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The effects of cortisol increase on long-term memory retrieval during and after acute psychosocial stress

Marieke S. Tollenaar [a,*], Bernet M. Elzinga [a], Philip Spinhoven [a,b], Walter A.M. Everaerd [c]

[a] University of Leiden, Section of Clinical, Health and Neuropsychology, Wassenaarseweg 15, 2300 RB Leiden, The Netherlands
[b] University of Leiden, Department of Psychiatry, P.O. Box 9600, 2300 RC Leiden, The Netherlands
[c] University of Amsterdam, Department of Psychology, Roetersstraat 15, 1018 WB Amsterdam, The Netherlands

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Abstract

In this study the effects of stress-induced cortisol increases on long-term memory retrieval during and after acute psychosocial stress were examined. Seventy male students were exposed to either a psychosocial stress task or to a non-stressful control task. During and after this task, retrieval was tested for idiosyncratic emotionally negative and neutral word pair associations that were learned 1 day or 5 weeks earlier. Within the stress condition, retrieval of negative words, 5 weeks after learning, was impaired both during and after the stress task compared to the control group. Further, during the stress task, when sympathetic activity was enhanced, impaired retrieval of both neutral and emotional words was significantly related to enhanced cortisol response. In contrast, after the stress task, when cortisol levels were still increased but sympathetic activity was low again, no association was found between cortisol increase and retrieval of either neutral or emotional material. These results are in line with the previous animal research showing that when arousal is high, cortisol increase can impair memory retrieval.

PsycINFO classification: 2343

Keywords: Long-term memory; Emotion; Stress; Cortisol; Arousal

1. Introduction

Glucocorticoid (GC) hormones and catecholamines are secreted by adrenal glands during stressful or emotional experiences. Besides regulating the bodily response to a challenging environment (Sapolsky, Romero, & Munck, 2000), these hormones also influence cognitive functions (de Kloet, Oitzl, & Joels, 1999; Roozendaal, 2002). One of the cognitive functions that is sensitive to stress hormones is memory, due to a high number of mineralocorticoid (MR) and glucocorticoid (GR) receptors in brain structures that play an important role in memory functioning, including the hippocampus, amygdala and prefrontal cortex (see Wolf, 2008; de Kloet et al., 1999; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Lupien & Lepage, 2001; Roozendaal, 2002).

While learning seems to be facilitated by increased levels of stress hormones (Andreano & Cahill, 2006; Buchanan & Lovallo, 2001; Cahill, Gorski, & Le, 2003; Kuhlmann & Wolf, 2006a), retrieval of previously learned material has repeatedly been found to deteriorate with increased levels of GCs. That is, placebo controlled studies administering exogenous doses of cortisol to humans have consistently found impaired memory retrieval (Buss, Wolf, Witt, & Hellhammer, 2004; de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Domes, Rothfischer, Reichwald, & Hautzinger, 2005; Het, Ramlow, & Wolf, 2005; Kuhlmann, Kirschbaum, & Wolf, 2005; Wolf et al., 2001). Other studies have used a psychosocial stress task like the Trier Social Stress Task (TSST: Kirschbaum, Pirke, &

* Corresponding author. Tel.: +31 (0) 71 5275236; fax: +31 (0) 71 5274678.
E-mail address: mtollenaar@fsw.leidenuniv.nl (M.S. Tollenaar).

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Hellhammer, 1993) to study the effects of endogenous cortisol increases on memory retrieval. Results are similar to, but less consistent than the pharmacological studies (Domes, Heinrichs, Rimmele, Reichwald, & Hautzinger, 2004; Kuhlmann, Piel, & Wolf, 2005; Oei, Everaerd, Elzinga, van Well, & Bermond, 2006; Wolf, Schommer, Hellhammer, Reischies, & Kirschbaum, 2002). While Kuhlmann et al. (2005) found impairing effects of stress on memory retrieval of both negatively and positively valenced (or arousing) material, Domes et al. (2004) found this effect only on the recognition of positive material. Oei et al. (2006) found a relation between increasing cortisol levels and impaired retrieval of only moderately and not highly arousing material, while Wolf et al. (2002) did not find any effect of stress or cortisol increase on the retrieval of neutral material.

The discrepancy between findings of pharmacological and psychosocial stress studies may be related to the level of cortisol, as cortisol levels obtained in stress studies are generally much lower than after exogenous administration of cortisol. However, the effects of endogenous cortisol levels on memory retrieval may also depend on several other modulating variables, e.g. the arousing properties of the material, concurrent activation of the noradrenergic system, and the time interval between learning and retrieval. Each of these variables will be discussed briefly.

First of all, stress-induced cortisol increases are found to affect retrieval of emotionally arousing material more than neutral material (Domes et al., 2004; Kuhlmann et al., 2005), possibly explaining the non-results of Wolf et al. (2002) using only neutral material. Recent animal studies have pointed to the role of the noradrenergic system in mediating the cortisol effects on retrieval. A number of such studies have shown that noradrenergic activation of the basolateral amygdala is necessary for effects of cortisol to occur on memory functioning in general, including memory retrieval (Roozendaal, de Quervain, Schelling, & McGaugh, 2004; Roozendaal, Griffith, Buranday, de Quervain, & McGaugh, 2003; Roozendaal, Hahn, Nathan, de Quervain, & McGaugh, 2004). This adrenergic activity could be elicited either by intrinsic arousing properties of the learned material (explaining the effects on emotional versus neutral material), or by the level of arousal induced by the environment, such as novelty stress (Okuda, Roozendaal, & McGaugh, 2004). In fact, a study by Elzinga and Roelofs (2005) has shown that in humans, cortisol-induced working memory impairments are only found under acute stress conditions, when sympathetic activation (as a measure of adrenergic activity) is elevated. They differentiated between a situation of acute psychosocial stress, during which participants had to perform in front of an audience (when both sympathetic activation and cortisol levels were high), and a situation where cortisol levels were high, while sympathetic activation was back to basal levels, that is, after the stress task. High cortisol responders showed impaired working memory compared to low cortisol responders only during, but not after the stress task. Testing after the stress task, when the audience has left and participants have been able to recover, is the usual approach in studies investigating the effects of psychosocial stress (and related cortisol increase) on memory functioning. Conflicting reports regarding the role of endogenous cortisol increases on memory retrieval might thus be due to the level of arousal that participants experience at the time of memory testing.

