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# Fear Without Context: Acute Stress Modulates the Balance of Cue-Dependent and Contextual Fear Learning

**Kathrin Simon-Kutscher, Nadine Wanke, Carlo Hiller, and Lars Schwabe**
Department of Cognitive Psychology, Institute of Psychology, University of Hamburg

## Abstract

During a threatening encounter, people can learn to associate the aversive event with a discrete preceding cue or with the context in which the event took place, corresponding to cue-dependent and context-dependent fear conditioning, respectively. Which of these forms of fear learning prevails has critical implications for fear-related psychopathology. We tested here whether acute stress may modulate the balance of cue-dependent and contextual fear learning. Participants ($N = 72$) underwent a stress or control manipulation 30 min before they completed a fear-learning task in a virtual environment that allowed both cued and contextual fear learning. Results showed equally strong cue- and context-dependent fear conditioning in the control group. Stress, however, abolished contextual fear learning, which was directly correlated with the activity of the stress hormone cortisol, and made cue-dependent fear more resistant to extinction. These results are the first to show that stress favors cue-dependent over contextual fear learning.

## Keywords

stress, fear conditioning, cue, context, cortisol, hippocampus, amygdala, open data, preregistered

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Fear learning is a highly adaptive process that enables the organism to predict future threats. Aberrant fear learning, however, may contribute to fear-related psychopathologies such as phobia, panic disorder, or posttraumatic stress disorder (PTSD; Duits et al., 2015; Mineka & Oehlberg, 2008). During Pavlovian fear conditioning, the most prominent form of fear learning, people learn to associate a neutral stimulus with an aversive unconditioned stimulus that leads to an unconditioned fear response. Eventually, the initially neutral stimulus alone, now referred to as the conditioned stimulus (CS), can elicit the fear. Importantly, during conditioning, fear may be linked to discrete cues or to the context in which the aversive event occurred (Maren, 2001). For instance, after a dog attack in a park, you may fear the barking of a dog or the park where the attack took place (or both). These forms of fear conditioning differ critically in the information-processing demands as well as in the underlying brain circuits. Unlike discrete cues that precede an aversive event, the complex sensory context is continuously present and temporally not precisely linked to the unconditioned stimulus (Phillips & LeDoux, 1992). Moreover, at the neural level, cue-dependent fear conditioning relies mainly on the amygdala, whereas context-dependent fear conditioning requires an intact hippocampus (Maren, 2001; Phillips & LeDoux, 1992).

Although it is obvious that, during a threatening encounter, an individual may acquire fear not only to cues preceding the threat but also to the context in which the threat occurred, to date most studies have focused on one form of fear conditioning only and tested cue- and context-dependent fear conditioning in separate tasks. Surprisingly little is known about the balance of cue- and context-related fear learning and the factors that may modulate this balance. Given that

**Corresponding Author:**
Lars Schwabe, University of Hamburg, Institute of Psychology, Department of Cognitive Psychology, Von-Melle-Park 5, 20146 Hamburg, Germany
E-mail: lars.schwabe@uni-hamburg.de

a decontextualization of fear and an overly strong responding to single threat-related cues are thought to be at the core of disorders such as PTSD (Liberzon et al., 1999), understanding which factors may bias the balance of contextual and cue-dependent fear learning is crucial.

Acute stress is known to be a powerful modulator of learning and memory processes (Diamond, Campbell, Park, Halonen, & Zoladz, 2007; Joëls, Fernandez, & Roozendaal, 2011; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). Through the action of neurotransmitters and hormones that are released in response to stressful experiences, stress may affect information processing in brain areas critical for contextual and cue-dependent fear conditioning (de Quervain et al., 2003; Henckens, van Wingen, Joëls, & Fernandez, 2010). Indeed, several studies have shown that stress and stress hormones may alter fear conditioning in humans, albeit virtually all of these studies focused on cue-dependent conditioning (Jackson, Payne, Nadel, & Jacobs, 2006; Lonsdorf & Merz, 2017; Merz, Elzinga, & Schwabe, 2016; Zorawski, Blanding, Kuhn, & LaBar, 2006). Rodent studies further demonstrated a critical role of stress hormones in the consolidation of contextual fear (Cordero, Kruyt, Merino, & Sandi, 2002; Cordero, Merino, & Sandi, 1998). Beyond the modulation of a specific form of learning, stress may bias the relative engagement of multiple anatomically and functionally distinct memory systems (Goodman, Leong, & Packard, 2012; Schwabe, 2017; Vogel, Fernandez, Joëls, & Schwabe, 2016). More specifically, acute stress biases learning toward rather simple automatic processes supported by the amygdala and basal ganglia, at the expense of cognitively more demanding processes that rely on the hippocampus and prefrontal cortex (Goldfarb, Mendelevich, & Phelps, 2017; Schwabe, Tegenthoff, Höffken, & Wolf, 2012; Schwabe & Wolf, 2012; Wirz, Wacker, Felten, Reuter, & Schwabe, 2017). Given this evidence, we hypothesized that stress may affect the balance of cue- and context-dependent fear conditioning in a manner that favors cue-dependent over contextual fear learning.

