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The role of incentive learning and cognitive regulation in sexual arousal

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Chapter 10

The Influence of Acute-Stress on the Down-Regulation of Sexual Arousal

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Abstract

Although it is hypothesized that dysregulated emotion regulation (ER) and vulnerability to stress play an important role in problematic sexual reward seeking behaviour, little is known about their interaction and neural correlates. In the present study, we investigated the neural effects of an emotion down-regulatory strategy during the processing of sexual stimuli, and the influence of acute stress thereon. It was hypothesized that activation within reward related structures (i.e. NAc, amygdala) decreases consistent with down-regulation, while activation in prefrontal control areas would increase, and that acute stress (induced by the Trier Social Stress Test; TSST) would affect the ability to down-regulate sexual arousal. Acute stress was thought to increase NAc and amygdala activation, and decrease activation in dorsolateral frontal control areas, while increasing activation in ventral frontal areas. Participants were randomly assigned to a stress (n=20), or control condition (n=18), and had to increase ('Sex-Up'), decrease ('Sex-Down') or maintain ('Sex-Equal') their sexual arousal response evoked by sexual explicit pictures inside a MRI-scanner. BOLD responses to sexual pictures were compared to neutral pictures on viewing trials ('Neutral-Equal'), and ratings of the ability to regulate sexual arousal were analyzed. Across both conditions, down-regulation of sexual arousal activated prefrontal regions. Crucially, compared to the control condition, induced stress resulted in increased activation in the right amygdala, right dorsal anterior cingulate cortex (ACC) and right inferior frontal gyrus pars triangularis (IFG) in Sex-Down vs Sex-Equal trials. Results suggest that acute stress may markedly impair the cognitive down-regulation of sexual arousal and highlights critical limitations of this technique to control sexual arousal under stress.

10.1. Introduction

Stress is widely acknowledged as a risk factor for the development of a wide range of disorders, including disorders of excessive appetite such as substance use disorders, gambling addiction, or sexual addiction (Adam & Epel, 2007; Uhart & Wand, 2009; Reid et al., 2008, 2012). Research has shown that individuals that manifest symptoms of hypersexual behaviour are more likely to experience vulnerability to stress and deficits in emotion regulation (ER) (Reid, 2014). Although it is hypothesized that ER and vulnerability to stress play an important role in sexual reward seeking behavior, much remains unknown about their interaction and neural correlate. Given the pervasive nature of stress in daily life, it is critical to understand how acute stress may influence this ability to modify sexual arousal.

Sexual arousal can be seen as an evolutionary preserved emotion (Everaerd, 1989; Frijda & Sundararajan, 2007; Janssen, Everaerd, Spiering, & Janssen, 2000). Sexual arousal is characterized by specific bodily reactions, like enhanced genital blood flow, by preparation of behavioural action, and by the experience of feelings of lust, excitement, and sexual desire, and can eventually result in overt sexual behaviour such as approach and consumption (Both et al., 2005; Dekker & Everaerd, 1989; Lang, 1971). Disturbances in the regulation of sexual arousal might be a key factor in the genesis of disorders in sexual motivation, such as hypersexuality, which may involve a chronic inability to suppress sexual arousal. ER is any process by which an individual modulates the intensity and direction of emotional response (Gross, 2002; Gross & Thompsom, 2007). Emotional down-regulation refers to the process of inhibiting the emotional response, or the intensity of the emotional response, regardless of its valence. The ability to regulate emotions when stressed is considered essential for mental health and deficit of such capacity confers risk

towards psychopathology (Gross, 2002; Heatherton & Wagner, 2011; John & Gross, 2004).

On a neural level, successful emotion down-regulation is thought to reflect the inhibition of subcortical brain areas related to emotional response, such as the amygdala, mediated by regions of the prefrontal cortex (PFC) that appear to act as control systems that implement the regulatory strategy (Frank et al., 2014, Ochsner et al., 2012; Ochsner & Gross, 2005). The technique ‘reappraisal’ (i.e. cognitive change, yielding an altered interpretation of an emotional stimulus or situation) has been proposed to be an effective ER strategy to down-regulate emotions because its influence begins at an early stage of emotion generation, before emotional responses have fully unfolded (Ochsner & Gross 2005; Richards & Gross, 2000). Research on the neural correlates of reappraisal of negative emotions has demonstrated that activation of the amygdala can be reduced during reappraisal (Ochsner et al., 2002; Phelps, 2006). This reduction in amygdala activation is negatively related to activity in a neural network including the anterior cingulate cortex (ACC), and frontal control areas, such as the orbitofrontal cortex (OFC), the inferior frontal gyrus (IFG) the middle frontal gyrus (MFG), and the parietal cortex (Banks et al., 2007; Etkin, Egner & Kalisch, 2011; Grecucci et al., 2013; Hamann, 2007; Kim & Hamann, 2007; Kim & Ochsner et al., 2002, 2004; Shenhav, Botvinick & Cohen, 2013). Moreover, it is important to keep in mind that the principles underlying ER also form the basis of cognitive-behavioral therapy (CBT), an intervention widely used in the clinic to treat individuals with hypersexuality (Birchard, 2015). This implies that the success of this technique for controlling maladaptive emotional responses relies on the availability of cognitive resources and intact executive function (Heatherton & Wagner, 2011; Raio, 2013). Despite the presumed importance, compared to the substantial amount of research on down-regulation of negative emotions, research assessing the dynamic interactions between regions within the subcortical