Two human studies have looked into the effects of arousal elicited by the testing situation in combination with cortisol increases during memory retrieval. Buchanan, Tranel, and Adolphs (2006) measured skin conductance (as a measure of sympathetic activity) and cortisol levels in response to a cold pressure test, after which memory retrieval was tested. They found that increased cortisol levels, but not the skin conductance levels, were related to impaired memory retrieval. From this study, however, we cannot conclude whether sympathetic arousal is necessary for the impairing effects of cortisol increases on memory retrieval to occur. Recently however, Kuhlmann and Wolf (2006b) reported a comparison of studies in which arousal related to the testing environment was manipulated while testing the effect of exogenous cortisol on retrieval. They compared two of their previous studies (Kuhlmann et al., 2005; Kuhlmann & Wolf, 2005) that were conducted in a standard formal testing situation, with a highly similar study in which they had changed the testing situation into a more relaxing, non-arousing, environment. The impairing effect of administered cortisol on retrieval that was found earlier in the standard formal testing situations did not occur in the more relaxed setting. While these results may suggest that in humans, adrenergic activation is also necessary for the effect of cortisol to occur on memory retrieval, they did not assess sympathetic activity (or a more direct measure of adrenergic activity) in their participants, and hence it remains undecided whether the different findings are indeed related to differences in sympathetic arousal levels.

Another factor that could influence the effect of cortisol on memory retrieval is the time frame between learning and recall. The usual paradigm in retrieval studies is to test recall of material that has been learned a few hours to a day before, not always allowing a clear separation between consolidation and retrieval processes. Whether memory retrieval remains sensitive to the effects of stress long time after learning is a topic that has not been well studied. To date, only the study of Wolf et al. (2002) examined the effects of a social stress task on the retrieval of material learned 4 weeks earlier. They did not find any effects of stress or cortisol increase on long-term memory retrieval, but this could also have been due to the nature of material that was learned (e.g., not emotionally arousing) and the testing situation (e.g. the arousing stressor was no longer present at the time of retrieval testing). Another issue might have been a floor effect, with only few words remembered after 4 weeks.

In summary, further work is clearly required taking into account the factors described above. The study we describe

here examines the effects of stress-induced cortisol on the retrieval of neutral and emotionally arousing words, learned either 24 h or more than a month before testing. Moreover, to test whether sympathetic arousal enables the effects of cortisol on memory, retrieval was tested both during an acute psychosocial stress task, with elevated cortisol levels and increased sympathetic activation, and after that stress task while cortisol levels are still high, but sympathetic activity is low again. During the acute stressor, we anticipated memory retrieval to be affected by cortisol increases, while after the stress task (the standard testing moment) this effect should be less evident. We expected that this distinction would be most prominent for the retrieval of neutral material, which elicits no intrinsic emotional arousal. In line with previous studies, we expected that retrieval of (negative) moderately arousing material might still be affected after the stress task, when sympathetic activation due to the stress task is low again.

2. Methods

2.1. Participants

Seventy healthy male Dutch students participated in the study. Their mean age was 21.34 ± 2.9 years (SD) with a minimum of 18 and maximum of 30. Their average body mass index (BMI) was 22.04 ± 3 kg/m^2 (SD). A male population was chosen to rule out potential effects of gender and endogenous estradiol on cortisol reactivity in response to stress (Kirschbaum, Pirke, & Hellhammer, 1995). Participants were included in the study if they were free of any medication and reported no serious illnesses, substance abuse, or mental problems (on AXIS 1 of the DSM-IV) in the last year. Participants were randomly assigned to one of the four experimental conditions (see below). The four groups did not differ in age or BMI (all $p > 0.10$).

All participants gave written informed consent and the study was approved by the ethics committee of the Leiden University Medical Center (LUMC). Participants received financial rewards or course credits for participation.

To minimize influences on baseline cortisol levels, cigarette smokers ($n = 14$) were instructed not to smoke at least 2 h before the start of both test sessions. Participants were also instructed to refrain from any heavy meals, sweets and coffee in the morning and not allowed to eat or drink anything but water in the hour previous to both testing sessions. In addition, participants were asked to minimize physical exercise or psychological distress in the hours prior to testing.

2.2. Procedures and tasks

The study consisted of two experimental sessions both starting at either 11.30 am or 1.30 pm, and lasting 1.5 h each. Participants were instructed to awake at least 3 h prior to both sessions to avoid the morning rise in cortisol. The second session was either one day after the first (1-day group) or 5 weeks later (5-week group). Participants were randomly assigned to the 1-day or 5-week group, so that both groups consisted of 35 participants. Within these two groups, 20 participants were assigned to the stress task and 15 to the control task in a random fashion. More participants were assigned to the stress groups to account for possible non-responders and to be able to perform within stress group correlation analyses. Fig. 1a shows a schematic representation of the random assignment of the participants.

