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Hydrocortisone reduces emotional distracter interference in working memory

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Summary Several studies have shown that stress and glucocorticoids can impair prefrontal-dependent working memory (WM) performance. WM is the ability to attend to the task at hand, and to maintain relevant information in mind during a delay while ignoring irrelevant stimuli. Here, it is investigated whether stress hormones impair WM by reducing the ability to suppress distracting, irrelevant neutral and emotional stimuli. Hydrocortisone (35 mg) ($n = 23$) or placebo ($n = 21$) was administered to young, healthy men, who performed a Sternberg WM task with neutral and emotional irrelevant distracters shown in the delay-phase of the task, between encoding and recognition of the relevant stimuli for WM. Contrary to expectations, enhanced WM performance with higher processing speed and a reduction of errors was found in the hydrocortisone group compared to placebo. Moreover, hydrocortisone significantly reduced the distraction by emotional stimuli. These findings show that cortisol effects on WM are not unambiguous and contrast with previous findings on the impairing effects of cortisol on WM. Dose—response studies could give more insight into the specific modulating effects of glucocorticoids on suppression of irrelevant emotional distraction.

1. Introduction

Deficits in prefrontal function, including working memory (WM) functioning, are found in a number of stress-related psychiatric disorders such as depression and posttraumatic stress disorder (PTSD). For instance, PTSD is associated with prefrontal dysfunction (Beckham et al., 1998; Bremner, 2002, 2006; Hou et al., 2007) and activation abnormalities in the prefrontal cortex (PFC) during WM performance (Galletly et al., 2001; Clark et al., 2003; Veltmeyer et al., 2005; Moores et al., 2008). Patients with stress-related disorders are also very susceptible to emotional distraction and poor at suppressing trauma-related or other (emotionally arousing) thoughts and feelings, possibly due to impaired prefrontal functioning (McNally, 1998; Elzinga and Bremner, 2002; Williams and Moulds, 2007). The failure to reduce emotional distraction might be associated with impairments in WM. Specifically, WM is thought to be crucial for reducing distrac-

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tion by its capacity to maintain relevant information in mind, and to suppress irrelevant information (Baddeley and Della, 1996; de Fockert et al., 2001; Arnsten and Li, 2005). Moreover, stress may play a role in modulating the ability to suppress emotional distraction, since stress hormones — specifically glucocorticoids (GCs) — have proven to impair WM (e.g., Lupien et al., 1999). In the present study, it is investigated whether GCs decrease the suppression of distractions.

Abundant evidence shows that memory depends on stress hormone levels and that it is sensitive to stress exposure (Wolf, 2003). When stressed, the hypothalamus–pituitary–adrenal (HPA) axis is activated, leading to the release of stress hormones that eventually enter the brain. In the brain, GC actions are mediated by mineralocorticoid and glucocorticoid receptors (GRs) in regions relevant for cognition and memory, such as the hippocampus and the PFC (De Kloet et al., 1998; Lupien and Lepage, 2001). GCs have found to enhance hippocampus-dependent declarative memory consolidation (Buchanan and Lovallo, 2001; Cahill et al., 2003; Kuhlmann and Wolf, 2006) and to impair memory retrieval (de Quervain et al., 2000; Roozendaal, 2002, 2003; Kuhlmann et al., 2005; Roozendaal et al., 2006; Buchanan et al., 2006). Impairing effects of stress on WM performance have mainly been ascribed to GC actions in the PFC (Lupien and Lepage, 2001). The PFC is densely packed with GRs and involved in regulating stress-induced HPA axis activity (Diorio et al., 1993; Lupien and Lepage, 2001; Sullivan and Gratton, 2002; Kern et al., 2008; Cerqueira et al., 2008). Both animal and human studies have shown associations between deficits in prefrontal cognitive functions and HPA axis dysregulations (Mizoguchi et al., 2004; Liberzon et al., 2007). In animal studies chronic stress was found to impair WM (Arnsten and Goldman-Rakic, 1998; Mizoguchi et al., 2000; Arnsten, 2000; Cerqueira et al., 2007). In humans, both chronic (Young et al., 1999) and acute GC administration (Lupien et al., 1999; Wolf et al., 2001) led to impaired WM. In addition, several studies in healthy people found that acute stress-induced GC elevations are related to impaired WM performance (Elzinga and Roelofs, 2005; Oei et al., 2006; Schoofs et al., 2008).