reward structures and the frontal circuit during the active cognitive control of sexual arousal is extremely scarce. Nevertheless, there is evidence for the involvement of prefrontal areas in the regulation of sexual arousal. For instance, using functional near-infrared spectroscopy, Leon-Carrion et al. (2007) demonstrated that even after sexual stimuli presentation ceased, dorsolateral PFC activation continued, supporting the involvement of frontal areas in the regulation of sexual arousal. Additionally, Beauregard et al. (2001) found that men, when instructed not to suppress becoming sexually aroused by sexual stimuli, demonstrated significantly enhanced activation in the right amygdala, right anterior temporal pole, and hypothalamus, whereas men that were instructed to suppress sexual arousal demonstrated activation in the right superior frontal gyrus and in the right ACC. In sum, successful ER appears to involve a balance between subcortical brain regions related to emotional response (e.g., amygdala) and prefrontal regions associated with cognitive control (Heatherton & Wagner, 2011).

A vast number of investigations using functional MRI have consistently shown that visual sexual stimuli evoke activations in the brain's reward system, such as the NAc and amygdala (Childress et al., 2008; Georgiadis & Kringelbach, 2012; Gillath & Canterberry, 2012; Hamann et al., 2004; Oei et al., 2012a; Rupp & Wallen, 2008; Stoléru et al., 2012). NAc activation is modulated by dopamine (DA) signaling (Richard et al., 2012), with higher activations in response to sexual reward cues when DA activity is increased, and lower activations when DA activity is decreased (Oei et al., 2012a). Interestingly, stress might increase sensitivity to potentially rewarding stimuli through its effects on DA signaling in the NAc (Cabib & Puglisi-Allegra, 2012; Oei et al., 2014). Additionally, a growing body of work has revealed that exposure to acute stress has deleterious effects on the successful execution of higher cognitive processes, including ER (Arnsten, 2009; Heatherton & Wagner, 2011; Kogler, Gur & Derntl, 2015; Raio et al., 2013). It

is thought that neuroendocrine responses to acute stress exposure impacts the functional integrity of the PFC (Arnsten, 2009; Arnsten, Wang & Paspalas, 2012), which is, as has become clear, crucial in successful cognitive ER (Beauregard, 2007; Hartley & Phelps, 2010; Ochsner et al., 2004; Ochsner & Gross, 2005; Ochsner, Silvers & Buhle, 2012; Levesque et al., 2003; Phan et al., 2005; Urry et al., 2006). Moreover, stress seems to activate ventral ‘affective’ brain areas, while deactivating dorsolateral ‘executive’ prefrontal areas during emotional inhibition (Oei et al., 2012b). Importantly, since impulse control is at the core of self-regulation (Heatherston & Wagner, 2011), increased neural activity in subcortical reward structures such as the amygdala and NAc as a result of induced stress (Oei et al., 2014), may further impede successful top-down control recruitment. This suggests an important paradox: top-down control may be compromised in regulating sexual arousal at times when such cognitive control is needed most, since acute stress can activate the brain reward system (Oei et al., 2014), resulting in increased bottom-up subcortical responses.

The aim of the present study is to investigate the influence of acute stress on the cognitive regulation of sexual arousal in an experimental design, in which young healthy men were randomly allocated to an experimental or control condition. The experimental condition underwent a stress procedure before they had to increase (‘Up’), decrease (‘Down’) or maintain (‘Equal’) their sexual arousal response evoked by sexual explicit pictures inside a MRI-scanner. We aimed at examining functional activations in regions associated with sexual reward, such as the NAc (Stoléru et al., 2012; Oei et al., 2012a), and amygdala (Hamann et al., 2004), and frontal regions involved in emotional response and implementing cognitive ER strategies, such as the IFG pars triangularis (Aron et al., 2007; Aron, Robbins & Poldrack, 2014; Hampshire et al., 2010; Shamay-Tsoory, Aharon-Peretz & Perry, 2009), the MFG (Etkin, Egner & Kalisch, 2011), and the dorsal ACC (Mohanty et al., 2007; Shenhav,

Botvinick & Cohen, 2013), during down-regulation of sexual arousal. It was predicted that activation within the NAc and amygdala would decrease consistent with emotional down-regulation, while activation in the IFG pars triangularis and MFG would increase (Amaral & Price, 1984; Baumann & Turpin, 2010; Ghashghaei et al., 2007; Ochsner et al., 2004; Phelps et al., 2004). Crucially, it was hypothesized that acute stress would affect the ability to down-regulate sexual arousal by increasing activations in ventral ‘affective’ areas, such as the amygdala, and decreasing activation in dorsolateral frontal control areas such as the MFG, while demonstrating increased activation in ventral ‘affective’ frontal areas, such as the IFG pars triangularis.

