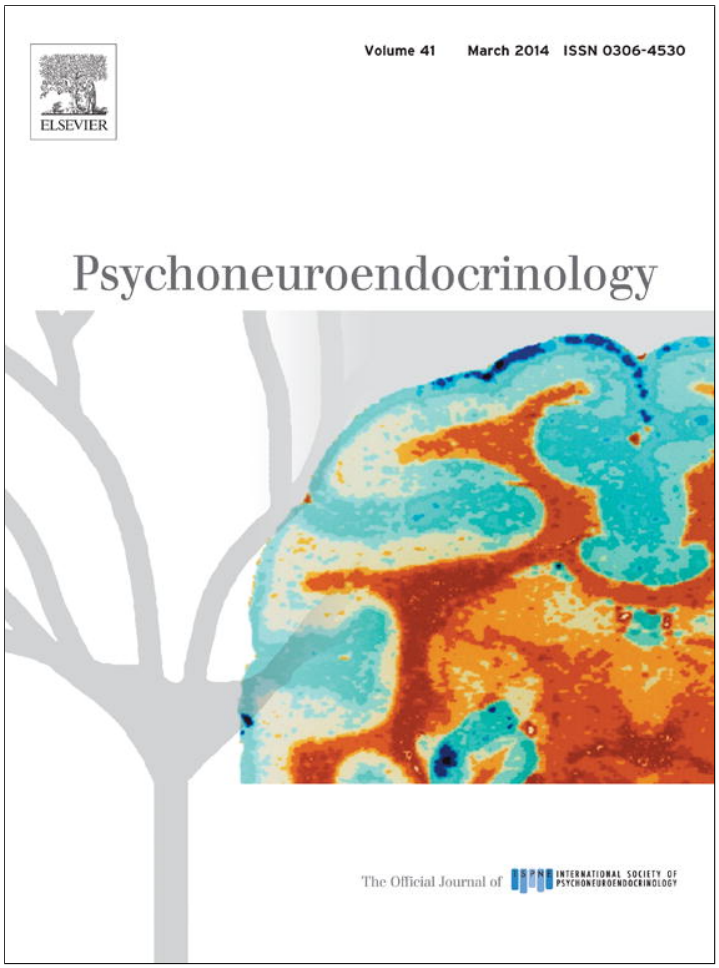

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Exposure to stress attenuates fear retrieval in healthy men

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Summary The stress hormone cortisol reduces retrieval of emotional memories, which has been suggested to support the treatment of psychiatric disorders characterized by exaggerated fear-related memories. Indeed, studies in patients with anxiety disorders have indicated that the success of exposure therapy can be enhanced with accompanying cortisol administration. Fear renewal refers to the clinically relevant phenomenon that successfully extinguished fear can return after a context change. It remains to be investigated whether the effects of stress hormones on fear retrieval also generalize across different contexts. Healthy men were exposed to a fear renewal design with fear acquisition in context A and extinction in context B. Pictures of rooms served as contexts, coloured lights were introduced as conditioned stimuli (CS), and an electrical stimulation served as the unconditioned stimulus (UCS). On the next day, participants were randomly assigned to a stress (Socially Evaluated Cold Pressor Test) or a control condition (n = 20 each). We tested for fear retrieval in contexts A and B during peak cortisol concentrations after stress induction. Overall, a context × stress interaction occurred, revealing that stress attenuated skin conductance responses in the extinction context B. Stress also reduced UCS expectancy in context B. Additionally, stress abolished the renewal effect (differentiation between CS in context A) at the electrodermal level. These results demonstrate a decreased return of fear after acute exposure to stress. Stress interferes with the retrieval of the original fear memory which in turn affects extinction responding. Thus, acute stress reduces rather than promotes the return of fear.

1. Introduction

Exaggerated retrieval of anxiety-related material leads to emotional disturbances in the case of pathological fear. Clinical observations suggest that a stressful situation might evoke or boost the return of fear (Jacobs and Nadel, 1985). Treatment strategies attempt to attenuate these maladaptive processes. For example, the stress hormone cortisol was administered prior to exposure therapy in patients with anxiety disorder (de Quervain et al., 2011; Soravia et al., 2006). Indeed, cortisol successfully reduced phobic fear, which points to its potential for augmenting extinction-based therapeutical strategies. Controversially, stress sometimes appears to increase fear while at other times it relieves fear.

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Basic research is needed to integrate these seemingly opposing findings.

