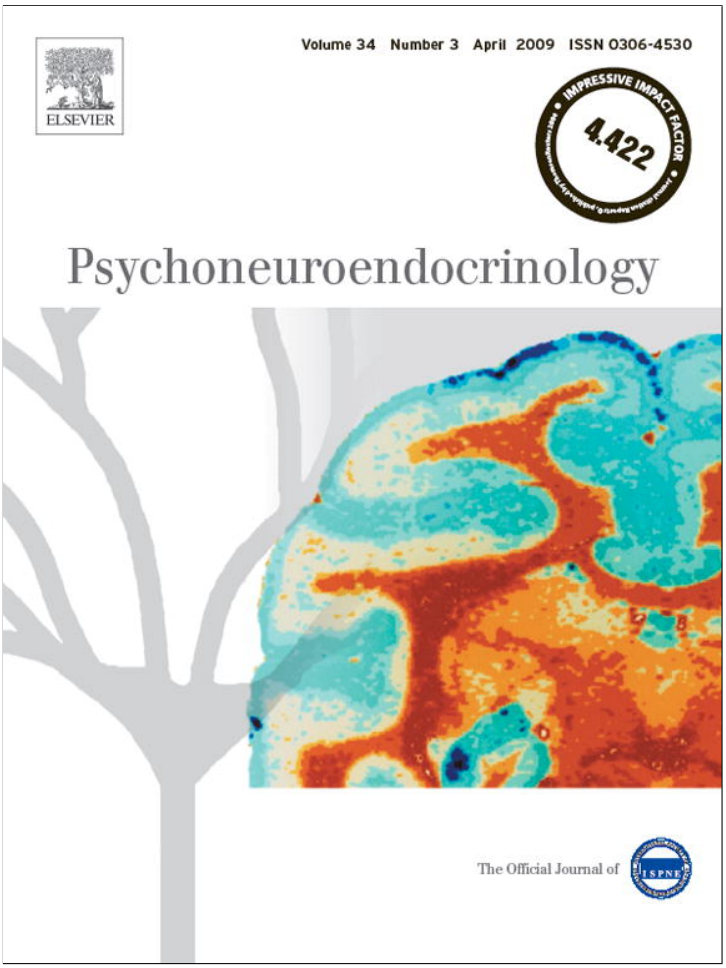

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Stress effects on declarative memory retrieval are blocked by a β-adrenoceptor antagonist in humans

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Summary Previous evidence indicates that stress hormone effects on memory consolidation depend on concurrent emotional arousal-induced noradrenergic activity. Here, we asked whether this is also true for stress effects on memory retrieval and hypothesized that administration of the β-adrenoceptor antagonist propranolol would block the effects of stress on declarative and procedural retrieval performance. In a double-blind, placebo-controlled, crossover study, 44 healthy young men learned a list of emotional and neutral words (declarative memory task) and completed a serial reaction time task (procedural memory task). On the following day, participants received either a placebo or 40 mg propranolol orally. One hour later, they were exposed to stress (socially evaluated cold pressor test (SECPT)) or a control condition 30 min prior to retention testing. Stress selectively enhanced the retrieval of emotionally arousing words. Pretreatment with propranolol had no effect on memory alone but blocked the stress-induced memory enhancement for emotional words, confirming the importance of noradrenergic activity in stress effects on memory retrieval. Memory for neutral words and the procedural task was neither affected by stress nor by propranolol. The present findings suggest that stress (hormone) effects on emotional memory retrieval require concurrent noradrenergic activation. Procedural memory retrieval and the retrieval of neutral verbal material appear to be less susceptible to stress.

1. Introduction

Stress elicits numerous physiological reactions including the release of catecholamines (epinephrine and norepinephrine) and glucocorticoids (GCs; cortisol in humans), which are known to influence memory function. Importantly, stress effects on memory depend critically on the timing of the stress (hormone) exposure. Converging evidence from animal and human studies shows that stress or GC administration immediately after learning facilitates memory *consolidation* (Cahill et al., 2003; Diamond et al., 2006; Roozendaal et al., 2006). By contrast, stress and GCs administered before retention testing impaired memory *retrieval* in rodents (de Quervain et al., 1998; Diamond et al., 2006). In humans,

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findings on the effect of stress and GCs on retrieval performance are mixed. While some authors reported stress- or GC-induced retrieval impairments (de Quervain et al., 2000; Kuhlmann et al., 2005a), others showed that stress and GCs can also enhance memory retrieval (Domes et al., 2005; Nater et al., 2007; Buchanan and Tranel, 2008).

A recent model that aims to explain the influence of stress and GCs on memory postulates that concurrent glucocorticoid and noradrenergic activity within the basolateral amygdala (BLA) is critical for stress effects on memory functions (McGaugh and Roozendaal, 2002). In line with this model, Roozendaal et al. (2006) reported that the consolidation enhancing effect of corticosterone is blocked by administration of a β-adrenoceptor antagonist. Furthermore, the authors showed that corticosterone (the main GC in rodents) injections after training in an object recognition memory task enhanced memory in naïve rats but not in rats that were previously habituated to the training context, i.e. in which novelty-induced arousal was reduced. Similarly, Cahill et al. (2003) found an enhancing effect of post-learning stress on memory for emotionally arousing but not for neutral material in humans.

