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## **Memory function after stress : the effects of acute stress and cortisol on memory and the inhibition of emotional distraction**

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# 6

## Stress shifts brain activation towards ventral "affective" areas during emotional distraction

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## 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 activations 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) (Luethi, Meier, & Sandi, 2008; Ramos & Arnsten, 2007; Arnsten, 2009; Lupien et al., 1999; Oei et al., 2006; 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, Hermans, Qin, & Fernandez, 2009), while also compromising the efficiency of conscious effortful information processing by decreasing prefrontal activation during WM performance (Qin, Hermans, van Marle, Luo, & Fernandez, 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 versus executive processing, revealing that “affective processing” is favored over “executive processing” (Drevets & Raichle, 1998). When comparing neutral versus 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 DLPFC (Mitchell et al., 2008; Anticevic, Repovs, & Barch, 2010; Morey et al., 2009; Perlstein et al., 2002; Dolcos & McCarthy, 2006).

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 disorders such as posttraumatic stress disorder (PTSD). PTSD, which

presumably is precipitated by acute traumatic stress, is associated with an overresponsive amygdala and impaired prefrontal function (Shin et al., 2006; Elzinga & Bremner, 2002). 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 activations in ventral affective brain regions, which was positively related to PTSD symptom severity, and conversely, higher activity in frontoparietal brain regions with lower PTSD symptom severity.

Although the acute stress response in healthy individuals is considered adaptive (De Kloet et al., 1999), its (temporary) effect on the brain shows similarities with PTSD, as even acute mild psychological stress impairs PFC function (Arnsten, 2009; Oei et al., 2006; Schoofs et al., 2008; Elzinga & Roelofs, 2005; Qin et al., 2009; Ramos & Arnsten, 2007), 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 to 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 to a non-stressful control condition. To examine our hypothesis, we analyzed behavioural 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., Mitchell et al., 2008; Dolcos et al., 2006). 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 colour 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 (a cut-off score for exclusion of 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 et al., 1985). Furthermore, a Body Mass Index (BMI;  $\text{kg}/\text{m}^2$ ) between 19 and 26, an age between 18 and 35 yrs, and right-handedness. 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 (Edinburgh, 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 Wechsler Adult intelligence Scale-III (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 no

more than 25 minutes. 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 is 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 sixteen 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). 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). Distracters consisted of validated pictures selected from the International Affective Pictures System (IAPS; Lang et al., 2001), of which 60 neutral pictures (rated on 9-points Likert scales (1 *very negative*, 9 *very positive*)  $M \pm SD$ , valence:  $5.09 \pm 0.54$ ; arousal (1 *not arousing at all*, 9 *highly arousing*):  $3.21 \pm 0.77$ ) and 60 negatively arousing pictures ( $M \pm SD$ , valence:  $2.86 \pm 0.93$ ; arousal:  $6.22 \pm 0.52$ ), that matched in background colour, and complexity, e.g. 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 pseudorandomized 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) 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-points Likert scales using the Self-Assessment Manikin (Bradley & Lang, 1994).

### ***Stress-induction***

To induce stress, the Trier Social Stress Task (TSST) was employed (Kirschbaum et al., 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 minutes to think of a movie to their liking, of which they were informed to having to answer open questions on paper for 5 minutes, in the same laboratory room, but without audience. Thereafter, they had 5 minutes to count backwards from 50 to zero 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  $-20^{\circ}\text{C}$  until assayed at Prof 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 3 T Philips Achieva MRI scanner (Philips, Best, The Netherlands), using an 8- channel SENSE head coil. For fMRI,  $T_2^*$ -weighted gradient echo, echo planar images (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 =  $80^{\circ}$ , SENSE factor = 3, 38 axial slices, FOV = 220x220 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 = 224x224 mm, in-plane resolution 0.875x0.875 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 = 220x220 mm, in-plane resolution 1.96x1.96 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 (to be reported elsewhere).

