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Arousal and Cortisol Interact in Modulating Memory Consolidation in Healthy Young Men

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Animal studies indicate that adrenal glucocorticoids enhance memory consolidation while impairing memory retrieval. In humans, beneficial effects on consolidation have been observed infrequently. In the current double-blind study, subjects ($N = 29$) received placebo or cortisol (30 mg) 10 min before viewing emotionally arousing or neutral pictures. Cortisol treatment had no effects on immediate recall. In the 24-hr delayed recall condition, cortisol led to an enhanced emotional memory facilitation because of decreased neutral and increased emotional memory recall. No effects of cortisol treatment were observed for recognition memory or mood. Results support the notion that glucocorticoids specifically enhance the consolidation of emotional material.

Keywords: memory, arousal, stress, cortisol, humans

Almost everybody has experienced emotional events that are better remembered than others. In line with this everyday observation are a wealth of laboratory experiments reporting better memory for emotional than neutral material (e.g., Kleinsmith & Kaplan, 1963). Arousal often has a stronger effect on immediate and delayed recall than valence (Bradley, Greenwald, Petry, & Lang, 1992), and there is evidence that both aspects are processed differentially in the brain (Kensinger, 2004). Animal studies have revealed that the basolateral amygdala (BLA; Pare, 2003) is the critical brain structure for memory performance modulated by arousal. In support of this, studies in human patients have found absent emotional memory enhancement after amygdala damage (Adolphs, Tranel, & Buchanan, 2005; Adolphs, Cahill, Schul, & Babinsky, 1997; Cahill, Babinsky, Markowitsch, & McGaugh, 1995). Additional evidence for a pivotal role of the amygdala in emotional memory enhancement comes from several recent neuroimaging studies in healthy subjects (Alkire, Haier, Fallon, & Cahill, 1998; Cahill et al., 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Kensinger & Corkin, 2004).

Converging evidence from animal and human studies illustrate that adrenergic activation in the BLA underlies the observed enhanced memory consolidation of emotionally arousing material. Researchers who conducted rodent studies reported that posttraining intra-BLA infusions of epinephrine or a β-adrenoceptor agonist enhances memory (McGaugh & Roozendaal, 2002). Also human participants receiving a beta blocker before learning did not show emotional memory enhancement when tested 1 week later (Cahill, Prins, Weber, & McGaugh, 1994). Recent human neuroimaging studies using a beta blocker have visualized in vivo that adrenergic activation in the amygdala is required for the occurrence of emotional memory enhancement (Strange & Dolan, 2004; van Stegeren et al., 2005).

Animal studies have helped to further elucidate the underlying neuroendocrine mechanisms involved. Emotionally arousing experiences lead to a neuroendocrine stress response. Initially, catecholamines (adrenalin and noradrenalin) are released from the adrenal medulla allowing a fast arousal response by the sympathetic nervous system. In the case of more severe or prolonged stress, glucocorticoids (GCs) are secreted with a slight delay to facilitate adaptation (De Kloet, Vreugdenhil, Oitzl, & Joels, 1998; McEwen, 1998).

Numerous researchers who have conducted experiments in rodents have reported that GCs can enhance as well as impair memory (De Kloet, Oitzl, & Joels, 1999; Lupien & McEwen, 1997; Roozendaal, 2002). Similarly, in humans, acute GC administration has beneficial or detrimental effects depending on several modulating factors. The tested memory phase (consolidation vs. retrieval) appears to be especially important (see for recent reviews Lupien, Maheu, & Weeks, 2005; Wolf, 2003, and for a recent meta analysis Het, Ramlow, & Wolf, 2005). Animal (de Quervain, Roozendaal, & McGaugh, 1998) as well as human (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Kuhlmann, Kirschbaum, & Wolf, 2005a; Kuhlmann, Piel, & Wolf, 2005b; Wolf et al., 2001a) studies have documented that elevated GC levels impair memory retrieval. In contrast, increased levels of GCs lead to enhanced memory consolidation in rodents (McGaugh & Roozendaal, 2002; Roozendaal, 2000; Flood et al., 1978; Oitzl, De Kloet, Joels, Schmid, & Cole, 1997; Sandi, Loscertales, & Guaza, 1997). These findings suggest that memory consolidation is enhanced by GC-sensitive pathways. It appears that a beta adrenergic activation of the BLA is essential for GC-mediated enhanced memory consolidation. Lesions to the BLA or infusions of a β-adrenoceptor antagonist blocked the memory-enhancing effects of GCs (McGaugh & Roozendaal, 2002; Roozendaal, 2000). These findings indicate that cortisol and epinephrine act

