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Stress following extinction learning leads to a context-dependent return of fear

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Abstract

It has been suggested that extinction-based therapy benefits from administration of the stress hormone cortisol. However, it is unclear whether similar effects can be obtained by inducing stress instead of administering cortisol, and whether the effects also persist if memory is tested in a different context (renewal test) or after exposure to an aversive stimulus (reinstatement). The present study therefore applied a fear conditioning (context A, day 1) and extinction (context B, day 2) paradigm in healthy men. After fear extinction, participants were exposed to a stress or control procedure ($n = 20$ each). Fear retrieval was tested in contexts A and B on day 3. Postextinction stress increased skin conductance responses to the extinguished stimulus in the retrieval and reinstatement test especially in the acquisition context. The context-dependent return of fear may reflect enhancing effects of stress on the consolidation of contextual cues.

Descriptors: Conditioning, Normal volunteers, Electrodermal, Learning/Memory, Emotion, Biochemical

Confrontation with a feared object or situation, either imagined or in reality, is an integral part of standard psychotherapeutic treatments of anxiety disorders, and typically results in a decline of pathological/exaggerated fear. However, fear can return after some time has passed (spontaneous recovery; Pavlov, 1927), when the context changes (renewal effect; Bouton & Bolles, 1979), or after exposure to an aversive stimulus (reinstatement; Rescorla & Heth, 1975). The etiology of anxiety disorders can be modeled experimentally with fear conditioning (Davey, 1992; Bouton, Mineka, & Barlow, 2001), which comprises pairing a stimulus to be conditioned (CS) with an aversive unconditioned stimulus (UCS; e.g., electrical stimulation). Extinction, an experimental analogue of exposure therapy, involves repeated presentations of the CS without the UCS and becomes manifest in a decline of conditioned fear. Retrieval of extinction memory can be tested by presenting the CS again at a later occasion and allows for a systematic investigation of the conditions under which the fear is more likely to return, modeling relapse (Rachman, 1989). Using similar designs as the basic paradigm described here, the return of fear phenomena mentioned above have been demonstrated both in laboratory animals and humans (for reviews on extinction memory and the return of fear, see Bouton, 2004; Myers & Davis, 2007; Quirk & Mueller, 2008; Vervliet, Baeyens, Van den Bergh, & Hermans, 2013). They indicate that extinction does not lead to a permanent erasure of the fear memory but rather results in the formation of a new memory trace, inhibiting the expression of fear.

This study aimed at investigating whether a short stress induction applied after extinction learning might serve to strengthen the consolidation of extinction memory, thereby improving its later retrieval, or whether it might exert impairing effects on the consolidation process. The stress hormone cortisol, which is the major glucocorticoid (GC) in humans, has already been shown to ameliorate exposure therapy of anxiety disorders (Bentz, Michael, de Quervain, & Wilhelm, 2010; de Quervain et al., 2011; Soravia et al., 2006, 2014), supposedly acting by impairing retrieval of aversive memories and/or by enhancing the consolidation of extinction memory formed during therapy (Bentz et al., 2010). In a previous fear conditioning study, we were able to show that stress exposure is also capable of reducing the retrieval of fear memories in healthy men (Merz, Hamacher-Dang, & Wolf, 2014). Therefore, the stress-induced increase in endogenous cortisol concentrations might be sufficient to achieve the beneficial effects previously shown with the administration of cortisol. Likewise, both stress induction and pharmacological administration of cortisol have typically been shown to enhance the consolidation of episodic memory (e.g., Buchanan & Lovallo, 2001; Cahill, Gorski, & Le, 2003; Kuhlmann & Wolf, 2006; Preuss & Wolf, 2009; Smeets, Otgaar, Candel, & Wolf, 2008; for a review, see Roozendaal & McGaugh, 2011), which has also been observed for the consolidation of fear acquisition in men (Zorawski, Blanding, Kuhn, & LaBar, 2006; for a review of stress hormone effects on emotional memories, see Krugers, Zhou, Joels, & Kindt, 2011). In addition,

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animal studies have also shown that GCs are necessary for the successful extinction of fear memories (Barrett & Gonzalez-Lima, 2004; Blundell, Blaiss, Lagace, Eisch, & Powell, 2011). In contrast, a rodent study inducing acute stress after initial extinction learning found that it disrupted extinction retrieval on the following day (Akirav, Segev, Motanis, & Maroun, 2009), indicative of an impairing effect on extinction memory consolidation. However, it remains unknown—at least in humans—how stress exposure directly after extinction specifically affects the consolidation of extinction memories.

An important factor that can modulate stress effects (Hamacher-Dang, Engler, Schedlowski, & Wolf, 2013; Schwabe, Bohringer, & Wolf, 2009; Schwabe & Wolf, 2009) and which plays an important role in extinction memory is the context. Extinction memory is highly context dependent, as indicated by the observation that testing extinction retrieval in a context different from the acquisition context leads to a stronger return of fear (renewal effect; for a review, see Bouton, 2004). Reinstatement has also been proposed to be context dependent, as fear is typically reinstated only if the reinstatement UCS is administered in the same context in which the subsequent reinstatement (retrieval) test is conducted (e.g., Bouton & Bolles, 1979; Bouton & King, 1983; LaBar & Phelps, 2005; but see Westbrook, Iordanova, McNally, Richardson, & Harris, 2002). Not only the return of fear phenomena themselves but also the impact of potential influencing factors has been reported to be context dependent. For instance, the extinction-enhancing effects of the α2-adrenergic receptor antagonist yohimbine (Morris & Bouton, 2007) and the partial NMDA (N-methyl-D-aspartate) receptor agonist d-cycloserine (Bouton, Vurbic, & Woods, 2008) appear to be context specific, reducing spontaneous recovery in the extinction context but leaving renewal unaltered. Whether effects of cortisol or stress induction on extinction memory can also be modulated by the context has, to our knowledge, not yet been investigated.

To this end, the present study also took into account the potential modulatory role of contextual cues by applying a fear renewal paradigm (adopted from Milad et al., 2007, 2009) in which healthy men underwent differential fear conditioning in context A on the first day. Electrical stimulation was used as UCS, and skin conductance responses (SCRs) served as a measure of conditioned responding. On the second day, fear was extinguished in context B. Directly after extinction training, half of the participants were exposed to acute stress by means of the Socially Evaluated Cold Pressor Test (SECPT; Schwabe, Haddad, & Schachinger, 2008), while the other half underwent a nonstressful control condition. Inducing stress after extinction learning makes it possible to identify the specific effects of stress on the consolidation of extinction memory without it interfering with extinction learning per se or its retrieval. On the third day, retrieval of extinction memory was tested in contexts A and B both before and after unsignaled UCS applications.