10.2. Methods and materials

Participants

A total of 40 men from the general population were recruited by means of advertisements. Eligibility criteria were: no current (or history of) psychiatric problems as determined by the Amsterdam Biographical interview (ABV; Wilde 1963) and the MINI International Neuropsychiatric Interview (MINI; Sheehan et al, 1998), a heterosexual orientation, no medical illness (or medical history) or use of medication, including over the counter hay fever medication; no current or recent use (less than 12 weeks before participation) of psychopharmacological medication or psychotropic drugs; alcohol usage below 20 units per week. Participants were randomly assigned to the stress or control condition in an experimental design. The study was approved by the medical ethical committee of the Leiden University Medical Center and written informed consent was given by all participants.

Stress-induction & physiological assessments

The stress induction procedure has been described in detail elsewhere (Oei et al., 2014). In brief, the Trier Social Stress Test (TSST; Kirschbaum et al., 1993)

consists of a 10-min period in anticipation of a 5-min free speech, and a 5-min arithmetic task (counting backwards from 1033 to zero, in steps of 13) in front of a selection committee and a camera. In contrast, in the control condition, participants have to prepare and conduct a speech without audience about a book or movie. Thereafter, they have 5 min to count backwards from 50 to zero at their own pace (Het et al., 2009). Salivary cortisol was assessed, using salivettes (Sarstedt, Germany). Systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), and heart rate (HR, bpm) were recorded using an automatic wrist blood pressure monitor (OMRON, R5-I) (see Oei et al., 2014).

Materials

An ER task was presented during fMRI scanning, and consisted of ten neutral images and 40 erotic pictures that were selected from the International Affective Picture Set (IAPS; Lang et al., 2008). Additional erotic images were selected from picture sets previously used in sexology research and depicted (partly) naked humans in a heterosexual erotic context (Both et al., 2004; Brom et al., 2015a). Each trial began with a brief written cue on screen (2 s), ‘equal’, ‘increase’ or ‘decrease’, that was immediately followed by a neutral or sexual picture (duration = 8 s), see Figure 1. The assignment of the images to instructions was randomized and counterbalanced across subjects, with the restriction that written instructions were equally matched to stimulus category (Neutral pictures: 10 trials do not modify, i.e. ‘Neutral-Equal’; Erotic pictures: 10 trials do not modify, i.e. ‘Sex-Equal’; 15 trials increase, i.e. ‘Sex-Up’; 15 trials decrease, i.e. ‘Sex-Down’). After each trial participants were asked to indicate whether they felt their emotions were successfully modulated according to the strategy when asked to apply, up- or down-regulation or not to modify their emotion on each of these trials, via button response on a 4-point scale (1 not successful – 4 very successful) (8s). There was an inter-trial interval showing a

gray fixation dot with a random duration between 2s and 6s for jitter. Stimuli were presented in an 800 X 600 pixel resolution, back-projected on a screen located at the end of the scanner bore via an LCD projector located outside the scanner room. Subjects viewed stimuli on a screen through a mirror located on the head coil. Stimulus software (E-prime 2, Psychology Software Tools, Inc.) was used for stimulus presentation. Refresh rate of both the task PC monitor and projector was 60 Hz.

Instructions: Three task conditions were randomly presented. In the view condition (i.e. Sex-Equal and Neutral-Equal), when the instruction '*equal*' (i.e. do not modify) was presented, participants attended the content of the picture but did not manipulate the emotional response to it. When participants received the instruction '*increase*' prior to a picture, they were instructed to increase or up-regulate any experienced or felt sexual response and arousal the picture might elicit. More specifically, they were instructed to identify as much as possible with the male actor or to imagine that they themselves were engaged in the sexual activities depicted in the picture (i.e. Sex-Up). When participants received the instruction '*decrease*', they were instructed to reappraise and down-regulate the emotional value of the images, so that the sexual impact was lessened (i.e. Sex-Down). Participants were instructed to generate a more distant interpretation of the scene depicted in the picture. More specifically, when presented with the instruction '*decrease*', they were instructed to remind themselves that they were simply watching a picture depicting actors playing a role. A comprehensive prescanning training procedure was used to assure that participants understood the cue-task associations and the reappraisal strategy.

