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The stress connection: Neuroimaging studies of emotion circuits in social stress, personality, and stress-related psychopathology

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CHAPTER 2

Stress shifts brain activation towards ventral affective areas during emotional distraction

Oei, N. Y. L., **Veer, I. M.**, Wolf, O. T., Spinhoven, P., Rombouts, S. A. R. B., & Elzinga, B. M. (2012). *Social Cognitive & Affective Neuroscience*, 7(4), 403-412.

ABSTRACT

Acute stress has been shown to impair working memory (WM), and to decrease prefrontal activation during WM in healthy humans. Stress also enhances amygdala responses towards emotional stimuli. Stress might thus be specifically detrimental to WM when one is distracted by emotional stimuli. Usually, emotional stimuli presented as distracters in a WM task slow down performance, while evoking more activation in ventral “affective” brain areas, and a relative deactivation in dorsal “executive” areas. We hypothesized that after acute social stress, this reciprocal dorsal–ventral pattern would be shifted towards greater increase of ventral “affective” activation during emotional distraction, while impairing WM performance. To investigate this, 34 healthy men, randomly assigned to a social stress or control condition, performed a Sternberg WM task with emotional and neutral distracters inside an MRI scanner. Results showed that WM performance after stress tended to be slower during emotional distraction. Brain activation during emotional distraction was enhanced in ventral affective areas, while dorsal executive areas tended to show less deactivation after stress. These results suggest that acute stress shifts priority towards processing of emotionally significant stimuli, at the cost of WM performance.

INTRODUCTION

Several studies in healthy humans showed that acute stress and stress hormones, catecholamines and glucocorticoids (GC), impair working memory (WM) (Arnsten, 2009; Luethi et al., 2008; Lupien et al., 1999; Oei et al., 2006; Ramos & Arnsten, 2007; Schoofs et al., 2008). WM is the ability to maintain relevant information in mind and to keep irrelevant information out of mind. Stress might be especially detrimental to WM by decreasing one's ability to keep irrelevant emotional information out of mind, because stress heightens the sensitivity towards potentially threatening stimuli (van Marle et al., 2009), while also compromising the efficiency of conscious effortful information processing by decreasing prefrontal activation during WM performance (Qin et al., 2009). The present study was, therefore, aimed at examining whether acute social stress enhances emotional distraction during WM, and at investigating the stress-induced changes in the underlying neural patterns, using functional magnetic resonance imaging (fMRI).

The preferential processing of emotional cues is considered adaptive, as these are likely to be important for our survival. Accordingly, healthy humans under stress-free circumstances attend to emotional stimuli, even when these are irrelevant to the WM task at hand, and consequently perform poorer at WM (e.g. Kensinger & Corkin, 2003). At the neural level, several studies found an antagonistic relationship between neural activations associated with emotional vs. executive processing, revealing that 'affective processing' is favored over 'executive processing' (Drevets & Raichle, 1998). When comparing neutral vs. emotional distracters in a WM task, ventral 'affective' brain areas, such as the inferior frontal gyrus (IFG) and amygdala show increased activation, along with a deactivation of more dorsal 'executive' brain areas, such as parietal regions and the right dorsolateral prefrontal cortex (DLPFC) (Anticevic, Repovs, & Barch, 2010; Dolcos & McCarthy, 2006; Mitchell et al., 2008; Morey et al., 2009; Perlstein, Elbert, & Stenger, 2002).

Attending to emotional stimuli becomes maladaptive when one is biased towards negative cues, and/or unable to disengage from negative information that is unrelated to the task, which is frequently observed in stress-related psychiatric disor-

ders such as post-traumatic stress disorder (PTSD). PTSD, which presumably is precipitated by acute traumatic stress, is associated with an over responsive amygdala and impaired prefrontal function (Elzinga & Bremner, 2002; Shin, Rauch, & Pitman, 2006). Recently, in a task combining emotional and executive processing (Morey et al., 2009) evidence for an imbalance in the interaction between ventral affective and dorsal executive brain areas was found in PTSD patients. PTSD patients showed higher activation in ventral affective brain regions, which was positively related to PTSD symptom severity, and, conversely, to higher activity in frontoparietal brain regions with lower PTSD symptom severity.

Although the acute stress response in healthy individuals is considered adaptive (de Kloet, Oitzl, & Joëls, 1999), its (temporary) effect on the brain shows similarities with PTSD, as even acute mild psychological stress impairs prefrontal cortex (PFC) function (Arnsten, 2009; Elzinga & Roelofs, 2005; Oei et al., 2006; Qin et al., 2009; Ramos & Arnsten, 2007; Schoofs et al., 2008), and heightens the sensitivity of the amygdala towards threatening stimuli (van Marle et al., 2009). We therefore expected that acute social stress would impair WM performance compared with a control condition, especially when distracters are emotional. We further hypothesized that the social stress would lead to an alteration in the reciprocal dorsal–ventral pattern during emotional distraction, with increased activations in ventral ‘affective’ brain areas compared with a non-stressful control condition. To examine our hypothesis, we analyzed behavioral performance and dorsal and ventral a priori selected regions of interest (ROIs) implicated in emotional distraction during WM (*dorsal system*: right DLPFC and bilateral parietal regions; *ventral system*: bilateral IFG and right amygdala) in previous studies (i.e., Dolcos & McCarthy, 2006; Dolcos, Kragel, Wang, & McCarthy, 2006; Mitchell et al., 2008). We also explored the role of GCs (salivary cortisol) in relation to behavioral performance and neural responses during distraction.