Findings from animal studies suggest that noradrenergic activity may also be essential for stress hormone effects on memory retrieval. For instance, Roozendaal et al. (2004) showed that retrieval impairing effects of corticosterone were blocked by a β-adrenoceptor antagonist administered before retention testing. Comparable data from humans are largely missing. Very recently, de Quervain et al. (2007) presented the first evidence that noradrenergic activity is required for the effects of pharmacologically (i.e. exogenously) raised GCs on memory retrieval in humans. Whether the effects of stress-induced (i.e. endogenous) GC elevations on memory retrieval in humans can be prevented by β-adrenoceptor blockade is not known. Moreover, most memory studies, including the study by de Quervain et al. (2007), focused exclusively on hippocampus-dependent declarative memory, while the effects of stress and β-adrenoceptor blockade on the retrieval of non-declarative, procedural memory have not been tested yet (for a recent review see van Stegeren, 2008).

The present study examined whether the influence of stress and stress-induced GCs on the retrieval of declarative and procedural memory can be blocked by administration of a β-adrenoceptor antagonist. We used a double-blind, placebo-controlled, within-subjects design. Healthy young men learned a list of 24 emotional and neutral words and performed a serial reaction time task. Twenty-four hours later, participants were exposed to a stress (socially evaluated cold pressor test) or control condition 1 h after they received propranolol or a placebo and 30 min before a free recall test for the words and a retention test for the serial reaction time task.

2. Materials and methods

2.1. Participants and design

Forty-four healthy, non-smoking men (age: $M = 23.7$ years, S.D. = 3.3 years, range: 19—33 years; BMI (kg/m^2): $M = 23.5$, S.D. = 2.2, range: 19—27) recruited at the University of Trier participated in this study. Exclusion criteria were checked by a physician and comprised current or chronic psychiatric disorders, any medical condition and current treatment with psychotropic medications, narcotics, beta-blockers or steroids. Participants had to refrain from excessive exercise (e.g. long run or weightlifting), caffeine, alcohol and meals within the 3 h prior to testing. The study was approved by the local ethics committee and all subjects provided written informed consent.

We used a double-blind, placebo-controlled, within-subject design. On the first day of each experimental session participants learned a list of words (declarative memory task; for details see below) and were trained in a serial reaction time task (procedural memory task; for details see below). Twenty-four hours later, subjects were administered orally either a placebo ($n = 22$) or a propranolol (40 mg, Dociton®, Mibe, Germany; $n = 22$) pill 1 h before they took part in a stress test (socially evaluated cold pressor test) or a control condition. Thirty minutes after the treatment (stress vs. control) subjects completed a free recall test for the word list and a retention test for the serial reaction time task. Dosage and timing of propranolol administration were chosen according to the study by Quervain et al. (2007). Propranolol reaches peak levels 60—90 min after tablet administration and has a half-life of about 3 h whereas the duration of pharmacological effect may be even longer (Wojcicki et al., 1999). Salivary cortisol concentrations in response to the socially evaluated cold pressor test reach peak levels after 20—30 min and return to baseline levels after about 90 min (Schwabe et al., 2008a,b). Thus, the beta-blocker was effective during both the stress/control condition as well as during retrieval testing and saliva cortisol peaked at retrieval testing.

After a 2-week washout period, participants returned to the laboratory and the procedure was repeated with another list of words and another version of the serial reaction time task. Subjects received the same pharmacological intervention (placebo vs. propranolol) as 2 weeks before but the treatment (stress vs. control) they had not received in the first session. We decided to vary the treatment and not the pharmacological intervention within-subjects because previous research showed that repeated exposure to a stressor might lead to habituation effects (Schommer et al., 2003). Order of treatment, word lists and versions of the serial reaction time task was counterbalanced across subjects. All tests took place between 1330 h and 1700 h to control for diurnal variation of cortisol.

2.2. Declarative memory task

Participants were presented a word list containing 24 German two-syllable nouns with variable emotionality, ranging from neutral (valence ($M \pm$ S.E.M.): 0.01 ± 0.01; word length ($M \pm$ S.E.M.): 5.9 ± 0.3 words) to positive (valence: 1.20 ± 0.05; word length: 5.6 ± 0.4) and negative words (valence: -1.35 ± 0.07; word length: 6.3 ± 0.6; eight words per category; two parallel word lists available). The words were drawn from a German word database (Hager and Hasselhorn, 1994). They were comparable with respect to word frequency and semantic cohesion (norms taken from a German internet database). Positive and negative words were associated with comparable

arousal scores ($M \pm$ S.E.M.; positive: 0.47 ± 0.14, negative: 0.61 ± 0.16; $t_{30} = 0.67$, $p = .51$). Both positive and negative words were significantly more arousing than neutral words (-0.04 ± 0.12; vs. positive words: $t_{30} = 2.68$, $p = .01$; vs. negative words: $t_{30} = 3.17$, $p < .01$). Memory performance was similar for the two parallel words lists ($t_{42} = 0.07$, $p = .82$).