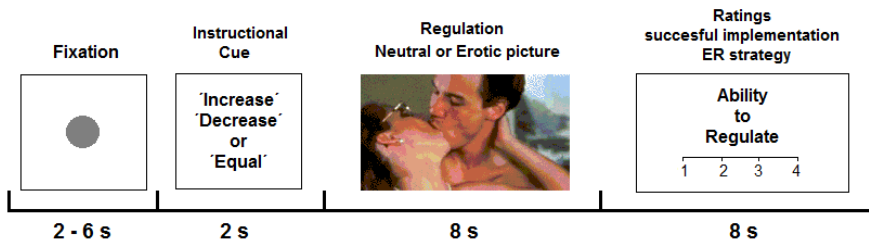


Figure 1. Experimental design for a single trial. The experiment consisted of 50 trials (10 neutral pictures and 40 erotic pictures). There were 10 trials each of do not modify (i.e. *equal*) emotional response in response to neutral pictures ('Neutral-Equal') and erotic pictures ('Sex-Equal'), and 15 trials of *increase* sexual arousal in response to erotic pictures ('Sex-Up'), and 15 trials of *decrease* sexual arousal in response to erotic pictures ('Sex-Down').

Scan protocol

Imaging was carried out on a 3 T Philips Achieva MRI scanner (Philips, Best, The Netherlands), using a 32-channel SENSE head coil. A standard T1-weighted structural volume and a high resolution gradient echo EPI scan were acquired for registration purposes. For fMRI during the emotion regulation task, T2*-weighted gradient echo planar images (EPI) sensitive to BOLD contrast were obtained in the axial direction (echo time 30 ms, flip angle 80°, isotropic voxels of 2.75 mm, 0.25 mm slice gap, 38 slices, repetition time 2.2 s).

Procedure

All participants arrived in the morning at either 08:00 h, or 09:15 h. The arrival time of the participants was balanced between and within stress and control condition, to keep morning cortisol levels as even as possible over groups. After informed consent was given, and the participants changed into the obligatory hospital clothing, the TSST protocol started with instructions (i.e., to prepare a presentation). After 10 min preparation time, participants were brought to a room, in which the committee was seated, and the TSST protocol was continued for 10 min (Kirschbaum et al., 1993; see Oei et al., 2014 for

detailed TSST-procedure). After the TSST, the participants were brought to the scanner, in which the emotion regulation task was delivered, approximately 20 min after the end of the TSST. The emotion regulation task was preceded by two other scanner tasks and structural scans. Saliva was sampled at four times: immediately before TSST instructions (“baseline”) and after the preparation phase of the TSST (“pre-speech”), at the end of the TSST, just before entering the scanner (“post-TSST”), and immediately after the scan procedure (“post-scan”). Blood pressure, heart rate and subjective stress were sampled at the same time points. After scanning, participants filled out questionnaires, and completed an exit interview. Thereafter, a debriefing regarding the TSST followed. Participants were thanked and received financial compensation for their participation.

Data processing and analysis

Physiological data and subjective ratings of stress Cortisol samples, blood pressure, heart rate and subjective stress were analyzed with repeated measures (RM) ANOVAs, and independent *t*-tests performed at baseline, after stress, and after scanning. Greenhouse- Geisser correction was applied when appropriate.

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied; motion correction; non-brain removal; spatial smoothing using a Gaussian kernel of FWHM 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $s = 25.0s$). Time-series statistical analysis was carried out with local autocorrelation correction. FMRI EPI data were registered to the high resolution EPI scan of each participant, which was registered to the individual T1-weighted structural scan, which was registered to the MNI-152 standard space template. Six explanatory variables (EV) were

included in the general linear model: the 4 target categories, neutral - no modified emotional response (Neutral-Equal), sexual - no modified emotional response (Sex-Equal), sexual - increased emotional response (Sex-Up), sexual - decreased emotional response (Sex-Down), and 'Rating' and 'Instruction', each time-locked to the target onset. Each EV was convolved with a double gamma hemodynamic response function. Contrasts of interest were Sex-Down versus Sex-Equal and Sex-Down versus Neutral-Equal. For whole brain analysis, the images of contrasts of parameter estimates and corresponding variances were fed into a higher-level mixed effects analysis, carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) with automatic outlier detection. To determine main task effects, irrespective of condition assignment, a one-sample *t*-test was done. Herein, whole brain *Z* (Gaussianised *T*) statistic images were thresholded by an initial cluster-forming threshold of $Z > 2.3$ and a (corrected) cluster significance threshold of $p = .05$.