WM deficits found after stress induction or GC administration could also be a consequence of enhanced distractibility. WM is defined not only by the ability to maintain relevant information in mind, but also by its ability to inhibit or suppress irrelevant information. A number of studies have shown that one of the functions of the PFC is to keep the mind free from distracting stimuli (Chao and Knight, 1995, 1998; Postle, 2005, 2006; D'Esposito et al., 2006). In patients and monkeys with frontal damage, WM maintenance functioning stays intact while performing various WM tasks under conditions of low distraction. For instance, monkeys with frontal lesions usually show deficits in delayed response tasks. However, they function well on the same task when kept in the dark during the delay, after the presentation of stimuli, thus free from visual distractions (D'Esposito and Postle, 1999; Muller and Knight, 2006). Also, patients with frontal lesions are more prone to interference, and their neurophysiological response to irrelevant sensory stimuli is stronger (e.g., Chao and Knight, 1995). Using functional imaging, Gazzaley et al., 2005 demonstrated that WM impairment in normal aging was associated with a PFC deficit in top-down suppression of irrelevant information, while enhancement of task-relevant activity was unimpaired. In sum, both evidence from neuropsychological and neuroimaging studies support the idea that the PFC mediates interference and distraction of irrelevant information during WM maintenance. It is therefore possible that what appears to be a WM (maintenance) impairment induced by stress and GCs, could also be explained by decreased suppression of distractions.

The ability to act upon relevant information and to ignore irrelevant info, however, is determined by the availability of WM capacity, with high cognitive load on WM leading to more distracter interference than low load (de Fockert et al., 2001; see Lavie, 2005, for cognitive load theory). Consistent with cognitive load theory, individual differences in WM capacity have found to be related to the ability to suppress self-relevant intrusive thought (Brewin and Smart, 2005), vulnerability to intrusions in general, and the ability to intentionally suppress intrusions (Schelstraete and Hupet, 2002). Interestingly, acute stress and GCs have shown to impair WM performance particularly at high loads and not low loads (Lupien et al., 1999; Oei et al., 2006). Stress might make individuals especially vulnerable to distractions when cognitive load is high.

In a few studies emotional stimuli were used to examine effects of distraction on WM maintenance (Dolcos and McCarthy, 2006; Dolcos et al., 2008). It is well-known that, generally, emotional distractions are more difficult to ignore, because emotional stimuli may be potential threats and get prioritized processing, even under conditions of limited attention (Windmann and Kutas, 2001; Ohman et al., 2001). In line with this, task-*irrelevant* emotionally arousing stimuli impaired WM performance to a higher degree than neutral irrelevant distracters (Kensinger and Corkin, 2003; Dolcos and McCarthy, 2006). It is, however, unclear how GCs might modulate this effect. Evidence with regard to GC effects on emotionally arousing stimuli is contradicting. One study found that GC administration caused heightened arousal in response to neutral stimuli without effects on mood (Abercrombie et al., 2005), whereas one other study found GCs to be mood uplifting (Het and Wolf, 2007). Fear-reducing effects of GCs have also been reported. GCs were found to diminish preconscious attention to emotionally negative distracters (Putman et al., 2007). Also, GCs led to a diminished startle reflex to emotional slides (Buchanan et al., 2001). Moreover, in a clinical study, GCs reduced phobic fear (e.g., Soravia et al., 2006). It could therefore be argued that GC administration leads to less interference from emotional distractions. GC administration, however, might also lead to more interference from *neutral* stimuli, if indeed these stimuli would become more arousing, although the evidence for this option is sparse (Abercrombie et al., 2005). Nonetheless, in both cases the distinction between neutral and emotional distraction would be less prominent.

In the present study, we studied the effects of a single dose of 35 mg hydrocortisone on WM performance with neutral and emotional distracters presented during the delay-phase of an item-recognition WM task. Since stress and GCs have shown to impair WM performance at high loads, we hypothesized that GCs would *impair* overall WM performance

especially at high loads, because of a reduced ability to suppress distracters. However, since we used emotionally negative and neutral distracting stimuli, we hypothesize that the differential effects of suppressing emotional and neutral distracters that are expected in the control group (i.e., slower performance when distracted by emotional stimuli compared to neutral ones) would not appear in the experimental group.

