Relax! Don’t do it…

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The psychological and physiological mechanisms underlying sexual inhibition

Dissertation

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CHAPTER 1.

General Introduction

In our everyday life we are faced with different kinds of rewarding stimuli that may evoke strong action tendencies. Whereas some of these stimuli are essential for survival (e.g. food), others are just very gratifying. Having evolved for reproduction purposes, sexual behaviour emerged as a strong incentive in life. However, as social organisms, human beings need regulatory mechanisms to express sexual behaviour in an adaptive manner. Whereas the capacities to inhibit sexual motivation and sexual behaviour are essential to avoid inappropriate or risky behaviours, a certain balance between sexual arousability and inhibition is needed so that an excess of inhibition does not lead to an undesired lack of sexual response. In this work, we aim to deepen our understanding on the mechanisms that allow individuals to control their sexual thoughts and behaviour.

A little bit of history…

Across time and culture, the failure to control sexual behaviour has been present and regarded as a deviant behaviour. The control of sexual behaviour was approached from different fields, such as philosophy, medicine, and religion. Regarding sexual compulsive behaviour, for instance, its characterisation as a medical condition has been described as early as 1800 and was referred to with different names such as ”don Juanism”, “satyriasis” for men, and “nymphomanism” for women. In 1953 the term “sexual addiction” was introduced and in recent years scholars and clinicians claimed for the recognition of “hypersexuality” as a psychiatric clinical condition (Carnes, 1953; Reid & Kafka, 2014). Explanations for other sexual deviant behaviours and preferences such as rape, sexual harassment, and paedophilia have also been targeted from the medical and sociological perspectives. However, in spite of the social and moral costs of out-of-control behaviours, the fundamental mechanisms that allow the control over sexuality have been poorly understood.

Almost one century ago Sigmund Freud proposed that the libido (sexual energy) was a central component and inherent motivational drive in human behaviour. Natural instincts and desires are part of individual’s psyche (id), some of which need to be suppressed or controlled. As the individual grows, he/she develops a superego, which comprises social rules and moral norms, avoiding that the id takes over the individual’s self (ego) (Freud, 1923). Later, Anna Freud described some defence mechanisms with which the *ego* could deal with ego threats (e.g. inconvenient sexual impulses), such as repression, denial, or sublimation (Freud, 1937).

Not much later, in 1930, but without aiming to study sexual behaviour, Paul Bucy and Heinrich Klüver, observed hyperorality, dampening in emotional expression, and hypersexuality (Klüver & Bucy, 1937) in monkeys after removal of the temporal lobe. A few decades further along, these symptoms were observed in humans after temporal lobectomy and other forms of brain damage in the same region (Terzian & Ore, 1955). The consistent presence of similar symptoms was characterised under the name of the Klüver-Bucy syndrome.

During the first half of the 20th century, experimental and physiological psychology evolved as scientific disciplines, and the methodological study of sexual behaviour came along briefly after. During the decades that followed an important advance in the scientific study of human sexual behaviour was made and even direct observations of human sexual behaviour were done in university laboratories (Masters & Johnson, 1966). Unfortunately, although a large body of valuable research was conducted on different forms of sexual disinhibition (e.g. sexual abuse), empirical research on the actual underlying inhibitory mechanisms and processes was entirely missing.

Sex is great, why worrying about sexual regulation?

As sexual stimulation is a highly rewarding behaviour, it can lead to many problematic situations, both on an individual and on a social level, if the proper regulatory mechanisms are absent. Like never before, modern societies are characterised by easy access to a wide and diverse sexual stimulation. It is estimated that at least 25 % of internet searches is pornography-related, being the most profitable revenue generator ("Internet Pornography", 2018). The use and abuse of pornography raises concerns about its role in generating addictive patterns, thereby interfering with the development and maintenance of satisfying interpersonal relationships, diminishing the ability to perform and enjoy regular sex, and portraying unequal gender representations, among others.

It has been suggested that the high accessibility, along with the privacy and anonymity implied in internet sex consumption, is an important risk factor for developing problems in, otherwise healthy but, vulnerable individuals. This implies that the continuous exposure to sexual material can develop preferences in a given person that he/she may have not previously considered or managed to control, such as sexual aggression or deviant interests. Along with habituation and tolerance symptoms, individuals could escalate their behaviours and act this out in real-life sexual encounters leading to risky practices or

violations of other's integrity (Young, 2008). To this regard, the study of the fundamental psychological mechanisms underlying the control of sexual thoughts, desires, and behaviour is paramount for providing new insight into the prevention and treatment of sexual disorders.

Sexual motivation and sexual inhibition

In order to conceptualise and understand the basic sexual inhibitory mechanisms, it is important to first characterise sexual motivation. Current views argue that unlike other biological needs, such as eating or drinking, sexual motivation is not an homeostatically driven mechanism, as no human being can die for not having sex. Instead, according to current incentive motivation models, sexual motivation can be elicited by (internal or external) stimuli and can be inferred from central, peripheral, or behavioural responses (Janssen, 2011). After a sexual stimulus is perceived, an automatic appraisal process takes place by concealing a motivational value towards it. When individuals process a positive conscious appraisal, a subjective sense of sexual desire and arousal is experienced, which further increases physical and subjective arousal. These ongoing responses may then trigger the motivation to actually engage in sexual activities (Toates, 2009). Without inhibition, sexual responses would most likely develop and unfold automatically (Everaerd, Laan, Both, & Spiering, 2001), thereby interfering with important relational and societal concerns. Inhibitory processes are in this sense a natural, adaptive reaction to contextual factors (Bancroft, 1999).

In line with the central role of sexual inhibition, John Bancroft and Eric Janssen developed the dual control model of sexual response, which states that the sexual response and associated sexual behaviours are the result of the interplay between inhibitory and excitatory mechanisms (Bancroft & Janssen, 2000). They identified two different types of sexual inhibition: a) a decrease of sexual arousal or sexual response related to fear of sexual performance failure and possibly related to a low inhibitory peripheral tone, and b) sexual inhibition caused by the threat of sexual performance consequences, such as the risk of sexual transmitted disease or undesired pregnancy. Thus, the first kind of inhibition is undesired, as the sexual response is inhibited when there is an intention to engage in sexual behaviour. On the contrary, the second type of inhibition is necessary as it constitutes an adaptive process to avoid potential harmful consequences. A certain balance between inhibitory processes and sexual excitation is required for adaptive behaviour, as an imbalance can lead to non-adaptive responses. For instance, if the levels of inhibition are high in

relation to the levels of excitation, this can lead to an impairment of the sexual response (i.e.- sexual dysfunction). On the contrary, low levels of inhibition (second type) in relation to high levels of sexual excitation can lead to out-of-control behaviour and risky sexual practices. Finally, a third type of inhibition has been proposed which is linked to the refractory period after the consummation of sexual activity and it is related to satiety mechanisms (Toates, 2009). However, this type of inhibition has been studied mainly from a physiological perspective in rodent models and goes beyond the scope of the present work.

The dual control model proposes that individuals vary in the extent in which they are inclined to become sexually aroused or inhibited. Sexual excitation and sexual inhibition have been widely studied with the Sexual Excitation/Inhibition Scales (Bancroft, Graham, Janssen, & Sanders, 2009) aiming to assess these inter-individual differences.

Conceptually, the incentive model theory and the dual control model may complement each other, as the first characterises the unfolding of sexual arousal responding and the second one refers to the interaction of excitatory and inhibitory mechanisms. Given that the processes determining sexual arousal operate at different levels, one may speculate that different parallel inhibitory mechanisms function at different levels as well (e.g. cognition, behaviour). However, a systematic study of these distinct and specific inhibitory mechanisms of sexual behaviour is currently missing.

The regulation of sexual behaviour from the brain

The neural mechanisms of the regulation of sexual behaviour are still scarcely understood. This is surprising and troublesome considering the possible negative consequences of unsuccessful sexual inhibition. From brain lesion studies it has been observed that impairments in the control of sexual behaviour can be caused by damage to frontal or temporal brain regions as well as to subcortical structures including the septal region, the pallidum, and the amygdala (Baird, Wilson, Bladin, Saling, & Reutens, 2007). Based on these lesion studies, it was proposed that ventral frontal brain damage causes sexual disinhibition as part of a generalised disinhibited behaviour while temporal lesions presumably increase sexual urges (Baird et al., 2007; Kühn & Gallinat, 2016). Nonetheless, the main limitation of lesion studies is the lack of focality which prevents a specific association between the damaged areas and affected fibers with particular cognitive (sub)processes.

The development of more detailed brain imaging techniques has clearly advanced our understanding of the human brain and its associated functions. As happened with Leeuwenhoek's curiosity to explore what sexual fluid looked like shortly after he invented the microscope, not a long time had to pass for researchers to investigate how brain activation looks during sexual cognition and even during orgasm (Komisaruk & Whipple, 2005; Tiihonen et al., 1994). However, the neural mechanisms underlying sexual regulation have been scarcely studied.

Different neuroimaging studies have aimed to identify functional and structural abnormalities in hypersexuality, pornography overuse, and paedophilia. In hypersexual individuals, an increased brain activity was observed in the right inferior frontal gyrus, the dorsal anterior cingulate cortex, the caudate, the ventral striatum, and the amygdala during the passive viewing of erotic stimuli (Seok & Sohn, 2015; Voon et al., 2014). Regarding pornography consumption, the more hours participants spent watching pornography, the less grey matter was observed in the right caudate and the less activation in the left putamen was observed while watching sexual images (Kühn & Gallinat, 2014). Paedophiles show a reduced size of the right amygdala and diverse functional differences during the passive viewing of erotic stimuli, including changes in the dorsolateral prefrontal and orbitofrontal cortices, and basal ganglia (Tenbergen et al., 2015). Finally, a recent study found that individuals who frequently performed risky sexual practices, engaged the anterior insula to a lesser extent during a response inhibition task involving sexual stimuli (Xue et al., 2018).

Without a doubt, studies that target to identify neural abnormalities are of high value and constitute an important scientific contribution. However, there are still many unresolved methodological issues that limit our understanding of causal brain-behaviour relationship in the domain of sexual regulation. On the one hand, even within the same kind of disorders, there is a high degree of variability regarding symptoms across individuals. For instance, regarding hypersexuality, some individuals may have symptoms that fit better into an addiction model whereas those from other individuals may resemble more obsessive-compulsive or impulse-control failure patterns (Bancroft & Vukadinovic, 2004). In the case of paedophiles, there is also a large difference among offenders and non-offenders. On the other hand, most of the functional neuroimaging studies have used paradigms that consist of the passive viewing of sexual stimuli, and very few have targeted functional differences during inhibitory processes.

We can observe that the wide and diverse spectrum of lack of control over sexuality may or may not involve another individual, may occur a single time or be repetitive, may or

may not comprise a moral component, may be phasic or continuous, and may be comprised at the cognitive or the action level. Compulsive masturbation, risky sexual practices, illegal pornography consumption, coercive sex, sexual harassment, and intrusive sexual thoughts, are some examples that illustrate the diversity of sexual dysregulation.

The book in your hands

As sexual regulation is a complex process, the purpose of this research line was to study the inhibitory processes that underlie sexual regulation in a systematic and differentiated manner. Several distinct questions need to be addressed. Is the regulation of sexual behaviour related to general self-regulation processes? And can we empirically separate the cognitive control of incoming sexual information from controlling a sexually motivated action?

In chapter two, we address these questions with a behavioural experiment in which participants performed computer-based tasks designed to assess two specific basic mechanisms of sexual regulation. We called these mechanisms *cognitive sexual inhibition* and *motivational sexual inhibition* as they target different psychological aspects of sexual regulation. To assess *cognitive sexual inhibition* we used a paradigm based on the negative priming phenomena (Negative Affective Priming). In brief, the negative priming effect consists of a delayed response to a stimulus caused by the previous inhibition of the same sort of stimulus. This process involves attentional inhibition and occurs automatically. To target *motivational sexual inhibition* we used a version of a widely used affective paradigm (Approach-Avoidance). This paradigm is inherently linked to motivational tendencies, as individuals intentionally control to either get closer or further away from a stimulus. Finally, to test the specificity of sexual inhibition and make comparisons with general response inhibition, we included a classic inhibition paradigm (Go/No-go task) which is related to a general non-affective control over impulses. We studied if these basic psychological processes were related to each other and if they could predict the frequency of real-life sexual thoughts and behaviours.

In chapter 3, we went one step further by investigating which brain regions are active when healthy individuals inhibit sexual incoming information versus controlling sexually driven actions (i.e. *cognitive sexual inhibition* and *motivational sexual inhibition*) in the MRI (Magnetic Resonance Imaging) scanner. This study revealed the specific neural correlates underlying the different sexual inhibitory processes. In addition, based on our within-subject-within-session functional MRI (fMRI) design, we were able to directly compare which brain

regions were commonly recruited by different kinds of sexual inhibition as well as general inhibition (Go/No-go task).

However, these data do not allow us to directly infer that the revealed brain regions or networks are indeed functionally necessary or essential for successful sexual inhibition. This question can only be addressed empirically by experimentally manipulating this brain activity using non-invasive neuromodulation techniques. Chapter four, describes a combined MRI-TMS (Transcranial Magnetic Stimulation) study, in which specific brain areas were experimentally and reversibly disrupted in order to investigate the functional necessity of different brain regions for the successful execution of different sexual inhibitory (sub)processes. Would the focal brain stimulation differentially affect distinct forms of sexual inhibition? Would the effect be the same for all participants?

FMRI and TMS are extremely helpful techniques to investigate the neural substrates of sexual inhibition. But the brain itself is part of a very complex organism, and multiple feedback mechanisms comprise the interaction between the brain and the rest of the body. Even more, our organism is designed to react to the environment demands and it does so along with the expression of different emotions. These emotions comprise important physiological changes in the body and influence cognition and behaviour. Chapter five takes a closer look into this topic. Specifically, we investigated the link between cortisol and the neural mechanisms of sexual approach-tendencies, to better understand the association between mood and sexual behaviour.

Finally, in a time where sexual graphic material is abundant and widely consumed, it is worth asking what factors could play a role in the emergence of excessive sexual interest and behaviour. Does it matter that individuals are easily aroused? And if a given individual is easily aroused, does it again not matter as long as he or she has proper regulation mechanisms in place? If human sexual behaviour is the result of biological, social, and psychological influences, what is the role of physiological mechanisms? To what extent can testosterone be relevant? Does the interaction of psychological traits and testosterone play a role? In chapter six we explored these questions.

The implications, limitations, and future directions of this series of studies are discussed in chapter seven.

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CHAPTER 2.

The role of inhibitory control mechanisms in the regulation of sexual behavior

Based on:

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Abstract

Sexual behavior is the open manifestation of a complex interplay between psychophysiological mechanisms that either facilitate or inhibit sexual thoughts, desires, and associated behaviors. Whereas sexual excitation has been widely studied, less is known about the impact of inhibitory control mechanisms that enable individuals to refrain from sexual cognition and behavior. The present study examined: (1) the relationship between general and sexual inhibitory mechanisms (as measured through self-reports and computer-based tasks), (2) the relation between sexual inhibitory processes at cognitive and motor-motivational levels and with sexual inhibition as an individual trait, and (3) the predictive value of these parameters on sexual thoughts (cognition) and behavior. We demonstrate that general inhibitory control (i.e., the ability to suppress any preponderant response) and the specific inhibition of sexual responses represent distinct processes that require at least partly different control mechanisms. Similarly, the ability to inhibit sexual visual input and the ability to suppress sexually driven responses seem to be two independent processes. The different inhibitory processes distinctively predicted the frequency of sexual thoughts and sexual behavior. We propose that these different inhibitory mechanisms are at play during different phases of sexual regulation (before and after the generation and unfolding of sexual arousal) and that a specific deficit in one of these processes may underlie the distinctive symptomatology and comorbidity of sexual disorders.

Introduction

Human sexuality is an essential part of our existence and comprises a broad range of aspects, including cognitive, emotional, behavioral, and physiological processes. These processes are modulated by a complex interplay between inhibitory (restrain, cancel, suppress) and excitatory (initiate, execute, promote) mechanisms, shaping the manifestation of sexual thoughts (cognition), desire (motivational state), and behavior. The successful inhibition of sexual expressions is a natural and adaptive reaction to contextual factors (Bancroft, Loftus, & Long, 2003) and enables the regulation of sexual behavior, thereby preventing undesired consequences for the individual and for society.

In spite of their relevance, sexual inhibitory mechanisms have been scarcely studied. When trying to understand sexual inhibition, it is important to specify its defining characteristics and differentiate it from other types of inhibition. A central question is whether the ability to regulate sexual cognition and behavior overlaps with an individual's general ability of behavioral control or whether it recruits inhibitory mechanisms specific to sexual behavior. On the one hand, there is evidence showing that both types of inhibition are interrelated. For example, efficient response inhibition of sexual stimuli was found to be inversely related to general impulsivity (Macapagal, Janssen, Fridberg, Finn, & Heiman, 2011). Likewise, high self-reported impulsivity was found to be related to a higher frequency of risky sexual behaviors (Curry et al., 2018; McCoul & Haslam, 2001), sexual compulsivity/hypersexuality (Miner, Raymond, Mueller, Lloyd, & Lim, 2009; Miner et al., 2016), low sexual restraint, and inclination towards infidelity (Gailliot & Baumeister, 2007). Additionally, the comorbidity of sexual disorders with other inhibition related disorders is not uncommon (e.g., ADHD, substance abuse; Bancroft & Vukadinovic, 2004). Further evidence comes from frontal brain damage patients, who sometimes exhibit inappropriate sexual behavior in the context of general disinhibition (Baird, Wilson, Bladin, Saling, & Reutens, 2007).

There is, however, also evidence pointing to the specificity of sexual inhibition, independently of general inhibition. For example, damage to non-frontal brain areas have led to specific forms of sexual disinhibition, such as compulsive masturbation, intrusive sexual thoughts, or sexual addiction in the absence of general inhibition deficits (Baird et al., 2007).

In addition, different sexual disorders are characterized by specific forms of sexual disinhibition. For example, while paraphilias are often characterized by obsessive sexual thoughts, pornography addiction leads to a compulsive urge to watch pornography, and some

forms of sexual addiction can lead to a promiscuous life, endangering health and personal and social relationships (Bancroft & Vukadinovic, 2004; Love, Laier, Brand, Hatch, & Hajela, 2015; Vella-Zarb, Cohen, McCabe, & Rowa, 2016). This suggests the involvement of various and specific inhibitory mechanisms in the regulation of sexual behavior.

To address the possibility of different sexual inhibitory processes, we refer to the process model of emotion regulation (Gross, 2002). Given that sexual arousal can be regarded as an emotion (Everaerd, Both, & Laan, 2006), this framework has a clear heuristic value for understanding sexual responding. According to this model, individuals can modulate their emotions either before they unfold via cognitive pathways, such as attention deployment or reappraisal, or after the emotions have unfolded via the suppression of the behavioral response. Accordingly, when an individual is aware of the risk of getting sexually aroused in inappropriate circumstances, he or she might redirect and focus the attention towards non-sexual stimuli or change the appraisal of the situation; but when the sexual arousal has initiated, it may be better suited to use avoidant actions or suppression mechanisms. We propose that these different regulatory processes, occurring at different phases in the regulation of sexual behavior, imply the existence of different inhibitory mechanisms, which in turn differentially overlap with certain aspects of one's general ability of inhibitory control.

However, in order to understand the regulation of the sexual response, not only the inhibitory mechanisms are relevant. According to the dual control model of male sexual response, it is the balancing between sexual inhibitory and sexual excitatory mechanisms that allows an adaptive sexual response consonant with the circumstances (Bancroft & Janssen, 2000). Whereas sexual excitation refers to the propensity to get sexually aroused or get an erectile response, sexual inhibition refers to processes that diminish that response.

Individuals vary in the degree to which they are sexually aroused and inhibited and these traits have been measured by the Sexual Excitation and Inhibition Scales (Janssen, Vorst, Finn, & Bancroft, 2002). Regarding sexual inhibition, two factors can be distinguished: SIS1–inhibition due to threat of performance failure, and SIS2– inhibition due to the threat of the consequences of the performance (Bancroft & Janssen, 2000). These factors measure psychophysiological traits, but far less is known about sexual inhibitory mechanisms measured as cognitive processes. Studying the basic processing of sexual inhibition is fundamental to understand the underlying mechanistic failure that lead to undesired consequences and sexual disorders.

Sexual Inhibition and General Inhibition

In this study, we primarily aimed to test whether general inhibition relates to sexual inhibition measured as traits and as processes. To study general and sexual inhibition traits, we selected the Brief Self-Control Scale (BSCS; Tangney, Baumeister, & Boone, 2004), which measures a general ability to control own behavior, and the second factor of the Sexual Inhibition Scale (SIS2; Janssen et al., 2002). We did not consider the first factor (SIS1) because it likely comprises a peripheral component (reflects the amount of effort needed to maintain an erection) and thus may reflect more a physiological-dependent process (Bancroft, Graham, Janssen, & Sanders, 2009). In contrast, the second factor (SIS2) constitutes an adaptive mechanism to prevent harmful consequences derived from the sexual performance (e.g., loss of arousal under the risk of getting a sexually transmitted disease).

To study general inhibition as a process, we selected the classic Go/No-go paradigm, in which individuals are required to restrain from responding to an infrequent stimulus. To assess sexual inhibition, we used the Approach-Avoidance (AA) task to measure the control over a motivationally driven motor response, thus comprising a peripheral inhibitory component.

We formulated the following propositions: Hypothesis 1–Sexual motor inhibition (AA) relates to general motor response inhibition (measured by the Go/No go task) as both processes require withholding a dominant motor response; Hypothesis 2–The second factor of Sexual Inhibition (SIS2) trait relates to general self-control (BSCS) as both traits comprise the ability to withhold actions that lead to pleasurable consequences by means of higher order processing such as preventing negative consequences or pursuing long-term goals.

Sexual Motor Inhibition, Sexual Cognitive Inhibition, and Sexual Inhibition as Trait

We further aimed to test whether different sexual inhibition processes relate to each other and to sexual inhibition as trait, or if they comprise distinct constructs. As we proposed that sexual inhibition does not compromise a unitary process, and that different mechanisms withhold the inhibition at different phases of the cascade of sexual arousal responding, we used two distinct paradigms to assess sexual inhibition. In addition to the AA task, which measures sexual motor inhibition, we selected the Negative Affective Priming (NAP) task. This task allowed us to study sexual inhibition at a central cognitive level, as subjects are required to ignore an affective distractor while attending a non-affective target; in a post-trial, the subjects are required to respond to a stimulus with the same content type than the one that was previous inhibited, which causes a response delay compared to non-priming trials.

We expected: Hypothesis 3–The two sexual inhibitory processes are not related, as one comprises cognitive processing (NAP) and the second (AA) comprises a rather "hot" component, as individuals are required to either approach or avoid sexual stimuli; Hypothesis 4–The second factor of Sexual Inhibition relates to sexual motor inhibition as process (AA) because both constructs imply the control over sexually rewarding actions and thus comprise a strong motivational and peripheral component.

Regulatory Mechanisms of Sexual Thoughts and Sexual Behavior

Finally, because we hypothesized that different inhibitory mechanisms play a distinct role at different levels of the sexual arousal unfolding, and because sexual responses and related behaviors result from the balance between excitatory and inhibitory mechanisms, we tested whether different general and sexual inhibition traits and processes along with sexual excitation (measured by the Sexual Excitation Scale; Janssen et al., 2002) predicted the frequency of typical sexual behaviors.

For this purpose, we selected sexual manifestations aimed to distinguish a cognitive and a behavioral component. Moreover, within the behavioral level, we distinguished between solitary and dyadic manifestations as dyadic sex involves social cognition and therefore may involve different inhibitory mechanisms. Specifically, we selected the frequency of sexual thoughts, for being a sexual process which does not manifest itself behaviorally; pornography watching, for being a private motivationally driven behavior; masturbation, for being a private behavior with a peripheral physiological output; and intercourse, for being a sexual behavior with a social component. We considered the frequency of those behaviors an indicator of the balance of the regulatory mechanisms in healthy conditions, as very high or very low frequencies could lead to undesired consequences or dissatisfaction.

In particular, we predicted that: Hypothesis 5–Sexual cognitive inhibition (NAP) predicts the frequency of sexual thoughts as sexual cognitive inhibition reveals the control over central processes through attention; Hypothesis 6–The sexual motor inhibition (AA) and general inhibition processes (Go/No-Go) relate directly to sexual behavior since they reflect the motor control over preponderant responses; Hypothesis 7–Sexual inhibition (second factor) and general inhibition (self-control) as traits have predictive value regarding sexual behavior, as both constructs measure the ability to control pleasurable actions at the foresight of long term consequences; and Hypothesis 8–Sexual excitability is a significant predictor of sexual thoughts and sexual behavior.

As women and men respond differentially during sexual cognitive and inhibitory processes (Dewitte, 2016; Sjoberg & Cole, 2018) and because women are less vulnerable to sexual inhibition impairments such as in hypersexuality (Kuzma & Black, 2008), we included only men in our sample to provide a first test of the role of inhibition in sexual responding.

Method

Participants

A total of 52 self-declared heterosexual male participants (18-35 years old; M age = 24.46; SD = 4.32) were recruited through advertising in Maastricht University halls and in a Facebook group created to recruit participants for research at Maastricht University. All of the participants were financially reimbursed for their participation with 10 Euros in vouchers. The study was approved by the local ethical committee. A total of 90.3% of participants were Bachelor or Master students; from the rest, three participants had completed university and two had completed high school. Approximately half of the participants were single (53.8%); the others had been in a relationship for an average period of 2.7 years (SD = 2.85). Single and coupled men did not differ in age nor in individual traits (sexual excitability, sexual inhibition, and self-control) measured by self-reports.

Procedure and Measures

After giving their informed consent, participants performed three computer-based tasks: two sexual (Negative Affective Priming task and Approach-Avoidance task) and one non-sexual (Go/No-go task). The order in which the two sexual tasks were presented was counterbalanced. The Go/No-go task was always presented between the sexual tasks to prevent habituation to sexual stimuli. The questionnaires were completed at the end of the session. To increase the confidence of participants on the anonymity of their answers and increase their comfort, their identities were registered as number codes and they were left alone in the room while answering.

Negative Affective Priming Task (NAP)

Our version of the task (adapted from Dewitte, 2016) consisted of three blocks containing 32 trial sequences each. There were four types of trial sequences which were presented randomly in equal proportion throughout each block. Each trial sequence consisted of a prime trial and a probe trial. During each, two pictures were simultaneously presented, one surrounded by a black frame and the other by a gray frame. Images were presented above

each other. Participants had to attend only to the black frame picture (target) while ignoring the one with the gray frame (distractor) and to indicate whether the target displayed sexual or non-sexual content by button-press.

During the experimental trial sequences (Priming), the content of the distractor picture in the prime trial matched the content type of the target in the probe trial, whereas in the control trial sequences (No Priming) the content of these two pictures differed. The target in the probe trial could be sexual or non-sexual. This way, there were four different conditions: Sex Priming (sexual distractor in the prime trial with a sexual target in the probe trial), Sex No Priming (non-sexual distractor in the prime trial with a sexual target in the probe trial), Non-Sex Priming (non-sexual distractor in the prime trial with a non-sexual target in the probe trial), and Non-Sex No Priming (sexual distractor in the prime trial with a non-sexual target in the probe trial) (Figure 1a). The prime and probe trials were presented for 1750 ms each, separated by a fixation cross presented for 1750 ms. The interval between the trial sequences was filled with the same fixation cross for 1750 ms and was not jittered so that the participants did not identify that the prime and probe trials were part of a predefined trial sequence (Figure 1b). The sexual stimuli were pictures (320 x 260 pixels) displaying sexual intercourse or oral sex between one man and one woman. The non-sexual stimuli were color pictures of one man and one woman exercising together. The neutral stimuli (distractors in the probe trials) were pictures of neutral objects (e.g., light switch). Pictures were displayed on light gray background and the picture frames were three pixels thick. Most of the images (85%) were drawn from validated data sets that were evaluated on the basis of valence and arousability (Dewitte, 2016; Rupp & Wallen, 2007). As there were not enough available images from the previous data sets, the remaining images were selected from the internet and approved by three judges considering that the content was similar to those of the rated photographs, mainly regarding body postures, positions, and dimensions.

As the inhibitory effect is implied from the response delay in priming conditions, we calculated a sexual priming index by subtracting the reaction times in Sex No Priming trials to those of Sex Priming trials. Because we were specifically interested in the sexual priming effect, we subtracted a non-sexual priming index to the sexual priming index ([Sex Priming–Sex No Priming] – [Non-Sex Priming–Non-Sex No Priming]) to exclude the non-sexual inhibitory component. This index was the main score used for this task. A higher index indicated a stronger sexual priming effect and thus, a stronger sexual inhibition.

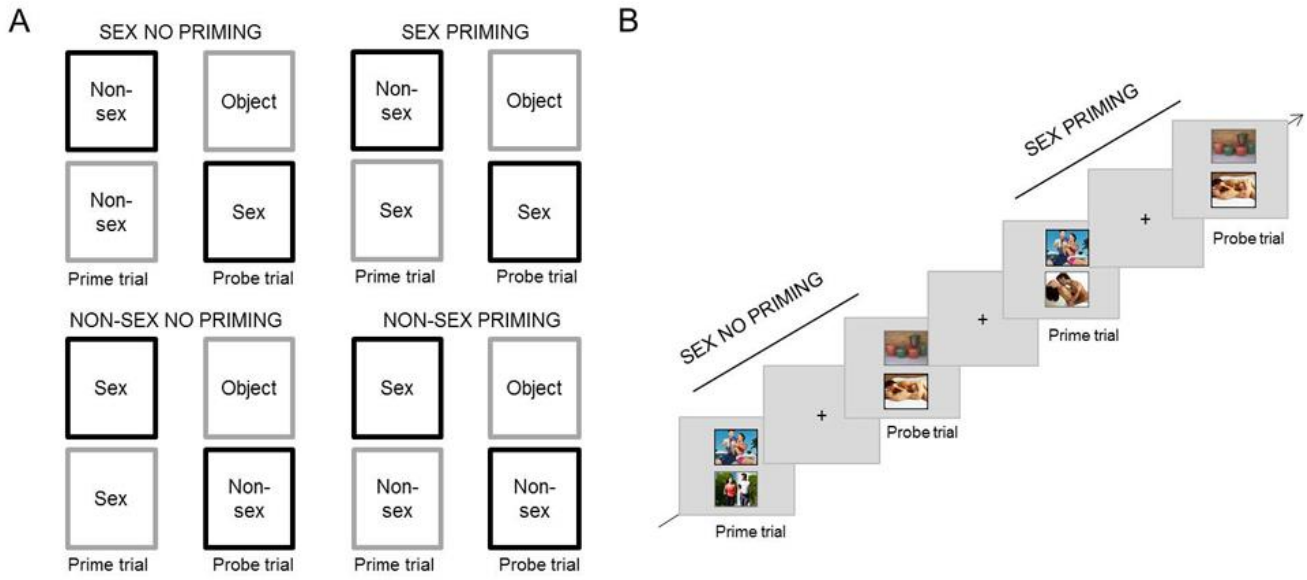

Figure 1. Negative Affective Priming task (NAP). (A) Four conditions: In the two priming conditions (Sex and Non-Sex) the content of the distractor in the prime trial matched the content of the target in the probe trial. In the no priming conditions, the content of the distractor in the prime trial was different from the content of the target in the probe trial. (B) Timeline: Example of a Sex Priming and a Sex No Priming trial.

Approach-Avoidance Task (AA)

This task consisted of four blocks with 48 stimuli each, half of them of sexual content and the rest with non-sexual content (adapted from Dewitte, 2016). Participants were told that in some blocks they would have to approach the sexual stimuli and avoid the non-sexual ones, whereas in other blocks they would have to do the opposite. To approach a stimulus, they were instructed to move the joystick towards them, mentioning that this implied the notion to bring the stimulus closer. With doing so, the image size increased. To avoid the stimulus, they had to push the joystick away from them, which implied the notion of pushing the stimulus away, and decreased the image size. They performed 20 practice trials, using plants and animals as stimuli, so that they got acquainted with associating the movement of the joystick with the respective resizing of the image.

Sexual stimuli consisted of 48 color photographs displaying sexual intercourse or oral sex between one man and one woman; these pictures were different from those used in the NAP task and 95% of them were drawn from a validated data set (Rupp & Wallen, 2007). The rest of photographs were selected from the internet on the same basis that the Negative Affective Prime task photographs. The purpose was that every image would be presented only once for every condition (approach-avoid). Non-sexual stimuli consisted of 48 color

photographs of one man and one woman dancing (Dewitte, 2016). The proportion of the exposition of the bodies (with special attention to the female body) in respect to the whole picture was comparable in both conditions. In half of the blocks, the photographs were horizontally (337 X 272 pixels) orientated, while in the other half vertically (257 X 400 pixels); this distribution was because there were not enough number of rated photographs with the same orientation. The image resizing halved or doubled the default size. Images were displayed on a light gray background. In two of the four blocks, participants were instructed to approach the sexual stimuli (presented in 50% of the trials included in the block) and to avoid the non-sexual stimuli. For the remaining blocks, they were instructed to do the opposite. Every trial consisted of the presentation of one sexual or non-sexual stimulus for 1750 ms followed by a randomized interval of 1750, 3500 or 5250 ms (Figure 2).

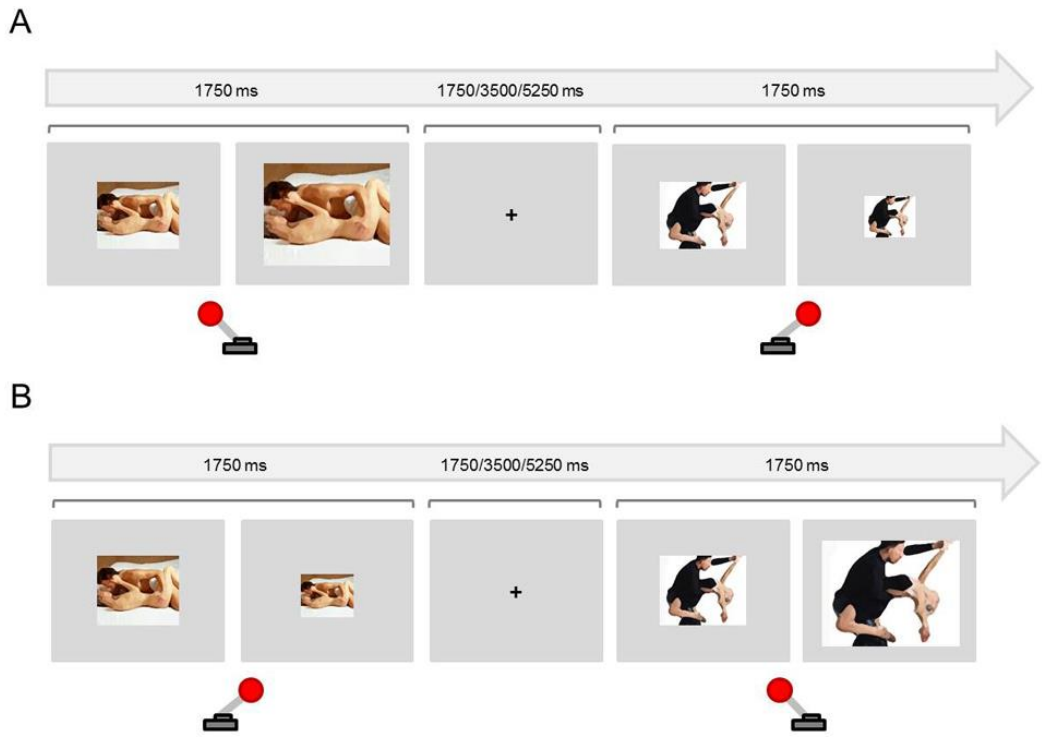

Figure 2. Approach-Avoidance Task (AAT). (A) Sex Approach block: Participants were instructed to approach (pull joystick towards themselves) images with sexual content and to avoid (pull joystick away from themselves) non-sexual photographs. Approach caused an increase, while avoidance caused a decrease in image size. (B) Sex Avoid block: Participants were instructed to avoid images with sexual content and approach images with non-sexual content.