During the learning phase on the first day of each experimental session, subjects saw the words (each word for 2 s) twice in a different order on a computer screen. To make sure that the words were encoded, participants were asked to read them aloud. Subjects were instructed to learn the words for later recall testing.

On the following day, participants completed a free recall test 30 min after the treatment (stress vs. control), i.e. 90 min after the pharmacological intervention (placebo vs. propranolol). They were asked to write as many words as they could remember on a sheet of paper.

2.3. Procedural memory task

Subjects were presented a response box consisting of five coloured lamps (from left to right: version A—yellow, white, green, red, blue; version B—yellow, white, red, blue, green) and five coloured buttons (from left to right: version A—green, red, blue, yellow, white; version B—blue, green, yellow, white, red). Lamps lit up one after another in a seemingly random order (inter-stimulus interval: 1 s) and participants were instructed to press with the tip finger of their dominant hand as fast and as accurate as possible the button which colour corresponded to the colour of the lit lamp (e.g. if the green lamp lit up, subjects should press the green button). In one trial each of the five lamps lit up 20 times, i.e. subjects were requested to respond 100 times per trial by pressing one of the five buttons. Importantly, the order in which the lamps lit up was not entirely random. Two sequences were included: a "goal sequence" and a "control sequence". In the "goal sequence", the sequence of two certain lamps was always followed by a certain third (target) lamp (version A: if the white lamp followed the red lamp, the next lamp was always the blue one; version B: if the blue lamp followed the white lamp, the next lamp was always the yellow one). In the "control sequence", however, the sequence of two certain lamps (version A: yellow—green; version B: green—red) was followed randomly by one of the other lamps. Participants were not informed about possible sequences in the serial reaction time task. Each of the two sequences was repeated 10 times per trial. Subjects performed 10 trials of the serial reaction time task during the learning phase on the first day of each of the two experimental sessions.

Twenty-four hours later, subjects completed another 5 trials immediately after the free recall task, i.e. 35 min after the treatment (stress vs. control) and 95 min after the pharmacological intervention (placebo vs. propranolol). After the final trial in the second experimental session, participants were asked whether they noticed certain regularity in the serial reaction time task. Importantly, none of the subjects could name one of the two sequences. Thus, performance in this task was implicit.

To take between-subject variation in reaction times into account, performance was expressed as the difference between individual reaction times for the target lamp in the "goal" sequence and the third lamp in the "control" sequence. Analyses were performed with the average difference score per trial.

2.4. Stress and control treatment

In the stress condition, participants were exposed to the SECPT as described in detail elsewhere (Schwabe et al., 2008b). Briefly, subjects were asked to immerse their right hand up to and including the wrist for 3 min into ice water (0—2 °C). During hand immersion, they were watched by a woman and videotaped (participants were informed that the video recordings would be analyzed for facial expression later on). The SECPT has been shown to elicit significant increases in cortisol and autonomic activity (Schwabe et al., 2008a,b). In the control condition, individuals immersed their right hand up to and including the wrist for 3 min into warm water (35—37 °C). They were neither watched by a woman nor videotaped.

2.5. Subjective stress ratings

Immediately after the stress or control condition, participants were asked to rate on an 11-point scale with 10-point increments from 0 ("not at all") to 100 ("very much") how stressful, painful and unpleasant they experienced the previous situation.

2.6. Saliva sampling and cortisol analyses

Subjects collected saliva samples themselves using standard Eppendorf tubes (1.5 ml, Eppendorf, Hamburg, Germany). Samples were taken immediately before as well as 5, 15, 25, 35, 50 and 65 min after stressor (or control condition) onset. Saliva samples were stored at room temperature until completion of the experimental session, and then kept at −20 °C until analysis. After thawing for biochemical analysis, the fraction of free cortisol in saliva was determined using a time-resolved immunoassay with fluorometric detection, as described in detail elsewhere (Dressendorfer and Kirschbaum, 1992). Inter- and Intra-assay variation was below 9%.

2.7. Blood pressure measurement

Blood pressure was measured for 5 min after subjects arrived in the laboratory (baseline) as well as before (pre), during and after (post) the stress and control condition using the Dinamap System (Critikon; Tampa, Florida, USA); the cuff was placed on the left upper arm. Beat-to-beat systolic and diastolic blood pressure was determined offline with the help of WinCPRS software (Absolute Aliens Oy, Turku, Finland).

