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Stress-induced cortisol elevations are associated with impaired delayed, but not immediate recall

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Abstract

Glucocorticoids are known to modulate memory functions, with elevated cortisol levels being associated with impaired declarative memory. This specific effect has been shown in several studies using pharmacological doses of cortisol. The present study was designed to assess the effects of stress-induced cortisol elevations on (1) the type of memory processing (encoding, consolidation and retrieval), and (2) on the emotional valence of the material under study. Sixteen healthy females were presented neutral and emotional material (words and paragraphs) before and after a stress challenge. Declarative memory was tested immediately after presentation and 24 h later (delayed recall). Delayed, but not immediate recall of the information presented after the stress challenge was significantly reduced compared with delayed recall of information presented before the stress challenge. In line with this, strong negative correlations were found for delayed recall of words and spatial memory presented after the challenge with post-stress cortisol levels, whereas no significant correlations were found between cortisol levels and delayed recall at day 1. These results suggest that stress-induced cortisol specifically affects long-term consolidation of declarative memories. These findings may have implications for understanding the effects of traumatic stress on memory functioning in patients with stress-related psychiatric disorders.

Keywords: Stress; Glucocorticoids; Memory; Hippocampus; Consolidation; Humans

1. Introduction

The relationship between stress and memory is currently a topic of considerable interest (Bremner, 1999; Lupien and Lepage, 2001; McGaugh, 2000;

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Roozendaal, 2002; de Kloet et al., 1999). Evidence that stress or arousal can have important effects on memory functioning dates back to almost a century ago when the Yerkes–Dodson law was proposed describing an inverted U-shaped relationship between arousal and memory performance (Yerkes and Dodson, 1908). Moderate as compared with low levels of arousal facilitate learning and memory up to an optimal point, beyond which additional arousal leads to a successive decrease in memory functioning. Also from a clinical punt of view, there are clear indications that chronic stress results in persistent memory impairments, given the disturbances in memory functions that are pervasive in stress-related psychiatric disorders, including depression, posttraumatic stress disorder, and dissociative disorders (Bremner et al., 1993; Elzinga and Bremner, 2003; Burt et al., 1995; Dorahy, 2001).

Hormones released during stress such as glucocorticoids (GCs) and catecholamines have effects on memory that may provide a mechanism for the inverted U relationship between stress and memory. There are indications that catecholamines and low to moderate levels of GCs strengthen memory formation in the short term (see McGaugh, 2000; Cahill et al., 2003), while high or chronic levels of GCs predominantly have an inhibitory effect on memory function (see McEwen, 2000, Lupien and McEwen, 1997). In humans, GC receptors are widely distributed in the hippocampus and other brain regions, including the prefrontal cortex (de Kloet et al., 1999). GC receptors in the hippocampus are the site of negative feedback regulation of hypothalamic-pituitary-adrenocortical (HPA) function. The hippocampus plays an important role in declarative memory, including the consolidation of short-term into long-term declarative memory (Zola-Morgan and Squire, 1990) and spatial memory (i.e., memory for 'spatial representation of the environment'; see Maguire et al., 2000).

In humans, administration of high doses of GCs (dexamethasone, hydrocortisone, prednisolone) has generally been associated with impairments in declarative memory, although findings are mixed (for a review, see Wolf, 2003). In several studies, treatment with GCs selectively impaired performance in hippocampal-dependent forms of memory (declarative memory tasks, e.g., paragraph recall, cued recall), leaving procedural memory (e.g., implicit memory) unaffected (Kirschbaum et al., 1996; Newcomer et al., 1999), suggesting that cortisol interacts with hippocampal neurons to induce memory deficits. Besides acute actions, chronic effects of GCs on memory functioning have also been reported. For example, Newcomer et al. (1994, 1999) found impaired paragraph recall after a 4-day administration of dexamethasone. Several studies did not find reduced declarative memory with GC administration before the learning phase (Lupien et al., 1999; de Quervain et al., 2000; Wolkowitz et al., 1990), although hydrocortisone did impair working memory (Lupien et al., 1999), and impaired delayed word recall when administered 1 h before retrieval (de Quervain et al., 2000), suggesting a role for prefrontal mediated memory impairments (see Lupien and Lepage, 2001).

Pharmacological studies may not be representative of the physiological effects of endogenous cortisol release in humans exposed to natural stressors. Some exogenously administered drugs (e.g., dexamethasone) are less able to penetrate the blood–brain barrier, and therefore they may not bind to hippocampal GC receptors (Lupien and McEwen, 1997). Moreover, during exposure to stress, other stress hormones, including cathecolamines, are released at the same time. Recent evidence from animal studies suggests that these may interact with the effects of GCs on memory functioning (Roozendaal, 2000). So far, only a few studies have addressed the effects of stress-induced cortisol elevations on memory performance in humans (Kirschbaum et al., 1996; Lupien et al., 1997; Domes et al., 2002). In the only study assessing a non-aged sample (Kirschbaum et al., 1996), elevated cortisol levels induced by a psychosocial stress challenge were associated with poorer immediate recall of word pairs. Word recall was not assessed at baseline, however, so it remains unclear whether memory was actually impaired as a result of the stressful task. Moreover, no control tasks were administered so that the specificity of the cognitive impairments remained unclear. In a sample of healthy elderly participants, a stressful public speaking task induced a significant decrease in learning and recall of word pairs (Lupien et al., 1997). Domes et al. (2002), in contrast, did not find any differences in memory performance among

middle-aged women who were either subjected to a public speaking task or a control condition. Moreover, in a subgroup of high cortisol responders, memory performance even increased.