Considering the well-known stress effects on episodic memory consolidation and the preliminary evidence for extinction memory, we expected postextinction stress to affect the return of fear in the retrieval and in the reinstatement test. Based on the important role of context for extinction memory as well as for stress effects on memory, and in line with previous findings (Hamacher-Dang et al., 2013; Merz et al., 2014), we assumed that the stress effects would differ depending on the test context. Thus, this study elucidates how stress modulates extinction memory consolidation, which is clinically relevant for the understanding and potential optimization of exposure therapy.

Method

Participants and General Procedure

A total of 40 healthy male students recruited via advertisements and flyers at the Ruhr-University Bochum participated in this study. In order to be eligible for participation, students had to go through a standardized telephone interview, in which compliance with inclusion criteria was checked. Students reporting color blindness, chronic or acute illnesses, current or past psychopathology, drug use including smoking, regular intake of medicine, working night shifts, or aged under 18 or over 40 years were not eligible.

Test sessions took place on the afternoons of 3 consecutive days, starting between 12:30 pm and 5:45 pm. Individual testing times were scheduled so that there were 24 h (± 2 h) between each session. During all of the 3 days of testing, participants were advised not to consume alcohol. In addition, participants were told to refrain from eating, physical exercise, and drinking anything except water within the 90 min prior to each test session. On arrival on the first testing day, participants provided written informed consent, were then screened for color blindness using a selection of four Ishihara plates (from Ishihara, 1990), completed questionnaires regarding demographic data and trait anxiety (State-Trait Anxiety Inventory, STAI; Laux, Glanzmann, Schaffner, & Spielberger, 1981), and underwent a fear acquisition procedure. On the next day, they were subjected to an extinction phase, followed by exposure to a stress or control procedure to which participants were randomly allocated ($n = 20$ in each group). On the third day, participants were tested for retrieval and reinstatement and afterwards completed a questionnaire to indicate UCS expectancies. At the end of the last test session, participants received 25€ for their participation and had the opportunity to obtain further information regarding the aims of the study. The experiment was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

Fear Acquisition, Extinction, and Retrieval Procedures

The stimuli and procedure were adopted from Milad and colleagues (Milad et al., 2007, 2009), as described in a previous study by our laboratory (Merz et al., 2014). In this fear conditioning paradigm, photos of two different rooms (office/library) were used as contexts A and B. In both contexts, a desk lamp was present, which indicated CS presence by different colors of the lamplight. Each trial consisted of 3 s of context-only presentation (during which the desk lamp was off) followed by 6 s of CS presentation (lamplight shining in red, blue, or yellow). Allocation of the three colors of light to the three CS was counterbalanced between participants. In the intertrial interval between the end of a CS presentation and the start of the next context presentation, a black screen with a white fixation cross was shown for a randomly set duration of 6–8 s. Stimuli were presented on a 19-inch computer screen with a distance of approximately 50 cm to the participant's head.

Throughout all phases of the experiment, participants were instructed that they may or may not receive electrical stimulation after a CS. Before the start of each phase, they were told to intently watch the presentation on the screen and encouraged to keep track of any regularities between stimuli and electrical stimulation that may occur. They were informed that in a situation where they discovered such a relationship, it would remain stable over all of the phases of the experiment: If a CS was safe, it would always be safe; if a CS was followed by electrical stimulation, this might or might not occur again. These instructions were used to facilitate

learning of contingencies (a prerequisite for studying the retrieval of extinction memory) and to preclude participants from expecting a complete reversal of contingencies in the extinction phase (i.e., expecting stimulation to occur after CS− presentations). However, note that participants were not informed about the actual CS–UCS contingencies.

The order of CS presentations was determined as follows: For all conditioning phases, an initial randomization procedure was applied with some restrictions (depending on the phase; for details, see supporting online information). For the acquisition and retrieval phase, two stimulus orders were derived from the randomization procedure and counterbalanced across participants. The stress and control group were matched, so that for each participant in the stress group, one participant in the control group received the same stimulus order in all conditioning phases. During fear acquisition, three CS were presented in context A, one of which was never followed by electrical stimulation (thus constituting the CS−), while the other two CS (CS+) were paired with the UCS in five of eight trials of each CS+. The CS− was presented 16 times, intermixed with eight presentations of each CS+.

At the beginning of the extinction phase on the subsequent day, stimulation electrodes were attached again, identical to the procedure in the conditioning phase, but did not deliver any electrical stimulation. During extinction in context B, one of the CS+ from the acquisition phase was presented 16 times without being followed by the UCS (CS+E, i.e., the extinguished CS+). The CS− was also presented 16 times, intermixed with the CS+E trials. The unextinguished CS+ (CS+U) was not shown during this phase.

On the third testing day, stimulation electrodes were again attached in the same way as in the previous days. The retrieval phase consisted of five presentations of the three CS in both contexts A and B without any electrical stimulation. The order of context and CS presentations was counterbalanced between participants. Then, the reinstatement phase followed, starting with the application of four unsignaled electrical stimulations at the level that had been individually determined in the first test session. The four stimulations were separated by intervals with a randomly varying duration of 14 to 16 s. During the whole UCS application period, the screen turned gray in order to avoid incidental conditioning to the background and fixation cross shown during usual intertrial intervals. Identical to the procedure in the retrieval phase, the three CS were then presented again in both contexts without electrical stimulation (five trials of each CS in each context).

Apparatus, Physiological Recordings, and SCR Data Analysis

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

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 of the nondominant hand. Raw SCR data were high-pass filtered with a cutoff frequency of 0.05 Hz. Conditioned SCRs were defined as the maximum amplitude (in μS) within a window of 1 to 6.5 s after CS onset and calculated as the baseline-to-peak amplitude difference of the largest deflection within a window of 1 to 6.5 s after CS onset. The baseline was the skin conductance level immediately preceding the inflexion point. Data were transformed with the natural logarithm to attain a normal distribution. Due to technical failure, one participant had to be excluded from analysis of the acquisition phase SCRs as his data could not be stored. One participant had to be excluded from analysis of the reinstatement test phase due to failure of the voltage stimulator system.

UCS Expectancy Ratings

After testing for retrieval and reinstatement in the third test session, participants were asked to indicate UCS expectancy for each of the context-stimulus combinations shown during the previous sessions. To state their UCS expectancies regarding the beginning of the retrieval testing, they marked crosses on 9-point scales ranging from 1 (*sure that the electrical stimulation will not follow the respective CS presentation*) to 5 (*unsure*) to 9 (*sure that it will follow the respective CS presentation*).

