Associations between Basal Cortisol Levels and Memory Retrieval in Healthy Young Individuals

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Abstract

■ Cortisol is known to affect memory processes. On the one hand, stress-induced or pharmacologically induced elevations of cortisol levels enhance memory consolidation. On the other hand, such experimentally induced elevations of cortisol levels have been shown to impair memory retrieval. However, the effects of individual differences in basal cortisol levels on memory processes remain largely unknown. Here we tested whether individual differences in cortisol levels predict picture learning and recall in a large sample. A total of 1225 healthy young women and men viewed two different sets of emotional and neutral pictures on two consecutive days. Both sets were recalled after a short delay (10 min). On Day 2, the pictures seen on Day 1 were additionally recalled, resulting in a long-delay (20 hr) recall condition. Cortisol levels were measured three times on Days 1 and 2 via saliva samples before encoding, between encoding and recall as well as after recall testing. We show that stronger decreases in cortisol levels during retrieval testing were associated with better recall performance of pictures, regardless of emotional valence of the pictures or length of the retention interval (i.e., 10 min vs. 20 hr). In contrast, average cortisol levels during retrieval were not related to picture recall. Remarkably during encoding, individual differences in average cortisol levels as well as changes in cortisol did not predict memory recall. Our results support previous findings indicating that higher cortisol levels during retrieval testing hinders recall of episodic memories and extend this view onto interindividual changes in basal cortisol levels. ■

INTRODUCTION

Glucocorticoids have a modulatory influence on memory processes. The effect of cortisol on memory strongly depends on the stage of memory consolidation (Schwabe, Joels, Roozendaal, Wolf, & Oitzl, 2012; de Quervain, Aerni, Schelling, & Roozendaal, 2009; Wolf, 2009). During memory formation, experimentally increased cortisol, pharmacologically or by stress induction, improves memory, in particular memory for emotionally arousing events (e.g., Cahill, Gorski, & Le, 2003; for a review, see Wolf, 2009). In contrast, cortisol impairs the retrieval of long-term memories. In rats, stress or systemic corticosterone administration before recall impairs recall of spatial memory of a water maze task acquired 24 hr earlier (de Quervain, Roozendaal, & McGaugh, 1998). In humans as well, administration of cortisone before retrieval testing impairs memory recall (Smeets, 2011; Tollenaar, Elzinga, Spinhoven, & Everaerd, 2008, 2009; de Quervain et al., 2003; de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000). Several studies show that the impairing influence of cortisol on retrieval of long-term memories is particularly pronounced for emotionally arousing material (Buchanan, Tranel, & Adolphs, 2006; Kuhlmann, Kirschbaum, & Wolf, 2005; Kuhlmann, Piel, & Wolf, 2005).

Effects of glucocorticoids on memory consolidation and retrieval depend on noradrenergic coactivation within the brain. Blockade of noradrenergic receptors in the amygdala diminishes cortisol-related memory enhancements (Roozendaal, Okuda, de Quervain, & McGaugh, 2006; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006; van Stegeren et al., 2005; Quirarte, Roozendaal, & McGaugh, 1997); on the other hand, cortisol-induced retrieval impairments are blocked by concurrent administration of the adrenergic antagonist propranolol (de Quervain, Aerni, & Roozendaal, 2007; Roozendaal, Hahn, Nathan, de Quervain, & McGaugh, 2004; for a review, see Krugers, Karst, & Joels, 2012).

Considering biological mechanisms underlying reactivity and feedback processes of the HPA axis, mineralocorticoid (MR) and glucocorticoid receptors (GR) play an important role in mediating glucocorticoid effects in the brain. They are highly expressed in the limbic system (hippocampus and amygdala), regions important for emotion and cognition (Lupien & McEwen, 1997). MRs have a higher affinity for glucocorticoids than GRs and are almost saturated under basal levels. GRs become occupied under stress or when circadian glucocorticoid levels are high (Roozendaal, Okuda, de Quervain, et al., 2006; Reul & de Kloet, 1985).

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It has been suggested that MRs are implicated in the maintenance of basal activities of the stress system. On the other side, GRs, in interplay with MRs, seem to be implicated in the recovery from a stress response, hence the suppression of the HPA axis. The balance between MRs and GRs is important for HPA activity as well as for neuronal excitability, stress responsiveness, and behavioral adaptation (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998). Furthermore, besides the intracellular effects of MR and GR, also a membrane-bound MR (Joëls, Karst, DeRijk, & De Kloet, 2008) and GR (Roozendaal et al., 2010) have been observed, which could be involved in rapid nongenomic effects on memory processes.

