

Preextinction Stress Prevents Context-Related Renewal of Fear

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Extinction learning, which creates new safety associations, is thought to be the mechanism underlying exposure therapy, commonly used for the treatment of anxiety disorders and posttraumatic stress disorder. The relative strength and availability for retrieval of both the fear and safety memories determine the response in a given situation. While the fear memory is often context-independent and may easily generalize, extinction memory is highly context-specific. “Renewal” of the extinguished fear memory might thus occur following a shift in context. The aim of the current work was to create an enhanced and generalized extinction memory to a discrete stimulus using stress exposure before extinction learning, thereby preventing renewal. In our contextual fear conditioning paradigm, 40 healthy men acquired (Day 1), retrieved and extinguished (Day 2) the fear memories, with no differences between the stress and the control group. A significant difference between the groups emerged in the renewal test (Day 3). A renewal effect was seen in the control group ($N = 20$), confirming the context-dependency of the extinction memory. In contrast, the stress group ($N = 20$) showed no renewal effect. Fear reduction was generalized to the acquisition context as well, suggesting that stress rendered the extinction memory more context-independent. These results

are in line with previous studies that showed contextualization disruption as a result of pre-learning stress, mediated by the rapid effects of glucocorticoids on the hippocampus. Our findings support research investigating the use of glucocorticoids or stress induction in exposure therapy and suggest the right timing of administration in order to optimize their effects.

Keywords: anxiety; cortisol; exposure therapy; extinction learning; fear conditioning

EXPOSURE THERAPY is a cognitive-behavioral psychotherapeutic procedure, commonly used for the treatment of posttraumatic stress disorder (PTSD) and anxiety disorders (Marks, 1979). During exposure sessions, the patient encounters the feared stimulus (e.g., snakes, heights, public speech) until the fear response subsides.

Two main models suggest different underlying mechanisms of exposure therapy. According to the emotional processing theory (Foa & Kozak, 1986; Rauch & Foa, 2006), the pathological fear structures are accessed and modified during a successful treatment. However, although (at least partial) erasure of the initial conditioning has been suggested (Delamater & Westbrook, 2014), the mainstream view sees exposure therapy as based on extinction, i.e., new inhibitory learning (Bouton, Westbrook, Corcoran, & Maren, 2006) in which the original memory itself is not affected (for a review of the theories of extinction, see Dunsmoor, Niv, Daw, & Phelps, 2015). That is, both fear and safety memories will co-exist after exposure therapy, and their relative strength and availability for retrieval will determine the response in a given situation (Bouton, 2004; Vervliet, Craske, & Hermans, 2013). However, the two memories are in general not of equal strength.

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While the fear memory is often context-independent and may easily generalize (Onat & Büchel, 2015), extinction memory is highly context-specific (Vervliet, Baeyens, Van den Bergh, & Hermans, 2013). It was suggested that the extinction, as the second thing that is learned about a stimulus, is coded as a conditional, context-specific exception to the rule (Bouton, 2002). Thus, a “renewal” of the extinguished fear memory might occur following a shift in context (Bouton, 2004, 2014), for example, when the patient leaves the clinical settings and goes back to daily life. Renewal and additional recovery phenomena pose a major challenge for the long-term success of psychotherapy (Craske, 1999; Vervliet, Baeyens, et al., 2013). However, studies suggest that the success of the treatment can be improved by the use of cognitive/behavioral modification (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Shiban, Pauli, & Mühlberger, 2013; Zbozinek, Holmes, & Craske, 2015) or pharmacological adjuncts, such as stress hormones (de Quervain et al., 2011).

In response to a stressful event, the sympathetic nervous system (SNS) supports the initial fight-or-flight response via adrenaline and noradrenaline. The hypothalamus-pituitary-adrenocortical (HPA) axis, slower to respond, secretes glucocorticoids (GCs; mainly cortisol in humans) that promote the adaptive physiological and behavioral response as well as the return to homeostasis (Joëls & Baram, 2009). The interaction of noradrenaline and GCs in brain areas relevant for learning (i.e., amygdala, hippocampus, prefrontal cortex) enhances the consolidation of emotional memories (Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006; Roozendaal, 2000). In contrast, it impairs the retrieval of competing emotional memories (Buchanan, Tranel, & Adolphs, 2006; Merz, Hamacher-Dang, & Wolf, 2014). This “memory consolidation mode” might be one critical reason for the strength and persistence of fear- and trauma-related memories. If the memory-enhancing properties of stress could be adapted for the benefit of treatment, the success of exposure therapy could increase, and the rate of relapses decrease. Promising findings were indeed demonstrated following the administration of cortisol in treatment of PTSD (Surís, North, Adinoff, Powell, & Greene, 2010; Yehuda et al., 2015), phobia of spiders (Soravia et al., 2006; Soravia et al., 2014), and of heights (de Quervain et al., 2011). However, it is yet unclear whether these effects generalize across contexts and resist relapse following context change.