One factor that has often been ignored in the studies on stress-related memory functions is the impact of stress on the different types of memory. Memory processing involves at least three phases; acquisition, consolidation, and retrieval. At each phase, stress-related factors can come into play to affect memory formation. Most previous studies could not detect possible differential effects of GCs on distinct phases of encoding, consolidation, and retrieval, because both learning and recall were tested immediately after the stress challenge or, in the case of exogenous GCs, treatment affected both acquisition and retrieval.

Recent findings indicate that cortisol enhancement does not uniformly affect memory performance for all information; rather it interacts with the emotional valence or degree of arousal at initial encoding of material in modulating memory for the material, presumably by interaction with noradrenergic activation (Buchanan and Lovallo, 2001; Cahill et al., 2003; Roozendaal, 2000; Okuda et al., 2004). So far, two studies reported selectively enhanced delayed recall of emotionally arousing pictures, one after pre-learning cortisol administration (Buchanan and Lovallo, 2001), the other after post-learning cortisol elevations induced by cold presser stress (Cahill et al., 2003). Rimmele et al. (2003) failed to replicate these findings, however. The present study was designed to assess the effects of stress-induced cortisol elevations on (1) the three types of memory processing (encoding, consolidation and retrieval), and (2) on the emotional valence of the material under study. Sixteen participants were presented neutral and emotional material (words and paragraphs) before and after a stress challenge. To differentiate between the effects of stress on the different phases of memory processing, half of the information was recalled shortly after presentation (i.e., to assess the effects of stress on encoding and retrieval), whereas the other half was recalled 24 h later (i.e., to assess the effects of stress on encoding and consolidation). Tests of declarative memory were used to assess the effects of stress on hippocampal functioning. Control tasks of memory and attention were included to assess the specificity of the declarative memory impairments.

2. Methods

2.1. Participants

Sixteen female paid volunteers (Yale University students) with a mean age of 21.4 ± 2.1 years participated in the study. They were recruited using local advertisements and were screened for general medical health and psychiatric disorders by a trained psychiatrist (A.B.) using the MINI International Neuropsychiatric Interview (Lecrubier et al., 1997). Participants were excluded for the presence of clinically significant medical illness or axis I psychiatric disorder, including any substance abuse disorder based on the MINI. Participants had to refrain from strenuous physical exercise, large meals, cigarette smoking, and coffee for at least 1 h before the experiment because of the known effects of these variables on HPA functioning. After a brief introduction to the study, all participants gave written informed consent for their participation in a protocol approved by the Human Investigation Committee of Yale University.

2.2. Stress challenge

The stress task consisted of a cognitive challenge performed under high levels of interpersonal pressure based on a protocol previously used in studies of aging (Seeman et al., 1995a,b) and PTSD (Bremner et al., 2003). Immediately before the challenge, a physician (A.B.) wearing a white laboratory coat entered the room and initiated a series of cognitively challenging tasks, including mental subtractions, substitution tasks, and general knowledge questions. Each individual task was scored by the rater and performed under time pressure. Negative feedback regarding the score and the time spent in the task was consistently given, and the level of difficulty was increased until participants were unable to complete the tasks. Because cortisol generally rises after 20–30 min of stress exposure, the challenge was continued for 20 min, so that cortisol levels were elevated when the second part of memory testing started.

2.3. Memory tasks

2.3.1. Word recall

Participants received two lists of 20 words, including 10 neutral words (e.g., 'picture,' 'building,' 'pencil'), and 10 emotional words (e.g., 'tortured,' 'blood,' 'scream'). Emotional words were rated as more fearful, sad, nervous, angry, and less happy than neutral words (all $P < 0.0001$). Two parallel forms of the word lists consisting of different words comparable in difficulty were presented, balanced between baseline (before the challenge) and after the challenge (see Fig. 1). The first investigator (B.E.) read the words out loud. Participants were instructed to rate how 'fearful' each word was on a five-point scale. After the first presentation, the words were read a second time, and participants were instructed to rate how 'aversive' each word was. This test was considered a test of incidental learning. To assess the effects of the stress challenge on encoding/consolidation, recall of the words was tested 24 h later in two declarative, hippocampus-dependent memory tasks (cued recall and recognition task). An implicit memory task (word stem completion), which is assumed to be independent of hippocampal functioning, was included to test the specific effects of the stressor on declarative memory.

For the cued recall task, 20 target word stems were presented corresponding to 10 neutral and 10 emotional words presented at day 1. Half of these words had been presented before the challenge, and the other half had been presented after the challenge. Participants were asked to "*fill in the word stems with words that were previously presented both before and after the stress challenge.*"

For the word stem completion task, the 20 remaining target word stems (not presented in the cued recall task) corresponding to 10 neutral and 10 emotional words presented at day 1, were presented intermixed with 20 filler word stems that did not correspond to any previously presented words, to obscure the goal of memory testing. Half of the target words were presented before, and the other half were presented after the stress challenge. Participants were instructed to "*fill in the first word that comes to your mind.*" The number of target completions served as a measure of implicit memory.

