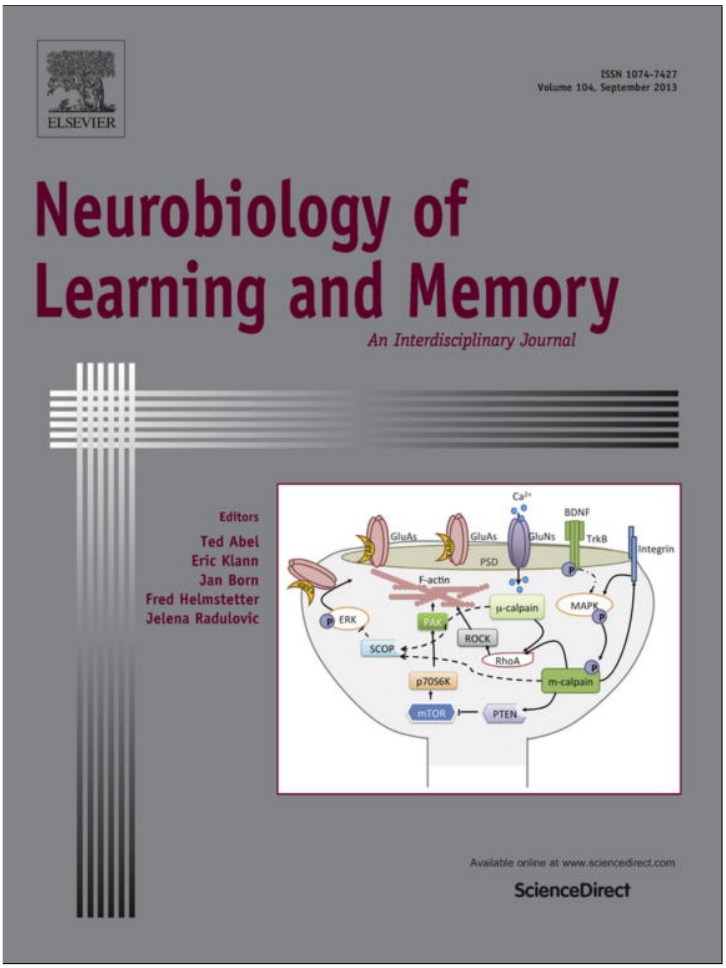

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Stress impairs retrieval of extinguished and unextinguished associations in a predictive learning task

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ABSTRACT

Recovery effects which can frequently be observed after a seemingly successful extinction procedure indicate that extinction does not lead to an erasure of the memory trace. Investigating factors which modulate the retrieval of extinction memory is highly relevant for basic science and clinical applications alike. This study investigated the effect of stress on the retrieval of extinguished and unextinguished stimulus-outcome associations in a predictive learning task. In this task, participants had to imagine being the doctor of a patient who sometimes suffers from stomach trouble after meals in his favorite restaurants. They were presented with different food stimuli while having to predict the occurrence or non-occurrence of stomach trouble. As extinction memory is modulated by context, we manipulated contextual cues so that initial acquisition of critical associations occurred in context (restaurant frame) A on day one, whereas associations were reversed in context B (extinction, day two). On the third day, participants were either stressed (exposed to the socially evaluated cold pressor task (SECPT); $n = 21$) or subjected to a control condition ($n = 21$) shortly before extinction memory retrieval was tested (in contexts A and B). Salivary cortisol and blood pressure measures as well as subjective ratings indicated that stress induction was successful. When retrieval of extinguished associations was tested on day three, participants' predictions reflected a renewal effect, as indicated by stronger recovery of responding in the acquisition context compared to the extinction context. Compared to controls, stressed participants showed impaired retrieval of extinguished and unextinguished associations. Contextual cues abolished the stress-induced memory impairment for unextinguished but not for extinguished associations. These findings might help to explain why stress leads to the reoccurrence of symptoms in affective disorders.

1. Introduction

To achieve a permanent extinction of a learned response is not an easy task to solve: often, the extinguished response recovers and shows up again (Bouton, 2002; Bouton & Swartzentruber, 1991; Delamater, 2004; Myers & Davis, 2007; Quirk & Mueller, 2008; Rescorla & Heth, 1975). This recovery indicates that extinction, which in Pavlovian conditioning is achieved by repeated exposure to the conditioned stimulus (CS) without presenting the unconditioned stimulus (US), does not lead to an erasure of the memory trace. Rather, extinction constitutes a form of new learning, which establishes a second meaning of the CS (Bouton, 1993, 2002; Myers & Davis, 2002). Which meaning of the now ambiguous CS will be retrieved depends on the context, with extinction being more context-dependent than acquisition. Thus, when the CS is encountered in a context different to the extinction context, a recovery of responding takes place. In animal (Bouton & Bolles, 1979; Bouton & Peck, 1989) as well as human (Milad, Orr, Pitman, & Rauch, 2005; Rosas, Javier, Lugo, & Lopez, 2001) studies, this has often been observed when conditioning in one context (A) was followed by extinction in another context (B): Retention testing back in context A leads to a recovery of responding (ABA renewal effect). Spontaneous recovery, which can be observed after some time has passed by since extinction took place (first described by Pavlov, 1927), can also be considered as a renewal effect, because the passage of time itself constitutes a temporal context (Bouton, 1993, 2004).