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interdependently in the BLA to enhance memory for emotionally arousing material.

Few studies have examined the effects of stress or stress hormones on the consolidation of emotional and neutral stimuli in the human. An initial experiment testing the effects of cortisol on consolidation of neutral and emotional memory was published in 2001. Subjects were treated with cortisol or placebo before viewing neutral or arousing pictures. Cortisol led to superior performance in a surprise delayed (1 week later) cued-recall test for arousing but not for neutral slides (Buchanan & Lovallo, 2001). In line with this finding is the result of a recent stress study, in which subjects participated in the cold-pressor stress or a control situation after viewing emotionally arousing and neutral images. Cortisol levels were enhanced by the stressor. Memory for arousing but not for neutral stimuli tested 1 week later was enhanced by stress (Cahill, Gorski, & Le, 2003). Although these two studies suggest that the observations made in rodents can be transferred to humans, other researchers have reported seemingly conflicting data. For example, cortisol treatment enhanced memory for details of a neutral story and impaired memory for details of an arousing story (Rimmele, Domes, Mathiak, & Hautzinger, 2003). Another recent memory study failed to find an interaction between cortisol and arousal (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003). An examination of the effects of a beta blocker and a cortisol synthesis inhibitor (metyrapone) on memory found an impairment of short- and long-term memory for emotional material by the beta blocker. In contrast, metyrapone decreased long-term memory for neutral and emotional stories (Maheu, Joober, Beaulieu, & Lupien, 2004). These results suggest that cortisol is important for long-term memory consolidation independent of emotional arousal. Finally, using an immediate recall paradigm, Tops et al. (2003) reported that cortisol-impaired memory for positive and neutral words but did not affect memory for negative words.

The previous discussion of the human studies on cortisol and memory consolidation makes apparent that the mixed picture of results calls for additional research. Hence, the aim of this study was to investigate the effects of cortisol administered shortly before viewing emotionally arousing and neutral (nonarousing) pictures on immediate and delayed (24 hr later) free recall. The use of an immediate and a delayed retrieval test allowed us to differentiate the effects of cortisol on initial encoding or working memory (immediate recall) from the effects of cortisol on consolidation (24-hr delayed recall).

Method

Subjects

Twenty-nine young healthy male university students between 20 and 35 years of age (mean ± *SE,* 24.75 ± 0.84 years) participated in this study. None had acute or chronic diseases or took medication (self-reported). No subject was obese (BMI <26, weight in kilograms/height in meters squared). The study was approved by an ethics committee, and all subjects provided written informed consent.

Each subject was tested on 2 consecutive days. In a double-blind placebo controlled design, participants randomly received either three cortisol pills (each containing 10 mg hydrocortisone) or three placebo pills. Sixteen subjects received placebo. On the first day, subjects signed the consent and answered demographic questions on arrival (between 11:00 and 13:00 hr). Afterward the treatment was administered and 10 min later, participants filled out a mood questionnaire (see below) and completed the intentional memory task (see below). To reduce the likelihood that subjects would prepare themselves for the delayed recall testing, we told them that they would view another set of pictures on the second day. The following day (24 hr later), they again filled out the mood questionnaire. Afterward, a delayed free recall of the images took place before recognition memory was tested. Subjects were not asked whether they had anticipated a surprise free recall of the pictures from the previous day.