Although the effects of experimentally increased glucocorticoid levels on memory are well established, the relationship between natural circadian variation of cortisol (basal cortisol) and memory has received less attention. Basal cortisol levels follow a circadian rhythm (e.g., Kirschbaum & Hellhammer, 1989) and strongly differ between individuals (Kudielka, Hellhammer, & Wust, 2009). Furthermore, glucocorticoid levels are altered in psychiatric diseases such as depression and posttraumatic stress disorders (PTSD), which are often accompanied by cognitive deficits (Yehuda, 2002; Belanoff, Gross, Yager, & Schatzberg, 2001). The few studies that have investigated the effects of basal cortisol on memory formation in healthy individuals do not show consistent results; positive as well as negative relations between basal cortisol levels and memory for emotional information have been reported (Preuss, Schoofs, & Wolf, 2009; Putman, Van Honk, Kessels, Mulder, & Koppeschaar, 2004; Van Honk et al., 2003). Furthermore, It has been shown that changes in cortisol levels over the study visit are associated with cognitive performance (Lee et al., 2007). In contrast to basal cortisol levels during encoding, to our knowledge, the relation between basal cortisol levels or changes in cortisol levels during retrieval testing and memory recall in healthy young individuals is still unknown.

In this study, we aimed at investigating whether basal cortisol levels as well as changes in basal cortisol levels during recall are related to memory performance in a short-delay and a long-delay episodic memory task in a large population (n = 1225) of healthy young individuals. In addition, we were interested whether we could replicate previous findings of basal cortisol during encoding and memory performance.

METHODS

Participants

We had complete data from 1253 participants. Twenty-eight participants had to be excluded because their cortisol measures exceeded our outlier criterion (4 *SD*s from group mean). Data from 1225 healthy young women and men (812 women, 413 men) between 18 and 35 years (mean age = 22.49 years, *SD* = 3.59 years) were included in the analyses. Of the 812 women participating in the study, 429 women were taking hormonal contraceptives, and 383 women were not taking hormonal contraceptives. Participants were students or employees from the Basel area and were paid for their participation. They did not take any medication (except hormonal contraceptives) and reported no neurological or mental illness. The study was approved by the local ethics committee and all participants gave written informed consent before participation.

Procedure

The experiments were conducted on two consecutive days (Figure 1). On Day 1, participants received instructions and were trained on the tasks. After training, participants viewed emotional and neutral pictures of the picture memory task (Set 1). Afterwards participants performed on a working memory task (n-back). This task was followed by an unannounced free recall test of the previously seen

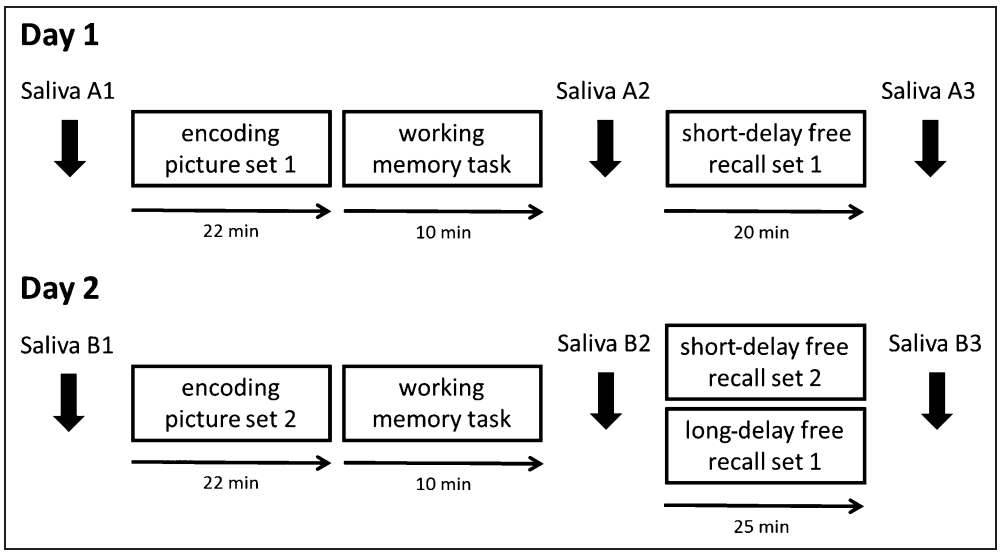

Figure 1. Study design and experimental procedure including point in time of cortisol measurements.

pictures (short-delay recall Day 1). Testing on Day 1 always occurred between 4:00 and 7:00 p.m. On Day 2 testing occurred between 1:00 and 3:00 p.m. Participants completed the same tasks again, although they saw a different set of emotional and neutral pictures (Set 2). On Day 2, participants were asked to freely recall all pictures seen 10 min earlier on the same day (short-delay recall Day 2) and the pictures seen 20 hr earlier on Day 1 (long-delay recall). On both days, saliva samples for cortisol determination were collected three times: before picture encoding, between picture encoding and picture recall, as well as after recall testing.

Picture Memory Task

The picture memory task consisted of 72 pictures taken from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008) as well as from in-house standardized picture sets. Stimuli consisted of two sets (Set 1 and Set 2) of 24 positive, 24 negative, and 24 neutral pictures interleaved with 24 scrambled pictures. Additionally, four pictures showing neutral objects were presented to control for primacy and recency effects (two pictures were shown in the beginning of the presentation, the other two at the end). These pictures were not included in the analysis. Set 1 was presented on Day 1, and Set 2 was presented on Day 2. The two sets were counterbalanced for ratings of arousal and valence as well as for visual complexity and presence of humans.