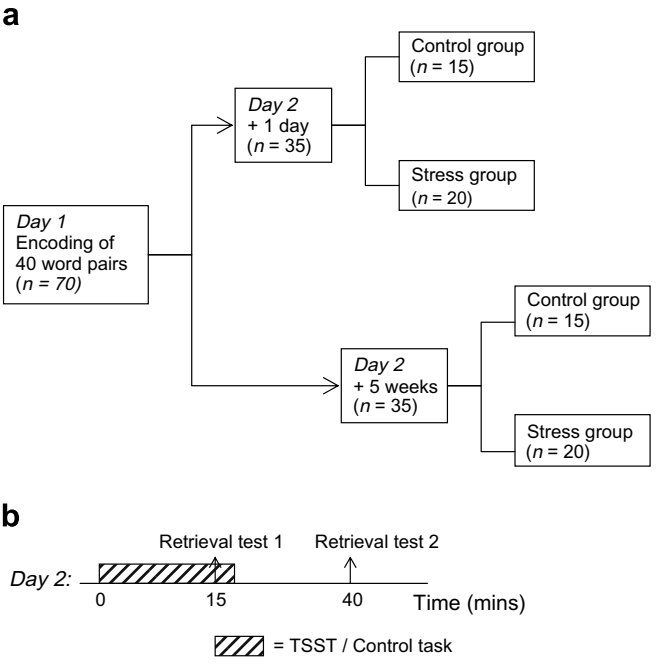

Fig. 1. (a) Randomization scheme of the groups. (b) Scheme of the protocol on day 2 for all groups.

2.2.1. Stress task

The Trier Social Stress Task (TSST) is a well established laboratory stress task that has been shown to consistently induce significant endocrine and cardiovascular responses in a large part of participants (Kirschbaum et al., 1993, see also Dickerson & Kemeny, 2004). The TSST consists of a short preparation period of 5 min, in which the participant is instructed to prepare for a 5-min speech in front of an audience. Participants were told that this audience consisted of a psychologist with 2 assistants, while in fact these were testing-assistants wearing white coats. Participants were told that the speech would mimic a job interview for a fictitious job in which they had to present themselves and convince the audience of their adequacy. In addition, they were videotaped and voice-recorded and were told that the psychologists were trained to monitor non-verbal behavior. They were also told the speech would be critiqued on content and presentation style. Following preparation time, the audience entered the room and switched on the camera and microphone in view of the participant. Participants were instructed to stand in front of a table

with the audience sitting at the other side, while the chairman led the interview. After the interview the chairman asked the participant to do a mental arithmetic task in which they had to serially subtract 13 from . The audience responded to any mistake by instructing participants to start over. This lasted for another 3 min before the experimenter came into the room to perform physiological measures and to administer the first part of the memory word task, while sitting between the audiences who attentively watched the participant. After this task, the audience left the room.

The control condition consisted of a reading period of 15 min, comparable to the timing of the TSST.

2.2.2. Memory task

For the present study an idiosyncratic word pair memory task was developed, which was tested in a pilot study for feasibility ($n = 9$). Idiosyncratic word pairs were used to increase emotionality and self relevance of the learning material, thereby increasing the generalization of the findings to autobiographical memories and to prevent a potential floor effect after 5 weeks.

On the first testing day participants were randomly given a list of 40 cue words, consisting of 20 neutral and 20 negative (emotion) words, similar in word length and frequency. Participants were asked to generate 2 associations to each word while having a clear image in mind of those associations (e.g. a participant named the words 'sport' and then 'water' in response to the cue word 'row'). After this was done for all words, the experimenter coupled the cue words with the second association words that participants had generated, forming word pairs (i.e. 'row' and 'water'). The cue word was coupled to the second word association to reduce mere implicit associative recall. The word pairs were read aloud twice. After the first repetition, recall was tested by asking the subject to name the coupled (second) word to each cue word. During the second repetition participants were asked to rate each word pair on two standardized, 9-point Likert scales on emotionality and valence from the Self-Assessment Manikin (SAM: Bradley & Lang, 1994). After this was done for all word pairs, recall was tested again.

On the second testing day, recall of word pairs was tested twice, once during (at $t = 15$) and once 20 min after the stress or control task (at $t = 40$) (see Fig. 1b). Cue words were randomly divided over the two trials, with the restraint that half would be neutral and half would be negative in valence, and that length and frequency of the 2 lists would be comparable. The cue words were read to the participants and they were asked to recall their second association to that word. Instructions were given to think back of the moment they associated these words. Recall performance was measured as the percentage of words remembered in relation to the number correctly recalled on the last recall trial of the learning day. This was done to account for possible between- and within-participant differences in initial learning on the two trials.

2.3. Stress measures

All physiological and subjective stress measures were taken at −10, 0, 15, 25, 40 and 60 min with reference to the stress task.

2.3.1. Cortisol assessment

Cortisol samples were obtained with Salivette collection devices (Sarstedt, Rommelsdorf, Germany). Saliva samples were stored at −20 °C before assay. Biochemical analysis of free cortisol in saliva was performed with a competitive electrochemiluminescence immunoassay (Elecsys 2010; Roche Diagnostics, Laval, Quebec, Canada), as described elsewhere (van Aken, Romijn, Miltenburg, & Lentjes, 2003).

2.3.2. Sympathetic activity

We used heart rate and blood pressure as measures of sympathetic activation. Heart rate was recorded continuously by an ambulatory monitoring system (VU-AMS, Version 3.6; Vrije Universiteit Amsterdam), a small battery-powered device for ambulatory recording. It was measured with three Ag–AgCl disposable electrodes (ConMed, Utica, NY), placed just above the sternum, at the left side of the chest and at the bottom right side of the chest. For each participant, heart rate was averaged over a period of 2 min after markers were given at each of the 6 assessment points. Systolic and diastolic blood pressure were measured from the non-dominant arm with an automatic blood pressure monitor (Model Omron R5-I). Measures were taken after each saliva sampling.