2.8. Statistical analyses

Declarative memory performance was analyzed with a 2 (treatment: stress vs. control) $\times$ 2 (drug: propranolol vs. placebo) $\times$ 2 (word category: emotional vs. neutral) mixed-design ANOVA. Paired t-tests were used to contrast stress effects on emotional and neutral words. Procedural memory performance was analyzed with a mixed-design

ANOVA with the between-subjects factor drug and the within-subjects factors treatment and time (for training: 10 trials; for retention testing: 5 trials). Similarly, blood pressure and cortisol were analyzed with mixed-design ANOVAs with treatment and time (three measurements for blood pressure, seven measurements for cortisol) as within-subjects factors and drug as between-subjects factor. Subjective stress assessments were analyzed with 2 (treatment) $\times$ 2 (drug) mixed-design ANOVAs. Reported *p*-values are two-tailed. $p < .05$ was accepted as statistical significance.

3. Results

3.1. Declarative memory performance

A recent model assumes that stress effects on memory retrieval require a co-occurrence of glucocorticoid and noradrenergic activity (Roozendaal, 2002; Roozendaal et al., 2006). The present study examined whether administration of the β-adrenoceptor antagonist propranolol given 90 min before a free recall test blocked the effects of stress induced by the SECPT 30 min prior to retention testing on memory performance. As positive and negative words did not differ in the associated emotional arousal (see above) and memory was comparable for positive ($M \pm$ S.E.M.: 26.7 $\pm$ 2.1%) and negative words (M: 25.2 $\pm$ 2.4%, $t_{42} = 0.73$, $p = .31$, $d = 0.16$; interaction between stress and word valence: $F_{1,42} = 0.05$, $p = .83$, $\eta^2 < 0.01$), they were averaged and combined to "emotional words".

3.1.1. Effects of stress and cortisol

Overall, stress tended to enhance retrieval performance, yet the referring main effect failed to reach statistical significance ($F_{1,42} = 3.01$, $p = .09$, $\eta^2 = 0.07$). However, we found a significant treatment $\times$ word category interaction ($F_{1,42} = 4.75$, $p < .04$, $\eta^2 = 0.11$) suggesting that stress enhanced memory for emotional ($t_{42} = 2.55$, $p < .02$, $d = 0.55$) but not for neutral words ($t_{42} = 0.29$, $p = .77$, $d = 0.06$; Fig. 1). In the same line, peak cortisol levels correlated significantly with memory for emotional ($r = .34$, $p < .05$) but not for neutral words ($r = .04$, $p = .81$; Fig. 2).

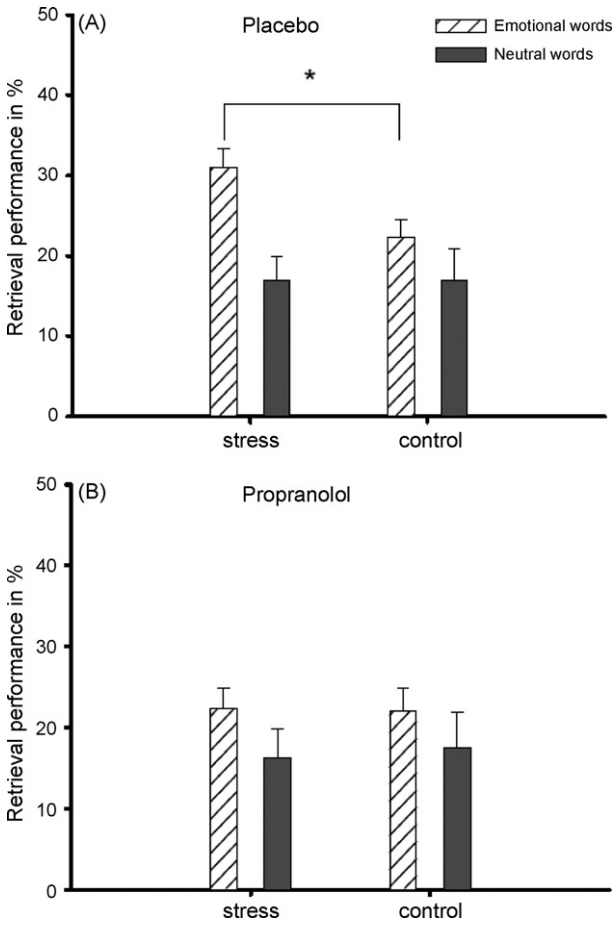

Figure 1 Retrieval performance for emotional vs. neutral words in (A) the placebo and (B) the propranolol group 30 min after stress or a control condition. The β-adrenoceptor antagonist propranolol blocked the stress-induced memory enhancement for emotional words. Data represent mean $\pm$ S.E.M. *$p < .05$.