The pictures were presented in a quasi-randomized order so that a maximum of four pictures of the same category followed consecutively. A fixation-cross appeared for 500 msec before each picture. Then the picture was presented for 2.5 sec. After presentation of each picture, participants rated the presented picture according to its emotional valence (negative = 1, neutral = 2, positive = 3) and arousal (low = 1, medium = 2, high = 3) on a 3-point scale. Trials were separated by variable intertrial periods (9–12 sec). Participants were not told to memorize the pictures (incidental encoding).

For the free recall task, participants had to write down a short description of each picture. The participants were instructed to recall as many pictures as possible. There was no time limit for this task. Participants were not told how many pictures they saw during picture presentation; therefore, no expectation of the amount of the to-be-recalled pictures was mentioned to the participants. Two independent and blind raters analyzed the recalled pictures and decided for each picture whether it could be recognized as one of the presented pictures. The interrater reliability added up to .96 (Cronbach's alpha). Afterwards a third independent and blind rater decided on pictures, which were rated differently.

Working Memory Task

Between picture presentation and recall, participants performed on the 0- and 2-back versions of the *n*-back working memory task (Gevins & Cutillo, 1993). In this task, letters are presented successively in the center of the screen. In the 0-back condition, participants had to respond to the occurrence of the letter "x," which is a baseline measure of general attention, concentration, and RT. The 2-back task requires participants to respond to a letter repetition with one intervening letter (g - S - f - s). The latter condition required both the maintenance of the last two letters in memory, and updating of these remembered stimuli as each new stimulus was presented. The difference in accuracy between the 2-back and the 0-back condition represents a reliable measure of working memory. *n*-Back data were available for 1100 participants.

Saliva Samples

Cortisol was measured via saliva samples using Salivette collection tubes (Sarstedt, Germany). On both days, saliva samples were taken before picture presentation (Figure 1 and Table 1; Day 1: Sample A1; Day 2: Sample B1) between picture presentation and picture recall (Day 1: Sample A2; Day 2: Sample B2) as well as after recall testing (Day 1: Sample A3; Day 2: Sample B3).

We were interested in the relation between cortisol during retrieval testing or picture encoding, respectively, and recall success and therefore investigated associations in relation to average cortisol levels during encoding (A1 and A2) and retrieval (A2 and A3) on Day 1 as well as on Day 2 (B1 and B2 as well as B2 and B3, respectively). Finally, we examined the relationship between changes in cortisol levels during encoding (A2 minus A1) and during retrieval (A3 minus A2) on Day 1 and Day 2 (B2 minus B1 and B3 minus B2, respectively). Because of circadian rhythm, cortisol levels generally showed a decrease during the experimental sessions. Therefore, the change in cortisol was mostly negative and can be seen as a measure of decrease of cortisol during the tasks.

Cortisol levels were analyzed by the Technical University of Dresden, Germany. For cortisol analysis, saliva samples were centrifuged at 3000 rpm for 3 min after thawing. Concentrations of salivary free cortisol were measured using a commercially available chemiluminescence immunoassay (IBL, Hamburg, Germany) with intra- and interassay precision of 2.5% and 4.7%, respectively.

Statistical Analysis and Data Reduction

Data were analyzed with bivariate Pearson's correlations, partial correlations, repeated-measure ANOVAs, and *t* tests (SPSS Statistics 20.0, 2011). Statistical comparison of correlation coefficients was performed using the software "R" (R Development Core Team, 2012). Recalled pictures are presented as percentage of presented pictures. p values of $< .05$ were considered significant; for correlation analyses, we applied correction for multiple testing: We first calculated the correlations independent of emotional valence, resulting in 16 correlations (eight for average

Table 1. Descriptives of Cortisol Levels, Mean Cortisol, Change in Cortisol, and Memory Performance (n = 1225)

Cortisol Levels Day 1 (nmol/L)			*Cortisol Levels Day 2 (nmol/L)*		
A1	*A2*	*A3*	*B1*	*B2*	*B3*
7.51 ± 4.36	5.32 ± 2.79	4.39 ± 2.22	12.03 ± 6.63	8.91 ± 4.25	6.76 ± 2.96

Mean Cortisol Levels Day 1 (Log-transformed)		*Mean Cortisol Levels Day 2 (Log-transformed)*	
Encoding (Mean A1A2)	*Recall (Mean A2A3)*	*Encoding (Mean B1B2)*	*Recall (Mean B2B3)*
1.72 ± 0.47	1.47 ± 0.45	2.23 ± 0.45	1.96 ± 0.41

Change in Cortisol Day 1 (Log-transformed)		*Change in Cortisol Day 2 (Log-transformed)*	
Encoding (Change A2-A1)	*Recall (Change A3-A2)*	*Encoding (Change B2-B1)*	*Recall (Change B3-B2)*
−0.33 ± 0.23	−0.19 ± 0.18	−0.27 ± 0.24	−0.26 ± 0.21