2. Methods

2.1. Participants

Male students were recruited by means of a sign-up board and advertisements posted at the faculty of social sciences of Leiden University. 54 participants who were part of a larger study (see for more details Tollenaar et al., 2009) were included and randomly assigned to an experimental and a control group in a double blind placebo-controlled between-subjects design. All participants were screened before inclusion. Eligibility criteria were: a Body Mass Index (BMI; kg/m^2) between 19 and 26, and age between 18 and 35 yr. No history of disease or chronic disease requiring medical attention, no current use of prescribed medication or the use of remedies containing corticosteroids, no use of psychotropic drugs, and no current and past psychiatric problems. Volunteers were asked whether they (ever) experienced psychological problems and/or were currently on medication or seeking help for psychological problems, or whether they had been seeing a psychologist or psychiatrist in the past. When answering 'yes' to any of these questions, they were excluded. Each participant gave signed informed consent in which confidentiality, anonymity, and the opportunity to withdraw without penalty were assured. The hydrocortisone group received a fixed oral dose of 35 mg of hydrocortisone. The dose of hydrocortisone used in this study was chosen because it can be considered to simulate endogenous physiologic secretion of cortisol under extreme stressful situations (Kirschbaum and Hellhammer, 1989, 1994). Furthermore, the dose of hydrocortisone selected for our trial was within the range used in other studies aiming at extreme acute stress levels (e.g., Abercrombie et al., 2003). The control group received similar looking placebo. Characteristics of the sample were as follows ($M \pm SD$): age, 20.6 ± 3.15 yr, range: 18–32 yr; BMI, 22.20 ± 2.17 kg/m^2; trait anxiety (STAI-trait version), 34.07 ± 9.25; levels of psychopathology (symptom checklist, SCL-90), 119.12 ± 24.17, and WM, as estimated using the Digit Span-subtest of the Wechsler Adult Intelligence Scale (WAIS-III, Wechsler, 1997), 10.70 ± 2.92. No significant differences between the two groups were found for BMI ($F[1, 53] = 0.49$; $p = 0.49$), STAI-trait ($F[1, 53] = 0.07$; $p = 0.79$), SCL-90 ($F[1, 53] = 0.09$; $p = 0.76$), and Digit Span ($F[1, 53] = 0.70$, $p = 0.41$. The hydrocortisone group ($M \pm SD$: 21.70 ± 3.99 yr) was older than the placebo group ($M \pm SD$: : 19.52 ± 1.37 yr) ($F[1, 53] = 7.22$; $p = 0.01$)[1]. The Medical Ethical Committee of the Leiden University Medical Center approved the study protocol. Participants received course credit or a monetary compensation for taking part in the study.

2.2. Cortisol

Cortisol was assessed via saliva samples, using Salivettes (Sarstedt, Germany). Saliva sampling is a stress-free method to assess unbound cortisol and α-amylase (Kirschbaum & Hellhammer, 1994). Saliva samples were centrifuged and stored at $-20\,^{\circ}$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 of 0.16 ng/ml (IBL, Hamburg, Germany). Inter- and intra-assay coefficients of variation were below 10%.

2.3. Working memory task

Working memory was measured using an adapted version of the Sternberg item-recognition task (Sternberg, 1966) previously used and described by Oei et al. (2006). The WM processing load was manipulated by varying the numbers of uppercase letters (1–4 targets) that had to be held in memory (1000 ms) for later recognition, and by varying the number of letters (1–4 displayed) presented in the recognition display after a short delay (1500 ms), which led to a load of 2, 4, 12 or 16 comparisons. For example, if the participant had to hold four items in memory (e.g., *E*, *R*, *F* and *S*), while searching for one of the items in a recognition display containing four items (*D*, *M*, *U*, and *Z*), this led to 16 possible comparisons (*E*–*D*, *E*–*M*, *E*–*U*, *E*–*Z*, *R*–*D*, *R*–*M*, *R*–*U*, *R*–*Z*, *S*–*D*, *S*–*M*, *S*–*U*, *F*–*D*, *F*–*M*, *F*–*U*, *F*–*Z* and *S*–*Z*). The delay-phase between target and recognition display originally contained a fixation cross (Lupien et al., 1999; Oei et al., 2006). In the current task version, distracters were presented during the delay-phase that consisted of pictures selected from the International Affective Pictures System (Lang et al., 2001). Half of the distracters were of negatively arousing content, e.g., aggressive people ($M \pm SE$: valence 2.9 ± 1.0, arousal 5.9 ± 0.9), the other half emotionally neutral, e.g., people on the sidewalk ($M \pm SE$: valence 5.2 ± 0.6, arousal 3.6 ± 0.9) on a 9-points Likert scale, using normative ratings for male subjects (Self-assessment Manikin, Lang, 1980). Pictures were matched for complexity, background color, and human or animal presence. A red fixation cross was shown at the centre of each picture. Participants had to ignore the distracters and press a 'yes' button indicating they had recognized a target (present-target trials), or a 'no' button, when no target letter was recognized (absent-target trials). Only one target letter was present in the present-target trials. Each block consisted of 12 emotional or neutral trials and was of low comparison load (loads 2 and 4) or high comparison loads (loads 12 and 16). It was chosen to use both two low and two high loads to keep the test challenging and diverse, without making it too long-lasting and tiresome. A total of 96 trials was randomly delivered, which lasted approximately 10 min. Stimulus presentation software (WESP) developed at the University of Amsterdam was used which randomizes and presents stimuli, and records reaction times and errors.