With regard to the underlying brain structures, the hippocampus (HC) and the prefrontal cortex (PFC) have been suggested to be crucially involved in the retrieval of extinction memory (Kalisch

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et al., 2006; Milad et al., 2007; for a review of the neuronal fear extinction network, see Herry et al., 2010). Importantly, these brain structures have been demonstrated to be specifically susceptible to the effects of stress (for reviews, see Arnsten, 2009; Herry et al., 2010; Kim, Song, & Kosten, 2006). Stress via its associated neuroendocrine alterations (in humans, mostly noradrenaline and cortisol are secreted during stress) has been shown to modulate learning and memory (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Roozendaal, McEwen, & Chattarji, 2009; Sandi & Pinelo-Nava, 2007; Schwabe, Wolf, & Oitzl, 2010; Wolf, 2009). Specifically, effects of stress or glucocorticoids (GCs) on memory have been reported to require an interaction between GCs and noradrenergic activation (Kuhlmann & Wolf, 2006; Roozendaal & McGaugh, 2011; Roozendaal et al., 2009).

Regarding memory retrieval, the impairing effects of stress on declarative/episodic memory are well known (for reviews, see Roozendaal & McGaugh, 2011; Wolf, 2009). For example, humans exposed to a laboratory stressor had more difficulties to retrieve a previously learned word list (Buchanan, Tranel, & Adolphs, 2006; Kuhlmann, Piel, & Wolf, 2005; Smeets, 2011). For the retrieval of extinction memory, the picture is less clear. Initial evidence for an impairing effect of acute stress on extinction memory retrieval in rats has recently been reported (Deschaux et al., 2013). Consistently, studies applying chronic stress in rodents (Garcia, Spennato, Nilsson-Todd, Moreau, & Deschaux, 2008; Miracle, Brace, Huyck, Singler, & Wellman, 2006) showed that chronic stress impairs the retrieval of extinction memory. A fear conditioning study in humans showed that the recall of the extinction memory is impaired in patients with posttraumatic stress disorder (PTSD) compared to healthy controls (Milad et al., 2009). However, whether acute stress is capable of impairing the retrieval of extinction memory in humans still has to be investigated.

As extinction is often applied in the psychotherapeutic treatment of anxiety disorders, this question is also of clinical importance. Are patients in a stressful situation thus more likely to experience relapse? Studies showing links between stress and relapse in alcohol and drug dependence (for reviews, see Breese et al., 2005; Schwabe, Dickinson, & Wolf, 2011; Uhart & Wand, 2009) or between stress and the return of fear in phobias (Jacobs & Nadel, 1985) suggest this might be the case.

Effects of stress on context-dependent declarative memory retrieval have been investigated in one previous study. Strong contextual cues were able to prevent the retrieval impairing effect of stress (Schwabe & Wolf, 2009). In order to investigate the potential modulatory role of stress on the context dependency of the extinction memory, we applied the ABA renewal paradigm in the form of a predictive learning task (adapted from Üngör & Lachnit, 2006). On three consecutive days, participants underwent an acquisition phase, an extinction phase during which feedback was reversed and a renewal test phase. As means of stress induction, we conducted the socially evaluated cold pressor test (SECPT; Schwabe, Haddad, & Schachinger, 2008) on day 3 shortly before the renewal test took place.

We expected that stress has a stronger effect on the retrieval of the more recently established extinction memory trace (Kuhlmann et al., 2005; Wolf, Schommer, Hellhammer, Reischies, & Kirschbaum, 2002), which is also more dependent on stress sensitive brain regions (PFC and HC). Moreover, since contextual cues have been shown to reduce the effects of stress on memory retrieval (Schwabe & Wolf, 2009), we predicted that stress would enhance the context dependency of the extinction memory, thereby potentiating the renewal effect. Regarding performance to unextinguished stimuli, we expected an impairing effect of stress on memory retrieval when the stimuli are shown in a context different from the one in which they have been trained.

2. Methods

2.1. Participants and general procedure

In total, 49 participants recruited via advertisement and flyers at the Ruhr University Bochum took part in this study. Due to outlier values in salivary cortisol (more than 1.5 inter-quartile-ranges above the upper quartile), one participant of the control condition was excluded from all analyses. Six more participants were excluded from analyses because they did not reach the learning criterion (adopted from Üngör & Lachnit, 2006, see below). The remaining sample comprised 12 men, 9 women in the stress group and 13 men, 8 women in the control group; age: $M = 24.0$ years, $SD = 4.1$; body mass index (BMI): $M = 22.7$ kg/m^2, $SD = 2.1$. Men and women were equally randomized to the experimental conditions.

Exclusion criteria checked beforehand in a telephone interview comprised use of hormonal contraceptives, smoking, chronic or acute illnesses, and intake of medicine. Women were tested only outside their menses (menstrual cycle phase was assessed via self-report). Furthermore, participants were advised to refrain from physical exercise and consumption of food and drinks except water within one hour prior to testing on the last testing day. In addition, participants were asked not to consume alcohol or any other kinds of drugs within the whole testing period. Participants provided written informed consent before the experiment started and were reimbursed with 25€ for their participation at the end of their testing session. The study was approved by the local ethics committee.