Short Delay Memory Recall Day 1		*Short Delay Memory Recall Day 2*	
Positive pictures	47.66 ± 14.55%	Positive pictures	47.92 ± 15.71%
Negative pictures	44.29 ± 13.72%	Negative pictures	47.47 ± 15.74%
Neutral pictures	26.79 ± 12.71%	Neutral pictures	33.44 ± 15.86%

	Long Delay Memory Recall Day 2	
	Positive pictures	33.69 ± 15.00%
	Negative pictures	30.99 ± 14.31%
	Neutral pictures	18.87 ± 11.77%

Reported are mean ± *SD*.

cortisol levels and eight for change in cortisol levels). Using Bonferroni correction to correct for multiple testing, a p value of <.003 (i.e., $p < .05/16$) was considered significant. In case of significant correlation after correction for multiple testing, we analyzed correlations for the different valences separately and investigated whether the correlation coefficients of the different emotional valences differed significantly. For exploratory purposes, we also report all correlation coefficients for all valences (Tables 3 and 4). Where not stated differently, values are presented as mean ± *SEM*. Because of the known sex differences in memory recall and cortisol levels, we conducted additional analyses controlling for the influence of sex and use of hormonal contraceptives.

RESULTS

Salivary Cortisol

Because cortisol data (Table 1) were not normally distributed, we used log-transformed data for all analyses. Cortisol levels showed a significant point in time of Cortisol Measurement × Day interaction as well as significant main effects for Point in Time of Cortisol Measurement and Day (all $p < .001$). On both days, cortisol levels decreased over the three measurement points, and on average, cortisol levels were lower on Day 1 (4:00 to 7:00 p.m.; mean = 5.74 ± 0.08 nmol/L) as compared with Day 2 (1:00 to 3:00 p.m.; mean = 9.23 ± 0.12 nmol/L). These findings are in accordance with the well-known circadian variation of cortisol levels.

With respect to change in cortisol levels (decrease in cortisol; lower values indicate larger decrease) during encoding (Day 1: A2-A1; Day 2: B2-B1) and recall (Day 1: A3-A2; Day 2: B3-B2; Table 1), data showed a significant Point in Time of Cortisol Measurement × Day interaction as well as a significant main effect for Point in Time of Cortisol Measurement (all $p < .001$). On Day 1, decrease in cortisol was significantly larger during encoding than during recall (all $p < .001$). On Day 2, change in cortisol during encoding was not different from change during recall ($p = .21$). Decrease in cortisol levels during encoding was larger on Day 1 as compared with Day 2 ($p < .001$), whereas decrease in cortisol levels during recall was larger on Day 2 as compared with Day 1 ($p < .001$).

Given the possible influence of sex and use of hormonal contraceptives in respect to cortisol levels, we additionally compared cortisol levels of women taking

hormonal contraceptives, women not taking hormonal contraceptives, and men. The groups differed with respect to the decrease measures as well as the mean cortisol levels during encoding and retrieval on both days (all $p < .05$; for single comparisons, see Table 2). Women taking hormonal contraceptives generally showed less decrease in cortisol than the other two groups.

Picture Recall

In the short-delay recall conditions we found a significant Picture Valence × Day interaction, as well as significant main effects for Valence and Day (all $p < .001$; Table 1). On both days, participants recalled more emotional than neutral pictures (all $p < .001$). On Day 1, participants recalled more positive pictures than negative pictures ($p < .001$), whereas on Day 2 recall of positive and negative pictures did not differ ($p = .25$). On Day 2, participants recalled more negative and neutral pictures than on Day 1 (both $p < .001$), recall of positive pictures did not differ ($p = .52$).

In the long-delay condition, we found a significant main effect of Picture Valence ($p < .001$). Participants recalled more emotional pictures than neutral pictures (both $p < .001$); furthermore, positive pictures were better recalled than negative pictures ($p < .001$).

Cortisol during Picture Recall

Mean Cortisol Levels

None of the average levels of cortisol during picture recall (mean of A2 and A3, respectively, mean of B2 and B3) was significantly associated with recall performance, neither in relation to long-delay recall nor short-delay recall (all $p_{(uncorrected)} \geq .12$; Table 3). To get a more complete overview, we additionally checked whether single cortisol levels are associated with memory recall. However, none of the correlations reached significance after correction for multiple testing.

Change in Cortisol Levels

We observed a significant association between the decrease in cortisol levels during recall on Day 2 (B3-B2) and long-delay recall performance ($r = -0.13$, $R^2 = 1.69\%$; $p_{(uncorrected)} = .00001$; $p_{(Bonferroni\text{-}corrected)} = .0002$; Figure 2). Because it has previously been found that cortisol effects on memory are particularly pronounced for emotional stimuli, we compared correlations of decrease in cortisol levels with the different picture valences separately. After correction for multiple testing, we found significant correlations for positive and negative picture valences (Table 4); however, the correlation coefficients for the different picture valences did not significantly differ (all $p \geq .15$).