Stressor and Control Procedure

Directly following electrode removal after the extinction phase on day 2, participants in the stress group were exposed to the SECPT as described by Schwabe and colleagues (2008). In brief, the stress induction protocol included the immersion of the participant's right hand and wrist into ice-cold water (0–3°C) for 3 min while being videotaped and observed by a neutral experimenter. The control group participants were instructed to immerse their hand into water at body temperature (36–37°C) and were neither videotaped nor observed. Immediately following the stress or control procedure, participants were asked to rate their feelings of stressfulness, painfulness, and unpleasantness during the preceding procedure on a scale ranging from 0 (*not at all*) to 100 (*very much*; rating method adopted from Schwabe et al., 2008).

Saliva Sampling and Analysis

As a marker of hypothalamus-pituitary-adrenal (HPA) axis activity, we assessed free salivary cortisol concentrations at the beginning of the second test session (before the start of the extinction phase), directly before the start of the SECPT/control procedure, as well as 1 min and 25 min after the stress induction/control procedure. In the waiting period between the last two saliva sampling time points, participants were allowed to read magazines provided by the experimenter. In addition, saliva samples were collected before and after fear acquisition (day 1), and before retrieval and after reinstatement testing (day 3). All samples were stored at −20°C until assayed. Free cortisol concentrations were analyzed with a commercial chemiluminescence immunoassay (IBL International, Hamburg, Germany). Inter- and intra-assay variations were below 10%. Due to insufficient amounts of saliva, the data of one participant from day 1, two participants from day 2, and four participants from day 3 were incomplete and had to be excluded from the corresponding cortisol analyses.

Blood Pressure Measurement

As a marker of sympathetic nervous system (SNS) activity, blood pressure was measured using a Dinamap vital signs monitor

Table 1. *Participant Characteristics and Mean Blood Pressure Responses to and Subjective Ratings of the SECPT/Control Procedure*

	Control	Stress	*p* values
Demographics			
Age (years)	25.5 ± 4.3	24.6 ± 4.3	.51
Body mass index (kg/m^2)	23.5 ± 2.5	22.9 ± 2.6	.46
STAI trait	47.6 ± 3.3	46.6 ± 3.2	.36
Systolic blood pressure (mmHg)			
Baseline	118.9 ± 9.3	122.4 ± 10.4	.27
During procedure	119.2 ± 9.8	142.7 ± 11.7	< .001
After procedure	113.4 ± 8.3	121.0 ± 11.5	.02
Diastolic blood pressure (mmHg)			
Baseline	66.3 ± 7.0	67.2 ± 7.6	.70
During procedure	66.9 ± 7.6	84.1 ± 6.9	< .001
After procedure	65.2 ± 7.7	68.6 ± 7.3	.16
Subjective ratings after procedure			
Stressful	4.5 ± 11.0	49.0 ± 33.5	< .001
Painful	0.5 ± 2.2	50.0 ± 33.6	< .001
Unpleasant	8.0 ± 18.2	47.5 ± 34.6	< .001

Note. Stressfulness, painfulness, and unpleasantness were rated on a scale from 0 (*not at all*) to 100 (*very much*). Data represents means ± standard deviation. *P* values of independent *t* tests regarding potential differences between the stress and control group are given. SECPT = Socially Evaluated Cold Pressor Test; STAI = State-Trait Anxiety Inventory.

(Critikon, Tampa, FL; cuff placed on the left upper arm) directly before, during, and 5 min after the stress or control manipulation (day 2).

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows 22.0. The statistical significance level was set to $\alpha = .05$. If assumptions of sphericity were violated, Greenhouse-Geisser corrected *p* values were used.

Results

There were no significant differences between the stress and control group regarding age, body mass index, and trait anxiety (see Table 1).

Stress Response

Analyses of salivary cortisol, blood pressure, and subjective ratings showed that stress induction on day 2 was successful.

Salivary cortisol. Figure 1 depicts free salivary cortisol concentrations separately for the stress and control group during the course of all of the three test sessions. On day 2, a repeated measures analysis of variance (ANOVA) with the between-subjects factor group (stress vs. control) and the within-subjects factor time (baseline, postextinction, +1 and +25 min after stress induction/control procedure) revealed that the stress group had significantly higher salivary cortisol concentrations in response to the stress induction than the control group (Time × Group interaction, $F(3,108) = 14.67$, $p < .001$, main effects of time, $F(3,108) = 3.49$, $p \leq .05$, and group, $F(1,36) = 4.15$, $p \leq .05$). The stress group had significantly higher cortisol concentrations than the control group at 25 min after the SECPT/control procedure, $t(36) = 4.57$, $p < .001$, while the two groups did not differ significantly at any other time point of measurement, as indicated by *t* tests (all *p*s > .10).

To test for incidental group differences on day 1 and day 3, two 2 × 2 repeated measures ANOVAs with the between-subjects factor group and the within-subjects factor time (baseline,