The order of the blocks was counterbalanced. We calculated a Sex Approach-Avoid index, by subtracting the reaction times in Sex Approach blocks from reaction times in Sex Avoid blocks. To control for non-sexual approach-avoidance reaction times, we subtracted the

analogous Neutral Approach-Avoidance index, which resulted in the main index used for this task. A larger index indicated a stronger control over sexual motivation, as this implied taking less time to avoid sexual stimuli and/or taking longer to approach them.

Go/No-go Task

In this task, participants were instructed to press the spacebar when they saw a frequent Go stimulus and to not respond to the infrequent No-go stimulus. As stimuli, the letters "C" and "M" were used and which letter was defined as the Go or No-go stimulus was counterbalanced among participants. White letters (3 X 2.3 cm) were displayed on gray background (adapted from Dambacher et al., 2014). Participants had to complete four blocks of 80 trials each (25% No-go trials). Every trial consisted of the presentation of the stimulus for 650 ms, followed by an inter-trial interval of 1500, 2350 or 4050 ms (Figure 3). Responses after 650 ms were not registered. Hits (responding to a Go trial), correct No-go's (not responding to a No-go trial), false alarms (responding to a No-go trial), and misses (not responding to a Go trial) were recorded. A higher number of false alarms indicated a low response inhibition. The three computer-based tasks were programmed and presented with PsychoPy (Peirce, 2007).

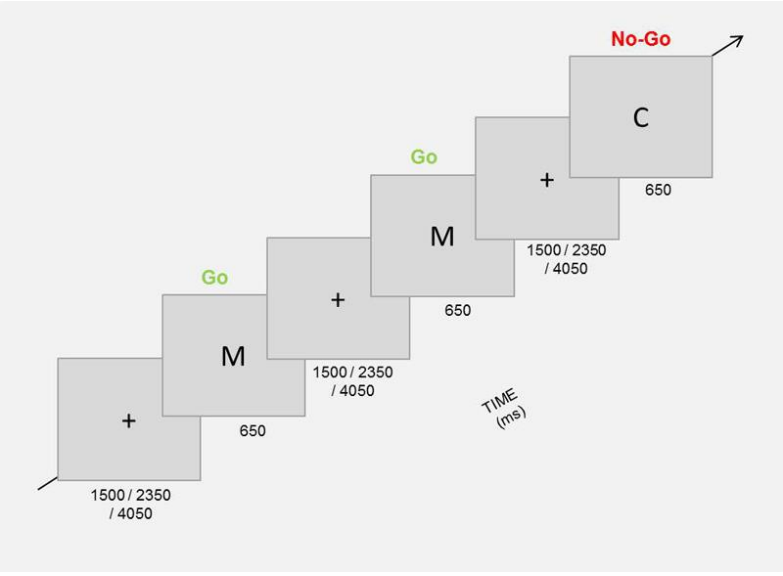

Figure 3. Go/No-go task design. Participants were asked to respond to the frequent stimulus (Go) and to not respond to the infrequent stimulus (No-go).

Brief Self-Control Scale (BSCS)

This scale consists of 10 items assessing the extent to which an individual is able to regulate his/her own behavior by resisting or inhibiting a preponderant response or desire in order to achieve long-term goals (Example item: "I am good at resisting temptation"). Participants could choose from a 1-5 point Likert scale ranging from *Not at all* to *Very much.* BSCS scores range from 13-65, with a higher number indicating more self-control. High internal consistency and test-retest reliability have been demonstrated for this scale (Tangney et al., 2004).

Sexual Inhibition/Sexual Excitation Scales (SIS/SES)

This 45 items scale measures the propensity for sexual inhibition and excitation. It contains one factor quantifying sexual excitation (Example item: "When an attractive person flirts with me, I easily become sexually aroused") and two factors quantifying sexual inhibition: (1) SIS1–Inhibition derived from threat of sexual performance failure, distraction, or lack of physical stimulation (Example item: "Once I have an erection, I want to start intercourse right away before I lose my erection"), and (2) SIS2–Inhibition due to the threat of performance consequences, such as risk of being caught or sexually transmitted diseases (Example item: "If I can be seen by others while having sex, I am unlikely to stay sexually aroused"). Response options were on a 4-point Likert scale (ranging from 1 = strongly agree to 4 = strongly disagree; Janssen et al., 2002). The raw scores were inversed in a way that a higher score would indicate a higher excitability (SES, possible range: 20-80) or inhibition (SIS1, possible range: 14-56; SIS2, possible range: 11-44). Previous studies showed solid internal consistency and test-retest reliability for the factors SES, SIS1, and SIS2 (Janssen et al., 2002).

Sexual Behavior

In order to have an index of the individual's sexual cognition and sexual behavior (solitary and dyadic), participants answered according to their experience during the last four weeks how often they: (1) Thought about sex, (2) Watched pornography, (3) Masturbated, and (4) Had sex (intercourse with penetration). Participants could answer on a 6-point Likert scale, ranging from *Not once* to *Several times a day.*

Results

Mean and SD for the self-report measures and sexual behaviors are shown in Table 1. As relationship status was expected to influence different aspects of sexual behavior (e.g.,

intercourse frequency), the descriptive statistics are shown for the total sample and for partnered and single men separately. Table 2 shows the percentage of participants reporting a determined frequency of sexual thoughts and sexual behaviors during the last four weeks.

Table 1. Descriptive and comparative statistics of partnered and single men.

	Total n = 52 M (SD)	Partnered n = 24 M (SD)	Single men n = 28 M (SD)	t [p]
Age	24.46 (4.32)	25.08 (4.46)	23.93 (4.21)	ns
Sexual Excitation Scale [a]	50.62 (7.19)	50.58 (6.37)	50.64 (7.9)	ns
Sexual Inhibition Scale 2 [b]	29.98 (4.41)	29 (4.14)	30.82 (4.53)	ns
Brief Self-Control Scale [c]	41.46 (7.79)	40.58 (9.23)	42.21 (6.39)	ns
Sexual thoughts	5.06 (.99)	5.29 (.75)	4.86 (1.14)	ns
Masturbation	3.77 (1.06)	3.75 (1.22)	3.79 (.91)	ns
Pornography watching	3.13 (1.21)	2.96 (1.23)	3.29 (1.18)	ns
Intercourse	2.52 (1.46)	3.45 (.21)	1.71 (.24)	-5.31*

* $p < .001$.

[a] Range: 30-64, [b] Range: 22-43, [c] Range: 27-61.

Table 2. Percentage of participants reporting a determined frequency of sexual thoughts and sexual behaviors during the last four weeks.

	Sexual thoughts	Masturbation	Pornography watching	Intercourse
Several times a day	40.4	3.8	0	0
Once a day	32.7	15.4	9.6	7.7
A few times a week	23.1	51.9	40.4	26.9
Once a week	0	13.5	13.5	17.3
One or two times per month	3.8	13.5	26.9	5.8
Not once	0	1.9	9.6	42.3
Total	100	100	100	100

Computer-Based Tasks

Negative Affective Priming Task (NAP)

A 2 (Stimuli: Sex vs. Non-Sex) X 2 (Condition: Priming vs. No Priming) ANOVA revealed a main effect of priming condition ($F(1, 50) = 15.52$, $p = .001$; Priming: $M = 837$, $SD = 143$, No Priming: $M = 811$, $SD = 145$), and an interaction between stimuli and condition ($F(1, 50) = 8.15$, $p = .006$; Table 3). No main effect was found for stimulus type ($F(1, 50) = 1.11$, $p = .29$; Sex: $M = 820$, $SD = 147$ ms, Non-Sex stimuli: $M = 829$, $SD = 145$; Figure 4a). Concordant with previous evidence (Dewitte, 2016), the priming effect was significantly larger for sexual than for non-sexual stimuli ($t = 2.85$, $p = .006$; Sexual Priming effect: $M = 42$ ms, $SD = 68$, Non-Sexual Priming effect: $M = 10$ ms, $SD = 53$), showing that the omission of visual sexual stimuli requires stronger inhibition.

Approach-Avoidance Task (AA)

A 2 (Stimuli: Sex vs. Control) X 2 (Condition: Approach vs. Avoidance) ANOVA revealed that participants were faster responding to sexual than to control stimuli ($F(1, 50) = 13.93$, $p = .001$; Sex trials: $M = 1024$, $SD = 198$ ms, Control trials: $M = 1055$, $SD = 183$ ms), which is in concordance with previous evidence (Dewitte, 2016; Hofmann, Friese, & Gschwendner, 2009). Reaction times on approach and avoid trials did not differ ($F(1, 50) = .28$, $p = .59$; Approach trials: $M = 1037$, $SD = 188$ ms, Avoid trials: $M = 1041$, $SD = 195$ ms), and there was a significant interaction between stimuli and condition ($F(1, 50) = 8.07$, $p = .006$), indicating a faster response approaching sexual stimuli over the other conditions (Table 3; Figure 4b).

Go/No-go Task

Participants committed on average 19.51 ($SD = 14.62$) false alarms and 7.86 ($SD = 8.91$) misses (Figure 4c). On false alarms, reaction times were faster than on Go trials (False alarms: $M = 242$, $SD = 36$ ms, Go trials: $M = 358$, $SD = 34$ ms; $t = -15.49$, $p = .001$). For further analyses, false alarms were log transformed to correct skewness. To examine whether relationship status would influence performance on the implicit measures, we conducted a series of tests, which revealed that single and partnered men did not differ significantly in their performance on none of the three tasks.

Table 3. Reaction times of the different conditions in the Negative Affective Priming and in the Approach-Avoidance tasks.

Negative Affective Priming task			
		M (SD)	
Sexual	*Priming*	*Sexual Priming*	*Sexual No Priming*
820 (147)	837 (143)	840 (155)	798 (147)
Non-sexual	*No Priming*	*Non-sexual Priming*	*Non-sexual No Priming*
829 (145)	811 (145)	834 (145)	824 (151)
Approach Avoidance task			
		M (SD)	
Sexual	*Approach*	*Sexual Approach*	*Sexual Avoid*
1024 (198)	1037 (188)	1004 (202)	1040 (206)
Non Sexual	*Avoid*	*Non-Sexual Approach*	*Non-Sexual Avoid*
1055 (183)	1041 (195)	1066 (181)	1040 (194)

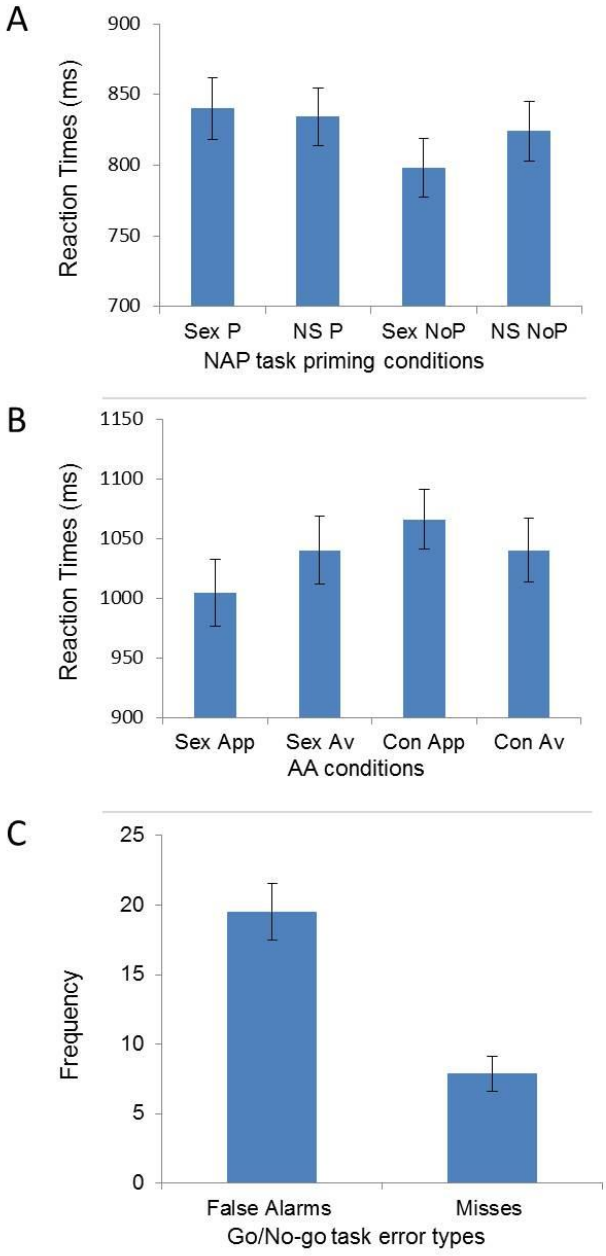

Figure 4. Descriptive statistics of the cognitive tasks. (A) NAP – Negative Affective Priming: Sex P – Sex Priming trials; NS P – Non-Sex Priming trials; Sex NoP – Sex No Priming trials; NS NoP – Non-Sex No Priming trials. (B) AA – Approach-Avoidance task: Sex App – Sex Approach trials; Sex Av – Sex Avoid trials; Con App – Control Approach trials; Con Av – Control Avoid trials.

Sexual Inhibition and General Inhibition

None of the relationships between general inhibition (Go/No-go task), self-control (BSCS), sexual cognitive inhibition (NAP), sexual motor inhibition (AA), and sexual inhibition as a trait (SIS2) were significant (Table 4).

Sexual Motor Inhibition, Sexual Cognitive Inhibition, and Sexual Inhibition as Trait

To investigate whether sexual motor inhibition, sexual cognitive inhibition, and sexual inhibition as a trait were related, we performed correlation analyses (Table 4). There were no significant relationships among these processes and trait.

Table 4. Correlational statistics between sexual inhibition, general inhibition, and self-control.

	Sexual Inhibition			General Inhibition and Self-Control	
	NAP CI (*p*)	AA CI (*p*)	SIS2 CI (*p*)	GNG FA log CI (*p*)	BSCS CI (*p*)
NAP	1	.07 [-12,.32] (.59)	.01 [-.23,.29] (.97)	.03 [-.28,.35] (.86)	-.21 [.45,.07] (.13)
AA		1	.6 [-.21,.32] (.68)	-.01 [-.26,.18] (.91)	.04 [.17,.25] (.77)
SIS2			1	.15 [-.12,.43] (.28)	.04 [.17,.25] (.77)
GNG-FA log				1	-.17 [.45,.04] (.21)
BSCS					1

NAP – Negative Affective Priming task; AA – Approach-Avoidance task; SIS2 – Sexual Inhibition Scale Factor 2; GNG FA log – Go/No-go false alarms (log-transformed); BSCS – Brief Self-Control Scale. CI – Confidence Intervals (95%, bootstrap resamples = 1000). In brackets: lower and upper limits. (*p*) – Alpha value.

Regulatory Mechanisms of Sexual Thoughts and Sexual Behavior

To investigate whether sexual inhibition, general inhibition, self-control, and sexual excitation were related to the frequency of different sexual manifestations, we performed correlation and multiple regression analyses. In Table 5, the correlation among these variables derived from the computerized-based tasks and the self-reports is shown. We conducted separated analyses to predict the frequency of sexual thoughts, solitary sexual behavior (pornography watching and masturbation), and dyadic sexual behavior (intercourse).

Table 5. Correlational statistics between sexual inhibition, general inhibition, and sexual excitation measurements, and sexual manifestations frequency.

	Tasks			Self-reports		
	NAP CI (*p*)	AA CI (*p*)	GNG FA log CI (*p*)	SES CI (*p*)	SIS2 CI (*p*)	BSCS CI (*p*)
Sexual Thoughts	-.36 [-.57, -.13] (.01)	.13 [-.21,.47] (.32)	.02 [-.26,.35] (.84)	.26 [.001, .48] (.06)	-.01 [-.28,.25] (.92)	-.04 [-.32,.21] (.77)
Masturbation	-.14 [-.38,.08] (.32)	.15 [-.21,.41] (.27)	.04 [-.23,.37] (.75)	-.004 [-.23,.24] (.97)	-.11 [-.39,.21] (.47)	-.23 [-.48,.04] (.08)
Pornography	-.04 [-.29,.21] (.76)	.27 [-.05,.52] (.04)	-.03 [-.34,.29] (.83)	.06 [-.18,35] (.62)	-.16 [-.36,.11] (.25)	-.26 [-.51,.01] (.06)
Intercourse	.01 [-.23,.32] (.91)	.08 [-.36,.21] (.56)	.23 [-.04,.49] (.11)	.11 [-.11,.38] (.46)	-.31 [.05,.52] (.02)	.03 [-28,.21] (.83)

NAP – Negative Affective Priming task; AA – Approach-Avoidance task; GNG FA log – Go/No-go false alarms (log-transformed); SES – Sexual Excitation Scale; SIS2 – Sexual Inhibition Scale Factor 2; BSCS- Brief Self-Control Scale. CI – Confidence Intervals (95%, bootstrap resamples = 1000). In brackets: lower and upper limit. (*p*) – Alpha value.

To predict the frequency of sexual thoughts, we entered sexual cognitive inhibition (NAP) index and Sexual Excitation (SES) scores to the model. To predict the frequency of pornography watching, masturbation, and intercourse, we entered the sexual motor inhibition (AA) and general inhibition (Go/No-go–log transformed number of false alarms) indices, along with the self-control (BSCS), sexual inhibition (SIS2), and sexual excitation (SES) trait scores in separate models. To exclude the fact that sexual cognitive inhibition (NAP) would predict the frequency of sexual behavior or that sexual motor inhibition (AA) and sexual inhibition as a trait (SIS2) would predict the frequency of sexual thoughts, we repeated the same analyses including both sexual inhibition processes and sexual inhibition as trait into the models. These variables were included stepwise into the model as we did not have a priori predictions about which variables would be more relevant in predicting the different sexual manifestations.

Table 6. Multiple regression models predicting sexual thoughts, individual sexual behavior, and intercourse.

	B	T	*p*
Sexual thoughts			
Negative Affective Priming task	-.37	-2.8	.007
Sexual Excitation Scale	.26	2.01	.05
Masturbation			
	--	--	ns
Pornography watching			
Approach-Avoidance task	-.29	-2.2	.03
Brief Self-Control Scale	-.29	-2.16	.03
Intercourse			
Sexual Inhibition Scale 2	-.29	-2.1	.04

The regression analysis showed that sexual cognitive inhibition (NAP) and sexual excitability predicted the frequency of sexual thoughts (R^2 = .21; p = .005; Table 6; Figure 5a and b). Results indicated that a higher frequency of sexual thoughts was associated with a lower sexual priming effect (less sexual cognitive inhibition) and a higher sexual excitability.

These results did not change when sexual motor inhibition (AA) and sexual inhibition as trait (SIS2) were entered into the model. None of the variables significantly predicted the frequency of masturbation. The frequency of watching pornography, on the other hand, was inversely predicted only by sexual motor inhibition (AA) and the degree of self-control (BSCS) (R^2 = .16; p = .016; Table 6; Figure 5c and d). The self-reported sexual inhibition due to sexual performance consequences (SIS2) inversely predicted the frequency of intercourse (R^2 = .08; p = .04; Table 6; Figure 5e). Including sexual cognitive inhibition (NAP) in the models to predict sexual behavior (masturbation, pornography watching, and intercourse frequency) did not add a predictive value.

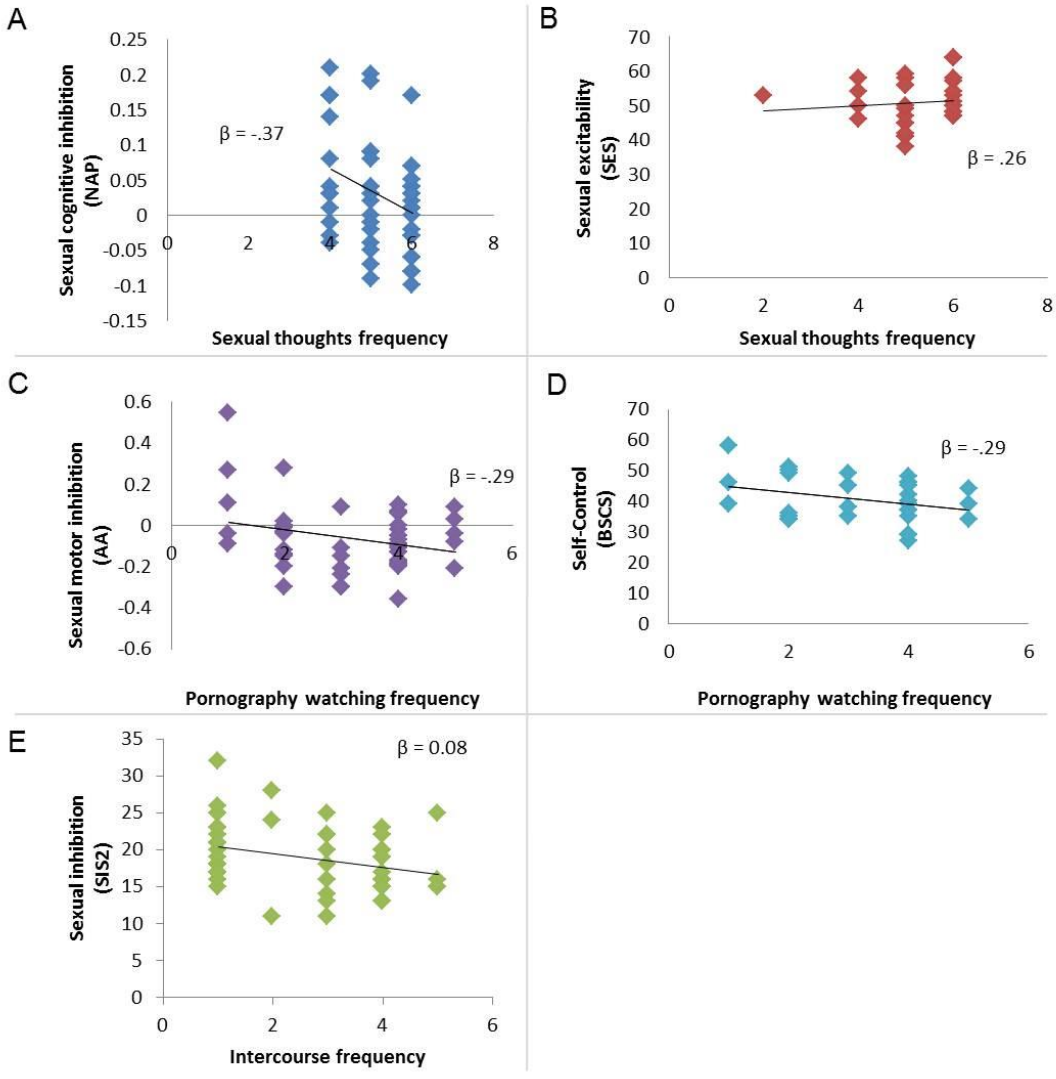

Figure 5. Significant predictors of the frequency of sexual thoughts, individual sexual behavior, and intercourse.

Discussion

In the current study, we aimed to deepen our understanding of the inhibitory mechanisms that are potentially involved in regulating sexual cognition and behavior. First, we aimed to study if sexual inhibition was related to general inhibition, measured both as processes and as traits. Additionally, we examined whether sexual inhibition would comprise distinct mechanisms that would work at different levels. Here, we considered cognitive and motor-motivational processes and if these would relate to sexual inhibition as a trait. Finally, we examined if the different inhibitory processes and traits (general and sexual) along with sexual excitation as a trait distinctively predicted the frequency of two spheres of sexuality: thoughts and behavior.

Sexual Inhibition and General Inhibition

Regarding the question of whether sexual inhibition and general inhibition as traits and processes would constitute different or related constructs, our results showed no significant relationship between sexual and general inhibition as processes. Contrary to our prediction in Hypothesis 1, the ability to inhibit a sexually driven response (AA) seems independent from the general ability to suppress a preponderant response (Go/No-go). Similarly, we did not find support for Hypothesis 2 which predicted that the general ability to control behavior regarded as trait (self-control) would relate to the degree to which individuals inhibit their sexual arousal due to the risk of undesired consequences (SIS2). Altogether, these findings do not support that sexual inhibition derives from a general inhibitory domain and instead requires specific cognitive mechanisms. Although general inhibition deficits can impact on sexual behavior as seen in frontal brain damage patients (Baird et al., 2007), our results indicate that additional mechanisms exist to inhibit different sexual manifestations.

Sexual Motor Inhibition, Sexual Cognitive Inhibition, and Sexual Inhibition as Trait

Hypothesis 3 predicted that sexual cognitive inhibition and sexual motor inhibition were not related, which was supported by our results. The sexual priming effect (measuring sexual cognitive inhibition) involves the capacity to inhibit sexual visual information. To this regard, it had been debated whether the negative priming effect reflected retrieval or inhibition processes (Mayr & Butchner, 2007; Frings, Shneider, & Fox, 2015). However, inhibition and retrieval are intrinsically linked in the negative priming effect: retrieving the content type of the distractor from the prime trial is a prerequisite for the inhibitory process to happen in the probe trial. In addition, we controlled for a neutral negative priming effect, in which the retrieval process was equivalent, and therefore, we can imply that we specifically targeted the inhibitory component.

In regard to sexual motor inhibition, the active avoidance of sexual stimuli implies control over the motor system to inhibit an inner reward-driven response. Typically, the automatic appraisal of a rewarding stimulus evokes approach tendencies. Avoiding this stimulus requires control over those motivational motor tendencies. This inhibitory component is reflected by the delayed response times in avoiding sexual stimuli as compared to approaching them. Thus, sexual cognitive inhibition and sexual motor inhibition comprise different processes and the lack of relationship between them supports the idea that there are different mechanisms to regulate sexual cognition and behavior. This diversity may constitute the core of the complexity and variety of sexual disorders.

Contrary to what was predicted in Hypothesis 4, the ability to inhibit sexually driven motor responses (AA) did not relate to sexual inhibition as a trait (SIS2). This may indicate that the approach-avoidance paradigm is not sensitive enough to reflect the inhibition of sexual arousal in quotidian circumstances. It is also possible that what is measured by this factor of the SIS (loss of sexual arousal and erection due to fear of sexual performance consequences) is inherently different from the motor response to approach or avoid a sexual stimulus; whereas the latter constitutes an intentional action, the former one refers to the automatic body response as a product of fear of the sexual performance consequences (even if the fear derives from a realistic risk).

Regulatory Mechanisms of Sexual Thoughts and Sexual Behavior

Finally, we examined whether the different inhibitory processes and traits, on the one hand, and sexual excitability, on the other hand, would distinctively predict specific sexual expressions. We expected that the sexual cognitive inhibition would predict the frequency of sexual thoughts (Hypothesis 5). Our results supported this hypothesis, which is in line with the process model of emotion regulation (Gross, 2002), stating that successful attentional direction prevents the emotional response (arousal) to take place, thereby preventing the sexual thoughts to interfere with quotidian goals. The fact that the sexual priming effect predicted only sexual thoughts but not sexual behavior, points to the specificity of this cognitive process and suggests that inhibiting sexual input information at a cognitive level may not be central in inhibiting actual overt behavior.

To inhibit sexual behavior, other inhibitory mechanisms are needed. Hypothesis 6 predicted that sexual motor inhibition and general inhibition as processes would directly relate to sexual behavior. The ability to inhibit sexually driven motor responses (sexual motor inhibition) predicted the frequency of watching pornography. This finding is in line with previous research showing that this task correlates with sexual behavior at the implicit level

(viewing time of erotic stimuli) but not at the explicit level (choosing a sex calendar over an art calendar) (Hofmann et al., 2009). It seems that the sexual AA reveals an inner motivation that is not overtly expressed but is still manifested at the individual behavior level.

General motor response inhibition (Go/No-go false alarms) did not predict the frequency of any sexual manifestation. This was unexpected, as in a previous study sexually compulsive individuals committed more false alarms and misses in the same task (Miner et al., 2009). It is possible that the relationship between general motor response inhibition and sexual inhibition is only present in extreme cases and that our sample did not include enough of these cases (individuals with a high frequency of sexual manifestations) to show this relationship. In this way, high or medium general inhibition may not be necessarily associated with high or medium sexual inhibition, but only extremely low general inhibition may be related to extremely low sexual inhibition. Furthermore, a previous study showed that in addition to self-reported impulsivity, the level of abstract intelligence was associated with the commission of false alarms in a Go/No-go task under a sexual arousing condition (Macapagal et al., 2011). Thus, it may not be the failure in general inhibition alone but its combination with other factors which causes a failure in sexual inhibition.

Hypothesis 7 predicted that inhibitory traits (sexual inhibition and self-control) would also predict sexual behavior. Self-control was also a significant predictor of the frequency of watching pornography. In quotidian life, one should overcome pleasant temptations in order to achieve mid- and long-term goals. In this regard, self-control is relevant to regulate a behavior that can be highly rewarding, and unlike intercourse, risk-free and easily accessible. The frequency of intercourse was predicted by sexual inhibition as a trait (SIS2). This construct emphasizes the decrease of sexual arousal and erectile response under the risk of future consequences. Therefore, the inhibition of sexual physiological responses occurring through higher order processing (anticipation of negative consequences or moral cognition) seems crucial in the regulation of dyadic sex. This is relevant since the failure of this inhibitory mechanism would presumably lead to harmful consequences for the individual and for others. In fact, this factor has been previously related to risky sexual behavior (Bancroft et al., 2004; Janssen & Bancroft, 2007). Additionally, this factor (SIS2) did not predict non-dyadic sexual aspects (i.e. sexual thoughts, masturbation, or pornography watching), which is not surprising as this trait taps into the inhibition involved when there is a threat, and non-dyadic sexual behaviors rarely pose any evident risk or danger. Noticeably, no process or trait was able to predict the frequency of masturbation. It is possible that this individual sexual behavior is more influenced by mood regulation and sexual attitudes (Bancroft &

Vukadinovic, 2004).

Finally, Hypothesis 8 predicted that sexual excitability would be a significant predictor of sexual thoughts and sexual behavior. Remarkably, sexual excitability predicted only the frequency of sexual thoughts. Because sexual thoughts are not manifest and belong to one's inner fantasy world, they require less inhibitory efforts to accomplish social and moral requirements and, thus, might be more susceptible to arousability levels. The fact that sexual excitability was not a predictor of either individual or dyadic sexual behavior emphasizes the dominant role of inhibitory and regulatory mechanisms in the expression of sexual behaviors. In this sense, while excitability and sexual inhibition modulate the amount of sexual thoughts, the behavior itself seems rather regulated by inhibitory mechanisms, which would imply that individuals who are easily aroused do not necessarily engage in more sexual behavior. Instead, the sexual behavior of individuals would depend mainly on inhibition and self-control rather than excitability levels, with different inhibitory processes regulating different aspects of sexual thoughts, desire, and behavior.

Limitations

This study supports the idea that multiple inhibitory mechanisms exist in the regulation of sexual cognition and behavior. These different inhibitory mechanisms modulate distinct aspects of sexual behavior and cognition and are at play during different phases of sexual regulation. Nonetheless, some aspects limit the generalization of our results. The sample of this study was mainly composed of Caucasian university students. It is, however, noteworthy that the study background of our participants was rather heterogeneous (e.g., medicine, engineering, business, psychology, economy). For ethical reasons, the participants were aware that the study would include erotic material which could also have resulted in a biased self-selected sample.

In addition, as occurs with small samples, the current study entails the risk of false negative results. However, the alpha values of the non-significant results were substantially far beyond the threshold of significance. Another problem of small samples is the potential inaccuracy in the magnitude of the correlation values (Schönbrodt & Perugini, 2013). In this regard, the confidence intervals generated by the bootstrapping procedure (in Tables 3 and 4) indicated that the significant correlation estimates were for the most part within the same direction (indicating either positive or negative relationships). This way, we cannot reassure the accuracy of the correlation parameters magnitude but we can have an approximation of its variability.

Although the present study shows that computer-based tasks can advance our understanding of the regulation of sexual behavior, we are also aware that these methods along with self-reports can capture only partial components of sexual cognition. Regarding sexual arousability, for example, we based our conclusions on merely one explicit measure (Sexual Excitation Scale). Future studies can include additional physiological indicators of sexual arousability (e.g., heart rate, skin galvanic response, or penile pletysmograhy) to have a more integrative perspective.

Although we tried to include ecologically valid measurements for sexual behavior (frequency of sexual thoughts, masturbation, pornography watching, and intercourse), we assessed those only via self-reports. To study sexual inhibition and sexual behavior, future studies can also consider to include behavioral non computer-based measurements (See Gailliot & Baumeister, 2007 and Hofmann et al., 2009 for examples) in order to achieve higher ecological validity and reliability. Finally, we studied sexual regulatory mechanisms in healthy participants and regarding healthy sexual behaviors. It remains to be investigated whether the same mechanisms are involved in undesired or unhealthy sexual behavior.

Conclusion

This work aimed to study the relationship between different inhibitory mechanisms and their specific role in regulating sexuality at the cognitive and at the behavioral level. The presented evidence supports the notion that sexual inhibition is distinct from one's general ability of inhibitory control. Along with clinical observations in brain damage patients showing that sexual disinhibition is not always accompanied by a general inhibition deficit (Baird et al., 2007), these results support the existence of different inhibitory mechanisms in the regulation of sexual cognition and behavior. Furthermore, in this study, we observed that sexual cognitive inhibition is not related to sexual motor inhibition and that both processes distinctively predicted different facets of sexuality (sexual thoughts and sexual behavior). Following the process model of emotion regulation (Gross, 2002), we propose that whereas sexual cognitive inhibition prevents the sexual arousal to take place, the sexual motor inhibition is involved to control an ongoing sexual emotional reaction. Future studies may examine whether the distinctive involvement of the examined mechanisms underlie specific symptomatology and comorbidity in sexual disorders.

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CHAPTER 3.

Putting out the blaze: The neural mechanisms underlying sexual inhibition

Based on:

Rodríguez-Nieto, G., Sack, A.T., Dewitte, M., Emmerling, F., & Schuhmann, T. (In revision). Putting out the blaze: the neural mechanisms underlying sexual inhibition.

Abstract

The successful inhibition of sexual thoughts, desires, and behaviors represents an essential ability for adequate functioning in our daily life. Evidence derived from lesion studies indicates a link between sexual inhibition and the general ability for behavioral and cognitive control. This is further supported by the high comorbidity of sexual compulsivity with other inhibition-related disorders. Here, we aimed at investigating whether sexual and general inhibition recruit overlapping or distinct neural correlates in the brain. Furthermore, we investigated the specificity of two different kinds of sexual inhibition: inhibition of sexually driven motor responses and inhibition of sexual incoming information. To this end, 22 healthy participants underwent functional Magnetic Resonance Imaging (fMRI) while performing a task requiring general response inhibition (Go/No-go), as well as cognitive and motivational sexual inhibition (Negative Affective Priming and Approach-Avoidance task). Our within-subject within-session design enabled the direct statistical comparison between general and sexual inhibitory mechanisms. The general inhibition task recruited mainly prefrontal and insular regions, replicating previous findings. In contrast, the two types of sexual inhibition activated both common and distinct neural networks. Whereas cognitive sexual inhibition engaged the inferior frontal gyrus, the orbitofrontal cortex and the fusiform gyrus, motivational sexual inhibition was characterized by a hypo-activation in the anterolateral prefrontal cortex. Both types of sexual inhibition recruited the inferior frontal gyrus and the inferotemporal cortex. However, the activity of the inferior frontal gyrus did not correlate with behavioral inhibitory scores. These results support the hypothesis of inhibitory processing being an emergent property of a functional network.

Introduction

Sexuality is one of the main driving forces underlying human behavior. Being essential for the individual's ability to reproduce, sexuality is a deeply rooted and highly rewarding behavior. Nonetheless, the ability to inhibit sexual stimuli and control sexual behavior is of utter importance to convey to societal norms or to prevent harmful consequences. The failure to control sexual impulses and behavior may lead to a wide range of undesired consequences such as compulsive masturbation and pornography watching, undesired pregnancy, sexual transmitted diseases contagion, relationships problems, and sexual offending. It is, thus, plausible that specific sexual inhibitory mechanisms underlie the ability to control sexual responding.