[1] This age difference was due to two participants in the hydrocortisone group who were 30 and 32 yrs of age, which is well below the 'critical' age of 35 set for inclusion.

2.4. Procedure

Participants arrived in the afternoon, between 1200 and 1500 h. They were seated on a chair in front of a 17″ CRT monitor with a fixed button box on the table before them. The first saliva sample was taken just before ingestion of the study-medication. After pill ingestion, 75 min was spent reading magazines and filling out questionnaires. Then, cognitive tests were done for the larger study (for details on the entire procedure see Tollenaar et al., 2009). At 115 min after the first saliva sample, another sample was taken. Immediately hereafter, WM task instructions appeared on the computer screen. The task was first explained and participants were given the opportunity to practice the WM task in a short practice block which consisted of 10 trials with only neutral distracters. Furthermore, they were asked to respond as quickly and accurately as possible. The last saliva sample was taken at 130 min after the first sampling, just after the WM task. An exit interview was done at the end of the larger experiment, in which was asked whether participants thought they had been given placebo, or one of the study-medications.

2.5. Statistics

Reaction times were checked for errors, misses and outliers. Errors and misses were counted and removed. Reaction times that were smaller than 300 ms were regarded as misses. Univariate outliers were detected using *z*-scores and replaced by mean + 2 *SD*s of each category. Data were analyzed using repeated measures ANOVAs, with as between-subjects factor Group (hydrocortisone vs. placebo) and Load (high vs. low), Target type (present vs. absent) and Distracter (emotional vs. neutral) as within-subjects factors. Greenhouse-Geisser corrections were applied when the sphericity assumption was not met. The data were analyzed using SPSS for Windows, version 14.

3. Results

WM data of two participants (from the placebo group) were not recorded because of a computer failure. Eight participants (2 from the placebo group and 6 from hydrocortisone group) had to be excluded from further analyses because of extreme numbers of errors (>25%). Before discarding these participants, the percentage of errors, however, did not differ between groups ($F(1, 51) = 0.02$, $p = 0.88$). A total of 21 participants in the hydrocortisone group and 23 in the placebo group were left for further analysis.

Table 1 Cortisol levels in nmol/l.

Time	Group	
	Placebo $M \pm SEM$	Hydrocortisone $M \pm SEM$
−10 min (baseline)	9.01 ± 0.93	7.6 ± 0.56
+115 min (pre-test)	4.57 ± 0.44	130.66 ± 15.53*
+130 min (post-test)	4.95 ± 0.56	96.39 ± 9.63*

* Significant difference between groups, $p < 0.0005$ (unpaired *t*-tests, equal variances not assumed).

3.1. Cortisol

Cortisol analyses showed the expected pill-induced increase in the hydrocortisone group, with significant effects of Time ($F[2, 84] = 94.8$), Group ($F[1, 42] = 121.56$), and Time by Group interaction ($F[2, 84] = 113.77$) (all *p*s < 0.0005) (see Table 1). Participants were not able to tell whether they had received placebo or hydrocortisone: just one participant correctly indicated noticing an effect of hydrocortisone, Chi-square = 4.02, $df = 4$, $p = 0.40$).