2.3.3. Subjective measures

Tension, anxiety, insecurity, mood and tiredness were assessed on a visual analogue scale ranging from 0 to 100 mm during each saliva sampling.

2.4. Statistical analyses

The effects of the stress task on both stress reactivity and memory were analyzed with repeated measure ANOVAs. Greenhouse-Geisser corrected p values were used when indicated by violated Sphericity, and follow-up analyses were done using two-tailed Holm-adjusted t-tests (Aickin & Gensler, 1996). To examine whether the levels of absolute cortisol increase were associated with impaired memory retrieval, follow-up analyses within the stress group were done using one-tailed Pearson's correlations. Analyses were performed with SPSS 14.0 (SPSS, Chicago, IL). The criterion for statistical significance was $p < 0.05$.

3. Results

3.1. Stress induction

3.1.1. Cortisol

Fig. 2a shows mean (±SEM) free salivary cortisol (nmol/L) before, during, and after the stress or control task

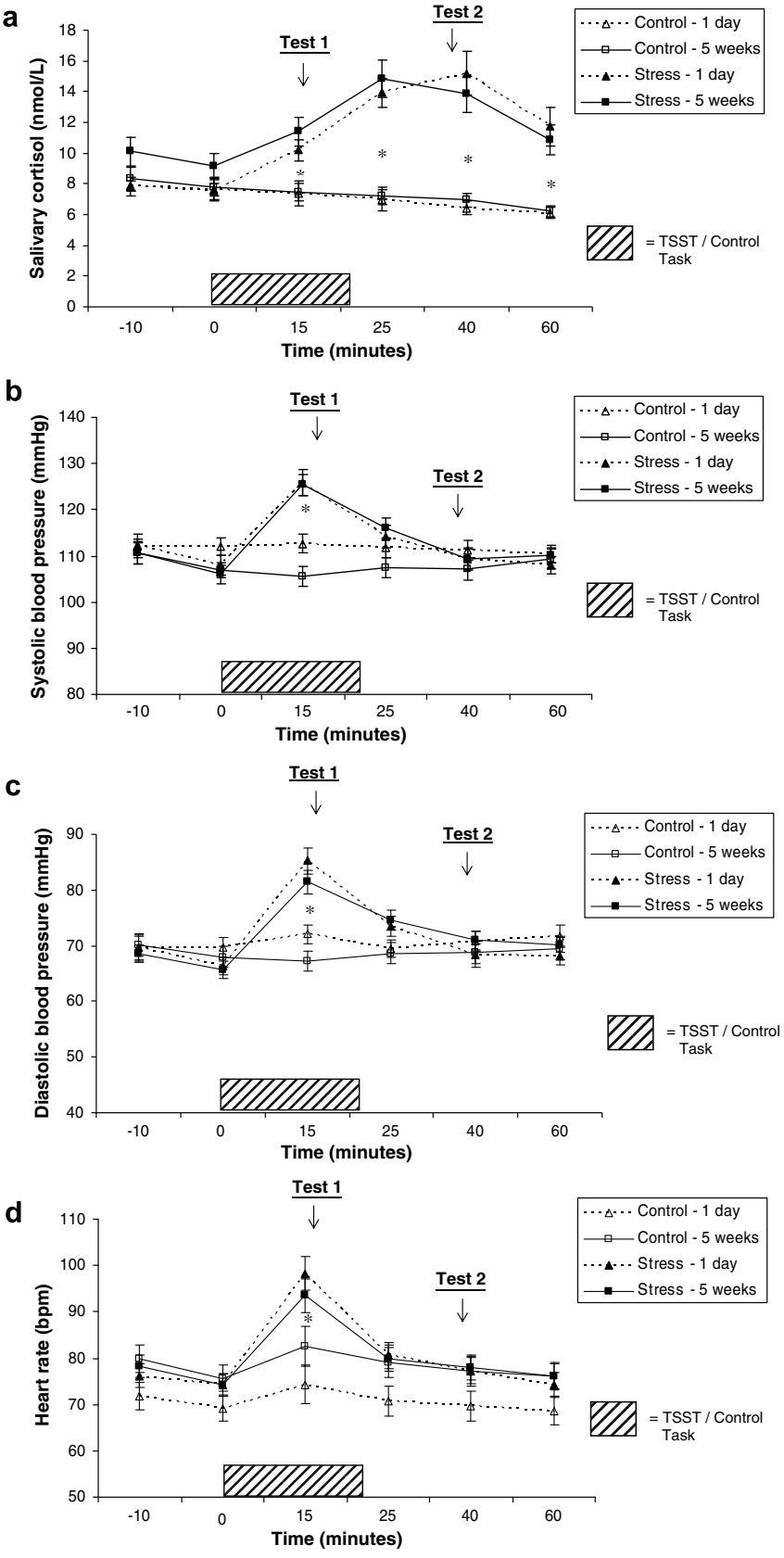

Fig. 2. Mean physiological measures before, during, and after the stress or control task in the two stress groups and two control groups. (a) Mean (± SEM) free salivary cortisol in nmol/L. (b) Mean (± SEM) systolic blood pressure in mmHg. (c) Mean (± SEM) diastolic blood pressure in mmHg. (d) Mean (± SEM) heart rate in bpm. Test 1 = Retrieval testing during stress / control task; Test 2 = Retrieval testing after stress / control task; * = significant differences between control and stress conditions at $p < 0.01$.

in the two stress groups and two control groups. Five participants (three from the 1-day stress group and two from the 5-week stress group) had missing values of cortisol during the stress task, due to low saliva levels at that time, and 1 participant in the 1-day stress group missed the first baseline value, and were therefore left out of the next analyses. An ANOVA with repeated measures for mean cortisol levels showed significant increases in cortisol over time in the stress conditions compared to the control conditions (time × condition; $F(2, 128) = 32.9$, $p < .001$). There was no effect of retrieval period (1 day vs. 5 weeks) ($F(2, 128) = 1{,}63$, *ns*), nor an effect of the starting time of the experiment (at 11.30am or 1.30 pm) ($F(2, 121) = 0.64$, *ns*).