The lack of control over sexual behavior has been studied in the context of compulsivity and addiction models. Hypersexual patients show typical addiction or compulsive symptoms, such as the interference with important occupational and social goals, and the repetitive and unsuccessful efforts in controlling their urges (Kafka, 2010).

The high prevalence of substance abuse, impulse-control, and obsessive-compulsive spectrum disorders among hypersexual patients (Bancroft & Vukadinovic, 2004; Kaplan & Krueger, 2010) raises the question whether the control of sexual thoughts, urges, and behavior, may derive from a general inhibition ability that generalizes across many modalities. Indeed, some evidence suggests that general inhibition shows a certain degree of domain generality (Cohen & Lieberman, 2010; Tabibnia et al., 2011). A well-established and simple task to assess and quantify general response inhibition is the classic Go/No-go paradigm. Participants are required to respond to a frequent Go signal while inhibiting their response to a rare interleaved No-go signal. This Go/No-go paradigm has been used to study inhibition processes in drug addiction (Goldstein & Volkow, 2011), aggression (Dambacher et al., 2014a), cigarette craving (Berkman, Falk, & Lieberman, 2011), and sexual risk behavior (Goldenberg, Telzer, Lieberman, Fuligni, & Galván, 2013; Xue et al., 2018).

Other studies have shown that the failure to respond to the Go stimulus (i.e. misses in the Go/No-go task) was associated with sexual arousability and sexual compulsivity (Macapagal, Janssen, Fridberg, Finn, & Heiman, 2011; Miner, Raymond, Mueller, Lloyd, & Lim, 2009). Moreover, convicted pedophiles were found to react slower to Go stimuli (Go/No-go task) compared to control participants (Habermeyer et al., 2013). Although it is debatable whether the omission errors (misses) or slow reaction times in the Go/No-go task

constitute an inhibition failure, these studies suggest a possible role of general inhibition in regulating sexual responses.

The link between general and sexual inhibition is further supported by observations from lesion studies, in which frontal damage often leads to general disinhibition as well as sexual inhibition deficits (Baird, Wilson, Bladin, Saling, Reutens, 2007). However, there are also lesion studies demonstrating that damage to specific temporal regions, the septal region, and the pallidum, trigger specific sexual compulsive or deviant behaviors in some patients. Specifically, damage to temporal regions seem to cause a dramatic increase of sexual drive, but overall, non-frontal lesions seem unrelated to general inhibition impairments, as observed in frontal lesion cases (Baird et al., 2007). The different symptoms and distinctive comorbidity of sexual disorders across patients suggest the existence of different sexual regulatory mechanisms that operate in addition to general inhibition networks in the brain. Although lesion studies provide valuable information on the link between inhibition and sexual behavior, an important limitation of these studies is that the damage is rarely focal. Epistemologically, even if a deficiency in general inhibitory mechanisms leads to a subsequent failure of inhibiting sexual behavior, that does not exclude the possibility that specific and/or additional sexual inhibitory mechanisms still exist. It is possible that different sexual manifestations (e.g. thoughts, behavior) engage different networks to be inhibited, which, depending on the process, could derive from a general and/or specific domain.

Previous neuroimaging studies have proposed the left lateral orbitofrontal cortex, the gyrus rectus, and the inferotemporal cortex to be tonic inhibitors of sexual arousal, showing distinct deactivation during the presentation of sexual stimuli (Stoléru, Fonteille, Cornélis, Joyal, & Moulier, 2012). In addition, the dorsolateral prefrontal cortex seems to play a regulatory role during and after the presentation of erotic films (León-Carrión et al., 2007). Probably the most direct evidence related to the neural correlates of sexual inhibition stems from a study in which participants were explicitly asked to inhibit any emotional reaction during the presentation of an erotic film. The superior frontal gyrus and anterior cingulate cortex (ACC) were active during the attempted inhibition of sexual responses (Beauregard, Lévesque, & Bourgouin, 2001).

On the other hand, neuroimaging studies investigating the neural correlates of general response inhibition using the Go/No-go paradigm, consistently describe mostly right-lateralized activation of the superior, middle, and inferior frontal gyri, the pre-supplementary motor area, the ACC, the inferior parietal lobe, the angular gyrus, basal ganglia, and anterior insula during the deliberate inhibition of a preponderant response (Chambers, Garavan, &

Bellgrove, 2009; Dambacher et al., 2014a&b; Swick, Ashley, & Turken, 2011). Similarly, an erotic Go/No-go task engaged the dorsolateral prefrontal cortex, the ACC, and the anterior insular cortices (Xue et al., 2018). It is therefore plausible to assume that a common inhibitory network exists involving the dorsolateral prefrontal cortex, the anterior insula, and the ACC. The possibility of an overlapping network for general and sexual inhibition has not been directly tested before. Moreover, the few neuroimaging studies that addressed sexual inhibition made mostly indirect inferences (i.e. based on the passive viewing of sexual stimuli). Hence, the question to what extent sexual inhibition comprises general inhibition mechanisms and which, if any, specific sexual inhibition networks are involved in different forms of sexual control is largely unanswered. For instance, it is possible that the mechanisms that allow the control of sexual thoughts are different from those that allow the control of sexually driven actions. To this regard, evidence comparing distinct aspects of sexual inhibition is missing.

Here, we aimed to characterize the neural substrates of sexual inhibition using functional Magnetic Resonance Imaging (fMRI) with two experimentally controlled paradigms assessing the motivational and cognitive aspects of sexual inhibition: Negative Affective Priming and Approach-Avoidance. We previously showed that the control of motivationally driven motor action tendencies (*motivational sexual inhibition* assessed by an Approach-Avoidance paradigm) behaviorally differs from the attentional control over sexual inputs (*cognitive sexual inhibition* assessed by a Negative Affective Priming paradigm) (Rodríguez-Nieto, Emmerling, Dewitte, Sack, & Schuhmann, in press). In addition, we included a classic response inhibition task (Go/No-go task) to directly investigate the potential overlap in neural correlates between sexual and general inhibition in a within-subject design.

Method

Participants

Twenty-four healthy male participants (18-34 years old) without neurological or psychiatric disorders took part in this study. One participant was excluded due to extensive head movements, and a second participant due to technical difficulties leading to an incomplete data set (final sample: N=22, mean age=24.77, SD=4.76). All participants were financially reimbursed for their participation and gave written informed consent. The study was

approved by the local Ethical Committee of the Faculty of Psychology and Neuroscience at Maastricht University.

Procedure and instruments

Participants performed two sexual (Approach-Avoidance and Negative Affective Priming task) and one non-sexual (Go/No-go task) paradigms in an MR scanner. The order in which the two sexual tasks were presented was counterbalanced. The Go/No-go task was always presented between the sexual tasks to prevent habituation to sexual stimuli.

Approach-Avoidance Task (AAT)

This paradigm was selected to measure *motivational sexual inhibition* as it targets approach-avoidance tendencies towards stimuli with affective or neutral content (Figure 1). Previous adaptations using sexual stimuli have shown to be sensitive to gender differences (Dewitte, 2016), to be related to the amount of viewing time of erotic stimuli (Hofmann, Friese, & Gschwendner, 2009), and to predict pornography watching frequency (Rodríguez-Nieto et al., in press).

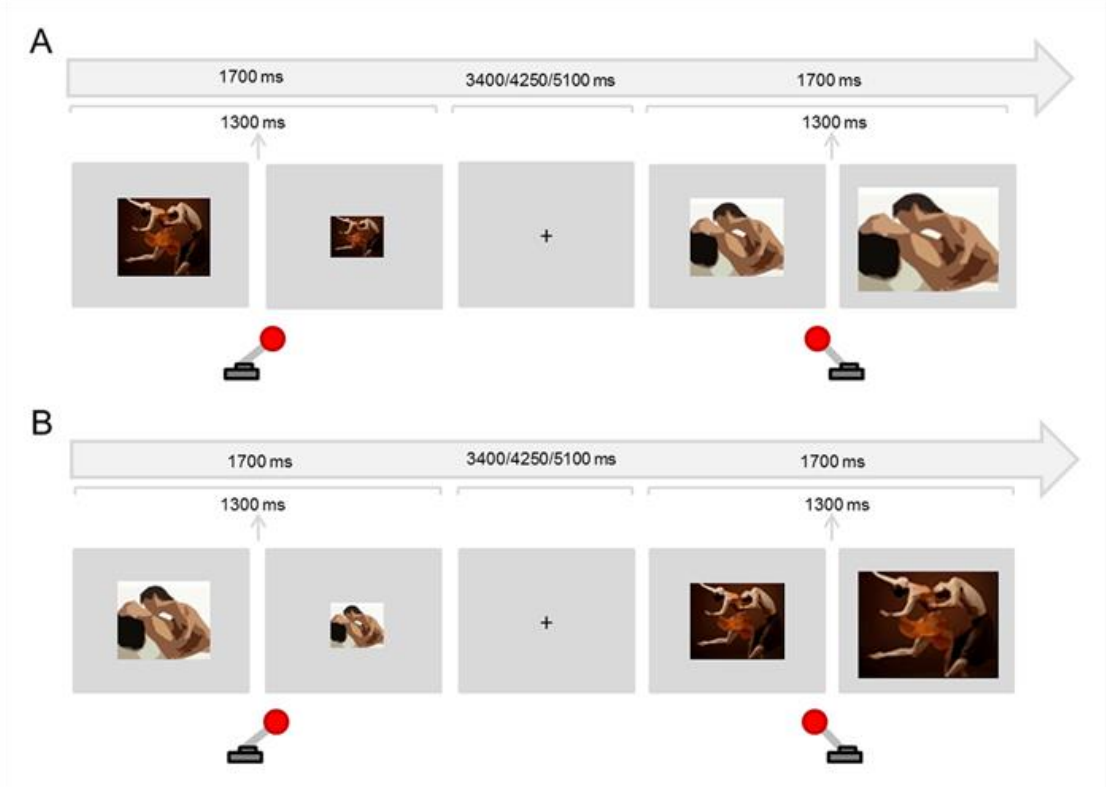

Figure 1. Motivational sexual inhibition - Approach-Avoidance Task. A) Sex Approach block: Participants approached sexual images (pulling the joystick towards themselves increasing the image size) and avoided non-sexual photographs (pushing the joystick away from themselves decreasing the image size). B) Sex Avoid block: Participants avoided sexual images and approached non-sexual images.

There were four blocks of 48 randomized trials each. In two blocks, participants were instructed to approach the sexual stimuli (presented in 50% of the trials) and to avoid the non-sexual stimuli. For the other two blocks, participants were instructed to do the opposite. To approach, participants had to pull a joystick towards them. This action doubled the image size. To avoid, they had to push the joystick away from them, which in turn halved the image size. In every trial, the presentation of the stimulus lasted 1700 milliseconds. To avoid variability in timing across trials and participants, the resizing always occurred 1300 ms after stimulus onset. Between trials, a fixation cross was presented for 3400, 4250, or 5100 ms (Figure 1). The four blocks were counterbalanced.

Sexual stimuli were color photographs displaying sexual intercourse or oral sex between one woman and one man; 95% of these pictures were previously evaluated and validated in terms of valence and arousability (Rupp & Wallen, 2007). The remaining pictures were selected from the internet. Non-sexual stimuli were color photographs of one woman and one man dancing (Dewitte, 2016). The proportion of the exposition of the bodies (with special attention to the female body) with respect to the whole picture was comparable in both conditions. Images were displayed on a light gray background and the default size of the image was 337,9 X 272,5 pixels (horizontal orientation) in half of the blocks and 257,6 X 400 pixels (vertical orientation) in the other half. We calculated a Sex Approach-Avoid index, by subtracting the reaction times in Sex Approach blocks from reaction times in Sex Avoid blocks. A major Sex Approach-Avoid index indicated a stronger control over sexual motivation, by taking less time to avoid sexual stimuli and/or taking longer to approach them.

Negative Affective Priming task (NAP)

This paradigm (adapted from Dewitte, 2016) addressed *cognitive sexual inhibition* (Figure 2). Participants had to attend to one stimulus while ignoring a simultaneously presented distractor. In the next trial, the participant had to respond to the kind of stimulus that was previously ignored which causes a response delay (priming effect). The link between two successive trials was not obvious to the participant and, therefore, it can be argued that this task measures automatic inhibition (for an overview see Moors & De Houwer, 2006). The priming effect has shown to be larger for sexual than for neutral stimuli presumably due to a major implication of inhibition (Dewitte, 2017; Rodríguez-Nieto et al., in press). In addition, this task predicted the frequency of sexual thoughts in daily life (Rodríguez-Nieto et al., in press).

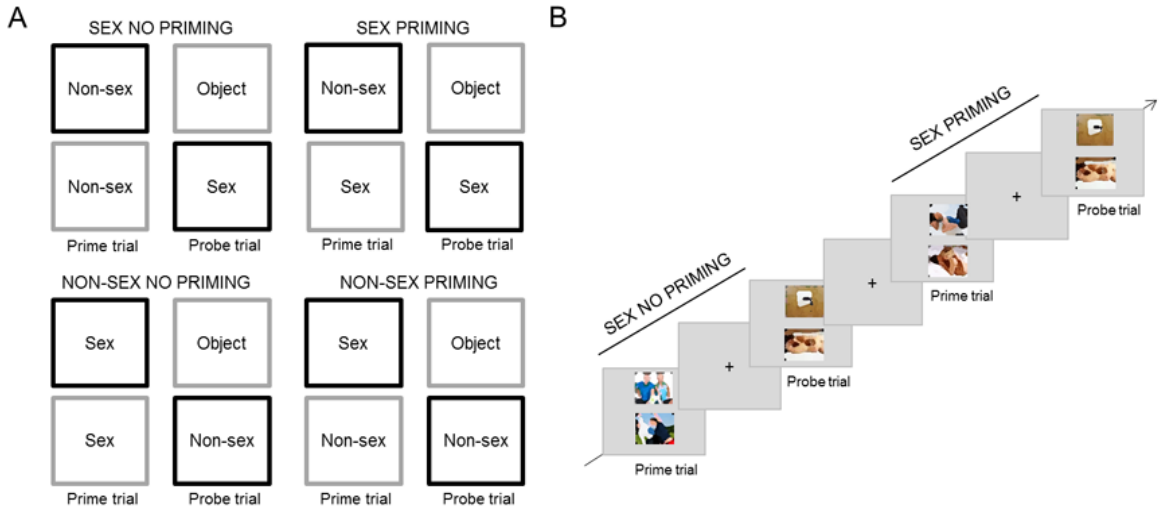

Figure 2. Cognitive sexual inhibition - Negative Affective Priming task. A) Priming conditions: the content of the distractor –gray frame- in the prime trial (Sex or Non-Sex) matched the content of the target –black frame- in the probe trial. Non Priming conditions: the content of the distractor in the prime trial was different from the content of the target in the probe trial. B) Timeline: Example of a Sex No Priming and a Sex Priming trial sequence.

The task consisted of four types of trial-sequences: a) Sex Priming, b) Sex No Priming, c) Non-Sex Priming, and d) Non-Sex No Priming. A trial-sequence contained a prime and a probe trial; during each, two pictures were presented simultaneously. The pictures were displayed one above the other; one surrounded by a black and the other by a gray frame. The instruction was to attend only to the picture with the black frame (target), therefore ignoring the one with the gray frame (distractor) and to indicate whether the target displayed sexual or non-sexual content. Participants responded by pressing a left or right button on a button box located below their right hand. During the priming trial-sequences, the content type of the distractor in the prime trial was the same as in the target picture of the probe trial. In the control trial-sequences (No Priming) the content type of the distractor in the primer trial and the target in the probe trial was different. The target of the probe trial could be sexual or non-sexual. Figure 2A provides an overview of the four different conditions.

The four types of trial-sequences were presented randomly in equal proportions throughout each of three blocks. Each block contained 32 trial-sequences and there were 24 trial-sequences in total for each condition. The prime and probe trials were presented for 1700 ms each. A fixation cross was displayed for 1700 ms between the prime trial and probe trial of the same sequence, and for 3400, 4250, or 5100 ms between different trial-sequences

(Figure 2B). The sexual stimuli were pictures (320 x 260 pixels) different from those used in the AAT but with the same content characteristics. The non-sexual stimuli were photographs of one man and one woman exercising together. The neutral stimuli (distractors in the probe trials) were pictures of neutral objects (e.g. pencil case). Pictures were displayed on a light gray background and the picture frames were three pixels in width. 85% of photographs were selected from previously used data sets (Dewitte, 2016; Rupp & Wallen, 2007), and the remaining were selected from the internet. A main sexual priming score was calculated by subtracting the sexual priming index (Sex Priming RT – Sex No Priming RT) minus the non-sexual priming index (Non-Sex Priming RT – Non-Sex No Priming RT). A higher index indicated a stronger sexual priming effect and thus, a stronger sexual inhibition.

Go/No-go task

This paradigm was used to target *general inhibition.* Participants were instructed to respond to a frequent Go stimulus and to not respond to an infrequent No-go stimulus. They responded with the right index finger on a button-box (Figure 3). As stimuli, the letters 'C' and 'M' were used and which letter was defined as the Go or No-go stimulus was counterbalanced across participants. Participants had to complete four blocks of 80 trials each (25% No-go trials). Every trial consisted of the presentation of the stimulus for 200 ms, followed by an inter-trial interval of 1500, 2350, or 4050 ms (Figure 3). Hits (responding to a Go trial), correct No-go's (not responding to a No-go trial), false alarms (responding to a No-go trial), and misses (not responding to a Go trial) were recorded. Responses after 650 ms with respect to stimulus onset were not registered. The letters (3 X 2.3 cm) were displayed in white color on a gray background (adapted from Dambacher et al., 2014b). The three computer-based tasks were programmed and presented with PsychoPy (Peirce, 2007).

Prior to entering the MR Scanner, participants performed a brief practice session for each task. There were twenty practice trials for the AAT, eight for the NAP, and ten for the Go/No-go task. The practice trials involved different stimuli than the actual tasks (animals and plants for the AAT and NAP tasks, and 'T' and 'K' letters for the Go/No-go task).

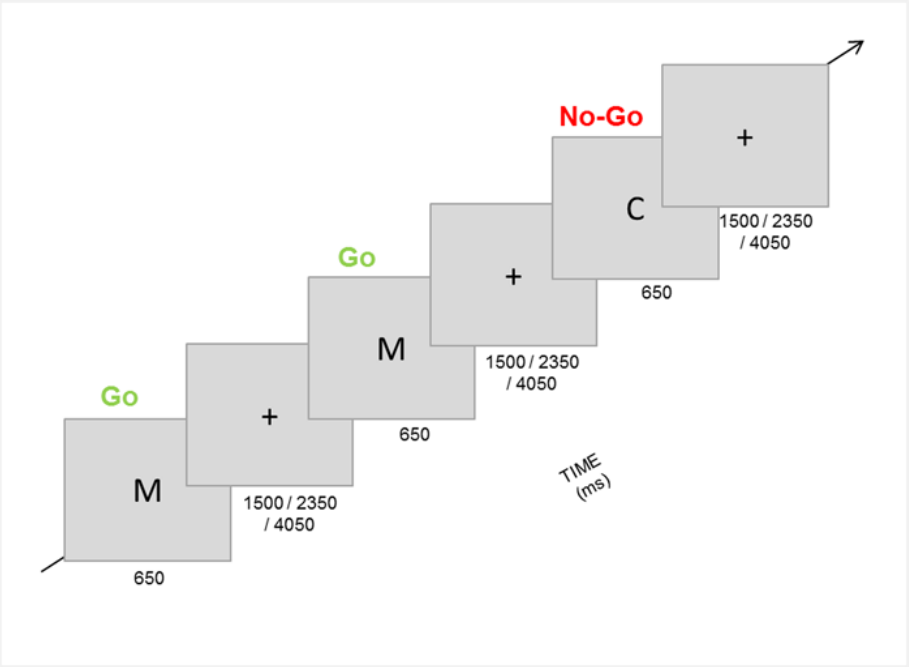

Figure 3. General inhibition – Go/No-go task. Example of a Go/No-go task trials sequence.

Technical details and fMRI acquisition

Participants performed all paradigms inside the MR Scanner. Data were acquired at the 3 T Siemens Prisma Scanner at the Maastricht Brain Imaging Center, Maastricht University. Functional EPI images were collected using an in-house developed multi-echo multi-band sequence (TR = 850 ms, TE = 15/30/44 ms, flip angle = 50°, FOV = 210 mm, 36 slices, isovoxel 3 mm^3). Online-scanner reconstruction was performed using the slice-GRAPPA algorithm (Setsompop et al., 2012) with leakage artifact reduction (Cauley, Polimeni, Bhat, Wald & Setsompop, 2014) as implemented in the reconstruction of the MGH blipped-CAIPI SMS-EPI distribution (software and complete documentation are available at https://www.nmr.mgh.harvard.edu/software/c2p/sms). This GRAPPA sequence was selected to optimize the BOLD signal in frontoventral regions.

High-resolution anatomical images were acquired with a MPRAGE sequence (TR = 2250 ms, TE = 2.21 ms, FOV = 256 mm, 192 sagittal slices, isovoxel 1 mm^3). The acquisition of anatomical images was done after the Go/No-go task (see above) to avoid cognitive fatigue.

fMRI analyses

The imaging data were pre-processed and analyzed with Brain Voyager QX Version 2.8.4.2645 (Brain Innovation, Maastricht, Netherlands).

Prior to the pre-processing, the echo images were combined using an optimized echo weighting method (Poser et al., 2006). The images were motion-corrected (trilinear/sinc interpolation and aligned to the first functional volume acquired after the anatomical sequence) and corrected for slice timing skew using temporal sinc interpolation. A temporal high pass filter (3 cycles) was applied. Images were co-registered to the individual T1 weighted images and normalized to Talairach stereotaxic space. Volume time courses were spatially smoothed using a 6mm full width half maximum Gaussian kernel.

To analyze the activation pattern of every task an event-related approach was implemented using a GLM model and a random-effects group analysis. For the sexual tasks, we executed 2 x 2 ANOVA analyses with Stimuli (Sex vs NonSex) and Inhibitory/Non-Inhibitory (AAT: Approach vs Avoid; NAP: Priming vs No Priming) conditions as factors. Further basic contrast analyses were executed to specifically compare sexual inhibitory conditions against the non-sexual inhibitory conditions (AAT: Sex Avoid > Dance Avoid; NAP: Sex Priming > Non-Sex Priming) and the sexual non-inhibitory conditions against the non-sexual non-inhibitory conditions (AAT: Sex Approach > Dance Approach; NAP: Sex No Priming > Non-Sex No Priming). In the case of the AAT, the resizing of the stimuli was the same in the conditions within each contrast (i.e. halving the stimuli size for avoid conditions and doubling it for approach conditions), therefore keeping the intensity of the stimuli constant. Motion correction parameters were included as confound variables in the GLM. In the case of the Go/No-go task, we calculated the No-go > Go contrast to identify regions active in motor response inhibition. For the three tasks, only successful trials were taking into account, excluding the trials where the participants did not respond or committed errors. The resulting maps were corrected for multiple comparisons by means of cluster threshold level estimation (1000 Monte Carlo simulation iterations; Forman et al., 1995). The nomenclature of the cluster peak values was defined with the software tool Talairach Client (Lancaster et al., 1997: Lancaster et al., 2000).

Conjunction analyses were conducted to investigate the common neural substrates underlying the different inhibition processes. First, we looked at the conjunction of the three processes as compared to their respective control condition (Sex Avoid > Sex Approach ^ Sex Priming > Sex No Priming ^ No-go > Hits) and of the paired combinations (i.e. Sex Avoid > Sex Approach ^ Sex Priming > Sex No Priming; Sex Avoid > Sex Approach ^ No-go > Hits; Sex Priming > Sex No Priming ^ No-go > Go).

Results

Behavioral data

Approach-Avoidance Task

A two-way repeated measures ANOVA (Stimulus Type [Sex, Dance] X Response [Approach, Avoid]) revealed a significant effect of stimulus type ($F_{(1,21)}$ = 12.11, p = .002) and an interaction between Stimulus Type X Response ($F_{(1,21)}$ = 10.84, p = .01, but no main effect of Response ($F_{(1,21)}$ = .07, p = .79). Consistent with previous studies (Hofmann, Friese, & Gschwendner, 2009; Dewitte, 2016; Rodríguez-Nieto et al., in press), participants reacted faster when responding to sexual stimuli versus neutral stimuli (Sex: M = 1172, SD = 342 ms; Dance: M = 1213, SD = 319 ms) and overall, reaction times were shorter when approaching sexual stimuli compared to approaching and avoiding neutral stimuli (Table 1).

Negative Affective Priming task

As expected, participants were slower to respond to Priming trials compared to No Priming trials ($F_{(1,21)}$ = 4.9, p = .04, Priming: M = 867, SD = 150; No Priming: M = 842, SD = 171 ms), and to non-sexual trials compared to sexual trials ($F_{(1,21)}$ = 7.51, p = .01; Sexual: M = 839, SD = 165 ms; Non-Sexual: M = 870, SD = 157 ms). No significant interaction was found between Stimulus Type and Priming condition ($F_{(1,21)}$ = .02; p = .88; Table 1).

Go/No-go task

Participants committed on average 11 (SD = 14.46) misses and 7 (SD = 6.3) false alarms.

Table 1. Average reaction times of the sexual inhibition tasks conditions.

Approach-Avoidance Task		
	Sex $\bar{x}$ (SD)	Dance $\bar{x}$ (SD)
Approach	1150 (357)	1238 (326)
Avoid	1193 (331)	1187 (319)
Negative Affective Priming Task		
	Sex $\bar{x}$ (SD)	Non-Sex $\bar{x}$ (SD)
Priming	851 (147)	883 (160)
No Priming	828 (194)	857 (160)

fMRI results

Approach-Avoidance Task

A two-way ANOVA (Stimulus Type [Sex, Dance] X Response [Approach, Avoid]) showed a significant Stimulus Type X Response interaction effect in the posterior cingulate, the parahippocampal gyrus, the cuneus, and the lentiform nucleus extending to the amygdala (CLTC [cluster-level threshold correction], $p < .001$; Table 2). When looking at the sexual avoidance condition map (Sex Avoid > Dance Avoid) a significant decreased BOLD response was observed in the middle temporal gyrus, the inferior parietal lobule, the anterolateral prefrontal cortex, and the cuneus (CLTC $p < .005$; Table 2; Figure 4). At a more liberal threshold (CLTC $p = .01$), a hypoactivation in the right caudate and an activation in the anterior cingulate was also observed (caudate: x, y, z = 12, 11, 13, cluster size = 397; anterior cingulate: x, y, z = -3, 41, 10, cluster size: 483).

When looking at the sexual approach condition map (Sex Approach > Dance Approach) an increased activation was observed in the right middle occipital gyrus and bilaterally in the amygdala, the lentiform nucleus, the hippocampus, and the parahippocampal gyrus (CLTC $p < .005$; Table 2; Figure 4). Because the anterolateral prefrontal cortex has been previously described as part of a self-regulation network (Volman, Toni, Verhagen, & Roelofs, 2011) and in the current paradigm showed to be hypoactive during the sexual inhibitory condition we explored its relation with behavior. A correlation analysis showed a negative relation between the activity of this region (spherical ROI: x, y, z = 30, 59, 2; size: 257 voxels) and the main Approach-Avoidance reaction times index, indicating that participants who showed a stronger sexual inhibition (higher sexual avoidance together with lower sexual approach) showed a stronger anterolateral prefrontal cortex deactivation during the Sexual Avoid trials ($r = -.46$, $p = .03$; Figure 5).

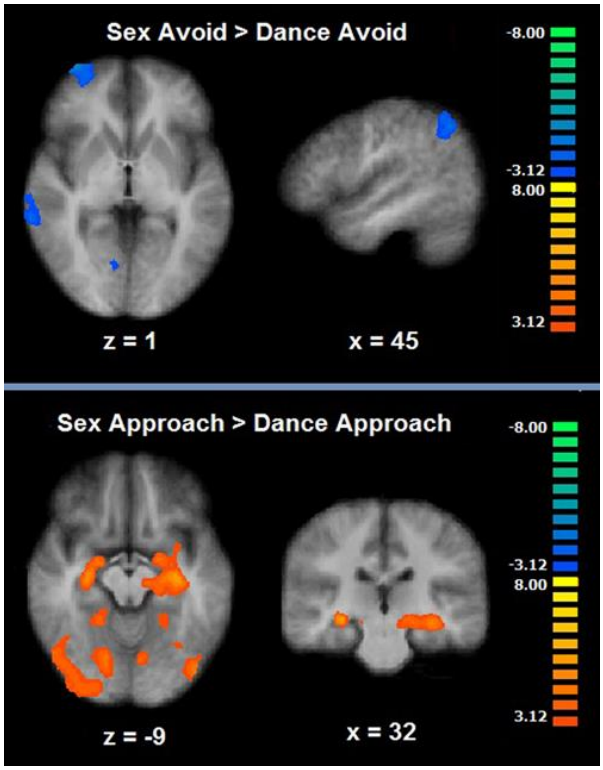

Figure 4. Motivational sexual inhibition - Approach-Avoidance task. Brain activation during the Sex Avoid (up) and Sex Approach trials (down) (CLTC, $p < .005$).

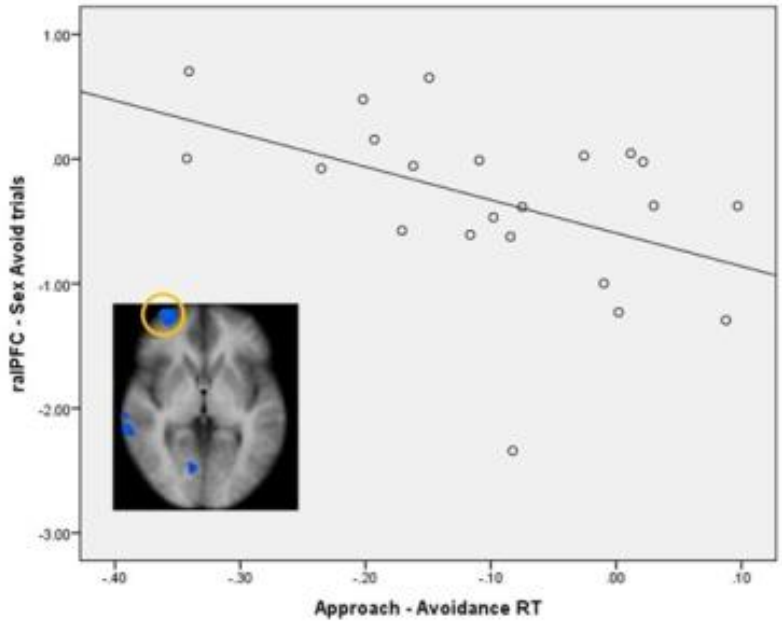

Figure 5. Brain activity correlates with the behavioral output in the Approach – Avoidance task. The activity of the right anterolateral prefrontal cortex during Sex Avoid trials negatively correlated with the Approach-Avoidance index (faster sexual avoidance and-or slower sexual approach reaction times).

Table 2. Brain regions active during the Approach-Avoidance task.

MOTIVATIONAL SEXUAL INHIBITION - Approach-Avoidance task							
	BA	x	y	z	Size (mm^3)	F / t	P
Stimuli x Movement Interaction							
Lentiform Nucleus		18	-4	-5	325	19.97	.0002
Cuneus	30	9	-67	7	1498	20.24	.0002
Posterior Cingulate	30	-12	-67	7	330	14.16	.0001
Parahippocampal Gyrus		-27	-13	-11	957	23.13	.00008
Sex Avoid > Dance Avoid							
Middle Temporal Gyrus	21	63	-31	-2	1628	-4.55	.0001
Inferior Parietal Lobule	40	45	-58	43	1117	-4.39	.0002
Middle Frontal Gyrus	10	33	62	1	712	-5.05	.00005
Cuneus	30	9	-67	7	639	-4.13	.0004
Sex Approach > Dance Approach							
Middle Occipital Gyrus	18	40	-85	1	38494	5.59	.00001
Parahippocampal Gyrus	28	27	-22	-5	3284	6.01	.000005
Hippocampus		-30	-16	-11	7379	6.75	.000001

CLTC $p < .005$

Negative Affective Priming task

A two-way ANOVA (Stimulus Type [Sex, Non-Sex] X Priming [Priming, No Priming]) showed a significant Stimulus Type X Priming interaction effect in the post-central gyrus (CLTC $p < .001$; Table 3). The sexual priming condition (Sex Priming > Non-Sex Priming) map revealed a significant increased BOLD response in the inferior frontal gyrus, middle frontal gyrus (orbitofrontal region), the medial prefrontal cortex, the middle temporal gyrus,

the fusiform gyrus, and the posterior cingulate (CLTC p < .001; Table 3; Figure 6). The sexual non-priming condition map (Sex No Priming > Non-Sex No Priming) showed a significant enhanced activation in the precentral and post-central gyri, the middle and superior temporal gyri, the precuneus, the middle occipital gyrus, the medial prefrontal cortex, and the lentiform nucleus (CLTC p < .001; Table 3; Figure 6). As the inferior frontal gyrus has been widely investigated in self-control and inhibition literature (Cohen, Berkman & Lieberman, 2013), we explored the relationship between its activation during the sexual priming trials and the sexual priming behavioral outcome (main NAP reaction times index). The relationship between the beta parameters in this region (spherical ROI: x, y, z = 46, 30, 13; size: 257 voxels) during the sexual priming condition and the NAP index was not significant (r = .21, p = .35).

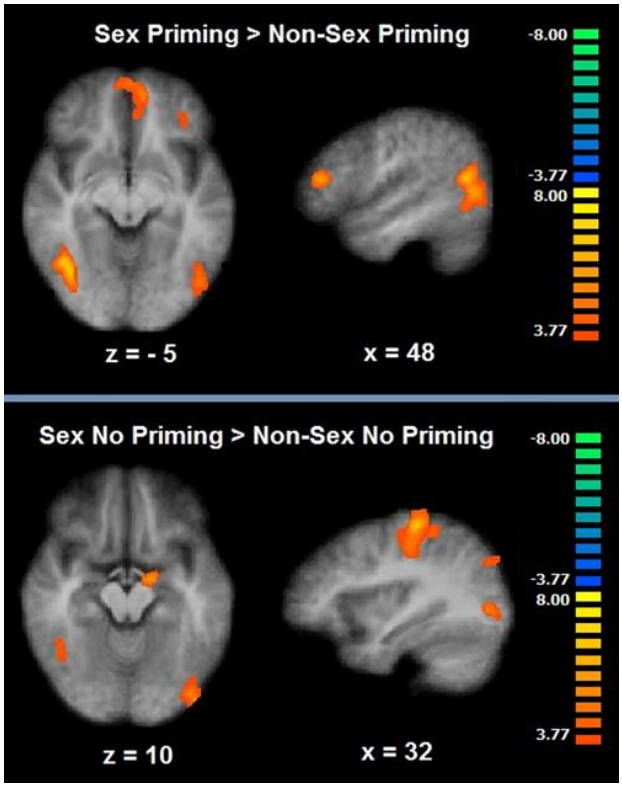

Figure 6. Cognitive sexual inhibition - Negative Affective Priming task. Brain activation during the Sex Priming (up) and Sex No Priming trials (down) (CLTC, p < .001).

Table 3. Brain regions active during the Negative Affective Priming task.