Subsequently, to investigate the effects of Condition (Stress vs Control) we focused on ROIs for which a role in sexual arousal, emotion regulation and inhibitory control in relation to urges has been demonstrated before, and which were a priori hypothesized to be affected by stress, i.e. the NAc (Stoléru et al., 2012; Oei et al., 2014), amygdala (Hamann et al., 2004; Oei et al., 2012b), dorsal ACC (Shenhav, Botvinick & Cohen, 2013), the MFG (Ochsner et al., 2012) the right IFG pars triangularis (Aron et al., 2007; Aron, Robbins & Poldrack, 2014; Hampshire et al., 2010), and OFC (Banks et al., 2007). *Z* (Gaussianised *T*/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = .05$ (Worsley 2001). The binarized images of the NAc and amygdala from the Harvard-Oxford Subcortical Probability Atlas were used as anatomical masks, set at a probability of 50%. Likewise, the binarized images of the OFC, MFG and IFG pars triangularis from the Harvard-Oxford Cortical Probability Atlas were used as anatomical masks, also set at a probability of 50%. For the dorsal ACC, an

atlas-based mask was made, removing the subgenual part of the ACC at MNI coordinate $y = 32$ (McCormick et al, 2006). In case the ROI analyses yielded significant differences between the two conditions, correlation analyses were performed between Featquery zstats of the a-priori defined ROIs and subjective ratings of successful implementation of the cognitive regulatory strategies. Correlation analyses were performed using IBM SPSS statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

10.3 Results

One participant was discarded in the analysis because of acute personal stress that he reported at arrival (initial stress was accompanied by extreme baseline salivary cortisol levels >50 nmol/L). One participant was excluded due to significant movement in the scanner. Both were from the control condition. The final sample thus consisted of 38 participants; 18 control participants (mean age 21.50 ± 2.90 years) and 20 participants who were exposed to psychosocial stress (mean age 22.42 ± 3.25 years). The stress and control condition did not differ in terms of age, BMI, psychoneuroticism as assessed with the Symptom Checklist-90, the sensitivity of two motivational systems (i.e. the appetitive and aversive system) as assessed with the Behavioral Inhibition Behavioral Activation Scales, BIS/BAS (Carver & White, 1994), and baseline heart rate, blood pressure or cortisol (see Oei et al., 2014). Although participants in both conditions scored within the normal range on the Sexual Inhibition (SIS) & Sexual Excitation Scale (SES) (Janssen et al., 2002a,b), the conditions differed in individual propensities to become sexually aroused and to be sexually inhibited (SIS1 [threat of performance failure], control condition: 36.61 ± 2.55 ; stress condition 36.53 ± 3.20 , $p = .93$; SIS2 [threat of negative consequences], control condition 27.89 ± 3.16 ; stress condition 25.42 ± 2.81 , $t(35) = 2.51$, $p < .02$; SES, control condition 50.94 ± 4.43 ; stress condition 45.89 ± 4.89 , $t(35) = 3.28$, $p < .01$). The control condition reported a higher propensity

to become sexually aroused and to be sexually inhibited compared to the stress condition.

Stress induction

For a detailed description of all physiological measures see Oei et al. (2014). A significant Group by Time interaction showed that the TSST led to significant increases in cortisol levels (directly after TSST, $t(34) = -2.02, p = .05$), higher heart rates, $F(3, 96) = 3.87, p = .01$, blood pressure, $t(35) = -2.12, p = .04$, and subjective stress, $t(35) = -4.99, p < .001$.

Emotion Regulation Task

Means and standard deviations of subjective ratings of successful instruction completion are shown in Table 1. Regarding the sexual stimuli, there were no differences in ratings of how well they were able to regulate in accordance with the instructions, between the stress condition and the control condition, all $ps > .50$. However, men in the stress condition declared they did better at not-modifying emotional response towards neutral pictures (Neutral-Equal), compared to men in the control condition.

	Neutral-Equal		Sex-Equal		Sex-Down	
	M	SD	M	SD	M	SD
Control	3.41	0.33	2.98	0.28	2.88	0.32
Stress	3.77*	0.17	3.07	0.47	2.91	0.45

Table 1. Means (*M*) and standard deviations (*SD*) of the ratings of successful emotion regulation completion. Notes: Neutral-Equal: neutral pictures, instruction was do not modify emotional response; Sex-Equal: sexual explicit pictures, instruction was do not modify emotional response; Sex-Down: sexual explicit pictures, instruction was to reappraise the emotional value of the images in order to decrease the emotional impact. * $t(36) = -4.10, p < .001$.

Main effects of task

It was expected that activation within reward related structures, such as the NAc and amygdala would decrease during down-regulation of sexual arousal, while activation in frontal control areas would increase. Significant clusters in the contrasts of interest and local maxima are presented in Table 2.