METHODS

PARTICIPANTS

Male volunteers from the general population were recruited by means of advertisements. Eligibility criteria were: no history of disease or chronic disease requiring medical attention, no dyslexia, no color blindness, no current use of prescribed medication or the use of remedies containing corticosteroids, no use of psychotropic drugs, no current or past psychiatric problems, determined by the Amsterdam Biographical interview (ABV; de Wilde, 1963). The Dutch version of the Symptom checklist (SCL-90) (Arrindell & Ettema, 1986) was used to assess psychoneuroticism (the cut-off score for exclusion was 145, following norm scores for a healthy population), the Dutch version of the Beck Depression Inventory, using a cut-off score for exclusion of > 10 (BDI; Bouman, Luteijn, Albersnagel, & Ploeg, 1985). Furthermore, a body mass index (BMI; kg/m²) between 19 and 26, an age between 18 and 35 years, and right-handedness was required. Lastly, participants were required to have a total IQ score of > 90, determined by the relevant subtests of the Wechsler Adult intelligence Scale-III (WAIS-III; Wechsler, 1997).

Altogether, 40 healthy male participants were included in the present study and randomly assigned to an experimental and a control group in a randomized two-group design. From this sample two participants with IQs lower than 90 were excluded from analyses in the present study. Four other participants were excluded from the analyses: two participants were outliers because of extreme cortisol levels at baseline, probably reflecting saliva sample contamination or an acute infectious disease (one from stress group, 120 nmol/l; one from the control group, 36 nmol/l). Data from one participant from the stress group could not be collected because of a computer failure. One other participant from the control group was a multivariate outlier with regard to task performance. Each participant gave signed informed consent in which confidentiality, anonymity, and the opportunity to withdraw without penalty were assured.

The study was approved by the Medical Ethics Committee of the Leiden University Medical Center and carried out according to the standards of the Declaration of Helsinki (2000).

MATERIALS

To ascertain that no pre-stress differences between groups existed on intelligence and WM performance, the subscales Picture Completion, Arithmetic, Information, Block Design, of the WAIS-III (Wechsler, 1997) were used to estimate total IQ (TIQ), while Arithmetic, Digit span and Numbers and Letters were used to assess WM Index (WMI). Also state and trait anxiety (State-Trait Anxiety Inventory, STAI; Spielberger, 1983) was assessed.

Emotional Sternberg task

WM was measured using an adapted version of the Sternberg item-recognition task (Sternberg, 1966), developed and described by Oei et al. (2009). In the present version, the task consisted of a total of 180 trials, which lasted not longer than 25 min. Half of the trials were of low load (i.e., comparison load 4) and the other half of high load (comparison load 16). Comparison load was defined by the number of targets (1 or 4) to hold in WM, multiplied by the number of stimuli (4) in the item-recognition display. Comparison load 16 (4:4; target:recognition display) means that four targets (e.g., RZAS) have to be held in WM while there are four stimuli on the item-recognition display (e.g., CDMA), leading to 16 possible comparisons to perform before answering (i.e., RC-RD-RM-RA-ZC-ZD-ZM-ZA-SC-SD-SA-SM-AC-AD-AM-AA, etc.). Each trial started with a blue fixation cross (500 ms), followed by the target presentation (1000 ms), a distracter (1500 ms) and a recognition display (< 2000 ms) (see **Figure 2.1**). Random jitter in between trials ranged from 1500 to 4500 ms. Participants were instructed to ignore the distracter pictures, and to fixate their eyes on a red cross centered in each distracter. The target letter then had to be recognized from four letters in a recognition display. Participants pressed a 'yes' button indicating they had recognized a target, or a 'no' button, when no target letter was present. A target was present (present-target trials) in half of the trials, in the other half the target was absent (absent-target trials).

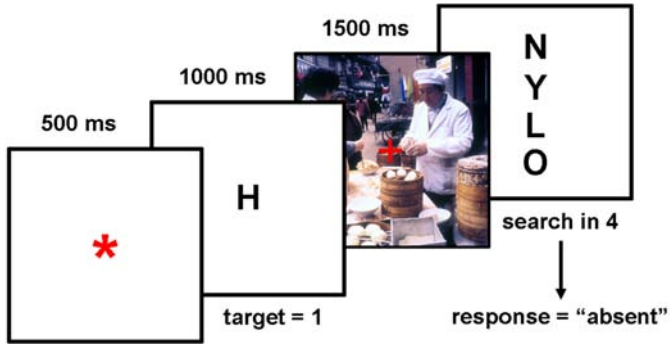


Figure 2.1 Example trial of the Sternberg task with distraction during the delay interval. In this example a low comparison load trial with a neutral distracter is depicted.