For the recognition task, the 20 (10 neutral and 10 emotional) words administered before and the 20 words administered after the challenge were presented intermixed with 40 (20 neutral and 20 emotional) new words. Participants had to rate how confident they were that they had seen the word before at day 1 using the following rating scale: 1. I'm sure that the word is new (not studied before); 2. The word is probably new; 3. The word is probably old; 4. I'm sure that the word is old (studied before). Participants were given 2 points each time they assigned a '4' (sure that the word is old) to a target word, 1 point for each '3,' −1 point for each '2,' and −2 points for each '1.' The total score served as a measure of recognition memory.

2.3.2. Paragraph recall

The Wechsler Memory Scale-Revised Logical Memory test (Wechsler, 1981) was used as a valid and sensitive measure of verbal declarative memory that has proved to be sensitive to GC effects in previous studies (Newcomer et al., 1994, 1999).

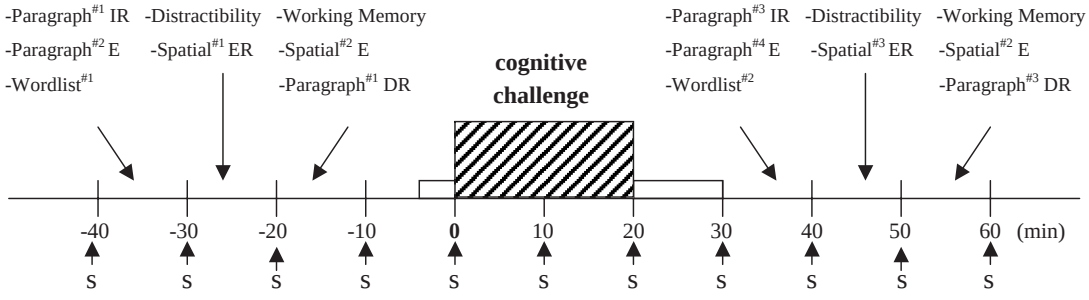

Fig. 1. Time line of memory tasks and saliva sampling.
Note: S—Salivette; DR—Delayed recall; E—Encoding only; IR—Immediate recall; ER—Encoding and retrieval.

Four paragraphs, each containing 25 pieces of information matched for difficulty, were constructed using an established method from the Wechsler Memory Scale-Revised Logical Memory. Two paragraphs were administered before the stress challenge serving as baseline measures, and two paragraphs were administered after the stress challenge. To distinguish the effects of stress on encoding, consolidation, and retrieval, two paragraphs were recalled immediately and after 30 min; the other two paragraphs were recalled only at day 2 (see Fig. 1). Percent retention was computed as 'delayed recall/immediate recall × 100%.' To avoid any non-random bias, presentation of the paragraphs was balanced over the four conditions, so that one paragraph was presented and tested before the challenge (baseline), one paragraph was presented before the challenge and tested at day 2, one paragraph was presented and tested after the challenge, and one paragraph was presented after the challenge and tested at day 2.

2.3.3. Spatial memory

The spatial memory test was a variation of a test developed by Kirschbaum et al. (1996), which proved to be sensitive to the effects of GCs. Participants were instructed to carefully read a short description of a walk in which they were 'guided' along a path with several 'attractions,' e.g., specific trees, flowers, and animals that were situated either on the right or the left side of the path. Additionally, the stroller 'saw' three bifurcations where she 'turned' left, right, or kept going straight ahead. Participants were given 3 min to memorize the description. Thereafter, they returned the description sheet to the investigator. For testing purposes, participants had to imagine that the stroller decided to return, walking back to the starting point of the walk. In a multiple choice test of 15 questions, participants had to choose the correct paths (at bifurcations) and describe whether an attraction was at the left or the right side of the path on the way back. Four parallel forms of descriptions of a walk were presented, so that for each participant (as in the paragraph recall) one story was presented and tested before the challenge, one story was presented before the challenge and tested at day 2, one story was presented and tested after the challenge, and one was presented after the challenge and tested at day 2 (see Fig. 1).

2.3.4. Working memory

Working memory was measured using the digit recall subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1987). Participants were presented two trials of six series of an increasing number of digits (from four to nine) that they had to repeat in the same order. In a second presentation, two trials of six series of digits (from three to eight digits) were presented that participants had to repeat in reversed order. This task was included to control for the specificity of the memory impairments, since working memory is not mediated by the hippocampus, but by the prefrontal cortex. Two parallel versions were presented in randomized order during baseline and after the challenge.

2.3.5. Continuous performance task

To control for attention, distractibility was measured using a computer-generated continuous performance task that presented a rapid, continual sequence of numbers in one of three positions, right, center, or left (Gordon Diagnostic System, GDS; Gordon and Mettelman, 1987). Participants were required to respond by pressing a key to each '9' that appeared immediately after a '1,' but only if they both appeared sequentially in the center position. The total number of correct responses and the reaction latencies were analyzed. The continuous performance task was administered during baseline and after the challenge.