In the contrast Sex-Down vs Sex-Equal four significantly activated clusters were found, with mainly activations in frontal structures. One cluster had its peak activation in the left OFC, with local maxima in the left IFG pars opercularis, temporal pole and frontal operculum cortex (see Figure 2). Other clusters were located in the left precentral gyrus, right lateral occipital cortex and left superior frontal gyrus with a local maximum in the left ACC.

In the Sex-Down vs Neutral-Equal contrast only one cluster was found with its peak activation in the left lateral occipital cortex, encompassing bilateral OFC, bilateral caudate and left thalamus.

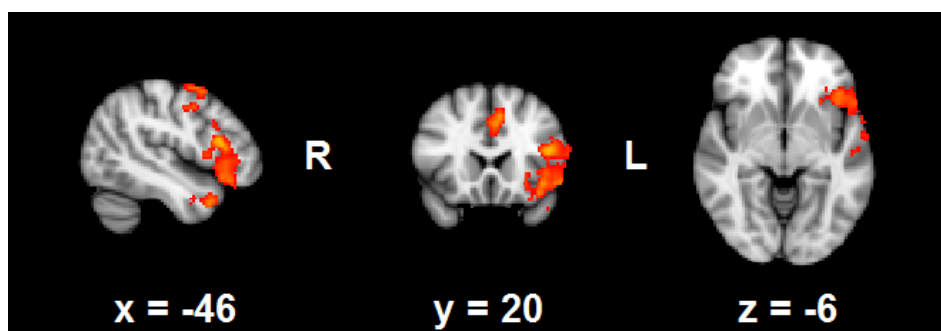


Figure 2. Main effects of the contrast Sex-Down vs. Sex-Equal. Note: (a) Sagittal, (b) coronal and (c) axial view of clusters of voxels ($Z > 2.3$, $p = .05$, cluster-corrected) when contrasting Sex-Down vs Sex-Equal (MNI coordinates, $x, y, z = -46, 20, -6$). Intensity values in this thresholded zstat map range from 2.3 (red) to 5 (yellow). Voxel size = 2 mm³ in standard space.

Region	Cluster Size	L/R	x	y	z	Z	P
• Local maxima							
Sex-Down > Sex-Equal							
Orbital frontal cortex	2412	L	-40	24	-10	4.51	<.001
• Inferior frontal gyrus		L	-46	20	16	4.31	
• Temporal pole		L	-48	12	-32	4.16	
• Frontal operculum cortex		L	-38	26	0	4.12	
Superior frontal gyrus	1027	L	-2	10	56	5.40	<.001
• Juxtapositional lobule cortex		L	-2	4	62	4.60	
• Paracingulate gyrus		L	-4	22	38	3.89	
• ACC		L	0	22	26	2.46	
Precentral gyrus	542	L	-52	0	50	4.34	.001
• Middle frontal gyrus		L	-38	4	52	3.05	
Lateral occipital cortex	413	R	44	-70	18	3.99	.004
Sex-Down > Neutral-Equal							
Lateral occipital cortex	54435	L	-42	-82	-2	8.61	<.001
• Orbital frontal cortex		R	34	22	-14	4.46	
• Orbital frontal cortex		L	-34	26	-4	4.94	
• Caudate		R	10	10	4	4.54	
• Caudate		L	-14	10	1	4.61	
• Thalamus		L	-16	-32	0	4.47	

Table 2. Cluster list of significant main effects and local maxima. Note: $Z > 2.3$, $p = .05$, cluster corrected. L/R = Left/right in the brain; X, Y, Z = mni coordinates. Voxel size is 2 mm isotropic.

ROI-analyses

To investigate if acute stress affected the ability to down-regulate sexual arousal, independent ROI-analyses were performed in the NAc, amygdala, dorsal ACC, OFC, MFG and IFG triangularis ($p < .05$, voxel corrected). It was hypothesized that acute stress would affect the down-regulation of sexual arousal by increasing activations in ventral affective brain areas, such as NAc

and amygdala (Oei et al., 2012), while leading to decreased activation in dorsolateral frontal areas such as the MFG. Significant differences in activation between conditions were found for the Sex-Down > Sex-Equal contrast in the right amygdala ($p < .02$), right dorsal ACC ($p < .04$), and right IFG pars triangularis ($p < .03$), with the stress condition demonstrating higher activation in these structures (see Figure 3). There were no significant differences between conditions in activation in NAc, OFC or MFG during the down-regulation of sexual arousal.

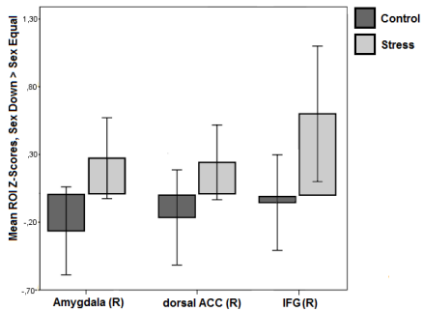


Figure 3. Mean ROI Z-scores (with standard error bars) for the contrast Sex Down vs. Sex Equal for the control and stress condition in the right amygdala, right dorsal ACC and right inferior frontal gyrus (IFG) pars triangularis.