Strong evidence from the literature on episodic memory (for reviews: Schwabe et al., 2010; Wolf, 2009) indicates that cortisol impairs memory retrieval, but facilitates memory consolidation, in particular concerning emotional material. When exposed to phobic stimuli, patients retrieve their aversive memories. It has been suggested that cortisol may enhance extinction-based psychotherapy via two mechanisms (Bentz et al., 2010; de Quervain and Margraf, 2008): by weakening the retrieval of aversive memories and by enhancing the consolidation of the corrective experience made during exposure therapy (i.e., enhancing the consolidation of extinction memory). Apart from patient studies, a recent experiment has indicated that acute stress prior to extinction decreases fear retrieval in healthy men (Bentz et al., 2013). Altogether, the opposing effects of cortisol on different memory phases are a promising phenomenon which may be utilized in the optimization of exposure treatment.

Critically, exposure relies on extinction (Graham and Milad, 2011) which brings with it the disadvantage of context-dependency (Bouton, 2004). Thus, when patients encounter their feared objects in a context that is different from the extinction context, phobic fear often returns. The phenomenon of recovery of the extinguished (fear) response in a context different from the extinction context is termed renewal (Bouton, 2004). It remains to be seen whether cortisol, besides alleviating fear retrieval in the extinction context, also shows a corresponding generalized effect in another context. In this framework, the original context in which fear was acquired constitutes the most fearful context. Successful treatment should reduce the fear response not only in the extinction context, but also in the powerful acquisition context, thus decreasing fear renewal.

In the present study, healthy men were subjected to a typical fear renewal design (cf. Milad et al., 2007, 2009) with fear acquisition in context A and extinction in context B. On the next day, they were either exposed to stress or a control condition. During peak cortisol concentrations the fear retrieval test was conducted in context A (to test for stress effects on fear renewal) and B (to investigate the influence of stress on fear extinction memory). Based on preliminary evidence that pre-extinction stress might reduce the retrieval of fear memory (Bentz et al., 2013) and in line with assumptions regarding the underlying mechanisms of cortisol enhancement in psychotherapy (Bentz et al., 2010; de Quervain and Margraf, 2008), we expect that stress will impair the retrieval of conditioned fear. This effect may be modulated by context, as has been observed for stress effects on episodic memory retrieval (Schwabe and Wolf, 2009).

2. Materials and methods

2.1. Participants

Forty healthy male students recruited at the Ruhr-University Bochum participated in this study and were randomized to two experimental groups (stress vs. control; Section 2.4). Compliance with inclusion criteria was checked beforehand in a standardized telephone interview; students reporting chronic or acute illnesses, colour blindness, regular intake of medicine, current medical or psychological treatment, drug use including smoking, body mass index (BMI) <18 kg/m^2 or >27 kg/m^2, age <18 years or >40 years were not eligible for participation.

During the two-day testing period, participants were advised not to drink alcohol and to refrain from exhausting physical exercise. In addition, they were instructed not to consume food or drinks except water and not to do any physical exercise 90 min before the start of the session on day 2. At the end of the second testing session, participants were reimbursed with 25€ for their participation and received additional information regarding the aim of the study. All procedures were in accordance with the Declaration of Helsinki and approved by the university's local ethical review board.

2.2. Stimulus material

The stimulus material was presented using Presentation (Neurobehavioral Systems) on a 19-inch computer screen located approximately 50 cm in front of the participants. All stimuli and the entire procedure were adopted from Milad and colleagues (2007, 2009). Pictures of an office room and a room with a shelf served as contexts A and B, respectively. Each of the contexts included a desk lamp for presentation of the conditioned stimuli (CS). The lamp switched on after 3 s of context presentation, shining either in red, blue or yellow for 6 s.

A pseudo-randomized stimulus order was used in which no more than two consecutive presentations of the same CS were allowed. Allocation of the three colours of light (red, blue, yellow) as CS+ and CS− as well as order of context and CS presentations on day 2 were counterbalanced between participants. On day 2, the six possible combinations of CS and contexts were presented in pseudo-randomized orders with the additional restriction that all six combinations have to occur once during the first six trials. A black screen with a white fixation cross was shown during the inter-trial intervals between the end of a CS presentation and the start of the next context presentation, randomly set between 6 s and 8 s.

A constant voltage stimulator (STM200; BIOPAC Systems, Inc.) provided transcutaneous electrical stimulation (100 ms) via two Ag/AgCl electrodes filled with isotonic electrolyte medium (Synapse Conductive Electrode Cream, Kustomer Kinetics Inc., Arcadia, CA) fixed to the middle of the left shin. Intensity was set individually to "unpleasant but not painful" using a gradually increasing rating procedure. The electrical stimulation was used as unconditioned stimulus (UCS) occurring immediately after CS+ offset (delay conditioning; 62.5% partial reinforcement rate).