2.4. Physiological assessment

Heart rate and blood pressure were assessed every 10 min using a Dynamap cuff (Critikon, parent company: GE Medical systems Informatics Technologies, Milwaukee, WI). During the stress challenge, heart rate and blood pressure were assessed every 2 min. For the analysis of heart rate and blood pressure, the means of the samples before (−40, −30, −20, and −10 min with reference to the beginning of the stressor), during (2–20 min after the start of the stressor), and after (+30, +40, +50, and +60 min) the stress challenge were calculated.

Cortisol samples were obtained during a 100-min period at 11 assessment points, at −40, −30, −20, −10, 0, +10, +20, +30, +40, +50, and +60 min with reference to the start of the stressor. Cortisol levels were monitored using saliva samplings to avoid the stress-inducing effects of blood sampling. Determination of cortisol in saliva provides a reliable measure of the free unbound fraction of cortisol (Tunn et al., 1992). In our laboratory, it was found that in subjects who had both plasma and salivary cortisol measures obtained simultaneously ($N=7$), there was a high degree of correlation between these measures ($r=0.64$, $df=6$, $P<0.001$). Saliva samples were collected using Salivette collection devices and stored at −70 °C. Salivette tubes were centrifuged (0 to 4 °C) to prepare saliva, which was analyzed for cortisol using a ^{125}I immunoradiometric assay kit available from Diagnostic Products Corporation (Los Angeles, CA). Samples and standards (200 μl) were determined in duplicate. For the analysis, repeated measures of the 11 cortisol samples were analyzed and cortisol peak with reference to baseline was computed by subtracting baseline (+0 min) and the cortisol peak at +40 min with reference to the beginning of the stressor (peak Cort). Day-to-day coefficients of variation for low (398 pg/ml) and high (4.12 ng/ml) concentration quality assessment samples were 10.1% and 8.4%, respectively.

2.5. Procedure

For the procedure, see Fig. 1. Because of cortisol's diurnal variations, testing was carried out between 1400 h and 1700 h. Participants were placed in a quiet room in a reclining chair with application of a Dynamap cuff for measurement of heart rate and blood pressure. After a resting period of 20 min, baseline memory testing was assessed for 30 min in the following order (see Fig. 1): paragraph$^{\#1}$ encoding and immediate recall; paragraph$^{\#2}$ encoding only; encoding of neutral and emotional words$^{\#1}$; distractibility task; spatial memory$^{\#1}$ encoding and recall; working memory; spatial memory$^{\#2}$ encoding only; and paragraph$^{\#1}$ delayed recall. After baseline memory testing, participants had a brief relaxation period of 5 min. Then the physician (A.B.) came in and carried out the stress challenge. After 20 min, the physician left the room, and the participants had a 10-min relaxation period during which heart rate and blood pressure returned to baseline levels to minimize the acute (adrenergic) stress effects on memory. After the relaxation period, the second part of memory testing took place for 30 min in the same order as during baseline (e.g., paragraph$^{\#3}$ encoding and immediate recall; paragraph$^{\#4}$ encoding only; encoding of neutral and emotional words$^{\#2}$; distractibility task; spatial memory encoding and recall$^{\#3}$; working memory; spatial memory$^{\#4}$ encoding only; and paragraph$^{\#3}$ delayed recall). At the end of day 1, participants were fully debriefed with respect to the purpose of the stress challenge (i.e., they were told that the negative feedback and the aversive attitude of the physician were fake). Participants were told that the purpose of the second appointment was to assess baseline memory functioning, and they were assured that no more stressful tests would be administered.

At day 2, participants came back for a 30-min surprise recall test. Testing took place in the following order: recall paragraph$^{\#2}$; spatial memory$^{\#2}$; word stem completion (words$^{\#1+\#2}$), cued recall (words$^{\#1+\#2}$), recognition (words$^{\#1+\#2}$), spatial memory$^{\#4}$, and paragraph$^{\#4}$. Afterwards, participants were fully debriefed.

2.6. Analyses

The main hypothesis of declarative memory performance before and after stress on day 1 and day 2 was tested using analysis of variance (ANOVA) to evaluate the repeated measures of paragraph recall, cued recall, recognition, and spatial memory. Effects on implicit memory (word stem completion), working memory, and distractibility were similarly tested to evaluate secondary hypotheses concerning the specificity of cortisol effects. Physiological responses of cortisol, heart rate, and blood pressure were tested by ANOVA, followed by pairwise comparisons with Bonferroni correction on the individual measures. To assess the relation between cortisol levels and memory performance, Pearson correlations were computed between the level of cortisol during presentation and recall at days 1 and 2. Analyses were performed using SPSS version 11.0.