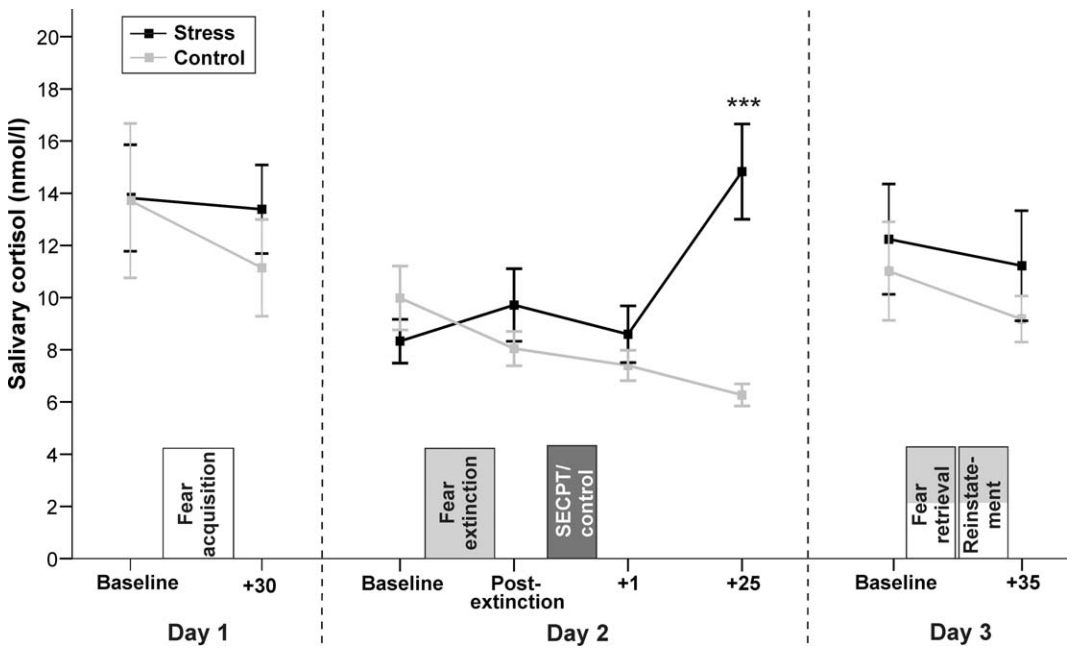

Figure 1. Mean salivary cortisol concentrations of the stress and control group along the three test sessions. Baseline measures were obtained before the start of the respective conditioning phase. On day 1, the second saliva sample was collected directly after fear acquisition and electrode removal (+30 relative to baseline). On day 2, the postextinction sample was collected 28 min after baseline. Further saliva sampling times are indicated relative to the end of the SECPT/control procedure (i.e., 1 min and 25 min after cessation of the stressor/control procedure). In response to the stressor, the stress group exhibited significantly elevated cortisol concentrations. On day 3, the last sample was obtained following electrode removal after the reinstatement test phase (+35 min relative to baseline). Error bars indicate standard errors of the mean. ***Significant difference between stress and control group, $p < .001$ in *t* test.

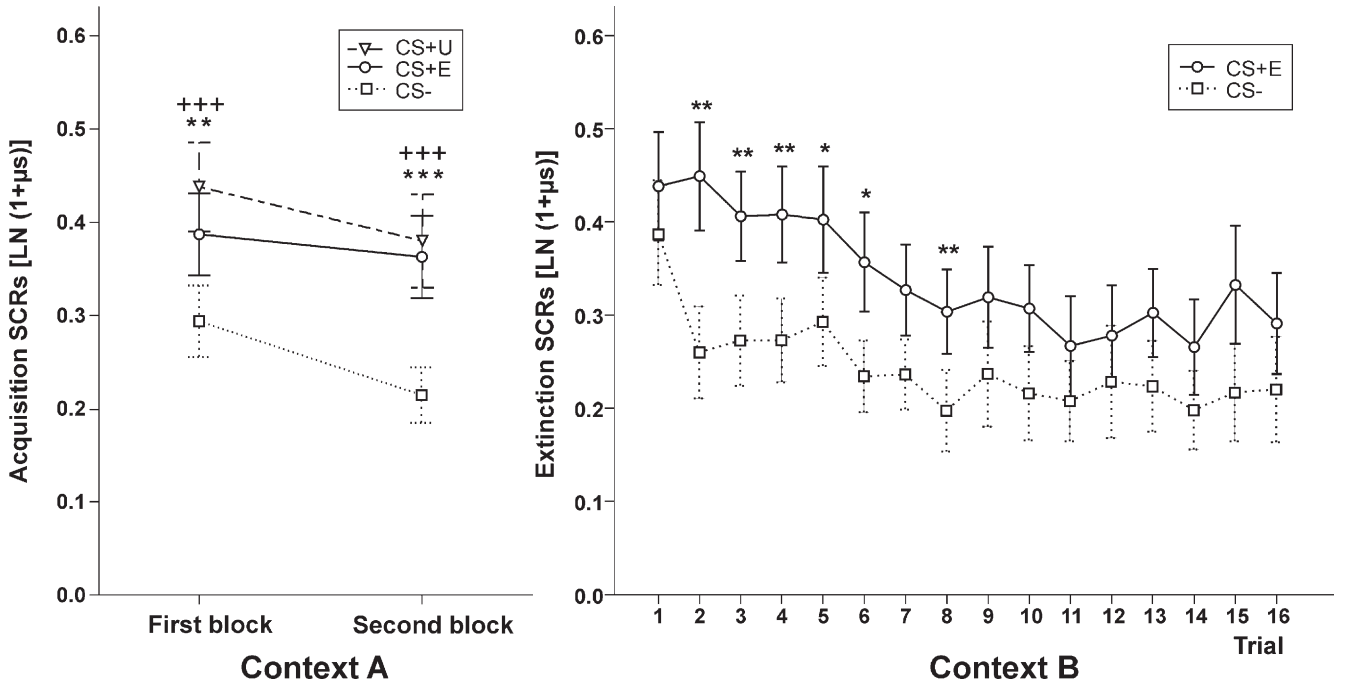

Figure 2. Mean conditioned SCRs during acquisition (day 1) in context A and extinction (day 2) in context B. Each block of acquisition comprised four trials of each CS+ and eight CS− trials. Extinction consisted of 16 unreinforced CS+E trials and 16 CS− trials. Both acquisition and extinction were successful. Significant differences between CS+E (extinguished stimulus) and CS− in dependent-sample *t* tests are indicated by ***$p < .001$, **$p < .01$, *$p < .05$. Significant differences between CS+U (unextinguished stimulus) and CS− are indicated by $^{+++}p < .001$. Error bars denote standard errors of the mean.

postconditioning) were conducted. Regarding day 1, no significant effects emerged (all *p*s > .10). Regarding day 3, the ANOVA revealed a trend towards a main effect of time, $F(1,34) = 4.03$, $p \leq .05$, reflecting a decline of cortisol concentrations from the beginning to the end of the test session. No other significant effects appeared (all *p*s > .10).

Blood pressure. Systolic and diastolic blood pressure data are given in Table 1 and were analyzed with two 2 × 3 repeated measures ANOVAs including the factors group and time (before, during, and after the SECPT/control procedure). Both ANOVAs revealed that stress increased systolic and diastolic blood pressure compared to the control condition (systolic blood pressure: Time × Group interaction, $F(2,76) = 64.22$, $p < .001$, main effects of time, $F(2,76) = 117.90$, $p < .001$, and group, $F(1,38) = 14.24$, $p < .01$; diastolic blood pressure: Time × Group interaction, $F(2,76) = 69.81$, $p < .001$, main effects of time, $F(2,76) = 91.01$, $p < .001$, and group, $F(1,38) = 10.85$, $p < .01$). *T* tests showed that systolic and diastolic blood pressure did not differ between the two groups before the experimental condition (both *p*s > .10). During hand immersion, the stress group displayed significantly elevated systolic, $t(38) = 6.89$, $p < .001$, and diastolic blood pressure, $t(38) = 7.45$, $p < .001$, compared to the control group. After the procedure, the stress group continued to show elevated systolic blood pressure, $t(38) = 2.57$, $p < .05$, while the diastolic blood pressure did not differ significantly between groups ($p > .10$).