Thus, in this preregistered experiment, we set out to directly test whether acute stress alters the balance of cue-dependent and contextual fear learning. Therefore, healthy participants underwent a standardized stressor or a control manipulation before they completed a novel fear-learning task in a virtual environment that was composed of three distinct contexts. In one of these contexts, but not in the others, participants repeatedly saw a light stimulus that was followed by a mild electric shock (CS+) as well as another light stimulus that was never paired with a shock (CS–), thus allowing fear conditioning to the context and to the cue in the same task. After this acquisition phase, participants completed an extinction phase, in which both CS+ and CS– were relocated to another context, thus enabling us to further dissociate cue- and context-dependent fear responses. In addition to using skin conductance responses (SCRs) as a key measure of conditioned fear, we collected subjective fear measures. We predicted that stress would impair contextual fear learning but enhance cue-dependent fear learning. Because cue-dependent conditioning is typically very robust in healthy individuals, which may lead to a ceiling effect during acquisition, we further hypothesized that the enhancement of cue-dependent fear learning might become apparent only during the extinction session.

## Method

### *Participants*

An a priori sample-size calculation with the software G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that 72 participants would be sufficient to detect a medium-size effect with a power of .95. We thus recruited 72 healthy volunteers (36 men, 36 women), in accordance with our preregistered intention. The assumption of a medium-size effect was based on previous studies from our lab on the influence of stress on related cognitive processes (Schwabe, Bohringer, & Wolf, 2009; Schwabe & Wolf, 2012). All participants were fluent German speakers, had no history of any psychiatric or neurological disorder, had no acute illness, did not take any prescribed medication, and had no background in psychology. Moreover, smokers and women taking hormonal contraceptives were excluded from participation because these factors may affect the endocrine stress response (Kudielka & Kirschbaum, 2005).

Fifteen participants had to be excluded: 4 because of technical failure, 3 because of motion sickness, 5 because they did not follow the instructions, 2 because they gained insight into the purpose of the experiment, and 1 because of experimenter error. To achieve the planned sample size, we recruited 15 new participants, with the same exclusion criteria listed above. Thus, our final sample consisted of 72 healthy young adults (41 women, 31 men; age: $M = 25.50$ years, $SD = 3.82$; body mass index: $M = 22.95$ kg/m$^2$, $SD = 2.05$). All participants provided written informed consent before beginning the experiment and received monetary compensation of €25. The study was carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki and approved by the local ethics committee.

### *Stress protocol*

Participants in the stress condition underwent the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993), a gold standard in experimental stress research that

reliably leads to robust subjective and physiological stress responses (Kudielka, Hellhammer, & Kirschbaum, 2007). In brief, the TSST is a mock job interview that consisted of two parts. In the first part, participants gave a 5-min free speech about why they were the ideal candidate for a job that was tailored to their interests and qualifications. In the second part, participants completed a 5-min mental arithmetic task, in which they were asked to count backward from 2,041 by steps of 17; whenever they made a mistake, they had to start anew from 2,041. Both the free speech and the mental arithmetic task were performed in front of a rather cold and nonreinforcing panel of two experimenters who were dressed in white coats and introduced as experts in behavioral analysis. In addition, participants were videotaped throughout the TSST and could see themselves on a large screen placed behind the panel. Overall, the TSST represents an ecologically highly valid stressor; in particular, this ecological validity made the TSST, in the face of the potential clinical relevance of a stress-induced bias from contextual to cued fear, ideally suited for studying the impact of stress on the mode of fear learning.