### ***Procedure***

Participants were invited on two occasions. The first time for further screening purposes (BDI, SCL-90, STAI, WAIS subtests). The second time for the scan session. Participants were asked to refrain from caffeine or sugar containing drinks, and not to eat two hours before arrival time. All participants arrived at either 8.30 AM, or 10.30 AM. 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 states scans were measured. Saliva was sampled at five times: 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 (“postscan”). Blood pressure and heart rate were sampled at all 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/HR was 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 standard deviations. Mahanobis

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 vs. Control), and as within-subjects factors Target (present vs. absent), Load (high vs. low) and Distracter (emotional vs. 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) was used for the analyses.

### **FMRI data**

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 4.1, part of FSL (FMRIB's Software Library, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl); Smith et al., 2004). The following pre-statistics processing was applied: motion correction (Jenkinson et al., 2002); non-brain removal (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 8 mm; grand-mean intensity normalisation of the entire 4D dataset 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 et al., 2001). 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 2mm MNI-152 standard space template (Jenkinson & Smith, 2001; Jenkinson et al., 2002). 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 2.5s) separate for load (low/high) x distracter type (Neu/Emo/Scr) on correct trials. Target-recognition periods on correct trials were modelled 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, modelling 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 FLAME (FMRIB's Local Analysis of Mixed Effects) (Woolrich et al., 2004; Beckmann, Jenkinson, & Smith, 2003). 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, i.e., the right amygdala, the bilateral inferior frontal gyrus, right dorsolateral PFC, and bilateral parietal lobe (Dolcos & McCarthy, 2006; Dolcos et al., 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 \*100) in the regions of interest, with as within-subjects factors neural system (dorsal, ventral), Load (Low vs High), Distracter type (neutral vs emotional), and Group as between-subjects factor. Note that analyses in which the group factor was not included might be biased by circularity to some degree and thus are marked with a C (see Kriegeskorte, Simmons, Bellgowan, & Baker, 2009).

## 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 1 for means and standard deviations).

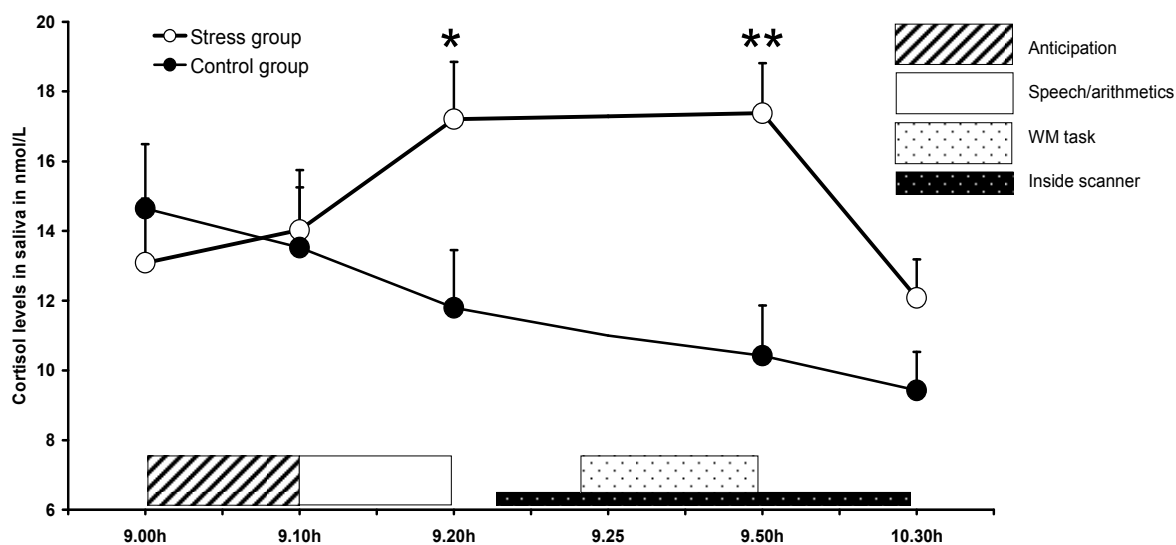
### ***Stress induction***

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 1). 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 higher in the stress group compared to 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,  $F(1, 32) = 2.19, p = .15$ .