2.3. Fear conditioning, extinction, and retrieval procedure

After arrival, participants were given a resting phase of 20 min in which they provided written informed consent, filled out questionnaires on demographic variables and were tested for red-green colour blindness using five Ishihara plates (selected from Ishihara, 1990). Furthermore, they were informed about the course of the experiment (SCR measurement, application of electrical stimulation, stress, saliva sampling) and given the possibility to ask questions.

In an AB(AB) renewal design, all participants were exposed to fear acquisition in context A as well as fear extinction in context B on day 1; recall was tested in both contexts on day 2. Participants were instructed throughout the whole experiment that they may or may not receive the electrical stimulation after a CS presentation. In addition, participants were told that if they discovered any regularity between the CS and UCS, this relationship would remain the same over the course of the experiment. If a CS was secure, this CS would always be secure; if a CS was followed by an electrical stimulation, this might or might not happen again after presentation of this particular CS.

During fear acquisition in context A, two CS (e.g. red and yellow light) were shown eight times each and both CS were paired with the UCS in five out of eight trials. A third CS (e.g., a blue light; CS−) was never paired with the UCS and shown 16 times intermixed with the CS+ presentations.

During subsequent extinction in context B, one of the CS+ was extinguished (CS+E) in 16 trials, whereas the other CS+ was not shown during extinction (CS+U). Intermixed with the CS+E trials, 16 CS− trials were presented. During the extinction session, the electrodes for delivery of the electrical stimulation remained attached to the shin but did not provide electrical stimulation.

On day 2, participants were either exposed to stress or to a control condition (Section 2.4). Twenty minutes after cessation of the stressor, the retrieval session started with five presentations of all conditioned stimuli (CS+E, CS+U, CS−) in both contexts (A and B). No electrical stimulation was delivered during the retrieval session.

2.4. Stress and control procedure

Individual testing sessions took place in the afternoons of two consecutive days (beginning between 1:30 pm and 4:30 pm) to guarantee low and relatively stable endogenous cortisol concentrations. For each participant, the two testing sessions were conducted at the same time of day (±30 min).

On day 2, participants were randomly assigned to the Socially Evaluated Cold Pressor Test (SECPT; Schwabe et al., 2008) or to a non-stressful control condition (cf. Schwabe et al., 2008). In the SECPT, participants were instructed to immerse their right hand, including the wrist, in a basin filled with ice-cold water (0–3 °C). After three minutes, they were told to remove the hand. During the SECPT, participants were video recorded and monitored by a neutral experimenter. The control procedure comprised hand immersion into warm water (36–37 °C) for three minutes without videotaping and monitoring.

2.5. Measurements and analyses of the stress response

We measured systolic and diastolic blood pressure using Dinamap vital signs monitor (Critikon, Tampa, FL; cuff placed on the left upper arm) before, during, and after hand immersion in each condition to verify activation of the sympathetic nervous system (SNS). Directly following the stress or control procedure, participants rated how stressful, painful, and unpleasant they experienced the respective procedure to be on a scale ranging from 0 (“not at all”) to 100 (“very much”; ratings adopted from Schwabe et al., 2008).

In order to assess activation of the hypothalamus–pituitary–adrenal (HPA) axis, we collected saliva samples using Salivette sampling devices (Sarstedt, Nümbrecht, Germany) one minute before the start of the stress or control procedure (baseline) and one minute, 20 min, and 35 min after the end of the procedure. Furthermore, saliva samples were taken on day 1 at baseline and after fear extinction. Without any further treatment (e.g. centrifuged), all samples were stored at −20 °C until assayed. Free cortisol concentrations were analyzed without prior extraction using a commercial Chemoluminescence Immunoassay (CLIA; IBL International, Hamburg, Germany) according to the manufacturer instructions. Chemoluminescence was read on an Ascent luminescence reader (Thermo Scientific); controls provided by the manufacturer were used to validate the assay. Inter- and intra-assay variations were below 10%. One participant had to be excluded from cortisol analyses as the day 2 baseline sample did not contain sufficient saliva to assess cortisol concentrations.

Participants in the control group showing an increase in salivary cortisol concentrations (>0 nmol/l) from baseline to the expected peak of the cortisol response (20 min later) after the control condition ($n = 2$), and stress group participants showing no increase during this time ($n = 6$) were excluded from analyses (cf. Buchanan et al., 2006). Thus, the final sample consisted of 18 men in the control group and 14 men in the stress group.

We conducted analyses of variance (ANOVA) separately for cortisol, systolic, and diastolic blood pressure including the repeated measurement factor time (four measurements for cortisol, three for blood pressure) as well as the between-subjects factor stress (stress vs. control) for day 2. ANOVA for changes in cortisol secretion on day 1 was calculated separately with the factors time (baseline vs. after fear extinction) and stress. Between group differences in perceived stressfulness, painfulness, and unpleasantness during the experimental condition were tested using two-sample t-tests.