In order to control for circadian variations in cortisol concentrations and in line with previous experiments from our group on stress and memory retrieval (e.g., Kuhlmann et al., 2005), testing took place in the mornings of three consecutive days (between 9 am and 12 pm). On day 1, participants received acquisition training in a computer-based predictive learning paradigm. On the following day, they proceeded with this task and underwent extinction training. On the third day, participants were exposed to a stressor or a control condition. Twenty minutes later, they were tested for renewal of the previously extinguished response.

2.2. Predictive learning task

A slightly modified version of the predictive learning task developed by Üngör & Lachnit, 2006, was applied. In this task, participants had to imagine being the doctor of a patient who sometimes suffers from stomach trouble after his meals in two different restaurants (named "the jar" and "the dragon" translated from German). The main ingredient of the meal and the respective restaurant (shown as a colored frame around the food stimulus in the centre) were presented to the participant who then had to predict whether the patient will suffer from stomach trouble after this meal. After responding, feedback about the correctness of the response appeared on the screen. As food stimuli, pictures of fruits and vegetables were used (e.g., apple, carrot, banana, cucumber).

Table 1 illustrates the allocation of stimuli to the two contexts and the respective outcomes (stomach trouble/no stomach trouble). In the acquisition and the extinction phase of the task, twelve stimuli were presented ten times each (so that there were ten trials for each stimulus). Trial order was randomized block-wise: In each block, all stimuli of the respective learning phase were presented two times. Thus, the acquisition and extinction phase comprised five blocks each. The order of presentation of the stimuli was randomized within each block. Directly before extinction started, one block of reminder trials from the acquisition phase were given.

In the renewal test phase, we tested the memory for four critical stimulus-outcome associations in two contexts. Stimuli a and b

Table 1
Stimuli presented during acquisition, extinction and renewal test. Letters a – v represent different stimuli (for each participant, fruit and vegetable pictures were assigned randomly to these letters); signs indicate the feedback given to the participant (+ causes stomach trouble, – does not cause stomach trouble, ? feedback omitted). The critical stimuli a, b, e and g are highlighted in bold.

	Day 1: Acquisition	Day 2: Extinction	Day 3: Renewal test
Context A	**a+, b+,** o+, c–, d–, p–	k+, l+, s+, m–, n–, t–	**a?, b?, e?, g?**
Context B	**e+,** f+, q+, **g–,** h–, r–	**a–, b**–, u–, i+, j+, v+	**a?, b?, e?, g?**

had been associated with stomach trouble in context A on day 1 (acquisition phase), whereas they had not been associated with stomach trouble anymore in context B on day 2 (extinction phase). In the renewal test phase, stimuli a and b were presented in both the former acquisition and the extinction context without feedback. As stimuli a and b were identical with respect to their contingencies, data was averaged over the two stimuli (subsequently named as stimulus a/b+ to indicate the stomach trouble association in the acquisition phase). In addition, memory for two stimuli which had only been presented during the acquisition phase but not during the extinction phase was tested. Stimulus e had been associated with stomach trouble (subsequently named e+), whereas stimulus g had not been associated with stomach trouble (indicated as g–). In the renewal test phase, stimuli e+ and g– were presented in both their former acquisition context B and the other context (A) in which they had not been shown before ('new' context). The renewal test phase consisted of four trials per stimulus-context combination; randomized in two blocks comprising two stimulus-presentations each (so that each block contained two presentations of all stimulus-context combinations in randomized order). Performance in the renewal test was assessed based on the first two presentations of each stimulus-context combination (first block).

Accomplishment of the learning criterion (adopted from Üngör & Lachnit, 2006) was assessed based on performance during the last two blocks of the acquisition and the extinction phase. Participants were excluded from analysis if they made more than 9 incorrect predictions during these four blocks. As mentioned above, six participants had to be excluded.

2.3. Stress and control procedure

The SECPT was conducted according to its description in Schwabe et al., 2008. In brief, the stress protocol comprised immersion of the participant's right hand into a basin with ice-cold water (0–3 °C) for three minutes while being videotaped and monitored by a reserved experimenter. In the control procedure, participants immersed their right hand into a basin filled with warm water (36–37 °C) without being monitored or videotaped.

2.3.1. Blood pressure measurements

As markers of SNS activity, blood pressure was measured before, during and after (five minutes post SECPT) stress induction. The measures were obtained using Dinamap vital signs monitor (Critikon, Tampa, FL; cuff placed on the left upper arm).

2.3.2. Saliva sampling and cortisol analysis

Saliva was collected to assess free cortisol levels (Kirschbaum & Hellhammer, 1994) as a marker of HPA axis activity. The samples were collected using Salivette sampling devices (Sarstedt, Nümbrecht, Germany) one minute before stress induction as well as 20 and 25 min after stress induction. Free salivary cortisol levels (ELISA; IBL International, Hamburg, Germany) have been analysed with commercial assays. Inter and intra assay variations were below 10%. Due to insufficient amounts of collected saliva or due to sample contamination, the data from six participants were incomplete and could thus not be included in the analysis of the cortisol data.