**Table 1. Means (*M*) and standard deviations (*SD*) of subject variables in each group**

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

**Figure 1. Mean cortisol levels and standard errors**

**Note.** Significant difference between groups, \* =  $p < .05$ ; \*\* =  $p < .005$

### **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 (SBP,  $F[3, 96] = 9.11, p < .0005$ , DBP,  $F[3, 96] = 8.64, p < .0005$ ) and Condition by Time (SBP,  $F[3, 96] = 12.52, p < .0005$ ; DBP,  $F[3, 96] = 8.00, p < .0005$ ). After the stress-induction, SBP and DBP was significantly higher in the stress group than the control group (resp.,  $t_{32} = -3.09, p = .004, t_{32} = -4.70, p < .0005$ ). 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 ( $M \pm SE = 79.25 \pm 1.79$ ) than in the control group ( $M \pm SE = 72.75 \pm 1.79$ ).

## **Emotional WM performance**

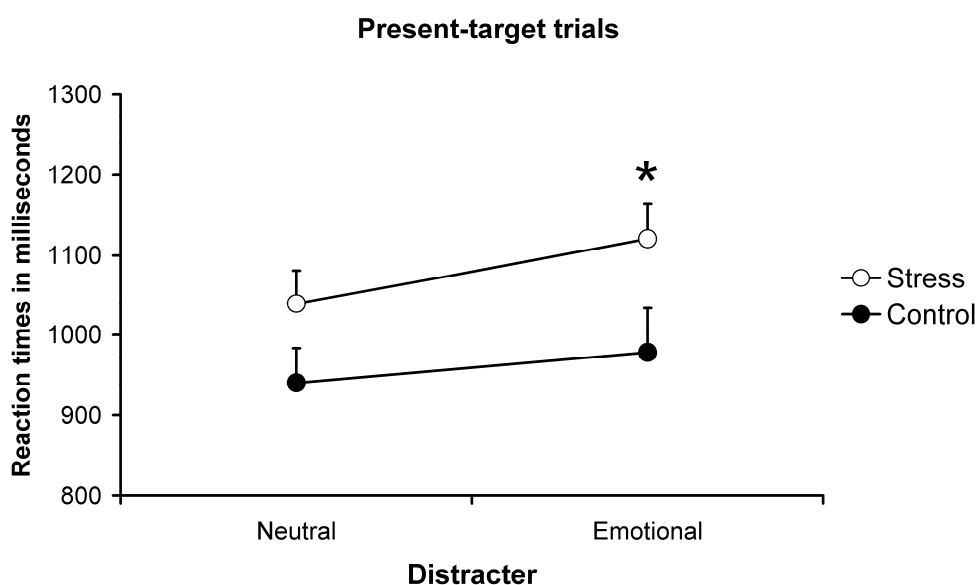
### **Reaction times.**

See means and standard deviations of RTs in Table 2. Within subjects, RTs were faster at low load compared to 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 ( $t_{32} = -1.65, p = .11$ ) (see Figure 2). 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.

### **WM errors.**

See Table 2 for means and standard deviations of Errors. Within subjects analyses showed that more errors were made at high compared to low load, more during present-target trials vs. absent target trials, and also more errors were made when distracters were emotional compared to neutral ( $F[1, 32] > 5.99, ps < .002$ ). There were no interactions with group, target or load, and there was no main effect of group ( $F[1, 32] = 0.70, p = .41$ ).

**Figure 2. Present-target trials: Mean reaction times (and standard errors) in emotional and neutral trials of the stress- and control group**



\*  $p < .05$

### ***Subjective ratings of neutral and emotional distracters***

Participants were subjectively more distracted by emotional pictures ( $M \pm SD = 1.78 \pm 0.57$ ) than by neutral pictures ( $M \pm SD = 1.21 \pm 0.22$ ) ( $t_{33} = 6.75$ ,  $p < .0005$ ), and rated emotional distracters ( $M \pm SD = 2.07 \pm 0.63$ ) as more arousing than neutral distracters ( $M \pm SD = 1.18 \pm 0.20$ ) ( $t_{33} = 9.99$ ,  $p < .0005$ ). The valence of emotional pictures was rated as more negative ( $M \pm SD = 3.83 \pm 0.46$ ) than the neutral pictures ( $M \pm SD = 2.72 \pm 0.35$ ) ( $t_{33} = -15.99$ ,  $p < .0005$ ). There was no difference between 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 3. Consistent with previous reports (e.g., Dolcos et al., 2006), the typical pattern of dorsal “executive” deactivations, and ventral “affective” activations was found (see Figure 3a). The four a priori ROIs (right DLPFC, bilateral LPC, right amygdala, bilateral inferior frontal gyrus) 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 atlases. Within the right DLPFC, the ROI was selected from the same region as reported by Dolcos and colleagues (2006).