Post hoc (Holm-adjusted) paired sample *t*-tests within the stress conditions showed that cortisol levels were higher during the TSST ($t = +15$), at the time of the first retrieval task (10.81 ± 3.42 nmol/L) compared to baseline, right before the TSST (8.45 ± 3.24 nmol/L, $t(34) = 10.20$, $p < 0.001$), as well as after the TSST ($t = +40$), at the time of the second retrieval task (13.62 ± 5.02 nmol/L, $t(34) = 6.83$, $p < 0.001$). Consistent with diurnal rhythm, in the control conditions there was a significant decrease between cortisol levels right before (7.70 ± 2.37 nmol/L) and after the reading phase, at the time of the second retrieval task, (6.69 ± 1.79, $t(29) = 3.26$, $p < 0.01$), but not at the time of the first retrieval task (7.45 ± 2.72, $t(29) = 1.04$, *ns*).

3.1.2. Heart rate and blood pressure

Fig. 2b–d show, respectively, mean (±SEM) systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and heart rate (bpm) before, during, and after the stress or control task in the 2 stress groups and 2 control groups. Repeated measure ANOVA's revealed significant condition by time interactions, due to increases in systolic blood pressure (SBP: $F(4, 276) = 36.46$, $p < 0.001$), diastolic blood pressure (DBP: $F(4, 267) = 39.21$, $p < 0.001$) and heart rate (HR: $F(2, 126) = 17.50$, $p < 0.001$) in the stress conditions compared to the control conditions. There was no effect of retrieval period (SBP: $F(4, 276) = 1.18$, *ns;* DBP: $F(4, 267) = 1.29$, *ns*; HR: $F(2, 126) = 0.97$, *ns*) or starting time of the experiment (SBP: $F(4, 253) = 0.98$, *ns;* DBP: $F(4, 242) = 1.30$, *ns*; HR: $F(2, 119) = 0.19$, *ns*).

Post hoc, Holm-adjusted, paired sample *t*-test within the stress conditions show that blood pressure and heart rate were higher during the TSST ($t = +15$), at the time of the first retrieval task compared to baseline, right before the TSST (SBP: $t(39) = 12.47$, $p < 0.01$; DBP: $t(39) = 10.87$, $p < 0.001$; HR: $t(39) = 9.69$, $p < 0.01$). After the stress task, at the time of the second retrieval task ($t = +40$), all three measures were significantly lower than during the stress task (SBP: $t(39) = 14.73$, $p < 0.01$; DBP: $t(39) = 14.86$, $p < 0.01$; HR: $t(39) = 9.51$, $p < 0.01$), but were still slightly elevated compared to baseline (SBP: $t(39) = 2.04$, $p < 0.05$; DBP: $t(39) = 3.87$, $p < 0.01$; HR: $t(39) = 3.80$, $p < 0.01$). In the control conditions there were no changes in blood pressure from baseline over time. Heart rate was slightly elevated at the time of the first retrieval task ($t(29) = 2.81$. $p < 0.05$), but returned to baseline after the reading phase ($t(29) = 0.53$, *ns*).

3.1.3. Subjective stress measures

Subjects tested under the stress condition showed a significant increase over time in tension, insecurity and anxiety compared to those tested under the control condition (all time by condition interactions in the repeated measure ANOVA's had *p*-values < 0.001, with no effect of retrieval period). Increases in these subjective stress measures during the stress task were still slightly elevated after the stress task (all paired samples *t*-tests; $p < .05$). Even though mood seemed to be decreased during the stress tasks, this effect was not significantly different from the control conditions, which was the same for tiredness (for both measures the interactions of time by condition; $p > 0.10$).

3.2. Memory task

3.2.1. Arousal and valence ratings

On day 1 (which was the same for all groups) word pairs were rated on level of arousal and valence. Both scales were rated on a 9 point scale ranging from 1 (low arousal) to 9 (high arousal), and 1 (very positive) to 9 (very negative). As expected, the word pairs we classified as negative were rated more negative in valence (6.6 ± 0.11) than the neutral word pairs (4.2 ± 0.07, $t(69) = 20.7$, $p < .001$) and elicited more arousal (4.6 ± 0.2) than the neutral word pairs (2.6 ± 0.16, $t(69) = 13.9$, $p < .001$). No group differences were found in the rating of the word pairs ($F(3, 66) = 0.32$, *ns*).

3.2.2. Memory retrieval

Data for all four groups on the retrieval task during and after the stress or control condition are shown in Fig. 3.

In the groups with a retrieval period of 1 day, both the stress and the control condition retrieved significantly less negative words than neutral words ($F(1, 33) = 49.32$, $p < .001$). Overall, participants in the stress condition recalled fewer word pairs than the control condition, but this was only a trend ($F(1, 33) = 3.02$, $p = .09$). No interactions were found with valence or moment of testing (during vs. after the stress task). However, these results should be interpreted with caution, as more than 50% of the participants scored a 100% correct on the retrieval of neutral words and 87% or more correct on the retrieval of negative words. This indicates a ceiling effect after 1 day, and the variance in this data is most likely not enough for reliable statistical analyses.