Distracters consisted of validated pictures selected from the International Affective Pictures System (IAPS; Lang, Bradley, & Cuthbert, 2008), of which 60 neutral pictures (rated on 9-points Likert scales; valence [1 very negative, 9 very positive]: 5.09 ± 0.54 [$M \pm SD$]; arousal [1 not arousing at all, 9 highly arousing]: 3.21 ± 0.77 [$M \pm SD$]) and 60 negatively arousing pictures (valence: 2.86 ± 0.93 [$M \pm SD$]; arousal: 6.22 ± 0.52 [$M \pm SD$]), that matched in background color and complexity, for example, amount of people or animals in the scene. A third category consisted of scrambled versions of both the neutral and emotional pictures (Dolcos & McCarthy, 2006). Trial order was pseudo-randomized using MATLAB, to optimize independence between regressors (the random generated order was confined by the rule that none of the categories would be presented more than three consecutive times). Task stimuli were 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, Psychology Software Tools) was used for stimulus presentation and recording of responses.

Subjective ratings

After the experiment participants rated all distracters on a 5-point Likert scale for distractibility (1 not distracting at all, 5 highly distracting), whereas arousal (1 not arousing at all, 5 highly arousing) and valence (1 very positive, 5 very negative) were assessed on 5-point Likert scales using the Self-Assessment Manikin (Bradley & Lang, 1994).

Stress induction

To induce stress, the Trier Social Stress Task (TSST) was employed (Kirschbaum, Pirke, & Hellhammer, 1993). The TSST protocol has consistently proven to raise cortisol levels (Kirschbaum & Hellhammer, 1994). This laboratory stressor 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 of three psychologists. One committee member responded to incorrect answers by saying out loud “incorrect, please start over”, while keeping up participant’s performance by means of a clearly visible scoreboard. In the control condition, participants used the same anticipation period of 10 min to think of a movie to their liking, of which they were informed to having to answer open questions on paper for 5 min, in the same laboratory room, but without audience. Thereafter, they had 5 min to count backwards from 50 to 0 at a slow pace.

Physiological assessments

Salivary cortisol was assessed using Salivettes (Sarstedt, Germany). Saliva sampling is a stress-free method to assess unbound cortisol (Kirschbaum & Hellhammer, 1994). Saliva samples were stored at -20 °C until assayed at Professor Kirschbaum’s laboratory (<http://biopsychologie.tu-dresden.de>). Cortisol concentrations in saliva were measured using a commercially available chemiluminescence-immuno-assay kit with high sensitivity (IBL, Hamburg, Germany). Inter- and intra-assay coefficients of variation were below 10 %. 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).

Scan protocol

Imaging was carried out on a 3T Philips Achieva MRI scanner (Philips Healthcare, Best, The Netherlands), using an 8-channel SENSE head coil for radiofrequency reception. For fMRI, T_2^* -weighted gradient-echo echo-planar images (GE-EPI) sensitive to BOLD contrast were obtained with the following acquisition parameters: repetition time (TR) = 2.2 s, echo time (TE) = 30 ms, flip angle = 80° , SENSE factor = 3, 38 axial slices, FOV = 220×220 mm, 2.75 mm isotropic voxels, 0.25 mm slice gap. A high-resolution anatomical image (T_1 -weighted ultra-fast gradient-echo acquisition; TR = 9.75 ms, TE = 4.59 ms, flip angle = 8° , 140 axial slices, FOV = 224×224 mm, in-plane resolution 0.875×0.875 mm, slice thickness = 1.2 mm), and a high-resolution T_2^* -weighted gradient echo EPI scan (TR = 2.2 s, TE = 30 ms, flip angle = 80° , 84 axial slices, FOV = 220×220 mm, in-plane resolution 1.96×1.96 mm, slice thickness = 2 mm) were acquired for registration purposes. The scan procedure consisted of EPI during the emotional WM task (< 25 min), the T_1 -weighted anatomical scan (6 min) and the high-resolution EPI (1 min). Furthermore, DTI and resting-state fMRI scans were acquired at the end of the procedure.

Procedure

Participants were invited on two occasions: The first time for further screening purposes (BDI, SCL-90, STAI, WAIS subtests), and the second time for the scan session. Participants were asked to refrain from caffeine or sugar containing drinks, and not to eat 2 h before arrival time. All participants arrived at either 8.30 a.m. or 10.30 a.m. Arrival time was balanced between and within groups, to keep morning cortisol levels as even as possible. After arrival, participants were given instructions regarding the protocol and the emotional WM task. Thirty minutes after arrival, the TSST protocol started. After the TSST, participant got into the scanner, where the emotional Sternberg task, the structural scan, high resolution EPI, DTI and resting-state scans were measured. Saliva was sampled at five time points: before ('baseline') and after the anticipation phase of the TSST ('pre-speech'), at the end of the TSST ('post-TSST'), after finishing the emotional WM task while still inside the scanner ('post-WM'), and after the scan procedure ('post-scan'). Blood pressure and heart rate were

sampled at all the same time points, except for those inside the scanner room. After scanning, participants were seated in front of a PC, to provide subjective ratings of the distracters on arousal, valence and distractibility. Hereafter, an exit-interview and a debriefing regarding the TSST followed. Participants were thanked and paid for their participation.