2.6. Skin conductance responses (SCRs) and analyses

SCRs were sampled (sampling rate: 1000 Hz) with a commercial SCR coupler and amplifying system (MP150 + GSR100C, BIOPAC Systems, Inc.; software: AcqKnowledge 4.2) using Ag/AgCl electrodes filled with isotonic electrolyte medium (Synapse Conductive Electrode Cream) attached to the hypothenar on the non-dominant hand. Raw SCR data were high pass filtered with a cutoff frequency of 0.05 Hz. We defined conditioned SCRs as the maximum amplitude (in μS) within a window of 1–6.5 s after CS onset. Data were transformed with the natural logarithm to attain a normal distribution.

Statistical comparisons of SCRs were conducted separately for each phase (acquisition, extinction, retrieval) in SPSS via ANOVA. For fear acquisition and extinction, the between-subjects factor stress was entered as well as the within-subjects factors CS and block (comprising four trials for each CS, except for the CS− in fear acquisition consisting of eight trials). Overall exploratory analyses of fear retrieval involved a CS × trial × context (A vs. B) × stress ANOVA. Hypotheses of group differences were directly and separately

tested during the first trial of fear renewal in context A and during that of extinction memory retrieval in context B, since cortisol might exert independent effects in both contexts. We focused on conditioned responding (CS+E vs. CS−) to emphasize learning-related contextual responding to extinguished stimuli. The corresponding analyses regarding the CS+U are added for completeness sake.

2.7. UCS expectancy ratings and analyses

After the retrieval test and the last saliva sample, participants indicated UCS expectancy for each of the context-stimulus combinations they had encountered during the fear conditioning task. For this rating, they had to mark a cross on a nine-point scale ranging from "sure that the electrical stimulation will not follow the respective CS presentation" (1) to "unsure" (5) to "sure that it will follow the respective CS presentation" (9) at the beginning of the retrieval testing.

UCS expectancy ratings were subjected to a CS (CS+ vs. CS−) × context × stress ANOVA, separately for CS+E and CS+U in line with the SCR analysis.

All statistical analyses were performed in IBM SPSS Statistics for Windows 21.0 with Greenhouse–Geisser correction if needed, the according (corrected) degrees of freedom are given in parantheses. The statistical significance level was set to $\alpha = .05$. Significant main or interaction effects were followed by appropriate post hoc tests.

3. Results

3.1. Sample description and stress induction

The control and stress groups did not differ significantly in age and BMI (Table 1).

Salivary cortisol concentrations of the stress and control group participants are shown in Fig. 1. Regarding day 1, ANOVA revealed a significant main effect of time ($F_{(1,30)} = 12.44$; $p = .001$), reflecting a decrease in cortisol concentrations from the beginning to the end of the testing session. There was no significant effect of stress ($F_{(1,30)} = 1.27$; $p = .268$) or time × stress interaction ($F_{(1,30)} = .20$; $p = .662$), indicating that cortisol concentrations did not differ significantly between groups during the first testing session.

Analyses of blood pressure measures (Table 1) and the cortisol data (Fig. 1) from day 2 indicated that stress induction was successful, as shown by significant time × stress interactions for systolic blood pressure ($F_{(2,60)} = 34.0$; $p < .001$), diastolic blood pressure ($F_{(2,60)} = 36.55$; $p < .001$) and cortisol ($F_{(1.9,55.5)} = 14.79$; $p < .001$). Post hoc tests indicated significantly higher blood pressure in the stress compared to the control group during hand immersion only (Table 1), whereas cortisol concentrations were significantly elevated 20 min ($p = .008$) and 35 min ($p = .011$) after the stressor, i.e. at the time of fear retrieval testing.

Compared to the control procedure ratings, participants of the stress group rated the SECPT as being significantly more stressful ($t_{(15.87)} = 4.69$; $p < .001$), painful ($t_{(13.0)} = 7.36$; $p < .001$) and unpleasant ($t_{(16.08)} = 5.48$; $p < .001$; Table 1).

3.2. Differential skin conductance responses (SCRs)

Fear acquisition was successful as indicated by a significant differentiation between the three CS (main effect CS; $F_{(1.9,55.9)} = 34.50$; $p < .001$; Fig. 2). Post hoc tests revealed significantly higher SCRs to the CS+E ($F_{(1,30)} = 74.93$; $p < .001$) and to the CS+U ($F_{(1,30)} = 44.55$; $p < .001$) compared to the CS−, while the CS+E and the CS+U were not significantly different from each other ($F_{(1,30)} = 0.21$; $p = .650$). Moreover, a main effect of block emerged ($F_{(1,30)} = 12.83$; $p = .001$), indicating habituation of CS responding from the first to the second block. No further significant effects were found, in particular regarding potential pre-existing differences between the stress and control group.