Correlational analyses

To further explore the significant differences between the stress and control condition in down-regulation of sexual arousal, zstats extracted from the right IFG, right amygdala and right dorsal ACC ROIs using Featquery were correlated with the participants' ratings of the ability to regulate sexual arousal. Because the right IFG pars triangularis is known to be involved in successful inhibition of emotion (Aron, Robbins & Poldrack, 2014; Grecucci et al., 2013), it was hypothesized that enhanced activation in the right IFG pars triangularis

would correlate with the perceived ability to down-regulate sexual arousal elicited by the sexual stimuli. For participants in the control condition, activity in the right IFG pars triangularis did not correlate to the ratings of successful down-regulation of sexual arousal, $p = .43$, whereas for participants in the stress condition, activity in the right IFG pars triangularis was significantly correlated to the ratings of successful down-regulation of sexual arousal ($r = .46$, $p < .05$; and when controlled for Neutral ratings $r = .48$, $p < .04$), see Figure 4. Likewise, correlational analyses were performed for the right amygdala and right dorsal ACC, but no significant correlations could be observed (all p s $> .13$).

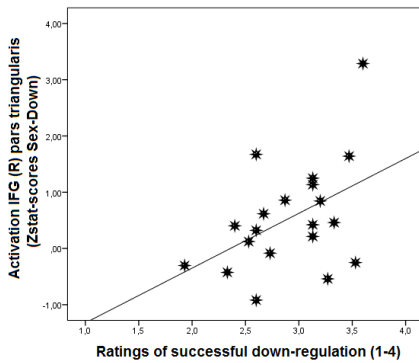


Figure 4. Scatter plot depicting that in the stress condition, greater activation in the right inferior frontal gyrus (IFG) pars triangularis in the contrast Sex-Down significantly correlated with reported greater sexual arousal down-regulation success ($r = .45$, $p < .05$).

10.4. Discussion

The present study investigated the effects of acute stress on the down-regulation of sexual arousal. The results presented here, accord well with previous neuroimaging studies on down-regulation of sexual arousal (Beauregard et al., 2001) and ER in general (Beauregard, 2007; Frank et al.,

2014; Ochsner, 2004; Phan et al., 2005), and extends these previous studies, exploring for the first time whether acute stress modulates brain responses during down-regulation of sexual arousal. First, when participants were instructed to down-regulate sexual arousal, increased neural activation was seen in frontal structures such as the IFG, superior frontal gyrus and frontal pole, and no activity was seen within reward related structures such as the NAc and amygdala. Crucially, acute stress increased activity in the right amygdala, right IFG and right dorsal ACC during the down-regulation of sexual arousal. Moreover, in stressed participants, activity in the right IFG correlated with the perceived ability to down-regulate sexual arousal elicited by the sexual pictures.

Like expected, our data suggest that stress has an impact on the down-regulation of sexual arousal. Although research has shown reduced amygdala activity during cognitive down-regulation (Frank et al., 2014; Kanske et al., 2011; Kim & Hamann, 2007; Ochsner et al., 2004; Townsend et al., 2013) in the present study, acute stress increased activity in the right amygdala during down-regulation of sexual arousal (compared to just watching sexual stimuli). This corroborates research that has demonstrated exaggerated amygdala response under stress (Oei et al., 2012b). This shift of amygdala function toward heightened sensitivity under stress may represent a state of indiscriminate hypervigilance and may correspond to broader dimensions of information processing (e.g. salience, significance, ambiguity, unpredictability, etc.), and may not map specifically onto emotion (Pessoa & Adolphs, 2010, 2011). Although this represents initial survival value in situations where the risk for false negatives in the detection of potential threats should be minimized, speculatively, it might similarly play a role in the development of disorders in sexual motivation, such as hypersexuality. For instance, several studies have demonstrated that activity in the ventral striatum (e.g. NAc) is associated with sexual risk behaviours over time in young adults (Demos et al., 2012; Victor et al., 2015), but results from the study by Victor et al. (2015) suggest that the