COGNITIVE SEXUAL INHIBITION - Negative Affective Priming Task							
	BA	x	y	z	Size (mm^3)	F / t	P
Stimuli x Priming Interaction							
Post-central Gyrus	2	30	-34	61	543	14.62	.0008
Sex Priming > Non-Sex Priming							
Inferior Frontal Gyrus	46	45	32	13	985	6.29	.000002
Middle Temporal Gyrus	39	45	-58	16	8621	7.39	.0000001
Medial Frontal Gyrus	10	-9	50	1	1804	5.91	.000005
Posterior Cingulate	23	0	-52	22	1229	6.25	.000002
Middle Frontal Gyrus	11	-36	38	-8	475	4.74	.000087
Middle Temporal Gyrus	39	-48	-58	7	6477	6.75	.000001
Fusiform Gyrus	37	-42	-40	-14	493	4.8	.000071
Sex No-Priming > Dance No-Priming							
Precentral Gyrus	4	33	-28	58	9777	7.62	.000001
Middle Temporal Gyrus	37	42	-55	-5	4258	7.75	.0000001
Precuneus	19	30	-76	34	619	4.52	.000153
Middle Occipital Gyrus	18	33	-79	1	727	5.32	.00021
Medial Frontal Gyrus	10	-9	50	1	6647	8.22	.0000001
Lentiform Nucleus		-12	-7	-8	797	6.55	.000001
Superior Temporal Gyrus	39	-45	-58	19	9002	8.07	.000001
Postcentral Gyrus	2	-54	-22	34	1175	6.83	.000001

CLTC $p < .001$

Go/No-go task

When performing the No-go > Go contrast an increased activation in the right superior frontal gyrus and bilateral insula, extending to the inferior frontal gyrus on the right side, was observed (CLTC p < .001; Table 4; Figure 7). As we did with the motivational sexual inhibition task, we explored a relationship between the activity in the inferior frontal gyrus during the No-go condition (spherical ROI: x, y, z = 44, 18, 10; size: 257 voxels) and behavioral measures (number of false alarms and misses). This region of interest was created from the No-go > Go activation map. No correlation was significant (False Alarms: rho = .04, p = .85; Misses: rho = -.19, p = .35).

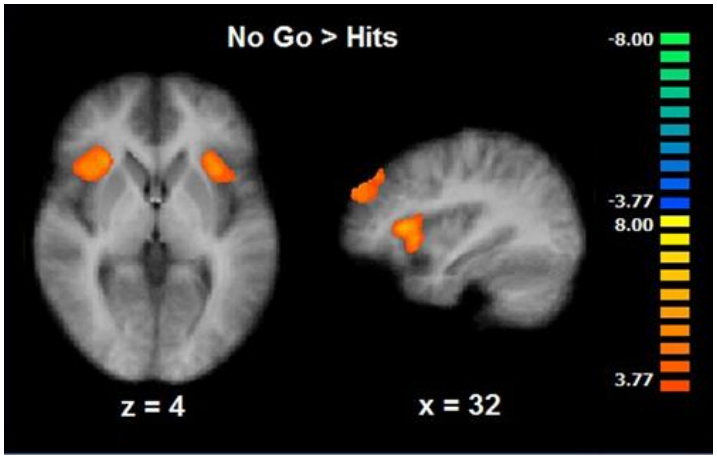

Figure 7. General inhibition – Go/No-go task. Brain activations during the No-go trials (CLTC p < .001).

Table 4. Brain regions active during the Go/No-go task.

GENERAL INHIBITION – Go/No-go task							
	BA	x	y	z	Size (mm^3)	t	P
No-go > Go							
Claustrum	13 / 44	27	14	-2	5445	7.5	.0000001
Superior Frontal Gyrus	9	30	50	31	1994	5.8	.000001
Insula	13	-33	20	13	2577	7.29	.0000001

CLTC p < .001

Conjunction Analysis

The conjunction analyses of the three inhibitory processes contrasted against their respective control condition (Sex Avoid > Dance Avoid ^ Sex Priming > Dance Priming ^ No-go > Go) did not reveal any overlapping region.

For the two sexual inhibitory processes (Sex Avoid > Dance Avoid ^ Sex Priming > Dance Priming), the analysis revealed an overlap in the inferior frontal gyrus and in the inferior and middle temporal gyri only at a liberal threshold of significance (CLTC $p < .05$). We also performed the conjunction of the two non-inhibitory sexual conditions from the two sexual tasks (Sex Approach > Dance Approach ^ Sex No Priming > Dance No Priming). This analysis showed a common activation in the anterior and posterior cingulate, in the thalamus, the precuneus, the inferior occipital gyrus and the lentiform nucleus (CLTC $p < .05$; Table 5; Figure 8). Regarding the conjunction analyses of the Go/No-go task individually with each of the sexual tasks, only a common deactivation of the No-go with the sexual priming condition (No-Go > Go ^ Sex Priming > Dance Priming) was found in the superior temporal gyrus (CLTC $p < .05$; Table 5).

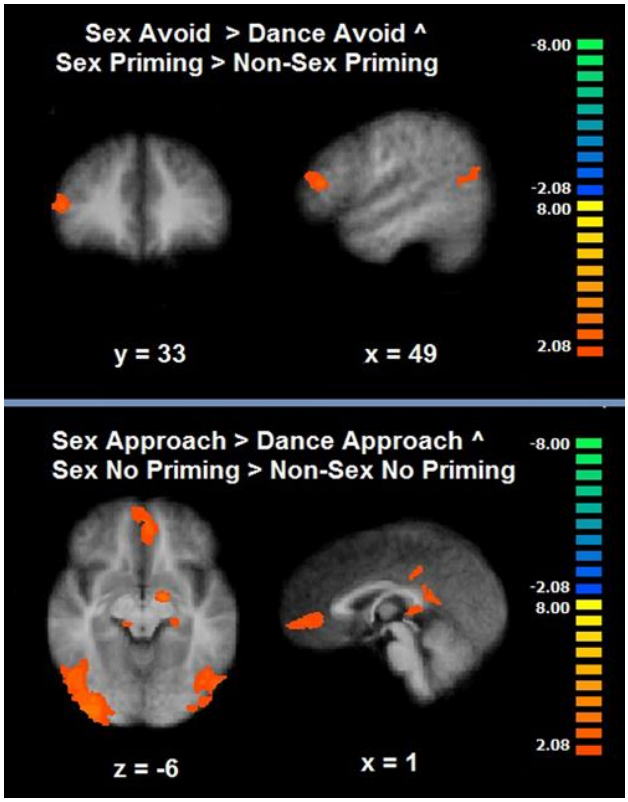

Figure 8. Conjunction of motivational and cognitive sexual inhibition. Common brain activation during the two sexual inhibitory conditions (up: Sex Avoid and Sex Priming) and during the two sexual non-inhibitory conditions (down: Sex Approach and Sex No Priming) (CLTC, $p < .05$).

Table 5. Conjunction analyses results for the three inhibitory processes and their paired combinations.

CONJUNCTION							
	BA	x	y	z	Size (mm^3)	t	P
Sex Avoid > Dance Avoid ^ Sex Priming > Dance Priming ^ No-go > Go							
	-	-	-	-	-	-	ns
Sex Avoid > Dance Avoid ^ Sex Priming > Dance Priming							
Inferior Frontal Gyrus	46	48	29	13	902	3.18	.004
Middle Temporal Gyrus	39	48	-63	19	785	2.81	.01
Middle Temporal Gyrus	37	41	-58	-5	1170	3.51	.002
Inferior Temporal Gyrus	37	-45	-64	-2	3253	3.36	.003
Sex Priming > Dance Priming ^ No-go > Go							
Superior Temporal Gyrus	22	-63	-4	5	1648	-2.71	.01
Sex Avoid > Dance Avoid ^ No-go > Go							
	-	-	-	-	-	-	ns
Sex Approach > Dance Approach Sex Approach > Dance Approach ^ Sex No Priming > Dance No Priming							
Anterior Cingulate	32	-6	41	-5	2696	3.34	.003
Posterior Cingulate	30	15	-52	13	1138	3.18	.004
Posterior Cingulate	29	0	-43	16	985	3.09	.005
Thalamus		-12	-31	4	3196	3.88	.0008
Lentiform Nucleus		-15	-4	-8	885	4.19	.0004
Precuneus	19	30	-79	37	1412	2.81	.011
Precuneus	19	-33	-79	40	1614	3.14	.005
Inferior Occipital Gyrus	18	33	-88	-5	15495	4.36	.0002
Inferior Occipital Gyrus	18	-43	-82	-11	9136	4.17	.0004
Sex Avoid > Sex Approach ^ Sex Priming > Sex No Priming							
	-	-	-	-	-	-	ns

CLTC $p < .05$

Discussion

In this study, we aimed at characterizing the neural correlates of sexual inhibition and at exploring whether there are common or distinct networks for cognitive versus motivational sexual inhibition, and how these networks relate to the networks recruited during general response inhibition. For this purpose, we used two different paradigms to target cognitive sexual inhibition (Negative Affective Priming) and motivational sexual inhibition (Approach-Avoidance), in addition to a classic Go/No-go paradigm to target general response inhibition. In a within-subject design, participants were required to execute all of these inhibition tasks while assessing their task-related whole-brain BOLD signal changes using fMRI.

To our knowledge, this is the first neuroimaging study that directly compares the neural networks underlying general inhibition and two types of sexual inhibition with a within-subject within-session design. The paradigms that we selected to target general inhibition, cognitive sexual inhibition, and motivational sexual inhibition differed considerably in their design. This is important as it has been argued that the neural network associated with classic inhibitory paradigms reflects non-inhibitory processes inherent to the design (e.g. infrequent stimuli detection during No-go trials in the Go/No-go task). Therefore, by using different designs we reduced the risk of finding common neural mechanisms of non-inhibitory psychological processes associated with one particular paradigm.

Our findings demonstrate that whereas the motivational sexual inhibition is distinguished by a prefrontal hypoactivation pattern, cognitive sexual inhibition is characterized by activation in the ventromedial and inferolateral prefrontal regions. Nonetheless, both sexual inhibitory processes show a common activation in the inferior frontal gyrus and in the inferotemporal cortex. The general inhibition paradigm engaged the insula and the right inferior frontal gyrus, which is in accordance with previous literature (Dambacher et al., 2014a&b). We will now discuss the activation pattern of every sexual inhibitory process followed by a discussion of the different inhibitory commonalities.

Motivational sexual inhibition

The inhibitory control to avoid sexual stimuli was characterized by a hypoactivation in the anterolateral prefrontal cortex, the inferior parietal lobe, the middle temporal gyrus, and the putamen, and by activation of the anterior cingulate. Of particular relevance is the observed hypoactivation of the anterolateral prefrontal cortex. This region was previously engaged in a

similar approach-avoidance paradigm, being active in incongruent conditions (approaching angry faces and avoiding happy faces) as compared to congruent conditions (Volman et al., 2011). It is intriguing that in the current study this region was hypoactive during the self-regulation (avoid sexual stimuli) condition.

It is possible that in our paradigm, a tonic inhibitory process was induced by the mere exposure of sexual pictures during the tasks, which was 'released' when participants deliberately aimed at avoiding the sexual images. Remarkably, the activation in this region correlated with the Approach-Avoidance main index. Individuals with a stronger inhibition of sexual stimuli (by avoiding them faster and/or taking longer to approach them) showed a stronger hypoactivation in the anterolateral prefrontal cortex during the sex avoiding trials. If it was the case that the anterolateral prefrontal cortex is sustaining a tonic inhibitory process, this would indeed explain why this mechanism was more active in individuals with a stronger motivational inhibition of sexual stimuli.

The proposed inhibitory mechanism could be regulating a reward expectancy processing sustained by the caudate. The right caudate, like the anterolateral prefrontal cortex, was deactivated during the avoidance of sexual stimuli. A previous study showed that the more hours participants spent watching pornography, the less grey matter was observed in the right caudate (Kühn & Gallinat, 2014) which could reveal either a diminished reward sensitivity or a diminished capacity to regulate reward anticipation. The specific role and dynamics of the anterolateral prefrontal cortex and the right caudate in sexual inhibition remains to be elucidated.

Ventral anterior cingulate cortex activation was observed during the avoidance of sexual stimuli. Although this activation was only significant at a liberal threshold, this observation is consistent with a previous finding showing the engagement of this region when individuals were instructed to inhibit their sexual arousal while watching an erotic film (Beauregard et al., 2001). To this regard, the anterior cingulate cortex plays a fundamental role in the regulation of autonomic responses, which is essential in emotion regulation processing (Critchley et al., 2003).

In contrast to the inhibitory control condition, approaching sexual stimuli largely engaged subcortical areas (amygdala and the lentiform nucleus) that have been associated with sexual arousal and penile tumescence (Stoléru et al., 2012). Lesions in the amygdala have led to hypersexuality in some patients (Baird et al., 2007). Similarly, an irregular functional activation has been found in the lentiform nucleus of sexual compulsive patients (Voon et al., 2014). This seems to indicate that not only the integrity of inhibitory networks

is relevant for successful control of sexual behavior, but also the integrity of regions engaged in sexual approach. This is in concordance with the dual control model of male response (Bancroft & Janssen, 2000), which states that the balance between sexual excitatory and sexual inhibitory mechanisms is essential for the regulation of sexual behavior and a disproportional high sexual excitation or disproportional low sexual inhibition can lead to hypersexual behavior.

Cognitive sexual inhibition

The Negative Affective Priming paradigm allowed us to target the neural correlates of inhibiting sexual information at a cognitive level. The left orbitofrontal cortex, the fusiform gyrus, and the right inferior frontal gyrus were engaged during cognitive sexual inhibition. Although an inhibitory role has often been ascribed to the right inferior frontal gyrus and generally to the ventrolateral prefrontal cortex (Cohen & Lieberman, 2010), previous work has shown that the temporal disruption of this region with transcranial magnetic stimulation led to an increase in cognitive sexual inhibition after accounting for sexual excitation scores (Rodríguez-Nieto, Sack, Dewitte, & Schuhmann, in press). Recent evidence shows that the inferior frontal gyrus is sensitive to processes inherent to inhibition paradigms such as target detection, and therefore not exclusive to inhibition itself (Erika-Florence, Leech & Hampshire, 2014). Moreover, in the current study, the activation level of this region did not correlate with the behavioral inhibitory index. Therefore, the inferior frontal gyrus seems to play a relevant role during cognitive sexual inhibition but it does not seem to code for sexual inhibition itself.

The left orbitofrontal cortex has been proposed to exert an inhibitory tonic control over sexual stimuli, as it has shown to be hypoactive during different sexual cognition paradigms (Stoléru et al., 2012). In addition, this proposed inhibitory mechanism is dependent on testosterone levels, as this pattern (orbitofrontal cortex deactivation towards sexual stimuli) is not observed in hypogonadal men and it is restored after testosterone administration (Redouté et al., 2005). In addition, the lesion to the orbitofrontal cortex often leads to impairments in socio-affective regulation including sexual inhibition (Baird et al., 2007). Its activation during the current study provides direct evidence for its engagement during the inhibition of incoming sexual stimuli (cognitive sexual inhibition). Because this inhibitory process occurs without the awareness of the individual (is not deliberate), it may actually constitute a default, or tonic, inhibitory mechanism.

Finally, we found that the fusiform gyrus was also active during cognitive sexual inhibition. The inferotemporal cortex, where the fusiform gyrus is located, has been

suggested to act as a tonic inhibitor in the control of sexual behavior, as its lesion or resection has led to hypersexuality (Stoléru et al., 2012; Komisaruk & Rodríguez del Cerro, 2015). However, it is unclear whether the fusiform gyrus was compromised in the brain damage. Although the function typically attributed to the fusiform gyrus is the recognition of complex visual patterns (Weiner & Zilles, 2016), there is growing evidence showing the involvement of the fusiform gyrus in inhibition, emotion regulation (e.g. Dambacher et al., 2014a; Kilts et al., 2001; LaBar et al., 2001; Parsons et al., 2000, Goldin, McRae, Ramel, & Gross, 2008) and in non-visual sexual cognition (Zhou & Chen, 2008; Georgiadis, Reinders, Paans, Renken & Kortekaas, 2009). Thus, it could also be possible that its engagement during this paradigm represents an adaptive signaling during the inhibitory process through pattern recognition that is functionally guided (e.g. through an increased attention in faces).

Overlap between motivational sexual and cognitive sexual inhibition

We posed the question whether inhibiting sexually driven motor actions and inhibiting sexually incoming information would share common neural substrates. The motivational sexual and cognitive sexual inhibitory conditions showed an overlap in the inferior frontal gyrus and in the inferior and middle temporal gyri. As was discussed before, although frequently associated with response inhibition (Aron, Robbins & Poldrack, 2014), the exclusively inhibitory role of the inferior frontal gyrus has been challenged and recent evidence suggests a role in detecting sexual salient cues during cognitive sexual inhibition (Rodríguez-Nieto et al., in press). Although the overlap was only present at a liberal significance threshold, the fact that this area was commonly active during the two sexual inhibitory but not in the sexual non-inhibitory conditions, suggests that this region is not only sensitive to detecting salient sexual stimuli but in detecting them in function of other cognitive demands, which is inhibition in this case.

The inferior and medial temporal gyri were also conjointly active during the two types of sexual inhibition. The posterior inferotemporal cortex has found to be active during the perception of sexual stimuli and to vary according to the levels of sexual arousal and penile tumescence (Ferreti et al., 2005, Redouté et al., 2000). It is noteworthy that in the current study the conjoint activation of the posterior inferotemporal cortex appeared in the sexual inhibitory conditions (cognitive sexual and motivational sexual inhibition) but not in the sexual non-inhibitory conditions. This observation seems to support the notion that posterior inferotemporal regions play a specific role during sexual inhibition. Similar to the role of the fusiform gyrus –also part of the posterior inferotemporal cortex- during cognitive

sexual inhibition, the posterior inferior and medial temporal gyri can play a part in recognizing patterns that are adaptively relevant during the inhibitory processes.

The pattern of activation during the two sexual inhibitory conditions largely contrasts with the pattern of the sexual non-inhibitory conditions from the two tasks. The latter revealed a common activation in the anteromedial prefrontal cortex which is associated with the subjective experience of sexual arousal (Stoléru et al., 2012). In addition, there was a conjoint activation in the globus pallidus which when lesioned has led to hypersexuality in some clinical cases (Baird et al., 2007). Research has shown that the structure and functionality of other basal ganglia regions are related to the frequency of sexual behavior and shows an abnormal pattern in hypersexual individuals (Kühn & Gallinat, 2014; Seok & Sohn, 2015; Voon et al., 2014). The neural activation pattern of sexual inhibition in this study did not reveal any activation in the basal ganglia. This shows once again, that the integrity of both, sexual excitatory and inhibitory networks, is important for the successful control of sexual manifestations.

Overlap between sexual and general inhibition

Given the coexistence of sexual and general inhibition deficits in different clinical conditions, we also investigated whether sexual inhibition shares common neural mechanisms with general inhibition. We did not find commonalities among cognitive sexual inhibition, motivational sexual inhibition, and general inhibition. The absence of common neural networks in sexual and general inhibition seems to contrast with clinical observations showing that frontal lobe damaged patients are unable to control both their sexual and non-sexual behavior. Different explanations may account for this finding: 1) The three inhibitory processes recruited different but adjacent portions of the ventrolateral prefrontal cortex, therefore an extensive lesion in the area would lead to a generalized impairment in different inhibitory modalities. 2) The Go/No-go paradigm lacks a socio-affective component; the general inhibition impairment reported in frontal lobe lesion patients often refers to a disregard for social or even moral norms (Bechara, Damasio, Damasio & Anderson, 1994; Ciaramelli, Muccioli, Làdavas & di Pellegrino, 2007). Thus, the link between general and sexual inhibition may rely on processes involving social and/or affective cognition. 3) Although the Go/No-go task does not relate to other sexual inhibitory processes *per se*, general inhibition may influence non-sexual processes that ultimately relate to sexual behavior; for instance, a lack of inhibition in social contexts could lead to more sexual encounters.

Another potential contradiction to our findings is that sexual compulsion is often comorbid with other disinhibition related behaviors such as substance abuse. Even if sexual and general inhibition recruited different neural substrates, some conditions could influence different networks indistinctively. For example, a deficit in dopamine would have an effect on cognitive, motor, and motivational circuits.

Limitations and future directions

While our study allowed the characterization of the neural circuits sustaining sexual inhibitory mechanisms, one should consider that a possible limitation of the study is that only male participants were tested. Since women are less vulnerable to sexual inhibition impairments such as in hypersexuality (Kühn & Gallinat, 2016), and women and men show important differences in sexual cognitive processes (Dewitte, 2016) and inhibitory ones (Hosseini-Kamkar & Morton, 2014; Sjoberg & Cole, 2018), we included only men in our sample to provide a first test of the role of inhibition in sexual responding. However, future studies should also target sexual inhibitory processes in women and see whether these differ from patterns observed in men.

Regarding the technical part of the method, future studies can benefit from two particular points in the acquisition and in the analysis of the data. First, future studies may benefit, as we did, from the use of fMRI sequences that optimizes the signal in frontoventral regions. These regions are generally susceptible to noise artifacts, but are nevertheless crucial in socio-affective processing. Second, although our design provided the spatial accuracy and functional specificity that was not given by other methods or paradigms, a better comprehension of the neural circuits sustaining sexual inhibition can be achieved by studying the network interactions through advanced methods such as dynamic causal modelling.

In sum, this study did not support the existence of common general and sexual inhibitory networks. However, the inhibition of a sexually motivated driven action and the attentional inhibition of sexual information commonly engaged the inferior frontal gyrus and the posterior inferotemporal cortex. The specific functional properties of these regions, as well as those of the individual networks (for cognitive sexual and motivational sexual inhibition) remain to be studied in order to understand the distinct symptomatology and comorbidity of sexual disorders.

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CHAPTER 4.

Inhibit my disinhibition: The role of the inferior frontal cortex in sexual inhibition and the modulatory influence of sexual excitation proneness

Based on:

Rodríguez-Nieto, G., Sack, A.T., Dewitte, M., & Schuhmann, T. (2018). Inhibit my disinhibition: The role of the inferior frontal cortex in Sexual Inhibition and the modulatory influence of sexual excitation proneness. *Frontiers in Human Neuroscience*.

Abstract

Sexual behaviour is the result of an interplay between distinct neural inhibitory and excitatory mechanisms. Individual differences in sexual excitation and sexual inhibition are proposed to play an important role in the processes sustaining the regulation of sexual behaviour. While much research has focused on the neural correlates of response inhibition, highlighting a prominent role of the inferior frontal gyrus (IFG), very little is known regarding the neural mechanisms underlying different aspects of sexual inhibition. Here, we experimentally combined functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) to i) test the functional role of IFG during motivational and cognitive sexual inhibition and ii) reveal whether this IFG involvement in sexual inhibitory processes depends on sexual excitation and sexual inhibition as traits. Twenty-two participants performed an Approach-Avoidance and a Negative Affective Priming paradigm to assess motivational and cognitive sexual inhibition respectively. Our fMRI study showed IFG being selectively activated during cognitive but not motivational sexual inhibition. Importantly, the level of this neural activity was modulated by individual sexual excitation scores. Interestingly, a transient disruption of IFG activity using TMS led to an improvement in cognitive, not motivational, sexual inhibition, but only when accounting for individual sexual excitation scores. These findings clearly document that sexual excitation modulates IFG activity levels during cognitive sexual inhibition, and at the same time determines the effects of TMS on IFG by improving cognitive control exclusively for individuals with high sexual excitation scores. These findings provide new insights regarding the functional role of IFG, and underscore the relevance of individual psychological differences in understanding the brain mechanisms underlying socioaffective processes.

Introduction

Sexuality is evolutionary relevant and individually rewarding and thus constitutes one of the leading motivating forces in human behaviour. Since sexual arousal can arise fairly automatically in response to sexual stimuli that are omnipresent in everyday life, adequate social behaviour requires the ability to inhibit sexual responses that potentially harm social norms and individual well-being.

The ability to inhibit unfolding sexual responses comprises different psychological and physiological mechanisms that occur in parallel with those processes that elicit sexual arousal. According to the dual control model of sexual response, any form of sexual behaviour is the consequence of the interplay and balance between mechanisms that activate and facilitate the unfolding of the sexual response (sexual excitation) and mechanisms that diminish or avoid this response (sexual inhibition). Sexual inhibition and sexual excitation cannot only be studied as a process but also as traits, as individuals differ in their propensity to become sexually aroused or inhibited (Bancroft & Janssen, 2000). According to the dual control model of sexual response, individuals with high sexual excitation and low sexual inhibition have an increased propensity to engage in inadequate sexual behaviour.

Individual variabilities in sexual excitation and sexual inhibition have been largely studied with the Sexual Excitation/Sexual Inhibition Scales (SES/SIS) (Bancroft, Graham, Janssen, & Sanders, 2009). Higher sexual excitation has repeatedly been observed in individuals with out-of-control sexual behaviour (Bancroft & Vukadinovic, 2004; Janssen & Bancroft, 2007; Rettenberg, Klein & Briken, 2016; Winters, Christoff & Gorzalka, 2010). On the other hand, sexual inhibition has shown to be weakly or not related to hypersexual behaviours (Miner et al., 2016; Rettenberger, Klein & Briken, 2016), but has shown to be lower in individuals who engage more in risky sexual practices (Bancroft et al., 2009).

As sexual arousal can impact cognition and the control of sexual behaviour (Ariely & Loewenstein, 2006), it is expected that individuals who are more easily sexually aroused also differ in their sexual inhibition processing. Macapagal et al. (2011), for example, showed that individuals high in sexual excitation (as measured by the SES) committed more omission mistakes during a sexual Go/No-go paradigm, which is a measure of sexual response inhibition, after watching an erotic film than individuals low in sexual inhibition. Sexual inhibition (as measured by the SIS) did not relate to omission or comission mistakes, presumably because the SIS tackles the inhibition due to potential negative consequences of sexual activity, which was not included in the experiment design (Macapagal, Janssen,

Fridberg, Finn, & Heiman, 2011). Thus, although sexual inhibition traits may influence complex socio-sexual behaviour (e.g. risky sexual practices), individual differences in sexual excitation seem to have more predictive value for understanding basic sexual inhibitory processing and their neural mechanisms.

In contrast to the large body of evidence regarding the neural mechanisms of sexual arousal (see Stoléru et al., 2012 for a review), much less is known about the neural mechanisms underlying sexual inhibition. A pionering study by Beauregard et al. (2001), aimed to characterise the neural network engaged when individuals deliberately regulate their sexual arousal. Participants were explicitly asked to inhibit their sexual arousal while watching erotic stimulus material. In comparison to passively viewing the same stimuli, an enhanced anterior cingulate activity, left inferior frontal gyrus, and the right superior frontal gyrus activity was observed during the attempted sexual inhibition (Beauregard et al., 2001). Interestingly, the inferior frontal gyrus (IFG) has also been proposed to be a tonic inhibitor of sexual arousal as it was deactivated during the passive viewing of sexual stimuli (Redouté et al., 2005).

These studies provide converging evidence that the IFG, is associated with sexual inhibition. This region has also been associated with different types of more classic response inhibition paradigms (e.g. Go/No-go and Stop Signal task) (Aron et al., 2014), self-regulation (Cohen & Lieberman, 2010; Tabibnia et al., 2011), and with exerting top-down control over rewarding stimuli (Goldstein & Volkow, 2011). Recent models have challenged this dominant view of the IFG being mainly an inhibitory module, arguing for its common role in multiple cognitive demands such as task switching or salience detection which are inherent to inhibitory paradigms (Erika-Florence et al., 2014; Hampshire & Sharp, 2015).

In the field of sexual cognition, the IFG is one of the regions that are more actively engaged during the passive viewing of erotic stimuli in hypersexual individuals as compared to controls (Seok & Sohn, 2015; Voon et al., 2014). The IFG has also been related to the amount of penile tumescence in response to sexual images (Moulier et al., 2006), and to levels of sexual addiction (Seok & Sohn, 2015). In addition, IFG activation in response to sexually appealing stimuli has shown to depend on testosterone levels in male participants (Redouté et al., 2005; Stoléru et al., 1999) and on the menstrual phase in females (Roberts et al.,2008; Zhu et al., 2010). These studies suggest that in addition to its potential role for sexual inhibition and control, also sexual excitatory mechanisms modulate activity in IFG during the perception of sexual stimuli. This apparent contradiction, i.e. IFG being activated during sexual inhibition while at the same time responding stronger to sexually arousing

stimuli, may become plausible when considering that the higher the arousal experienced by a given individual, the higher the demand for inhibitory control. This would also explain why this increased IFG response to arousing stimuli is dependent on, e.g., testosterone levels or levels of sexual addiction as a trait.

In the current study, we aim to directly investigate whether the IFG is causally engaged in sexual inhibition, and whether this potential functional engagement of the IFG is dependent on sexual excitation and/or sexual inhibition proneness, under the assumption that individuals that are more prone to be sexually aroused or less prone to inhibit their sexual response, have different cognitive demands when trying to inhibit their sexual thoughts and behaviour. Two sexual paradigms were used to assess sexual inhibition: the Negative Affective Priming (NAP) paradigm assessing the cognitive component of inhibitory control, and the Approach-Avoidance paradigm (AA) designed to involve a motivational-motor driven component of sexual inhibition. Previous research has shown that both paradigms were sensitive to predict the frequency of sexual thoughts and pornography watching respectively, and represent two independent inhibitory mechanisms (Rodríguez-Nieto, Emmerling, Dewitte, Sack, & Schuhmann, in press). Functional magnetic resonance imaging (fMRI) was combined with transcranial magnetic brain stimulation (TMS) in two separate experimental studies. In Experiment 1, participants performed the NAP and AA while their task-related brain activity changes were measured using fMRI, identifying the exact brain regions specifically involved in sexual inhibition. We expected sexual inhibitory processes to be intrinsically connected to the extent to which individuals are prone to being sexually aroused and/or inhibited, accordingly, we hypothesised that individual differences in sexual excitation and/or sexual inhibition (measured by the Sexual Excitation/ Inhibition Scales; Janssen et al., 2002) would modulate the IFG neural response during sexual inhibition. In the second experiment, we tested whether the revealed brain activations are essential in encoding for the inhibitory process itself by assessing the behavioural effects of disrupting IFG activity with TMS in the NAP and AA paradigms. We hypothesised that the IFG dysruption effect might be modulated by individual differences in sexual excitation and/or sexual inhibition. Finally, in both studies, we included a classic Go/No-go paradigm as a non-sexual inhibitory reference task, which has consistently shown to also recruit the IFG in the context of general response inhibition (Aron et al., 2014; Dambacher et al., 2014; Levy & Wagner, 2011).

Experiment 1: Functional magnetic resonance imaging (fMRI) to identify brain regions activated during sexual inhibition

Method

Participants

Twenty-four healthy male participants (18-34 years old) with no neurological or psychiatric disorders took part in this study. One participant was excluded due to extensive head movements and a second participant due to technical difficulties leading to an incomplete data set (final sample: N = 22, mean age = 24.77, SD = 4.76). All participants received a written description of the experiment and the relevant practicalities about the use of MRI prior to accepting to participate. They gave written informed consent and were financially reimbursed for their participation. The study was approved by the local Ethical Committee of the Faculty of Psychology and Neuroscience at Maastricht University.

Design

The experiment consisted of one session in which participants performed two sexual (Approach-Avoidance and Negative Affective Priming) and one non-sexual (Go/No-go) inhibition paradigm inside the MR scanner. The order in which the two sexual tasks were presented was counterbalanced. The Go/No-go task was taking place between the sexual tasks to prevent habituation to sexual stimuli. At the end of the session participants filled out the computerised self-reports (Sexual Excitation/Sexual Inhibition Scales; see description below).

Paradigms

Approach-Avoidance Task

To address *motivational sexual inhibition* we adapted the approach-avoidance task using sexual and neutral stimuli (adapted from Dewitte, 2016) (Figure 1). Similar versions have shown to be related to the amount of viewing time of erotic stimuli (Hofmann et al., 2009), to be sensitive to gender differences (Dewitte, 2016), and to predict pornography watching frequency (Rodríguez-Nieto et al., in press).

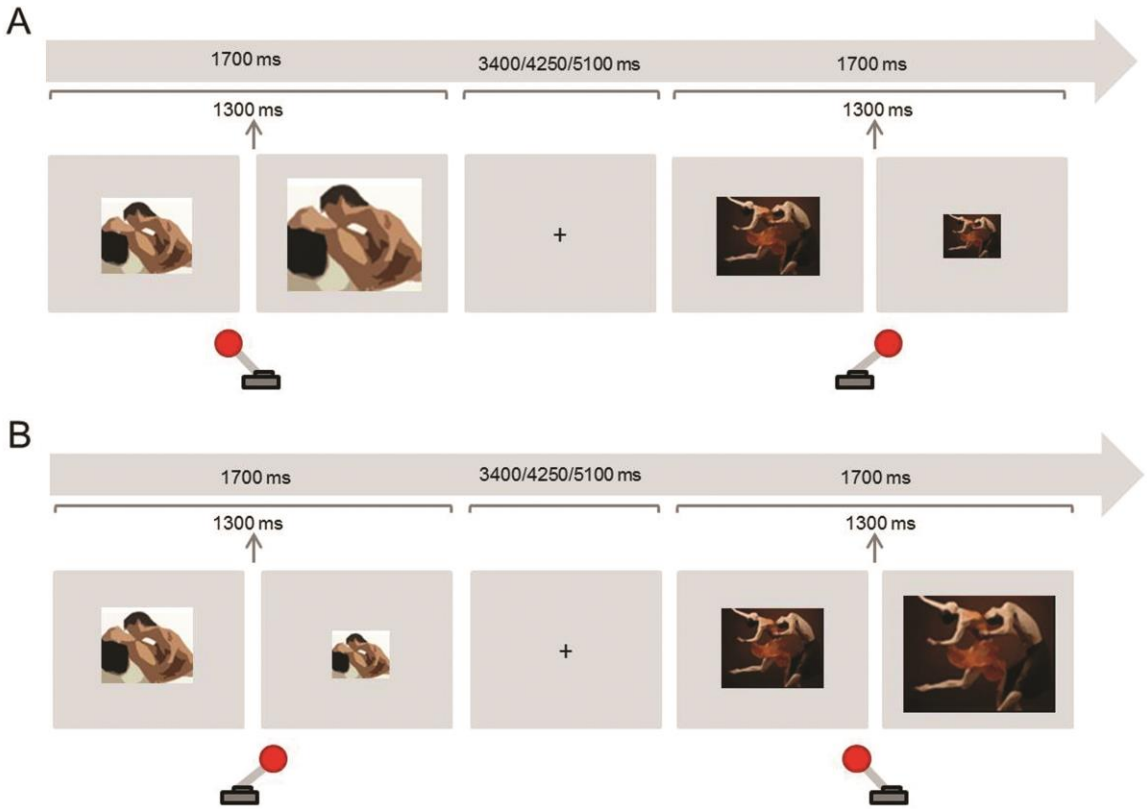

Figure 1. Experimental paradigm Approach-Avoidance task (motivational sexual inhibition). Participants were instructed to approach (pull the joystick towards them) sexual stimuli and avoid (push the joystick away) non-sexual stimuli in half of the blocks (A), and to avoid sexual stimuli and approach sexual stimuli in the remaining blocks (B). Approaching and avoiding stimuli produced a respective doubling or halving of the images.

There were two congruent and two incongruent blocks. In congruent blocks participants were asked to approach sexual stimuli and avoid non-sexual stimuli whereas they were asked to do the opposite in the incongruent blocks. To approach a stimulus, participants pulled a joystick towards them which doubled the image size. To avoid, participants pushed the joystick away from them, which in turn halved the image size. The block order was counterbalanced across participants. Each block contained 24 sexual and 24 non-sexual randomised stimuli. Sexual stimuli were colour photographs displaying dyadic heterosexual intercourse or oral sex. In order to avoid habituation and the impact of individual sexual preferences, we aimed to present each stimulus only once for every condition. Stimuli were drawn from a previously evaluated and validated dataset (Rupp & Wallen, 2007). As not enough photographs were available, 5 % were selected from the internet and evaluated by three judges to assure that the content and arousing properties were comparable to the

previously validated pictures. Non-sexual stimuli were colour photographs of one woman and one man dancing (Dewitte, 2016). The proportion of the bodies' dimensions (with particular attention to the female body) with respect to the whole picture was comparable in both conditions. Images were displayed on a light grey background and the default size of the image was 337,9 X 272,5 pixels (horizontal orientation) in half of the blocks and 257,6 X 400 pixels (vertical orientation) in the other half. The presentation of the stimulus in each trial lasted 1700 ms and these were intercalated with fixation crosses presented for 3400, 4250, or 5100 ms. The resizing of the image took place after 1300 ms of the image presentation to avoid variations according to the response reaction times.