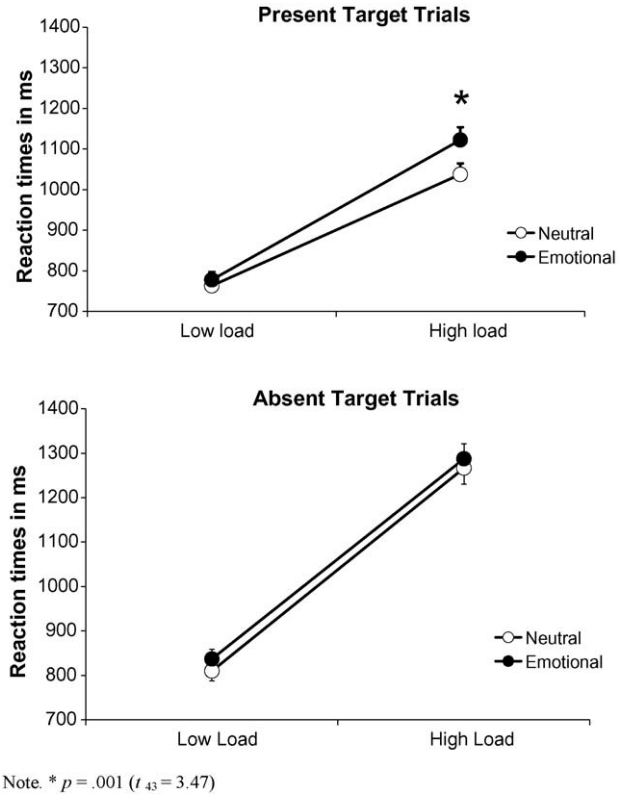
3.2. Working memory

Mean reaction times and standard errors are shown in Table 2. The repeated measures ANOVA revealed several main effects: first, a trend was found for the between-subjects factor group, with shorter RTs in the hydrocortisone group (946.74 ± 31.39) compared to the placebo group (1028.91 ± 29.99), $F(1, 42) = 3.58$, $p = 0.06$. Within-subjects, RTs were longer at high load (1178.54 ± 27.59) than at low load (797.11 ± 18.89), $F(1, 42) = 413.72$, $p < 0.0005$.

Table 2 Mean (*M*) reaction times and standard error (*SE*).

Load	Distracter	Group			
		Hydrocortisone		Placebo	
		Target: present $M \pm SE$	Target: absent $M \pm SE$	Target: present $M \pm SE$	Target: absent $M \pm SE$
Low	Emotional	736.27 ± 27.92*	824.20 ± 31.05	819.94 ± 26.68*	849.68 ± 29.67
	Neutral	743.74 ± 29.17	795.03 ± 32.56	783.06 ± 27.87	824.97 ± 31.11
	Total	740.00 ± 27.05	809.611 ± 30.35	801.50 ± 25.84	837.32 ± 28.99
High	Emotional	1051.40 ± 45.74*	1219.04 ± 48.47	1192.96 ± 43.70*	1356.52 ± 46.31
	Neutral	1008.48 ± 39.10	1195.77 ± 52.54	1066.59 ± 37.36	1337.57 ± 50.21
	Total	1029.94 ± 38.71	1207.41 ± 46.68*	1129.78 ± 36.99	1347.04 ± 44.61*
Total	Emotional	893.84 ± 33.15*	1021.62 ± 34.66	1006.45 ± 31.67*	1103.09 ± 33.12
	Neutral	876.11 ± 31.85	995.39 ± 38.41	924.83 ± 30.44	1081.27 ± 36.70

* Significant difference between groups, $p < 0.05$.

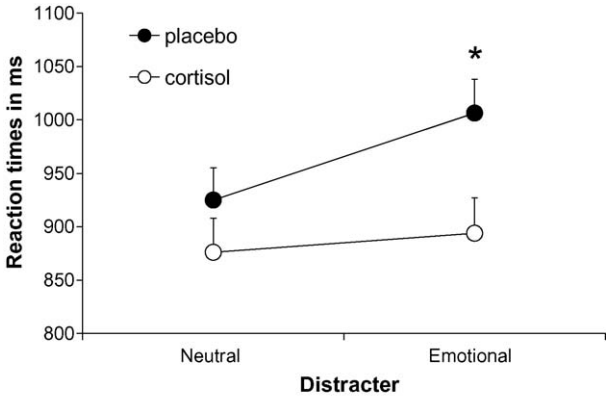


Note. * $p = .001$ ($t_{43} = 3.47$)

Figure 1 Load by Distracter interaction in present- and absent-target trials.

RTs of present targets (925.31 ± 21.36) were significantly faster than that of absent targets (1050.35 ± 23.90), $F(1, 42) = 91.61$, $p < 0.0005$. RTs during trials with emotional distracters (1006.25 ± 21.93) were longer than when neutral distracters were shown (969.40 ± 22.85), $F(1, 42) = 11.20$, $p = 0.002$. Group interacted with Load, with shorter RTs at high load in the hydrocortisone group as compared with the placebo group, $F(1, 42) = 4.01$, $p = 0.05$. Finally, there was a triple interaction of Target by Load by Distracter, $F(1, 42) = 4.21$, $p = 0.046$ (see Fig. 1).