3. Results

3.1. Physiological measurements

The cognitive challenge resulted in an increased heart rate (78.13 ± 3.47 bpm) relative to baseline (68.82 ± 2.55 bpm) and recovery (68.65 ± 2.88 bpm) (main effect for time: $F_{2,14}=13.01$, $P<0.001$; post hoc pairwise comparisons with Bonferroni correction of 'challenge versus baseline,' $P<0.0001$; 'challenge versus recovery,' $P<0.0001$; 'baseline versus recovery,' P=NS). The cognitive challenge also resulted in an increased systolic blood pressure (115.51 ± 2.73 mmHg), relative to baseline (105.28 ± 2.33 mmHg) and recovery (106.32 ± 1.86 mmHg) (main effect for time: $F_{2,14}=10.36$, $P<0.01$; pairwise comparisons of 'challenge versus baseline,' $P<0.001$; 'challenge versus recovery,' $P<0.001$; 'baseline versus recovery,' P=NS). This was the same for diastolic blood pressure ($F_{2,14}=24.51$, $P<0.0001$), with a mean diastolic blood pressure of 73.09 ± 1.27 mmHg during challenge; 63.83 ± 1.46 mmHg during baseline; and 65.22 ± 1.57 mmHg during recovery (pairwise comparisons of 'challenge versus baseline,' $P<0.0001$; 'challenge versus recovery,' $P<0.0001$; 'baseline versus recovery,' P=NS). Analysis of the cortisol levels resulted in a cubic interaction ($F_{1,\ 11}=5.70$, $P<0.05$). The increase between the lowest point before the challenge (t_0, 10.6 ± 1.2 μg/dl) and the peak cortisol response after the challenge (t_{40}, 15.0 ± 2.8 μg/dl) was 41.5% ($F_{1,15}=4.32$, $P<0.05$, 1-tailed); see Fig. 2.

3.2. Memory

For memory performance on day 1, see Table 1; for day 2, see Table 2.

3.2.1. Wechsler memory task

When tested 24 h later, participants tended to recall fewer items from the paragraph presented after exposure to the stress challenge than before. No differences were found on day 1 between immediate, delayed, and percentage recall (delayed/immediate recall × 100) before and after the stress challenge.

3.2.2. Spatial memory

When tested 24 h later, participants made more errors in the questions on the descriptions of walks that were presented after the stress challenge than before. No differences were found between performance on the spatial task on day 1 before and after exposure to the stress challenge.

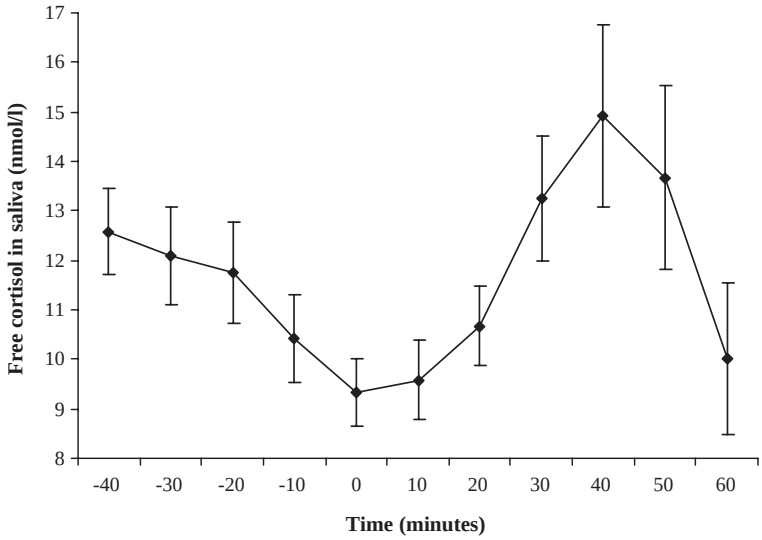

Fig. 2. Mean salivary cortisol levels (±S.E.M.).

Table 1
Memory performance at day 1 on spatial memory, Wechsler memory, working memory, and distractibility task during baseline and after the challenge (mean ± S.E.M.)

Memory task	Baseline	After challenge	*F*-value	*P*-value
	Mean ± S.E.M.	Mean ± S.E.M.		Two-tailed
Spatial memory	14.00 ± 0.30[#1]	13.75 ± 0.36[#3]	0.60	0.45
Paragraph recall				
Immediate recall	18.97 ± 0.74[#1]	18.19 ± 0.95[#3]	0.52	0.48
Delayed recall	17.28 ± 0.76[#1]	16.56 ± 1.03[#3]	0.40	0.54
% retention (delayed/immediate)	91.14 ± 1.96[#1]	90.62 ± 2.63[#3]	0.03	0.86
Working memory	17.63 ± 1.09	19.00 ± 0.74	6.15	0.03
Distractibility task				
# correct answers	27.06 ± 1.12	28.50 ± 0.93	0.76	0.40
Reaction time	45.56 ± 1.89	46.25 ± 1.85	0.19	0.67

[#1]corresponds to spatial memory[#1] and paragraph[#1]; [#3] corresponds to spatial memory[#3] and paragraph[#3] (see Fig. 1).

3.2.3. Words

3.2.3.1. Cued recall. When tested 24 h later, words that were presented before exposure to the stress challenge were somewhat better recalled than words presented after the stress challenge, but in the cued recall task, this difference did not reach significance. When tested separately, recall of neutral words was impaired by the stress challenge, whereas recall of emotional words was not. Overall, emotional words were better recalled than neutral words ($F_{1,15}=10.10$, $P<0.01$).