Memory for Pictures

Thirty pictures were selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1999). Ten were neutral (e.g., no. 7150, umbrella), 10 were positive (e.g., no. 1460, kitten), and 10 were negative (e.g., no. 2800, crying child). The positive slides did not contain erotic material. The norms for pleasure and arousal were chosen from the IAPS database (Lang et al., 1999). The scale for each image ranged from 1 to 9. The mean pleasure score for neutral pictures was 4.93 ± 0.05 (mean ± *SE*), 2.12 ± 0.10 for the negative pictures, and 7.81 ± 0.17 for the positive pictures. The mean arousal scores for negative (5.25 ± 0.51) and positive (5.35 ± 0.78) slides did not differ significantly, $t(18) = -0.324$); $p = .75$. However, the neutral slides were significantly lower in arousal rating (2.74 ± 0.73) than the positive, $t(18) = -7.67$; $p < .01$, and the negative, $t(18) = -8.85$; $p < .01$, slides.

Each picture was presented for 3 sec on a computer screen. The order of the pictures was randomized but the same presentation order was used for all participants. In the subsequent immediate free-recall task, the participants were instructed to write down as many images as they could remember by describing the pictures with only a few words and by not placing emphasis on details. Previously, a list of possible correct answers had been established in pilot experiments with this picture set. The number of correctly recalled slides was defined as the test score. In addition, emotional enhancement was calculated at immediate and delayed recall as a specific measure for amygdala-related memory. This was calculated as ([emotional slides recall/neutral slides recall]*100) − 100, indicating a percentage gain (Wagner, DeGirmenci., Drosopoulos, Perras, & Born, 2005). Delayed free recall was tested 24 hr later and was scored in a similar fashion.

Recognition Task

Recognition memory was only tested on the second day immediately after the delayed free-recall testing. The participants viewed 60 pictures (5-sec duration) randomly, of which half were the original images and the other half distractors. The distractors were matched to the target pictures for arousal and valence. On a piece of paper, subjects indicated which of the pictures were old and which new. Recognition performance was evaluated using signal detection theory (Green & Swets, 1974). The sensitivity (d') indicates the ability to discriminate old from new stimuli and is calculated by the difference of hits and false alarms. The response bias (β) describes the tendency to call a stimuli "old" or "new" in case of uncertainty.

Mood Assessment

An adjective checklist for the assessment of good mood versus bad mood, wakefulness versus tiredness, and calmness versus restlessness was used. Each scale contains eight adjectives (Steyer, Schwenkmezger, Notz, & Eid, 1994).

Hormone Analysis

Saliva was collected using Salivette collection devices (Sarstedt, Nümbrecht, Germany). Samples were taken before treatment, 10 min (imme-

diately before viewing), 20 min (after viewing), and 40 min after treatment. On the second day, the samples were collected at the beginning and the end of cognitive testing. Free cortisol was measured using a commercially available immunoassay (IBL, Hamburg, Germany).

Statistical Analysis

Data were analyzed first with analyses of variance (ANOVAs) and then by *t* tests.

Results

Cortisol Levels

The cortisol group showed significantly higher cortisol levels than the placebo group after treatment (see Table 1). ANOVA with the factors Time and Treatment for the first day revealed a significant main effect of Time, $F(3, 81) = 22.79$, $p < .01$; Treatment, $F(1, 27) = 45.78$, $p < .01$; and a Time × Treatment interaction, $F(3, 81) = 23.16$, $p < .01$. Post hoc *t* tests showed that the two groups did not differ at baseline. Cortisol levels were significantly ($p < .01$) higher in the treatment group 10, 20, and 40 min after cortisol intake. For the second day, ANOVA showed no effect of Time, $F(1, 27) = 0.11$, $p = .74$; Treatment, $F(1, 27) = 0.03$, $p = .86$; or the Time × Treatment interaction, $F(1, 27) = 0.65$, $p = .44$ (see Table 1 for mean and *SE*).