The timing of stress exposure is critical in determining its effects on learning and memory. It was previously shown that acute stress exposure before extinction retention test prevents the return of fear (Merz et al., 2014). Stress induction after

extinction learning, however, enhances the contextualization of extinction memory, thus leading to an enhanced renewal (Hamacher-Dang, Merz, & Wolf, 2015). The effects of timing the stress induction before extinction learning on the renewal of fear are yet unclear, but other studies suggest that stress exposure or GCs treatment before a learning task can disrupt contextualization (Meir Drexler, Hamacher-Dang, & Wolf, 2017; Schwabe, Bohringer, & Wolf, 2009; van Ast, Cornelisse, Meeter, Joëls, & Kindt, 2013). Thus, the aim of the current study was to create a stronger and more context-independent extinction memory to a discrete stimulus using stress exposure before extinction learning. A context-independent memory might generalize from the extinction context to the acquisition context, and thus would be more resistant to renewal after context change (Bouton, 2004; Vervliet, Baeyens, et al., 2013).

Materials and Methods

PARTICIPANTS AND GENERAL PROCEDURE

As extinction memory can be modulated by sex hormones and their alteration during the female menstrual cycle (e.g., Milad et al., 2010), we tested only men in the current study. Forty men participated in this study. The participants were aged 18–35 with a body mass index (BMI) of 19–28 kg/m². To avoid additional confounds on the cortisol response following stress (Hellhammer, Wüst, & Kudielka, 2009), all participants were healthy (i.e., no somatic, endocrine, psychiatric or neurological diseases) non-smokers with no regular medication intake. In addition, as the learning paradigm involved stimuli of different colors, color-blindness was an additional exclusion criterion. All participants were students to either a bachelor or master’s degree at the Ruhr-University Bochum, Germany. They were recruited via advertisements on the campus and received a financial reimbursement of 30 € (approximately \$35) for their participation. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. All participants signed an informed consent in the presence of the research experimenter.

The test sessions took place on the afternoons of three consecutive days (starting between 12:30 PM and 5:45 PM): acquisition on Day 1, stress/control condition followed by extinction on Day 2, and renewal test on Day 3. The individual testing schedules were timed so that there were 24 h (± 2 h) between each session to allow memory consolidation after each phase (Dudai, 2012) and to avoid immediate extinction deficit (Maren, 2014; Merz, Hamacher-Dang, & Wolf, 2016). Participants were asked not to consume alcohol during the three testing days. In addition, they

were told to refrain from eating, drinking (anything but water), and physical activity 90 min prior to each testing session. The 3-day testing schedule was conducted in the presence of the same experimenter (either the study leader or a trained student). In addition, on Day 2, a novel experimenter was introduced for the stress procedure only (see below). A sealed partition in the experiment room separated the experimenter and participant during the learning tasks.

THE CONTEXTUAL FEAR CONDITIONING PARADIGM

In the contextual fear conditioning paradigm, developed by Milad and colleagues (2007; Milad, Pitman, et al., 2009), the CS (conditioned stimulus) is paired with the UCS (unconditioned stimulus) in one context but not the other. Adaptation to this design was used in several additional studies, which investigated the effects of stress hormones either preextinction (Merz, Hamacher-Dang, Stark, Wolf, & Hermann, 2018), postextinction (Hamacher-Dang et al., 2015), or preretrieval (Merz et al., 2014) on fear and extinction memory retrieval, and was also used in the current study. The validity of using two-dimensional pictures as different contexts, as practiced in this paradigm, has been demonstrated in previous studies showing a renewal effect or contextually gated fear responding (e.g., Lonsdorf, Haaker,

& Kalisch, 2014; Milad, Orr, Pitman, & Rauch, 2005).

In this paradigm (see Figure 1), photos of two different rooms were used as contexts: the office was used as context A (acquisition context) and the library, as context B (extinction context). A desk lamp, located in each of the rooms, indicated the CS by different colors of light (red, blue, or yellow; allocation of the three colors of light to the three CS was counterbalanced between participants). In all learning phases, each trial began with 3 s context-only presentation (the room is presented, but the lamp is off) and was followed by 6 s of CS presentation within the same context (the lamp in the room is red, blue, or yellow). The CS co-terminated with the UCS on reinforced trials (acquisition only). During the inter-trial interval (between the end of CS and the beginning 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, at a distance of approximately 50 cm of the participant's head.

Day 1: Fear Acquisition Training

Upon arrival on the first testing day, the participants provided written informed consent and were screened for color blindness using a selection of four Ishihara plates (Ishihara, 1990). The participants completed