Subjective ratings. Subjective ratings obtained after the SECPT/control procedure indicated that the stress group experienced the preceding situation to be significantly more stressful, $t(38) = 5.64$, $p < .001$, painful, $t(38) = 6.58$, $p < .001$, and unpleasant, $t(38) = 4.51$, $p < .001$, than the control group (see Table 1).

Skin Conductance Responses

Acquisition and extinction. Success of fear acquisition (see Figure 2) was tested separately for the CS+E and the CS+U relative to the CS− via two ANOVAs with the within-subjects factors CS (CS+ vs. CS−) and block (first half vs. second half of the acquisition trials) and the between-subjects factor group. Significant main effects of CS emerged (CS+E: $F(1,37) = 25.53$, $p < .001$; CS+U: $F(1,37) = 45.11$, $p < .001$), indicating differentiation between the respective CS+ and the CS−. Significant main effects of block reflect habituation of responding from the first to the second block (CS+E: $F(1,37) = 16.54$, $p < .001$; CS+U: $F(1,37) = 21.66$, $p < .001$). No other significant effects were found (all *p*s > .05).

Regarding extinction, an ANOVA with the factors CS (CS+E vs. CS−), trial (16 extinction trials), and group revealed significant main effects of CS, $F(1,38) = 16.12$, $p < .001$, and trial, $F(15,570) = 4.30$, $p < .001$, indicating habituation over successive trials. No other significant effects emerged (all *p*s > .10). As can be seen in Figure 2, there was no significant differential responding to the CS+ compared to the CS− in the last eight trials of extinction, indicating that extinction was successful.

Retrieval test phase. Figure 3 shows SCRs to the first trial of each CS in the retrieval test. Fear retrieval was analyzed separately for the CS+E and the CS+U with two ANOVAs including the within-subjects factors CS (CS+, CS−) and context (A vs. B), and the between-subjects factor group.

Analyses of group differences in responding to the extinguished CS+ compared to the CS−. Postextinction stress differentially affected SCRs to the CS+E compared to the

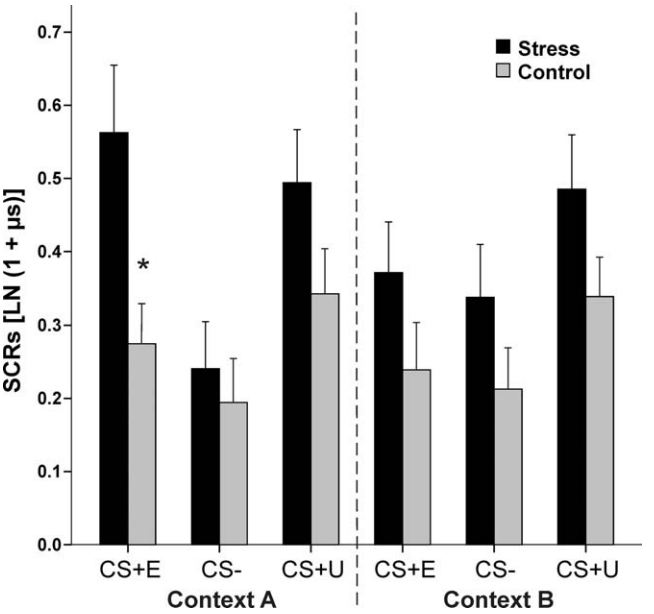

Figure 3. First trial SCRs in the retrieval test phase. Mean SCRs to the CS+E (extinguished), the CS+U (unextinguished), and the CS− are shown separately for the acquisition context A and the extinction context B (left). Compared to the control group, the stress group showed an increased fear response to the CS+E in the acquisition context, whereas the two groups' fear responses did not differ from each other in the extinction context. *Significant difference between stress and control group, $p < .05$ in t tests. Error bars indicate standard errors of the mean.

CS− (significant CS × Group interaction, $F(1,38) = 4.81$, $p < .05$), which could be traced back to higher SCRs to the CS+E in the stress group (follow-up independent sample t tests, $t(38) = -2.24$, $p < .05$), while responding to the CS− did not differ between groups ($p > .10$). In addition, the ANOVA revealed a significant main effect of CS, $F(1,38) = 16.97$, $p < .001$, and a CS × Context interaction, $F(1,38) = 4.53$, $p < .05$, indicative of a renewal effect, as participants showed differential responding to the CS+E compared to the CS− in context A (dependent sample t tests; $t(39) = 3.86$, $p < .001$), but not in context B ($p > .10$).

As we specifically hypothesized that distinct stress effects might occur in the acquisition and extinction context for the extinguished conditioned response (analogous to our previous study, Merz et al., 2014), we tested this hypothesis with two ANOVAs (one for each context) with the factors CS (CS+E, CS−) and group. Regarding context A, we found a significant main effect of CS, $F(1,38) = 16.74$, $p < .001$, and a CS × Group interaction, $F(1,38) = 5.91$, $p < .05$, reflecting that compared to controls, the stress group had larger SCRs to the CS+E, $t(38) = -2.57$, $p \leq .01$, while no such difference occurred for the CS− ($p > .10$). In context B, the ANOVA did not detect any significant effects (all ps > .10). Thus, the effects of stress appeared to be specifically apparent when retrieval was tested in the acquisition context.

Analysis of group differences in responding to the unextinguished CS+ compared to the CS−. The ANOVA involving the CS+U revealed a significant main effect of CS, $F(1,38) = 29.35$, $p < .001$, reflecting larger SCRs to the CS+U than to the CS−. No other significant effects emerged (all ps > .10). Stress did therefore not affect responding to the CS+U compared to the CS−.

Analyses of group differences in responding to the extinguished CS+ compared to the unextinguished CS+. ANOVA involving the factors CS (CS+E, CS+U), context, and group revealed a significant CS × Context interaction, $F(1,38) = 4.25$, $p < .05$, indicating that responses to the CS were modulated by context, and a trend towards a main effect of group, $F(1,38) = 3,51$, $p < .01$, reflecting a tendency of the stress group to show higher SCRs to both CS+.

