

Brief Report

# Effects of oral cortisol treatment in healthy young women on memory retrieval of negative and neutral words

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## Abstract

Studies in rodents have demonstrated that glucocorticoids enhance memory consolidation but impair delayed memory retrieval. Similar findings have been reported in humans. Emotional items are better remembered than neutral items. However, it is unknown if emotional valence influences the effects of cortisol on retrieval. In this double-blind crossover study, 16 healthy women learned a wordlist containing 15 neutral and 15 negative words. Delayed recall was tested 5 h later. Cortisol administered before recall testing significantly reduced retrieval ( $p < .01$ ). Exploratory follow-up analysis revealed that cortisol significantly impaired retrieval of negative words ( $p < .01$ ), while having no significant effect on neutral words ( $p = .47$ ). The current findings could suggest that emotional material is especially sensitive to the memory modulating effects of stress hormones.

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## 1. Introduction

Glucocorticoids (GCs) secreted during stress are a crucial component of the body's response aimed at adapting to the perceived challenge. These hormones exert effects in multiple target tissues including the brain. Acute GC treatment has enhancing as well as impairing effects on memory (Lupien & Lepage, 2001; Wolf, 2003). Based on findings in rats, Roozendaal and McGaugh proposed that GCs together with adrenergic activation in the basolateral nucleus of the amygdala enhance memory consolidation (see for recent review Roozendaal, 2002) and for related observations (Sandi, 1998). In contrast, GCs impair delayed memory retrieval (Roozendaal et al., 2003) and working (short-term) memory (Roozendaal, McReynolds, & McGaugh, 2004) seemingly via the very same mechanisms. Roo-

zendaal (2002) suggests that GCs put the brain into a 'consolidation mode', which is accompanied by impaired retrieval. De Kloet, Oitzl, and Joels (1999) alternatively suggest that stress within the context of a learning experience enhances memory, while stress out of context impairs it. Three studies in humans observed impairing effects of cortisol treatment on delayed memory retrieval (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; de Quervain et al., 2003; Wolf, Convit et al., 2001), thereby replicating the results obtained in rodents (see above).

The emotional valence of an item influences the likelihood of its later recall, with emotional items being remembered better than neutral items (Kleinsmith & Kaplan, 1963; Quevedo et al., 2003). Human neuroimaging studies have demonstrated that activation of the amygdala is associated with this effect (Cahill, 2003). Several recent human studies have investigated the interaction of glucocorticoids with emotional valence. Buchanan and Lovallo (2001) found that cortisol

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enhanced the consolidation of slides rated as arousing by the subjects. Similar results were obtained in a study using cold pressor stress immediately after learning, in the phase of consolidation (Cahill, Gorski, & Le, 2003). Using a different experimental paradigm another study failed to find any modulatory influence of valence (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003). Most recently, Tops and colleagues reported that cortisol impaired immediate recall of neutral and positive words, while having no effect on negative words (Tops et al., 2003). While these experiments are far from conclusive they nevertheless demonstrate that emotional valence can interact with the effects of cortisol on memory. Since no previous study tested the interaction of cortisol and emotional valence on memory retrieval of words the present experiment was conducted.

Sixteen young healthy female students participated in this study. None of the women had acute or chronic diseases or were taking medications. Subjects were lean (body mass index (BMI) <25 (kg/m<sup>2</sup>)) and did not use hormonal contraceptives. Each participant was tested on two experimental sessions both times during the first half of their menstrual cycle with an between session interval of approximately 4 weeks. Subjects were between 21 and 33 years old ( $26.56 \pm 3.86$  (means  $\pm$  SE)). The study was approved by an Ethic Committee and subjects provided written informed consent.