expression of ventral striatum-associated sexual risk behaviour is moderated by the magnitude of amygdala activity, especially in men. They found that increased ventral striatum activity is associated with a greater number of sexual partners over time, only in the context of relatively decreased amygdala activity. Speculatively, increased reward sensitivity in combination with low amygdala activity could translate in a heightened drive to pursue immediate (sexual) rewards, but in absence of the ability to recognize and avoid threat. Additionally, individuals who frequently encounter sexual rewarding stimuli when under stress would run the risk of amplified incentive salience of rewards and ultimately addictions (Robinson & Berridge, 1993; Oei et al., 2014). The finding that exposure to acute stress impacts the functional integrity of the PFC (Arnsten, 2009; Arnsten, Wang & Paspalas, 2012), and has deleterious effects on the successful execution of ER (Arnsten, 2009; Raio et al., 2013) may further compromise the ability to regulate sexual arousal in men. However, to date, no controlled experimental studies have investigated emotion down-regulation and functional connectivity in subjects with hypersexuality, which could elucidate trait-level dysfunction in suggested key neural circuitry. The current study did not investigate if the activity in the ventral striatum was also associated with sexual risk behaviour, and whether this was moderated by the magnitude of amygdala activity, but recent research from our lab demonstrated that acute stress-induced cortisol elevations mediate NAc activity during the subconscious processing of sexual stimuli (Oei et al., 2014) and that high stress-induced cortisol responses were negatively correlated with amygdala responses during emotional inhibition (Oei et al., 2012b). Although no differences were seen in activity in the NAc between control and stressed participants in the present study (but see Oei et al., 2014), the above suggest that individuals with a certain phenotype (increased NAc activity as a result of high stress induced cortisol, in combination with low amygdala activity) may be vulnerable for

developing problematic sexual behaviour. However, as has become clear, more research is warranted.

It is thought that ventrolateral PFC dysfunction may explain the failure to modulate or inhibit limbic regions underlying affect, including the amygdala. The right IFG pars triangularis is known for stopping action, and to be specific, for stopping action tendencies (Aron, Robbins & Poldrack, 2014). Results from the present study might point at the contribution of the ventrolateral PFC in controlling sexual arousal. Sexual stimuli evoke automatic (approach) responses, and the right IFG pars triangularis might be involved in suppressing these tendencies (Both et al., 2005; Dekker & Everaerd, 1989; Lang, 1971), especially when this suppressing is further compromised by the induction of stress. Results from the correlational analyses suggest that, speculatively, additional right IFG pars triangularis resources were specifically recruited as the acute-stress induction costs for providing top-down control of sexual arousal increased. However, another explanation might be that this enhanced right IFG activation may reflect increased emotional coping mechanisms, as a result of high stress (Anderson, 1976; Yuen et al., 2009).

Research has shown that dorsal regions of the ACC are involved in appraisal and expression of negative emotion, but also in reward-based decision making (Bush et al., 2002; Etkin, Egner & Kalisch, 2011). Moreover, the dorsal ACC has strong interconnections with lateral PFC (Bush, Luu & Posner, 2000). Therefore, the enhanced recruitment of the dorsal ACC in the stress condition while down-regulating sexual arousal may reflect the guidance of behaviour by evaluating motivation and encoding reward values, which may then influence attention allocation, and even motor preparation and motor responses (Bush et al., 2002).

Although this study highlights the potential deleterious effect of acute stress in controlling sexual arousal, there are some limitations of this study that must be considered before definitive inferences can be made. First, an

important caveat to consider when interpreting these findings is that on each trial subjective and physiological sexual desire or arousal was not assessed directly and assessment of regulation success was limited to self-report. Therefore, firm conclusions about patterns of brain activation and actual levels of sexual arousal and desire cannot be drawn. Second, the current study sample only comprised of healthy sexually functional men. Therefore, we can only speculate about the suggested key neural circuitry involved in hypersexual behaviours. Moreover, research suggests that men and women may differ in their ability to regulate emotions (Whittle, 2011), including sexual arousal (Brom et al., 2015). Since, imaging studies in women on the regulation of sexual arousal are lacking in the literature, future research on the influence of stress on the regulation of sexual arousal in women is warranted. Moreover, the present study only investigated the reappraisal strategy. Different strategies, including attentional control (e.g. distraction) may be adopted to achieve successful emotion down-regulation. Therefore, the effect of the emotional down-regulatory strategy in the present study does not reflect the complexities of the emotion regulation repertoire (Aldao, 2013).

Clinically, these data might imply that if patients with hypersexuality are impaired in the ability to suppress the impact of sexual material, this might reflect a decreased ability -at least in some patients- of the ventrolateral PFC to suppress a pathological increased NAc response to sexual stimuli as a result of experienced stress in combination with a relatively decreased amygdala activity (Demos et al., 2012; Oei et al., 2014; Victor et al., 2015). Stress has been related to an increased vulnerability to develop drug intake or relapse (Sinha, 2008). This makes clear that future studies using the current tasks should explore possible deficits in this proposed neural circuitry in patients with substance use disorders or sexual addiction. Nevertheless, targeting the effects of stress on the regulation of sexual arousal might be helpful in predicting individual susceptibility to relapse. Furthering our understanding of how stress may impair

ER may lead to better interventions that foster resistance to stress-induced regulatory impairments and offer better treatment options for clinical populations.

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