Negative Affective Priming task

This task was selected to target *cognitive sexual inhibition* (adapted from Dewitte, 2016) (Figure 2). The inhibition process is assessed through the negative priming effect, which consists in a delay of a response towards a stimulus that has been previously inhibited (see description below). This phenomenon is not noticeable to the participant and, therefore, is believed to measure automatic inhibition (for an overview on automaticity see Moors & De Houwer, 2006). The priming effect has shown to be larger for sexual than for neutral stimuli presumably due to a major implication of inhibition (Dewitte, 2016; Rodríguez-Nieto et al., in press). This task predicted the frequency of sexual thoughts in daily life (Rodríguez-Nieto et al., in press).

There were four types of trial-sequences: a) Sex Priming, b) Sex No Priming, c) Non-Sex Priming, and d) Non-Sex No Priming. A trial-sequence consisted of a prime trial and a probe trial; during each, two pictures were presented simultaneously. The pictures were displayed one above the other, and one was surrounded by a black frame and the other by a grey frame. The instruction was to attend only to the black frame picture (target), therefore ignoring the grey frame one (distractor) and to indicate whether the target displayed sexual or non-sexual content through button pressing. During the priming trial-sequences, the content type of the distractor in the prime trial matched the content of the target picture in the probe trial. In the control trial-sequences (No Priming) the content type of the distractor in the prime trial was different from the target in the probe trial. The target of the probe trial could be sexual or non-sexual. Figure 2a provides an overview of the four different conditions (Sex – Non-Sex X Priming – No Priming).

The four types of trial-sequences were presented randomly in equal proportions throughout each of three blocks. Each block contained 32 trial-sequences. The prime and

probe trials were presented for 1700 ms each and were separated by a fixation cross displayed for the same duration. The probe and prime trials from different sequences were separated by the same fixation cross which lasted for 3400, 4250, or 5100 ms (Figure 2b). Sexual stimuli were pictures (320 x 260 pixels) different from those used in the AA task but with the same content characteristics. The non-sexual stimuli were colour photographs of one man and one woman exercising together. The neutral stimuli (distractors in the probe trials) were pictures of neutral objects (e.g. pencil case). Pictures were displayed on a light grey background and the picture frames were three pixels in width. 85% of photographs were selected from Rupp & Wallen (2007) and Dewitte (2016), and the remaining ones were selected from the internet, for the same reasons and on the same criteria basis as those selected for the Approach-Avoidance task.

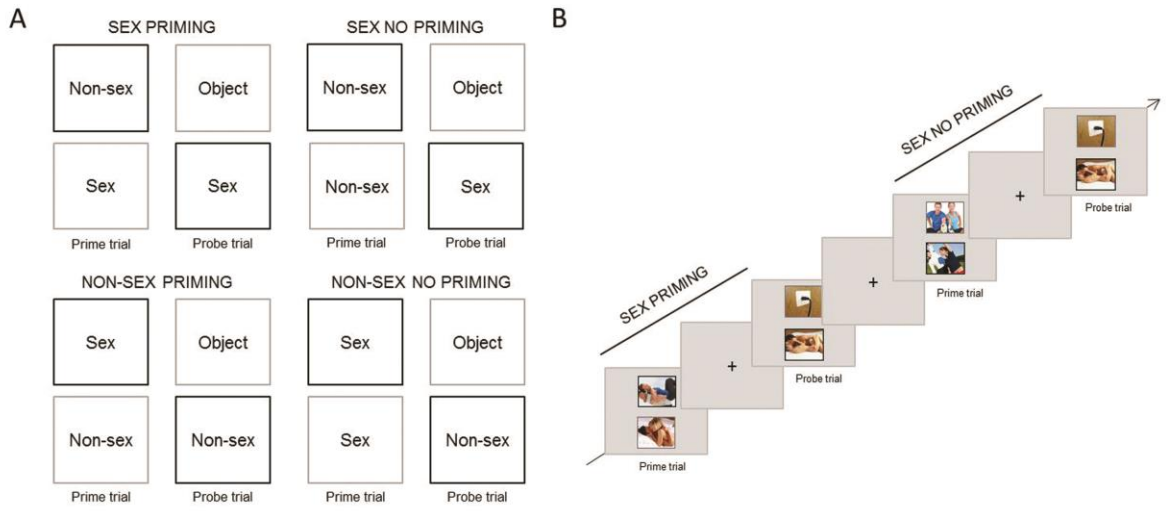

Figure 2. Experimental paradigm Negative Affective Priming task (cognitive sexual inhibition). A) Design of the four different trial-sequences (Stimuli [Sex vs Non-sex] X Type [Priming vs No Priming]). In priming probe trials participants had to respond towards the stimuli type (in black) that they ignored in the prime trial (in grey) of the same sequence. In no priming trials, the target content type (in black) in the probe trial did not match the distractor (in grey) in the prime trial. B) Example of a Sex Priming sequence followed by a Sex No Priming sequence.

Go/No-go task

This paradigm was used to target *general inhibition.* Participants were instructed to respond to a frequent Go stimulus and to not respond to an infrequent No-go stimulus. They responded with the right index finger on a button-box (Figure 3). As stimuli, the letters ‘C’

and ‘M’ were used and which letter was defined as the Go or No-go stimulus was counterbalanced across participants. Participants had to complete four blocks of 80 trials each (25% No-go trials). Every trial consisted of the presentation of the stimulus for 200 ms, followed by an inter-trial interval of 1500, 2350, or 4050 ms (Figure 3). Responses after 650 ms with respect to stimulus onset were not registered. The letters (3 X 2.3 cm) were displayed in white color on a grey background (adapted from Dambacher et al., 2014).

Before entering the MRI room, participants performed twenty practice trials for the Approach-Avoidance task (AA), eight trial sequences for the Negative Affective Priming task (NAP), and ten for the Go/No-go task. The number of practice trials was decided according to the complexity of every task. The practice trials involved different stimuli than the actual tasks to avoid habituation (animals and plants for the sexual tasks and ‘T’ and ‘K’ letters for the Go/No-go task). All tasks described in this manuscript were programmed and presented with PsychoPy software (Peirce, 2007).

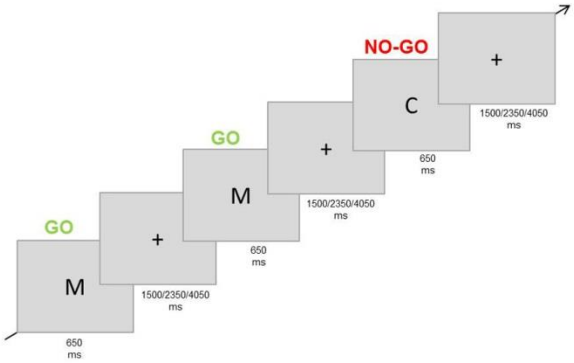

Figure 3. Experimental paradigm Go/No-go task (non-sexual inhibition task). Participants were asked to respond to a frequent stimulus (letter “M”) and to refrain from responding when the infrequent stimulus was presented (letter “C”).

Questionnaires

Sexual Inhibition/Sexual Excitation Scales (SIS/SES). This 45 items-scale measures the individual propensity for sexual inhibition and excitation. It contains one factor quantifying sexual excitation and two factors quantifying sexual inhibition: a) SIS1 – Inhibition derived from threat of sexual performance failure, distraction or lack of physical stimulation (14 items), and b) SIS2 – Inhibition due to the threat of performance consequences, such as risk of being caught, unwanted pregnancy, sexually transmitted diseases, feeling or causing pain, and partner’s too young age (11 items). Answers were registered on a four-point Likert scale

(Janssen et al., 2002). Previous studies showed solid internal consistency and test-retest reliability for the factors SES, SIS1, and SIS2 (Janssen, et al., 2002; Current study: SES Cronbach's alpha = .82; SIS1 - Cronbach's alpha = .73; SIS2 - Cronbach's alpha = .74).

Technical details and fMRI acquisition

Participants performed all paradigms inside the MR Scanner as described above. Data were acquired at the 3T Siemens Prisma Scanner at the Maastricht Brain Imaging Center, Maastricht University. Functional EPI images were collected using an in-house developed multi-echo multi-band sequence (Poser et al., 2006; TR = 850 ms, TE = 15/30/44 ms, flip angle = 50°, FOV = 210 mm, 36 slices, isovoxel 3 mm^3). Online-scanner reconstruction was performed using the slice-GRAPPA algorithm (Setsompop et al., 2012) with leakage artifact reduction (Cauley et al., 2014) as implemented in the reconstruction of the MGH blipped-CAIPI SMS-EPI distribution (software and complete documentation are available at https://www.nmr.mgh.harvard.edu/software/c2p/sms). The echo images were combined using an optimised echo weighting method as described in Poser et al., 2006. This GRAPPA sequence was used to optimise the BOLD signal in frontoventral regions. High-resolution anatomical images were acquired with an MPRAGE sequence (TR = 2250 ms, TE = 2.21 ms, FOV = 256 mm, 192 sagittal slices, isovoxel 1 mm^3).

fMRI analyses

The imaging data were pre-processed and analysed with Brain Voyager QX Version 2.8.4.2645 (Brain Innovation, Maastricht, Netherlands). The images were motion-corrected (trilinear / sinc interpolation and aligned to the first functional volume acquired after the anatomical sequence) and corrected for slice timing skew using temporal sinc interpolation. A temporal high pass filter (3 cycles) was applied. Images were co-registered to the individual T1 weighted images and normalised to Talairach stereotaxic space. Volume time courses were spatially smoothed using a 6mm full width half maximum Gaussian kernel.

We conducted a random-effects general linear model (GLM) analysis for every task. An event-related approach was considered for every task and each condition was entered as a regressor in the design matrix (AA: Sex Avoid, Sex Approach, Dance Avoid, Dance Approach; NAP: Sex Priming, Sex No Priming, Non-Sex Priming, Non-Sex No Priming; Go/No-go: Go, No-go). For each sexual task we contrasted the sexual inhibitory condition (AA: Sex Avoid; NAP: Sex Priming) against their respective control inhibitory condition (AA: Dance Avoid; NAP: Non-Sex Priming). Motion correction parameters were included as confound variables in the GLM. In separate models, we performed the same analyses

including the Sexual Excitation and Sexual Inhibition Scales scores as covariates. The resulting maps were corrected for multiple comparisons by means of cluster threshold level estimation (1000 Monte Carlo simulation iterations; Forman et al., 1995). Although we were particularly interested in the IFG, we report whole brain analyses results since sexual inhibition neural mechanisms have been barely explored. However, for the ANCOVA analyses, we limited the computation to the right prefrontal cortex with the aid of a mask circumscribed to this region.

Results

Approach-Avoidance task

The motivational sexual inhibition condition (Sex Avoid > Dance Avoid) led to decreased activation in the middle frontal gyrus, middle temporal gyrus, inferior parietal lobule, and cuneus (Table 1; CLTC $p < .005$).

Table 1. Regions active during the avoidance of sexual stimuli.

MOTIVATIONAL SEXUAL INHIBITION - Approach-Avoidance Task						
	BA	x	Y	z	Size (mm^3)	t
Middle Temporal Gyrus	21	63	-31	-2	1628	-4.55
Inferior Parietal Lobule	40	45	-58	43	1117	-4.41
Middle Frontal Gyrus	10	33	62	1	712	-5.05
Cuneus	30	9	-67	7	639	-4.13

CLTC $p < .005$

Negative Affective Priming task

During cognitive sexual inhibition (Sex Priming > Non-Sex Priming), increased activation was observed in the right inferior and middle frontal gyri, the posterior cingulate, the inferior and middle temporal gyri, and the fusiform gyrus (with some areas showing also task-related activity decrease, for a complete list see Table 2; CLTC $p < .005$; Figure 4). To exclude the possibility that the inferior frontal gyrus would be linked to a general sexual cognition

component, we also executed the Sex No Priming > Non-Sex Priming analysis. The inferior frontal gyrus was not activated under this condition (CLTC p = .01).

Table 2. Regions active during the sexual priming condition.

COGNITIVE SEXUAL INHIBITION – Negative Affective Priming Task						
	BA	x	y	z	Size (mm^3)	t
Middle Temporal Gyrus	37	42	-64	10	6472	6.21
Inferior Frontal Gyrus	46	45	29	13	870	4.67
Inferior Frontal Gyrus	47	30	29	-12	517	5.27
Posterior Cingulate	23	0	-52	22	1857	5.05
Medial Frontal Gyrus	10	0	56	-6	1454	4.21
Cingulate Gyrus	24	-9	-4	49	305	-4.08
Precentral Gyrus	6	-21	-16	64	443	-3.97
Middle Frontal Gyrus	11	-36	35	-9	861	4.04
Inferior Temporal Gyrus	19	-45	-73	1	7769	5.37
Fusiform Gyrus	37	-45	-37	-11	559	4.41

CLTC p < .005

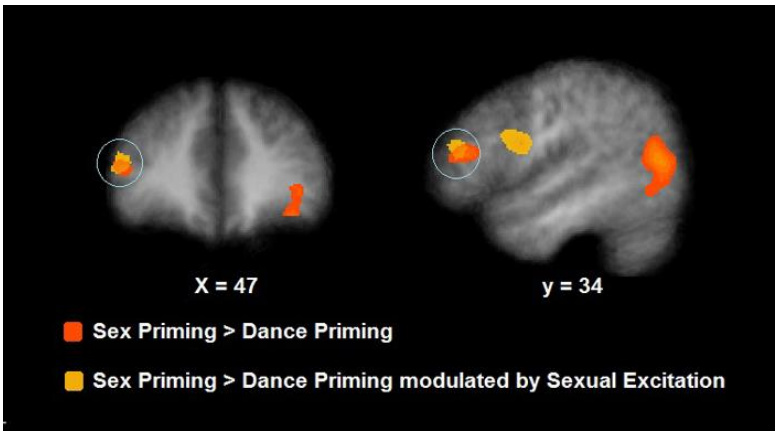

Figure 4. Neural activation during cognitive sexual inhibition (Negative Affective Priming task; in orange) and its correlates with Sexual Excitation (in yellow). During sexual priming trials, participants showed an increased activation in the right inferior frontal gyrus which also correlated with Sexual Excitation (maps showed at a p = .01, CLTC).

Go/No-go task

During the inhibitory trials (No-go > Go) an increased activation was observed in the right superior frontal gyrus and bilaterally in the insula, extending to the IFG on the right side (CLTC $p < .001$; Table 3).

Table 3. Regions active during the No-go trials.

GENERAL INHIBITION – Go/No-go task							
	BA	X	y	z	Size (mm^3)	t	P
Claustrum	13 / 44	27	14	-2	5445	7.5	.0000001
Superior Frontal Gyrus	9	30	50	31	1994	5.8	.000001
Insula	13	-33	20	13	2577	7.29	.0000001

CLTC $p < .001$

Modulatory role of Sexual Excitation/Inhibition Scales scores

The *Sexual Excitation Scale* (SES) scores of participants significantly correlated with the neural response during cognitive sexual inhibition (NAP: Sex Priming > Non-Sex Priming) within the IFG and in the middle frontal gyrus extending to the IFG (Table 4, CLTC $p < .005$). The latter cluster overlapped with the cluster engaged during the cognitive sexual inhibitory condition (Figure 4). The *Sexual Inhibition Scales* (SIS1 and SIS2) scores did not modulate the IFG neural response during the same condition (CLTC $p = .01$). The SES, SIS1, and SIS2 scores did not hold significant correlation with the IFG neural response during the sexual no priming trials of the NAP task (Sex No Priming > Non-Sex No Priming; CLTC $p = .01$), nor during the sexual avoiding trials of the AA task (Sex Avoid > Dance Avoid; CLTC $p = .01$). Unexpectedily, SIS1 scores -but not SES or SIS2-, modulated the IFG (pars orbitalis) neural response during the non-sexual inhibitory trials (No-go > Go; peak values: 39,26,1; Size (mm^3): 1823; CLTC $p = .001$). This cluster extended to the insula, where it showed an overlap with the non-modulated neural activation during the No-go trials (No-go > Go; Table 3).

Table 4. Sex Priming > Dance Priming correlates with Sexual Excitation scores.

COGNITIVE SEXUAL INHIBITION – Negative Affective Priming Task Neural correlates with Sexual Excitation Scale scores.						
	BA	x	y	z	Size (mm^3)	r
Inferior Frontal Gyrus	44	48	2	19	1060	.74
Middle Frontal Gyrus	46	48	35	19	460	.63

CLTC $p < .005$

Discussion

This study aimed at directly investigating the involvement of the IFG during sexual inhibition and the potential modulating role of individual differences in sexual excitation and/or sexual inhibition traits. To this end, we used functional neuroimaging during the execution of cognitive and motivational sexual inhibition using the established Negative Affective Priming and Approach-Avoidance paradigms.

The IFG was recruited during the execution of the cognitive sexual inhibition (Negative Affective Priming) but not during the execution of the motivational sexual inhibition (Approach-Avoidance) task. As expected, the IFG was also recruited during the non-sexual inhibitory Go/NoGo task. However, whereas the portion of the IFG recruited by cognitive sexual inhibition was located dorsally in the pars triangularis, the region engaged during the non-sexual inhibition was located ventrally in the opercular subdivision, in concordance with previous evidence (Dambacher et al., 2014). The disparity within the IFG regarding different types of inhibition and associated processes has been previously observed and a functional subdivision has been proposed (Cohen et al., 2013). In contrast to the non-sexual inhibition task (Go/No-go), the cognitive sexual task requires controlling bottom-up salient affective information during a cognitive process which implies more executive control and the inhibitory process occurs in an implicit rather than an explicit manner.

Unexpectedly, the IFG was not engaged during the motivational sexual inhibition task, which requires motor response control. It has been argued that the involvement of the IFG in inhibition paradigms is associated with the detection of infrequent stimuli (Erika-Florence et al., 2014). In the motivational sexual inhibition task, the inhibitory condition was presented in half of the trials which may have caused a tonic rather than an acute inhibitory demand.

We also aimed to investigate whether sexual excitation and/or sexual inhibition as traits modulated the IFG neural response during sexual inhibition processes. We observed that the degree to which an individual is, in general, more easily sexually aroused (according to SES scores) indeed significantly modulated the neural activity of the IFG during cognitive sexual inhibition but not during motivational sexual inhibition. This finding supports that individuals who are more prone to be sexually aroused have more inhibitory demands during cognitive sexual inhibition, resulting in an increased IFG activity during sexual inhibition which is modulated by sexual arousal proneness.

Sexual inhibition traits did not predict the IFG neural response during sexual inhibitory processes. Whereas the sexual inhibition traits assess the proneness to inhibit the sexual response and sexual arousal due to the threat of sexual performance, our paradigms targeted sexual inhibition at a cognitive and at motor-motivational levels. These processes may not be related at all or they may relate in other components of socioaffective cognition networks.

Although we did not have specific predictions regarding the modulation of sexual individuals traits over the IFG neural response during general response inhibition, we observed that individuals higher in the first factor of sexual inhibition (SIS1 - inhibition of the sexual response due to the threat/fear of sexual performance failure) recruited to a higher extent the IFG pars orbitalis during the No-go trials. This factor of sexual inhibition has been related to general anxiety and also proposed to be related to inhibitory tone (Bancroft et al., 2009). Both factors, anxiety and inhibitory tone could make the individual less prone to peripherically react, which would facilitate motor response inhibition but prevent the sexual response when it is desired.

In conclusion, the dorsal portion of the IFG pars triangularis (pt) showed to be specifically activated during the execution of cognitive sexual inhibition and its activity correlated with sexual excitation scores. Although these results seem to support the idea of IFGpt being an inhibitory node during cognitive sexual inhibition, the findings do not provide conclusive evidence for its causal involvement. From our correlational data we still cannot exclude alternative explanations, such as that the IFGpt processes the saliency of incoming information, increasing activity in individuals who are more easily sexually aroused when presented with sexual primed stimuli. In order to investigate whether the engagement of the IFGpt was indeed of inhibitory nature, we performed a subsequent brain stimulation experiment.

Experiment 2; Transcranial Magnetic Brain Stimulation

In our previous neuroimaging study, we could demonstrate that the right IFGpt is engaged during cognitive but not motivational sexual inhibition. Moreover, the activation during cognitive sexual inhibition correlated with sexual excitation as a trait.

Although this region has been typically associated with inhibitory and self-regulation processes (Aron et al., 2014; Cohen & Lieberman, 2010; Tabibnia et al., 2011), it has also been argued that its involvement during inhibitory tasks maybe derived from non- inhibitory processes such as salient stimuli detection (Erika-Florence et al., 2014; Hampshire & Sharp, 2015).

To assess whether the BOLD activations that we observed were indeed associated with inhibitory processing, we employed a brain stimulation design. We tested whether the experimental deactivation of the right IFGpt using TMS would result in an experimentally-induced change in sexual inhibition capacity. Considering the specificity of its activation to cognitive sexual inhibition, we expected that brain stimulation-induced disruption would influence exclusively this inhibitory process while leaving unaffected other types of sexual inhibition or non-sexual inhibition processes. Finally, our design enabled us to experimentally assess whether brain stimulation-induced effects depend on the sexual excitation propensity of participants, considering that the level of neural activity within this region has shown to be correlated with sexual excitation as a trait during cognitive sexual inhibition (see experiment 1).

To further increase the specificity of potential findings, we also targeted the precuneus, as this region was active during the sexual trials of both sexual inhibition tasks and did not show activation specificity for the inhibitory conditions. Thus, this region seems to play a role in sexual cognition that is not specific to the inhibitory component. Therefore, disrupting this area could modulate sexual inhibition by generally dysregulating sexual cognition in a non-specific way. To pursue our goals, we used a repeated-measures design in which participants performed the same tasks as described in Experiment 1 to target cognitive sexual and motivational sexual inhibition (Negative Affective Priming and Approach-Avoidance) as well as a motor-response general inhibition task (Go/No-go) to additionally control for possible effects on a non-sexual inhibitory process.

Method

Participants

Twenty-five healthy and self-reported heterosexual males were recruited for this study. One participant did not attend the third session and two participants stopped during the first session as they experienced the stimulation as uncomfortable. All participants were informed about the risks and effects of the TMS and signed an informed consent. Neither of the participants had a history of neurological disorders and all of them were right-handed (Final sample: n = 22; mean age = 21.8, SD = 6.25). The study was approved by the same ethical committee as in Experiment 1.

Design

Participants underwent three TMS sessions and an initial MRI session in case no prior anatomical MR data set was available (n = 15). During the TMS sessions, participants received continuous theta burst stimulation (cTBS) (Huang et al., 2005) on one of two target sites (IFGpt and precuneus) and sham stimulation; the session order was counterbalanced. Sham stimulation was delivered to the supplementary motor area, being an intermediate location between the two target sites. All sessions were scheduled at least one week apart from each other to diminish a learning or habituation effect. In every session, before the stimulation, participants performed few practice trials of the computerised tasks. In the first session, the individual motor threshold was determined by delivering single pulses to the right motor cortex with an increasing intensity until we observed a motor response in the left abductor pollicis brevi muscle. In each session, participants performed three computerised tasks following the cTBS stimulation (see below for details). The non-sexual task (Go/No-go) was always presented between the two sexual tasks to avoid habituation from sexual stimuli. The order of the two sexual tasks was counterbalanced across participants but the order remained constant within participants across sessions. At the end of the third session, participants were asked to fill in the same computerised questionnaires as in Experiment 1. They were identified with a number to ensure the anonymity of their responses.

Paradigms

As the cTBS effects start to dissipate after 45 minutes (Huang et al., 2005) we adapted the timing of the computerised tasks described in the Method section of Experiment 1 as described below. Beyond this adaptation, the tasks remained with the same characteristics.

Approach-Avoidance task

The total exposition of the sexual and neutral pictures lasted for 1700 milliseconds, and the resizing time occurred immediately after a joystick response was executed. The interstimulus fixation cross lasted for 1300, 1500, or 1700 milliseconds. We calculated a Sex Approach-Avoid index, by subtracting the reaction times in Sex Approach blocks from reaction times in Sex Avoid blocks. A major Sex Approach-Avoid index indicated a stronger control over sexual motivation, by taking less time to avoid sexual stimuli and/or taking longer to approach them.

Negative Affective Priming task

Every prime and probe trial, and every inter-trial fixation cross lasted for 1500 milliseconds. In order to get priming effect indices for the sexual and non-sexual conditions, the reaction times in the probe trial of the No Priming condition were subtracted from the reaction times in the probe trial of the Priming condition for Sex and Non-Sex conditions. We further calculated a main sexual priming score by subtracting the non-sexual priming index from the sexual priming index. A higher index indicated a stronger sexual priming effect and thus, a stronger sexual inhibition.

Go/No-go task

Every trial consisted of the presentation of the stimulus for 200 ms, followed by an inter-trial interval of 650, 850, or 1050 ms. Responses after 650 ms with respect to stimulus onset were not registered. False alarms (responding to a No-go trial), and misses (not responding to a Go trial) were recorded.

Questionnaires

Participants filled in the same questionnaires as in Experiment 1.

Localisation of TMS target regions

As new participants (n = 19) were recruited for the present TMS study and since TMS effects are highly dependent on spatial precision, we used cortex based-alignment (CBA) for individualised TMS coil positioning. Unlike Talairach coordinates, the CBA method takes the macroanatomical differences of participants into account by aligning the individual anatomical data with pre-existing functional data in a surface space. Therefore, this method preserves a functional-anatomical correspondence, resulting in a higher spatial stimulation specificity over the region of interest and consequently stronger TMS effects (Duecker, et al., 2014).

To this end, every anatomical data was segmented and a cortex reconstruction was created (80 000 vertices) from which a curvature map was extracted and transformed into a spherical space. The individual spherical space of each participant in this study was aligned to the group average spherical space from the fMRI sample proceeding from most prominent to most fine anatomical landmarks. After the alignment, the individual space was back-transformed to the individual brain anatomy and the target regions in the average surface map from fMRI were copied to the individual surface maps. Anatomical images from the participants were collected with the same methodology as in Experiment 1.

As a target area, we selected the IFG cluster that was active during the cognitive sexual inhibition paradigm (NAP) in Experiment 1 and whose activity was shown to be modulated by the sexual excitation scores. The selection of the area was based on the surface map GLM for the Sex Priming > Non-Sex Priming contrast (x, y, z = 40, 28, 20). We also executed a conjunction analysis of the sexual conditions of both sexual inhibition tasks (Sex Approach ^ Sex Avoid ^ Sex Priming ^ Sex No Priming); from the resulting map we extracted a patch of interest in the precuneus (x, y, z = 25, -70, 40, CLTC p = .001).

TMS parameters

The TMS protocol was applied using a MagPro X100 stimulator (MagVenture A/S, Farum, Denmark) and a figure-of-eight coil (MC-B70). The co-registration of the participant's head with their MRI anatomical data was done with the Brain Voyager TMS Neuronavigator (Brain Innovation, BV, Maastricht, The Netherlands), which allowed the localisation and targeting of the regions of interest. The coil was manually held tangentially to the scalp and oriented at 45°, 90° and 45° to the central sulcus for the IFG, pre-supplementary motor area (sham), and precuneus respectively. cTBS was applied at 100 % of the individual resting motor threshold (Average Maximal Stimulator Output = 32.87, SD = 3.98; Realised di/dt = 49 A/us). For the sham stimulation a placebo coil was used (MC-P-B70).

Results

A repeated measures ANOVA revealed no main stimulation effect on sexual inhibition as there were no significant differences on the AA ($F(2, 42) = 1.53$, $p = .22$) or the NAP ($F(2, 42) = 2.47$, $p = 0.09$) main indexes across the three sessions. Similarly, a Friedman's two-way ANOVA by ranks showed no differences in the number of Misses and False Alarms in

the Go/No-go task (False Alarms: p =.21; Misses: p = .57). Table 5 shows the average main index for the AA and NAP tasks and the median of the frequency of False Alarms in the Go/No-go task for every session.

When accounting for sexual excitation scores, however, a significant main effect of stimulation on the NAP task (F (2, 40) = 6.24, p = .004) was observed with participants showing a higher sexual priming effect after TMS over IFGpt as compared to the precuneus and the sham stimulation sessions (p = .02 and p = .05; Figure 5). No such main effects was found for the AA task (F (2, 40) = .72, p = .49). After adjusting for multiple comparisons, the difference between the two experimental conditions (IFGpt and precuneus stimulation) remained significant (p = .05) while the difference between the sham and the IFGpt stimulation conditions did not (p = .16). Stimulation had different effects on participants depending on their sexual excitation scores (Interaction effect: F (2, 40) = 5.73, p = .01). Regression analyses showed that higher sexual excitation scores predicted a smaller sexual priming effect during the sham session (R^2 = .22, t = - 2.38, p = .03; Figure 6a), but the inverse pattern was observed during the IFGpt stimulation session (R^2 = .24, t = 2.49 p = .04; Figure 6c). No association was found between these two variables in the precuneus stimulation session (R^2 = .008, p = .67; Figure 6b).

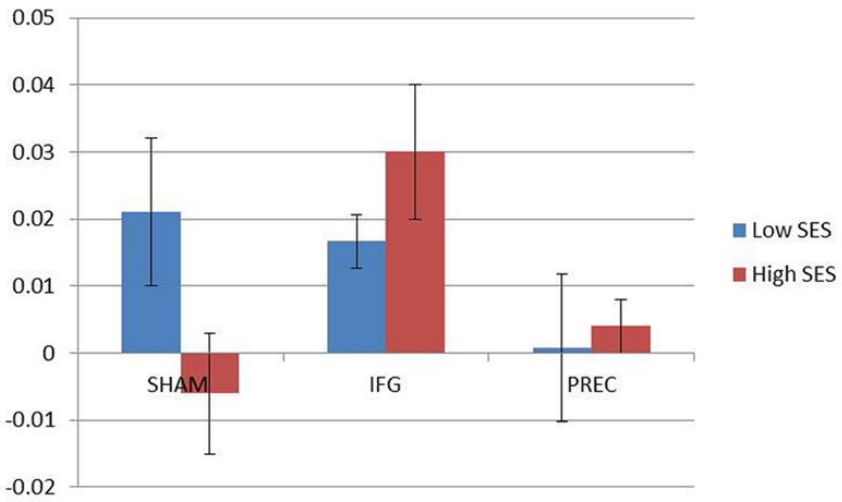

Figure 5. **Mean indices of the cognitive sexual inhibition task (Negative Affective Priming) across the three sessions.** For illustration purposes, the sample was median-split according to the Sexual Excitation Scale (SES) scores (Blue: low; Red: high). Participants high in sexual excitation proneness showed an increased cognitive sexual inhibition after the cTBS in the inferior frontal gyrus (IFG) compared to the control condition (sham) and to the cTBS in the precuneus (PREC) (F = 4.79, p = .03).

Table 5. Behavioural outcomes of the three inhibitory tasks across the three TMS sessions.

APPROACH-AVOIDANCE TASK					
Reaction Times	*Sex Approach Mean (SD)*	*Sex Avoid Mean (SD)*	*Dance Approach Mean (SD)*	*Dance Avoid Mean (SD)*	*Main Index Mean (SD)*
Sham	784 (138)	805 (168)	819 (128)	827 (145)	-13 (82)
IFG	791 (113)	822 (131)	845 (137)	823 (115)	-52 (84)
Precuneus	808 (134)	837 (136)	862 (130)	842 (135)	-48 (119)
NEGATIVE AFFECTIVE PRIMING TASK					
Reaction Times	*Sex Priming Mean (SD)*	*Sex No Priming Mean (SD)*	*Neut Priming Mean (SD)*	*Neut No Priming Mean (SD)*	*Main index Mean (SD)*
Sham	572 (61)	579 (048)	559 (54)	575 (55)	8.6 (35)
IFG	586 (57)	579 (043)	566 (53)	581 (46)	22 (24)
Precuneus	575 (53)	582 (047)	565 (54)	573 (52)	2.3 (28)
GO/NO-GO					
Frequency		*False Alarms Median (min, max)*		*Misses Median (min, max)*	
Sham		10 (1,36)		1.5 (0,24)	
IFG		10.5 (0,22)		2 (0,8)	
Precuneus		10 (0,28)		1 (0,16)	

IFG – Inferior frontal gyrus.

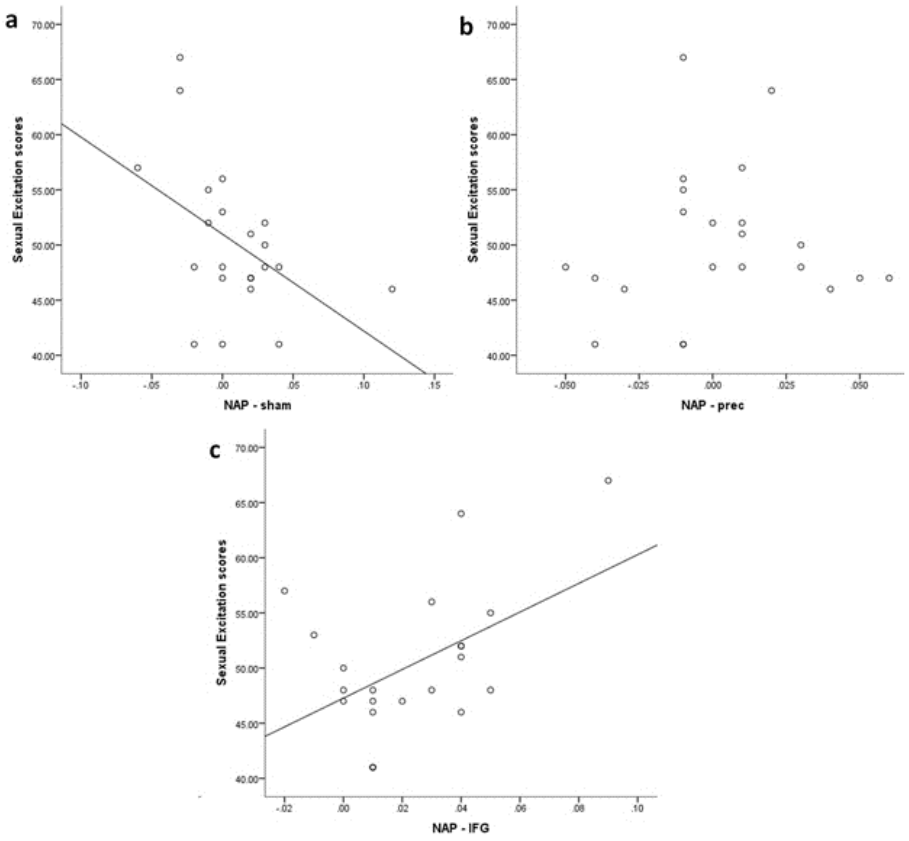

Figure 6. Relationship between Sexual Excitation scores and cognitive sexual inhibition (NAP index) through the three sessions. Sexual excitation negatively predicted cognitive sexual inhibition during the control condition (a) (R^2 = .22, t = - 2.38, p = .03), which was reversed after the cTBS in the inferior frontal gyrus (c) (R^2 = .24, t = 2.49 p = .04). No significant relationship was found after the cTBS in the precuneus (b) (R^2 = .008, p = .67).

Discussion

In this non-invasive brain stimulation study, we aimed to test whether the involvement of the right IFGpt during cognitive sexual inhibition observed in Experiment 1, was actually encoding for an ongoing inhibitory process. According to the results of Experiment 1, we expected: a) IFGpt disruption to induce changes specifically in cognitive sexual inhibition -not in motivational sexual inhibition or general motor-response inhibition-, and b) sexual excitation as a trait to modulate these behavioural effects induced by the IFGpt disruption.

We observed that disrupting the IFGpt did modulate sexual inhibition in a specific way. Whereas brain stimulation affected cognitive sexual inhibition, it did not produce significant changes in motivational sexual inhibition or general motor-response inhibition.

Importantly, this effect was significant only when taking into account sexual excitation proneness.

The present findings are relevant in two crucial ways. First, the effect was specific to cognitive sexual inhibition and did not affect other forms of inhibition. In our previous study, the different sexual inhibitory mechanisms were not related with each other behaviourally, and they distinctively predicted the frequency of different aspects of sexuality (sexual thoughts and pornography watching) (Rodríguez-Nieto et al., in press). Importantly, we here showed that only cognitive sexual inhibition recruited the IFGpt (Experiment 1). Second, the stimulation effect was only significant when accounting for sexual excitation which is in line with our fMRI study, in which participants with higher sexual excitation scores showed a stronger response in the IFGpt during cognitive sexual inhibition.