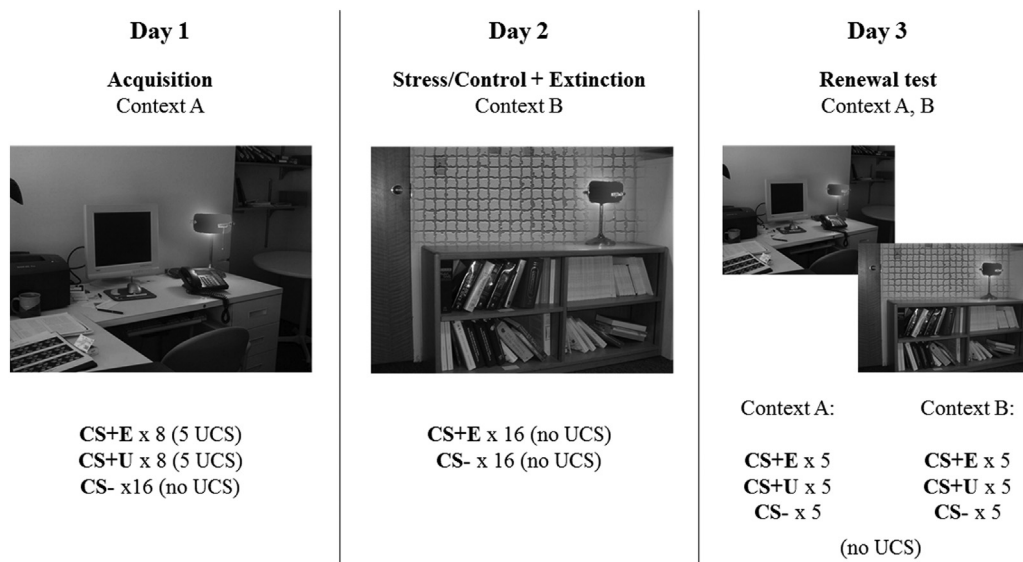


FIGURE 1 *Experimental timeline.* In this contextual fear conditioning paradigm (adapted from: Milad et al., 2007; Milad, Pitman, et al., 2009), photos of two different rooms were used as contexts: the office was used as context A and the library was used as context B. A desk lamp, located in each of the rooms, indicated the conditioned stimulus (CS) by different colors of light (red, blue, or yellow; counterbalanced between participants). In this paradigm, CS + E was paired with UCS (unconditioned stimulus) in context A, extinguished in context B, and tested for renewal in both contexts. CS + U (un-extinguished stimulus) and CS- (non-paired stimulus) were used as control stimuli. The numbers of each stimulus type presented during the acquisition, extinction learning, and renewal test are indicated.

questionnaires regarding demographic data and trait anxiety (State-Trait Anxiety Inventory, STAI-T; Spielberger, Gorsuch, & Lushene, 1970). The participants then underwent the acquisition procedure. During fear acquisition, three CS were presented, intermixed, in context A. Two stimuli, CS+E and CS+U, were presented eight times each and in five out of these eight trials, both CS were paired with the UCS (62.5% reinforcement rate). The CS- was presented 16 times and was never paired with the UCS. CS presentations were pseudorandomized (Hamacher-Dang et al., 2015; Merz et al., 2014).

Day 2: Stress/Control and Extinction Training

On the second day, the participants were exposed to stress ($N = 20$) or a control procedure ($N = 20$). Twenty-five minutes after the initiation of the stress/control procedure, the extinction phase began. This interval was chosen because cortisol reaches peak levels 20–30 min after stress (Dickerson & Kemeny, 2004). During extinction training, which was performed in context B, one of the previously reinforced stimuli (CS+E; the letter E represents “extinguished”) was presented 16 times, but was not followed by electrical stimulation. The CS- was also presented 16 times and was not followed by electrical stimulation. CS+U (the letter U represents “unextinguished”) was not presented on this day at all. CS presentations were pseudorandomized (Hamacher-Dang et al., 2015; Merz et al., 2014).

Day 3: Renewal Test

On the third day, the participants were tested for renewal. The retrieval phase consisted of five presentations of the three CS in both contexts in a pseudo-randomized order. None of the stimuli was followed by electrical stimulation (Hamacher-Dang et al., 2015; Merz et al., 2014). Immediately after the renewal test, we included a reinstatement test (Hamacher-Dang et al., 2015). Due to the lack of reinstatement effect in both the control and stress groups, the results of this test are not reported here.

Instructions

Before each of the experiment phases, the participants were instructed (both orally and in a written form) that they may or may not receive electrical stimulation after the presentation of a visual stimulus. They were encouraged to pay attention to the task and look for any regularities. Such regularities, they were informed, would remain stable during the experiment: If a stimulus was safe, it would always be safe, if a stimulus was coupled with the electrical stimulation, this might happen again. After each phase, they were asked to report the context (i.e., the room) they had seen (all reported correctly, data not shown). Although contingency awareness reported

on Day 1 was not used as exclusion criteria in the study, the participants were asked to report any contingencies they witnessed. This was used to facilitate contingency learning and to preclude participants from expecting contingency reversal. At no point were the participants explicitly informed about the actual CS-UCS contingencies (during acquisition) or the change in reinforcement rate (during extinction and renewal).

UCS Administration, SCR Recording, and Analysis

In line with previous fear conditioning studies (e.g., Agren et al., 2012; Milad et al., 2005; Schiller et al., 2010), skin conductance response (SCR) served as a measure of the conditioned fear response. Stimulation (UCS) and SCR electrodes were attached during all learning phases

An electric shock immediately beginning after the offset of the CS+E and CS+U on reinforced trials (acquisition phase only) served as UCS. The transcutaneous electrical stimulation (100 ms) was produced by a constant voltage stimulator (STM200; BIOPAC Systems) and was delivered to the left shin through two Ag/AgCl electrodes (0.5cm² surface) filled with isotonic (0.05 M NaCl) electrolyte medium (Synapse Conductive Electrode Cream; Kustomer Kinetics, Arcadia, CA). The UCS was individually adjusted for each of the participants before acquisition to ensure a “subjectively uncomfortable but not painful” level. Adjustment to this level was conducted on experimental Day 2 and Day 3 to promote shock expectancy, yet no shocks were given during these days.