DATA PROCESSING AND ANALYSIS

Physiological data

Cortisol, BP, and HR were analyzed using repeated measures (RM) ANOVA, and unpaired *t*-tests.

Task data

Reaction times (RTs) were checked for errors, misses and outliers. Errors and misses were scored and removed. Univariate outliers were replaced by the mean per load by distracter type + 2 *SD*. Mahalanobis distance was calculated to check for multivariate outliers ($p[D^2] < .05$). RTs of correct trials were analyzed using RM ANOVAs, with as between-subjects factor Group (stress/control), and as within-subjects factors Target (present/absent), Load (high/low), and Distracter (emotional/neutral). Errors were analyzed similarly. Follow-up analysis of RM ANOVA effects, if relevant, was done with *t*-tests. Greenhouse–Geisser corrections were applied when the sphericity assumption was not met. SPSS Version 16.0 (SPSS Inc.) was used for the analyses.

FMRI data

FMRI data processing was carried out using FMRI Expert Analysis Tool (FEAT) Version 4.1, part of (FMRIBs Software Library [FSL], www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). The following pre-statistics processing was applied: motion correction (Jenkinson, Bannister, Brady, & Smith, 2002); non-brain removal (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 8mm; grand-mean intensity normalization of the entire 4D data set by a single multiplicative factor; high-

pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma = 50.0$ s). Time-series statistical analysis was carried out with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). FMRI EPI data were registered to the high resolution EPI scan of each participant, which was registered to the individual T_1 -weighted structural scan, which was registered to the 2 mm MNI-152 standard space template (Jenkinson et al., 2002; Jenkinson & Smith, 2001). For each participant, eight explanatory variables (EVs) were included in the general linear model: Six EVs describing the period between target onset and distracter offset (total length 2.5 s), separate for Load (low/high) \times Distracter type (Neu/Emo/Scr), on correct trials. Target-recognition periods on correct trials were modeled in one EV, independent of load or preceding distracter type, with variable durations depending on the response times of the participants. A last EV was included describing error trials, modeling the entire trial from target onset to target-recognition response.

Each EV was convolved with a double gamma hemodynamic response function to account for the hemodynamic response. The images of contrasts of parameter estimates and corresponding variances were then fed into a higher level mixed effects analysis, carried out with FMRIBs Local Analysis of Mixed Effects (FLAME) (Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). The significance level of the z -statistic image of the contrast of interest (Emo > Neu) was set to $p < .001$ ($z > 3.1$, uncorrected). Before further analysis, the whole-brain activation map, consisting of all participants, was used to select ROIs, defined as clusters of significantly activated contiguous voxels in the four a priori chosen ROIs involved in coping with emotional distraction, that is, the right amygdala, bilateral IFG, right dorsolateral PFC, and bilateral parietal lobe (Dolcos et al., 2006; Dolcos & McCarthy, 2006; Mitchell et al., 2008). These activated clusters were further confined within boundaries of preselected atlas-based ROIs (from the anatomical Harvard–Oxford cortical probability atlas, with the exception of the right amygdala, which was confined by boundaries from the Harvard–Oxford subcortical probability atlas). Then, from these ROIs, parameter estimates (PE) were extracted (Emo and Neu at both Low and High Load) with zero determined by each individual’s implicit baseline (Poldrack, 2007). Then, to examine whether stress modulated

the specific pattern of more activity in ventral areas, and less activity in dorsal areas during emotional distraction, and the differential (interaction) effects of Load and Distracter, a RM ANOVA was performed on the percentage change of the MR signal (PE/implicit baseline \times 100) in the regions of interest, with as within-subjects factors neural system (dorsal/ventral), Load (low/high), Distracter type (neutral/emotional), and Group (stress/control) as between-subjects factor.

RESULTS

There were no significant differences in the remaining groups with regard to Age, BMI, BDI, SCL-90, Total IQ, WMI, and state anxiety, although trait anxiety showed a trend towards higher anxiety in the stress group (see **Table 2.1** for means and standard deviations).

Table 2.1 Means (*M*) and standard deviations (*SD*) of subject variables in stress and control group

	Control	Stress	<i>F</i> (1, 33)	<i>p</i>
	<i>M</i> \pm <i>SD</i>	<i>M</i> \pm <i>SD</i>		
Age	24.00 \pm 2.62	24.47 \pm 4.13	0.16	.69
BMI	22.70 \pm 1.55	22.29 \pm 2.56	0.32	.57
BDI	2.71 \pm 3.53	3.53 \pm 3.61	0.45	.51
SCL-90	103.24 \pm 16.78	104.82 \pm 11.51	0.10	.75
STAI-trait	29.82 \pm 6.78	34.06 \pm 7.45	3.01	.09
STAI-state	29.76 \pm 6.24	32.47 \pm 7.32	1.34	.26
TIQ	113.35 \pm 14.66	114.00 \pm 15.30	0.02	.90
WMI	114.47 \pm 13.39	109.41 \pm 10.13	1.54	.22

Note: BMI = body mass index; BDI = Beck Depression Inventory; SCL-90 = Symptom Checklist-90; STAI-trait= Trait version of the State-Trait anxiety index; TIQ = Total Intelligence Quotient; WMI = Working memory index.