2.3.3. Subjective ratings

Immediately after the SECPT or control manipulation, participants rated on a scale from 0 ("not at all") to 100 ("very much") how stressful, painful and unpleasant they had felt during the previous situation (rating method adopted from Schwabe et al., 2008).

2.4. Statistical analyses

For all statistical tests, the level of significance was set to .05. For repeated measures analyses of variance (ANOVA), Huynh-Feld corrected p-values were reported if assumptions of sphericity were not met. P-values of exploratory t-tests were corrected for unequal variances if appropriate. Partial correlation analysis controlling for the factor 'group' (stress vs. control) included the following variables: Salivary cortisol concentration directly before the renewal test (i.e. 20 min after SECPT/control condition), systolic blood pressure during SECPT/control, an interaction between cortisol and systolic blood pressure, subjective stressfulness rating, and a performance variable reflecting the overall difference between performance in the acquisition context vs. the extinction/'new' context (averaged over the stimuli a/b+, e+, and g–; subsequently named as context dependency). Cortisol, systolic blood pressure, and their interaction were also included as independent variables in a linear regression analysis to assess whether one of them explains a significant proportion of variance in the dependent variable context dependency.

3. Results

3.1. Physiological and subjective stress responses

Both physiological as well as subjective measures confirmed that the SECPT successfully induced stress.

3.1.1. Salivary cortisol

Compared to the control condition, the SECPT elicited a significant increase in salivary cortisol concentrations (see Table 2). This is reflected by a significant group x time interaction ($F(2, 68) = 3.71$, $p = .05$, $\eta^2 = .10$) in a 3 × 2 ANOVA with the within-subjects factor time and the between-subjects factor condition. Main effects of group or time were not significant (both $p > .10$). The two groups did not show a significant difference before the treatment ($t(34) = 0.82$, $p > .41$). Twenty minutes after the SECPT or control condition (at the beginning of the renewal testing), the stressed participants had significantly higher cortisol concentrations than the controls ($t(34) = 2.88$, $p = .01$). After the renewal testing the two groups continued to differ ($t(34) = 2.31$, $p = .03$).

3.1.2. Blood pressure

During hand immersion, systolic and diastolic blood pressure significantly increased in the stress group, but not in the control condition (group × time interactions for systolic and diastolic blood pressure, both $F(2, 80) > 24$, both $p < .001$, both $\eta^2 > .37$).

Table 2
Subjective ratings of and salivary cortisol as well as blood pressure responses to the stress vs. control condition.

	Control	Stress
Salivary cortisol (nmol/l)		
Before treatment	13.90 ± 6.4	16.02 ± 7.1
20 min after treatment	10.97 ± 4.9	17.38 ± 8.8*
25 min after treatment	10.64 ± 5.6	16.66 ± 9.1*
Systolic blood pressure (mmHg)		
Before treatment	122.1 ± 11.9	118.9 ± 14.7
During treatment	118.6 ± 12.7	129.4 ± 15.2*
After treatment	114.3 ± 11.7	112.8 ± 13.3
Diastolic blood pressure (mmHg)		
Before treatment	69.0 ± 8.6	68.0 ± 10.6
During treatment	67.6 ± 7.1	77.6 ± 10.1**
After treatment	67.1 ± 7.8	64.5 ± 8.7
Subjective ratings		
Stressfulness	4.2 ± 7.8	41.7 ± 28.7**
Painfulness	1.7 ± 4.8	54.2 ± 28.4**
Unpleasantness	5.8 ± 9.3	49.6 ± 25.8**

Stressfulness, painfulness and unpleasantness were rated on a scale from 0 ("not at all") to 100 ("very much"). Data represent means ± standard deviation (SD).
* Significant difference between stress and control group, $p < .05$.
** Significant difference between stress and control group, $p < .001$.

Both before and after hand immersion, the two groups did not differ in this respect (see Table 2).

3.1.3. Subjective ratings

As shown in Table 2, participants of the stress group rated their experience significantly more stressful ($t(40) = 6.03$, $p < .001$), painful ($t(40) = 8.05$, $p < .001$), and unpleasant ($t(40) = 7.21$, $p < .001$) than participants of the control group.

3.2. Predictive learning task

Fig. 1 presents the mean percentage of participants making a stomach trouble prediction on each trial across the acquisition and extinction phase.

To assess performance during acquisition and extinction, we calculated the mean percentage of stomach trouble predictions across the first two trials (beginning) and the last two trials (end) of each phase. For the acquisition phase, data was averaged over stimuli a/b+ and e+ as they reflected identical contingencies during this phase.