SCR was sampled using Ag/AgCl electrodes (0.5cm² surface) filled with the same isotonic electrolyte medium as for shock electrodes. Electrodes were placed at the hypothenar of the nondominant hand. A commercial SCR coupler and amplifying system (MP150+GSR100C; BIOPAC Systems; Software: AcqKnowledge 4.2) sampled the SCR with a sampling rate of 1000 Hz. The maximal base-to-peak difference in SCR during 1–4.5 s after CS onset was used as a measure of conditioned response during acquisition, extinction and renewal test. The data was transformed with the natural logarithm to attain a normal distribution.

STRESS/CONTROL PROCEDURES

Participants in the stress group completed the Socially Evaluated Cold-Pressor Test (SECPT) as originally described in Schwabe, Haddad, and Schächinger (2008). In this task, participants immersed their right hand into a metal basin filled with ice-cold water (0–3°C) for 3 minutes while being recorded by a video camera and observed by a reserved experimenter. The experimenter was

unknown to the participant and was involved in the stress procedure only (i.e., did not take part in any of the other phases during the three testing days). In the control condition, the participants immersed their hand into a basin filled with warm water (35–37°C) and were neither watched by an experimenter nor recorded by a video camera.

Stress/Control Assessment

Saliva was collected to assess free cortisol levels (Kirschbaum & Hellhammer, 1994) as a marker of HPA axis activity. Samples were taken on Day 2 (5 min before the beginning of the stress/control procedure, and 1, 20 and 35 min afterward), as well as on Day 1 and 3 (at the beginning and the end of each testing day). The samples were collected using Salivette sampling devices (Sarstedt, Nümbrecht, Germany). Free salivary cortisol concentrations were analyzed with a commercial assay (ELISA; Demeditec Diagnostics, Kiel-Wellsee, Germany). Inter- and intra-assay variations were below 10%.

To obtain measures of SNS activity, systolic and diastolic blood pressure were recorded before, during, and 5 minutes after the stress/control procedure using Dinamap Vital signs monitor (Critikon, Tampa, FL; cuff placed on the left upper arm). For each phase, three measurements were averaged to gain a more reliable measure of the blood pressure.

Subjective ratings were collected immediately following the stress/control condition. On a scale from 0 (*not at all*) to 100 (*very much*), participants had to specify how stressful, painful, and unpleasant the previous situation was. The rating method was adopted from Schwabe et al. (2008).

STATISTICAL ANALYSIS

All statistical analyses were performed using IBM SPSS Statistics for Windows 22.0. The statistical significance level was set to $\alpha = .05$. Greenhouse-Geisser corrected *P*-values were used if assumptions of sphericity were violated. Significant ANOVAs were followed by Bonferroni-adjusted *post-hoc* tests.

Results

The two groups did not significantly differ in age, BMI, and STAI-T score (all $p > .05$; not shown).

STRESS RESPONSE

As indicated by the cortisol data, blood pressure measures and stress ratings, the SECPT procedure successfully induced stress.

We ran independent *t*-tests to compare the groups in the cortisol, blood pressure and rating variables. *T*-tests revealed that the stress procedure induced higher cortisol concentrations, compared with the control procedure, after 20 min ($t_{37} = 2.35, p < .05$

and 35 min ($t_{38} = 2.46, p < .05$) from its initiation. As expected, no group differences in cortisol concentrations were seen in the samples taken before (-5 min) and immediately after (+1 min) stress, and neither in the samples taken on Day 1 and Day 3 (all $p > .1$). Also, the stress procedure induced a significantly higher blood pressure response compared to the control procedure. This was indicated by significant group differences for systolic blood pressure ($t_{38} = 5.68, p < .001$) and diastolic blood pressure ($t_{37} = 5.72, p < .001$) during the procedure. No group differences were found for baseline- and postprocedure values (for all comparisons, $p > .1$). Moreover, participants of the stress group experienced the procedure to be significantly more stressful ($t_{20.44} = 4.73, p < .001$), painful ($t_{19.30} = 10.59, p < .001$), and unpleasant ($t_{29.84} = 5.54, p < .001$) compared with the control group. See Table 1 for cortisol, blood pressure, and rating values.

SCR DURING THE LEARNING PHASES

Acquisition in Context A

In the acquisition phase, performed in context A, two stimuli (CS+E, CS+U) were paired with the UCS, while a third stimulus (CS-) was never paired. To test whether acquisition was successful in leading to differential SCR, we compared the mean response to each of the three stimuli. ANOVA with the within-subjects factor CS (CS+E, CS+U, CS-) and the between-subjects factor Group (Stress, Control) revealed a significant CS effect ($F_{2,76} = 11.80, p < .001$). As illustrated in Figure 2, CS+E and CS+U did not significantly differ from each other, but both led to a higher SCR compared to the “safe” CS-. For all other comparisons (including Group), $p > .05$.