In fear extinction, we found significant differences between CS+E and CS− ($F_{(1,38)} = 35.98$; $p < .001$), a habituation over blocks ($F_{(2.6,100.2)} = 7.96$; $p < .001$) as well as a CS × block interaction ($F_{(2.8,107.8)} = 4.09$; $p = .010$; Fig. 2).

Table 1 Mean (±SEM) age, body-mass-index as well as day 2 blood pressure data and subjective ratings by the stress and control group. *p*-Values of independent-sample *t*-tests are given for comparison between stress and control group data.

	Control	Stress	*p*-Values
Demographics			
Age	24.50 ± 1.14	25.29 ± 0.62	.525
Body-mass-index	23.08 ± 0.44	24.16 ± 0.48	.110
Systolic blood pressure (mmHg)			
Baseline	129.93 ± 3.45	124.90 ± 2.77	.285
During hand immersion	126.26 ± 2.95	140.64 ± 4.49	.009
5 min after SECPT/control	120.33 ± 2.90	118.33 ± 2.61	.623
Diastolic blood pressure (mmHg)			
Baseline	67.26 ± 2.08	71.74 ± 1.89	.132
During hand immersion	65.44 ± 1.81	81.10 ± 2.85	<.001
5 min after SECPT/control	64.48 ± 1.63	67.19 ± 2.41	.344
Subjective ratings after stress/control condition			
Stressful	3.33 ± 1.98	32.86 ± 5.97	<.001
Painful	0.00 ± 0.00	50.00 ± 6.79	<.001
Unpleasant	5.00 ± 2.46	46.43 ± 7.16	<.001

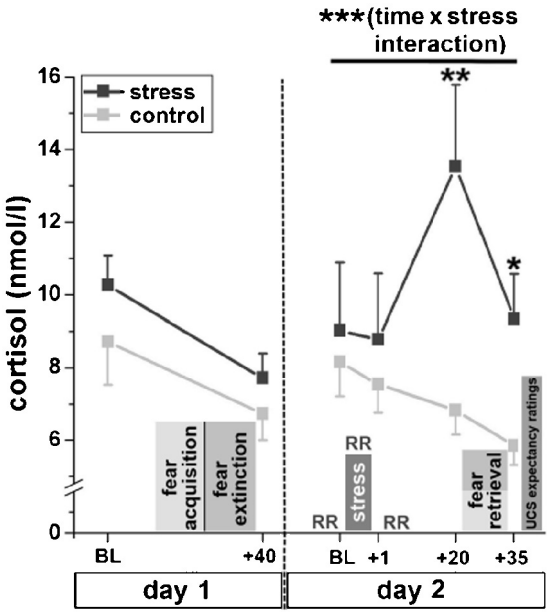

Figure 1 Display of the experimental timeline and mean cortisol concentrations (±SEM). On day 1, fear acquisition in context A and fear extinction in context B were carried out. Cortisol concentrations were determined at baseline (BL) and after the conditioning procedure (+40 min; relative to BL). Cortisol concentrations significantly dropped from BL to +40, reflecting the circadian cortisol rhythm. On day 2, stress induction took place after a BL measurement of cortisol and blood pressure (RR). During hand immersion into ice-cold or warm water and 5 min afterwards, RR was measured a second and third time. Immediately after the stress or control procedure, a second saliva sample was collected; further sampling took place 20 min and 35 min after the end of the respective condition. Cortisol concentrations were significantly higher in the stress compared to the control group over the course of the experiment, in particular before and after fear retrieval (conducted in context A and B) tested during the peak of the cortisol response. UCS expectancy ratings for the different CS were given at the end of day 2. $^{***}p < .001$; $^{**}p < .01$; $^{*}p < .05$ (compared to the control group).

Post hoc tests indicated higher SCRs to the CS+E compared to the CS− in the first ($F_{(1,38)} = 47.57$; $p < .001$), second ($F_{(1,38)} = 8.33$; $p = .006$), and third block ($F_{(1,38)} = 14.73$; $p < .001$), but not in the fourth block ($F_{(1,38)} = 2.80$; $p = .102$). Altogether, fear extinction was effective in diminishing conditioned responding over time, while no group differences were observed.