General discussion

In Experiment 1 we found that the right IFGpt is explicitly activated during cognitive sexual inhibition but not during motivational sexual inhibition or general motor-response inhibition. Supporting our hypothesis, we found that sexual excitation modulated the IFGpt activation, yet specifically during cognitive sexual inhibition. This seemed to suggest that individuals who are more easily sexually aroused have higher inhibitory resource demands which translate into more activity within IFGpt during sexual inhibition. In Experiment 2, we used TMS to disrupt the neural activity within the IFGpt and the precuneus. We observed an increase in cognitive sexual inhibition when disrupting activity within IFGpt, only when taking into account sexual excitation scores. This finding is in contradiction with the traditional role that has been adjudicated to this region because temporally disrupting the inhibitory function of rIFG with TMS should according to this classical view result in a decreased inhibition.

Although the region that we disrupted (dorsal IFGpt) has previously been engaged in inhibitory paradigms (Amin et al., 2006; Levy & Wagner, 2011), the role of the right IFG as an inhibitory module was challenged in a previous study where the manipulation of a classic inhibition paradigm (Stop Signal Reaction Time) showed that this region was not exclusively sensitive to inhibition itself but supported different processes such as the detection of salient cues and infrequent stimuli (Erika-Florence et al., 2014). This region has also shown to be relevant in visual detection of changes in the environment (Verbruggen et al., 2010) and

seems to be part of the ventral attentional network which is involved in reorienting processing driven by bottom-up salient stimuli (Corbetta et al., 2008).

Remarkably, both studies (Experiment 1 and 2) were consistent in showing the modulatory effects of sexual excitation over the IFGpt during cognitive sexual inhibition. If the IFGpt is sensitive to detecting salient information, we would expect that the underlying mechanism is more prominent in individuals who are more sensitive to sexual cues during a cognitive sexual inhibition paradigm. In line with this, disrupting this process would cause a lower sensitivity to affective salient information resulting in a better affective cognitive inhibition. This reasoning is in concordance with the current results. The TMS effects were dependent on sexual excitation with individuals scoring higher in this trait showing larger benefits in cognitive sexual inhibition as a consequence of the experimentally-induced IFGpt disruption. This is, whereas individuals that scored high in sexual excitation showed less sexually cognitive inhibition during the baseline condition, this relationship was reversed when IFGpt activity was disrupted with cTBS. It can be expected that individuals who are more easily sexually aroused have a lower threshold to detect sexual cues. This salience detection mechanism interferes with their inhibitory demands. However, when this mechanism is disrupted, they can more easily ignore sexual cues facilitating their inhibitory processing.

In conclusion, this pair of studies shows that the right IFGpt is a relevant node during sexual inhibition (and in particular to cognitive sexual inhibition). However, the current evidence did not support that this region sustains the inhibitory processing, as the temporal disruption of the IFGpt produced an increase in cognitive sexual inhibition. The present evidence supports the role of the right IFGpt as a reorienting system driven by salient stimuli detection. Importantly, our study highlights the role of individual differences in psychological processes and their underlying neural mechanisms. The IFGpt activity during cognitive sexual inhibition was modulated by sexual excitation and, in line with this, the effect of TMS on the participants' performance was also dependent on the levels of sexual excitation. These findings showed that sexual excitation proneness influence basic sexual inhibition processing and the underlying neural mechanisms. This was specific to cognitive sexual inhibition and presumably due to a higher sensitivity to sexual cues. Finally, the modulation of sexual excitation trait over the rIFG during sexual inhibition provides empirical support to the dual control model of male sexual response which states that the interplay of excitatory and inhibitory mechanisms determine the occurrence of sexual responses and associated behaviours (Bancroft & Janssen, 2000).

Deepening our understanding of the neural mechanisms underlying sexual inhibition does not only advance our knowledge on the symptomatology of sexual disorders but also provides insights for treatment improvements. In particular, the use of TMS represents an alternative to the use of medicaments to treat sexual disorders which often have undesired side effects (e.g. nausea, mood changes, bone reduction) or are contra-indicated because of the use of other pharmaceuticals. Although more research is needed, the rIFG activity could be a potential biomarker for detecting the suitability of TMS treatment. Alternatively, the modulation of cognitive sexual processes can be addressed by targeting different sub-processes such as reward processing (Prause et al, 2016). Future studies may examine the clinical suitability of the present protocol or examine different sexual inhibitory processes through different networks.

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CHAPTER 5.

Keep calm and regulate your sexual behaviour: The neuromodulatory role of cortisol during the approach of sexual stimuli

Based on:

Rodríguez-Nieto, G., Sack, A.T., Dewitte, M., Emmerling, F& Schuhmann, T. (*submitted*) The neuromodulatory role of cortisol during the approach of sexual stimuli.

Abstract

The regulation of sexual arousal and sexual behaviour is essential in everyday life. It has recently been shown that these regulatory processes are differentially affected by mood. For example, individuals vary in how a particular mood (anger, anxiety, and sadness) affects their proneness to be sexually aroused, to perform sexual acts, or to be sexually disinhibited. However, the physiological mechanisms linking sexual arousal, sexual regulation, and mood are poorly understood. The hypothalamic-pituitary-adrenal axis is considered to be crucial for this association, as cortisol has been shown to influence sexual arousal as well as to play a neuromodulatory role during emotion regulation. Here, we used functional magnetic resonance imaging for investigating the potential neuromodulatory role of cortisol in the association between sexual arousal, mood, and sexual regulation. Specifically, we investigated whether cortisol modulates the neural response during the approach of sexual stimuli in an approach avoidance task and whether these neural correlates underlie the individual differences in sexual inhibition as well as the association between mood and sexual desire and behaviour. We revealed that cortisol modulated the neural response of the anteromedial prefrontal cortex during the approach of sexual stimuli. Moreover, the anteromedial prefrontal cortex activation was dependent on individual differences in sexual inhibition and the improvements of negative mood as a result of sexual activity. Network connectivity analyses showed that the coupling between the anteromedial prefrontal cortex and the amygdala was related to the likelihood of individuals to perform sexual actions that could be later regretted. The anteromedial prefrontal cortex processes bottom-up information, reward, and risk estimation. The neuromodulatory role of cortisol in this region during sexual approach may be a key element in the regulation of sexual behaviour.

Introduction

The regulation of sexual desires and behaviour is essential to maintain health and social harmony. The impairment of the ability to regulate sexual behaviour can result in a wide spectrum of undesired consequences including sexual risk behaviour, hypersexuality, and sexual offense. Dysregulated sexual behaviour can be caused by an imbalance between the proneness to be sexually aroused (sexual excitation) and the ability to inhibit such arousal (sexual inhibition) (Bancroft & Janssen, 2000). It can be implied that the ability to inhibit sexual arousal has an impact on motivational tendencies, reducing the probability of sexual approach behaviours.

Among possible factors influencing sexual regulation and sexual approach behaviours, mood is assumed to play an important role by affecting either sexual excitation or sexual inhibition. However, current evidence reveals conflicting results, pointing to a facilitative, inhibitory, or even no effect of negative mood (e.g. anxiety and stress) on sexual arousal, sexual interest, and sexual activity (Bodenmann, Atkins, Schar, Poffet, et al., 2010; Bradford & Meston, 2006; Crepaz & Mark, 2001; Koukonas & McCabe, 2001; Mitchell, DiBartolo, Brown & Barlow, 1998; Nobre et al., 2004). This inconsistency may be partly due to individual differences as some individuals seem more prone than others to experience sexual arousal when being in a negative mood (e.g. sad, angry, or anxious). There seems to be a link between the association mood-sexual arousal and the manifestation and regulation of sexual behaviour. Individuals who experience sexual desire and arousal while being sad or depressed, report a higher number of sexual partners and lifetime one night-stands (Bancroft, Janssen, Strong & Vukadinovic, 2003; Bancroft et al., 2003). In relation to sexual regulation, sex addicts reported to have an increased interest to engage in sexual behaviour in states of depression or anxiety (Bancroft & Vukadinovic, 2004; Rettenberg, Klein & Briken, 2016; Young, 2008) and show a higher comorbidity with mood disorders (Kuhn & Gallinat, 2016). Furthermore, sexual offenders are more likely to respond to stress with sexual fantasies or acts, thereby being at increased risk of sexual recidivism during certain emotional states (Cortoni & Marshall, 2001; Hanson & Harris, 2000; McKibben, Proulx, & Lusignan, 1994).

The physiological mechanisms underlying the relationship between sexual approach behaviours and mood can be partly rooted in the hypothalamic-pituitary-adrenal (HPA) axis. During stressful circumstances, the release of cortisol activates the sympathetic system preparing the body for fight/flight responses. Cortisol also influences cognitive processes such as learning, memory, and emotional arousal processing, which in turn influence

approach-avoidance tendencies and behaviour (Kaldewaij, Koch, Volman, Toni, & Roelofs, 2016; Wolf, 2009). Regarding sexual cognition, baseline cortisol levels positively relate to the degree of sexual arousal induced by sexual thoughts (Goldey & van Anders, 2012) and to the amount of physical effort made to visualise female erotic images (Chumbley et al., 2014). By increasing the arousal towards emotional salient stimuli, cortisol levels may impact the regulation of sexual arousal and sexual approach behaviour. On the other hand, a disruption in the HPA axis potentially leads to a dysregulation of homeostatic processes including sexuality. For instance, in hypersexual individuals, cortisol levels negatively correlate with the severity of their disorder and they also show an irregular HPA endocrine suppression pattern. These patients may engage in more intense and frequent sexual activity to compensate an irregular endogenous mechanism. Interestingly, these patients report more depression symptoms and more childhood trauma (Chatzittofis et al., 2016).

Beyond the changes induced in the autonomous nervous system, the HPA axis activity also yields important effects in the central nervous system. In the brain, limbic structures and the medial prefrontal cortex (PFC) – essential in processing and regulating emotional arousal (Mc Klveen, Myers, & Herman, 2015; Phelps & LeDoux, 2005) – are rich in glucocorticoids receptors (Sánchez, Young, Plotsky, & Insel, 2000; Ulrich-Lai & Herman, 2009). An increasing number of neuroimaging studies show that cortisol levels modulate the activity and connectivity of these regions during resting state and during emotion regulation paradigms (Henckens, Wingen, Joels & Fernández, 2011; Kern et al., 2008; Kogler et al., 2016; Veer et al. 2012; Urry et al., 2006). The medial PFC has been assigned a crucial role in the regulation of the HPA axis and has been suggested to coordinate different cognitive functions to create context-specific responses (Mc Klveen, Myers, & Herman, 2015). Its connectivity with the amygdala during approach-avoidance behaviours, points to a regulatory feedback mechanism (Volman, Roelofs, Koch, Verhagen, & Toni, 2011). The connection between the medial PFC and the amygdala also mediates the response to stress and shows abnormal patterns in mood disorders such as anxiety disorder and depression (Pagliaccio et al., 2015).

These lines of evidence converge to the notion that cortisol plays a role in neuromodulating brain regions involved in emotion regulation such as the amygdala and medial PFC. Moreover, cortisol levels have not only been implicated in the behavioural response towards stress and mood states but also in sexual arousal. Therefore, it may be hypothesised that cortisol is involved in the physiological and neural mechanisms underlying the relationship between mood and sexual regulation. In the current study, we aimed at

replicating evidence showing a relationship between endogenous cortisol and sexual arousal and we aim to investigate whether cortisol relates to the degree to which individuals feel in control during a sexual arousing condition. In addition, we hypothesise that moods that elicit a fight-flight response (anxiety, stress, and anger) relate to endogenous cortisol and sexual arousal, according to the proposition that mood relates to sexual arousal due to the enhanced arousing state of the organism. Furthermore, we aim to investigate if cortisol modulates the neural activity during sexually motivated approach behaviour. For our purposes, we implemented an Approach-Avoidance paradigm, as this simulates natural motivational tendencies towards affective stimuli. As cortisol has shown to influence a wide spectrum of cognitive processes but its neuromodulatory role in sexual cognition has not been studied yet, we aim to perform an exploratory whole-brain analysis. We are, however, particularly interested in the modulating role of cortisol within the medial PFC and its interaction with the amygdala. Finally, we aim at investigating whether potential brain activity modulated by cortisol during sexual approach-avoidance behaviours relates to sexual regulation traits. More specifically, we examined sexual inhibition trait and the degree to which individuals' sexual interest and behaviour is associated to mood (i.e. anger, sadness, and anxiety). To assess sexual inhibition we considered the second factor of sexual inhibition from the dual control model of sexual response. This factor refers the proneness to inhibit the sexual response and arousal due to the negative consequences of sexual performance (e.g. contagion of sexual transmission disease) (Bancroft & Janssen, 2000) and therefore, it has been shown to be related with risky and non-solitary out-of-control sexual behaviours (Bancroft et al., 2004; Bancroft and Vukadinovic, 2004). To assess individual differences in the relationship mood-sexual interest and behaviour, we consider the effect of mood on sexual desire, the benefits on mood from sexual activity, and the effects of mood on regrettable sexual behaviour (Janssen, Macapagal, & Mustanski, 2013).

Method

The current analyses are derived from a dataset that was previously used to compare the neural mechanisms of different inhibitory processes (see Rodríguez-Nieto, Sack, Dewitte, Emmerling, & Schuhmann, submitted). The research question and goal of the current study is not related to the previous one and therefore all the here presented analyses and associated results have not been reported elsewhere.

Participants

Twenty-five healthy male participants without neurological or psychiatric disorders participated in this study. One participant was excluded due to excessive head motion, and a second participant due to technical difficulties leading to an incomplete data set (final sample: N=22, mean age = 24.77, SD = 4.76). Participants gave written informed consent and were financially reimbursed. This study was approved by the Ethical Committee of the Faculty of Psychology and Neuroscience at Maastricht University.

Procedure and instruments

Participants were asked to abstain from eating or drinking (anything besides water), brushing their teeth, and vigorously exercising 45 minutes prior their appointment and were recommended to drink water ten minutes before to facilitate saliva collection. Appointments were made between 8:30 and 10:30 in the morning. Upon their arrival and after signing the inform consent, participants were instructed to drool their saliva into a 3.6 ml hormonal tube assay with the aid of a small straw.

Following the saliva collection, participants performed three computer-based tasks in the Magnetic Resonance Imaging (MRI) scanner. For the purposes of this study we only report the Approach-Avoidance procedure. After completing the tasks, participants were asked to fill in questionnaires on the computer. Participants were identified with a four digits number as their ID to increase their confidence over the anonymity of their answers.

After the experiment, saliva samples were stored at 4°C.

Questionnaires

Revised Mood and Sexuality Questionnaire (MSQ-R) (Janssen, Macapagal, Mustanski, 2013). This instrument assesses the likeliness of experiencing sexual interest and arousal, masturbating, or performing a sexual act that could later be regretted, when being in a particular mood (anxiety, sadness, anger, or happiness). In addition, it assesses the effects of sexual activity on mood and attachment. Participants answered on a five-point Likert scale ranging from *Much less than usual* to *Much more than usual* (e.g. "When I feel angry I think about sex…"). For this study, we considered the following indices: a) Effect of negative mood on sexual desire – Refers to the effects of anger, sadness, and anxiety on sexual interest (*AngDes, SadDes, and AnxDes*), b) Positive effects of sex on mood – Refers to the benefits on mood from sexual activity (i.e. decreasing negative mood, increasing attachment with partner, and feeling better about oneself) (*PositFx*), and c) Effect of negative mood on regrettable behaviour – Concerns the effects of negative mood (anger, sadness, and anxiety) on the likelihood of doing something sexual that might be regretted later (*RegrSx*).

Sexual Inhibition/Sexual Excitation Scales (SIS/SES) (Janssen et al., 2002). This 45 items-scale measures the individual propensity for sexual inhibition and excitation. For this study we only considered the second factor of sexual inhibition (SIS2) which assesses inhibition (unlikeliness to stay aroused or to maintain an erection) due to the threat of performance consequences (e.g. risk of being caught, unwanted pregnancy, sexually transmitted diseases). Answers were registered on a four-point Likert scale (ranging from 1 = *strongly agree* to 4 = *strongly disagree*).

Mood and task effects. Before entering the scanner participants answered to what extent they felt in a particular mood (happy, anxious, sad, stressed, relaxed, excited, angry) on a five-point Likert scale (*Not at all – Very much*). After the scanning, they filled in a SAM (self-assessment manikin) type questionnaire indicating to what extent they liked or disliked the task (valence), to what extent they felt aroused (arousal) and to what extent they felt in control of the stimuli (dominance). To answer, they could select one of five images which ranked from *Very pleasant to Very unpleasant* (valence), *Very arousing to Not arousing* (arousal) and *High control to Low control* (dominance).

Cortisol assay

After shipping, cortisol samples were frozen at -20 °C. Analyses were performed at Ghent University, Belgium. Cortisol concentrations in saliva (in µg/dL) were obtained using competetitive luminiscence immunoassay kits with sensitivity for cortisol of 0.1 ng/mL. Intra-assay coefficient of variation was 4.6 %.

Approach-Avoidance Task

This paradigm assesses approach-avoidance tendencies towards emotional stimuli. Previous versions with sexual content proofed sensitive to gender differences (Dewitte, 2016), to the viewing time of other erotic stimuli (Hofmann, Friese, & Gschwendner, 2009), and to predict the frequency of pornography watching (Rodríguez-Nieto, Emmerling, Dewitte, Sack, & Schuhmann., in press).

The current version consisted of four counterbalanced blocks of 48 randomised trials each. In half of the blocks, participants were instructed to approach the sexual stimuli (50% of the trials) and to avoid the non-sexual stimuli. Participants were instructed to do the opposite in the other two blocks. To approach the stimuli, participants pulled a joystick towards them which doubled the picture size. Participants avoided the stimuli by pushing the joystick away, which halved the picture size. The presentation of every stimulus lasted 1700 milliseconds and the resizing occurred 1300 ms after the presentation onset to avoid

variability across trials and participants. An inter-trial fixation cross was presented for 3400, 4250, or 5100 ms (Figure 1).

As sexual stimuli, colour photographs of heterosexual couples having intercourse or oral sex were used. 95% of these stimuli were previously evaluated in terms of valence and arousability (Rupp & Wallen, 2007). The additional pictures were selected from the internet making sure that they had similar characteristics and features. Non-sexual stimuli were colour photographs of a woman and a man dancing (Dewitte, 2016). The proportion of body exposition (with special attention to the female body) with respect to the whole picture was comparable in both conditions. Due to the limited number of evaluated images, in half of the blocks the default size of the pictures was 337,9 X 272,5 pixels (horizontal orientation) and in the other half was 257,6 X 400 pixels (vertical orientation). Images were displayed on a light grey background. The task was programmed in programmed in PsychoPy (Peirce, 2007).

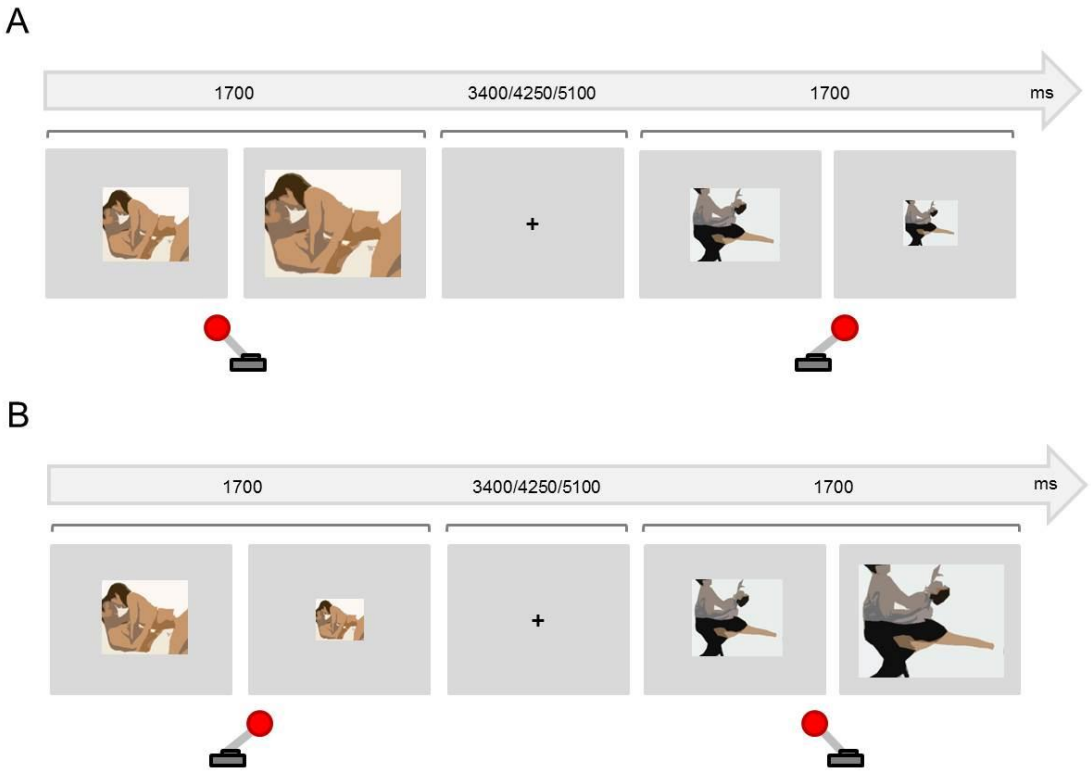

Figure 1. Experimental paradigm Approach- Avoidance task. Participants were instructed to approach (pull the joystick towards them) sexual stimuli and avoid (push the joystick away) non-sexual stimuli in half of the blocks (A), and to avoid sexual stimuli and approach non-sexual stimuli in the remaining blocks (B). Approaching and avoiding stimuli doubled of halved the image size.

fMRI acquisition

Data were acquired at the 3 T Siemens Prisma Scanner at the Maastricht Brain Imaging Center, Maastricht University. High resolution anatomical images were acquired with a MPRAGE sequence (TR = 2250 ms, TE = 2.21 ms, FOV = 256 mm, 192 sagittal slices, isovoxel 1 mm^3). Functional EPI images were collected using an in-house developed multi-echo multi-band sequence (TR = 850 ms, TE = 15/30/44 ms, flip angle = 50°, FOV = 210 mm, 36 slices, isovoxel 3 mm^3). Online scanner reconstruction was performed using the slice-GRAPPA algorithm (Setsompop et al., 2012) with leakage artifact reduction (Cauley, Polimeni, Bhat, Wald, & Setsompop, 2014) as implemented in the reconstruction of the MGH blipped-CAIPI SMS-EPI distribution (software and complete documentation is available at https://www.nmr.mgh.harvard.edu/software/c2p/sms). This GRAPPA sequence was used to optimise the BOLD signal in frontoventral regions.

fMRI analyses

The imaging data were pre-processed and analysed with Brain Voyager QX Version 2.8.4.2645 (Brain Innovation, Maastricht, Netherlands).

Prior to the pre-processing, the echo images were combined using an optimised echo weighting method (Poser et al., 2006). The images were motion-corrected (trilinear / sinc interpolation and aligned to the first functional volume acquired after the anatomical sequence) and corrected for slice timing skew using temporal sinc interpolation. A temporal high pass filter (3 cycles) was applied. Images were co-registered to the individual T1 weighted images and normalised to Talairach stereotaxic space. Volume time courses were spatially smoothed using a 6mm full width half maximum Gaussian kernel.

To analyse the activation pattern of every task an event related approach was implemented using a GLM model and a random-effects group analysis. Motion correction parameters were included as confound variables in the model. A contrast analysis was made to compare the sexual approaching trials with the sexual avoiding trials including the cortisol levels as a covariate. The resulting activations were corrected for multiple comparisons by means of cluster threshold level estimation (1000 Monte Carlo simulation iterations; Forman et al., 1995). The nomenclature of the cluster peak values was defined with the software tool Talairach Client (Lancaster et al., 1997: Lancaster et al., 2000).

Functional connectivity

To explore functional connections between prefrontal and subcortical regions during the approach of sexual stimuli, we extracted a medial prefrontal region of interest from the resulting ANCOVA (covariate: cortisol) activation map (see Results section) to use it as a seed in psychophysiological interaction (PPI) analyses (Friston et al., 1997). As we were particularly interested in the functional connectivity with the amygdala, we use an anatomically defined mask for this region. The resulting activations were corrected for multiple comparisons by means of cluster threshold level estimation (1000 Monte Carlo simulation iterations; Forman et al., 1995).

Results

Cortisol, mood, and traits

The average cortisol levels and self-report scores are reported in Table 1. The correlations between cortisol and self-report scores are shown in Table 2. According to what we expected, participants with higher cortisol levels reported higher arousal in response to the task. However, cortisol levels did not correlate with the degree to which participants felt in control over the sexual stimuli (dominance). Although cortisol did not show a significant correlation with anxiety or stress, it showed a trend towards significance with anger. In addition, cortisol levels correlated positively with the levels of sadness and negatively with happiness and excitation reported prior to entering the scanner. Contrary to our expectations, sexual arousal did not relate to anger or anxiety. On the contrary, sexual arousal correlated with sadness (rho = .49, p = .01), but this correlation was no longer significant after controlling for cortisol levels (rho = .34, p = .11).

Table 1. Average of cortisol levels and self-reports.

	Cortisol	SIS2	MSQ-R AnxDes	MSQ-R PositFx	MSQ-R RegrSx	Valence	Arousal	Dominance
Mean (SD)	.31 (.21)	25.17 (6.58)	4.61 (1.83)	23.34 (9.19)	1.82 (1.03)	2.56 (.72)	3.35 (1.07)	2.35 (.88)
	Happy	Anxious	Sad	Stressed	Relaxed	Excited	Angry	
Mean (SD)	3.22 (1.11)	1.59 (.96)	1.22 (.68)	1.72 (.82)	3.41 (.85)	3 (.98)	1.13 (.46)	

SIS2: Sexual Inhibition (second factor); MSQ–R: Revised Mood and Sexuality Questionnaire; AnxDes – Degree of sexual interest experienced while being anxious; PositFx – Positive effects of sexual activity over mood; RegrSx – Likelihood of regrettable sexual behaviour while being in a negative mood state.

Table 2. Correlations between cortisol levels and self-reports.

	SIS2	MSQ-R AnxDes	MSQ-R PositFx	MSQ-R RegrSx	Valence	Arousal	Dominance
Cortisol	-.02 (.91)	-.19 (.37)	-.11 (.61)	.03 (.87)	.17 (.43)	.44 (.03)	.27 (.19)
	Happy	Anxious	Sad	Stressed	Relaxed	Excited	Angry
Cortisol	-.61 (.002)	-.13 (.55)	.55 (.007)	-.07 (.73)	-.36 (.09)	-.77 (.001)	.38 (.08)

SIS2: Sexual Inhibition (second factor); MSQ–R: Revised Mood and Sexuality Questionnaire; AnxDes – Degree of sexual interest experienced while being anxious; PositFx – Positive effects of sexual activity over mood; RegrSx – Likelihood of regrettable sexual behaviour while being in a negative mood state.

Brain correlates of sexual approach with cortisol

In Table 3, we display the regions that were active during sexual approach as compared to sexual avoidance. These regions include the amygdala, the hippocampus, the parahippocampal gyri, and visual processing regions (p = .005, CLTC). Endogenous cortisol levels significantly modulated activation in the anteromedial prefrontal cortex (amPFC), the insula, the superior temporal gyrus, the precentral gyrus, and the precuneus when participants approached sexual stimuli, as compared to the avoidance of the same stimuli (p = .005, CLTC; Table 4; Figure 2a). At a more liberal threshold, cortisol levels modulated the activity in the bilateral inferior and superior frontal gyri, the middle temporal gyrus, the inferior occipital gyrus, and the caudate (p = .01, CLTC; Table 4). A functional mask was created from the area in the medial prefrontal cortex modulated by cortisol and the model parameters (beta) of this region during sexual approach were extracted for every participant. These activation parameters were negatively correlated with sexual inhibition (SIS2) (r = -.51, p = .01; Figure 2b) and positively with the degree to which participants reported mood improvement (when being sad, anxious or angry) as result of sexual activity (*MSQ R – PositFx)* (r = .48, p = .02; Figure 2c). To address specificity, we also conducted a correlation analysis between sexual excitation scores and the amPFC activation parameters, which was not significant (r = .31, p = .14).

Table 3. Active regions during the approach of sexual stimuli as compared to the avoidance condition.

Sex Approach > Sex Avoid							
	BA	x	y	z	Size (mm^3)	t	P
Lingual gyrus	18	-9	-76	-2	66855	9.92	.000000
Parahippocampal gyrus	28	27	-19	-8	360	4.58	.0001
Amygdala		21	-7	-8	917	5.01	.00005
Parahippocampal gyrus	30	18	-40	-5	397	4.22	.0003
Hippocampus		-27	-13	-11	3776	5.68	.00001
Middle Occipital gyrus	19	-45	-82	4	619	3.81	.0009

CLTC .005

Table 4. Brain activations correlating with endogenous cortisol during the approach of sexual stimuli.

Sex Approach > Sex Avoid – CORTISOL							
	BA	x	y	z	Size (mm^3)	r	P
Sex Approach-Sex Avoid							
Insula	22	42	-28	-2	1514**	.73	.00005
Superior Temporal Gyrus	22	51	-13	-8	891**	.76	.00002
Precuneus	19	42	-70	40	1443**	.71	.0001
Precentral gyrus	9	36	8	37	705**	.69	.0002
Medial Frontal Gyrus	10	-12	56	4	782**	.65	.0006
Posterior Lobe/Cerebellum		-27	-79	-27	1107**	.68	.0002
Superior Temporal Gyrus	22	-48	-34	1	715**	.65	.0007
Inferior Frontal Gyrus	45	51	26	7	1386*	.63	.001
Middle Temporal Gyrus	19	36	-64	19	771*	.65	.0006
Inferior Occipital Gyrus	17	18	-91	-8	1104*	.73	.00007
Superior Frontal Gyrus	9	21	35	34	1097*	.68	.0003
Caudate (Head)		9	14	-2	763*	.65	.0007
Inferior Frontal Gyrus	46	-45	29	7	827*	.69	.0002

** CLTC $p < .001$; * CLTC $p < .01$

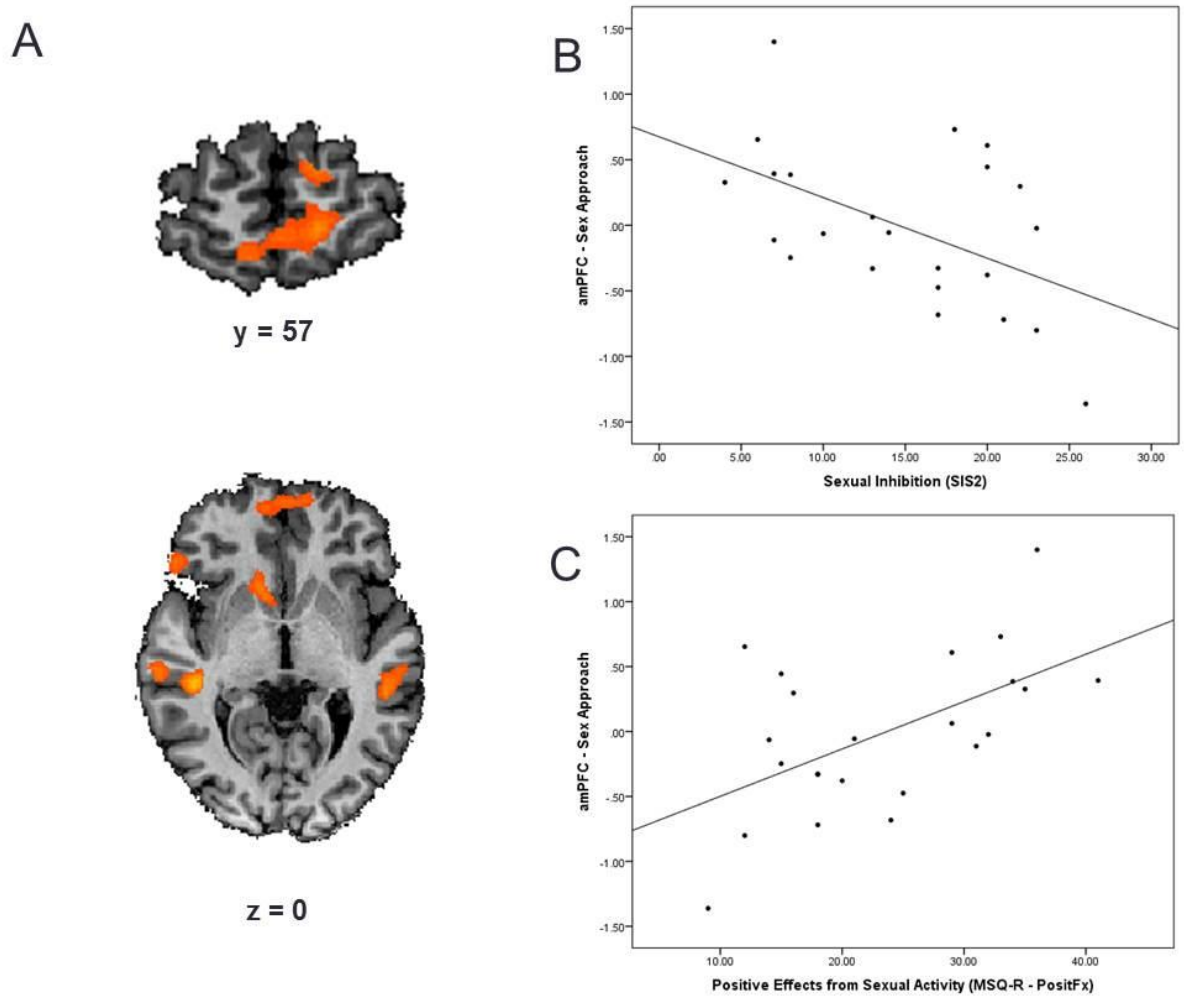

Figure 2. **Neural correlates of cortisol during the approach of sexual stimuli and its relationship with individual psychological differences**. **A –** Neural correlates of cortisol during the approach of sexual stimuli as compared to the avoidance of the same stimuli (p = .01, CLTC). **B –** The activity of the anteromedial prefrontal cortex (amPFC) during the approach of sexual stimuli negatively correlated with sexual inhibition (SIS2 scores were reversed so that higher values would indicate higher sexual inhibition). **C –** The amPFC activity during the Sex Approach condition also related (positively) with the degree to which participants reported mood improvement (when being sad, anxious or angry) as result of sexual activity (*MSQ R – PositFx).* Activation is displayed on the anatomical data of one participant from the sample.

Functional connectivity

PPI analyses revealed significant functional connectivity between the amPFC and the right amygdala (p = .05, CLTC; Figure 3a). There was a significant positive correlation between the amPFC-amygdala connectivity and the degree to which participants reported the likelihood of sexual acts while being in a negative mood (angry, sad, or anxious) that could later be regretted (*MSQ R- RegrSx*; rho = .59, p = .003; Figure 3b).

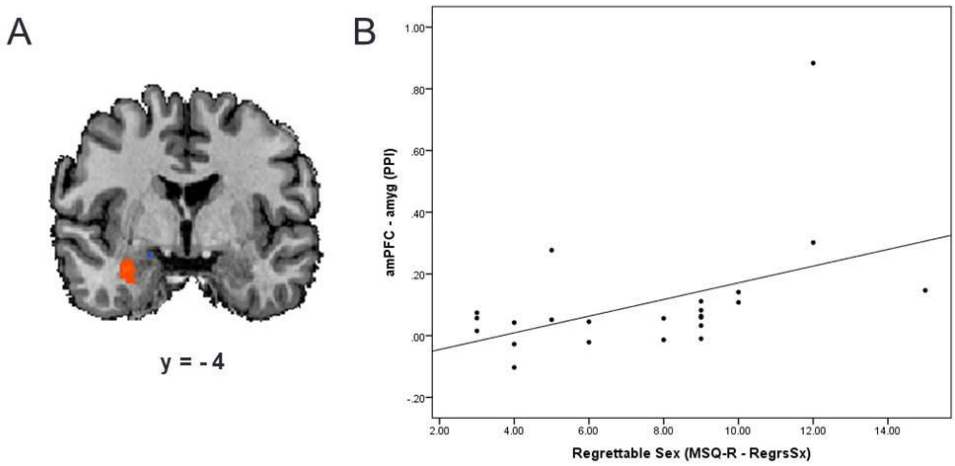

Figure 3. Anteromedial prefrontal cortex – amygdala functional connectivity and its relationship with sexual regrettable acts. A – Psychophysiological interaction map revealing a functional connectivity between the anteromedial prefrontal cortex (amPFC) and the amygdala during the approach of sexual stimuli. **B –** The strength of this functional connectivity related to the degree to which participants reported being likely to comit a potentially regrettable sexual act while being in a negative mood (angry, sad or anxious) (MSQ R- RegrSx). Activation is displayed on the anatomical data of one participant from the sample.