Extinction in Context B

The extinction was performed in context B. Here, only the previously paired stimulus CS+E was extinguished (i.e., presented without any shocks). CS- was also presented and remained unreinforced. CS+U, the unextinguished stimulus, was not presented on this day. First, we calculated a mean for the early phase (trials 1-8) and the late phase (trials 9-16) of extinction for the two stimuli. We then examined whether the acquired fear was successfully retrieved at the early phase of extinction. ANOVA (factors: CS, Group) for the early phase of extinction revealed a significant effect of CS ($F_{1,37} = 9.75, p < .005$), indicating fear retrieval: higher responses were detected for the CS+E compared to the CS-. Then, we examined whether the conditioned response was extinguished. ANOVA (factors: CS, Phase - early vs. late, Group) showed a significant Phase effect ($F_{1,37} = 17.76, p < .001$), i.e., a general reduction in SCR from the early to the late phase, and a main CS effect

Table 1
Mean Ratings, Blood Pressure Responses and Cortisol Concentrations in the Stress/Control Group

	Stress (n=20)	Control (n=20)
Subjective ratings after procedure		
Stressful	36.0 ± 31.5	2.0 ± 6.1**
Painful	59.5 ± 24.8	0.5 ± 2.2**
Unpleasant	45.0 ± 27.4	6.0 ± 15.3**
Blood pressure responses		
Systolic blood pressure (mmHg)		
Baseline	119.6 ± 14.5	123.3 ± 13.2
During procedure	144.3 ± 14.3	122.4 ± 9.5**
5 min after procedure	125.4 ± 13.5	120.4 ± 12.8
Diastolic blood pressure (mmHg)		
Baseline	66.5 ± 10.2	64.1 ± 6.2
During procedure	87.7 ± 13.8	67.4 ± 7.6**
5 min after procedure	68.7 ± 9.8	67.6 ± 9.7
Cortisol concentrations (nmol/l)		
Baseline (-5 min before stress/control procedure)	8.6 ± 5.3	10.3 ± 10.0
+1 min after stress/control procedure	9.8 ± 6.0	10.3 ± 11.4
+20 min after stress/control procedure	17.4 ± 12.5	9.3 ± 8.9*
+35 min after stress/control procedure	15.2 ± 9.8	8.5 ± 7.4*

Note. Stressfulness, painfulness, and unpleasantness were rated on a scale from 0 ("not at all") to 100 ("very much"). Data represents means ± SD. ** $p \leq .001$, * $p \leq .05$, a significant difference between stress and control group (independent t -tests).

($F_{1,37}=9.58$, $p < .005$). Indeed, we examined the response to the stimuli at the late extinction phase, and no significant CS differences were seen when comparing the two stimuli (ANOVA; factors: CS, Group) at the end of extinction ($p > .05$). For all additional comparisons (including Group), $p > .05$. These results demonstrate an initial fear retrieval and extinction of CS+E with no significant difference between groups (see Figure 3).

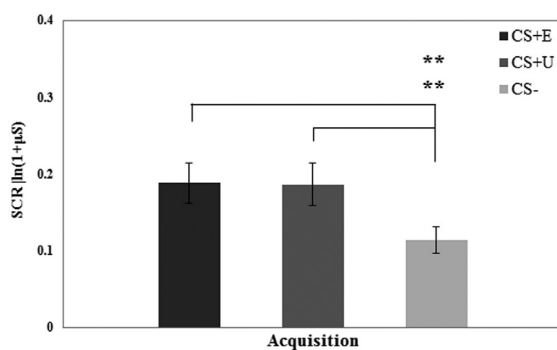


FIGURE 2 Day 1: Fear acquisition in context A. The skin conductance response (SCR) to the three stimuli (mean of 8 trials for CS+E and CS+U, mean of 16 trials for CS-). SCR to the unreinforced CS- is significantly lower than the SCR to the reinforced CS+E and CS+U (with no difference between the two reinforced stimuli) demonstrating a successful fear acquisition. The graph presents both groups combined ($N=40$; Stress group: $n=20$, Control group: $n=20$) as no interaction and no main effect of group were found. Error bars represent SEM and thus between-subject variance. ** $p < .001$. CS, conditioned stimulus.

Renewal Test: Context A vs. B

Renewal is the relapse phenomenon that occurs when the response to an extinguished stimulus is higher when shifting from the extinction context to another context, in particular when returning to the acquisition context (Bouton & Bolles, 1979;

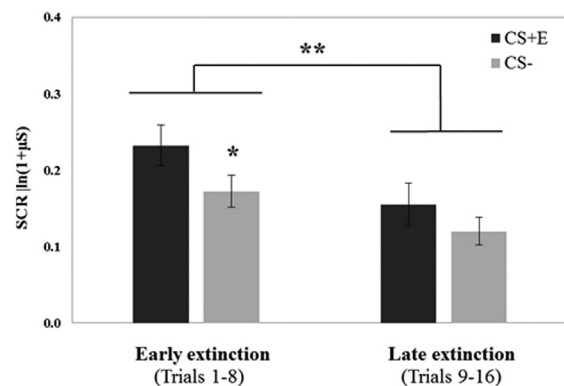


FIGURE 3 Day 2: Fear extinction in context B. Extinction took place on the second testing day, approximately 25 min after the initiation of the stress/control procedure. In this phase, only CS+E and CS- were presented (both not reinforced). This graph illustrates the skin conductance response (SCR) to both stimuli at early extinction (trials 1–8) vs. late extinction (trials 9–16). The significant difference between CS+E and CS- (* $p < .05$) in early extinction indicates fear memory retrieval; the significant effect of Phase (** $p < .001$) and the lack of difference between the stimuli at the later phase indicate fear extinction. As no interaction or main effect of group was found, the graph presents both groups combined ($N=40$; Stress group: $n=20$, Control group: $n=20$). Error bars represent SEM and thus between-subject variance. CS, conditioned stimulus.