Participants in the control condition gave a free speech about a topic of their choice and did a simple mathematical task (counting by steps of 15). There was no panel in the room, and participants were not videotaped. To assess whether the TSST successfully induced stress, we took subjective, autonomic, and endocrine measures at several time points before and after the experimental manipulation. Participants completed a German mood questionnaire (Steyer, Schwenkmezger, Notz, & Eid, 1994) before and after the TSST/control manipulation. Furthermore, they rated the stressfulness, unpleasantness, and difficulty of the task on a scale from 0 (*not at all*) to 100 (*very much*) immediately after the end of the TSST and control manipulation, respectively. We measured blood pressure and pulse as indicators of autonomic-nervous-system activity, using a Dinamap system (Critikon, Tampa, FL) immediately before, during, and after the TSST or control manipulation. Finally, we analyzed the concentration of the stress hormone cortisol from saliva samples that were collected before and immediately after the TSST and control manipulation, respectively, as well as 30, 70, and 95 min after the onset of the experimental manipulation. Cortisol was analyzed with a luminescence assay (IBL International, Hamburg, Germany).

## *Fear-learning task*

For the fear-learning task, we created a virtual environment using the real-time game engine Unity (Unity Technologies, San Francisco, CA), which was composed of three highly distinct rooms—a library, an open-plan office, and a biochemical laboratory—that were connected via a hallway. In all three rooms, there was a light bulb in the right upper corner of the screen. Participants could move through the virtual environment with the arrow keys of a customary keyboard. The fear-learning task consisted of an exploration phase, an acquisition phase, and an extinction phase (see Fig. 1).

***Exploration phase.*** In a 3-min exploration phase, participants were allowed to move freely through the virtual environment. They started in the hallway, from which they could access all rooms. Participants were instructed to explore each room at least once. Shortly after participants entered a room for the first time, the screen (and time) froze, and participants were asked to rate the valence (positive vs. negative) and arousal level (not at all arousing vs. highly arousing) associated with the respective room on a 4-point scale. During the exploration phase, the light bulb never lit up.

***Acquisition phase.*** Participants were informed that they would now be allowed to move further through the three rooms and that they would repeatedly receive mild electric shocks to their left lower leg. In the acquisition phase, a trial started with the participant being placed in one of the three rooms. One trial lasted 60 s, during which time participants could freely move through the room but could not leave the respective room. Between 3 and 6 s after the beginning of a trial, the screen (and time) froze again, and participants rated on a 4-point scale their current arousal level and their expectation that they would receive a shock (very unlikely vs. very likely). These ratings provided indices of subjective context-dependent fear learning. For each participant, one of the three rooms was determined to be the risk context, and the other two rooms were Safe Context 1 and Safe Context 2, respectively. Which room served as the risk context was counterbalanced across participants and experimental groups.

In the risk context, the light bulb in the right upper corner of the screen lit up four times for 2 s, twice in blue and twice in yellow. One of the lights (blue vs. yellow) was paired with a 100-ms shock with a real probability of 80% (CS+), whereas the other stimulus was never followed by a shock (CS–). Shocks were presented with a delay of 1.9 s after CS+ onset and coterminated with the CS+. Whether the blue or yellow light served as the CS+ was counterbalanced across participants and groups. Importantly, the light bulb lit up for the first time from 8 to 10 s (random jitter: 0–2 s) after trial onset; between CS+ and CS– there was an interval of 5 to 12 s (random jitter: 0–7 s). These intervals ensured that the SCR windows that were analyzed for entering the specific context, the CS+ or the CS–, did not overlap. The screen (and time) froze again and participants gave arousal and shock-expectancy ratings