3.2.3.2. Recognition. Words that were presented before the stress challenge were better recognized than words presented after the stress challenge. Overall, emotional words were better recognized than neutral words ($F_{1,15}=19.00$, $P<0.001$). Moreover, recognition of neutral words presented after the challenge was relatively more impaired than recognition of emotional words, but this interaction between valence and time was not significant ($F_{1,15}=2.47$, $P=$NS).

3.2.3.3. Word stem completion. Words presented before exposure to the stress challenge tended to be more often completed than words presented after the stress task, but this effect was not significant. Neutral words were completed as often as emotional words ($F_{1,15}=0$, $P=1$). No differences were found between neutral and emotional word stem comple-

Table 2
Memory performance at day 2 on spatial memory, Wechsler memory, cued recall, word stem completion and recognition of information presented at day 1 before and after the challenge (mean ± S.E.M.)

Memory task	Baseline	After challenge	*F*-value	*P*-value
	Mean ± S.E.M.	Mean ± S.E.M.		Two-tailed
Spatial memory	12.38 ± 0.56[#2]	9.94 ± 0.76[#4]	6.67	0.02
Paragraph recall	10.28 ± 0.70[#2]	7.53 ± 1.56[#4]	3.20	0.09
Cued recall (total)	1.09 ± 0.17[#1]	0.84 ± 0.14[#2]	1.71	0.21
Neutral words	0.81 ± 0.21	0.31 ± 0.15	3.75	0.07
Emotional words	1.38 ± 0.15	1.38 ± 0.29	0.00	1.0
Word stem completion (total)	0.33 ± 0.08[#1]	0.17 ± 0.06[#2]	3.95	0.07
Neutral words	0.31 ± 0.15	0.19 ± 0.10	0.48	0.50
Emotional words	0.34 ± 0.12	0.16 ± 0.09	1.22	0.29
Recognition (total)	14.06 ± 1.07[#1]	9.06 ± 1.44[#2]	35.19	0.000
Neutral words	11.06 ± 1.73	4.25 ± 2.18	16.23	0.001
Emotional words	17.06 ± 1.12	13.89 ± 1.41	8.34	0.011

[#1]corresponds to words[#1]; [#2] corresponds to paragraph[#2] and spatial memory[#2], words[#2]; [#4]corresponds to spatial memory[#4] and paragraph[#4] (see Fig. 1).

tion before and after the stress challenge ($F_{1,15}$= 0.40, P=NS).

3.2.3.4. Distractibility task. No differences were found in distractibility before exposure than after exposure to the stress challenge in reaction latency or number of errors.

3.2.3.5. Working memory. Participants repeated more digits correctly after exposure to the stress challenge than before the stress challenge.

3.3. Relationship between cortisol and memory performance

To further evaluate the relationship between cortisol and memory functioning, Pearson correlations were calculated. To calculate correlations between cortisol levels and memory performance at day 1 and post-stress cortisol levels during encoding and delayed memory performance at day 2, task performance was correlated with the absolute cortisol levels, based on the salivette that was closest in time to the task at hand (30 min post stress level for paragraph recall, 40 min for word recall, and 50 min for spatial memory). Correlational analyses on day 1 immediately before and after the stress challenge between cortisol levels and memory performance on Wechsler immediate and delayed recall, spatial memory and working memory did not yield any significant correlation (all P>0.10). At day 2, strong negative correlations were found between cortisol levels during encoding and cued word recall at day 2 (see Table 3 and Fig. 3), as well as a

Table 3
Pearson correlations between delayed recall at day 2 of information learned before the stress challenge and peak cortisol (40 min post stress level) and between information learned after the stress challenge and post-stress cortisol levels during encoding

Memory tests at day 2	R_{before}	R_{after}
Paragraph recall	$0.08^{\#2}$	$0.02^{\#4}$
Spatial memory	$0.06^{\#2}$	$-0.46^{\#4}$
Cued recall total	$0.21^{\#1}$	$-0.76^{\#2}$ ***
Neutral	$0.45^{\#1}$	$-0.23^{\#2}$
Emotional	$-0.31^{\#1}$	$-0.62^{\#2}$ **
Word stem completion	$-0.44^{\#1}$	$-0.22^{\#2}$
Neutral	$-0.27^{\#1}$	$-0.13^{\#2}$
Emotional	$-0.36^{\#1}$	$0.13^{\#2}$
Recognition	$0.18^{\#1}$	$0.37^{\#2}$
Neutral	$0.20^{\#1}$	$0.23^{\#2}$
Emotional	$0.03^{\#1}$	$0.09^{\#2}$

R_{before}=Pearson correlation between peak cortisol level and delayed recall of information learned before the stress challenge.
R_{after}=Pearson correlation between cortisol levels at encoding and delayed recall of information learned after the stress challenge.
** P<0.01.
*** P<0.001.