Analogous to the analyses of the CS+E/CS− responses reported above, we conducted follow-up ANOVAs separately for each context. When tested in the acquisition context, the stress group showed a higher return of fear to the CS+E compared to the CS+U than the control group (significant CS × Group interaction, $F(1,38) = 4.31$, $p < .05$; additional main effect of group, $F(1,38) = 4.39$; $p < .05$; main effect of CS, *n.s.*, $p > .10$). In the extinction context, participants exhibited generally larger SCRs to the CS+U than to the CS+E (significant main effect of CS, $F(1,38) = 7.78$, $p < .01$). However, stress did not affect responding in the extinction context (all other ps > .10).

Reinstatement

Analyses of group differences in responding to the extinguished CS+ compared to the CS−. A potential reinstatement effect would be indicated by increased conditioned responding in the first reinstatement test trial compared to the last retrieval test trial (data shown in Figure 4) and was analyzed with an ANOVA including the factors time (last retrieval test trial, first reinstatement test trial), context (A, B), CS (CS+E, CS−), and group. The analysis revealed a significant main effect of time, $F(1,37) = 5.23$, $p < .05$, interactions between time and group, $F(1,37) = 5.99$, $p < .05$, and time and CS, $F(1,37) = 4.15$, $p < .05$, as well as a four-way interaction between all factors, $F(1,37) = 4.86$, $p < .05$. Follow-up analyses were then conducted separately for the acquisition and the extinction context. Regarding the acquisition context, the significant main effect of time, $F(1,37) = 5.63$, $p < .05$, and the interactions between time and group, $F(1,37) = 6.29$, $p < .05$, as well as time and CS, $F(1,37) = 10.24$, $p < .01$, persisted; trends for a main effect of group, $F(1,37) = 3.10$, $p < .10$, and an interaction between time, CS, and group, $F(1,37) = 2.95$, $p < .10$, emerged. Groupwise analysis showed that the stress group exhibited a stimulus-specific reinstatement effect (CS × Time interaction, $F(1,18) = 9.38$, $p < .01$) due to increased responding to the CS+E in the first reinstatement test trial compared to the last retrieval test trial, $t(18) = -3.57$, $p < .01$, while responding to the CS− did not increase significantly ($p > .10$). The control group showed neither a generalized nor a CS-specific reinstatement effect (all ps > .10). Regarding the extinction context, neither significant reinstatement effects nor any other effects were observed (all ps > .10).

Analyses of group differences in responding to the unextinguished CS+ compared to the CS−. Furthermore, we conducted the same analysis for the CS+U, again including the factors time, context, CS (CS+U, CS−), and group. We found significant main effects of time, $F(1,37) = 12.59$, $p \leq .001$, and CS, $F(1,37) = 4.94$, $p < .05$, and a significant interaction between time and CS, $F(1,37) = 8.80$, $p < .01$, reflecting a stimulus-specific reinstatement effect, as SCRs increased to the CS+U, $t(38) = -3.87$, $p < .001$, but not to the CS− ($p > .10$). Moreover, a significant Time × Group interaction, $F(1,37) = 8.05$, $p < .01$, indicated that the stress group showed a stronger reinstatement effect than the control group. Neither the main effect of context nor any interactions with this factor were significant (all ps > .10), suggesting that the context did not modulate reinstatement of the unextinguished CS+.

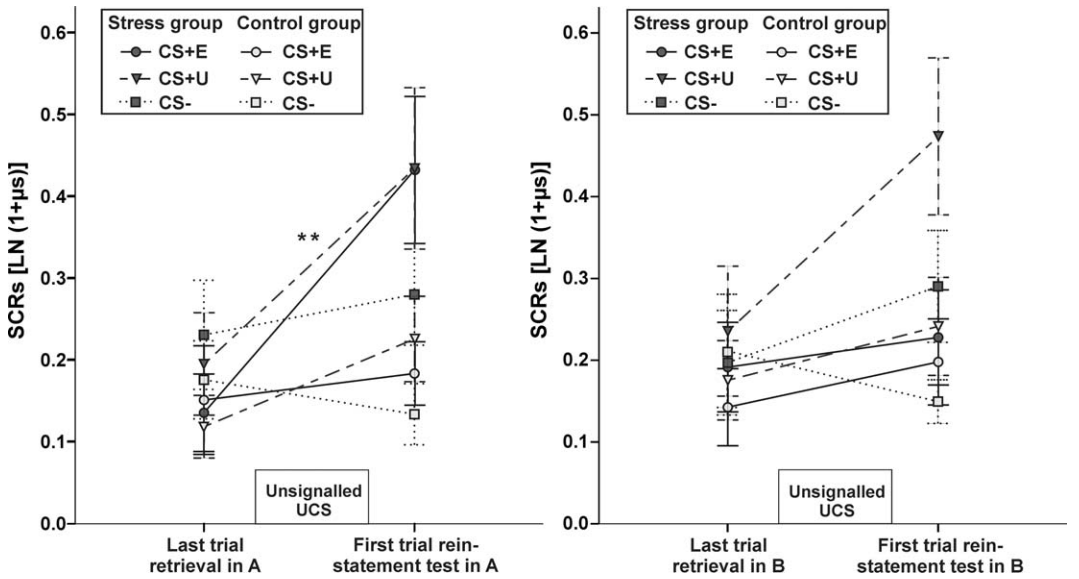

Figure 4. Conditioned SCRs in the last trial of the retrieval test phase and the first trial of the reinstatement test phase, shown separately for acquisition context A (left) and extinction context B trials (right). Compared to the control group, the stress group showed a pronounced reinstatement of fear responses to the extinguished CS+E in the acquisition context (see Results section for further effects). **Significant increase in responding to the CS+E and the CS+U in the stress group, both *p*s < .01 (*t* tests; main effects and interactions are reported in the Results section). Error bars indicate standard errors of the mean.

Analyses of group differences in responding to the extinguished CS+ compared to the unextinguished CS+. ANOVA involving the factors CS (CS+E, CS+U), context, time, and group revealed significant main effects of time, $F(1,37) = 20.12$, $p < .001$, and CS, $F(1,37) = 4.84$, $p < .05$, reflecting an increase in SCRs in the reinstatement test and generally higher SCRs to the CS+U than to the CS+E. Compared to controls, the stress group showed a more pronounced reinstatement effect, as indicated by a significant interaction between time and group, $F(1,37) = 5.30$, $p < .05$. Additionally, trends for a main effect of group, $F(1,37) = 3.29$, $p < .10$, and a four-way interaction between CS, context, time, and group emerged, $F(1,37) = 2.79$, $p \leq .10$; all other *p*s > .10.