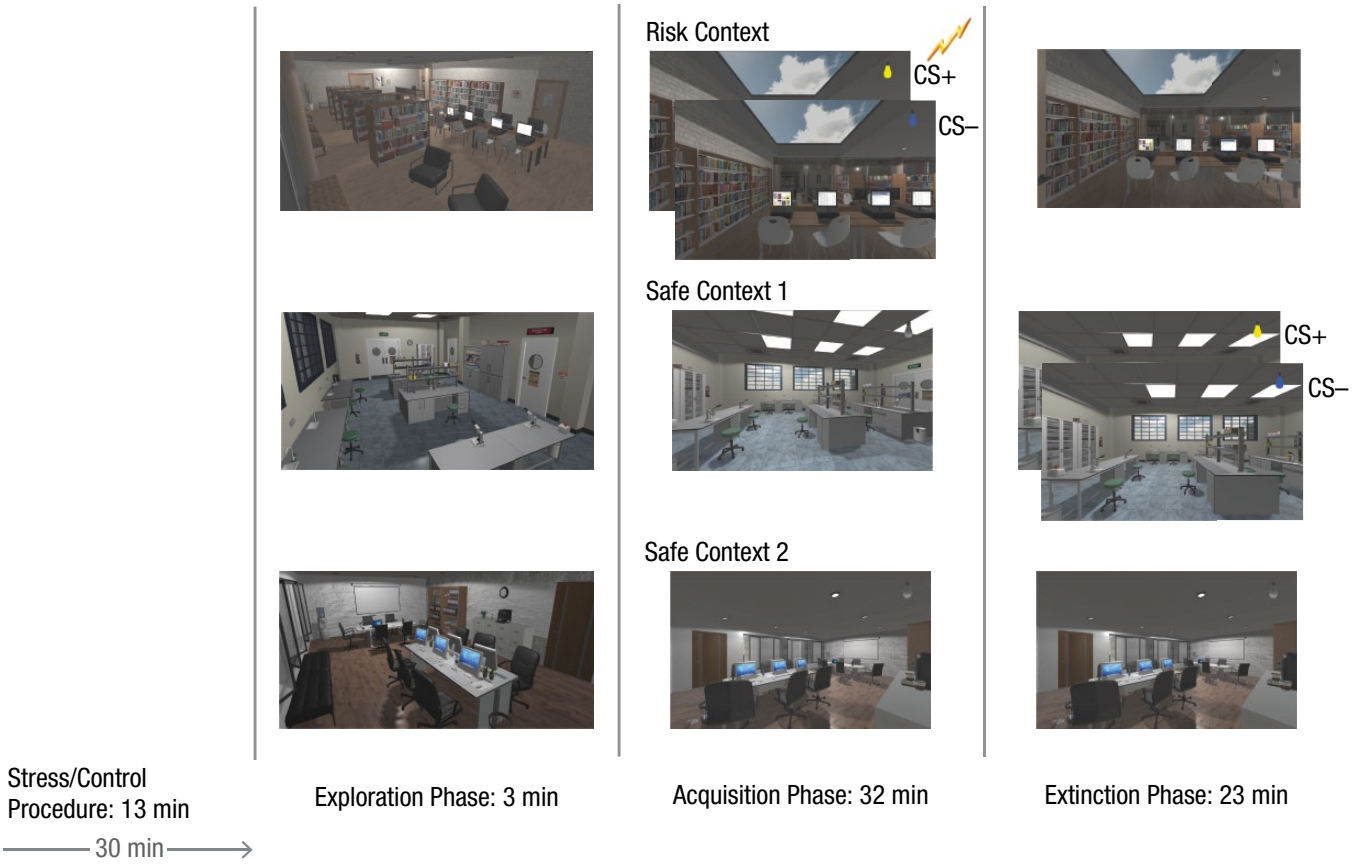


**Fig. 1.** Overview of the fear-learning task and experimental procedure. Thirty min after the start of a 13-min stressor (or control manipulation), participants explored three rooms in a virtual environment. During acquisition, a blue light and yellow light repeatedly lit up in one of the three rooms (risk context). One of the lights was followed by an electric shock in 80% of the trials (positive conditioned stimulus, or CS+), whereas the other light stimulus was never paired with a shock (negative conditioned stimulus, or CS–). In the other two rooms (Safe Context 1 and Safe Context 2), no light lit up, and participants never received electric shocks. During extinction, light cues (CS+ and C–) were relocated to Safe Context 1, but electric shocks were no longer presented.

once per trial after CS+ onset and once after CS– onset, providing cue-related subjective fear ratings.

The trial procedure for the Safe Context 1 and Safe Context 2 trials was exactly the same during the acquisition phase. In both safe contexts, no light lit up, and participants never received an electric shock. The timing of the second and third arousal and shock-expectancy ratings was matched to the timing of the CS+ and CS– related ratings in the risk context. Participants completed 8 trials per context during the acquisition phase (i.e., 24 trials in total). Between trials there was a fixation period of 1 to 2 s (random jitter: 0–1 s). The order of risk context, Safe Context 1, and Safe Context 2 trials was pseudorandomized to ensure that the same context was not presented two times in a row.