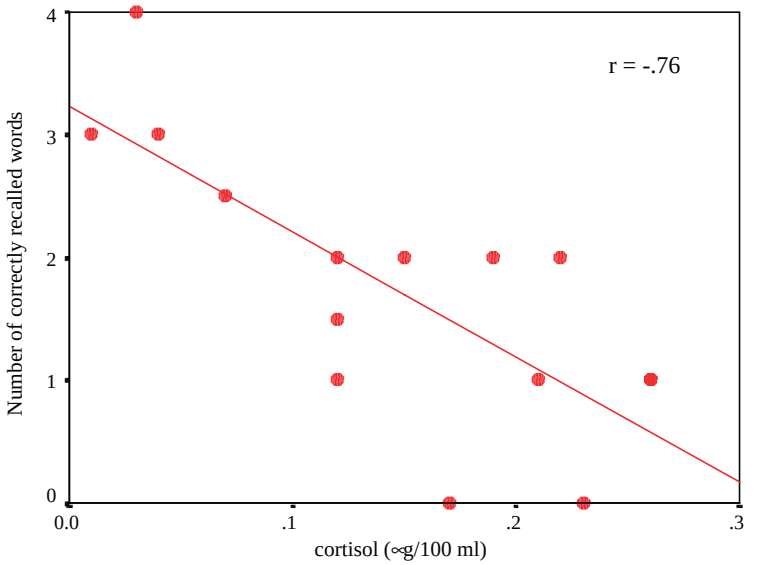

Fig. 3. Correlation between cortisol levels (40-min post-stress level) and total number of neutral and emotional words recalled at day 2 in the cued recall task.

negative correlation between spatial memory and cortisol levels, which went up to $r=-0.71$, $P<0.01$ one cortisol measurement later, after 60 min (see Table 3). To evaluate the potential effects of stress-induced cortisol elevations on memory consolidation of information presented *before* the stress challenge, correlations were calculated between the peak cortisol response to the stress challenge (at +40 min) and delayed recall of information presented before the challenge. Except for the word stem completion task, all correlations were small and in a positive direction (see Table 3).

In addition to the association of memory performance with absolute cortisol levels, the association with net increases of cortisol was also investigated. These analyses yielded similar results, i.e., negative correlations with post-stress net increase and spatial memory and explicit word recall at day 2, and no significant correlations on any other task at day 2 or day 1.

4. Discussion

The results of this study suggest that stress exposure may specifically affect long-term memory consolidation, as we found a reduction in the delayed recall of information presented *after* a stressful event compared with the delayed recall of information presented *before* stress exposure. In line with these findings, delayed recall of (emotional) words and spatial information learned after the stress challenge was negatively correlated with cortisol levels during encoding, whereas correlations with delayed recall of information presented *before* the stress challenge were all non-significant. Interestingly, exposure to the stress challenge did not affect memory performance immediately after the challenge. Consistent with these findings, no significant correlations were found between cortisol levels and memory performance at day 1, either before or immediately after the stress challenge. In line with previous studies, declarative memory (i.e., recognition, spatial memory, and paragraph recall) was especially affected by the stress challenge, whereas performance on hippocampus-independent tasks was unaffected (i.e., distractibility), or even improved after the challenge (i.e., working memory).

The observation that exposure to the stress challenge selectively affected delayed recall of information without directly affecting performance immediately after acquisition is consistent with the genomic actions of GCs, as few GC actions in the hippocampus are executed until about an hour after the onset of the stressor (see McGaugh, 2000; Lupien and McEwen, 1997). The crucial question is what specific processes may have mediated the decrease in delayed recall of information presented after the stress challenge relative to information administered before the stressor? Given the fact that cortisol levels remained elevated after cessation of the stressor for 30 min, stress-induced cortisol increases may potentially have affected both acquisition and consolidation of information presented *after* the challenge, while for information learned *before* the stress challenge, only consolidation can have been influenced. Following this line of reasoning, the pattern of result can be interpreted as both (i) impaired acquisition of information learned *after* the stressor, and (ii) enhanced consolidation of information learned *before* the stress challenge.

Pertaining to the first interpretation, the significant negative correlations between cortisol and delayed recall of information learned after the stressor would argue for a role of GC-related impaired acquisition. Moreover, GC-induced impaired acquisition would be in line with previous findings of decreased word recall (immediately) after stress-induced cortisol increases (see Kirschbaum et al., 1996; Lupien et al., 1997), although findings are mixed (see Wolf, 2003, for a review), and word recall could also be caused by impaired retrieval processes instead of acquisition. GC-related enhanced memory consolidation, on the other hand, would be consistent with several recent studies in animals, showing that systemic injections of moderate doses of corticosterone administered shortly *after* a training experience enhance long-term memory (Roozendaal, 2002). Moreover, recent evidence indicates that GC effects on memory consolidation are mediated, in part, by adrenergic activity in the basolateral nucleus of the amygdala (see Roozendaal, 2000; Okuda et al., 2004). Because adrenergic activity reverted to baseline during the second memory testing phase, noradrenergic activation can only have affected consolidation of information learned before the stressor. This could have contributed to enhanced

consolidation of information learned before the stress challenge. Although pre-clinical evidence for GC-induced enhanced memory consolidation is compelling, direct empirical support is weak, given the small correlations that have been found between cortisol levels and delayed recall of information learned before the challenge. Correlational data on cortisol and memory consolidation should be interpreted with caution, however, given the fact that memory consolidation is a process of hours or even days, and the salivary cortisol sample represents only a relatively arbitrary fraction of the total amount of GCs a person is exposed to during this period. In conclusion, the significant negative correlations between cortisol and delayed recall suggest a role for GC-induced impaired acquisition. Future studies are clearly needed to disentangle the effects of stress exposure on acquisition and consolidation.