**Table 2. Means (*M*) and standard deviations (*SD*) of reaction times and errors in the stress and control group on the emotional working memory task**

		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

### ***Effects of stress on patterns of activation pertaining to dorsal 'cognitive' and ventral 'affective' neural systems***

The RM ANOVA performed on the percentage change of the MR signal in the ROIs showed that there was one main effect, System, which indicated higher mean percentage of signal change in the ventral system than in the dorsal system ( $F(1, 32) = 4.61, p = .04, \underline{(C)}$ ). There were three significant interactions: First, consistent with previous reports (e.g., Dolcos et al., 2006), the RM ANOVA yielded a highly significant interaction between Neural system and Distracter ( $F(1, 32) = 69.13, p < .0001, (C)$ ), revealing significantly greater deactivation (i.e., higher magnitude of below zero signal change) of the dorsal system when distraction was emotional compared to neutral ( $t_{33} = 3.57, p = .001$ ) and compared to the ventral system ( $t_{33} = -4.02, p < .0001$ ). Also, emotional distracters evoked more activation than neutral distracters in the ventral system ( $t_{33} = -6.47, p < .0001$ ). When distraction was neutral, there was no between-systems difference in activation ( $t_{33} = 0.25, p = .81$ ) (see Figure 3b for mean signal change and standard error of the individual ROIs, as a function of group and distracter type).

Secondly, there was a Group by Distracter type 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 inspected this interaction in the dorsal and ventral system separately. Separate ANOVAs showed that in the stress group compared to the control group there was a trend for smaller deactivation in the dorsal system during emotional distraction ( $F(1, 33) = 3.09, p = .08$ ), and significantly greater activation of the ventral system ( $F(1, 33) = 4.74, p = .04$ ).

Finally, Neural system interacted with Load ( $F(1, 32) = 15.05, p < .0001$ ), 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 to 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 group ( $r = -.37, p = .06$ ), but not in the control group ( $ps > .13$ ). In the stress group, the cortisol response was negatively correlated with