Memory: Free Recall

Both groups together recalled more positive (5.38 ± 0.27) and negative (6.03 ± 0.28) slides than neutral (4.21 ± 0.25) at immediate recall. Also in delayed recall more positive (4.17 ± 0.34) and negative (4.79 ± 0.26) slides were remembered than neutral slides (3.28 ± 0.23). No significant difference in the recall of positive and negative slides was observed. Hence, we created the new category, *emotionally arousing stimuli* (positive + negative images)/2), on the basis of this initial observation and on the results of previous studies that showed that emotional arousal rather than valence interacts with the effects of stress hormones on memory consolidation (Buchanan & Lovallo, 2001; Cahill et al., 2003) or retrieval (Kuhlmann et al., 2005b).

An ANOVA with the factors Time (immediate vs. delayed recall), Treatment (placebo vs. cortisol), and Arousal (neutral vs. arousing) was conducted. A significant main effect of Time, $F(1, 27) = 89.75$, $p < .01$; and Arousal, $F(1, 27) = 34.39$, $p < .01$; and an Arousal × Treatment interaction, $F(1, 27) = 5.36$, $p < .03$, were detected. In addition, a significant three-way interaction—Time × Treatment × Arousal, $F(1, 27) = 4.56$, $p < .04$—was observed. To investigate this three-way interaction further, we performed two separate calculations, one for immediate and one for delayed recall. For immediate recall, a main effect of Arousal, $F(1, 27) = 32.40$, $p < .01$, was observed, but no Treatment × Arousal interaction was found, $F(1, 27) = 1.23$, $p = .28$ (see Figure 1a). In contrast, a main effect of Arousal, $F(1, 27) = 22.66$, $p < .01$, and a Treatment × Arousal interaction, $F(1, 27) = 8.80$; $p < .01$, were apparent for delayed recall (see Figure 1b).

In the placebo group, no differences between neutral and emotionally arousing images occurred in the delayed retrieval condition, $t(15) = -1.23$, $p = .24$. However, the cortisol group remembered emotionally arousing slides significantly better than neutral ones, $t(12) = -5.91$, $p < .01$. Between-group analysis revealed a significantly reduced delayed memory retrieval for neutral images in the cortisol group, $t(27) = 2.08$, $p < .05$, compared with the placebo group, whereas the emotionally arousing pictures tended to be better remembered after cortisol treatment, $t(27) = -1.53$, $p = .14$.

The emotional enhancement scores are also presented in Table 1. Emotional enhancement did not differ between the two groups during immediate recall. However, emotional enhancement was significantly stronger in the cortisol group in the delayed recall task, $t(27) = -2.38$, $p < .03$.

Effect Size Calculation

To further characterize the observed significant cortisol effects in the delayed recall task, we calculated effect sizes (Het et al., 2005). We used the formula provided by Hedges and Olkin (1985).

Table 1
Effects of Cortisol or Placebo Treatment on Salivary Cortisol Levels, Emotional Memory Enhancement, and Recognition Memory Performance (Mean ± SE).

	Placebo ($n = 16$)	Cortisol ($n = 13$)
Cortisol (nmol/l) at baseline	11.50 ± 1.88	16.92 ± 3.15
Cortisol (nmol/l) 10 min after administration (before viewing)	10.18 ± 1.43	213.54 ± 38.64*
Cortisol (nmol/l) 20 min after administration (after viewing)	11.47 ± 1.51	198.77 ± 36.35*
Cortisol (nmol/l) 40 min after administration	9.46 ± 1.30	144.71 ± 19.25*
Cortisol (nmol/l) on the second day before retrieval testing	9.66 ± 1.30	11.41 ± 1.99
Cortisol (nmol/l) on the second day after retrieval testing	9.56 ± 1.17	11.09 ± 1.75
Immediate free recall: emotional enhancement score (%)	49.43 ± 22.00	57.37 ± 17.17
Delayed free recall: emotional enhancement score (%)	30.26 ± 16.32	87.18 ± 17.34*
Recognition task sensitivity index d' (neutral slides)	2.49 ± 0.13	2.80 ± 0.16
Recognition task sensitivity index d' (emotional slides)	2.73 ± 0.18	2.81 ± 0.18
Recognition task response bias β (neutral slides)	0.54 ± 0.22	0.32 ± 0.22
Recognition task response bias β (emotional slides)	0.99 ± 0.29	0.79 ± 0.13

Note. For the description of the formulas used for the memory indices as well as for analyses of variance, see Results section.
* $p < .05$ in independent sample *t* tests.