Social stress and emotional working memory

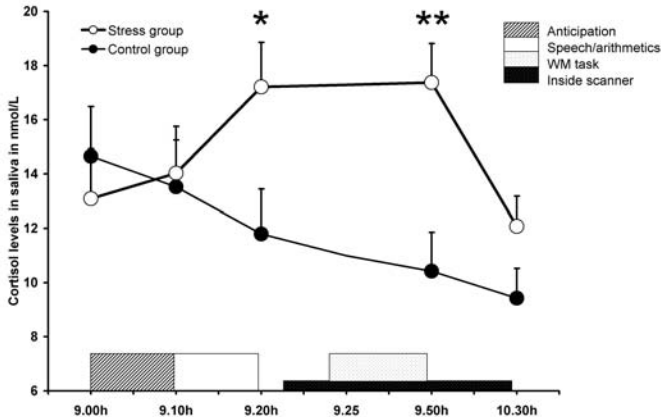


Figure 2.2 Mean levels of cortisol in saliva and standard errors in the stress and control group. Note: significant difference between groups, * $p < .05$, ** $p < .005$

Stress induction

As expected, the stress induction raised the cortisol levels in the stress group, as evidenced by a Group-by-Time interaction, $F(1.81, 57.83) = 6.95$, $p = .003$ (see **Figure 2.2**). Follow-up t -tests showed that the groups did not differ at baseline, $t(32) = 0.59$, $p = .55$, while right after the stress induction, cortisol levels were significantly higher in the stress group compared with the control group $t(32) = -2.32$, $p = .027$. After the task, cortisol levels were still higher in the stress group, $t(32) = -3.42$, $p = .002$. The between-subjects factor Group was not significant, $F(1, 32) = 2.19$, $p = .15$.

Heart rate

There were no significant differences between groups in heart rate (all $ps > .05$).

Blood pressure

There were significant within-subjects effects of Time on systolic (SBP), $F(3, 96) = 9.11$, $p < .001$, and diastolic blood pressure (DBP), $F(3, 96) = 8.64$, $p < .001$, as well as of Condition-by-Time on SBP, $F(3, 96) = 12.52$, $p < .001$, and DBP, $F(3, 96) =$

8.00, $p < .001$. After the stress-induction SBP and DBP were significantly higher in the stress group than the control group, $t(32) = -3.09$, $p = .004$, and $t(32) = -4.70$, $p < .001$, respectively. There was also a significant between-groups effect of DBP, $F(1, 32) = 6.56$, $p < .02$, with a higher mean in the stress group ($M = 79.25$, $SE = 1.79$) than in the control group ($M = 72.75$, $SE = 1.79$).

Emotional WM performance

See means and standard deviations of RTs in **Table 2.2**. Within subjects, RTs were faster at low load compared with high load, at present vs. absent target trials, and when the distracter was neutral vs. emotional (all $ps < .001$). Overall, the stress group tended to be slower than the control group, $F(1, 32) = 3.66$, $p = .06$. Group, Target, and Distracter interacted at trend levels, $F(1, 32) = 3.61$, $p = .07$. Post hoc t -tests showed that during present-target trials, the stress group was slower than controls when distracters were emotional, $t(32) = -2.03$, $p = .05$, but not when they were neutral, $t(32) = -1.65$, $p = .11$ (**Figure 2.3**). In the control group, there was no significant difference in RTs between neutral and emotional trials. There were also no differences during absent-target trials.

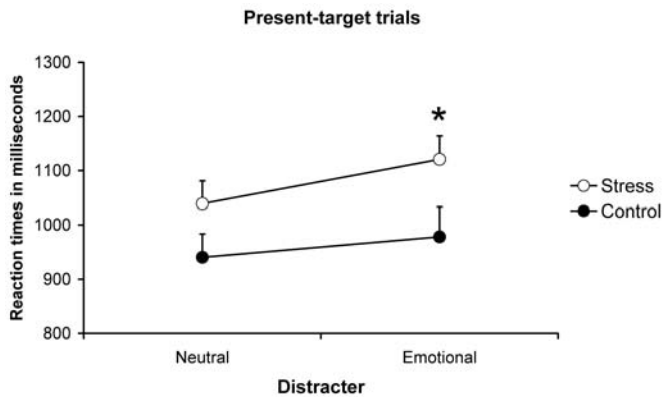


Figure 2.3 Present-target trials: Mean RTs (and SE 's) in emotional and neutral trials of the stress- and control group. * $p < .05$.

Social stress and emotional working memory

Table 2.2 Means (*M*) and standard deviations (*SD*) of reaction times and errors on the emotional Sternberg task in the stress and control group.