On Day 2, decrease in cortisol levels during recall (B3-B2) also correlated with short-delay recall of pictures on Day 2: $r = -0.11$, $R^2 = 1.21\%$; $p_{(uncorrected)} = .00006$; $p_{(Bonferroni\text{-}corrected)} = .001$; Figure 2). The correlation between cortisol levels during recall on Day 1 (A3-A2) and short-delay recall of pictures reached nominal significance but did not withstand correction for multiple testing (Day 1: $r = -0.08$, $p = .006$; $p_{(Bonferroni\text{-}corrected)} = .10$). Comparing correlations of cortisol levels with the different picture valences separately, on both days we found the highest correlation with short-delay recall of negative pictures, the lowest correlation with positive pictures and correlation with recall of neutral pictures in between (Table 4). On Day 2, the correlation coefficients for short delay of negative pictures and

Table 2. Comparison of Cortisol Levels between Women Taking Hormonal Contraceptives (whc; $n = 429$), Women Not Using Hormonal Contraceptives (wnc; $n = 383$) and Men ($n = 413$)

	whc	*wnc*	*Men*	*Single Comparisons*
Mean Cortisol Levels				
Encoding day 1 (mean A1A2)	1.75 ± 0.42	1.60 ± 0.51	1.81 ± 0.45	wnc < whc; wnc < men
Recall day 1 (mean A2A3)	1.55 ± 0.42	1.30 ± 0.48	1.53 ± 0.42	wnc < whc; wnc < men
Encoding day 2 (mean B1B2)	2.17 ± 0.42	2.24 ± 0.47	2.26 ± 0.47	whc < men
Recall day 2 (mean B2B3)	2.00 ± 0.39	1.92 ± 0.41	1.96 ± 0.43	wnc < whc
Change in Cortisol				
Encoding day 1 (change A2-A1)	−0.24 ± 0.17	−0.37 ± 0.22	−0.37 ± 0.27	wnc < whc; men < whc
Recall day 1 (change A3-A2)	−0.16 ± 0.14	−0.21 ± 0.18	−0.20 ± 0.22	wnc < whc; men < whc
Encoding day 2 (change B2-B1)	−0.17 ± 0.16	−0.33 ± 0.25	−0.33 ± 0.26	wnc < whc; men < whc
Recall day 2 (change B3-B2)	−0.19 ± 0.15	−0.32 ± 0.22	−0.29 ± 0.24	wnc < whc; men < whc

Reported are mean ± *SD*. Cortisol levels are log-transformed. Reported are significant post hoc comparisons (Bonferroni corrected). p values of <.05 are considered significant.

Table 3. Correlations between Average Cortisol Levels and Memory Recall (n = 1225)

	Cortisol Levels Day 1		*Cortisol Levels Day 2*	
	Encoding (Mean A1A2)	*Recall (Mean A2A3)*	*Encoding (Mean B1B2)*	*Recall (Mean B2B3)*
Short-delay Recall Day 1				
Positive				
r	−.00	−.01		
p	.91	.86		
Negative				
r	−.00	−.01		
p	.94	.63		
Neutral				
r	.02	.01		
p	.58	.81		
Short-delay Recall Day 2				
Positive				
r			.00	.01
p			.93	.84
Negative				
r			.05	.02
p			.10	.40
Neutral				
r			−.01	−.03
p			.65	.24
Long-delay Recall				
Positive				
r	−.02	−.01	−.02	−.04
p	.44	.64	.53	.22
Negative				
r	−.01	.00	−.03	−.05
p	.74	.99	.35	.07
Neutral				
r	−.01	−.01	.00	−.02
p	.76	.62	.98	.45

None of the correlations reached significance: Bonferroni-corrected p values ($p < .002$; i.e., 0.05/24) are considered significant.

short delay of positive pictures were significantly different ($t = 2.06$; $p = .04$). All other correlation coefficients for the different pictures valences did not differ (all $p \geq .17$).

To rule out the possibility, that the decrease measure (B3-B2) is influenced by the size of the first cortisol measure B2 (i.e., a larger first measure could lead to a larger decrease), we included B2 as covariate in an additional analysis. Including B2 as covariate did not alter the result pattern (association with long-delay recall performance: $r = -0.14, R^2 = 1.96\%; p_{(\text{uncorrected})} = .000001$; association with short-delay recall performance: $r = -0.11$, $R^2 = 1.21\%$; $p_{(\text{uncorrected})} = .00007$).

Given the differences in responses to stress effects on memory in women using hormonal contraceptives and women not using hormonal contraceptives (e.g., Nielsen, Segal, Worden, Yim, & Cahill, 2013), we additionally conducted separate analyses in women taking hormonal contraceptives and women not using hormonal contraceptives. Descriptively, associations were stronger for women not using hormonal contraceptives ($r = -0.19$, $R^2 = 3.61\%$; $p_{(\text{uncorrected})} = .0003$) than for women taking hormonal contraceptives ($r = -0.10$, $R^2 = 1.0\%$; $p_{(\text{uncorrected})} = .04$); for association between decrease in cortisol levels during recall on Day 2 (B3-B2) and long-delay recall performance. Effects in men were similar to the effects in women not using hormonal contraceptives ($r = -0.17$, $R^2 = 2.89\%$; $p_{(\text{uncorrected})} = .0004$). However, statistically, the correlation coefficients were not significantly different (all $p \geq .22$).