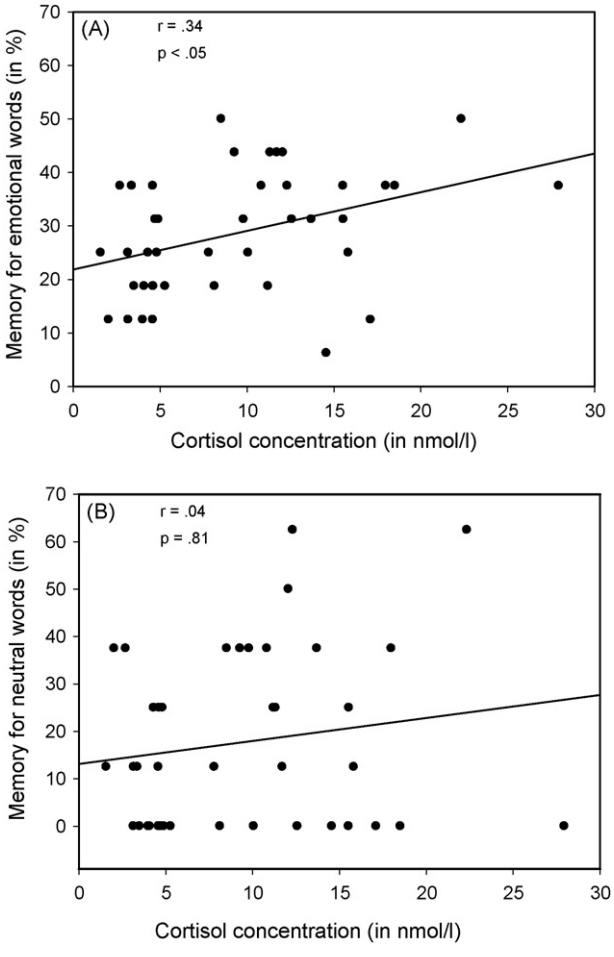

Figure 2 Peak cortisol concentrations (20 min after cessation of the stress manipulation; in nanomoles per liter) plotted against memory performance for (A) emotional and (B) neutral words. Peak cortisol concentrations correlated significantly positive with memory for emotional words while there was no correlation between cortisol and memory for neutral words.

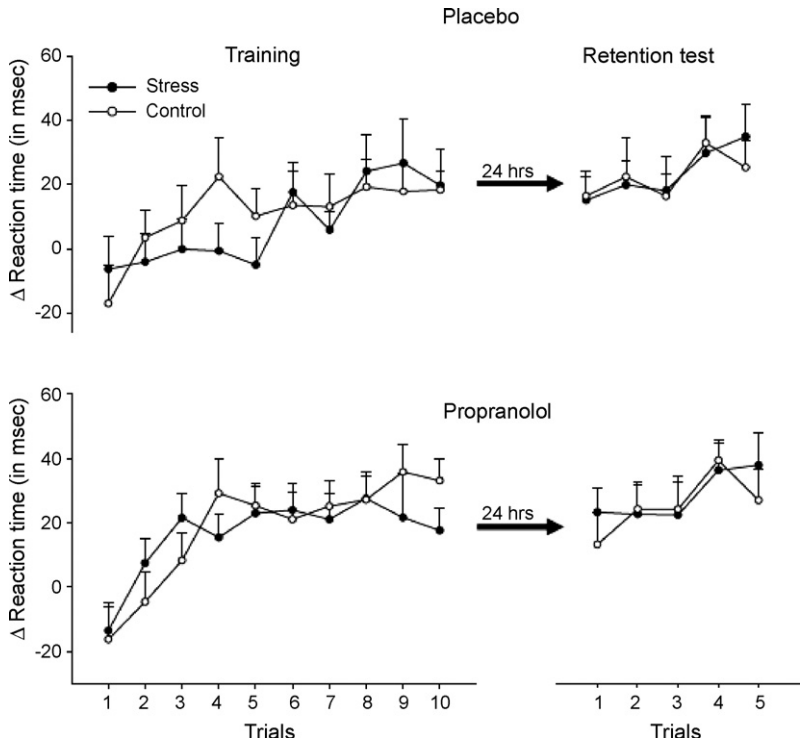

Figure 3 Performance in the procedural task during training and in the retention test 35 min after stress or a control condition expressed as difference between the reaction time for the target in the "goal" sequence and the (random) third lamp in the control sequence (averaged per trial). Increasing difference scores during training indicate that subjects improved over trials. Retrieval of procedural memory was not affected by stress or propranolol. Data represent mean ± S.E.M.

3.1.2. Interaction between stress and propranolol

ANOVA results revealed a significant treatment × drug interaction ($F_{1,42} = 4.23$, $p < .05$, $\eta^2 = 0.10$) showing that stress had different effects on retrieval performance in the placebo and propranolol groups (Fig. 1). Exposure to the SECPT enhanced memory retrieval in the placebo group ($F_{1,21} = 6.97$, $p < .02$, $\eta^2 = 0.23$) while no such effect was found in the propranolol group ($F_{1,21} = 0.08$, $p = .78$, $\eta^2 < 0.01$). Furthermore, we obtained a three-way interaction between treatment, drug and word category that was close to significance ($F_{1,42} = 3.32$, $p = .07$, $\eta^2 = 0.07$). Bonferroni-adjusted post hoc tests revealed that the stress-induced memory enhancement in the placebo group was owing to enhanced memory for emotional words ($t_{21} = 3.75$, $p < .01$, $d = 1.13$) whereas retrieval of neutral words was unaffected by stress ($t_{21} = 0.02$, $p = .96$, $d < 0.01$). In the propranolol group, neither emotional nor neutral word retrieval was influenced by stress.