Irrespective of the phase of learning, recall of emotionally arousing material was enhanced relative to neutral information. Extensive animal research suggests that enhanced memory for emotional material is related to an interaction between stress hormones (e.g., cortisol and epinephrine) and the degree of arousal at initial encoding of the material to be learned (Roozendaal, 2000). The association between cortisol and memory for neutral versus emotionally arousing material has not yet been systematically explored in humans, however. So far, two studies reported selective enhanced delayed recall of emotionally arousing pictures, one after pre-learning cortisol administration (Buchanan and Lovallo, 2001), the other after post-learning cortisol elevations induced by cold presser stress (Cahill et al., 2003). Rimmele et al. (2003) failed to replicate these findings, however. Despite the enhanced recall of emotional material, we could not detect significant positive correlations between cortisol levels and the recall of emotional words presented either before or after the stress challenge, as may be expected if cortisol activity is causally related to enhanced memory consolidation of emotional information. Instead, we found a strong negative correlation between cortisol levels and recall of words learned *after* the challenge, which was strongest for emotional words. One explanation for this discrepancy might be that words are not arousing enough to induce strong emotion. This issue needs to be explored in future studies.

Our failure to find immediate effects of GC-induced cortisol levels on memory performance is in line with two recent studies (Wolf et al., 2001; Domes et al., 2002), but is in contrast with two earlier studies showing memory impairments immediately after stress exposure (Kirschbaum et al., 1996; Lupien et al., 1997) or after cortisol administration (Newcomer et al., 1994, 1999; Kirschbaum et al., 1996). Several factors may account for these discrepant findings. Participants in our study consisted of young female participants, whereas the samples in the studies showing immediate memory impairments after stress consisted either of elderly (Lupien et al., 1997) or male participants (Kirschbaum et al., 1996). Cortisol increases are known to have a stronger (negative) impact on memory functioning in elderly than in a young population, presumably because baseline cortisol levels are higher among the elderly. Second, consistent gender differences in cortisol responses to psychological stress have been reported, with females generally showing smaller cortisol responses than males and less pronounced associations between cortisol and memory performance (see Kirschbaum et al., 1999). For example, only men showed clear cortisol elevations after a stress challenge in the study of Kirschbaum et al. (1996), and negative correlations between cortisol and immediate memory recall were found only in men (Wolf et al., 2001). In a similar vein, no immediate memory impairments appeared in a study in which only women participated (Domes et al., 2002). Third, compared with pharmacological studies, peak cortisol levels in response to the cognitive challenge were moderate in size (41%) and far below those obtained in pharmacological studies (e.g., Lupien et al., 1999; Newcomer et al., 1999). Given the fact that the cognitive challenge was clearly perceived as stressful in terms of subjective distress, heart rate, and blood pressure, the moderate cortisol increase may in part be related to the fact that only females participated. Pharmacological studies have demonstrated a dose–response curve of cortisol and memory performance, showing that low doses did not impair memory performance (Newcomer et al., 1999; Lupien et al., 1999). It could be speculated that more pronounced stress-induced cortisol increases are required for detection of significant effects on immediate memory performance.

Several limitations of the study need to be kept in mind when evaluating the present findings. Most importantly, the study did not include a control condition without a stressor. It is therefore difficult if not impossible to disentangle the effects of the stressor from other potential factors like interference, practice effects (which may have played a role in the enhanced working memory), or changes in motivation. In our opinion, the pattern of selective interference with delayed declarative recall, and not with immediate recall, working memory, and attention, argues against a major influence of these non-specific factors on memory performance. Future studies examining memory performance in a stress and a control condition, including a male and a female sample, are needed to elucidate the effects of stress on memory performance. Second, the correlational data in the present study should be interpreted with caution, given the increased risk of false positives with multiple comparisons. Finally, there are limitations in not controlling for oral contraceptives and menstrual cycle, factors that may modulate memory performance in women.

To conclude, the results of this study suggest that increases in stress-related cortisol may specifically affect delayed recall of stress-related experiences. To our knowledge, this is the first study that has directly compared immediate and delayed effects of cortisol on memory functioning. Given the genomic effects of GCs that may take hours or even days, studying the delayed effects of GCs may be a viable way to understand the relation between stress and memory functioning. To study the relevance of the present findings for traumatized individuals, it would be interesting to assess the effects of endogenous GC levels and other stress-related hormones and transmitters on (distinct phases of) memory functioning in patients with stress-related disorders, such as depression or PTSD. Also, studies are needed that assess GC levels during and immediately after traumatic events, and during the course of the development of PTSD in association with memory changes (see also Sapolsky, 2000). These studies can make an important contribution to our understanding of the complex effects of stress on memory, and can be of potential help in the treatment and prevention of memory disturbances in stress-related disorders.

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