With respect to the association between the decrease in cortisol levels during recall on Day 2 (B3-B2) and short-delay recall performance, correlations were descriptively strongest in men ($r = -0.23$, $R^2 = 5.29\%$; $p_{(\text{uncorrected})} = .000004$), followed by women taking hormonal contraceptives ($r = -0.14$, $R^2 = 1.96\%$; $p_{(\text{uncorrected})} = .003$) and women not using hormonal contraceptives ($r = -0.12$, $R^2 = 1.44\%$; $p_{(\text{uncorrected})} = .02$). However statistically, the correlation coefficients did not significantly differ (all $p \geq .14$).

Cortisol during Encoding

Mean Cortisol Levels

None of the mean levels of cortisol during picture encoding (mean A1 A2 and mean B1 B2, respectively) were significantly associated with picture recall, neither in relation to long-delay recall nor in relation to short-delay recall (all $p_{(\text{uncorrected})} \geq .51$; Table 3).

Change in Cortisol Levels

In contrast to decrease in cortisol during recall, decrease in cortisol during encoding of pictures (A2-A1) did not predict long-delay recall ($r = 0.04$, $p_{(\text{uncorrected})} = .15$; $p_{(\text{Bonferroni-corrected})} > .99$; Table 4). In respect to short-delay recall, we did not find any significant correlations with decrease in cortisol levels during encoding (A2-A1 and B2-B1, respectively; both $p \geq .11$; $p_{(\text{Bonferroni-corrected})} > .99$; Table 4).