Lonsdorf et al., 2017; Vervliet, Baeyens, et al., 2013). Therefore, for the renewal test, we compared the response to all three stimuli (CS+E, CS+U, CS-) in both contexts A (acquisition context) and B (extinction context). For this comparison, a mean was calculated for the five presentations of a stimulus in a context. ANOVA (factors: CS, Context, Group) revealed a significant CS \times Context ($F_{2,76}=4.56, p < .005$) interaction, indicating a higher response to CS+E in the acquisition context, as well as a Context \times Group ($F_{1,38}=6.57, p < .005$) interaction. To further investigate the latter interaction, and considering the additional CS \times Context interaction, we re-ran the ANOVA (factors: CS, Context) on each group separately. In the control group, a CS \times Context interaction ($F_{2,38}=4.47, p < .005$) was found. We then compared the response to each CS across contexts (ANOVA for each of the three stimuli; factor: Context) and found a Context effect for CS+E ($F_{1,19}=16.01, p < .001$), i.e., higher SCR in the acquisition context compared to the extinction context. No significant Context effects were found for the unextinguished CS+U and the “safe” CS- (all $p > .05$). The higher response to the extinguished stimulus upon context change confirms renewal in the control group. In contrast, no renewal effect (nor any CS, Context effects; all comparisons: $p > .1$) was found in the Stress group. In this group, the response to the extinguished CS+E has not recovered when

tested in the original acquisition context. These results, illustrated in Figure 4, demonstrate a stronger and more generalized extinction memory in the stress group.

Discussion

The use of GCs in combination with exposure therapy was suggested for the treatment of PTSD and phobias (de Quervain, Schwabe, & Roozendaal, 2017). In this combined treatment, cortisol is thought to disrupt the retrieval of aversive memories and, at the same time, enhances the newly acquired extinction memories (de Quervain & Margraf, 2008). Indeed, the results of these studies show improved treatment retention and reduction in symptoms (de Quervain et al., 2011; Soravia et al., 2006; Soravia et al., 2014; Yehuda et al., 2015). Nonetheless, it remained unclear whether the observed effects generalize across contexts. Context shift can lead to the renewal of extinguished fear after successful treatment (Bouton, 2002; Vervliet, Baeyens, et al., 2013) and can play a role in additional recovery phenomena, such as spontaneous recovery and reinstatement (Haaker, Golkar, Hermans, & Lonsdorf, 2014; Vervliet, Baeyens, et al., 2013). Our aim in the current work was to create an enhanced and generalized extinction memory to a discrete stimulus using stress exposure. While stress exposure after learning can enhance

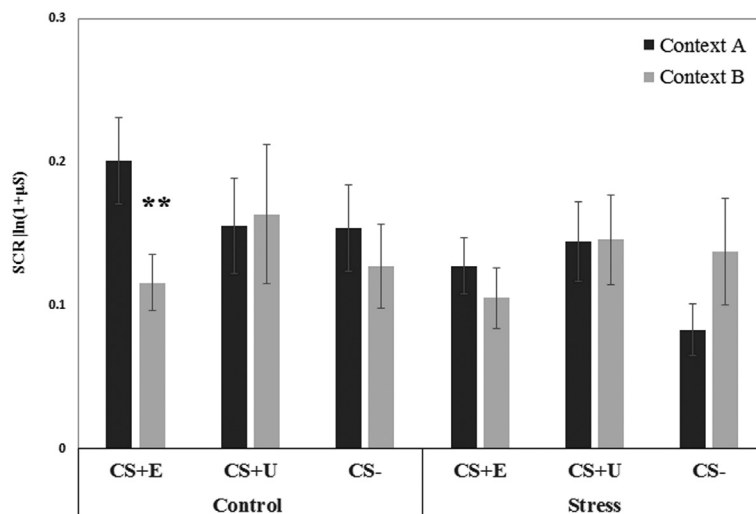


FIGURE 4 Day 3: Renewal test. The renewal test compared the mean skin conductance response (SCR) to the stimuli (CS+E, CS+U, CS-) in both contexts A (acquisition context) and B (extinction context). The control group (left panel; $n=20$) showed renewal of the extinguished fear response (** $p < .001$ in repeated measures ANOVA: the response to the previously extinguished CS+E in context A is higher than in context B), the stress group (right panel; $n=20$) showed no renewal. These results suggest a stronger and more generalized extinction memory in the stress group. Error bars represent SEM and thus between-subject variance. CS, conditioned stimulus.

contextualization (Hamacher-Dang et al., 2015), thus enhancing the renewal effect, stress exposure before learning tends to disrupt contextualization (Schwabe et al., 2009). Indeed, it was recently shown that preextinction stress enhances and generalizes extinction memory in a predictive learning task, a neutral task of contingency learning (Meir Drexler et al., 2017). Therefore, we timed stress exposure prior to the extinction session.