***Extinction phase.*** The trial procedure and timing during the extinction phase were identical to those in the acquisition phase. However, there were two critical differences. First, the CS+ and CS– were moved from the risk context to Safe Context 1 (see Fig. 1), which enabled us to explicitly dissociate fear responses provoked by the CS+ from those elicited by the risk context (or the combination of cue and context). Second, participants were tested in extinction, that is, they no longer received any electric shocks (shock electrodes, however, were still connected). During the extinction session, participants were placed in each context six times, that is, they completed 18 trials in total. Trial order was again pseudorandomized so that the same context was not presented in two trials in a row.

## *Measurement and analysis of SCRs*

SCR served as a key parameter of fear conditioning, in line with previous fear-conditioning research (Jackson et al., 2006; Lonsdorf & Merz, 2017; Öhman & Mineka, 2001; Zorawski et al., 2006). SCRs were measured during all phases of the fear-learning task with a BIOPAC MP-150 system (BIOPAC Systems, Goleta, CA), with electrodes placed on the distal phalanx of the index and middle

fingers of the left hand. SCR data were analyzed using continuous decomposition analysis as implemented in Ledalab (Version 3.4.9; Benedek & Kaernbach, 2010). Specifically, we derived the average phasic driver within 0 to 4 s after entering a specific context and 0 to 4 s after the onset of the CS+ and CS–, respectively. SCR data were downsampled to a resolution of 50 Hz and optimized using four sets of initial values. The minimum amplitude threshold was set to 0.01 μS.

### *Procedure*

We controlled for the diurnal rhythm of the stress hormone cortisol by conducting all testing between 1 p.m. and 7 p.m. All participants were tested individually. After providing written informed consent, participants completed the Beck Depression Inventory (Beck & Steer, 1987), the State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Luchene, 1970), and the Trier Inventory for Chronic Stress (Schulz, Schlotz, & Becker, 2004), which controlled for group differences in depressive mood, anxiety, and chronic stress level, respectively. Next, we collected baseline measurements of subjective mood, blood pressure, and pulse as well as a first saliva sample. Each participant was then randomly assigned to either the stress or control condition and underwent the TSST and control manipulation. Blood pressure and pulse were also measured during the experimental manipulation. Immediately after the TSST or control manipulation, autonomic parameters and subjective mood were measured again and another saliva sample was collected. Afterward, the electrodes for SCR measurement were attached to the fingers of the left hand, and the shock electrode was placed on the left lower leg. We then set the shock intensity in a stepwise procedure to a level that was experienced by the individual participant as unpleasant but not painful. Thirty minutes after the beginning of the stress or control procedure, participants gave another saliva sample, and the fear-learning task started. This interval between stressor and task was chosen because cortisol levels are known to increase with a delay and to reach peak levels at about 30 min after stressor onset (Kirschbaum et al., 1993; Kudielka et al., 2007). Thus, the chosen timing of the task made it very likely that the acquisition phase would be performed under elevated cortisol levels. Between the acquisition and extinction phases as well as after the extinction phase, participants gave further saliva samples. At the end of the experiment, participants completed a questionnaire in which they indicated what they had learned during the task, whether they noticed any changes between the second phase (acquisition) and third phase (extinction) of the task, and their experience with computer or video games in general.

### *Statistical analyses*

Subjective and physiological stress parameters were subjected to mixed-design analyses of variance (ANOVAs) with group (stress vs. control) as the between-subjects factor and time point of measurement as the within-subjects factor. Stress-induced changes in cue-dependent fear conditioning were analyzed in an ANOVA with the between-subjects factor group and the within-subjects factors CS type (CS+ vs. CS–) and block (1 vs. 2 vs. 3 vs. 4). Likewise, stress-induced changes in context-dependent fear learning were analyzed by a Group × Context (risk vs. Safe Context 1 vs. Safe Context 2) × Block (1 vs. 2) ANOVA. Subjective ratings of arousal and fear expectancy were entered into the same ANOVAs. To create an index of the cortisol response to the stressor, we subtracted baseline cortisol concentrations from peak cortisol concentrations and correlated this difference with indicators of cue- and context-dependent conditioning. The difference between fear responses to the CS+ and CS– was used as an indicator of cue-dependent conditioning, and the difference between fear responses to the risk context and the averaged responses to the two safe contexts served as an indicator of context-dependent conditioning. To directly test the influence of stress on the relative strength of cue- and context-dependent conditioning, we performed a mixed-design ANOVA with the between-subjects factor group and the within-subjects factor type of conditioning (indicator of cue-dependent conditioning vs. indicator of context-dependent conditioning). Significant main or interaction effects were followed by post hoc tests that were Bonferroni corrected ($p_{corr}$) if indicated. In the case of violation of the sphericity assumption, Greenhouse-Geisser correction was applied. All reported $p$ values are two tailed, unless stated otherwise. All statistical analyses were performed with SPSS Version 22.