Apparently, absent-target trials slopes were not differentially affected by distracters, which might indicate that another strategy was used when targets were absent, than



Note. * $p < .02$ ($t_{42} = 2.46$)

Figure 2 Present-target trials: Group by Distracter interaction.

when targets were present, respectively, the exhaustive search strategy vs. a self-terminating search strategy (Sternberg, 1969). This may possibly have abolished the sensitivity to detect distracter interference in absent-target trials. Moreover, absent-target trials may also have obscured (interaction) effects of the primary factors of interest, namely Group, Load and Distracter. Therefore, separate analyses were performed, splitting up the significant main effect of target. Analysis of the reaction times on present-target trials showed a trend for group, which indicated somewhat faster RTs in the hydrocortisone group compared to the placebo group ($F[1, 42] = 3.56$, $p = 0.07$). At low load, RTs were shorter than at high load ($F[1, 42] = 310.93$, $p < 0.0005$), and RTs were longer when distracters were emotional, than when they were neutral ($F[1, 42] = 12.60$, $p = 0.001$). Also, a Group by Distracter interaction was revealed, with shorter RTs during emotional trials in the hydrocortisone group than in the placebo group ($F[1, 42] = 5.21$, $p = 0.028$) (see Fig. 2). A Load by Distracter interaction was found, with slower RTs in emotional than in neutral trials at high load than at low load, $F(1, 42) = 6.70$, $p = 0.013$ (see Fig. 1). There were no other interactions (Fs < 1.20, ps > 0.28).

See Table 3 for means and standard errors of error rates. Analysis of errors during present-target trials showed no effect of Group ($F[1, 42] = 1.29$, $p = 0.26$). There were significant main effects of Load ($F[1, 42] = 48.77$, $p < 0.0005$),

Table 3 Mean error rates and standard errors.

	Distracter	Group			
		Hydrocortisone		Placebo	
		Target: present $M \pm SE$	Target: absent $M \pm SE$	Target: present $M \pm SE$	Target: absent $M \pm SE$
Low Load	Emotional	1.05 (0.20)	0.43 (0.15)	0.57 (0.20)	0.44 (0.14)
	Neutral	0.76 (0.22)	0.71 (0.17)	0.57 (0.21)	0.44 (0.16)
	Total	0.91 (0.16)	0.57 (0.12)	0.57 (0.15)	0.44 (0.11)
High Load	Emotional	2.14 (0.38)	0.52 (0.17)	3.00 (0.37)	0.48 (0.16)
	Neutral	1.52 (0.34)*	0.62 (0.20)	2.57 (0.33)*	0.70 (0.19)
	Total	1.83 (0.32)*	0.57 (0.14)	2.78 (0.31)*	0.59 (0.13)

* Significant difference between groups, $p < 0.05$

and Distracter ($F[1, 42] = 4.66$, $p < 0.04$), with more errors at high load ($M \pm SE$, 2.31 ± 0.22) than at low load ($M \pm SE$, 0.74 ± 0.11), and more errors when distracters were neutral ($M \pm SE$, 1.69 ± 0.16) than when they were emotional ($M \pm SE$, 1.35 ± 0.15). A significant interaction was found between Group and Load ($F[1, 42] = 8.19$, $p < 0.007$, indicating that the placebo group made more errors at high load than the hydrocortisone group (see Table 3). There were no further significant interactions (all Fs < 1.74, all ps > 0.19).

In absent-target trials, the between-subjects factor Group showed a trend towards faster RTs in the hydrocortisone group (1008.51 ± 33.03) than the placebo group (1092.18 ± 34.56), $F(1, 42) = 3.06$, $p = 0.09$. There was a main effect of Load ($F[1, 42] = 302.63$, $p < 0.0005$), with faster RTs at low load than at high load. There was no significant effect of Distracter ($F[1, 42] = 2.10$, $p = 0.16$). A Group by Load interaction ($F[1, 42] = 4.60$, $p = 0.038$) indicated faster RTs in the hydrocortisone group at high load (1207.41 ± 35.65) compared to the placebo group (1347.04 ± 52.38) (see Table 2). There were no other significant interactions (all Fs < 0.05, all ps > 0.83). A repeated measures ANOVA on error rates showed no significant main effects or interactions (all Fs < 1.86, all ps > 0.18).

4. Discussion

In the present study, against our expectations, the administration of 35 mg hydrocortisone enhanced working memory performance in healthy young men. Hydrocortisone administration tended to result in higher overall processing speed, and its enhancing effects were specifically evident at high load: at high load, WM performance was faster with fewer errors. Moreover, hydrocortisone greatly reduced the distraction of emotional stimuli.

The finding that working memory performance was enhanced after hydrocortisone administration was not in line with our expectations. These results are inconsistent with several studies that found WM impairments after stress and GC administration (Lupien et al., 1999; Oei et al., 2006; Schoofs et al., 2008). However, it is in line with the one dose–response study that found evidence for both GC-induced WM impairment and enhancement (Lupien et al., 1999). Lupien et al. (1999) infused hydrocortisone (40, 300 or 600 μg/(dl/kg)) or placebo in young healthy men and assessed WM using the same task as was used in the present study, albeit without distracters. They found that the highest cortisol dose impaired WM at high comparison loads, as compared with the 40 and 300 μg/dl-groups. Importantly, the latter two experimental groups treated with intermediate doses performed *better* than the placebo group at high comparison loads. It could therefore be possible that the oral dose used in the current study resembles the intermediate doses infused in Lupien's study (1999). However, comparisons between hydrocortisone infusion, and administering a fixed oral dose cannot easily be made and as of yet it is unknown whether different doses – and which doses – of hydrocortisone would result in a similar inverted *U*-curved association using the emotional WM task.