When focusing on SCRs in the acquisition context, no effects or interactions of CS were detected (all *p*s > .10), indicating that in the acquisition context, participants did not distinguish between the extinguished and the unextinguished stimulus. However, a significant main effect of time, $F(1,37) = 20.59$, $p < .001$, reflecting an increase in SCRs, and a trend towards a main effect of group, $F(1,37) = 3.92$, $p < .10$, emerged. Stress affected SCRs in the acquisition context: Compared to the control group, the stress group showed a stronger increase in SCRs to both CS+ (Time × Group interaction, $F(1,37) = 7.08$, $p \leq .01$).

In the extinction context, in contrast, participants appeared to distinguish between the CS+U and the CS+E, as the extinguished CS elicited less fear than the unextinguished CS (significant main effect of CS, $F(1,37) = 6.88$, $p \leq .01$). Furthermore, participants showed a reinstatement effect, as indicated by an increase in SCRs to both CS+ after the reinstatement shocks (main effect of time, $F(1,37) = 6.0$, $p < .05$). No other significant effects emerged (all *p*s > .10).

Correlational analyses. Correlational analyses focused on the retrieval and reinstatement test responses to the extinguished CS+E in the acquisition context. Partial correlation analyses controlling for the factor group (stress vs. control) involved the SCRs to the CS+E in the acquisition context in the first trial of the retrieval test and the increase in SCRs from the last trial of the retrieval test to the first trial of the reinstatement test (both in the acquisition context). We did not observe any significant correlations between these two variables and the increase in cortisol concentrations in response to the stressor (day 2, calculated as area under the curve with respect to increase, according to Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) or the subjective rating of stressfulness (all *p*s > .05).

UCS Expectancy

Separate ANOVAs for the CS+E and the CS+U including the within-subjects factors CS (CS+, CS−) and context and the between-subjects factor group did not detect any effects of stress (main effects of group and interactions involving the factor group were not significant, all *p*s > .10; data shown in Table 2). The ANOVAs showed significant main effects of CS (CS+E: $F(1,38) = 109.43$, $p < .001$; CS+U: $F(1,38) = 123.03$, $p < .001$) and context (CS+E: $F(1,38) = 80.69$, $p < .001$; CS+U: $F(1,38) = 40.56$, $p < .001$), indicating higher UCS expectancy for the CS+ compared to the CS− and higher UCS expectancy in the acquisition context compared to the extinction context. In addition, a significant CS × Context interaction occurred (CS+E: $F(1,38) = 30.06$, $p < .001$, CS+U: $F(1,38) = 8.47$, $p < .01$), reflecting a higher UCS expectancy of the respective CS+ compared to the CS− in the acquisition context than in the extinction context (dependent sample *t* tests; CS+E: $t(39) = 5.55$, $p < .001$; CS+U: $t(39) = 2.95$, $p < .01$).

Comparing UCS expectancy regarding the extinguished and the unextinguished CS+ via ANOVA showed that participants indicated a higher UCS expectancy in the acquisition context than in the extinction context (main effect of context, $F(1,38) = 64.23$, $p < .001$) and a higher UCS expectancy for the CS+U than for the CS+E (main effect of CS, $F(1,38) = 6.48$, $p < .05$), which was

Table 2. *Mean UCS Expectancy of the Stress and Control Group in the Acquisition and Extinction Context (A or B, Respectively) Obtained after the Reinstatement Test Phase*

	Control	Stress
Context A		
CS+E	6.6 ± 2.3	6.0 ± 2.3
CS+U	6.3 ± 2.3	6.7 ± 2.2
CS–	2.4 ± 1.8	1.9 ± 1.4
Context B		
CS+E	3.6 ± 2.5	2.9 ± 1.9
CS+U	4.5 ± 2.1	4.7 ± 2.3
CS–	1.9 ± 1.5	1.1 ± 0.3

Note. UCS expectancy referred to the beginning of the retrieval test phase and was rated on 9-point scales ranging from 1 (*sure that the electrical stimulation will not follow the respective CS presentation*) to 5 (*unsure*) to 9 (*sure that it will follow the respective CS presentation*). Stress did not significantly affect UCS expectancy ratings.

modulated by the context (significant CS × Context interaction, $F(1,38) = 7.24$, $p \leq .01$; no other significant effects emerged, all ps $> .10$). Follow-up dependent sample t tests revealed that participants did not distinguish between the CS+E and the CS+U in the acquisition context ($p > .10$), but exhibited a lower UCS expectancy for the CS+E compared to the CS+U in the extinction context, $t(39) = -3.21$, $p < .01$.

Discussion

The present study investigated the effects of stress on the consolidation of fear extinction memory in a 3-day fear acquisition, extinction, and retrieval/reinstatement paradigm. Participants demonstrated successful fear acquisition and extinction, which, as expected, did not differ between the two experimental groups. Success of stress induction directly following the extinction learning phase was demonstrated by increased salivary cortisol concentrations, blood pressure, and subjective ratings in the stress group. In the retrieval test conducted 24 h later, we observed renewal and reinstatement of fear responses in the acquisition context, while participants did not show a return of fear in the extinction context, thus demonstrating good retention of extinction memory. Consistently, fear responses to the extinguished CS did not differ from responses to the unextinguished CS in the acquisition context, but were significantly lower in the extinction context. Postextinction stress predominantly affected responding in the acquisition context, as in this context specifically the stress group showed a stronger fear response to the extinguished CS+ than the control group. This was evident in both the retrieval and the reinstatement tests. Fear responses to the unextinguished CS+ did not differ between groups in the retrieval test; however, the stress group exhibited a generally stronger increase in responding compared to the control group.

The context-dependent return of fear in response to the CS+E in the stress group might be due to stress enhancing the consolidation of contextual cues, thus making extinction memory more context dependent. This would be in line with findings from animal studies showing that GCs contribute to the consolidation of contextual fear (Pugh, Tremblay, Fleshner, & Rudy, 1997). Similarly, we also found context-dependent effects of postextinction stress on the consolidation of extinction memory in a predictive learning task (Hamacher-Dang et al., 2013). However, the direction of effects was somewhat contrary to the present results as, in the former study, the stress group exhibited a reduced recovery of responding in the extinction context, whereas responding in the acquisition context did not differ between groups (Hamacher-Dang et al., 2013). This could be explained by differences in the applied tasks (fear conditioning vs. predictive learning), the emotionality (aversive vs. neutral), and/or the dependent measures (SCRs vs. button-press responses). Likewise, we also observed a discrepancy between predictive learning and fear conditioning with regard to stress effects on extinction memory retrieval (Merz et al., 2014). An alternative explanation for the observed effects could be that stress impaired the consolidation of extinction memory, which would be in line with the results of a rodent study (Akirav et al., 2009). However, as we did not find reduced retrieval of extinction memory in the extinction context, neither in the retrieval nor in the reinstatement test, the account of a generally impaired extinction memory in the stress group seems rather implausible.