Discussion

In this study we investigated the role of cortisol regarding the relationship between mood and sexual arousal and sexual regulation. Moreover, we investigated the neuromodulating role of cortisol during sexual approach behaviour. We also investigated if the cortisol-related brain response during sexual approach behaviour was related to sexual inhibition trait and sexual mood-related behaviour. Although we found a relationship between cortisol, mood, and sexual arousal, the pattern observed did not support that cortisol and sexual arousal relate to each other due to the co-occurrence with fight/flight responses. Regarding the neuromodulating role of cortisol, we observed that higher levels of cortisol were related to an

increased activation in the amPFC, the insula, the superior temporal gyrus, the precentral gyrus and the precuneus during sexual approach behaviour. During this condition, the amPFC was functionally connected to the amygdala. Remarkably, the activation in the amPFC was negatively related to sexual inhibition trait and positively related to the benefits on mood from sexual activity. Moreover, the strength of the connectivity between the amPFC and the amygdala related to the extent to which individuals reported the likeliness of doing a regrettable sexual act while being in a negative mood.

Relationship between cortisol, sexual arousal, and mood

Our results showed a relationship between endogenous baseline cortisol levels and the level of sexual arousal evoked by the sexual stimuli during the task, which is consistent with previous evidence (Goldey & van Anders, 2012). The link between sexual arousal and cortisol can be explained from a functional perspective because cortisol activates the sympathetic autonomous system and promotes fast metabolization to generate energy which is needed to facilitate sexual arousal. In line with this, both sexual arousal and states of anxiety/stress are characterised by a high heart rate and blood pressure (Goldey & van Anders, 2012). Note, however, that we did not find a relationship between cortisol levels and the level of anxiety, anger, or stress reported by participants prior to entering the scanner. In addition, we did not find a relationship between most mood states and sexual arousal. Only sadness directly related to sexual arousal, but this relationship was no longer significant when controlling for cortisol. This suggests that the heart rate and blood pressure associated to negative mood is not enough to elicit an enhanced sexual arousal. Supporting this is the fact that not only negative mood induces an increase in heart rate and blood pressure, but also happiness (Schwartz et al., 1981). As the mood reports and cortisol were taken before the task performance and the sexual arousal was reported afterwards, it might be that baseline cortisol, which was higher in individuals with higher reports of negative mood, had an additive role in increasing the sympathetic activity triggered by emotional stimuli. It is also important to mention that cortisol has short (non-genomic) and long-term (genomic) effects (Henckens et al., 2011). Whereas baseline cortisol levels are related to the reported degree of sexual arousal, research has shown that there is no change in cortisol in response to increasing levels of sexual arousal but there is a significant decrease in cortisol after penile rigidity (Ückert et al., 2003; Goldey & van Anders, 2012). Therefore, it is possible that the association between cortisol, mood, and sexual arousal is due to genomic rather than non-genomic effects.

Cortisol, brain response, and psychological traits

In the sexual approach condition, individuals higher in cortisol showed an increased brain response in the precentral gyrus, the caudate, and the insula. This may indicate a stronger proneness to act (approach the sexual stimuli) accompanied by an enhanced visceral sensitivity. Likewise, an increased activity in the bilateral inferior frontal gyrus was associated to higher cortisol levels. The inferior frontal gyrus is engaged in the detection of salient stimuli and its temporal disruption leads to an increase in inhibition of sexual cues (Erika-Florence, Leech, & Hampshire, 2014; Rodríguez-Nieto, Sack, Dewitte, & Schuhmann, in press). Thus, via this circuit, cortisol may increase the perception sensitivity towards arousing relevant cues in the environment. In the same condition (approaching sexual stimuli) cortisol related to an increased response in supramodal regions: the amPFC, precuneus, and the superior temporal gyrus. The amPFC cortisol-modulated pattern during the sexual approach condition implies a negative modulation during the comparing condition (i.e. less amPFC activity according to more cortisol levels during sexual avoidance) in which individuals restrain a motivationally-driven motor response. This is in concordance with previous evidence where higher levels or non-normative circadian patterns of cortisol related to a decrease of amPFC activity during emotion regulation compared to an emotional but non-regulatory condition (Kern et al., 2008; Urry et al., 2006). Thus, the higher activation of the amPFC during the non-regulatory condition associated with higher cortisol levels may indicate a higher demand to control autonomous responses. In line with this, individuals higher in cortisol reported being more sexually aroused by the task and they also showed an increased amPFC response while approaching sexual stimuli.

Remarkably, individuals with a higher neural response of the amPFC during the approach sexual behaviour reported being more sexually disinhibited and reported benefits on mood (improvement in sad, angry, or anxious mood) as a consequence of sexual activity. Whereas the medial prefrontal cortex seems to play a role in the regulation of the HPA axis, its most anterior portion (i.e. frontal pole) is associated to higher-order processing such as the maintenance of higher-order goals, hierarchical processing, anticipation of consequences, mentalizing, and self-reflection (Burgess, Gilbert, & Dumontheil, 2011; Ramnani & Owen, 2004; Roca et al., 2011). These functions are not mutually exclusive, as the hierarchical processing and goal maintenance can switch according to environmental demands which in turn require the organism to adapt (including autonomous responses). Accordingly, it has also been argued that the vmPFC (overlapping with our amPFC cluster) integrates high social values with basic emotional processes (e.g. visceroaffective), thereby modulating approach-

avoidance behaviours (Bzdok et al., 2013). Our results show that individuals who are less likely to inhibit their sexual arousal neglecting higher order values and/or long term goals (e.g. having sex in spite of pain or health risks), show an increase in amPFC when they approached sexual stimuli. This counterintuitive finding (i.e. enhanced regulation activity in more disinhibited individuals) may reflect a higher demand to control autonomous responses during a sexually arousing condition, in particular in a context where individuals cannot unfold their sexual response. Alternatively, the activation of this region, by processing buttom-up information and memory-informed reward and risk estimation (Bzdok et al., 2013) may be reflecting a stronger weighting of rewarding stimuli, reducing risk perception, and favouring approach behaviours.

The amPFC also shown to be more active in individuals who reported higher benefits on mood (e.g. feeling less angry, sad, or anxious, or feeling better about themselves) from sexual activity. It has been suggested that some individuals use sex to cope with their mood, as sexual activity can act as an anxiolytic (Bancroft & Vukadinovic, 2004). An enhanced amPFC activation could be reflecting that individuals who reported higher benefits on mood from sex recruit more bottom-up regulatory mechanisms (immediately rewarding and potentially anxiolytic) to cope with negative emotional states, perhaps as opposed to recruiting more dorsal top-down processes.

Note, that the amPFC activity was related to sexual inhibition trait but not to sexual excitation. Likewise, the amPFC did not correlate with the degree to which individuals show sexual desire or sexual interest during negative moods, but specifically to the mood ameliorating effects of sexual activity (e.g. feeling less anxious after sexual activity). This observation seems to support the involvement of amPFC in the integration of visceroaffective information in homeostatic mechanisms, and not solely in evaluating or processing the arousal state inputs.

Furthermore, the strength of the functional connectivity between the amPFC and the amygdala while approaching sexual stimuli was associated with the likelihood that participants reported to engage in sexual activity while being in a negative mood that might be subsequently regretted. Once more, it remains unclear whether this neural pattern constitutes an enhanced compensatory regulation mechanism, or an integrative process favouring immediate gratification in spite of consequences. In the first case, participants who are more likely to perform potentially regrettable acts when being in a negative mood would recruit this circuitry more because their regulatory demands are higher. In the second possibility, an enhanced signalling from the amygdala could represent a stronger integration

of arousing information, leading to an emotionally driven behavioural output. A previous approach-avoidance study showed a negative coupling between the anterior PFC (a more laterally located cluster relative to ours) and the amygdala while participants overrode a natural avoidance tendency (i.e. approach angry faces), suggesting a downregulation mechanism (Volman et al., 2016). In this study instead, we observed a positive coupling during the non-regulatory condition which may actually underlie a positive feedback mechanism rather than a downregulation one.

Whereas cortisol did not held a direct relationship with the degree to which individuals felt in control over the sexual stimuli, with sexual inhibition trait, or mood associated sexual behaviour, cortisol modulated the activity in the amPFC during sexual approach behaviour. Thus, the amPFC neural response of individuals with higher levels of cortisol resembled the neural activity of sexually disinhibited individuals and individuals who reported an improvement in sadness, anger, or anxiety mood as a consequence of sexual activity. This seems to indicate that the enhancement of sympathetic reactivity produced by cortisol leads to a higher sexual arousing state that can interfere with the regulation of sexual approach behaviour similar to that of individuals with regulatory impairments.

This study is not without limitations. A first limitation is its correlational nature which prevents us to conclude that high cortisol levels increases the regulatory circuitry demands by increasing arousal. Alternatively, high cortisol levels could directly cause an increase in such circuitry as an adaptive response in challenging situations. Furthermore, it remains unclear whether this mechanism favours an approach sexual behaviour by an enhanced bottom-up processing of what is momentarily relevant (Bzdok et al., 2013). In this sense, cortisol may enhance the weighting and integration of rewarding and potentially anxiolytic stimuli as a compensatory mechanism to achieve homeostasis. Whereas moderate levels of cortisol are adaptive and even have anxiolytic effects (Dominique & Magraf, 2008; Soravia et al., 2006), the continuous exertion of the system may lead to abnormal regulatory mechanisms. To this regard, individuals with an irregular HPA axis activity may lack adequate endogenous means and make use of external factors (e.g. sexual activity or substance abuse) to cope with negative mood which eventually could develop into an addiction, as seems to be the case of hypersexual individuals (Chatzittofis et al., 2016).

Future studies may test the different posed hypotheses and examine to what extent they apply in clinical conditions where HPA mechanisms are disrupted. Another interesting avenue for research aiming to understand the relationship between mood and sexual regulation is exploring the interaction of cortisol with monoamines, as serotonine and

dopamine have shown to influence both mood and sexual regulation (Kafka, 2010). Finally, the Approach-Avoidance paradigm can be tested as a training tool for individuals with sexual regulation impairments. To this respect, emotional training with an Approach-Avoidance paradigm has shown to be successful in socially anxious individuals (Rinck et al., 2013).

Conclusion

In sum, this study showed that cortisol modulates the response of the amPFC during sexual approach. Moreover, the activation in the amPFC and the strength of its connectivity with the amygdala was related to individual differences in sexual inhibition and perceived benefits on moof from sexual activity. These results imply that during sexual approach, cortisol levels are associated with the brain activity of areas comprised in sexual regulation. These circuits may, at least in part, underlie the association between negative mood states and the dysregulation of sexual behaviour –neglecting social values and/or long-term consequences- during arousing situations.

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CHAPTER 6.

The interactive role of excitatory and inhibitory mechanisms with testosterone in hypersexuality tendencies

Based on:

Rodríguez-Nieto, G., Dewitte, M., Sack, A.T., & Schuhmann, T. (submitted) The simultaneous role of excitatory and inhibitory mechanisms and testosterone in hypersexuality tendencies.

Abstract

The high exposure to sexual graphic material in modern societies has raised concerns about the increased risk of developing sexual disorders. One of the most common sexual disorders is hypersexuality, characterised by strong sexual desires and excessive sexual behaviour that interferes with daily life goals. The dual control model of sexual response proposes that an imbalance between sexual excitation and sexual inhibition mechanisms may lead to sexual dysregulation. Whereas some evidence supports this notion, the potential role of interindividual differences in certain personality traits and hormonal level have been neglected. In this study we aimed to investigate the potential contributing role of sexual excitation and inhibition, but also self-control traits and testosterone levels, for the proneness of individuals to display interfering sexual urges and behaviour (hypersexual tendencies). 70 healthy young males provided a sample of their saliva for testosterone level assessments and filled in the Sexual Inhibition/Sexual Excitation Scales, Brief Self-Control Scale, and Sexual Compulsivity Scale. In addition, the frequency of their individual and dyadic sexual behaviours was assessed. We found that high levels of testosterone and low levels of self-control were associated with higher hypersexual tendencies. Interestingly, sexual excitation and sexual inhibition also showed to predict hypersexual tendencies (in accordance with dual control model), but did so in interaction with testosterone levels. Testosterone levels negatively predicted the frequency of dyadic sexual behaviour and none of the independent variables predicted the frequency of individual sexual behaviour. The identification of potential risk or protector factors in the development of sexual disorders from a biopsychosocial perspective is essential in the understanding of the etiology and has potential implications in the prevention and treatment of these disorders.

Introduction

Modern generations are characterised by their high exposure to sexual graphic material mainly through the web. It has been proposed that being continuously exposed to diverse explicit sexual material at an earlier age causes neurobiological and cognitive changes that increase the vulnerability of the contemporary youth to develop sexual disorders, such as sexual addiction (Riemersma & Sytsma, 2013). The ease of accessibility and anonymity in the consumption of sexual material contribute to the risk of using sexual stimulation to escape daily life problems, thus, engaging in addictive-like patterns (Young, 2008). This pattern can involve dependence, an excessive manifestation of sexual urges, interference with daily life goals, and failure to control behaviour. In case all of these symptoms are present, a diagnosis of hypersexuality can be made (Kafka, 2010). Symptoms can emerge in different patterns and at different levels of intensity, thereby not always reaching clinical levels of hypersexual behaviour (Kafka, 2010). This implies that many people may show hypersexual tendencies that have an impact on daily (sexual) behaviour, without being diagnosed as hypersexuals. In college students, for example, the interference of excessive sexual preoccupation in daily life has been associated with an increased frequency of risky sexual behaviours (Dodge, Reece, Cole & Standfort, 2004).

In spite of the widespread consumption of sexual material, not every individual develops hypersexual patterns. To identify protective or risk factors for developing a clinical level of hypersexuality, individual differences need to be studied. The dual control model of sexual response has clear heuristic and empirical value to understand such individual differences in hypersexual tendencies. The model proposes that the sexual response is indicated by a balance between excitatory and inhibitory mechanisms and that individuals vary in their propensity to be sexually excited versus sexually inhibited (Bancroft & Janssen, 2000). In this model, sexual excitation refers to the processes that increase the likelihood of sexual arousal and penile erection, whereas sexual inhibition refers to processes that decrease the likelihood of its occurrence. Based on self-reports (Sexual Inhibition Scale - SIS) Bancroft and Janssen identified two types of sexual inhibition: a) Sexual Inhibition (SIS1) caused by a threat of performance failure which likely comprises peripheral mechanisms; and b) sexual inhibition (SIS2) caused by the threat of performance consequences (e.g. risk of getting a contagious disease).

The dual control model postulates that individuals who are more easily sexually aroused (i.e. higher in sexual excitation) and are low in the second factor of sexual inhibition

(SIS2 – sexual inhibition due to negative consequences of sexual activity), are more prone to develop hypersexuality (Bancroft, Graham, Janssen, & Sanders, 2009). Indeed, some studies have consistently found that higher scores on the Sexual Excitation Scale (SES) are associated with hypersexuality (Bancroft & Vukadinovic, 2004; Janssen & Bancroft, 2007; Rettenberg, Klein & Briken, 2016; Winters, Christoff & Gorzalka, 2010). However, the relationship between hypersexuality and low sexual inhibition has found to be non-existing or modest (Bancroft & Vukadinovic, 2004; Miner et al., 2016; Rettenberg, et al., 2016) which may be masked by the fact that sexual inhibition (SIS2) is low specifically in sexual addicts whose main way of acting out is not solitary sexual activity (Bancroft & Vukadinovic (2004).

The dual control model refers specifically to sexual inhibitory mechanisms but does not take into account general inhibitory mechanisms that could also play a role. Self-control as the capability to override one's desires and thoughts and control actions may be crucial in the control of sexual motivation. In a previous study, it was shown that individuals low in self-control reported being more prone to fail at restraining their sexual behaviour and also showed a larger likelihood to engage in sexual infidelity (Gailliot & Baumeister, 2007). Although self-control has been studied in the context of other compulsive behaviours (e.g. binge eating), to our knowledge so far it has not been linked with (hyper) sexual behaviour.

The dual control model underscores a biopsychosocial perspective and ascribes an important role to physiological mechanisms sustaining sexual arousal and sexual inhibition (Janssen & Bancroft, 2007). To align with the model when trying to explain hypersexual tendencies, it is thus important to consider both biological and psychological mechanisms. Among the most studied biological factors affecting sexual behaviour are androgens. Androgens affect sexuality both at a peripheral and central level. It has been shown that testosterone depletion in men not only alters levels of sexual functioning, but also decreases sexual cognition, sexual motivation, and sexual behaviour (Jordan, Fromberger, Stolpmann & Müller, 2011; Finkelstein et al., 2013; Schmidt et al., 2009). Similarly, hypogonodal men who are treated with testosterone show a higher sexual interest than non-treated patients (Redouté et al., 2005; Osterberg, Bernie, & Ramasamy, 2014). Regarding the relationship between endogenous levels of testosterone and sexual motivation and behaviour in healthy men, a large amount of studies shows changes in testosterone levels in anticipation and as a consequence of sexual activity. For instance, testosterone levels in men increase after brief encounters with a woman (Roney, Mahler & Maestripieri, 2003), correlate with the viewing time of erotic stimuli (Rupp & Wallen, 2007), and increase during in vivo sexual stimulation

and as consequence of sexual intercourse (Escasa, Casey & Gray, 2011). Note that null-findings have been reported as well (e.g. Goldey & van Anders 2015), which could be explained by the relevance of the context, as it has been proposed that increased testosterone levels are manifested in sexual behaviour mainly when there is competence or challenge involved (Goldey & van Anders, 2015; Wingfield, Hegner, Dufty & Ball, 1990). However, the literature linking hypersexuality and testosterone levels is scarce. To our knowledge, only one study targeted the question, showing that there were no differences in the testosterone plasma levels of hypersexual and control men (Chatzitoffis et al., 2017).

The integration of psychological traits and biological factors is rarely considered in empirical research regarding the control of sexual behaviour. In this study, we aimed to investigate the relative value of sexual excitation, sexual inhibition, self-control, and endogenous testosterone levels in the manifestation of hypersexual tendencies in a sample of young healthy men. We hypothesise that whereas high sexual excitation and high testosterone levels can be associated with hypersexuality proneness, a high sexual inhibition and a high self-control may counteract and reduce such susceptibility. Moreover, we aimed to investigate the predictive value of the interaction between testosterone levels and individual traits, as we expected that these bio-psycho interactions may be particularly relevant to explain hypersexual behaviour. Specifically, we hypothesise that individuals with higher levels of testosterone in combination with high sexual excitation, low self-control, or low-sexual inhibition, may be more prone to show hypersexual tendencies. The lack of control over sexual urges can be characterised by a high frequency of sexual behaviour that can occur in solitude or with a partner. For this reason, we differentiated between solitary and dyadic sexual behaviour and examined the contributing role of excitation, inhibition, self-control, and testosterone in predicting the frequency of these different types of behaviour.

Method

Participants

70 self-declared heterosexual male participants (18-35 years old, mean age = 24.7, SD = 4.4) were recruited through advertising in Maastricht University halls and in a Facebook group created to recruit participants for research at Maastricht University. All of the participants were financially reimbursed for their participation. The study was approved by the Ethics Review Committee Psychology and Neuroscience at Maatricht University and conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinski). 92.1% of participants were Bachelor or Master students; of the remaining participants, 3 had

completed university and 2 had completed high school. Approximately half of the participants were single (47.6%), the others had been in a relationship for an average period of 2.7 years (SD = 2.6).

Procedure

Participants were instructed to abstain from eating, drinking any beverage (except water), brushing their teeth, and vigorously exercising 45 minutes before arrival and were suggested to drink water ten minutes before to facilitate saliva collection. Appointments for the sessions were made at 9 or 10 am to avoid variations due to testosterone daily cycle.

At arrival, participants gave their written informed consent. Next, they were instructed to drool their saliva to the top of a 3.6 ml hormonal tube assay with the aid of a small straw. Following the saliva collection, participants performed computer-based tasks for a different study. After completing the tasks, participants were asked to fill in questionnaires on the computer. Participants were identified with one single four digits number as their ID and left alone while filling in the questionnaires to increase their comfort and confidence over the anonymity of their answers. After the experiment, saliva samples were stored at 4°C.

Testosterone assay

Centrifugation was performed at 2000 g for five minutes and 250 µl supernatant from the sample was stored at -80°C until further LC–MS/MS analysis. For this later one, inter-assay coefficient of variation was 8.2% at 0.23 ng/dL (8 pmol/L) with a limit of quantification of 0.07 ng/dL (2.4 pmol/L).

Questionnaires

Sexual Inhibition/Sexual Excitation Scales (SIS/SES). This scale measures the individual propensity to be sexually aroused or sexually inhibited. It contains one factor quantifying sexual excitation (20 items) and two factors quantifying sexual inhibition: a) SIS1 – Inhibition derived from threat of sexual performance failure, distraction, or lack of physical stimulation (14 items), and b) SIS2 – Inhibition due to the threat of performance consequences, such as risk of being caught, unwanted pregnancy, sexually transmitted diseases, feeling or causing pain, and partner's too young age (11 items). Answers were registered on a four-point Likert scale (ranging from 1 = strongly agree to 4=strongly disagree; Janssen et al., 2002). The raw scores were inversed in a way that higher scores would indicate higher sexual excitation (SES, Possible range: 20-80) or inhibition (SIS1, Possible range: 14-56; SIS2, Possible range: 11-44). For this study we considered only the second factor of Sexual Inhibition because this subscale is particularly relevant in terms of

explaining hypersexual tendencies (SES - Cronbach's alpha = .82; SIS2 - Cronbach's alpha = .73).

Brief Self-Control Scale (BSCS). This scale consists of ten items assessing the extent to which an individual is able to regulate his/her own behaviour by resisting or inhibiting a preponderant response or desire in order to achieve long-term goals. Participants answered in a five-point Likert scale ranging from *Not at all* to *Very much.* BSCS scores range from 10-50 with a higher number indicating more self-control. High internal consistency and test-retest reliability have been demonstrated for this scale (Tangney et al., 2004; Current study Cronbach's alpha = .79).

Sexual Behaviour self-reports. In order to have an index of the individual's sexual behaviour (solitary and with a partner), participants answered how often they had masturbated and had sexual intercourse during the last four weeks. Participants could answer using a six-point Likert scale ranging from *Not once* to *Several times a day.*

Sexual Compulsivity Scale (SCS). This scale contains 10 items that measure the failure to control sexual impulses and interference in quotidian life because of sexual behaviour (e.g. "My desires to have sex have disrupted my daily life") (Kalichman & Rompa, 1995). These items are scored on a four-point Likert scale from *Not at all like me* to *Very much like me*. This scale has proven to have high reliability and be associated with sexual risky behaviours (Ballester-Arnal, Gómez-Martínez, Llario, & Salmerón-Sánchez, 2013; Current study Cronbach's alpha = .81).

Results

Table 1 displays the average and standard deviations of the self-report scores and testosterone levels, in the total sample and separated by relationship status. We explored whether single and partnered men differed in the psychological traits, testosterone levels, frequency of sexual behaviours, or hypersexuality tendencies with a series of independent t - tests. Single and partnered men differed only in the frequency of intercourse with partnered men having significantly more sex than single men ($t = -6.01$, $p = .001$).

Table 1. Descriptive and comparative statistics of coupled and single men.

	Total **n = 70** **Mean (SD)**	**Partnered men** **n = 36** **Mean (SD)**	**Single men** **n = 34** **Mean (SD)**	**T[p]**
Age	24.77 (4.41)	25.83 (4.61)	23.68 (3.93)	-2.07*
Testosterone	7.57 (3.88)	6.7 (4.39)	8.42 (3.17)	1.58
SES	50.55 (7.32)	50.77 (5.96)	50.32 (8.58)	.35
SIS2	29.73 (4.91)	29.02 (5.01)	30.47 (4.75)	-1.41
BSCS	41.57 (7.82)	40.97 (8.86)	42.18 (6.65)	.21
Sexual Compulsivity Scale	14.74 (4.18)	15.06 (4.58)	14.41(3.74)	-.62
Masturbation frequency	3.71 (1.04)	3.63 (1.21)	3.79 (.85)	.37
Intercourse frequency	2.56 (1.49)	3.43 (1.17)	1.67 (1.24)	- 6.01**

SES – Sexual Excitation Scale; SIS2 – Sexual Inhibition Scale Factor 2; BSCS – Brief Self-Control Scale; ns – non significant. ***** p = .04, ** p = .001

The correlations between the predictor variables (i.e. sexual excitation, sexual inhibition, self-control, and testosterone levels) and the dependent variables (i.e. hypersexuality tendencies, masturbation, and intercourse frequency) are displayed in Table 2. Testosterone and intercourse frequency showed a negative association. Because intercourse frequency differed significantly between single and partnered men and previous evidence has shown that testosterone levels are lower in partnered men (van Anders & Watson, 2007), we ran a partial correlation analysis between testosterone levels and intercourse frequency controlling for relationship status to exclude that this variable would mediate the observed association. The relationship remained significant (r = -.29, p = .02).

Table 2. Correlation between predictor and dependent variables.

	SES	SIS2	BSCS	Test.
SCS	**.26 (.02)**	.01 (.93)	**-.47 (.001)**	**.34 (.001)**
Masturbation	-.02 (.88)	.16 (.17)	-.09 (.42)	.14 (.23)
Intercourse	.01 (.88)	**-.29 (.03)**	-.02 (.84)	**-.37 (.001)**

Predictor variables: SES – Sexual Excitation Scale; SIS2 – Sexual Inhibition Scale Factor 2; BSCS – Brief Self-Control Scale. Test. – Testosterone. Dependent variables: SCS – Sexual compulsivity Scale; Masturbation and Intercourse frequencies.

Regression analyses

Sexual excitation, sexual inhibition, self-control, and testosterone levels were simultaneously entered in three different regression models to predict the level of hypersexuality tendencies, and masturbation and intercourse frequencies.

None of the independent variables revealed a significant relationship with frequency of masturbation. Intercourse frequency, on the other hand, was negatively predicted by testosterone levels and the sexual inhibition scores, indicating that the lower the level of sexual inhibition and the lower the level of testosterone levels, the more frequent intercourse men reported (Table 3; $F = 10.26$, $R^2 = .23$, $p = .001$).

Contrary to what was found for intercourse frequency, testosterone showed a positive association with the level of hypersexuality tendencies. The opposite pattern was found for self-control, indicating that higher scores on self-control were associated with lower hypersexuality tendencies (Table 3; $F = 13.71$, $R^2 = .29$, $p = .001$). Because sexual excitation was significantly correlated with testosterone ($r = .28$, $p = .02$) and with hypersexual tendencies ($r = .26$, $p = .03$), we conducted a Sobel test, to examine whether the relationship between testosterone and hypersexuality tendencies would be mediated by sexual excitation, which was not the case (indirect effect = .06, LI = .003, UI = .17). Figure 1 displays the relationship between self-control, hypersexuality tendencies, and testosterone. For illustration purposes the sample was median-split in high and low-testosterone individuals and divided in four groups (by quartiles) according to self-control scores.

Table 3. Regression models for hypersexuality reported levels, and masturbation and intercourse frequencies.

	β	T	P
SCS			
Testosterone	.31	2.94	.004
BSCS	-.41	-3.95	.001
Masturbation			
	--	--	ns
Intercourse			
Testosterone	-.35	-3.21	.002
SIS2	-.32	-2.91	.005

SCS – Sexual Compulsivity Scale; BSCS – Brief Self-Control Scale; SIS2 – Sexual Inhibition Scale Factor 2.

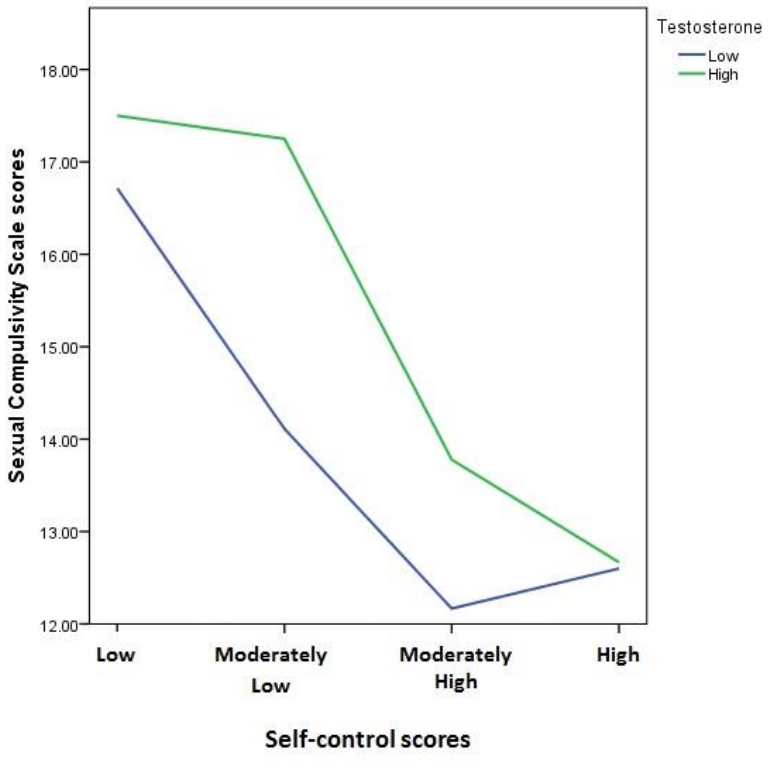

Figure 1. Individuals low in self-control and high in testosterone reported higher hypersexuality tendencies as assessed by the Sexual Compulsivity Scale.

To align with the biopsychosocial view on sexual responding, we also ran additional models to assess the interaction between testosterone and the individual traits (sexual excitation, sexual inhibition, and self-control). The interaction term of testosterone and self-control did not reach significance ($F = 9.91$, $R^2 = .31$, $p = .001$, Testosterone x Self-control: $\beta = -.14$, $t = -1.38$, $p = .17$). However, the interaction between testosterone and sexual excitation, and the interaction between testosterone and sexual were significant (Testosterone X SES; $F = 6.91$, $R^2 = .24$, $p = .001$, $\beta = .34$, $t = 2.85$, $p = .006$; Testosterone X SIS2; $F = 9.48$, $R^2 = .31$, $p = .001$; $\beta = -.44$, $t = -4.21$, $p = .001$). Additional slope analyses showed that sexual excitation showed a significant and positive association with hypersexual tendencies only when testosterone levels were high (Table 4). Similar analyses showed that sexual inhibition was a positive predictor of hypersexual tendencies when testosterone levels were low but was a negative predictor when testosterone levels were high (Table 5).

Table 4. Conditional effects of Sexual Excitation on Hypersexual tendencies at different values of testosterone.

Testosterone	β	T	P
3.45	-.12	-1.19	.23
7.44	.06	1.03	.31
11.42	.26	3.08	.003

Table 5. Conditional effects of Sexual Inhibition (SIS2) on Hypersexual tendencies at different values of testosterone.

Testosterone	β	T	P
3.45	.41	3.08	.002
7.44	.01	.13	.89
11.42	-.38	-3.01	.003

Our analyses aimed to study the relationship among continuous variables. However, in order to make a direct comparison with a previous study (Chatzitoffis et al., 2017), we performed a median-split on the sample based on the hypersexuality tendencies and examined whether they differed in testosterone levels. Although individuals high in hypersexuality tendencies showed higher levels of testosterone, the difference was not significant (High: $M = 8.13$, $SD = 4.12$; Low: $M = 6.87$, $SD = 3.58$; $t = 1.34$, $p = .18$).

Discussion

The aim of this study was to investigate individual differences in the manifestation of hypersexual tendencies in healthy young males. In particular, we explored the role of inhibition, excitation, self-control, and testosterone as possible explanatory mechanisms. Our results showed that higher levels of self-control were related to lower levels of hypersexuality tendencies, whereas higher levels of testosterone showed a positive association with hypersexual tendencies, thus, suggesting a protective role of self-control in the development of hypersexuality. In addition, the individual traits of sexual excitation and sexual inhibition were found to predict hypersexual tendencies but only in interaction with testosterone levels. Finally, whereas sexual excitation, sexual inhibition, self-control, or testosterone did not predict the frequency of masturbation, we did find that sexual inhibition and testosterone levels negatively predicted the frequency of intercourse.

Regarding the role of inhibitory mechanisms, lower levels of self-control predicted a higher tendency to display hypersexual behaviour. This corresponds with the idea that self-control comprises the ability to control immediate reward in the pursue of long-term benefits and this ability predicts better adjustment, less addictive behaviours, and better personal relationships (Tangney, Baumeister, & Boon, 2004). Self-control targets a general ability to control temptations and behaviour, thus, its association with hypersexual tendencies may explain the frequent comorbidity of substance abuse disorders in hypersexual individuals (Kühn & Gallinat, 2016).

Sexual inhibition was positively related to hypersexual tendencies only when testosterone levels were low, but in individuals with high testosterone the pattern was inversed: the lower the sexual inhibition, the stronger the hypersexual tendencies. Sexual inhibition as measured by the SIS2 scale refers to the loss of arousal due to the threat of negative consequences of sexual performance, mainly in dyadic sexual contexts. It has been proposed that testosterone favours sexual activity and related behaviours in competing or challenging contexts (Goldey & van Anders, 2015; Wingfield, Hegner, Dufty & Ball, 1990), which most likely involves dyadic sex and not solitary sexual practices. Thus, individuals who are high in testosterone and low in sexual inhibition (little regard for sexual performance consequences) may be at higher risk of developing sexual disinhibition problems and likely risky sexual behaviour. On the contrary, higher levels of sexual inhibition seem to counterweight the effect of high testosterone in predicting hypersexual tendencies. This

supports that like self-control, sexual inhibition acts as a protective factor in the emergence of hypersexual tendencies.

The finding that high sexual inhibition in combination with low testosterone showed a positive relation with hypersexual tendencies seems counter-intuitive at first sight. This pattern could potentially be linked to mood effects and to the use of sex as a coping mechanism (Bancroft & Vukadinovic, 2004) as low levels of testosterone may contribute to poor mood and irritability (Johnson, Nachtigall, & Stern, 2013) and sexual inhibition can be linked to behavioural inhibition and harm avoidance (Bancroft et al., 2009) which in excess can be an indicator of anxiety.

Higher sexual excitation was related to stronger hypersexual tendencies only in individuals with high levels of testosterone. This seems to indicate that sexual excitation is not *per se* at the core of hypersexuality tendencies, but higher levels of testosterone may trigger the enhancement of urges in individuals who are already more prone to be sexually aroused. Testosterone, by itself, showed a positive association with hypersexuality tendencies. Note that the association between hypersexuality tendencies and testosterone was not mediated by sexual excitation, but could possibly be mediated by more general traits. Research has shown, for example, that testosterone levels are related to substance abuse (Tajima-Pozo et al., 2015), sensation seeking (Sakaguchi, Oki, Honma, & Hasegawa, 2006), and risk taking (Mehta, Welker, Zilioli & Carré, 2015), features that are often present in individuals with hypersexuality (Kafka, 2010). Hence this might suggest that the interaction between testosterone and monoamines, which is important for sexual appetite (Kafka, 2010), is likely generalised to non-sexual behaviours. In fact, testosterone has been positively related to reinforcement sensitivity and MRI data supports a testosterone effect over the reward dopaminergic circuit during a non-sexual motivational paradigm (Hermans et al., 2010). Thus, in some individuals high testosterone may increase a susceptibility to seek and, under certain contexts, abuse rewarding stimuli.