There was no main effect of drug ($F_{1,42} = 0.01$, $p = .91$, $\eta^2 < 0.01$) indicating that propranolol alone did not affect memory performance. However, we obtained a significant effect of word category ($F_{1,42} = 208.71$, $p < .001$, $\eta^2 = 0.84$) with significantly better memory for emotional than for neutral words.

3.2. Procedural memory performance

To examine whether stress affects also the retrieval of procedural material and whether such an effect would be blocked by the β-adrenoceptor antagonist propranolol, we trained participants in a serial reaction time task. Memory for this task was tested on the following day, 35 min after exposure to the SECPT (or control condition) which was given 60 min after propranolol or placebo administration. As shown in Fig. 3, procedural memory retrieval was not influenced by stress.

3.2.1. Training

A mixed-design ANOVA showed a significant time effect ($F_{9,306} = 10.54$, $p < .001$, $\eta^2 = 0.24$). Differences between reaction times to the target in the "goal" sequence and the third lamp in the "control" sequence increased over the 10 training trials indicating that subjects improved during training (Fig. 3). The acquisition of the serial reaction time task was comparable in the stress and control condition ($F_{1,42} = 0.24$, $p = .63$, $\eta^2 = 0.02$) as well as in the placebo and propranolol groups ($F_{1,42} = 0.02$, $p = .89$, $\eta^2 < 0.01$; all possible interactions: all Fs < 1.5, all ps $> .35$, all $\eta^2 < 0.02$).

3.2.2. Retention test

Performance in the five retention test trials 24 h after training was not affected by prior stress ($F_{1,42} = 0.24$, $p = .63$, $\eta^2 < 0.01$) or propranolol administration ($F_{1,42} = 1.32$, $p = .26$, $\eta^2 = 0.03$; Fig. 3). Subjects tended to improve also during retention testing, but the referring time effect failed to reach statistical significance ($F_{4,144} = 2.13$, $p = .08$, $\eta^2 = 0.06$). The mixed-design ANOVA showed no significant interactions between treatment, drug and time (all Fs < 1, all ps $> .60$, all $\eta^2 < 0.01$).

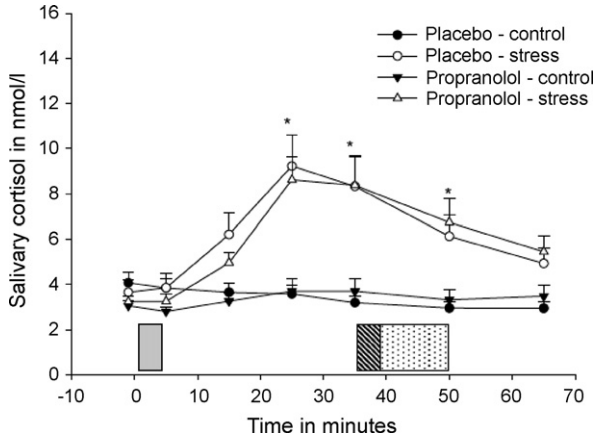

Figure 4 Salivary cortisol responses (mean ± S.E.M.) to the stress (socially evaluated cold pressor test, SECPT) and control condition in the placebo and propranolol groups. The grey bar denotes the time point and duration of the SECPT and control condition. Time point and duration of the free recall test for the words and the retention test for the procedural task are indicated by the striped and dotted box, respectively. *Significant difference between the stress and control conditions (Bonferroni-adjusted *p*s < .05).

3.3. Cortisol responses

As shown in Fig. 4, cortisol was significantly increased in response to the socially evaluated cold pressor test with a different time course from the control condition (treatment: $F_{1,42} = 21.34$, $p < .001$, $\eta^2 = 0.34$; time: $F_{6,246} = 19.93$, $p < .001$, $\eta^2 = 0.33$; treatment × time: $F_{6,246} = 19.47$, $p < .001$, $\eta^2 = 0.32$). Bonferroni-adjusted post hoc tests indicated significant differences in cortisol between the stress and control condition 20, 30 and 45 min after cessation of the treatment. There was neither a main effect of the drug on cortisol responses ($F_{1,42} = .04$, $p = .85$, $\eta^2 < 0.01$), nor an interaction between drug and any of the other factors (all Fs < 3, all ps > .10, all $\eta^2 < 0.06$).

3.4. Blood pressure responses

Exposure to the socially evaluated cold pressor test elicited significant increases in blood pressure (Table 1). A mixed-design ANOVA revealed for both systolic and diastolic blood pressure (bp) a significant treatment effect (systolic bp: $F_{1,42} = 32.2$, $p < .001$, $\eta^2 = 0.41$; diastolic bp: $F_{1,42} = 37.1$, $p < .001$, $\eta^2 = 0.44$) and a significant time × treatment interaction (systolic bp: $F_{3,141} = 146.0$, $p < .001$, $\eta^2 = 0.76$; diastolic bp: $F_{3,141} = 153.7$, $p < .001$, $\eta^2 = 0.77$). Post hoc tests found significant differences between the stress and control

Table 1 Systolic and diastolic blood pressure (in mmHg) after arrival at the laboratory (baseline) as well as before (pre), during, and after (post) treatment (stress vs. control condition) in the placebo and propranolol groups.