In a double-blind crossover placebo controlled fashion participants received either three pills containing 10 mg hydrocortison (Hoechst, Germany) or three similar looking placebo pills. The current dose (30 mg) was chosen to be similar to previous studies showing impairing effects of cortisol on retrieval (de Quervain et al., 2000, 2003; Wolf, Convit et al., 2001). The order of the treatment was randomized. Upon arrival (between 10.00 and 11.00 a.m.) the participants filled out a mood questionnaire (see below) and learned a list containing 15 neutral and 15 negative words (see below). Four hours later they received cortisol (30 mg) or placebo orally. Another hour later (between 3:00 and 4:00 p.m.) participants filled out the mood questionnaire again, followed by a free and cued recall of the word list (details below). Thereafter, working memory and attention was assessed (details below). The additional tests and the questionnaires were employed to be able to exclude that effects of cortisol on retrieval were secondary to changes in mood or attention. The working memory task was used since we had found negative effects of cortisol in this task in a previous study (Wolf, Convit et al., 2001).

The following tests and questionnaires were used:

### 1.1. Memory for words

A word list (with two parallel versions available) containing 15 negative (e.g., pain, explosion, and prison) and 15 neutral words (e.g., street, blouse, and stone)

was used. In a pilot study ( $n = 18$ ) the emotional valence of the words had been verified by having the subjects rate the emotional valence of the words on a seven point scale ranging from negative (1) over neutral (4) to positive (7). Negative words received an average rating of  $1.57 \pm .11$  (range 1.0–2.5) while neutral words received a rating of  $4.7 \pm .11$  (range 3.8–5.5). This difference was significant ( $t(17) = -18.13$ ;  $p < .001$ ). There were no differences between neutral and negative words or between the two lists with respect to word frequency or word length.

The list was presented to the subjects on a piece of paper and subjects were instructed to learn the list (intentional learning). They were given 2 min to learn the list with immediate free recall being tested. This procedure was repeated immediately once more leading to two learning trials.

In the afternoon (5 h after initial learning, 1 h after oral cortisol or placebo treatment) free recall of the words was tested. To account for possible within and between subject variance in initial learning, free recall performance in the afternoon was expressed as the percentage of words remembered in relation to the second (and last) learning trial in the morning.

Immediately after free recall cued recall was assessed by presenting the first two letters of each learned word on a piece of paper in a random order with the instruction to complete the word stem to the previously learned words. Then working memory and attention was tested (see below).

### 1.2. Working memory (digit-span test)

A series of numbers with increasing length were read to the subjects. They had to repeat the digits in the same order or in the reversed order. Each length was tested twice. One point was given for each correctly repeated set.

### 1.3. d2 test of attention/psychomotor speed

Out of a series of d's and p's with one or two lines above and/or beneath each letter the participants had to mark as quickly and correctly as possible the d's with two lines. The test score is the number of the correctly marked letters minus the number of errors.

### 1.4. Mood assessment

An adjective checklist for the assessment of bad versus good mood, awake versus tired, and calm versus restless was used.

Saliva was collected using Salivette collection devices (Sarstedt, Rommelsdorf, Germany). Samples were taken before the treatment, 60 min after treatment (immediately before cognitive testing) and 90 min after

treatment (after cognitive testing). Free cortisol levels were measured using an immunoassay (IBL, Hamburg, Germany).

Results revealed the expected treatment induced increase in cortisol (see Table 1).

Cortisol treatment led to a significant reduction in free recall of all words. Subjects under cortisol recalled  $74.10 \pm 2.68\%$  while recalling  $80.87 \pm 2.25\%$  under placebo ( $t(15) = 3.67$ ;  $p < .01$ ). The effects of valence and cortisol were analyzed using two approaches. The first approach consisted of four Bonferroni adjusted paired  $t$  tests ( $p < .0125$ ), the second consisted of an ANOVA with the factors treatment and valence.

Bonferroni adjusted paired  $t$  tests revealed a significant difference between placebo and cortisol for the negative words ( $t(15) = 3.92$ ;  $p < .01$ ) but not for the neutral words ( $t(15) = 0.74$ ;  $p = .47$ ). There was a trend for better recall of the negative words ( $t(15) = 1.62$ ;  $p < .13$ ) in the placebo condition, while no such trend was apparent in the cortisol condition. See Fig. 1 for means and standard errors.

ANOVA with the factors treatment (cortisol versus placebo) and valence (negative versus neutral) revealed a significant main effect of treatment ( $F(1,15) = 14.00$ ;  $p < .01$ ) but failed to find a significant interaction between treatment and valence ( $F(1,15) = 1.87$ ;  $p < .19$ ).