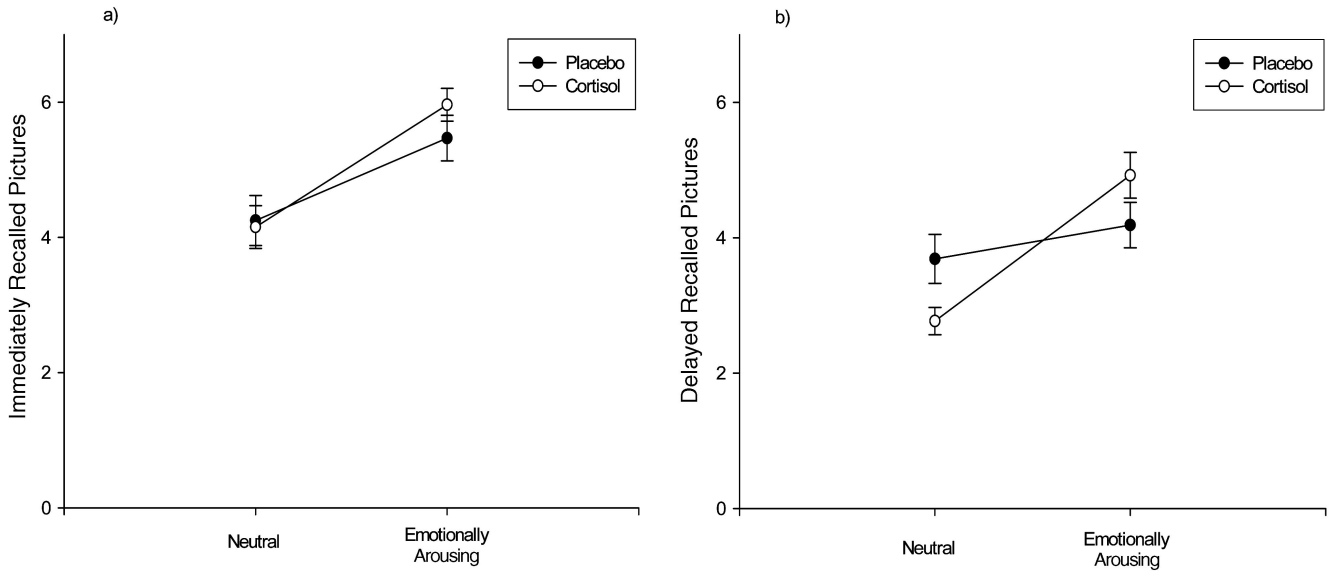

Figure 1. Recalled neutral and emotionally arousing pictures of placebo and cortisol treated subjects for immediate (a) and delayed recall (b). Analysis of variance revealed a significant three-way interaction (Treatment × Arousal × Time). For further statistical analysis, see the Results section.

The effect size (g_{Hedges}) is defined as the difference between the mean of the experimental group (M_{EG}) and the placebo control group (M_{CG}) standardized by the pooled standard deviation (S_{Pooled}). Calculation was performed using the free meta-analytic software program META (Schwarzer, 1989). According to Cohen (1988), an effect size of .50 can be classified as moderate, whereas an effect size of .80 can be considered large. In the delayed recall condition, we calculated an effect size of $d = -.755$ for the impairing effect on neutral slides. For the enhancing effects on emotional slides, the effect size was $d = .555$. The effect size for the cortisol-induced increase in the emotional enhancement score was $d = .863$. Thus, the effects observed in the delayed recall condition ranged between moderate and large.