## Results

### *Subjective and physiological stress responses*

Subjective and physiological measures confirmed that the TSST successfully induced stress. Participants in the stress condition experienced the experimental manipulation as significantly more stressful, $t(70) = 8.77$, $p < .001$, $d = 2.07$; unpleasant, $t(70) = 6.66$, $p < .001$, $d = 1.57$; and difficult, $t(70) = 9.08$, $p < .001$, $d = 2.14$, than did those in the control condition. Moreover, positive mood decreased, Group × Time: $F(1, 70) = 13.24$, $p = .001$, $\eta_p^2 = .16$, and restlessness increased, Group × Time: $F(1, 70) = 19.89$, $p < .001$, $\eta_p^2 = .22$, from before to after the experimental manipulation in the stress

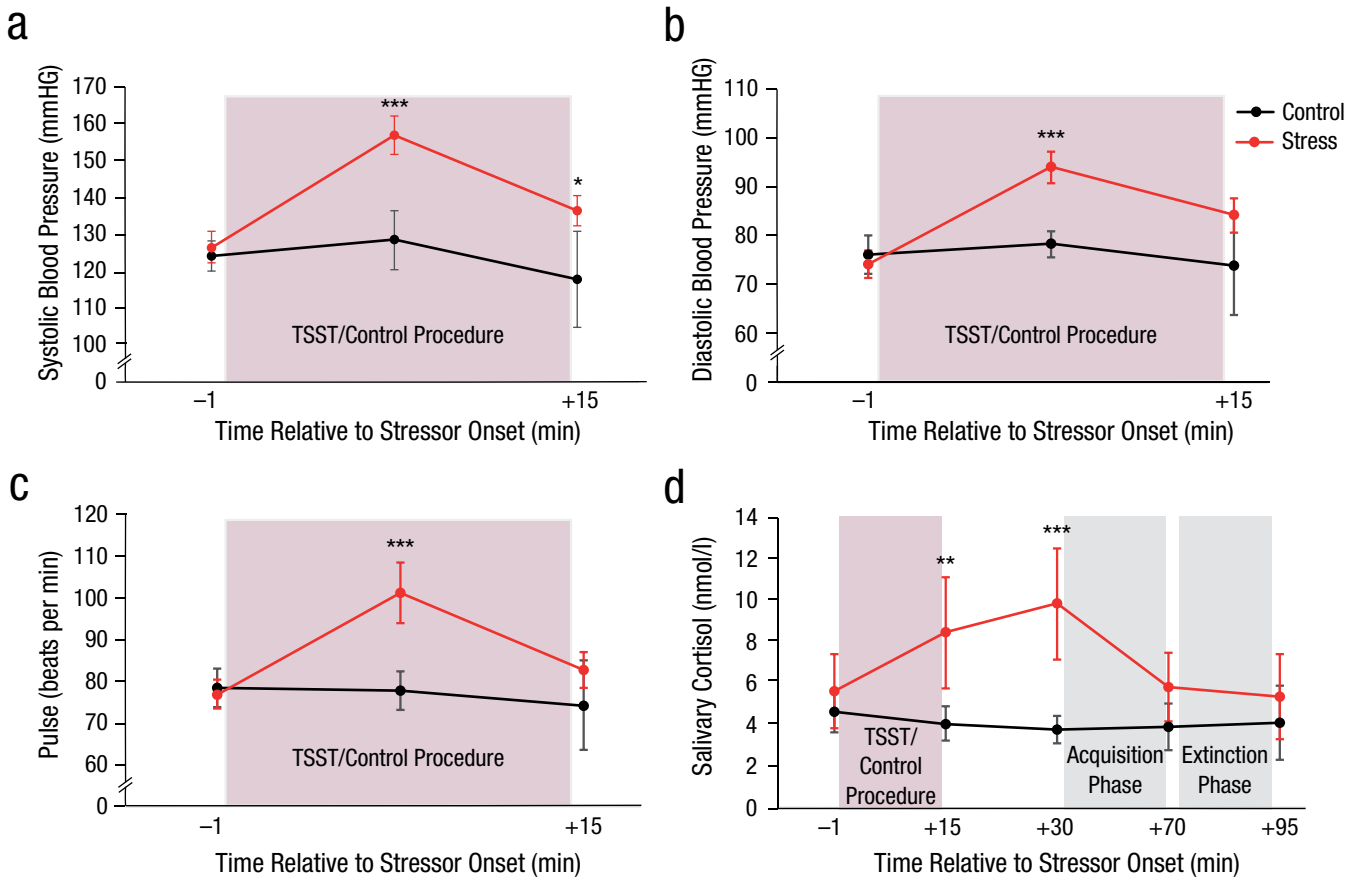


**Fig. 2.** Physiological stress responses. Mean (a) systolic blood pressure, (b) diastolic blood pressure, (c) and pulse rate are shown immediately before, during, and immediately after exposure to the Trier Social Stress Test (TSST) and the control procedure. Mean (d) salivary cortisol is shown before and immediately after the TSST and control procedure, as well as 30, 70, and 95 min after the onset of the experimental manipulation. Asterisks indicate significant differences between groups (**$p < .01$, ***$p < .001$). Error bars indicate 95% confidence intervals.

condition but not in the control condition, whereas there was no treatment-related change in wakefulness, Group × Time: $F(1, 70) = 0.13$, $p = .724$, $\eta_p^2 < .01$ (see Table S1 in the Supplemental Material available online).

At the physiological level, exposure to the TSST resulted in a significant increase in systolic blood pressure, Group × Time: $F(1.517, 104.694) = 9.28$, $p = .001$, $\eta_p^2 = .12$; in diastolic blood pressure, Group × Time: $F(1.214, 84.950) = 7.79$, $p = .004$, $\eta_p^2 = .10$; and in