Furthermore, in the present study, hydrocortisone enhanced WM accuracy at high load during the present-target trials. Participants were also faster, which excludes that speed was traded off with accuracy. Different doses of hydrocortisone administration, have, as far as we know, not yet shown to affect WM accuracy in a Sternberg task (Lupien et al., 1999). Accuracy has been shown to deteriorate due to psychosocial stress (Oei et al., 2006; Schoofs et al., 2008). Oei and colleagues found that stress impaired accuracy in the Sternberg paradigm specifically at high loads during present-target trials, whereas Schoofs et al. (2008) found group effects of stress, with decreased accuracy in the stress group, that was most pronounced at high load using the *n*-back task.

An explanation for the inconsistency between our results and those of other studies that found WM impairment after stress or hydrocortisone, could be the 'time of day' effect (Het et al., 2005). It appears that the inverted *U*-curved function between GC and memory, with very high and low GC doses causing impairment, and moderate doses causing enhancement, depends on the ratio of MR/GR receptor occupancy (Lupien et al., 2002; Lupien and Lepage, 2001). Because of the circadian cortisol peak in the morning, GC administration would be memory impairing, whereas in the afternoon, when basal levels are very low, GC administration would have enhancing effects. In a meta-analysis of studies on the effects of GC treatment on specific memory phases (encoding, consolidation and retrieval), Het et al. (2005) found that the effect size of GC administration was greatly determined by the time of testing. Therefore, time of day might modulate WM performance in a similar vein. Of the GC treatment studies that found WM impairment, one was conducted in the morning (Lupien et al., 1999) and the other in the morning and early afternoon, i.e., 1230 h (Wolf et al., 2001). Both studies found GC-induced WM impairment. However, as mentioned above, Lupien et al. (1999) also found WM enhancement in their morning study, which suggests that the effect of dose might be more important, and consequently a better explanation for our unexpected results, than time of day. Taken together, it cannot be ruled out that time of day has influenced the present results, that were obtained in the afternoon. However, more studies should first be conducted using comparable WM tasks, and different GC doses, to be able to draw conclusions on the effect of time of day on WM performance.

The coactivation of the beta-adrenergic system, is believed to be an important determinant of enhancing and impairing effects of cortisol on declarative memory of emotional material (Cahill et al., 1994; de Quervain et al., 2007). In rats, it was shown that both lesions of the basolateral amygdala, and propranolol administration blocked the WM impairment induced by corticosterone (Roozendaal et al., 2004). In line with these animal studies, WM impairment has specifically been found *during* stress (Elzinga and Roelofs, 2005), or in the first part of the WM study assessed after stress exposure (Schoofs et al., 2008), which might be associated with the influence of concurrent adrenergic activation. However, it should be noted that using the Sternberg task we also found WM impairment *after* the stressor was terminated (Oei et al., 2006). Moreover, it is unclear to what extent adrenergic activation is necessary for WM impairments after GC administration, as WM impairment after GC administration has been found by others using neutral WM tasks (Lupien et al., 1999; Wolf et al., 2001), which seems contradictory to the notion that GC administration only leads to impairment when the adrenergic system is activated. Although in the

present study only GCs were administered, the emotionally negative pictures that were shown during the task may have induced some arousal. Given the fact that our results were specific to the emotional trials, adrenergic activation may have added to the enhancing effects on WM.