Memory: Recognition

Cortisol did not significantly influence any of the recognition measures. Neither the sensitivity index nor the response bias was modulated by the treatment (see Table 1).

Mood

Cortisol treatment had no significant effect on the three mood scales of the questionnaire (data not shown).

Discussion

The main finding of this study is that cortisol enhanced long-term consolidation of emotional stimuli while also impairing consolidation of neutral stimuli. The sum of correctly recalled slides did not differ between the two treatment groups, but the emotional enhancement was much stronger in the cortisol group. Cortisol levels in the treatment group were already elevated before viewing and at the time of immediate recall. Although we cannot exclude possible effects of cortisol on initial acquisition, there was no difference in immediate memory recall performance between the cortisol and the placebo groups. Yet our data show that the cortisol effect increases over time. Therefore, we suggest that memory consolidation of neutral and emotional stimuli is modulated by GCs, whereas the initial acquisition process as well as short-term or working memory is less affected. At the very least, our data show that the cortisol effect increases over time. In future studies, the subjects could be treated with cortisol immediately after acquisition to demonstrate effects on consolidation more purely. Investigators in such future studies might consider administering cortisol intravenously because oral cortisol treatment results in a somewhat slow cortisol increase.

Studies in rodents (Okuda, Roozendaal, & McGaugh, 2004) and humans (Cahill et al., 2003) indicate that emotional arousal during initial learning is essential for the occurrence of GC effects on memory consolidation. In the present study, we induced emotional arousal with the use of slides, even though we did not measure activity of the sympathetic nervous system.

Our results are in line with findings of previous studies. We used IAPS images like Buchanan and Lovallo (2001) but chose a shorter retention delay and a shorter presentation time for each image. Buchanan and Lovallo (2001) reported better performance for emotionally arousing stimuli in the cortisol group during the cued recall but not in the free recall condition. These discrepancies might be explained by differences in the delay, which probably led to differences in task difficulty. Because these authors did not use an immediate recall test, they could not exclude the possibility that cortisol affected initial encoding. However, our current finding shows that the effects of cortisol are most likely selective for memory consolidation or at least cannot be detected in an immediate recall task. This idea is further supported by the study of Cahill et al. (2003) in which IAPS pictures were also used and memory performance was tested 1 week later. Memory for arousing stimuli was better in those subjects who received the cold-

pressor stressor immediately after watching the slides (Cahill et al., 2003). The assumption that cortisol modulates memory consolidation but not initial learning is also supported by other recent results (Maheu et al., 2004). In this study, metyrapone impaired long-term memory (even though the effect was independent of arousal) but had no effect on short-term memory. In sum, GC-mediated pathways seem to be important for memory consolidation.

However, there are also studies with findings that appear to be in contrast to our current findings. Abercrombie et al. (2003) failed to find an interaction between cortisol and emotional arousal despite using emotional-laden words as well as slides. Similarly, another study observed an interaction between cortisol and emotional arousal, but cortisol actually impaired memory for emotional details, while enhancing it for neutral details (Rimmele et al., 2003). Finally, cortisol elevations caused by psychosocial stress were associated with poorer memory consolidation in another recent study (Elzinga, Bakker, & Bremner, 2005). These studies indicate that additional research on this issue is warranted. Differences in the used tasks as well as in the time of day might at least partially reconcile these discrepancies (Het et al., 2005).

Our findings of nonsignificant effects for immediate recall are in contrast to the study of Tops et al. (2003) who observed that cortisol impaired immediate recall for neutral and positive but not for negative words. In their study, immediate recall was tested 2 hr rather than, as in our study, 20 min after treatment. A previous study had observed that cortisol effects on working memory (digit span) are only apparent 2 hr but not 20 min after treatment (Wolf et al., 2001a), which would fit to the observed differences between the current and the Tops et al.(2003) study. In addition, the tasks used in both studies differed substantially.