The only study that has targeted the relationship between testosterone and hypersexuality so far, showed that testosterone levels of hypersexual individuals did not differ from those of controls (Chatzinoffis et al., 2017). Even though we studied a random non-clinical sample that included individuals on a continuum between low and high hypersexuality tendencies, our results fit with previous evidence when splitting the sample into a high and a low hypersexuality tendencies group. That is, the association between testosterone and hypersexuality tendencies became less apparent when splitting the sample,

indicating that testosterone may be a contributing but not crucial factor in the manifestation of hypersexuality.

We also explored the contributing role of sexual excitation, sexual inhibition, self-control, and testosterone levels in predicting individual and dyadic sexual behaviour. Surprisingly, none of the variables explained the frequency of masturbation. It may be that sexual excitation and sexual inhibition did not have predictive value because they exert their influence mainly in contexts involving other people (e.g. getting aroused by the touch of somebody or getting sexually inhibited during intercourse). Although being an easily accessible rewarding behaviour, masturbation frequency did not relate to self-control. Moreover, testosterone levels did not predict the frequency of masturbation which suggests that testosterone does not equal a mere physiological sexual drive. It is possible that the frequency of masturbation is related more to social attitudes and mood regulation than only biological drive.

In contrast, and contrary to a prevalent view, testosterone showed a negative relation with intercourse frequency and this was not accounted by their relationship status. This pattern -less testosterone in more sexually active men- has been reported previously (Kraemer et al., 1976; Sakaguchi, Oki, Honma, Uehara & Hasegawa, 2007). In addition, previous research has revealed a negative relationship between endogenous testosterone levels and number of sexual partners during the last year (Puts et al., 2015). Other studies have revealed an interesting pattern of findings on this behalf. When exploring the association between sexual responding and testosterone within subjects, testosterone levels increase after sexual stimulation and orgasmic activity (Escasa, Casey & Gray, 2011; Kraemer et al., 1976). However, when considering the association between testosterone and sexual activity between subjects, the opposite is found (Kraemer et al., 1976). From our findings, it is not possible to infer whether the endogenous levels of testosterone influence sexual intercourse, whether sexual intercourse influences testosterone levels, or both. Thus, different explanations seem plausible. For instance, it has been proposed that men with lower testosterone may respond with high frequency of sexual activity to reach an ideal homeostatic point (Kraemer et al., 1976). It is also possible that low sexual activity induces the organism to increase testosterone levels as an adaptive response, increasing the propensity of individuals for mating behaviours (e.g. increasing sexual excitation and sensitivity to sexual cues). In fact, a previous study showed that basal testosterone levels of individuals, who were in a stable relationship and had regular sex, increased after three weeks of abstinence (Exton et al., 2001). Thus, the hypothesis of a negative feedback

mechanism seems feasible. The negative feedback possibility fits in the frame of the Challenge Hypothesis (Wingfield, Hegner, Dufty & Ball, 1990). This states that testosterone variations in response to mating and reproductive behaviours are not absolute, but that they are related to those behaviours in the context of challenging environments, as they would prepare the organism for mating process challenges. Another possibility is that baseline testosterone levels related with certain traits have an indirect influence on the sex frequency. For instance, testosterone has been associated with antisocial traits (Dabbs & Morris, 1990; Tajima-Pozo, Bayón, Díaz-Marsá, & Carrasco, 2015) which may reduce mating success and bonding behaviours. From a broader perspective, the enhanced antisocial traits may be the evolutionary result of preparing the organism to compete for resources (territory or mating) but those traits are no longer necessarily adaptive in today's civilized contexts.

Finally, it is important to note that even when testosterone was negatively related to sex frequency and positively to hypersexuality tendencies, these two variables –sex frequency and hypersexuality tendencies- were not interrelated. This discards the possibility that individuals reported higher hypersexual tendencies (e.g.- increase in sexual urges) due to a lack or scarce sexual activity, which would then increase testosterone levels as suggested by the proposed feedback mechanisms.

In this study, we mainly aimed to identify potential risk or protective factors in the emergency of hypersexuality in healthy individuals. One of the limitations is its correlational nature, so, although some possible explanations were discussed, we cannot make direct causal inferences. Moreover, it remains to be studied whether the associations that we found are replicable in clinical samples. Whereas sexual excitation, sexual inhibition, and to a lesser extent testosterone, have been studied in clinical samples, this is not the case for self-control. Future studies may target this trait in hypersexual diagnosed individuals and assess whether self-control training can be useful in clinical interventions. Most importantly, this study took a biopsychological perspective by simultaneously studying psychological and biological factors. This may encourage future research to focus more on the interactions between different processes of different modalities when trying to understand sexual behaviour.

In sum, this study showed that self-control and testosterone are associated with hypersexuality tendencies, potentially as protective and risk factors, respectively. These two factors did not show an interaction effect, thus, suggesting that self-control can reduce the likelihood of developing hypersexuality in spite of the testosterone levels of the individual. The entrainment of self-control can therefore be a particularly useful tool in the prevention

and treatment of hypersexuality. This study also showed that sexual excitation and sexual inhibition play a risk and protective factor respectively, but this effect is dependent on testosterone levels. Overall, our results support the idea that hypersexuality does not just consist of an enhanced sexual arousal but also a failure to control such arousal. These findings underscore the interaction between psychological traits and biological factors in modelling and shaping sexual behaviour.

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CHAPTER 7.

General Discussion

This series of studies aimed at deepening our understanding of how individuals regulate their sexual behaviour by systematically investigating basic inhibitory mechanisms, on a psychological, physiological, and neurological level. In general, our studies provide support that different mechanisms and processes are necessary to regulate distinct aspects of sexuality and that basic sexual inhibitory mechanisms are also independent from general inhibitory processes. We observed that different sexual inhibitory (sub)processes could differentially predict distinct aspects of sexuality and also recruit distinct neural networks in the brain. Interestingly, we also revealed that individual traits modulate the functioning of these networks and their effect on sexual regulation. In addition, we investigated the role of different hormones in relation to sexual regulation. In particular, we observed that cortisol modulates the neural response during approach behaviour towards sexual stimuli, which may be one of the mechanisms underlying the relationship between mood and sexual regulation. Our results further showed that testosterone is related to hypersexual tendencies. Interestingly, self-control and sexual inhibition seem to counteract the role of testosterone in the emergence of hypersexual tendencies.

Different sexual inhibitory processes

In chapter two we studied the underlying mechanisms of cognitive and motivational sexual inhibition. We observed that these basic sexual inhibitory processes are not related to each other and predict different aspects of sexuality. This has important theoretical and practical implications.

From a theoretical perspective, sexual inhibition has been studied mainly as the mechanism that automatically diminishes the sexual response and/or sexual arousal. Sexual arousal can be regarded as an emotion (Everaerd, Both & Laan, 2006), and according to the process model of emotion regulation different mechanisms are involved in the regulation of emotions (Gross, 2002). Therefore, we hypothesised that sexual arousal would also engage different regulatory mechanisms. In this sense, we extended the concept of sexual inhibition to those mechanisms that prevent the emotion to take place and function at a cognitive level and those that prevent the manifestation of undesired sexual behaviour once the arousal response has started, thus involving motivational components. Our results confirmed that sexual inhibition is not a unitary construct with cognitive sexual inhibition not being related to motivational sexual inhibition, and each being distinctively associated to different sexual aspects (i.e. sexual thoughts and solitary sexual behaviour).

One should note that we only measured sexual excitation as a trait but we did not measure it as a process. Sexual arousal can be experienced at a subjective and at the physiological level, and those levels do not always converge (Janssen, 2011). For instance, physiological arousal can occur without the conscious appraisal of the stimulus and without the subjective experience of being aroused. In our study, cognitive sexual inhibition was measured by the sexual priming effect which is an automatic process. It would be interesting to investigate whether automatic and controlled cognitive inhibition have different effects on subjective and physiological arousal. To this regard, recent studies showed that controlled cognitive strategies can modulate the level of sexual arousal but do not prevent the conditioning of sexual stimulation with neutral stimuli (Brom et al., 2015; Both, Laan, & Everaerd, 2011). This may suggest that cognitive sexual inhibition may prevent subjective but not physiological arousal to happen. Whether this is actually the case and if this also applies to an automatic kind of cognitive sexual inhibition (e.g. sexual priming effect) remains to be explored.

Sexual arousal, as other emotions, implies an action tendency. We measured motivational sexual tendencies using an approach-avoidance paradigm. It has been shown that individuals are less likely to inhibit themselves when being aroused (Ariely & Loewenstein, 2006). Future studies could compare the role of subjective and physiological arousal in relation to motivational sexual inhibition. Given that emotion regulation would be more challenging when physiological changes have taken place (e.g. increase heart rate and heart pressure) (Gross, 2002), the inclusion of physiological variables can be particularly beneficial to address the association between the level of physiological sexual arousal and motivational sexual inhibition. If this association would turn out to be significant, future research could be directed at studying the strategies to regulate body reactions and its effect on motivational sexual inhibition performance.

Finally, other directions for research may include the characterization of basic sexual inhibitory mechanisms in sexual disorders and its training for prevention and treatment interventions.

Sexual inhibition and general inhibition

In chapter two we showed that cognitive and motivational sexual inhibition were not related to general motor response inhibition. In chapter three we further support the idea of distinct processes by showing that there was no common neural network of sexual inhibition and

general motor response inhibition. This highlights the specificty of sexual inhibition neural mechanisms. Unlike general motor response inhibition, sexual inhibition comprise important affective processes, such as the appraisal of rewarding stimuli. Both chapters showed that the control over neutral impulses (predominant motor responses) is essentially different from the cognitive and motor control over motivationally loaded stimuli.

However, chapter four illustrated that sexual inhibition as a trait (first factor of the dual control model) modulated the neural activity in the inferior frontal gyrus and insula during the general motor inhibition task. This trait factor refers to an undesired inhibition of the sexual response due to the threat of performance failure and/or low peripheral tone and therefore it is essentially different from the basic cognitive sexual inhibitory processes that we studied. As was argued in that chapter, the observed relationship can be due to a common temper feature. For instance, individuals who show an enhanced sensitivity to salient cues during the Go/No-go task, may also be hyperaware of environmental cues during sexual intercourse causing a reduced sexual response. This hyperawareness and a reduced peripheral tone could be influenced by harm avoidance or anxiety.

In chapter six we observed that self-control levels were inversely related to sexual compulsivity scores. At first sight, this seemed to contradict the findings observed in chapter two. There are different explanations for this inconsistency. Self-control is a complex construct that comprises not only inhibition, but also other processes such as persistence, the capacities to override temptation and to foresee long-term consequences (Baumeister, 2014; Tangney, Baumeister, & Bonne, 2004). Importantly, like sexual inhibition, self-control comprises motivational components that are not captured by the general motor response paradigms. In this sense, the expectations about less levels of sexual compulsivity scores being related to higher levels of self-control were confirmed. It is possible that whereas general response inhibition may be more related to temper features such as harm avoidance or impulsivity, self-control may be a more environmentally developed trait.

Neural substrates underlying the regulation of sexual behaviour

We observed that cognitive sexual inhibition recruited the inferior frontal gyrus, the orbitofrontal cortex, and the fusiform gyrus. Motivational sexual inhibition involved functional differences in the activation of the alPFC. From these regions, the orbitofrontal cortex has for a long time been studied in the context socio-affective regulation (Elliott, Dolan, & Frith, 2000) and the alPFC had been previously engaged in emotion regulation

(Volman, Roelofs, Koch,Verhagen, & Toni, 2011) and seems crucial in motivational sexual inhibition, as its activity correlated with the behavioural outcome. The fusiform gyrus, although rarely mentioned in the context of self-control or inhibitory behaviour, has been previously engaged in inhibition and emotion regulation paradigms (e.g. Dambacher et al., 2014; Goldin, McRae, Ramel, & Gross, 2008), and therefore it remains to investigate its particular role in sexual regulatory processes.

Although cognitive and motivational sexual inhibition showed an overlap in the right inferior frontal gyrus at a low threshold, this region was only active during cognitive sexual inhibition when considering a stricter threshold. Moreover, we showed that individuals high in sexual excitation exhibited performance benefits in cognitive sexual inhibition –but not motivational- when this region was temporally disrupted by non-invasive brain stimulation.
The areas described above are regions engaged during basic sexual inhibitory processes in overall healthy individuals. However, as was demonstrated throughout the research project, the functioning of these and other areas varies as a function of individual differences, and therefore some relevant regions may not show in the average activation maps. One example is the amPFC, which as we saw is dependent on cortisol levels and is also related to sexual regulation traits and to the association between mood and sexual activity.

Additional analyses on this data set showed that the caudate activity during the avoidance of sexual stimuli was dependent on sexual compulsivity scores and showed a negative functional coupling with the amPFC (Rodríguez-Nieto, Emmerling, Dewitte, Sack, & Schuhmann, 2017), which is consistent with a previous study that showed an association between the structure and functionality of basal ganglia and the amount of hours that participants watched porn in quotidian life (Kühn & Gallinat, 2014).

Finally, as was mentioned in chapter three, not only the integrity of sexual inhibitory networks seems to be important for the regulation of sexual behaviour, but also the integrity of sexual excitation. This may be the case with the amygdala. Its activation seemed to be downregulated during the sexual inhibitory conditions in comparison to the sexual non-inhibitory ones. Different brain lesion studies, including Klüver-Bucy syndrome cases, where the amygdala was comprised, report hypersexuality as a consequence. It is possible that the tracts that allow downregulation were damaged in these cases.

Specifying cognitive profiles and neural networks linked to different sexual regulatory processes can eventually expand intervention possibilities through non-invasive brain stimulation techniques.

Neuroendocrinological mechanisms

Endocrine systems are dynamic and are designed to respond to environmental and organism demands, therefore inducing changes in the body and in cognition through their action in the peripheral and central nervous system. Chapter five and chapter six explored the role of cortisol and testosterone in the regulation of sexual behaviour.

It was shown in chapter five that cortisol plays a neuromodulatory role during sexual approach and that such neural pattern resembles the one observed in individuals with low sexual inhibition and who show higher benefits on negative mood as a result of sexual activity. The characterization of the underlying physiological patterns of sexual inhibition and its etiology is important to further our understanding of sexual disorders and provide indications for prevention and treatment. For instance, if chronic stress can disrupt the regular functioning of endocrine systems and generate addiction proneness, this underscores the need for on-time intervention in vulnerable populations in order to diminish the risk of future disorders including sexual disorders. The link between cortisol and low sexual inhibition somehow fits with the idea that hypersexuality would involve a dysregulated stress coping response, being triggered by and resulting in increased levels of distress.

Regarding testosterone, additional analyses showed that this hormone also modulates the neural response during sexual approach-avoidance behaviours. Specifically, testosterone levels were positively related to neural activation in the left orbitofrontal cortex and in the left putamen during the avoidance of sexual stimuli (implying a negative relation during sexual approach) (Rodríguez-Nieto, Emmerling, Dewitte, Sack, & Schuhmann, 2017b). This is relevant as the left orbitofrontal cortex had been previously proposed to sustain a tonic sexual inhibitory mechanism and to show a distinctive pattern response in hypogonodal patients (Redouté et al., 2005 ; Stoléru et al., 2003). Moreover, orbito-striatal circuits have found to be engaged in self-regulation processes (Fettes, Schulze, & Downar, 2017). The results of chapter six further suggested a contributing role of testosterone in the interference of sexual urges in daily life. Our results showed that sexual excitation did not mediate the relationship between testosterone and sexual compulsivity scores. Furthermore, testosterone levels were inversely related to the frequency of sexual intercourse. Thus, it seems plausible that the modulating role of testosterone over sexual motivation is not driven by sexual desire but by non-sex-specific motivational processes such as reward expectancy.

Given the conjoint evidence supporting a modulatory role of testosterone in sexual regulation, future studies may target the effect of exogenous testosterone on sexual inhibitory

processes which might be highly relevant considering the over-prescription of testosterone and the vast amount of commercial "testosterone boosters" in some countries.

Limitations and future considerations

In sum, this line of studies showed that the study of sexual regulation can gain from differentiating between basic sexual inhibitory processes, as different mechanisms are engaged at different levels of sexual responding. In addition, the simultaneous consideration of psychological and physiological variables showed to be particularly valuable in understanding different mechanisms of sexual inhibition.

Nonetheless, we drew our conclusions based on a sample of healthy individuals, so it remains to be studied whether the basic sexual inhibitory processes identified here can be used to elaborate cognitive profiles in clinical samples. This line of research requires the simultaneous study of inhibitory processes, individual traits, and hormone levels as possible biomarkers. In addition, the inclusion of autonomous response measures such as skin galvanic response, peripheral temperature, plethysmography, or heart rate can be useful to study regulation during different phases of sexual arousal. To this end, we only addressed sexual excitation through a single self-report, but the use of other variables may increase our understanding of the interaction between excitatory and inhibitory mechanisms.

Although we included self-reports targeting real-life behaviours and some of these correlated with the paradigms that we used, the ecological validity still remains limited. Some complementary methods could be behavioural measurements such as viewing time of erotic material, forced-choice between an erotic calendar or art calendar, or word puzzles with socially risqué words related to sex (See Gailliot & Baumeister, 2007; Hofmann, Friese, & Gschwendner, 2009). Moreover, real-life sexual inhibition/disinhibition related behaviours can be assessed with correlational methods in clinical or forensic samples.

It is also worth mentioning that in real-life sexual regulation, moral cognition is essential. Thus, we can distinguish between the capacity to inhibit sexual behaviour and the actual willingness to do so. Moral cognition was not included in this research line but may be considered in future research lines.

Finally, the introduction of internet pornography induced an important switch in society that permeates different spheres of sexuality. The study of its effect on individuals has been approached from different disciplines and scientific fields and, although controversial, different studies show a negative impact of excessive porn watching on

different psychological and social factors (e.g. Love et al., 2015; Wright & Tokunaga, 2016). On the other hand, a growing internet community is promoting the "no fap challenge" (abstention from pornography watching with the option of masturbation abstinence; see www.nofap.com and www.yourbrainonporn.com), who claims different benefits on emotional and physiological wellbeing on an anecdotal base. Although the complete restraint from porn watching is probably not necessary for all individuals, the no fap challenge can be used as a research model to study psychological and physiological aspects of sexual regulation.

In conclusion, given that sexual regulation is a complex biopsychosocial response, it remains a challenge to implement a holistic and integrative view that considers the dynamics between physiological, psychological, and environmental systems. The presented research line shows that the methodological and integrative study of fundamental psychological and physiological mechanisms can increase our insight in understanding sexual regulation. The different sexual inhibitory processes predicted the frequency of distinct aspects of sexuality, engaged different neural circuits, and were distinctiviley affected by brain stimulation. The existence of different and independent mechanisms related to diverse aspects of sexuality have important implications, as this could potentially refine the characterisation of sexual disorders, their prevention, and their treatment. Moreover, the fundamental mechanisms of sexual inhibition can be affected by sexual and non-sexual individual differences. We identified that mood, self-control, sexual excitation, testosterone, and cortisol play a role in sexual inhibition. The systematic study of potentially influential factors is essential to better understand the regulation of sexual behaviour. Future studies may further incorporate environmental information (e.g. pornography exposure or socio-sexual attitudes) and measure sexual and inhibitory responses in naturalistic contexts to have a more comprehensive view on the role of sexual inhibition in sexual responding.

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SUMMARY

The aim of this series of studies was to better understand the fundamental mechanisms that allow humans to control their sexual cognition and behaviour. For this purpose a series of experiments were performed using a sample of healthy young males.

In a first study –Chapter 2-, we aimed to examine whether the ability to control sexual cognition and behaviour derives from a general inhibitory capacity or whether it comprises separate mechanisms. Moreover, we aimed to examine whether the ability to inhibit sexual cognition was related to the ability to inhibit sexual behaviour. The results indicated that the abilities to inhibit sexual cognition and sexual behaviour comprise different processes and predict different outcomes (sexual thoughts vs sexual behaviour). In addition, these abilities are not related to a general inhibitory process.

The finding that different inhibitory processes comprise distinct processes was further supported by a study in which we used functional Magnetic Resonance Imaging (Chapter 3) to demonstrate that cognitive sexual inhibition, motivational sexual inhibition and general inhibition engaged different neural networks. Whereas the anterolateral prefrontal cortex showed changes in activation during the motivational sexual inhibition, the orbitofrontal cortex and the inferior frontal gyrus were active during cognitive sexual inhibition.

The inferior frontal gyrus is typically involved in inhibitory and self-regulation processes. In Chapter 4, we took a closer look at this region and observed that its activation was found to be modulated by the sexual excitability of participants. In a follow-up experiment, we stimulated the inferior frontal gyrus with Transcranial Magnetic Stimulation with the aim to temporally disrupt the region. The functional inhibition of this region led to improvements in cognitive sexual inhibition in individuals who are easily sexually aroused. This finding indicates that the inferior frontal gyrus is involved in sexual inhibition but does not code inhibition *per se*.

Given the central role of hormones in sexual responding, we also investigated whether and how cortisol and testosterone are implicated in sexual inhibition. In Chapter 5, we found that cortisol modulated brain activity in the anteromedial prefrontal cortex during the approach of sexual stimuli. This region is associated with the integration of autonomic processes with higher-order processes, among others. The activation of this region was also related to the degree to which participants reported being able to inhibit their sexual arousal in unappropriated contexts. Moreover, the strength of the functional connectivity between this

region and the amygdala was related to the reported likelihood of individuals to perform sexual actions (while being angry, sad or anxious) that could be later regretted. These findings suggest that the anteromedial prefrontal cortex activity and its coupling with the amygdala underlie the relationship between mood states, sexual arousal and sexual inhibition.
In a final study (Chapter 6) we observed that lower levels of self-control were associated with higher hypersexual tendencies. In addition, testosterone levels were positively correlated with hypersexual tendencies, but negatively associated with intercourse frequency. Trait sexual inhibition and trait sexual excitation also correlated with hypersexual tendencies but only in interaction with testosterone, in a way that individuals with low sexual inhibition in combination with high testosterone or high sexual excitation in combination with high testosterone reported more hypersexual tendencies.
Gaining deeper insight into the working mechanisms of sexual inhibition and approaching this from a biopsychosocial perspective can eventually help to further improve current prevention and treatment protocols of sexual disorders.

SAMENVATTING

Het algemene doel van deze studies was een dieper begrip van de fundamentele mechanismen die beheersing geven over seksuele cognitie en het bijbehorende gedrag. Tot dit doeleinde werd een reeks experimenten uitgevoerd met gezonde, jongvolwassen mannen. In de eerste studie – Hoofdstuk 2 – werd onderzocht of het inhibitie mechanisme dat ten grondslagen ligt aan de beheersing van seksuele cognitie van algemene of specifieke aard was. Tevens werd onderzocht in hoeverre het vermogen om seksuele cognitie te remmen gerelateerd was aan de inhibitie van seksueel gedrag. De resultaten suggereerde dat verschillende processen verantwoordelijk waren en dat er geen sprake was van een algemeen remmend proces

De bevinding dat verschillende remmende processen beïnvloed worden door verschillende mechanismen, werd verder ondersteund door functionele Magnetic Resonance Imaging onderzoeken (fMRI; Hoofdstuk 3). In deze studie konden we aantonen dat cognitieve seksuele inhibitie, motivationele seksuele inhibitie, en algemene inhibitie verschillende neurale netwerken omvatten. Cognitieve inhibitie kon geassocieerd worden met hogere activatie in de orbitofrontale cortex en de inferieure frontale gyrus, terwijl motivationele inhibitie met een verandering in de activiteit van de anterolaterale prefrontale cortex.

Omdat de inferieure frontale gyrus wordt vaak geassocieerd met remmende en zelfregulerende processen, werd deze nader onderzocht in een stimulatie studie (Hoofdstuk 4). Een vervolgexperiment maakte gebruik van Transcraniële Magnetische Stimulatie (TMS) om de inferieure frontale gyrus tijdelijk te verstoren. De functionele remming van deze regio leidde tot verbeteringen in cognitieve seksuele remming bij individuen die gemakkelijk seksueel opgewonden zijn. Dit suggereert dat de inferieure frontale gyrus betrokken is bij seksuele remming, maar niet op zich remming codeert.

Gezien de centrale rol van hormonen bij seksueel gedrag, is er ook onderzoek gedaan naar de betrokkenheid van cortisol en testosteron bij seksuele inhibitie. In Hoofdstuk 5 staat beschreven hoe cortisol de hersenactiviteit in de anteromediale prefrontale cortex moduleert bij het verwerken van seksuele stimuli. Deze regio wordt geassocieerd met de integratie van autonome processen en hogere orde processen. De activatie in de prefrontale cortex was ook gerelateerd aan de mate waarin deelnemers seksuele opwinding in ongepaste context konden remmen. Bovendien was de mate van functionele connectiviteit tussen prefrontale cortex en amygdala gerelateerd aan de waarschijnlijkheid dat een individu seksuele handelingen zou

uitvoeren die zij later zouden betreuren, met name tijdens emotionele momenten (woede, verdriet, of angst). Deze resultaten suggereren dat de anteromediale prefrontale cortex activiteit en de connectie met de amygdala, een basis vormen voor de relatie tussen gemoedstoestand, seksuele opwinding, en seksuele remming.

In het laatste onderzoek lag de nadruk op de werking van testosteron (Hoofdstuk 6). De resultaten lieten een positieve correlatie zien tussen testosteron en hyperseksuele neigingen, een negatieve verband tussen zelfcontrole en hyperseksuele neigingen, en een negatieve associatie tussen testosteron en frequentie van seksuele gemeenschap. De relatie tussen testosteron, hyperseksuele neigingen, seksuele remming, en seksuele opwinding was complexer. Hogere hyperseksuele neigingen waren gerelateerd aan lage seksuele inhibitie of/en hoge seksuele opwinding, maar alleen in individuen met een hogere mate van testosteron.

Het verkrijgen van een dieper inzicht in de werking van het mechanismen achter seksuele inhibitie vanuit een biopsychosociaal perspectief kan uiteindelijk helpen om de huidige preventie- en behandelingsprotocollen van seksuele aandoeningen verder te verbeteren.

RESUMEN

El objetivo de esta serie de estudios fue entender los mecanismos fundamentales que permiten el control de la cognición y comportamiento sexuales en humanos. Para este fin, una serie de experimentos fueron realizados en una muestra de jóvenes sanos.

En un primer estudio –Capítulo1-, examinamos si el control de la cognición y comportamiento sexuales derivan de una capacidad general inhibitoria o si conforman mecanismos independientes. También examinamos si el procesamiento de la inhibición de la cognición sexual se relaciona con la inhibición del comportamiento sexual. Los resultados indicaron que la inhibición de la cognición sexual y la inhibición del comportamiento sexual conforman procesos independientes. Adicionalmente, estos procesos no se relacionaron a una capacidad general inhibitoria.

El hallazgo de que los procesos inhibitorios constituyen procesos distintos fue una vez más sustentado en un estudio realizado con Resonancia Magnética Funcional (Capítulo 3). Este estudio mostró que la inhibición de la cognición sexual, la inhibición de acciones motivadas sexualmente y un tipo de inhibición no sexual, son procesadas por distintas redes neurales. Mientras la corteza prefrontal anterolateral mostró cambios en la activación durante la inhibición de acciones sexualmente motivadas, la corteza orbitofrontal y el giro frontal inferior incrementaron su actividad durante la inhibición de la cognición sexual.

Típicamente, el giro frontal interior se ha relacionado con procesos inhibitorios y de auto-control. En el Capítulo 4 observamos que la activación de esta región es modulada por diferencias individuales en la excitabilidad sexual. En un experimento con Estimulación Magnética Transcraneal, interrumpimos temporalmente la actividad del giro frontal inferior. Esto generó mejoras en la inhibición de la cognición sexual en individuos que reportaron tener alta excitabilidad sexual. Estos resultados indican que el giro frontal inferior actúa durante la inhibición de la cognición sexual pero no codifica este proceso de manera directa.

Ya que las hormonas juegan un papel central en la respuesta sexual, investigamos si la testosterona y el cortisol están implicados en procesos inhibitorios. En el Capítulo 5, encontramos que el cortisol modula la actividad en la corteza prefrontal anteromedial durante la aproximación de estímulos sexuales. Esta región se asocia con la integración de respuestas autónomas con procesos de alto orden, entre otros procesos. La activación de esta región también se relacionó con el grado en la habilidad para inhibir respuestas sexuales en contextos inapropiados de acuerdo con el reporte de los participantes. Más aún, el grado de la

conectividad entre la corteza prefrontal anteromedial y la amígdala se relacionó con el grado en que los individuos reportaron ser propensos a realizar un acto sexual (al estar tristes, enojados o ansiosos) que podrían lamentar después. Estos hallazgos sugieren que la actividad de la corteza anteromedial y su conectividad con la amígdala, subyacen, al menos en parte, la relación entre estados de ánimo y la excitación e inhibición sexuales.

En un último estudio (Capítulo 6) observamos que bajos niveles de auto-control se asociaron con tendencias hipersexuales. Adicionalmente, los niveles de testosterona correlacionaron positivamente con tendencias hipersexuales, pero negativamente con la frecuencia de relaciones sexuales. La inhibición y excitación sexuales como rasgos psicológicos también correlacionaron con tendencias hipersexuales pero solo en interacción con la testosterona, de modo que individuos con baja inhibición sexual en combinación con altos niveles de testosterona o individuos con alta excitación sexual y altos niveles de testosterona reportaron mayores tendencias hipersexuales.

Profundizar nuestro entendimiento sobre los mecanismos de la inhibición sexual desde una perspectiva biopsicosocial puede eventualmente mejorar las intervenciones en la prevención y tratamiento de desórdenes sexuales.

VALORISATION

Humans are naturally provided with curiosity and exploratory behaviour. Along with its particular intellectual skills, humanity has gained a sophisticated and considerable amount of knowledge. Much of this knowledge is useless, but that does not mean that it is meaningless or negligible. Knowing that there is a supermassive black hole at the centre of the Milky Way or that dinosaurs inhabited Earth hundreds of million years ago may be useless (by now), but still fascinating. Therefore, the request of 'create value from knowledge' may seem redundant as knowledge already has value itself.

Much of the sophisticated technology used nowadays evolved from observations of natural phenomena that had no apparent application. For instance, when Heinrich Hertz was asked about what the electromagnetic waves could serve for he replied: 'Nothing, I guess'. Thus, it is uncertain to tell and predict what could be the use of certain knowledge.

We may, however, talk about a utilitarian valorisation of knowledge. For this purpose, we have to ask who decides what is valuable, for whom and on what basis. According to the values of society and institutions, the emphasis may be put on the benefits on individuals' quality of life and in society, on financial gains, or on reputation, among the most common ones. In this sense, it is relevant to reflect where do we put the emphasis and why.

Science may always lead us to go faster, higher and further. In today's world, not only machines can land in Mars or beat human calculations but they are now designed to execute precise surgeries, and to learn to learn. Still, machines cannot answer the most fundamental questions, like what is this for? Where are we going? What are our priorities? And why?

In this utilitarian valorisation, I will argue on how the present research can be of social value.

The need to understand the mechanisms that allow human beings to control their sexual cognition and sexual behaviour is fundamental, as by today, sexual harassment and sexual offenses are still present even in the most modern societies. Moreover, the sequelae of these offenses involve long-term effects on the mental life of the victim.

It has been proposed that in today's society there is an increased risk of developing a sexual disorder given the increase in the accessibility of sexual material. The overconsumption of sex on the internet has different consequences, like undermining the development and maintenance of interpersonal relationships, diminishing the ability to perform and enjoy regular sex, and portraying unequal gender representations (i.e., objectification of women's sexuality). The lack of control over sexual material consumption does not only jeopardise the

quality of life of individuals. In some cases, the overconsumption of sexual material may escalate to real-life behaviours that may compromise the integrity of other individuals.

Far beyond, illegal pornography is directly linked to world large crimes implying human trafficking, sexual exploitation, and children abuse. Human trafficking for sexual exploitation, is an alarming problem, as it has been estimated that there are 4.8 million persons for forced sexual practices, which involves street prostitution, night clubs, escort sites, and the pornography industry, among others.

Thus, given the large accessibility of sexual consumption, the increased risk of developing sexual disorders, and the large amount of effects derived from the lack of control of sexual behaviour, the need to understand the psychological and physiological processes underlying the regulation of sexual behaviour is essential in order to improve the prevention and treatment of sexual disorders. One of these processes is sexual inhibition, as this comprises the ability to inhibit sexual arousal and associated behaviours. A balance in sexual inhibition is essential, as this process is necessary to restrain inappropriate sexual behaviour, but an excess can lead to other problems such as sexual dysfunction or relationship problems.

The studies here presented investigated the basic processes of sexual regulation and sexual inhibition in a sample of healthy young men. The conclusions derived from this thesis may help to create psychological profiles of individuals at risk for developing sexual disorders. Such profiles may include the characterization of different sexual inhibitory and excitatory processes and traits, emotion regulation, self-control, and hormone levels. This characterization can serve as a first step to develop concrete guidelines to further improve the diagnosis, prognosis and intervention programs.

An individualized treatment could make use of different techniques depending on the area of impairment. Accordingly, treatment protocols can be directed towards different targets such as increasing self-control, emotion regulation training, training awareness and control of autonomic responses, or hormonal interventions.

The development of non-invasive brain stimulation protocols represents an important treatment alternative, given the invasive side-effects caused by some medicaments used to treat sexual disorders. Given that sexual inhibition is not a unitary construct and that the underlying processes are sensible to individual differences, the study of the associations between neural and endocrine mechanisms and individual differences in specific processes is indispensable to design and improve those protocols.

Finally, a better characterisation of (individual differences in) inhibition could help to improve the prognosis of individuals with sexual problems and help to maximize therapeutic benefits. This is highly relevant to prevent harmful consequences.

The present work investigated the fundamental mechanisms of sexual inhibition in a sample of young healthy males. Whereas there is no warranty that every fundamental research study will lead to a crucial transformation in reality applications, it is highly dubious that a social impact can occur without it. To this regard, it is noteworthy that a recent study showed that the creation of the most transformative medicines between 1985 and 2009 had their origins in fundamental research. Likely, this principle is suitable for research in mental health as well, as by understanding the aetiology and underlying mechanisms of certain behaviour, we can design more effective interventions by targeting specific processes.

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CURRICULUM VITAE

Geraldine Rodriguez Nieto was born in Mexico City on November 10th 1985. She completed her secondary education at the National High School from the National Autonomous University of Mexico. In 2007, she started her bachelor in Psychology at the National Autonomous University of Mexico, Mexico. She finished her last period of undergraduate studies at University of California, San Diego, as part of an exchange program. For her bachelor thesis, she studied the basis of executive functions in pre-schoolers through neuropsychological tests under the supervision of Prof. Feggy Ostrosky. After graduating with honours, she moved to Queretaro, Mexico, to do postgraduate studies in Neurobiology at the Institute of Neurobiology, Querétaro, Mexico. During this period, she joined the lab group of Prof. Fernando Barrios, where she investigated the gender differences in the neural functional connectivity of compassion. At the end of her master studies she did an internship at Instituto D'Or de Pesquisa e Ensino, Rio de Janeiro with the research group of Dr. Jorge Moll. During this visit, Geraldine participated in a project that aimed to study the neural basis of altruistic decisions on patients with brain damage. In 2014, she moved to Maastricht, Netherlands to join the Brain and Cognition Group of Prof. Alexander T. Sack as a PhD candidate. Under the supervision of Prof. Alexander T. Sack, Dr. Teresa Schuhmann and Dr. Marieke Dewitte, Geraldine investigated the psychological and neural mechanisms underlying sexual inhibition and the potential contributing role of testosterone and cortisol. By October, 2018, she defended her doctorate thesis.

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- 38th ANNUAL MEETING OF INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY; Acapulco, 2010. *Relationship between Executive Functions and Mathematical Skills in Preschool Children*.
- 42nd ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE; New Orleans, 2012. *Gender differences for hemodynamic responses in brain regions activated while experiencing compassion.*
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- ORGANIZATION FOR HUMAN BRAIN MAPPING ANNUAL MEETING; Vancouver, 2017. *Avoiding Erotic Stimuli: Neural Mechanisms of Sexual Inhibition.*