pulse, Group × Time: $F(1.713, 118.193) = 11.70$, $p < .001$, $\eta_p^2 = .15$. As shown in Figures 2a to 2c, these markers of autonomic-nervous-system activity were comparable in the two groups before the experimental manipulation, all $t$s(70) < 0.82, all $p$s > .41, but significantly higher in the stress group relative to the control group during the manipulation—systolic blood pressure: $t(70) = 5.77$, $p_{corr} < .001$, $d = 1.36$; diastolic blood pressure: $t(70) = 7.32$, $p_{corr} < .001$, $d = 1.72$; pulse: $t(57.77) = 5.29$, $p_{corr} < .001$, $d = 1.25$.

Finally, the TSST also led to a significant increase in salivary cortisol, Group × Time: $F(1.538, 107.626) = 8.43$, $p = .001$, $\eta_p^2 = .11$. Whereas groups did not differ in their cortisol concentrations at baseline ($p = .33$), cortisol concentrations increased in response to the TSST but not in response to the control manipulation (see Fig. 2d). The stress-induced cortisol elevation reached peak levels 30 min after stressor onset, $t(70) = 4.28$, $p_{corr} < .001$, $d = 1.01$, when the fear-learning task started, and returned to the level of the control group before the beginning of the extinction phase—before extinction: $t(70) = 1.88$, $p_{corr} = .320$, $d = 0.44$; after extinction: $t(70) = 0.826$, $p = .412$, $d = 0.20$.

## *Exploration phase*

During the exploration phase, participants rated the virtual environment overall as low arousing ($M = 0.49$, $SD = 0.51$) and as neutral to slightly positive ($M = 2.03$, $SD = 0.43$), without any differences between groups or the three contexts (all $F$s < 2.26, all $p$s > .109). Moreover, SCRs were comparable in the three contexts and between groups, and both groups spent a comparable

amount of time in each of the three contexts (all $F$s < 1.61, all $p$s > .202; see Table S2 in the Supplemental Material).