In the groups with a retrieval period of 5 weeks, no main effect of condition on memory retrieval was found. Also, no main effect of effect of valence or moment was indicated, but the repeated measures ANOVA did show a trend for an interaction of condition by valence ($F(1, 33) = 3.23$, $p = 0.08$). Explorative follow-up analyses showed that within the stress condition, significantly fewer negative words were retrieved than neutral words ($F(1, 19) = 8.49$,

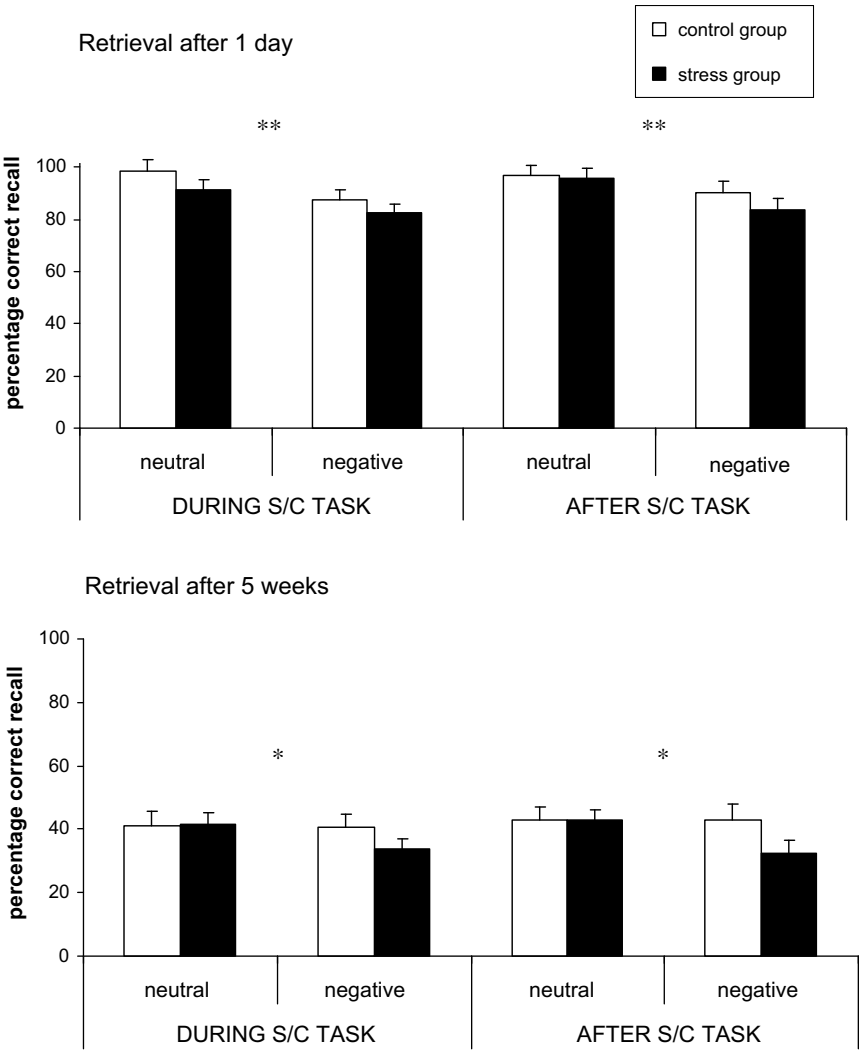

Fig. 3. Performance (mean ± SEM) on the word pair retrieval task, both during and after the stress vs. control (S/C) task, in the groups with a retrieval period of 1 day vs. 5 weeks. Results are expressed as percentage recall of the last learning trial, for neutral and negative word pairs. ** = significant difference between neutral and negative words at $p < 0.001$; * = significant difference between neutral and negative words in the stress group at $p < 0.01$.

$p < 0.01$), an effect not present in the control condition ($F(1, 14) = 0.00$, *ns*). Moreover, participants in the stress condition tended to recall fewer negative words compared to the control condition ($t(33) = 1.77$, $p = 0.09$), with no effect of moment of testing. Contrary to expectations, no effect of the stress condition was found on neutral words during the stress task.

3.2.3. Cortisol increase and retrieval performance

To investigate the relation between absolute cortisol increase and retrieval performance within the stress condition, one-tailed Pearson's correlations were calculated between absolute cortisol increases (test moments minus baseline level) and memory retrieval, both during and after the stress task (at $t = 15$ and $t = 40$). Because of the ceiling effect in the group with a retrieval period of 1 day, we analyzed these effects only in the 5 week stress group. In this group, two participants missed cortisol data at the moment during or after the stressor and were therefore removed from the analyses ($n = 18$).

Table 1 shows the results for the correlation analyses between retrieval performance and cortisol. Correlations to baseline cortisol levels and to increases in cortisol from baseline to $t = 15$ (during the stress task) and to $t = 40$ (after the stress task) are shown. During the stress task, cortisol increase (at $t = 15$) was significantly associated with impaired performance on the retrieval task ($r = -0.58$, $p < 0.01$). Correlations were significant for the retrieval of both neutral ($r = -0.48$, $p < 0.05$)[1] and negative

[1] It may seem puzzling that even though there is no group effect of stress on the retrieval of neutral words, we do find a correlation between retrieval and cortisol. This can be explained by the fact that a small increase in cortisol may actually increase memory retrieval, as has been found before (inverted-U function relationship; Domes et al., 2004; Lupien & McEwen, 1997). We did not find a significant quadratic association between cortisol increase and retrieval ($F(2, 30) = 2.06$, *ns*), but when we perform a median split on the cortisol response, low cortisol responders do score higher on retrieval than controls ($M = 52.6$, $SD = 30$ vs. $M = 41.1$, $SD = 17$) and high cortisol responders perform worst of all groups ($M = 28.8$, $SD = 14$).