	Placebo		Propranolol	
	Control	Stress	Control	Stress
Systolic blood pressure				
Baseline	121.3 ± 2.5	121.6 ± 2.6	119.9 ± 2.0	119.8 ± 1.8
Pre	118.5 ± 2.3	117.8 ± 2.4	111.8 ± 1.8[¶]	110.8 ± 1.4[*,¶]
During	117.5 ± 2.3	**144.5 ± 3.2**[*]	109.6 ± 1.6[¶]	**131.4 ± 2.8**[*]
Post	115.5 ± 2.1	119.5 ± 2.5	107.8 ± 1.8[¶]	109.8 ± 1.4[¶]
Diastolic blood pressure				
Baseline	66.0 ± 1.6	66.0 ± 1.9	66.1 ± 1.5	65.8±1.3
Pre	66.3 ± 1.6	67.7 ± 1.6	67.2 ± 1.7	65.5 ± 1.3
During	66.5 ± 1.5	**86.8 ± 2.2**[*]	66.8 ± 1.6	**84.8 ± 1.8**[*]
Post	66.5 ± 1.4	68.6 ± 1.7	65.6 ± 1.6	65.8 ± 1.3

Bold—significant difference within the stress conditions ($p < .05$). Data represent mean ± S.E.M.
[*] Significantly higher than in the control condition ($p < .05$).
[¶] Significantly lower than the baseline value and the referring values of the placebo group ($p < .05$).

Table 2 Subjective assessments of painfulness, stressfulness and unpleasantness of the stress and control condition in the placebo and propranolol groups.

	Placebo		Propranolol	
	Control	Stress	Control	Stress
Painful	0.4 ± 0.4	68.3 ± 3.5[*]	1.6 ± 1.2	65.2 ± 3.8[*]
Stressful	2.1 ± 1.3	47.1 ± 5.0[*]	2.0 ± 0.8	49.2 ± 5.2[*]
Unpleasant	5.0 ± 2.0	60.9 ± 4.0[*]	6.8 ± 2.6	60.8 ± 4.8[*]

Data represent means ± S.E.M.
[*] Significantly higher than in the control condition ($p < .01$).

condition only during hand immersion in cold and warm water, respectively (see Table 1). As expected, propranolol decreased systolic blood pressure (drug: $F_{1,42} = 7.4$, $p < .01$, $\eta^2 = 0.14$; time × drug: $F_{3,141} = 11.35$, $p < .01$, $\eta^2 = 0.19$). However, it did not block the stress-induced increase in systolic blood pressure (treatment × drug: $F_{1,42} = 0.7$, $p = .40$, $\eta^2 = 0.02$). Diastolic blood pressure was not affected by propranolol (drug and time × drug effects: both Fs < 1, both ps $> .50$, both $\eta^2 < 0.02$).

3.5. Subjective stress ratings

As expected and shown in Table 2, participants rated the SECPT as significantly more painful, stressful and unpleasant than the control condition (all Fs > 120, all ps $< .001$). There were no drug or treatment × drug interaction effects on subjective stress ratings (all Fs < 1.2, all ps $> .30$).

4. Discussion

Previous rodent studies indicated that GC effects on memory retrieval require concurrent noradrenergic arousal (Roozendaal et al., 2004). For the first time, we show here that stress effects on declarative memory retrieval can be blocked in humans by administration of a centrally acting β-adrenoceptor antagonist. Propranolol inhibited the stress-induced memory enhancement for emotional verbal material; propranolol alone did not influence retrieval performance. Furthermore, we demonstrate for the first time that the retrieval of non-declarative, procedural memory is not affected by stress.

In line with earlier reports, we found overall better memory for emotional than for neutral words (Abercrombie et al., 2003; Payne et al., 2006; Schwabe et al., 2008a). Importantly, stress and cortisol affected selectively the memory for emotional words; memory for neutral words was unaffected by stress and cortisol. This is consistent with the literature (Buchanan and Lovallo, 2001; Cahill et al., 2003; Kuhlmann et al., 2005a; de Quervain et al., 2007). For instance, Buchanan and Lovallo (2001) showed that cortisol administration before learning enhanced memory for emotionally arousing pictures but not for neutral pictures. This may be explained by the finding that stress hormone effects on memory retrieval require concurrent activation of the hippocampus and the amygdala (Roozendaal et al., 2004) and that emotionally arousing but not neutral information is capable of activating the amygdala (Cahill et al., 1996; Canli et al., 2000; Strange and Dolan, 2004). It was argued that β-adrenoceptor antagonists block stress and GC effects on memory by inhibiting this activation in the amygdala (Roozendaal et al., 2006; Van Stegeren et al., 2007).