Of interest for the discussion of the current results is also a recent sleep study. Here the authors observed that lowering cortisol levels with metyrapone impaired neutral but enhanced emotional memory consolidation, which is a behavioral result almost identical to that in our present study (Wagner et al., 2005). Lowering cortisol levels during sleep at night appears to have similar effects on memory consolidation as raising cortisol levels during wakefulness in the daytime. This study, along with previous research from this group, seems to suggest that memory consolidation during sleep is differentially influenced by cortisol than is memory during wakening (Born & Wagner, 2004; Gais & Born, 2004).

In their landmark article, Kleinsmith and Kaplan (1963) reported that retrieval of emotionally arousing word pairs was initially impaired but enhanced over time. Although this effect has not been replicated consistently, other studies have at least observed that the arousal effects are more pronounced in delayed than in immediate recall tasks (e.g., Quevedo et al., 2003). In contrast to these findings, we observed in our placebo group that the advantage of emotional memory over neutral memory diminished over time and was only significant for immediate recall. Differences in the memory task used, the instructions (intentional vs. incidental learning) used, and the number of recall tests conducted might contribute to these seemingly opposing results (for review and discussion, see Christianson, 1992). Possibly related to our finding is the observation by Strange, Hurlemann and Dolan (2003) that emotional words (in an immediate recall task) lead to a retrograde amnesia, which is mediated by beta adrenergic activity in the amygdala. Because the presentation of neutral and emotionally arousing slides was intermixed in our study, it is conceivable that the enhanced immediate recall of emotionally arousing slides also represents such a phenomenon. Although cortisol treatment (in contrast to treatment with a beta receptor blocker; Strange et al., 2003) had no effect on immediate recall in our study, the behavioral results for the delayed recall consisted of enhanced emotional memory at the cost of neutral memory. Cortisol might have enhanced the emotion-induced amnesia by interacting with the adrenergic system in the amygdala (Roozendaal, 2002). Although our memory paradigm was not designed to investigate serial position effects in a fashion comparable to that of Strange et al. (2003), it would be interesting to investigate the effects of cortisol in such a paradigm in future studies.

The present findings replicate the finding that arousal is a stronger determinant of memory performance than valence (Bradley et al., 1992). Similarly, the effects of cortisol on memory were modulated by arousal and not by valence, which is in line with the findings of previous work (Buchanan & Lovallo, 2001). Kensinger and Corkin (2004) have suggested that two different pathways for the effects of valence and arousal exist in the human brain. For arousing items, the amygdala plays a critical role in memory enhancement, which is supported by imaging work in this area (Cahill et al., 1996; Canli et al., 2000). In contrast, the effects of valence appear to be in part modulated by the prefrontal cortex (Kensinger et al., 2004).

Men and women differ in emotional memory performance and in the neuroanatomical substrates involved (see for review Cahill, 2003). For example, beta blockade impaired emotional memory for gist in men, while impairing emotional memory for details in women (Cahill & van Stegeren, 2003). In addition, animal studies have shown that stress often has opposing effects on memory of male and female animals (Conrad et al., 2004; Luine, 2002; Shors, 2004). Also in humans the relationship between stress-induced cortisol secretion and memory differs between men and women (Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001b). In our present study, we investigated only men. Clearly future studies should attempt to study both sexes. The previous pharmacological cortisol study by Buchanan and Lovallo (2001) did not observe sex differences.

In sum, the present results suggest that memory consolidation of emotional stimuli is especially enhanced by GCs. In the current study, this occurred at the expense of memory for neutral material. Former work from our group has shown that memory retrieval of emotional stimuli is especially impaired by cortisol or stress treatment (Kuhlmann et al., 2005a, 2005b). All these observations are in line with the findings of previous studies in both humans (Buchanan et al., 2001; Cahill et al., 2003) and animals (Roozendaal, 2002) and suggest that cortisol switches the brain into a consolidation mode, which is associated with impaired retrieval. Arousing material seems to be especially sensitive for these stress hormone–mediated effects.

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