For the acquisition phase, a 2 × 2 × 2 ANOVA with the within-subjects factor time (beginning vs. end), outcome (stimuli a/b+ and e+ vs. stimulus g−) and the between-subjects factor group (stress vs. control) was conducted. The ANOVA revealed a significant main effect of time ($F(1, 40) = 13.79$, $p < .01$, $\eta^2 = .26$) and a main effect of outcome ($F(1, 40) = 654.0$, $p < .001$, $\eta^2 = .94$), reflecting a greater number of stomach trouble predictions to stimuli a/b+ and e+ than to stimulus g−. The analysis also showed a significant interaction between time and outcome ($F(1, 40) = 125.12$, $p < .001$, $\eta^2 = .76$) indicating the increased differentiation between the stimuli associated with stomach trouble (stimuli a/b+ and e+) and the stimulus which was not associated with stomach trouble (stimulus g−) at the end of the learning phase compared to its beginning. Neither the main effect of group nor any interactions between group and the other factors reached significance (all $p > .55$, all $\eta^2 < .01$), confirming that the stress group did not differ from the control group during acquisition.

For the extinction phase, a 2 × 2 ANOVA with the factors time (beginning vs. end) and group (stress vs. control) revealed a significant main effect of time ($F(1, 40) = 149.72$, $p < .001$, $\eta^2 = .79$), indicating a decreased number of stomach trouble predictions to stimulus a/b+ at the end of extinction compared to its beginning. The factor group and the interaction between group and time were not significant (all $p > .39$, all $\eta^2 < .02$), demonstrating that the two groups did not differ during extinction.

For the renewal test phase, "Yes"-predictions to stimulus g− as well as "No"-predictions to stimulus e+ were considered incorrect, thus reflecting impaired memory retrieval. Performance regarding stimulus e+ was therefore recoded to indicate the percentage of incorrect predictions (i.e., the percentage of "No"-responses) in the renewal test. Data was then averaged over CS e+ and g− (subsequently named stimulus e+/g−), as they had a similar learning history. Fig. 2 shows the mean percentage of participants making incorrect predictions to the extinguished stimulus a/b+ and the unextinguished stimulus e+/−g during the renewal test phase (averaged across the first two stimulus presentations). Performance is shown separately for acquisition context trials and extinction context/new context trials. A 2 × 2 × 2 ANOVA with the within-subjects factors stimulus (extinguished stimulus a/b + vs. unextinguished stimulus e+/g−) and context (acquisition

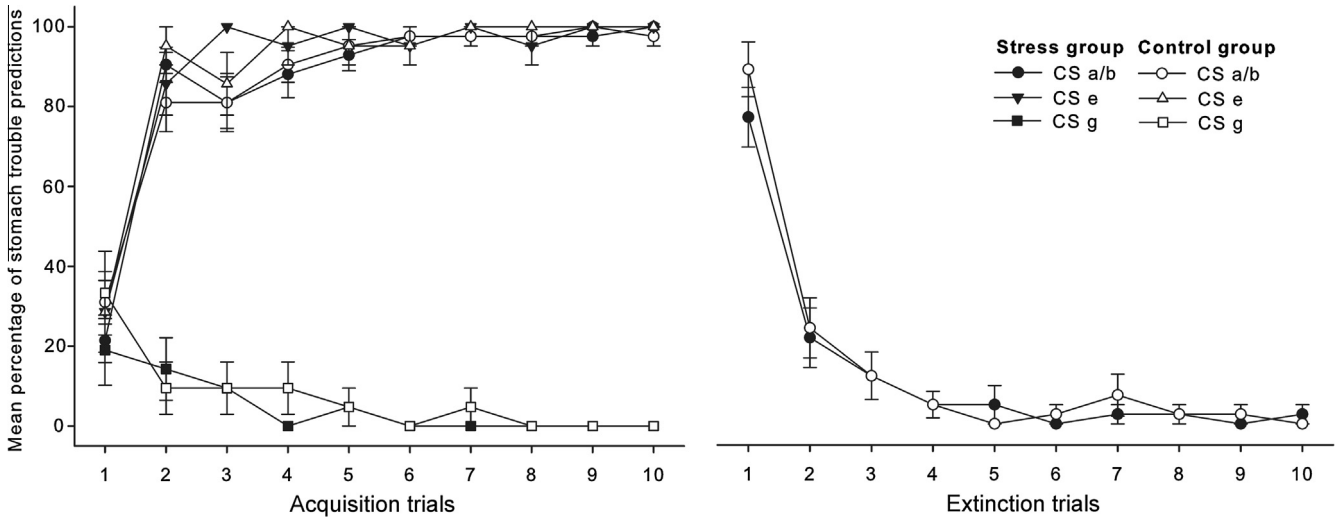

Fig. 1. Mean percentage of stomach trouble predictions to stimuli (CS) a/b+, e+, and g− during the ten trials of the acquisition phase (day 1, left side of the graph) and to CS a/b+ during the ten extinction trials (day 2, right side). CS a/b+ were presented in context A during acquisition and in context B during extinction. CS e+ and g− were presented in context B during acquisition and not shown during the extinction phase. Error bars denote standard errors of the mean.

phase context vs. extinction phase/'new' context) and the between-subjects factor condition (stress vs. control) revealed a significant main effect of stimulus ($F(1, 40) = 38.53$, $p < .001$, $\eta^2 = .49$), indicating that the unextinguished associations were retrieved better than the extinguished ones. Participants made more incorrect predictions in the acquisition context than in the extinction context, which is reflected by a significant main effect of context ($F(1, 40) = 9.20$, $p < .01$, $\eta^2 = .19$). The main effect of condition ($F(1, 40) = 9.57$, $p < .01$, $\eta^2 = .19$) indicated that control participants showed better memory retrieval than stressed participants. The analysis also revealed significant interactions between stimulus and context ($F(1, 40) = 35.13$, $p < .001$, $\eta^2 = .47$) and a three-way interaction between stimulus, context, and condition ($F(1, 40) = 4.97$, $p = .03$, $\eta^2 = .11$). Interactions between stimulus and condition ($p = .35$, $\eta^2 = .02$) as well as between context and condition ($p = .42$, $\eta^2 = .02$) were not significant.