Table 1  
Cortisol levels during the course of the study (mean  $\pm$  SE)

Time	Placebo (nmol/L)	Cortisol (30 mg) (nmol/L)
Baseline	7.84 $\pm$ 1.01	10.49 $\pm$ 1.42
+60 min (pre-testing)	6.38 $\pm$ 0.61	88.06 $\pm$ 10.54*
+90 min (post-testing)	5.19 $\pm$ 0.94	80.06 $\pm$ 9.84*

\*  $p < .01$  in paired  $t$  tests.

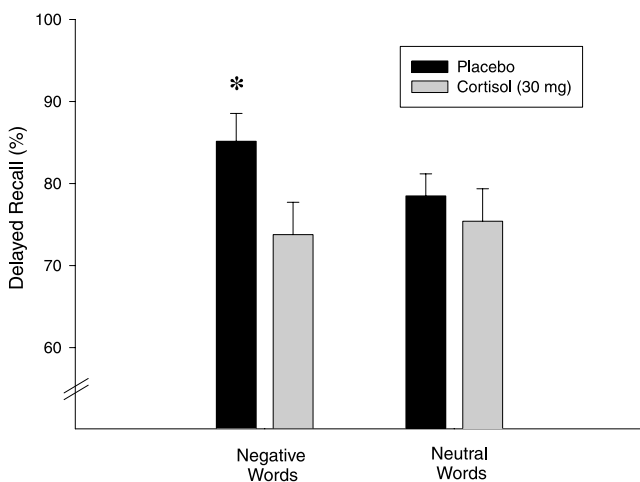


Fig. 1. Effects of oral cortisol treatment on delayed free recall of negative and neutral words. Performance is presented as percentage of words remembered from the learning trial. \* $p < .01$  in paired  $t$  tests.

Cortisol treatment had no effect on cued recall ( $t(15) = .28$ ;  $p = .78$ ). Similarly working memory, attention as well as mood were not affected by cortisol (all  $ps > .20$ ).

The means and standard errors of all cognitive test scores are presented in Table 2.

The present study in young healthy women replicates an impairing effect of cortisol on memory retrieval, as reported previously in studies investigating young men and women (de Quervain et al., 2000), young men (de Quervain et al., 2003), or young and older men (Wolf, Convit et al., 2001). For the first time the effect of cortisol on retrieval of neutral and negative words was tested. If negative and neutral words were presented in one word list, only retrieval of negative words was significantly affected as revealed by Bonferroni adjusted  $t$  tests. However, no significant treatment by valence interaction was observed in the ANOVA, which reflects the fact that the effects for neutral and negative words were going into the same direction as well as the relatively small sample size and its associated lack of power. Previous studies found impairing effects when using only assumingly neutral words (de Quervain et al., 2000, 2003; Wolf, Convit et al., 2001) thereby demonstrating that negative valence of the learning material is not a prerequisite for the occurrence of an impairing cortisol effect.

Only women in one phase of their menstrual cycle were tested. Sex differences have been reported for emotional memory (Cahill, 2003) as well as for the effects of stress on memory in animals (Luine, 2002; Shors & Leuner, 2003) and humans (Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001). Future studies will have to investigate the effects of sex and sex hormones systematically.

In the present study, negative words only tended to be better remembered under placebo than neutral words. The length of the wordlist or the delay (5 h)

Table 2  
Mean ( $\pm$  SE) cognitive test scores of subjects treated with placebo or cortisol