In our contextual fear conditioning paradigm (adapted from Milad et al., 2007; Milad, Pitman, et al., 2009; for a 3-day design), the participants were able to acquire (Day 1), retrieve and extinguish (Day 2) the fear memories, with no group differences. The lack of an immediate effect of stress exposure on fear retrieval or extinction learning itself is in line with some previous findings involving cortisol administration (Soravia et al., 2014), but not others (de Quervain et al., 2011). A significant difference between the groups emerged in response to the extinguished stimulus during the renewal test on the third day. In the control group, a renewal effect was seen, i.e., a higher response to the extinguished stimulus in the acquisition context compared to the extinction context. This suggests that the extinction memory was highly context-dependent. In contrast, the stress group showed no renewal effect. Their response to the extinguished stimulus was not different in the original acquisition context compared to the extinction context, suggesting that their extinction memory was more generalized and less context-dependent.

MECHANISMS OF CONTEXTUALIZATION UNDER STRESS

During learning, the hippocampus encodes the relations between stimuli in a given context. High hippocampal activation during the extinction phase was previously found to be related to a stronger renewal effect—that is, to greater contextualization (Lissek, Glaubitz, Schmidt-Wilcke, & Tegenthoff, 2016). The ventromedial prefrontal cortex (vmPFC) is critical for the retrieval of the extinction associations (Milad et al., 2007). Its disruption during stress exposure and the related rise in GCs (Kinner, Merz, Lissek, & Wolf, 2016) can lead to stress-related retrieval deficits which might contribute to relapse, e.g., experimentally tested using reinstatement procedures (Haaker et al., 2014)

Whether the aim is to promote or disrupt memory contextualization, timing is critical. Indeed, the timing of the stressor relative to the memory phase of encoding (Buchanan & Lovallo, 2001; Schwabe et al., 2009), consolidation (Cahill, Gorski, & Le, 2003), retrieval (Merz et al., 2014), and reconsolidation (Meir Drexler & Wolf, 2017) is a major factor in

determining its effects. It was previously shown that enhanced contextualization could result from post-extinction stress (Hamacher-Dang et al., 2015). In clear contrast, preextinction stress in the present study led to a generalized, context-independent extinction memory. The extinction memory retrieval was not limited to the extinction context, but generalized to the acquisition context. These results are in line with previous works that showed contextualization disruption in declarative memory tasks as a result of pre-learning stress (Schwabe et al., 2009) or GC administration (van Ast et al., 2013). Lissek et al. (2016) suggested that the stress-related contextualization disruption is mediated by reduced hippocampal activation. This can result from the rapid effects of GCs, which occur when cortisol is administered 30 min before learning (van Ast et al., 2013). This timing corresponds to our paradigm, as our participants went through the extinction phase approximately 25 min after stress exposure. More generally, stress leads to shifting from the hippocampal-dependent memory system, which integrates multiple cues in a context, to the more rigid striatal system, which supports simple cue-response relationships (Schwabe & Wolf, 2013). In contrast, the slow effects of GCs (i.e., when administered 210 min before learning) tend to enhance contextualization (van Ast et al., 2013).

FEAR RETRIEVAL AND EXTINCTION LEARNING UNDER STRESS

In contrast to the model suggested by de Quervain and Margraf (2008), in the current study we could not find any effects of stress exposure on fear retrieval, and participants from both groups could retrieve the memory of the CS at the beginning of extinction. Some authors suggested that fear retrieval might actually be beneficial to the treatment, as the retrieval and emotional processing of the feared stimulus is needed to promote the extinction process and to avoid fear conservation (Foa & Kozak, 1986; Solomon & Wynne, 1954; Stampfl, 1987, 1988). High responding in extinction might thus allow more learning of the direct inhibition of the response (Bouton, García-Gutiérrez, Zilski, & Moody, 2006). In addition, like some animal studies (Miracle, Brace, Huyck, Singler, & Wellman, 2006), we could not find any effects of stress on the extinction learning itself, and so the observed effects were only seen at the retention test performed one day later. In contrast, several other works emphasized the role of GCs as enhancers of the extinction process in exposure therapy (Bentz et al., 2013; Bentz, Michael, de Quervain, & Wilhelm, 2010; de Bitencourt, Pamplona, & Takahashi, 2013; de Quervain et al., 2017), while others

reported stress-induced impairment of extinction learning (Akirav & Maroun, 2007; Holmes & Wellman, 2009). Methodological differences (e.g., exogenous GCs administration vs. stress induction, alternations in treatment timing, and emotional vs. neutral paradigms) may account for these conflicting findings. For a review on the modulatory role of stress on extinction, see Stockhorst and Antov (2016).