In this study, we did not observe significant correlations between responses to the extinguished CS+ in the retrieval and reinstatement tests (day 3) and the increase in cortisol concentrations in response to the stressor (day 2, calculated as area under the curve with respect to increase, according to Pruessner et al., 2003) or the subjective rating of stressfulness. The observed differences between the stress and control group possibly do not reflect a linear dose-response relationship, or were driven by SNS activation in interaction with cortisol (according to the model proposed by Roozendaal, McEwen, & Chattarji, 2009; Roozendaal & McGaugh, 2011). Further reasons for the absence of a significant correlation may include interindividual differences in cortisol sensitivity and the relatively small sample size.

Studies administering GCs as adjuncts to exposure therapy sessions have typically observed superior extinction memory retention at follow-up testing (Bentz et al., 2010; de Quervain et al., 2011; Soravia et al., 2006, 2014). However, these studies differed in several aspects from the current one. Perhaps most importantly, they administered GCs at the beginning of the exposure therapy sessions, which, as we suggest, might render stress or cortisol effects on memory less dependent on the context (Schwabe et al., 2009) instead of increasing the context dependency. Consistently, a recent study reported timing-dependent effects of cortisol on memory contextualization in healthy men and found that rapid effects of cortisol (administered 30 min before learning) impaired memory contextualization (van Ast, Cornelisse, Meeter, Joels, & Kindt, 2013). Furthermore, differences may also be due to stress-induced concurrent activation of the SNS, which is usually absent in pharmacological studies, and/or due to different cortisol concentrations (a moderate increase caused by the SECPT compared to supraphysiological cortisol concentrations following GC administration). Future studies could rule out these possibilities by directly comparing pre- and postextinction GC and stress effects. Importantly, our findings indicate that the timing of stress induction or GC administration may be very critical, which is in line with well-known timing-dependent effects of stress on declarative memory (for reviews, see Joels, Fernandez, & Roozendaal, 2011; Schwabe, Joels, Roozendaal, Wolf, & Oitzl, 2012). This is also highly relevant for the clinical application of GCs, because suboptimal timing of GC administration might favor the context-dependent return of fear rather than reduce it. In addition, the findings of this study suggest that exposure to stress should be avoided after extinction-based psychotherapeutic treatments, as it might increase the probability for relapse outside the therapeutic context.

Interestingly, we observed a stimulus-specific (differential) reinstatement of fear in the stress group. Such a differential return of fear has been reported in several studies on reinstatement in humans (e.g., Hermans et al., 2005; LaBar & Phelps, 2005; Norrholm et al., 2006), although the question still remains which specific factors lead to differential reinstatement or rather cause a generalized return of fear to all CS, which has also frequently been found (Dirikx, Vansteenwegen, Eelen, & Hermans, 2009; Haaker, Lonsdorf, Thanellou, & Kalisch, 2013; Kull, Müller, Blechert, Wilhelm, & Michael, 2012; Milad, Orr, Pitman, & Rauch, 2005). A potential explanation based on our results could be that timing-dependent effects of stress or stress hormones might play a role in this. As reinstatement is a clinically relevant phenomenon that has frequently been used as a model for drug relapse in animal studies (for a review, see Bossert, Marchant, Calu, & Shaham, 2013) and could also serve to explain reemergence of phobic fear in contexts that induce a feeling of anxiety or insecurity, further research on the underlying mechanisms of differential and generalized reinstatement would be desirable.

Another important factor influencing reinstatement may be the context: In this study, we administered unsignaled UCS during presentation of a gray screen, similar to previous reinstatement studies (Kull et al., 2012; discussed in more detail in Haaker et al., 2013). In the control group, UCS application alone could have been not strong enough to trigger fear to the CS+E, which itself was embedded in the context of the room pictures. In the stress group, with their assumedly more context-dependent extinction memory, UCS application might have preferably activated fear acquisition memories in the associated context, thereby leading to a return of fear to the CS+E specifically during acquisition context presentation. The assumption that stress made extinction memory more context dependent is also supported by the observation that the return of fear to the CS+U, which was not shown during extinction, was not modulated by the context, and did not differ between groups in the retrieval test.

This study focused on male participants only, which potentially limits the generalizability of our results. Stress or cortisol effects on fear acquisition and extinction have been shown to differ between men and women (e.g., Jackson, Payne, Nadel, & Jacobs, 2006; Merz et al., 2010, 2013), and fear extinction memory has been reported to be influenced by sex hormones (e.g., Lebron-Milad & Milad, 2012; Milad et al., 2010). Thus, future studies should also focus on potential sex differences in stress effects on extinction memory consolidation.

In our study, we applied a previously established fear conditioning paradigm, which has been used to study extinction and renewal in human participants and patient population (e.g., Milad et al., 2007, 2009). This design, however, could be criticized for its fixed trial order and the number of CS− trials relative to CS+ trials. For instance, due to the different numbers of trials showing the unextinguished CS+ (i.e., eight) compared to the CS− (i.e., 16), and the extinguished CS+ (i.e., eight) compared to the CS−, it is possible that at least a portion of the differential responses to the two CS+ compared to the CS− during acquisition are due to nonassociative processes (i.e., differential orienting responses or differential habituation). In order to rule out these alternative explanations, future study designs should fully counterbalance CS presentation order and the number of trials per CS in the acquisition phase.

In the present study, we did not find an effect of stress on UCS expectancy ratings. This might indicate that stress affected mostly the more emotional component of fear (SCRs) while leaving more cognitive aspects (UCS expectancy) unaltered. However, in order not to interfere with SCRs, ratings were obtained only after the end of the reinstatement test, which potentially limits their sensitivity. Future studies could aim at incorporating expectancy ratings at several time points of the conditioning procedure to allow for a tracing of changes over time (e.g., as in Haaker et al., 2013).

To conclude, our findings suggest that stress after extinction learning exerts an enhancing effect on the consolidation of contextual cues, leading to a stronger return of fear in the acquisition context. This could be especially relevant for clinical studies trying to reduce the return of fear, as in these cases, stressful events directly after exposure sessions should be avoided.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1: This section presents additional information on the randomization procedure used to define the stimulus presentation order in the acquisition, extinction, and retrieval/reinstatement test phases.