Cognitive test	Placebo	Cortisol (30 mg)
2nd Learning trial (all words)	20.75 $\pm$ 1.26	21.06 $\pm$ 0.93
2nd Learning trial (negative words)	10.13 $\pm$ 0.69	10.81 $\pm$ 0.53
2nd Learning trial (neutral words)	10.50 $\pm$ 0.72	10.25 $\pm$ 0.71
Delayed recall (all words)	17.00 $\pm$ 1.30	15.69 $\pm$ 0.98
Delayed recall (negative words)	8.56 $\pm$ 0.66	7.93 $\pm$ 0.53
Delayed recall (neutral words)	8.44 $\pm$ 0.76	7.69 $\pm$ 0.65
Cued recall (all words)	18.31 $\pm$ 1.62	17.88 $\pm$ 1.26
Cued recall (negative words)	8.63 $\pm$ 0.76	8.75 $\pm$ 5.36
Cued recall (neutral words)	8.94 $\pm$ 0.86	9.00 $\pm$ 0.88
Digit span (forwards)	9.69 $\pm$ 0.36	9.19 $\pm$ 0.32
Digit span (backwards)	8.13 $\pm$ 0.44	7.94 $\pm$ 0.47
Attention (Correct hits minus errors)	174.25 $\pm$ 13.43	171.38 $\pm$ 15.40

might account for this. In addition, a better recall of negative words is not always observed (e.g., [Tops et al. \(2003\)](#)). Emotional pictures or stories might be more powerful to produce reliable strong effects of valence on memory and therefore might be better suited for the investigation of cortisol effects on emotional memory ([Buchanan & Lovallo, 2001](#)).

Three previous studies investigated the possible interaction of cortisol with the emotional valence of the learning material. These studies, however, investigated different phases of the memory process. For example, [Buchanan and Lovallo \(2001\)](#) tested the effects of cortisol on memory consolidation. Cortisol given before the initial learning of pictures enhanced recognition tested 3 weeks later for those pictures, which were rated as arousing (positive as well as negative pictures). [Tops et al. \(2003\)](#) observed that cortisol given before initial learning impaired immediate free recall for neutral and positive words, but not for negative words. A third study observed no interaction between emotional valence and cortisol ([Abercrombie et al., 2003](#)).

Studies in rodents have stimulated the model that glucocorticoids together with norepinephrine interact in the amygdala leading to enhanced memory consolidation. The same mechanism appears to be responsible for the negative effects of glucocorticoids on delayed retrieval ([Roosendaal, 2002](#)). It is thus conceivable that the beneficial effect of cortisol on memory consolidation is enhanced for emotional or arousing material ([Buchanan & Lovallo, 2001](#)), while the impairing effect of cortisol on memory retrieval might also be enhanced, as suggested by the present study. The recent findings by [Tops et al. \(2003\)](#), however, appear to argue against this interpretation, but these authors tested immediate recall only. One could speculate that the interaction of cortisol with emotional valence differs between immediate recall, presumably mediated by the prefrontal cortex, and delayed retrieval, presumably mediated by the hippocampus ([Lupien & Lepage, 2001](#); [Wolf, 2003](#)). Since only negative and neutral words were used as learning material in the current study no conclusion can be drawn regarding positive words. As already discussed, one study found that the effects of cortisol are different for positive and negative words ([Tops et al., 2003](#)). Similarly, in male rats fear provoking stress (cat exposure) but not positive arousal (presence of a receptive female) is associated with impaired memory ([Woodson, Macintosh, Fleshner, & Diamond, 2003](#)). Future studies are needed to disentangle the possibly distinct effect of arousal and valence.

No effects on working memory as tested somewhat crudely with digit span forwards and backwards was observed. This is in contrast to some previous studies reporting impairing effects of cortisol treatment on working memory (see for review: [Lupien & Lepage, 2001](#); [Wolf, 2003](#)). The time of day (afternoon versus morning; [Lupien et al., 2002](#)) or the sex of the partici-

pants ([Wolf, Schommer et al., 2001](#)) might explain these discrepancies.

The oral cortisol treatment lead to salivary cortisol levels in the upper physiological range reflective of severe psychological stress (e.g. first parachute jump ([Deinzer, Kirschbaum, Gresele, & Hellhammer, 1997](#))). It therefore remains to be shown whether a more moderate cortisol increase as induced by a standardized laboratory stressor like the ‘Trier Social Stress Test’ ([Wolf, Schommer et al., 2001](#)) leads to similar retrieval deficits.

In sum, the present study replicates a negative effect of oral cortisol treatment on delayed memory retrieval. For the first time it is reported that retrieval of negative words appears to be more affected than retrieval of neutral words if both are presented in one wordlist. Emotional material thus might be especially sensitive for the memory modulating effects of cortisol.

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