IMPLICATIONS FOR THE UNDERSTANDING AND TREATMENT OF STRESS-RELATED DISORDERS

Exposure to a stressful event activates the SNS and the HPA axis and changes cognition and behavior (Joëls et al., 2006). According to the cue utilization hypothesis (Easterbrook, 1959), increasing levels of emotional arousal result in a restricted attention to cues. Indeed, learning under stress might lead to a narrow focus on the cues related to the memory task, and not to contextual cues (Schwabe et al., 2009; Schwabe & Wolf, 2013). Together with the enhancing effect of stress and GCs on memory consolidation (Roosendaal, 2000; Wolf, 2008), this can explain why fear- and trauma-related memories are so strong and often easily generalized to other contexts. Yet the same properties can be used in psychotherapy to enhance extinction memory (de Quervain & Margraf, 2008; de Quervain et al., 2017) and—as our results suggest—to promote its generalization.

In this study, we used stress exposure, and not GC administration, as a pre-learning manipulation. Stress induction leads to a complex physiological and emotional response (Joëls & Baram, 2009), yet its effects on memory processes are often comparable to those of GC administration (Buchanan & Lovallo, 2001; de Quervain, Roosendaal, & McGaugh, 1998; but see Meir Drexler & Wolf, 2017). Our results thus present further support to research on the use of GCs in psychotherapy (de Quervain et al., 2011; Soravia et al., 2014; Surís et al., 2010; Yehuda, Bierer, Pratchett, & Malowney, 2010). Moreover, these findings might inspire the incorporation of additional behavioral (e.g., stress induction) interventions into psychotherapy.

Several critical factors are to be taken into account if this method is to be tested to promote the generalization of extinction memory in clinical populations. First, a retrieval of a consolidated fear memory needs to be promoted, and avoidance or other safety behaviors should be discouraged. Fear retrieval, as opposed to avoidance or safety behaviors, is important to allow the emotional processing required for the extinction process (Foa & Kozak, 1986; Levis & Stampfl, 1972). Second, since retrieval can lead to either memory reconsolidation or extinction (Monfils, Cowansage, Klann, &

LeDoux, 2009), the proper paradigm should be used to avoid triggering memory reconsolidation instead, as this could lead to the opposite effects (e.g., fear memory enhancement in the case of GCs use; Meir Drexler, Merz, Hamacher-Dang, Tegenthoff, & Wolf, 2015). Typically, repeated exposure to the CS in the absence of the UCS leads to extinction while a very brief presentation of the CS, leading to a prediction error, triggers reconsolidation (Kindt, Soeter, & Vervliet, 2009; Merlo, Milton, Goozee, Theobald, & Everitt, 2014). Last, it is crucial to see the right timing of intervention. This should take into account the length of the session as well as the timing-dependent physiological effects of the use of either pharmacological treatment (and its dosage; Buchanan & Lovallo, 2001) or stress exposure (Joëls & Baram, 2009). The rapid effects of cortisol impair contextualization (van Ast et al., 2013), and so timing the behavioral intervention approximately 30 min before the beginning of a short exposure session might achieve the desired generalized extinction. In contrast, prolonged exposure therapy is longer, usually consists of 8 to 15 weekly or twice-weekly sessions, each lasting about 90 minutes (Foa, Hembree, & Rothbaum, 2007). The stress response would subside during this time (Joëls & Baram, 2009), suggesting GC administration (Buchanan & Lovallo, 2001) or time of day manipulation (Lass-Hennemann & Michael, 2014) as preferable intervention under these conditions.

Our findings have two main limitations. First: the exclusion of women from our study. Women are more susceptible to anxiety and stress-related disorders than men (Kessler et al., 2005). It has to be determined whether the same beneficial results reported here in men can be replicated in women and whether the effects interact with additional factors (e.g., the alternating sex hormones during the menstrual cycle or following the use of hormonal contraceptives; Merz et al., 2012; Milad et al., 2010; Milad, Igoe, et al., 2009; Nielsen, Ahmed, & Cahill, 2013). Second: the use of a single index to measure the fear response. While SCR represents autonomic arousal in response to a stimulus and is more directly linked to contingency knowledge, such as expectancy ratings (Kindt et al., 2009; van Dooren, de Vries, & Janssen, 2012), the fear-potentiated startle provides an index of affective state (Grillon, 2002). The two indices are sometimes affected differently by the same manipulation (Kindt et al., 2009), and concurrent measurements bear some caveats (cf. Lonsdorf et al., 2017; Sjouwerman, Niehaus, Kuhn, & Lonsdorf, 2016). Thus, future studies should investigate whether the effects shown using SCR could also be found in additional indices, such as expectancy ratings, fear ratings, or the startle response.

Conclusion

Stress can disrupt the ability to integrate contextual cues into a memory trace. This effect can be detrimental, leading to a strong, generalized fear, as seen in anxiety disorders and PTSD. Extinction memory, in contrast, is usually more context-specific, and thus less resistant to context change. Here we demonstrate that stress exposure can also be used to promote the treatment of these disorders (i.e., in exposure therapy), and—with the correct timing and design—lead to a stronger, more generalized extinction memory, which is resistant to relapse following context change. Thus, preexposure stress might facilitate learning and memory processes in patients with anxiety disorders or PTSD and eventually enhance the efficacy of exposure therapy by reduction of relapses.

Conflict of Interest Statement

The authors declare no competing financial interest.

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