		Control		Stress	
Target		Present	Absent	Present	Absent
		<i>M</i> ± <i>SD</i>	<i>M</i> ± <i>SD</i>	<i>M</i> ± <i>SD</i>	<i>M</i> ± <i>SD</i>
Load	Distracter	Reaction times			
Low	Emo	784.10 ± 180.74	794.50 ± 220.72	949.40 ± 202.67	943.00 ± 183.97
	Neu	736.53 ± 141.68	798.66 ± 222.85	849.29 ± 165.43	973.02 ± 206.98
High	Emo	1168.38 ± 302.61	1431.22 ± 415.09	1301.25 ± 194.71	1590.8 ± 281.41
	Neu	1138.61 ± 253.51	1357.21 ± 397.44	1240.20 ± 208.66	1537.74 ± 275.57
		Errors			
Low	Emo	1.12 ± 1.11	0.18 ± 0.39	0.64 ± 0.86	0.65 ± 0.86
	Neu	0.06 ± 0.68	0.35 ± 0.61	0.35 ± 0.61	0.47 ± 0.72
High	Emo	3.41 ± 2.48	0.65 ± 0.79	2.94 ± 1.98	1.18 ± 1.19
	Neu	2.82 ± 1.63	0.35 ± 0.99	3.11 ± 2.29	1.06 ± 1.30

WM errors

See **Table 2.2** for means and standard deviations of Errors. Within subjects analyses showed that more errors were made at high compared with low load, more during present-target trials vs. absent target trials, and also more errors were made when distracters were emotional compared with neutral, $F_s(1, 32) > 5.99$, $p_s < .002$. There were no interactions with Group, Target, or Load, and there was no main effect of group, $F(1, 32) = 0.70$, $p = .41$.

Subjective ratings of neutral and emotional distracters

Participants were subjectively more distracted by emotional pictures ($M = 1.78$, $SD = 0.57$) than by neutral pictures ($M = 1.21$, $SD = 0.22$), $t(33) = 6.75$, $p < .001$, and rated

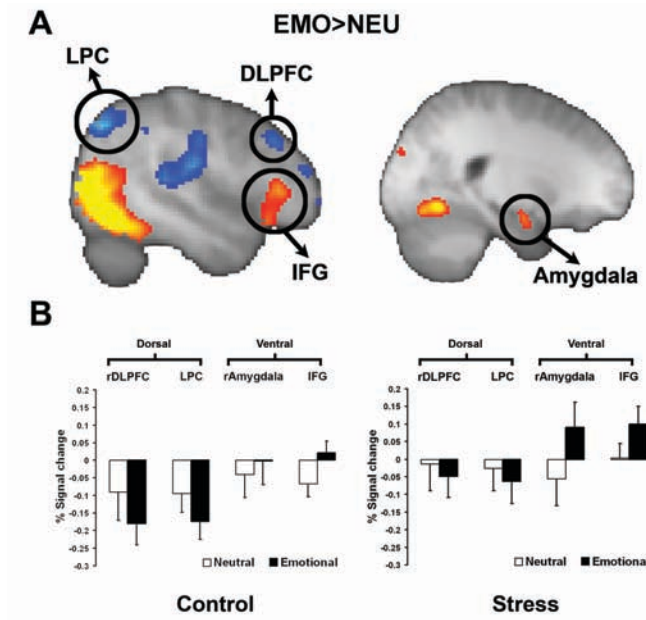


Figure 2.4 Brain activation during emotional compared with neutral distraction, and percent signal change in the ROI. **(A)** Combined group activation showing the typical pattern of dorsal deactivation and ventral activation in the presence of emotional distraction. LPC = lateral parietal cortex; DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus. **(B)** Graphs depict mean percent signal change and standard error in the four regions of interest in control (left) and stress group (right) as a function of distracter.

emotional distracters ($M = 2.07$, $SD = 0.63$) as more arousing than neutral distracters ($M = 1.18$, $SD = 0.20$), $t(33) = 9.99$, $p < .001$. The valence of emotional pictures was rated as more negative ($M = 3.83$, $SD = 0.46$) than the neutral pictures ($M = 2.72$, $SD = 0.35$), $t(33) = -15.99$, $p < .001$. There was no difference between the stress and control group in these ratings (all F s < 2.34 , and p s $> .14$).

FMRI analyses

The results from the Emo vs. Neu contrast in the whole-brain analysis of the combined groups are presented in **Table 2.3**. Consistent with previous reports (e.g., Dolcos & McCarthy, 2006), the typical pattern of dorsal ‘executive’ deactivations and ventral ‘affective’ activations was found (**Figure 2.4a**).

The four a priori ROIs (right DLPFC, bilateral LPC, right amygdala, bilateral IFG) were selected from these activations, discarding extended activation in voxels outside these regions (specifically in bilateral orbitofrontal regions) as determined by the probabilistic Harvard–Oxford cortical and subcortical atlases. Within the right DLPFC, the ROI was selected from the same region as reported by Dolcos and McCarthy (2006).