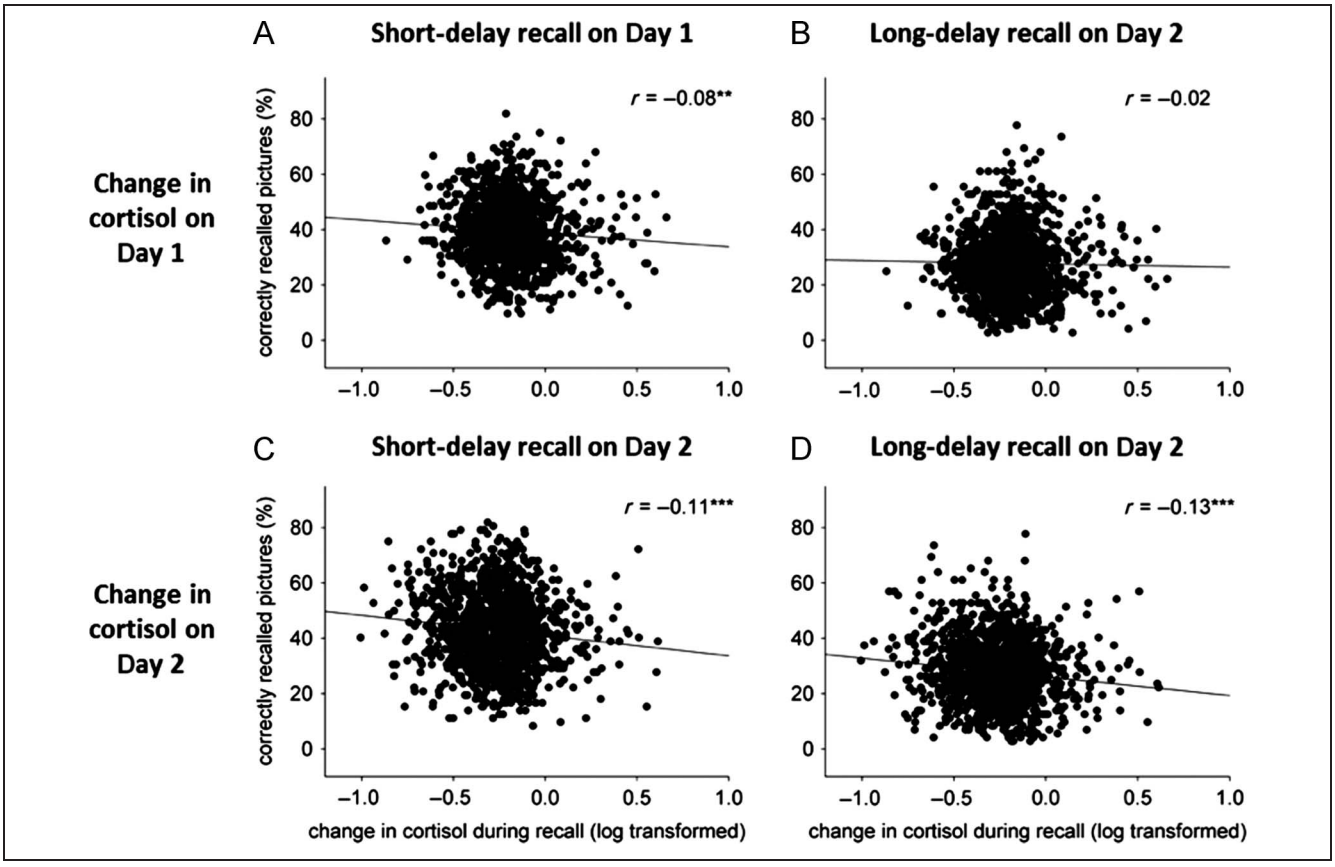

Figure 2. Associations between changes in cortisol levels during picture recall and recalled percentage of presented pictures (independent of valence). (A) Change in cortisol on Day 1 (A3-A2) and short-delay recall on Day 1. (B) Change in cortisol on Day 1 (A3-A2) and long-delay recall on Day 2. (C) Change in cortisol on Day 2 (B3-B2) and short-delay recall on Day 2. (D) Change in cortisol on Day 2 (B3-B2) and long-delay recall on Day 2. **p (uncorrected) < .01; ***p (uncorrected) < .001.

Table 4. Correlations between Change in Cortisol and Memory Recall (n = 1225)

	Cortisol Levels Day 1		*Cortisol Levels Day 2*	
	Encoding (Change A2-A1)	*Recall (Change A3-A2)*	*Encoding (Change B2-B1)*	*Recall (Change B3-B2)*
Short-delay Recall Day 1				
Positive				
r	.04	−.05		
p	.22	.07		
Negative				
r	.02	−.09		
p	.44	.003		
Neutral				
r	.01	−.06		
p	.74	.04		
Short Delay Recall Day 2				
Positive				
r			.08	−.07
p			.008	.01
Negative				
r			.02	**−.12***
p			.58	**<.001**
Neutral				
r			.03	**−.10***
p			.33	**<.001**
Long Delay Recall				
Positive				
r	.05	−.01	.04	**−.10***
p	.11	.71	.16	**<.001**
Negative				
r	.05	−.01	.04	**−.13***
p	.09	.73	.22	**<.001**
Neutral				
r	.00	−.03	−.00	−.09
p	.90	.31	.94	.003

Bonferroni-corrected p values ($p < .002$; i.e., 0.05/24) are considered significant. **Bold** font indicates significant results.

*Significant p values after Bonferroni correction.

In additional analyses controlling for possible effects of gender and use of hormonal contraceptives, results stayed similar; associations generally increased. Results did not change when correcting for valence or arousal ratings.

Working Memory

No significant correlations were found between working memory performance and basal cortisol levels or change in cortisol levels (all $p > .36$).

DISCUSSION

In this study, we investigated possible associations of naturally varying cortisol levels with free recall of emotional and neutral pictures. Stronger decreases in cortisol levels during recall testing predicted better memory recall in the long-delay as well as in the short-delay condition of Day 2 (the correlation with short-delay recall on Day 1 did not reach significance after correcting for multiple testing), independent of picture valence. We did not find any significant results for the average of cortisol during retrieval and recall performance. To have a more complete picture, we additionally investigated correlations of single cortisol levels with recall performance in an exploratory analysis; however, none of the results reached significance after correction for multiple testing. Furthermore, neither average cortisol levels during encoding nor changes in cortisol levels from baseline to encoding predicted memory performance in the short- or long-delay conditions. In respect to the natural variation of cortisol, these results point to an involvement of decrease of cortisol levels in the process of retrieving memories, rather than in memory acquisition. It is to note that the strength of the observed associations—although statistically highly significant—is rather small and explains only roughly 1–2% of the variation in memory performance. However, considering that we did not induce stress but investigated subtle variations in circadian cortisol levels during performance of the tasks, we in fact did expect small rather than large effects.

Our results are in line with previous studies examining glucocorticoid effects on memory retrieval. Administration of glucocorticoids before retrieval testing impaired memories acquired on the day before in animals and humans while leaving immediate recall unaffected (de Quervain et al., 1998, 2000). Increasing glucocorticoid levels by stress induction before retrieval lead to similar effects (de Quervain et al., 2009; Wolf, 2009, for reviews). In studies using different methods to induce an elevation of glucocorticoids, the impairing influence of cortisol on retrieval is particularly pronounced for emotionally arousing stimuli (Smeets, 2011; Smeets, Otgaar, Candel, & Wolf, 2008; Tollenaar et al., 2008; Buchanan et al., 2006; Kuhlmann, Kirschbaum, et al., 2005; Kuhlmann, Piel, et al., 2005). In our study, the association between change in cortisol during recall and recall was independent of picture valence, although the effect was most pronounced for negative pictures. In several previous studies, effects have also been found with respect to recall of neutral stimuli (Smeets, 2011; de Quervain et al., 2000, 2003). Besides differences in the method used to induce an elevation of glucocorticoids, studies also greatly differed in respect to the memory task, mode of recall (e.g., recognition vs. free recall), and time elapsed between encoding and recall.