During fear retrieval on day 2, we detected higher SCRs to the CS+E compared to the CS− (main effect CS; $F_{(1,30)} = 15.43$; $p < .001$). Furthermore, context modulated SCRs to the CS+E and CS− (CS × context interaction; $F_{(1,30)} = 6.95$; $p = .013$): The two CS differed from each other in context A ($F_{(1,30)} = 23.59$; $p < .001$), but not B ($F_{(1,30)} = 2.57$; $p = .119$). Additionally, stress tended to reduce overall SCRs (main effect stress; $F_{(1,30)} = 4.18$; $p = .050$) depending on the context (stress × context interaction; $F_{(1,30)} = 4.31$; $p = .047$): Stress diminished SCRs in context B ($F_{(1,30)} = 8.22$; $p = .007$; Fig. 3A), but not A ($F_{(1,30)} = .66$; $p = .422$). In addition, a CS × stress interaction

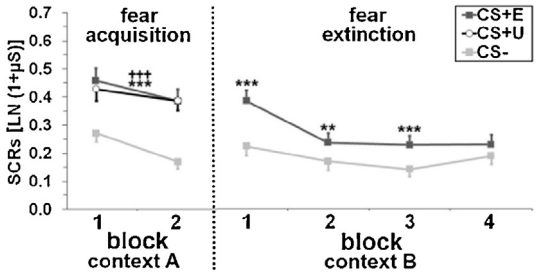

Figure 2 Mean (±SEM) conditioned SCRs during blocks of four trials (except for eight CS− trials in fear acquisition) on day 1. Successful fear acquisition (conducted in context A) and fear extinction (conducted in context B) could be observed. $^{***}p < .001$ (CS+E [extinguished] compared to CS−); $^{+++}p < .001$ (CS+U [unextinguished] compared to CS−); $^{**}p < .01$ (CS+E [extinguished] compared to the CS−).

was observed in context A ($F_{(1,30)} = 4.96$; $p = .034$), revealing reduced CS+E/CS− differentiation after exposure to stress compared to the control condition ($F_{(1,30)} = 4.38$; $p = .046$). Thus, stress attenuated the fear renewal effect (CS+/CS− differentiation in the acquisition context).

Furthermore, we examined whether cortisol-increases were related to the CS+E/CS− differentiation in context A. Cortisol-increases were operationalized as the area under the curve with respect to increase (AUC_i; Prüssner et al., 2003) over the course of the four times of measurement. Indeed, higher cortisol-increases were significantly negatively correlated with the CS+E/CS− differentiation in context A ($r = -.36$; $p = .049$), while no correlation occurred in context B ($r = -.14$; $p = .440$) in the entire group. Thus, the higher the cortisol-increase, the lower the CS+E/CS− differentiation (i.e. the fear renewal) in context A.

In addition to the main analysis concerning CS+E responding, we detected higher SCRs to the CS+U compared to the CS− (main effect CS; $F_{(1,30)} = 25.30$; $p < .001$). Again, stress significantly modulated SCRs depending on the context (stress × context interaction; $F_{(1,30)} = 5.61$; $p = .025$): Stress tended to diminish SCRs in context B ($F_{(1,30)} = 3.11$; $p = .088$), but not A ($F_{(1,30)} = 0.06$; $p = .806$). No further significant effects were observed (all $F_{(1,30)} < 3.77$; $p > .06$).

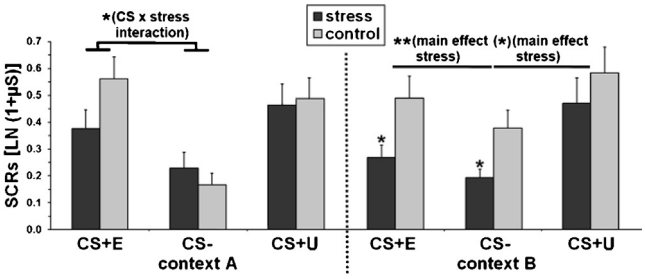

Figure 3 Mean (±SEM) conditioned SCRs for CS+E (extinguished), CS− and CS+U (unextinguished) are depicted separately for the stress and the control group in context A and B during the first trial of the fear retrieval testing on day 2. Stress reduced fear renewal in context A and overall conditioned responding in context B. Only main and interaction effects with the factor stress are indicated with $^{**}p < .01$; $^{*}p < .05$ (compared to the control group); $^{(*)}p < .10$.