The RM ANOVA performed on the percentage change of the MR signal in the ROIs showed that there was a Group-by-Distracter interaction, $F(1, 32) = 5.06$, $p = .03$, which indicated more activation during emotional distraction in the stress group than in the control group, but not during neutral distraction. To specifically address our hypothesis that ventral activation would be enhanced, and dorsal activation decreased during emotional distraction, we further inspected this interaction in the dorsal and ventral ROIs. Separate ANOVAs revealed that the stress group compared to control group had a smaller deactivation in the dorsal system during emotional distraction at trend levels, $F(1, 33) = 3.09$, $p = .08$, and significantly greater activation of the ventral system, $F(1, 33) = 4.74$, $p = .04$ (see **Figure 2.4b** for mean signal change and standard error of the individual ROIs, as a function of group and distracter type). Finally, Neural system interacted with Load, $F(1, 32) = 15.05$, $p < .001$, with at low load, more activation in the ventral system than in the dorsal system, $t(33) = -3.29$, $p = .002$, and a tendency for less deactivation of the dorsal system at high compared with low load, $t(33) = -1.74$, $p = .09$.

Correlational analyses

Higher increases in cortisol levels at the time of task performance (mean pre- and post-WM minus baseline) were associated with less interference by emotional distraction (RTs emotional trials minus RTs neutral trials) at trend levels in the stress

Chapter 2

Table 2.3 Peak voxels of significantly activated clusters in brain areas during distraction (Emotional vs Neutral distracters and vice versa), in the whole sample ($n = 34$).

Contrast	BA	voxels	L/R	MNI-Coordinates			z
				x	y	z	
Emo>neu							
Occipital fusiform gyrus	37	4544	R	42	-62	-12	7.24**
Inferior lateral occipital	19	3924	L	-52	-70	12	6.97**
Inferior orbitofrontal cortex		1766	L	-36	30	-2	5.20**
Inferior frontal gyrus		1182	R	52	30	4	4.58**
Amygdala		72	R	22	-4	-18	3.98
Temporal fusiform cortex		60	L	-30	-10	-36	4.11
Temporal pole	21	24	R	54	8	-32	3.65
Insular cortex		14	R	38	0	-16	3.48
Neu>Emo							
Superior temporal gyrus	22	3656	R	62	-4	-4	5.12**
Superior temporal gyrus	22	3391	L	-66	-28	8	5.14**
Precentral gyrus	3	1466	R	24	-26	70	4.76**
Pre-/postcentral gyrus		777	L	-24	-30	66	4.55**
Frontal pole		399	R	42	52	-10	4.23**
Precuneus		224		0	-70	22	3.95
Occipital pole		180	R	30	-94	-10	4.41
Middle frontal gyrus	6	125	L	-30	22	54	4.12
Superior frontal gyrus		115	R	24	38	46	4.34
Middle frontal gyrus	9	84	R	50	28	32	4.05
Lateral occipital cortex	39	79	L	-36	-60	38	3.54
Frontal pole (DLPFC)	46	62	R	46	44	16	3.79
Supramarginal gyrus		49	R	54	-38	52	3.55
Postcentral gyrus		29	R	52	-22	56	3.52
Pre/postcentral gyrus		25	R	36	-24	48	3.33
Middle frontal gyrus		16	L	-24	34	34	3.39
Supramarginal gyrus	40	13	R	46	-42	38	3.39

Note: *** = cluster-corrected ($z > 3.1$), $p < .05$. All other areas significant at $z = 3.1$, $p < .001$ (uncorrected). No small volume corrections were applied. BA = Brodmann area; L/R = left/right in the brain; voxel size is 2 mm isotropic.

group ($r = -.37, p = .06$), but not in the control group ($ps > .13$). In the stress group, the cortisol response was negatively correlated with neural response in the ventral system during emotional distraction ($r = -.50, p = .04$; amygdala: $r = -.45, p = .07$; IFG: $r = -.30, p = .24$). There was no significant relation between cortisol response and dorsal activation in stress or control group.

DISCUSSION

In the present study, healthy men were exposed to acute social stress before entering the MRI scanner. Inside the scanner, when cortisol levels were high, participants performed a Sternberg WM task with emotionally negative and neutral distracting pictures, shown during the delay phase of each trial. Emotional distracters evoked more ventral activation after acute social stress, and a tendency towards less deactivation (i.e., a smaller magnitude of below-implicit baseline BOLD signal) in dorsal areas compared to the control group. Furthermore, compared to the control group, WM performance tended to be impaired in the stress group during emotional distraction.

The present study is the first to use a validated stress procedure, the TSST, to test the stress effects on emotional distraction in WM. Our findings lend support to the recent accumulation of ideas on acute stress effects, that, although tackling different memory systems or processes, stress modulates the interaction between “higher executive” and “lower emotional” processes (Luethi et al., 2008; Schwabe & Wolf, 2009; van Marle et al., 2009). Intuitively, the idea that acute effects of stress on memory and cognition have survival value is attractive, as it seems adaptive to prioritize attending to dangerous instead of neutral stimuli, for later superior recall, and to be more ready to flee than ponder (Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006). For instance, Luethi et al. (2008) showed that stress enhanced implicit memory of negative emotional stimuli, while impairing explicit memory and WM. Stress also induced a shift from goal-directed behavior towards habits in instrumental stimulus–response processes (Schwabe & Wolf, 2009). Other recent imaging studies reported either enhanced ventral activation after stress (van Marle et al., 2009), or reduced

dorsal prefrontal activations during WM (Qin et al., 2009). We found comparable effects within one task design, which enhances the convergent validity of the idea that stress facilitates emotional processing at the cost of executive processing. Moreover, consistent with the idea that stress shifts brain activation towards ventral areas during emotional distraction, a recent study (Chuah et al., 2010) reported increased amygdala activation associated with increased emotional distraction during WM after 24 h sleep deprivation, which can be considered as an acute stressor (McEwen, 2006).