In order to characterize the 3 way interaction further, two 2 × 2 ANOVAs with the factors stimulus (extinguished CS a/b+ vs. unextinguished CS e+/g−) and condition (stress vs. control) were conducted. With regard to performance in the acquisition context, the ANOVA showed a significant main effect of stimulus ($F(1, 40) = 85.98$, $p < .001$, $\eta^2 = .68$) as well as a significant stimulus × condition interaction ($F(1, 40) = 6.23$, $p = .02$, $\eta^2 = .14$). The main effect of condition did not reach significance ($p = .08$, $\eta^2 = .08$). Exploratory t-tests indicate that stressed participants exhibited a more severe impairment of extinction memory retrieval than controls, as they made significantly more incorrect predictions to stimulus a/b+ in the acquisition context than participants of the control group ($t(40) = 2.41$, $p = .02$, $d' = 0.74$). In contrast, memory of the unextinguished stimulus-outcome associations was not affected by stress, as the predictions of the two groups to stimulus e+/g− in the acquisition context did not differ significantly ($p > .42$, $d' = .25$). Regarding performance in the extinction/new context, the ANOVA revealed a main effect of condition ($F(1, 40) = 9.14$, $p < .01$, $\eta^2 = .19$), indicating that in this context, memory retrieval of both the extinguished and the unextinguished stimulus-outcome associations was impaired under stress. The main effect of stimulus ($p = .70$, $\eta^2 < .01$) and the interaction between stimulus and condition ($p = .33$, $\eta^2 = .02$) were not significant.

To assess effects of stress on renewal of stimulus a/b+, we conducted a 2 × 2 ANOVA with the factors context (acquisition vs. extinction) and group (stress vs. control). The ANOVA showed a significant main effect of context, $F(1, 40) = 27.66$, $p < .001$, $\eta^2 = .41$, indicating that on day 3, participants made more incorrect predictions to stimulus a/b+ in the acquisition context A than in the extinction context B (renewal effect). Stressed participants showed a higher number of incorrect responses than the controls, which is indicated by a significant main effect of condition ($F(1, 40) = 6.41$, $p = .02$, $\eta^2 = .14$). The interaction between context and condition was not significant ($p > .39$, $\eta^2 = .02$).

Regarding stimulus e+/g−, which had not been presented during the extinction phase, a 2 × 2 ANOVA with the factors context (old vs. 'new'), and condition (stress vs. control) showed a significant main effect of context ($F(1, 40) = 20.25$, $p < .001$, $\eta^2 = .34$)