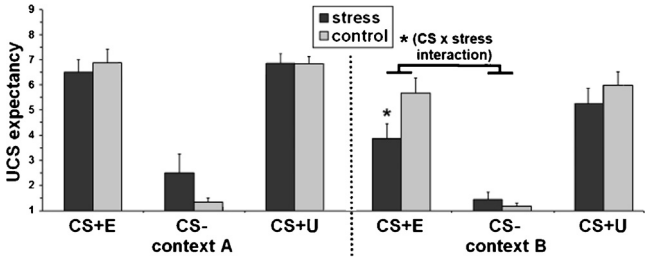

Figure 4 Mean (±SEM) UCS expectancy for CS+E (extinguished), CS− and CS+U (unextinguished) is shown separately for the stress and the control group in context A and B during fear retrieval testing on day 2. Stress significantly attenuated UCS expectancy for the CS+E (extinguished). Only main and interaction effects with the factor stress are indicated with $^{*}p < .05$ (compared to the control group).

3.3. UCS expectancy ratings

As expected, UCS expectancy was significantly higher in context A compared to context B (main effect context; $F_{(1,30)} = 21.13$; $p < .001$) and higher for the CS+E compared to the CS− (main effect CS; $F_{(1,30)} = 144.46$; $p < .001$). Both factors also interacted (CS × context interaction; $F_{(1,30)} = 4.20$; $p = .049$): The UCS expectancy in context A compared to B was higher for the CS+E as opposed to the CS− ($t_{(31)} = 2.04$; $p = .050$). Additionally, stress influenced UCS expectancy concerning CS (CS × stress interaction; $F_{(1,30)} = 6.99$; $p = .013$) and context processing (context × s- stress interaction; $F_{(1,30)} = 4.39$; $p = .045$). While there were no differences between groups in context A ($F_{(1,30)} = 2.34$; $p = .137$), a significant CS × stress interaction was observed in context B ($F_{(1,30)} = 5.90$; $p = .021$; Fig. 4). In context B, stress reduced UCS expectancy for the CS+E ($t_{(30)} = 2.09$; $p = .046$), but not for the CS− ($t_{(30)} = 0.90$; $p = .374$). No correlations between cortisol-increase and differential UCS expectancy were found in context A ($r = -.27$; $p = .148$) or B ($r = -.15$; $p = .435$).

Comparable to the results regarding the CS+E, UCS expectancy was significantly higher in context A compared to context B (main effect context; $F_{(1,30)} = 10.69$; $p = .003$) and higher for the CS+U compared to the CS− (main effect CS; $F_{(1,30)} = 182.08$; $p < .001$). However, the experimental manipulation did not influence these results, because no interaction with stress occurred (all $F_{(1,30)} < 2.38$; $p > .13$).

4. Discussion

The current experiment demonstrates that acute stress, when applied before testing fear retrieval, attenuates fear renewal and fear responding in the extinction context. Stress presumably exerts beneficial effects on the return of fear by inhibiting the retrieval of emotional information (i.e. the original fear trace), an effect comparable to the effect it has on episodic memory (cf. Schwabe et al., 2010; Wolf, 2009). This effect is not only observable in the extinction context, but also in the original acquisition context, in which fear renewal was significantly reduced after stress exposure.

More precisely, the significant stress × context interaction could be traced back to the extinction context, in which acute stress generally lowered SCRs. Accordingly, studies examining patients with anxiety disorders have revealed that cortisol administration attenuates phobic fear without context change from one exposure session to the next (de Quervain et al., 2011; Soravia et al., 2006). These findings indicate that cortisol decreases fear when tested in the extinction context. This fits in well with the findings of the current study applying acute stress in healthy men. In the same line, exposure to stress diminished UCS expectancy towards the extinguished CS+, pointing to a specific reducing effect of stress on a prior fear-associated stimulus which underwent extinction learning in the same context. Extending these observations concerning extinction memory retrieval, stress also prevented fear renewal, i.e. CS+/CS− differentiation in the acquisition context. Moreover, cortisol-increases were negatively associated with differential SCRs in context A. Even when revisiting the most fearful acquisition context, stress hormones appear to be capable of attenuating subsequent fear responding.

Comparing the results of both response levels, stress reduced conditioned SCRs in the acquisition context, but UCS expectancy in the extinction context. Such a divergence gives an important hint to carefully include several response levels to get a more complete overview of how stress can affect emotional (SCRs) and cognitive (UCS expectancy) aspects of fear and extinction retrieval. Apparently, acute stress influenced emotional responding in the more arousing acquisition context (in which UCS application occurred once before), but cognitive aspects were tackled in the safe extinction context (in which conditioned responding is under cognitive control during the test phase).