Table 1
Pearson correlations between memory retrieval, baseline cortisol levels ($t = 0$) and increases in cortisol from baseline, during ($t = 15$) and after ($t = 40$) the stress or control task ($n = 18$)

	Retrieval test 1 ($t = 15$)		Retrieval test 2 ($t = 40$)	
	Neutral words	Negative words	Neutral words	Negative words
Baseline cortisol ($t = 0$)	−0.17	−0.10	0.15	0.17
Increase in cortisol ($t = 15$-0)	−0.48*	−0.45*	0.00	−0.18
Increase in cortisol ($t = 40$-0)	−0.12	0.16	−0.05	−0.02

* $p < 0.05$.

words ($r = -0.45$, $p < 0.05$). No associations were found between cortisol increase during the stress task and performance afterwards (for neutral words: $r = 0.00$, *ns*; negative words: $r = -0.18$, *ns*).

After the stress task, no significant associations were found between retrieval performance and cortisol increase (at $t = 40$) (for neutral words: $r = -0.05$, *ns*; negative words: $r = -0.02$, *ns*). No associations were found between cortisol increase after the stress task and performance during the stress task either (for neutral words: $r = -0.12$, *ns*; negative words: $r = 0.16$, *ns*). No significant associations were found between retrieval performance at any time point and absolute baseline cortisol levels.

We hypothesized that only when arousal is high, cortisol can impair memory retrieval. During the stress task sympathetic activity was indeed significantly elevated, and only then associations between cortisol increase and memory retrieval were found. However, not all subjects in the stress group responded with a similar heightened sympathetic arousal. Therefore we separately analyzed the correlation between cortisol increase and memory retrieval during the stress task, excluding subjects that responded with an increase in heart rate less than 10 bpm and an increase in systolic blood pressure less than 10 mmHg ($n = 5$). Including only subjects that responded with heightened arousal during the stress task ($n = 13$), correlations between cortisol increase and memory retrieval were even stronger (total: $r = -.83$, $p < 0.001$; for neutral words: $r = -0.66$, $p < 0.01$; for negative words: $r = -0.76$, $p = 0.001$).

4. Discussion

The present study examined the role of cortisol increases on long-term memory retrieval both during and after acute psychosocial stress. In the groups with a retrieval period of 5 weeks, the retrieval of negative, moderately arousing word pairs was affected compared to the retrieval of neutral words, both during and after acute stress. This is in line with previous research showing an impairing effect of psychosocial stress on the retrieval of emotional memory (Kuhlmann et al., 2005; Domes et al., 2004), but not of neutral memory (Wolf et al., 2002). Interestingly, increase in cortisol was significantly associated with impaired memory retrieval only during and not after the stress task (the standard testing time for stress studies, when the audience of the TSST has exited). This effect was found for the retrieval of both negative and neutral words. Thus, even though no overall effect of stress was found on the retrieval of neutral words during the stress task, within the stress group a significant association between increase in cortisol and impaired retrieval of neutral words was revealed. Apparently, only during acute stress, at a time of heightened sympathetic and subjective arousal, and in the presence of an audience, cortisol increases are associated with impaired retrieval of neutral and emotionally arousing material learned 5 weeks before. From the results in the groups with a retrieval period of 1 day, little can be concluded due to a ceiling effect leading to only slight variance in performance for appropriate statistical testing. Overall, there seemed to be a negative effect of stress on memory retrieval of material learned 1 day before, but no different effects for neutral and negative word pairs or for moment of testing could be discerned.

Several explanations can be put forward for the specific relation between cortisol and memory during, but not after the TSST (after 5 weeks). First of all, these findings are consistent with findings in animal studies that adrenergic arousal is needed for cortisol effects to occur on memory retrieval (Roozendaal et al., 2003; Roozendaal, de Quervain et al., 2004; Roozendaal, Hahn et al., 2004). Moreover, these findings are also in line with the study of Kuhlmann and Wolf (2006b), who found indications in humans that an arousing environment is necessary for the impairing effects of exogenous cortisol on memory retrieval to occur. Indeed, in our study cortisol increases no longer influenced memory retrieval after the stress task, when the social evaluative stressor was gone. On group level, however, retrieval of emotional words 5 weeks after learning was still affected *after* the stress task. At that time in the stress group, sympathetic and subjective arousal due to the stress task was again comparable to the control group, but not completely back to baseline. It is possible that in combination with noradrenergic activation in the amygdala elicited by the retrieval of the emotionally arousing words, cortisol may still have had an impairing effect on retrieval performance. This would be consistent with and increasing number of studies showing that the amygdala is activated during emotional memory retrieval (Dolcos, LaBar, & Cabeza, 2005; Sharot, Delgado, & Phelps, 2004; Smith, Henson, Dolan, & Rugg, 2004; Sterpenich et al. 2006). No correlations were found, however, between retrieval of emotional words and cortisol increases after the stress task. Altogether, the effects of cor-

tisol on memory retrieval in interaction with adrenergic activation in the amygdala, due to either emotionally arousing material or environmentally evoked arousal, should be further explored. An interesting approach would be to block the adrenergic system while testing memory retrieval under high cortisol levels. This would be even more informative in combination with functional MRI. Functional MRI studies could also shed more light on which brain areas are specifically involved in long-term memory retrieval (for a discussion see: Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006).