Our results extend previous findings suggesting that the effect of stress on memory functions is not solely detrimental but that stress may also enhance memory performance (Cahill et al., 2003; Schwabe et al., 2008a). Several authors, however, found declarative memory retrieval to be impaired when subjects were stressed or administered GCs prior to retention testing (Kuhlmann et al., 2005a,b; de Quervain et al., 2007). In our view there are two possible explanations for these seemingly discrepant findings. First, stress might have different effects on memory retrieval depending on the time of day and the referring basal cortisol concentrations. The release of cortisol underlies a circadian rhythm with peak levels in the morning as well as after lunch and an evening nadir (Rosmond et al., 1998). Earlier studies that reported impaired memory retrieval after stress tested subjects in the morning (Kuhlmann et al., 2005b). In the present study, participants were examined in the afternoon when basal cortisol levels were relatively low. Lupien et al. (2002) examined the effect of GCs on memory in the morning and in the afternoon. Interestingly, GC administration had a detrimental effect in the morning while GC administration in the afternoon enhanced memory functions. Corroborating the findings of Lupien et al. (2002), a recent meta-analysis showed that the effects of GCs on memory performance depend on the time of day with impairing effects in the morning and positive effects in the afternoon (Het et al., 2005). These findings are interpreted in light of a differential activation of mineralocorticoid receptors (MR) and glucocorticoid receptors (GR), the two receptor types that mediate GC actions in the brain (Lupien et al., 2002). During the circadian trough of GCs in the afternoon high affinity MR are occupied whereas low affinity GR are not. Stress or pharmacologically induced elevations of GCs activate GR which might enhance cognitive functions (de Kloet et al., 1998).

Second, the discrepancy between our findings and those of previous studies reporting stress- or GC-induced retrieval impairments could be related to the obtained GC concentrations. Pharmacological studies in animals and humans typically induce GC concentrations at the upper physiological range (e.g. Kuhlmann et al. (2005a) reported cortisol concentrations of 80—90 nmol/l). Even in the stress studies by Buchanan and Tranel (2008) and Kuhlmann et al. (2005b) GC levels were more than two times as high as in our study; most likely owing to the different time of testing as discussed above. Thus, the differences in the direction of the stress (hormone) effect on declarative memory retrieval might be due to dose-dependent effects of GCs. Indeed, evidence supporting this interpretation comes from a study by Domes et al. (2005). These authors subdivided participants that were administered a moderate dose of hydrocortisone into subjects with high cortisol concentrations (high cortisol group) and subjects with low cortisol concentrations (low cortisol group). They found impaired retrieval of verbal memory in the high cortisol group but a retrieval enhancement in the low cortisol group.

Future studies are clearly needed to test these possible explanations for the observed memory retrieval enhancement after stress. Most importantly, however, our findings indicate that also the stress (hormone)-induced retrieval enhancement is blocked by the β-adrenoceptor antagonist propranolol. It appears that noradrenergic activity is required for stress and GC effects on memory retrieval per se, irrespective of whether the effect is enhancing or impairing.

Recent ideas regarding stress effects on memory functions emphasize the convergence of noradrenergic and GC activity in the BLA, which would then regulate memory processes in other brain systems (McGaugh and Roozendaal, 2002; Roozendaal, 2002). The present study examined the effects of stress and propranolol on the retrieval of both hippocampal declarative and non-hippocampal procedural memory. Contrary to declarative memory retrieval, procedural memory

retrieval was not influenced by stress. This could suggest that there is a specific interaction between the BLA and other medial temporal lobe (MTL) structures, instead of a broad regulatory effect of the BLA on multiple, MTL-dependent and MTL-independent memory systems. Alternatively, the lack of a stress effect on procedural memory retrieval could be due to a lack of task-induced emotional arousal. Participants might have experienced the procedural task as rather less arousing, similar to the neutral verbal material for which we obtained also no stress effect. Future studies are needed to contrast these alternative explanations by employing a more arousing procedural task.

Here, we examined men only to keep our sample more homogenous with respect to sex hormones. The interaction between sex hormones and glucocorticoids in memory is complex and not well understood (Andreano and Cahill, 2006). Previous studies suggested that stress effects on memory might be different in men and women (Wolf et al., 2001; Cahill, 2005; Andreano and Cahill, 2006). Wolf et al. (2001) showed that memory was affected by stress-induced cortisol in men but not in women. Moreover, men tended to show higher cortisol responses to laboratory stressors than women (Kudielka and Kirschbaum, 2005). Thus, it could be predicted that the memory of men is especially susceptible to the influences of stressors such as the SECPT. Future studies are clearly required to replicate our findings in women.

The present findings indicate that stress effects on MTL-dependent memory retrieval require, same as stress effects on memory consolidation, a co-occurrence of GCs and noradrenergic activity and thus support the assumption of a common mechanism underlying the effects of stress on both memory phases (Roozendaal, 2002). A challenge for future research will be to understand the relevance of the interaction between noradrenergic and GC systems in memory processes depending on other brain areas than the MTL.

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Conflict of interest

All authors report no conflict of interest.

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