Considering neuronal activity, the reduction in brain activity in medial-temporal lobe regions was predictive for the degree of memory impairment induced by preretrieval administration of corticosterone (de Quervain et al., 2003). In addition, cortisol effects on memory retrieval depend on concurrent noradrenergic activation of the amygdala, a brain region highly involved in emotional processing that has rich reciprocal projections with hippocampal brain regions (McGaugh, 2004). In human imaging studies, interaction between the hippocampus and the amygdala is greater during retrieval of emotional as compared with neutral information (Smith, Stephan, Rugg, & Dolan, 2006; Dolcos, LaBar, & Cabeza, 2005). Taken together, noradrenergic coactivation and amygdala–hippocampal interactions appear to be a prerequisite for cortisol-induced retrieval impairments, which may also underlie the effects of cortisol on recall performance in our study. However, with respect to change in cortisol levels during picture recall, we not only found an effect on recall of emotional pictures but also on recall of neutral pictures.

The encoding of emotional pictures might have induced an increase in emotional arousal and noradrenergic activity across the encoding of emotional and neutral pictures. This might in part explain why we found an effect not only on recall of emotional pictures but also on recall of neutral pictures. Yet, we did not find an association of cortisol levels with arousal ratings during picture viewing.

Furthermore, the effects of glucocorticoids on memory are mediated by binding to GR and MR. In respect to memory, the ratio of occupation of GR and MR is important (de Kloet et al., 1998). Therefore, we speculate that less cortisol decrease during the task might point to a ratio of GR/MR occupancy that is less sustentative for recall of memory.

Although change in basal cortisol measures sampled during retrieval testing predicted recall of memories, we did not observe a significant association with change in basal cortisol levels measured during encoding of these memories on the previous day. Stress- or pharmacological-induced cortisol elevations during memory formation are typically beneficial for storing emotional memories (Payne et al., 2007; Roozendaal, Okuda, de Quervain, et al., 2006), whereas reports on basal cortisol levels during encoding and memory have been inconsistent (Putman et al., 2004; Van Honk et al., 2003). In a similar experimental approach as in the current study, Preuss and colleagues (2009) reported a positive association between basal cortisol during encoding and free recall of emotional stimuli only when participants knew that their memory would be tested one day later (intentional encoding). The authors reported no association when participants were unaware that they had to remember the pictures later (incidental encoding), which is consistent with our findings, as in our study picture encoding and picture recall were incidental.

In addition to cortisol, the noradrenergic system is critically involved in memory formation (Roozendaal, Okuda, de Quervain, et al., 2006; Roozendaal, Okuda, Van der Zee, et al., 2006; van Stegeren et al., 2005;

Quirarte et al., 1997) and possibly also played a central role in memory formation in this study. As we did not measure noradrenergic activity, future studies need to further examine this important point.

Previous studies have reported substantial gender differences for the relationship between cortisol and memory (Andreano & Cahill, 2006; Jackson, Payne, Nadel, & Jacobs, 2006; Stark et al., 2006; Zorawski, Blanding, Kuhn, & LaBar, 2006; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001). We did not find substantial differences between men and women. However, a limitation of the current study is the missing information of women's cycle. There might be differences in the association of cortisol and memory in women in different stages of the cycle. We additionally conducted separate analyses for women taking hormonal contraceptives and women not using hormonal contraceptives given the reported differences in responses to stress effects on memory (e.g., Nielsen, Segal, Worden, Yim, & Cahill, 2013). However, we did not find any significant differences between correlation coefficients between these groups.

Furthermore, age might have an influence on the association between cortisol and memory. In our sample of young healthy individuals with a relatively narrow age range (18–35 years), we did not find an influence of age on the associations between cortisol and memory measures. However, it is possible that the picture might be different when investigating participants across a broader age span. In elderly participants, chronic elevation of cortisol over several years has been associated with worse declarative memory performance (e.g., Lupien et al., 2005). Therefore, it would be interesting to investigate whether chronically elevated cortisol levels in younger individuals are related to later memory complaints at an older age. It has previously been shown that in elderly participants elevated cortisol levels over several years lead to deficits in hippocampus-dependent memory and reduced hippocampal volume (Lupien et al., 1998).

Our results might have some clinical implications. Reduced basal cortisol levels have been observed in patients with PTSD (for a review, see Yehuda, 2002). On the background of the current findings, larger decrease in cortisol during memory recall might be related to facilitated recall of traumatic memories and could therefore influence disease status. Compatible with this notion, attempts to treat PTSD patients with cortisol lead to reduction of PTSD symptoms (de Quervain, 2006; Aerni et al., 2004). Furthermore, people with lower basal cortisol levels are at higher risk of developing PTSD after a traumatic event than people with higher basal cortisol levels (de Quervain et al., 2009). Our findings that less decrease in cortisol during retrieval hinders memory recall also in healthy participants adds to the notion that basal cortisol appears to be an important modulator for the accessibility and resistance of memories. This may be an implication for the development of new treatment options of PTSD. Our study strengthens and extends previous findings of glucocorticoids on memory by showing that also without any drastic experimental manipulation, less reduction in cortisol levels during memory retrieval is related to reduced recall of memories.

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