The present findings are also consistent with results from other studies showing that stress induces WM impairment (Oei et al., 2006; Schoofs et al., 2008). However, it remains unclear what the specific contribution of GCs is to these stress effects. On the one hand, GCs released during (Elzinga & Roelofs, 2005) and after stress (Oei et al., 2006; Schoofs et al., 2008) have been related to reduced WM performance. On the other hand, GC actions appear to be beneficial in dealing with emotional distraction (Oei et al., 2009; Putman, Hermans, Koppeschaar, van Schijndel, & van Honk, 2007). Here, individuals that responded to stress with high cortisol levels, showed less interference by emotional distraction and a smaller neural response to emotional distracters in the ventral ROIs, especially the amygdala. Although these effects were significant at trend levels, they are consistent with a previous study from our lab, showing that administration of 35 mg hydrocortisone significantly reduced emotional distraction using the same task (Oei et al., 2006). Hydrocortisone administration has also found to reduce selective attention for threat (Putman et al., 2007). Cortisol might act to suppress the first wave stress activity (e.g., noradrenergic [NA] activity) towards emotional stimuli. High NA activity has been shown to increase amygdala responses towards emotional stimuli (Onur et al., 2009), and is also associated with impaired WM performance and PFC function (Arnsten, Mathew, Ubriani, Taylor, & Li, 1999; Birnbaum, Gobeske, Auerbach, Taylor, & Arnsten, 1999; Mao, Arnsten, & Li, 1999; Ramos & Arnsten, 2007; Ramos et al., 2005). Moreover, blocking NA activity has shown to reduce interference by emotional distraction in the present task, which was partially mediated by individual cortisol levels (Oei, Tollenaar, Elzinga, & Spinhoven, 2010). Thus, future studies (e.g., using pharmacological manipulations) aimed at further disentangling the specific contributions and interactions of cortisol

and NA activity during stress on processing of emotional stimuli should monitor both cortisol and NA.

Given that WM is especially impaired after stress or GCs at high loads (Lupien et al., 1999; Oei et al., 2006), it could be expected that our stressed participants would be particularly distracted by emotional pictures at high load. This was, however, not confirmed. At high load, overall performance speed was quite low and only differentiated between emotional or neutral trials at the descriptive level. This might have been a drawback from having to perform the task inside the scanner, resulting in slightly altered behavioral response patterns compared with similar task data (Oei et al., 2009). At the neural level, more ventral activity was evoked when load was low than when load was high, which is consistent with other reports. Interference by similar emotionally negative distracting pictures was only observed under low- but not high load (Erthal et al., 2005), while amygdala responses to negative distracters under high load were shown to be reduced compared with low load, presumably because high load claims so much attention, that not enough attentional resources were left to be captured by emotional distracters (Pessoa, Padmala, & Morland, 2005). Furthermore, similar to Dolcos and McCarthy (2006) amygdala activity was higher when contrasting emotional vs. neutral distraction. In the control group, however, amygdala activity was not increased when comparing emotional distraction with baseline. As several studies have shown a higher sensitivity to threatening stimuli in women than in men (Canli, Desmond, Zhao, & Gabrieli, 2002a; Hamann, 2005), the fact that we only tested males, whereas Dolcos and McCarthy tested females, might explain why they found increased amygdala activation during emotional distraction compared to baseline.

Furthermore, only present-target trials appeared sensitive enough to detect effects of distraction in this paradigm, whereas absent-target trials did not differentiate between neutral and emotional distraction (Oei et al., 2009). Present- and absent-target trials usually produce different performances, probably because they elicit/evoke different search strategies (i.e., for present-target trials a self-terminating, and for absent-target trials an exhaustive search strategy) (Corbin & Marquer, 2008). Nonetheless, because neural activation during the delay of each trial preceded the

participants/knowledge of target presence or absence, we did not analyze the imaging data for present-targets only. Discarding half of the imaging data would also have greatly reduced the power to detect differences.

Together, the present results show greater activation in ventral “affective” areas after stress, and smaller deactivation in dorsal “executive” areas, during emotional distraction. This was related to slower WM performance during emotional distraction. These results might suggest that acute stress shifts priority towards processing of emotionally significant stimuli, at the cost of WM performance. Further research into the effects of stress on cognitive functioning and attention to (distracting) emotional stimuli in the environment should be aimed at elucidating the specific effects of cortisol and other stress hormones on neural and behavioral performance.

Social stress and emotional working memory