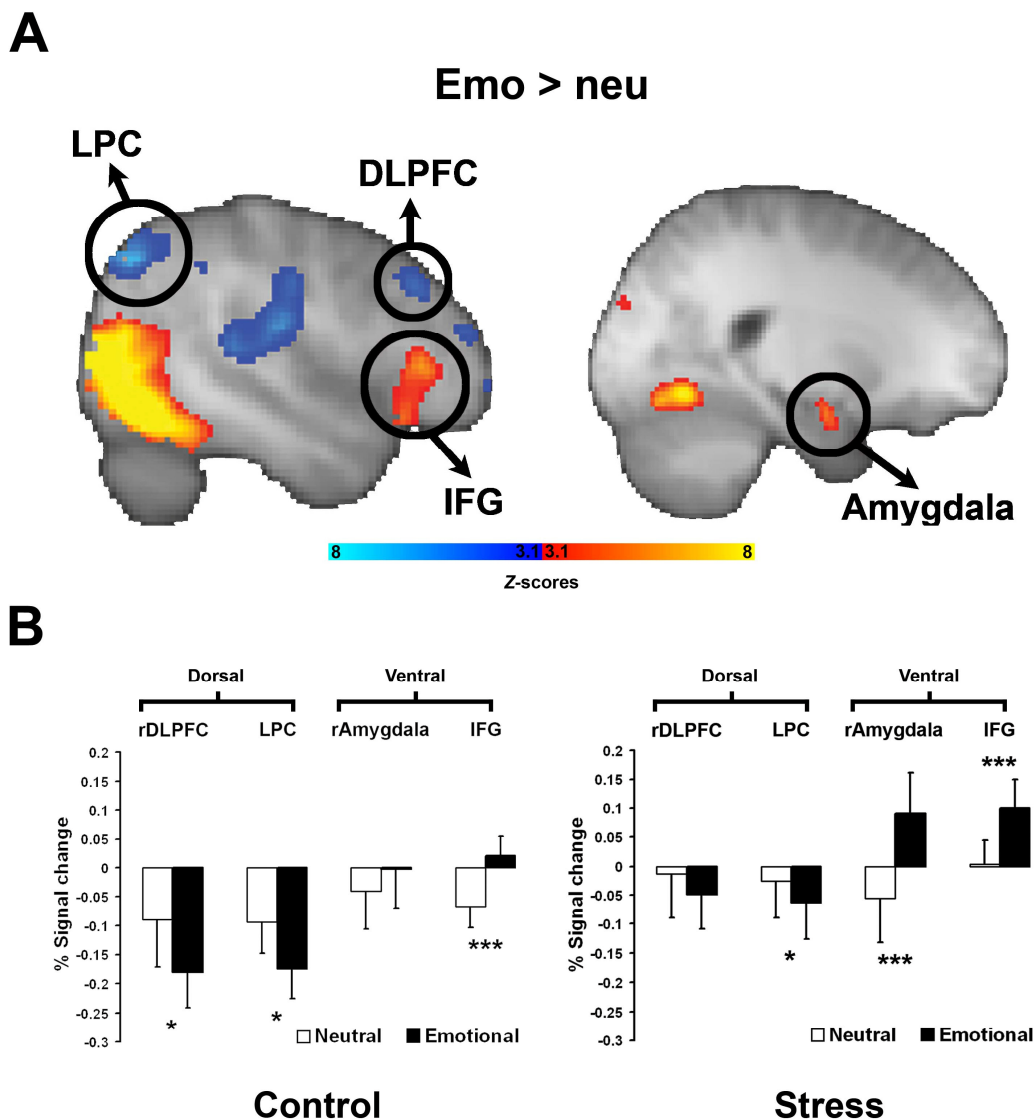
**Table 3. Peak voxels of significantly activated clusters in brain areas during distraction (Emotional vs Neutral distracters and vice versa), in the whole sample (N = 34)**

Area	BA	voxels	L/R	Coordinates			Z
				x	y	z	
<b>Emo&gt;Neu</b>							
Occipital fusiform gyrus	37	4544	R	42	-62	-12	7.24***
Inferior lateral occipital cortex	19	3924	L	-52	-70	12	6.97***
Inferior orbitofrontal cortex		1766	L	-36	30	-2	5.20***
Inferior frontal gyrus, triangularis		1182	R	52	30	4	4.58***
Amygdala		72	R	22	-4	-18	3.98
Anterior 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
<b>Neu&gt;Emo</b>							
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, superior division	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 significant at  $Z > 3.1$ ,  $p < .05$ . All other areas significant at  $Z = 3.1$ ,  $p < .001$  (uncorrected). BA = Brodmann area; L/R = Left/right in the brain. Voxelsize is 2mm isotropic.

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.

**Figure 3.** Brain activation during emotional compared with neutral distraction, and percent signal change in the regions of interest



*Note.* 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; \* =  $p < .05$ ; \*\*\*  $p < .0001$

## 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 (Schwabe & Wolf, 2009; van Marle et al., 2009; Luethi et al., 2008). 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 et al., 2006). For instance, Luethi and colleagues (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, for instance, that stress induced heightened amygdala and inferior temporal activity towards threat-related stimuli (van Marle et al., 2009), or that stress 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.

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 et al.,

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., 2009). 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 (Birnbaum et al., 1999; Ramos & Arnsten, 2007; Ramos et al., 2005; Mao et al., 1999; Arnsten et al., 1999). 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 (for example, using pharmacological manipulations) aimed at further disentangling the specific contributions and interactions of cortisol and noradrenergic (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 (Oei et al., 2006; Lupien et al., 1999), it could be expected that our stressed participants would be particularly distracted by emotional pictures at high load. This was, however, was 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 to 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 to 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, 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). However, 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.