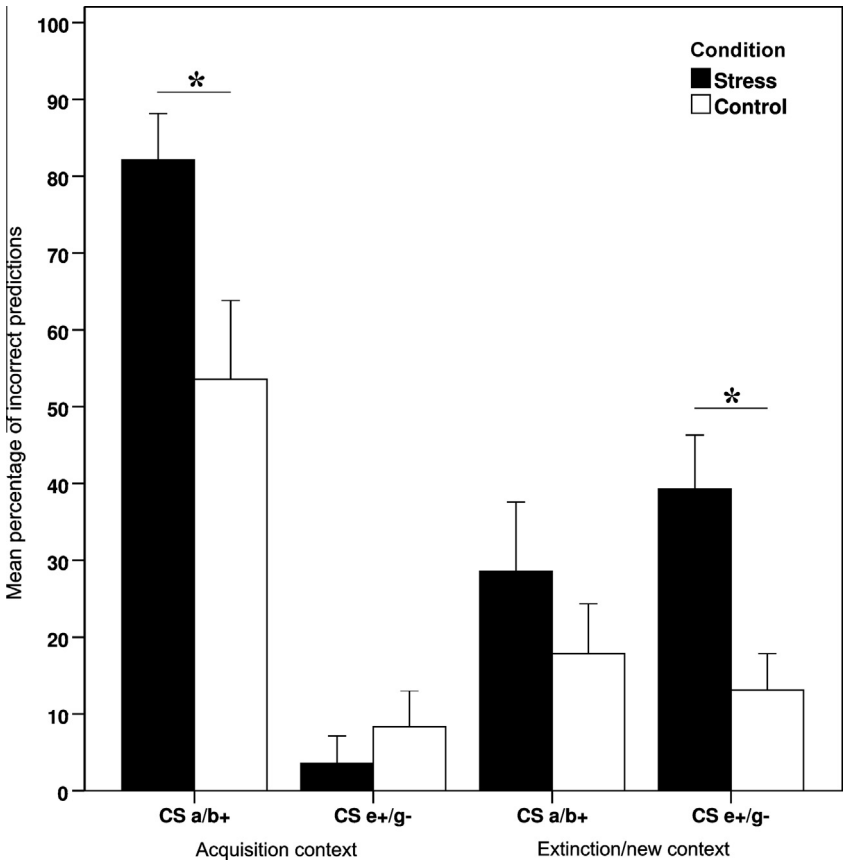

Fig. 2. Mean percentage of incorrect predictions to stimuli a/b+ and e+/g− averaged over the first two stimulus presentations during the renewal test phase (day 3). Signs indicate whether the CS had (+) or had not (−) been associated with stomach trouble during the acquisition phase (day 1). 'Yes'-predictions to the extinguished CS a/b+ were considered incorrect; 'no'-predictions to CS e+ and 'yes'-predictions to CS g− were averaged to represent the percentage of incorrect predictions to the unextinguished stimuli. CS a/b+ was presented in both the former acquisition context and the extinction context. CS e+/g− was presented in the context in which it had been shown during the acquisition phase and in the context in which it had not been shown before ('new' context). *Significant difference between stress and control group (two-tailed exploratory t-tests, $p < .05$). Results of the analysis are reported in more detail in Section 3.2 following the ANOVA results. Error bars denote standard errors of the mean.

and an interaction between context and condition ($F(1, 40) = 11.84$, $p < .01$, $\eta^2 = .23$). The main effect of condition did not reach significance ($p = .07$, $\eta^2 = .08$).

Based on the *t*-test result mentioned above, this indicates that stressed participants' predictions did not differ from those of the control participants when stimulus e+/g− was presented in the acquisition context ($p > .42$, $d' = .25$). In contrast, the stressed group made significantly more incorrect predictions than the control group when stimulus e+/g− was presented in the 'new' context ($t(40) = 3.09$, $p < .01$, $d' = .95$).

3.3. Correlation and regression analyses

Partial correlation analysis showed that the performance variable reflecting the overall difference between performance in the acquisition vs. extinction/'new' context during the renewal test (subsequently named context dependency) correlated with the interaction between cortisol concentration before renewal test and systolic blood pressure during SECPT/control condition ($r = .35$, $p = .03$). It was neither correlated with cortisol concentrations ($p = .56$) nor systolic blood pressure alone ($p = .38$). There was no significant partial correlation between the subjective rating of stressfulness and context dependency ($p = .95$).

A stepwise linear regression analysis with the three predictors cortisol concentration directly before renewal test, systolic blood pressure during SECPT/control condition and the interaction between cortisol and systolic blood pressure only kept the interaction between cortisol and systolic blood pressure as significant predictor of context dependency in the model ($\beta = .40$, $p = .03$). It explained a significant proportion of variance in context dependency ($R^2 = .10$, $F(1, 37) = 5.32$, $p = .03$). Neither cortisol concentration before renewal test ($\beta = -.07$, $p = .73$) nor systolic blood pressure during the SECPT/control condition ($\beta = -.14$, $p = .39$) significantly predicted context dependency.

4. Discussion

The current study investigated the effect of stress on the retrieval of extinction memory in a predictive learning task designed as a renewal paradigm. Salivary cortisol data as well as blood pressure measures and subjective ratings confirmed that stress induction was successful. During the retrieval test, a renewal effect was found, as indicated by generally stronger (''stomach trouble''-) responding to the extinguished stimulus in the acquisition context compared to the extinction context. Moreover, stress impaired retrieval of extinguished and unextinguished associations in the renewal test. With regard to unextinguished associations, memory retrieval was in general more strongly impaired when the stimuli were presented in a new context than when they were shown in the context in which they had been presented in the acquisition phase. Stressed participants' memory retrieval performance did not differ from controls when the stimuli were presented in this acquisition context. In contrast, when the stimuli were presented in a new context, stressed participants did not retrieve the original associations as well as the control group did. Thus, exposure to stress rendered memory retrieval of unextinguished associations more dependent on contextual cues.

The renewal effect found in this study is in line with previous research demonstrating impaired retrieval of extinction memory after a context change (e.g., Bouton & Bolles, 1979; Milad et al., 2005; Rosas et al., 2001). In line with our hypothesis, we found an effect of stress on extinction memory retrieval, as reflected by stronger memory impairment in stressed participants than in controls. This finding is consistent with a recent study reporting reemergence of extinguished fear after acute stress in rats (Deschaux et al., 2013) and studies investigating chronic stress effects on extinction memory retrieval in rodents (Garcia et al., 2008; Miracle et al., 2006). Moreover, our results seemingly parallel those which have been found for declarative memory: In extinction as well as declarative memory (Buchanan et al., 2006; Kuhlmann et al., 2005; Smeets, 2011), stress has an impairing effect on retrieval. The effect of stress on memory can be modulated by contextual cues (Schwabe & Wolf, 2009), as we also found in this study. When no appropriate contextual cue was present ('new' context trials), stressed participants remembered the outcome associated with the specific stimulus less well than the control group. If, however, a contextual cue reminding of the acquisition phase was present, the stress group did not differ from the controls. Thus, appropriate contextual cues abolished the impairing effect of stress on memory retrieval of unextinguished associations (in line with Schwabe & Wolf, 2009). However, this was not the case for extinguished associations, whose retrieval was generally impaired under stress.