In sum, although it is unclear to what extent dose of hydrocortisone administration, time of day or adrenergic activation may be involved in the finding of enhanced WM performance after hydrocortisone administration, it is unlikely that these factors completely explain the findings. Probably the best alternative explanation for finding GC-induced WM enhancement is task-related. Our task contained distracters, and is therefore not the same as the WM task version used in previous studies (Lupien et al., 1999; Oei et al., 2006; Schoofs et al., 2008; Wolf et al., 2001; Elzinga and Roelofs, 2005). The addition of distracters has changed the WM task significantly. It could be hypothesized therefore, that the enhanced WM performance after hydrocortisone administration was a direct effect of GCs on emotional distracter suppression. Unfortunately, we did not test performance on the WM task without distracters, so we cannot disentangle whether the GC effects on (emotional) distraction were direct, or whether the effects were an indirect consequence of enhanced WM performance. An indication, however, that GC effects on emotional distracter were direct, and not indirect via WM enhancement, was the remarkable finding that GCs reduced the interference of emotional distraction regardless of load. Overall, groups performed slower in trials with emotional than with neutral distracters, especially at high load. This finding is in line with the cognitive load theory, that predicts more distracter processing when cognitive load is high (Lavie, 2005). In several studies that used emotional distracters this effect was consistently present (Kensinger and Corkin, 2003; Dolcos and McCarthy, 2006). However, in the hydrocortisone group, interference by emotional distracters was similar to interference of neutral distracters. So, the distinction between neutral and negatively arousing stimuli disappeared. Importantly, emotional distraction in the hydrocortisone group did also not differ from neutral distraction in the control group. This indicates that GCs did not heighten arousal levels of neutral stimuli. On the contrary, the enhanced distractibility by irrelevant emotional stimuli that generally emerges, was greatly reduced by hydrocortisone. The fact that this was regardless of load, might indicate that GCs directly affected emotional distraction. This finding is consistent with other studies that found evidence suggesting fear-reducing effects of GC administration (Buchanan et al., 2001; Soravia et al., 2006; Putman et al., 2007). Our data extend those findings and may indicate that GCs decrease distractibility, particularly by emotional stimuli.

GC effects on distracter interference were only found during present-target trials. A different performance is generally found when having to detect the presence or absence of a target (Corbin and Marquer, 2008). For present-target trials, a self-terminating search is triggered, that is ended when the target is encountered. For absent-target trials, an exhaustive search strategy is displayed, where each stimulus is examined before the search can end. It is possible that the differential effects of emotional and neutral distracters were masked because of the exhaustive search strategy when a target is absent. Nevertheless, similar to present-target trials, overall performance during absent-target trials tended to be better in the hydrocortisone group, and was better at high loads.

It is unclear how GCs might affect the suppression of emotional distraction. Recently, however, Etkin et al. (2006) proposed that interference by emotional distracters may be overcome by an inhibitory rostral anterior cingulated cortex (rACC)—amygdala interaction, in which the ACC reduces the responsiveness of the amygdala toward task-irrelevant emotional stimuli. In line with this, it was found that conflict from non-emotional distraction is resolved by a lateral prefrontal 'cognitive control' system, showing enhanced processing in sensory cortices of task-relevant stimuli, whereas emotional distraction was resolved by a rACC 'emotional control' system, which was associated with decreased responses to emotional stimuli in the amygdala (Egner et al., 2008). This inhibitory relationship was also associated with blunted autonomic responses to emotional stimuli. Moreover, in another recent study, baseline cortisol levels were found to modulate activity in the rACC cortices (Liberzon et al., 2007). It could be speculated that the present dose of hydrocortisone has strengthened the rACC inhibitory control over the amygdala. However, this should be studied using imaging methods, preferably using a dose—response study.

Some limitations to our study should be mentioned. First, we have not used different doses of hydrocortisone. Without lower and higher doses than the one used in the present study, it remains uncertain whether different doses will give impairing effects on WM, and specifically whether this will be accompanied by more distracter interference. Also, we did not assess subjective valence and arousal ratings of the distracters. Therefore, we cannot tell whether the hydrocortisone group would have rated the emotionally negative pictures as less arousing or not. Also, only males were tested which reduces generalisation of these effects to females. Finally, because of the relatively small sample size the generalisability and statistical power of these data are confined.

Here, we show for the first time in healthy men that GCs enhance the ability to suppress interference from emotional distractions during the implementation of a WM task. Enhancing the ability to suppress intrusions is highly desirable for patients suffering from aversive and traumatic memories. There are several publications suggesting the possibility that administration of GCs may be suitable for treatment (and prevention) of PTSD and phobic fears by reducing traumatic memory retrieval and enhancing consolidation of fear extinction memories (Aerni et al., 2004; Schelling et al., 2004; Soravia et al., 2006; de Quervain and Margraf, 2008). Given the present results, it could be hypothesized that GC administration enhances suppression of intrusions by decreasing distraction by emotional stimuli directly, or indirectly by improving WM. In a recent study, GC administration showed to enhance WM performance in elderly PTSD patients (Yehuda et al., 2007). It would thus be interesting to see whether cortisol-induced WM enhancements in PTSD patients are related to enhanced distracter suppression. As a first step, at our lab it is currently investigated how female PTSD patients and healthy female controls perform on the same task using functional imaging. Further research in a healthy population should be done to see whether these enhancing

effects would also arise after chronic hydrocortisone administration and whether higher or lower doses would lead to opposite effects.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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