There is another possible explanation, however, for the finding of impaired retrieval in relation to cortisol increases during stress. During the stress task, participants perform the retrieval task in the presence of an audience. Performing a memory task while being socially evaluated asks of the participant to inhibit the processing of environmental cues and to focus on the memory task. Animal data have shown that whereas cortisol may facilitate the encoding of relevant stimuli (i.e. the stressful context), it may at the same time impair cognitive functions unrelated to the stressor (i.e. the memory task) (see de Kloet et al., 1999). The amount to which a subject is able to inhibit thoughts and feelings related to the audience could depend on cortisol levels, therewith indirectly affecting memory retrieval. However, on group level there was no performance difference during and after the stress task, so it is questionable whether this is happening. To evaluate this hypothesis, measures of distraction and/or memory for the psychosocial task itself should be taken into account in future research using comparable designs.

One should also keep in mind that performance was tested at two moments, with the condition of high cortisol and high arousal always before the condition with high cortisol and low arousal. Time effects could thus have played a role, for example, fast cortisol responders might differ in their cognitive functioning from late cortisol responders. However, increase in cortisol during the stress task did not correlate to performance after the stress task or vice versa, so cortisol reactivity of participants cannot explain their overall performance.

Although a large sample of 70 participants was recruited for the present study, when divided over treatment and retrieval period, the groups were rather small. Despite this, our results do confirm our expectations and could therefore be considered as evidence for impairing effects of stress-induced cortisol elevations on long-term memory during stress. For stronger conclusions, additional research is necessary in larger samples. Further, earlier studies have found differences in the effects of stress on memory between men and women (Wolf, Schommer, Hellhammer, Mcewen, & Kirschbaum, 2001). Since only males were included in the present study, it is still to be investigated whether similar findings will be found in a female population.

The new paradigm we developed for idiosyncratic word pair generating proved effective as a sensitive memory task after 5 weeks. Delayed recall rates might have been a problem in the study of Wolf et al. (2002), where a floor effect could potentially have explained the non-results. However, the effectiveness on long-term memory retrieval in our study was at the cost of a low sensitivity of this task after 1 day, where we ran into a ceiling effect. Since idiosyncratic words were used, this task is more autobiographic than a standard word pair task and it makes a clear distinction in the valence and arousal ratings of the negative and neutral word pairs. We intended to measure episodic memory with the task, but subjects might possibly have been guessing on parts of the memory task if they did not directly recall their second association. This might have led to a more semantic type of memory testing which we did not control for but should be done with future use of the task. It is also interesting to note that this task shows opposite results of what is usually found in retrieval of neutral and emotional material. Usually emotionally arousing material is remembered better than neutral material (Cahill, 1999), which might be due to amygdala-related arousal effects on consolidation (Strange & Dolan, 2004; van Stegeren et al., 2005), while in our study recall of emotional words was lower than recall of neutral words. This might be related to a higher semantic cohesion in emotion words (Buchanan, Etzel, Adolphs, & Tranel, 2006; Dillon, Cooper, Grent-'t-Jong, Woldorff, & LaBar, 2006), making the emotional word pairs more difficult to keep apart.

To summarize, while exogenously induced cortisol levels seem to be able to impair memory retrieval as long as testing is performed in a formal research setting (Kuhlmann & Wolf, 2006b), stress-induced cortisol levels may only have an impairing effect on emotional memory retrieval or on memories retrieved during acute stress, with heightened sympathetic activation or a distracting evaluative component. Since psychological stress is a common real life condition, the effects of cortisol on memory retrieval may have implications in different fields. The results of our study suggest for a way to pharmacologically treat stress related memory problems like blackouts during stressful situations as exams or job interviews. If stress-induced cortisol is blocking memory only when adrenergic arousal is high, administration of beta-adrenergic blockers like propranolol before a stressful experience may be able to reduce the impairing effects of cortisol, while leaving cortisol levels intact, which might be of importance for cognitive functioning (Lupien & McEwen, 1997). Whereas beta-blockers are already frequently in use by people with anxiety problems, the independent effects on memory retrieval have never been thoroughly studied before (Chamberlain, Muller, Blackwell, Robbins & Sahakian, 2006). Another area of interest is the field of psychiatric disorders like post traumatic stress disorder (PTSD) and depression. Patients troubled with these disorders show disturbed patterns of basal cortisol levels or cortisol reactivity (Burke, Davis, Otte, & Mohr, 2005; Nemeroff & Vale, 2005; Raison & Miller, 2003; Yehuda, 2001) and also show problems in cognitive functions related to memory (Barnhofer, Kuehn, & de Jong-Meyer, 2005; Elzinga & Bremner, 2002; McNally,

1998; Raes et al., 2006). If increases in cortisol can block the retrieval of emotionally arousing memories, administration of cortisol might be a useful treatment in patients that are bothered by involuntary recall of (emotional) memories. Recent pharmacological studies involving the administration of exogenous cortisol to PTSD patients (Aerni et al., 2004) and phobic patients (Soravia et al., 2006) have shown promising results.

In conclusion, the present study is the first to measure sympathetic activity in combination with cortisol elevations while studying memory retrieval during and after acute stress. It confirmed our hypothesis that acute stress and/or emotional arousal is necessary for endogenous cortisol effects on memory retrieval to occur, and is consistent with the study by Kuhlmann and Wolf (2006b) using exogenous cortisol elevations, and animal studies measuring and manipulating the adrenergic activity of the amygdala under cortisol administration (Roozendaal, de Quervain et al., 2004; Roozendaal, Hahn et al., 2004). The effects of stress hormones on memory in patient studies should shed more light on the use of pharmacologic stress hormones either in blocking unwanted memories or blocking the impairing effects of elevated stress hormones on memory retrieval. Furthermore, long-term outcomes of retrieving memories under stress hormones are still unknown and should therefore also be a subject of future investigations.

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