Taken together, our results suggest that, irrespective of contextual cues, patients might profit from a mild stressful experience shortly prior to encountering a feared object, which is highly relevant for clinical applications. The finding that cortisol decreases fear has already been demonstrated following cortisol administration in patients with specific phobia (de Quervain et al., 2011; Soravia et al., 2006). Likewise, cortisol treatment diminishes symptoms in PTSD patients (Aerni et al., 2004; Suris et al., 2010; Yehuda et al., 2010). According to the literature on episodic memory (Schwabe et al., 2010; Wolf, 2009), stress hormones dampen memory retrieval especially concerning emotional material. In this line, the acquisition context can be considered as more emotional compared to the extinction context due to the application of the UCS during fear acquisition. Thus, acute stress might primarily reduce the retrieval of fear memory acquisition (as indicated by the reduced fear renewal effect). The effects observed in both the acquisition and the extinction context could be ascribed to the same mechanism: Stress weakens fear retrieval, which can be observed not only in the extinction context, but also in the original fear context. Therefore, stress can indeed overrule fear renewal and does not evoke an extinguished conditioned response to heavily return after a context change. However, an unextinguished conditioned response is not affected (cf. results of the CS+U), suggesting that the impact of stress does not generalize across cues.

Remarkably, our current experiment suggests that pharmacologically induced cortisol-increases, evoking supraphysiological concentrations, are not necessarily required for inducing reduced fear memory retrieval. A moderately

stressful intervention such as the SECPT used in the present study leads to comparably beneficial effects. A recent fear conditioning study was also able to show that the cold pressor test without its socio-evaluative components decreases fear retrieval in healthy men when applied before extinction learning (Bentz et al., 2013). However, our study is the first to test the influence of stress on fear and extinction memory retrieval in order to assess the impact of contextual cues, thus examining the renewal effect. The inhibition of fear after cortisol-increases and its relevance for contextual processing constitute a promising phenomenon for future clinical research, which could provide important treatment strategies.

In contrast to the current results, stress enhanced the renewal effect in a rather neutral predictive learning task in humans (Hamacher-Dang et al., 2013). This suggests that the task itself might interact with stress effects: Whereas fear conditioning is a highly emotional paradigm, the predictive learning task does not incorporate any emotional components. If at all, a slight emotional component may occur in the predictive learning task during extinction in terms of a prediction error signal, when the CS is no longer coupled with an aversive outcome. Thus, these recent results (Hamacher-Dang et al., 2013) point to an enhanced renewal after exposure to stress, which might be driven by stress hormones reducing extinction memory retrieval. Extinction memory in this task represents the more emotional information; therefore, it should be more susceptible to the influence of stress compared to the neutral acquisition memory.

Furthermore, the present results also contradict clinical reports on stress evoking or enhancing the return of fear (Jacobs and Nadel, 1985). However, this discrepancy can be resolved by taking into account that our stressor is acute. Chronic stress might indeed lead to impaired extinction recall and increased reemergence of fear, as has been shown to occur in male rats (Garcia et al., 2008; Miracle et al., 2006; Wilber et al., 2011). Additionally, chronic stress was applied before fear acquisition and extinction in these rodent studies, so a direct effect on fear retrieval cannot be derived.

Moreover, the exact timing of stress-induction has a major impact on learning and memory processes (cf. Schwabe et al., 2010; Wolf, 2009). We tested fear renewal during the cortisol peak (between 20 and 35 min after stress onset), when the stress-induced activation of the SNS had already subsided. If fear renewal had taken place immediately after stress induction, stress might have increased fear responding, as has been demonstrated in male rats (Deschaux et al., 2013). Such a timing-related effect has also been shown for influences of stress on decision making (Pabst et al., 2013) and might reflect opposing effects of the SNS and the HPA axis.

In the present study, only male participants were included, so our conclusions do not necessarily also apply to women. Indeed, several hints point to pronounced sex differences in fear acquisition and extinction after stress exposure or cortisol administration (Jackson et al., 2006; Merz et al., 2010, 2012, 2013; Shors, 2004; Stark et al., 2006). Moreover, low concentrations of estradiol, either released endogenously over the course of the menstrual cycle or due to the intake of hormonal contraceptives, are associated with increased fear recall (Graham and Milad, 2013; Milad et al., 2010; Zeidan et al., 2011). Future experiments should take this neurobiological evidence of the impact of sex (hormones) on fear recall into account, in particular concerning possible applications in psychotherapy by studying both sexes.

In summary, stress appears to reduce rather than to promote the return of fear. This is another example of the adaptive nature of the acute biobehavioral stress response. Clinicians might profit from these basic research findings in order to optimize existing treatment strategies such as exposure therapy. A moderately stressful experience before exposure could enhance the treatment outcome. Since patients are usually afraid before exposure sessions, this anticipation evokes a stress response, which in turn might help them to better cope with their expected fear.

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Conflict of interest statement

None declared.

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