Besides the role of contextual cues, the different age of the memory traces could be an additional factor explaining parts of our findings: Extinction memory is more recently established than acquisition memory and thus probably more likely to be impaired by stress. Some initial evidence for such a temporal gradient of stress sensitivity can be derived from previous studies on episodic/declarative memory retrieval (Kuhlmann et al., 2005; Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009; Wolf et al., 2002). Nevertheless, we also found impairing effects of stress on memory for the stimuli which had not been presented in the extinction phase. It seems therefore unlikely that the differential susceptibility of older vs. younger memories to stress can account for our results.

Obviously, there are various procedural differences between a predictive learning task and a classical conditioning paradigm as, for instance, the biological significance of the stimuli used. Nevertheless, many researchers share the assumption that predictive learning and classical conditioning are governed by similar mechanisms (e. g., Allan, 1993; Dickinson, 1980; Gluck & Bower, 1988; Miller & Matute, 1996). This view is mainly based on two considerations. First, besides differences, there are also fundamental similarities between both learning situations. In either case, organisms predict the occurrence of an event on the basis of the presence or absence of specific stimuli. Second, and perhaps more compelling, a large number of phenomena observed in classical conditioning can be found in analogous observations in predictive learning. For instance, factors known to influence the rate of conditioning as contingency and cue-competition are also shown to affect predictive learning (for an extensive review see, Shanks, Holyoak, & Medin, 1996). This parallel between predictive learning and classical conditioning is also evident in extinction. Within both types of learning, extinguished behavior recovers with the passage of time (spontaneous recovery; e.g., Pavlov, 1927; Vila & Rosas, 2001a), after exposure to the outcome (reinstatement; e.g., Bouton & Bolles, 1979; Vila & Rosas, 2001b), and when contextual cues are changed (renewal; e.g., Bouton & King, 1983; Üngör & Lachnit, 2006). Nevertheless, it would be important to investigate the effects of stress on extinction memory retrieval also in emotional learning tasks, such as fear conditioning. At least in rodents, a recent study reported similar effects of stress on the reemergence of conditioned fear (Deschaux et al., 2013).

Bearing in mind that the conclusions derived from a predictive learning paradigm cannot be directly translated to clinical implications, the similarities to classical conditioning procedures stated above may allow for some preliminary considerations. The finding of a stronger renewal effect under stress relates to studies which established a connection between stress and symptom reoccurrence in anxiety disorders and relapse in drug dependence (for reviews, see Breese et al., 2005; Jacobs & Nadel, 1985; Schwabe et al., 2011; Uhart & Wand, 2009). In view of our results, a potential

mechanism for this might be that stress impairs the retrieval of extinction memory, thus blocking access to the corrective experiences made during exposure therapy or related approaches. In addition, this might be of relevance for studies which aimed at enhancing extinction or extinction-based psychotherapy by administration of GCs (de Quervain et al., 2011; Soravia et al., 2006; Suris, North, Adinoff, Powell, & Greene, 2010; Yehuda, Bierer, Pratchett, & Malowney, 2010): Although GCs have been shown to be beneficial for the treatment of anxiety disorders and PTSD (de Quervain & Margraf, 2008), presumably by impairing fear memory retrieval and enhancing consolidation of extinction memory (Bentz, Michael, de Quervain, & Wilhelm, 2010), a continued GC administration during follow-up tests might lead to an impairment of extinction memory retrieval.

The observed correlations indicate that a combination of sympathetic activation and heightened cortisol concentrations predicted context dependency in the renewal test, but neither factor alone. These findings correspond to the model proposed by Roozendaal and colleagues (Roozendaal & McGaugh, 2011; Roozendaal et al., 2009) stating that effects of GCs on memory require arousal-induced noradrenergic activation of the amygdala, which has also been found for declarative memory retrieval in humans (de Quervain, Aerni, & Roozendaal, 2007; Kuhlmann & Wolf, 2006). For example, eliminating the arousal induced by a formal test situation also eliminated the impairing effect of oral GC administration on memory retrieval (Kuhlmann & Wolf, 2006).

In conclusion, this study shows that presenting the acquisition context at retrieval testing leads to a renewal of extinguished associations in predictive learning. Moreover, stress causes a stronger recovery of responding, thus indicating that the retrieval of extinction memory is impaired under stress (consistent with the findings of Deschaux et al., 2013). Furthermore, retrieval of unextinguished stimulus-outcome associations is seemingly unaltered by stress if contextual cues are identical to those present during training. However, if contextual cues diverge from the learning context, stress impairs memory retrieval (in line with Schwabe & Wolf, 2009). Thus, the context plays an important role in modulating stress effects on memory for unextinguished associations. Whether our results can be extended to more emotional tasks in humans, such as fear conditioning, remains a question for future work. At least in rodents, acute stress impairs the retrieval of fear extinction as well (Deschaux et al., 2013). Studying the effects of stress on context-dependent retrieval of fear extinction memory would allow for more direct conclusions regarding stress as a potential risk factor for relapse in patients with anxiety disorders.

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