## *Acquisition phase*

SCR data showed strong cue-dependent fear conditioning that developed across the acquisition phase—CS Type × Block: $F(2.65, 185.29) = 3.26$, $p = .028$, $\eta_p^2 = .04$; main effect of CS type: $F(1, 70) = 15.51$, $p < .001$, $\eta_p^2 = .18$. Whereas SCRs were comparable for the CS+ and CS– in the first acquisition block ($p = .649$), SCRs were significantly higher for the CS+ than for the CS– in the second block, $t(71) = 2.93$, $p_{corr} = .020$, $d = 0.33$; third block, $t(71) = 3.09$, $p_{corr} = .012$, $d = 0.34$; and fourth block, $t(71) = 3.61$, $p_{corr} = .004$, $d = 0.41$. Importantly, cue-dependent fear conditioning during the acquisition phase was comparable in the stress and control groups—CS Type × Group and CS Type × Group × Block: both $F$s < 1.49, both $p$s > .226 (see Figs. 3a and 3b). Accordingly, there was also no association between cue-dependent fear conditioning and the cortisol response to the experimental manipulation ($r = –.13$, $p = .257$).

Our analysis of the SCRs to the context, however, revealed striking group differences (see Figs. 3c and 3d). In particular, a mixed-design ANOVA yielded a significant Context × Group interaction, $F(1.806, 126.019) = 6.60$, $p = .003$, $\eta_p^2 = .09$. In the control group, SCRs indicated strong context-dependent conditioning, main effect of context: $F(1.64, 57.49) = 8.97$, $p = .001$, $\eta_p^2 = .20$, with significantly higher SCRs when entering the risk context than when entering Safe Context 1 ($p_{corr} = .005$) or Safe Context 2 ($p_{corr} = .007$). This context-dependent conditioning effect developed quickly, with significantly stronger responding to the risk context (vs. average safe contexts) after only four trials (Block 2: $p_{corr} = .004$; Block 1: $p_{corr} = .18$). In the last block of acquisition, the difference between SCRs to risk contexts versus safe contexts was weaker ($p_{corr} = .291$), most likely because of a general habituation of SCRs across blocks, $F(2.234, 156.369) = 21.49$, $p < .001$, $\eta_p^2 = .24$, which occurred irrespective of context or group (all $p$s > .421). In sharp contrast to the pattern in the control group, there was no indication of context-dependent conditioning in the stress group, main effect of context: $F(2, 70) = 0.09$, $p = .911$, $\eta_p^2 < .01$. Interestingly, the degree of contextual fear conditioning, indicated as the difference between SCRs to the risk context and the average SCRs to the safe contexts, was negatively correlated with the cortisol response to the experimental manipulation ($r = –.30$, $p = .010$).

To directly compare the relative balance of cue- and context-dependent fear conditioning in the stress and control groups, we ran a Group × Type of Conditioning ANOVA with the differences between CS+ and CS– and between risk and safe contexts as indices of cue- and context-dependent conditioning, respectively. This analysis yielded a significant Group × Type of Conditioning interaction, $F(1, 70) = 4.70$, $p = .034$, $\eta_p^2 = .06$, indicating significantly stronger cue-dependent than context-dependent fear conditioning in the stress group, $F(1, 35) = 4.57$, $p = .040$, $\eta_p^2 = .12$, whereas the extent of cue-dependent and contextual fear conditioning was comparable in the control group, $F(1, 35) = 1.69$, $p = .202$, $\eta_p^2 = .05$.

Cue-related subjective arousal ratings remained unaffected by CS type and group (all $F$s < 2.14, all $p$s > .097; see Table S3 in the Supplemental Material). Arousal ratings, however, were significantly higher after participants entered the risk context than the safe contexts, with differential responding increasing across blocks—Context × Block: $F(4.63, 324.09) = 9.87$, $p < .001$, $\eta_p^2 = .12$; main effect of context: $F(1.55, 108.26) = 30.99$, $p < .001$, $\eta_p^2 = .31$. Furthermore, there was a nonsignificant trend for a Group × Context interaction, $F(1.55, 108.26) = 2.91$, $p = .072$, $\eta_p^2 = .04$; Group × Context × Block, $F(4.63, 324.09) = 1.92$, $p = .097$, $\eta_p^2 = .03$. Follow-up tests suggested that context-related subjective arousal was significant in both groups but stronger in the control group, $F(1.42, 49.74) = 22.91$, $p < .001$, $\eta_p^2 = .40$, than in the stress group, $F(2, 70) = 8.84$, $p < .001$, $\eta_p^2 = .20$. Finally, analyses of shock-expectancy ratings showed that participants cognitively learned the association of the CS+ and risk context, respectively, with the shock, irrespective of the experimental group. More specifically, we obtained a significant CS Type × Block interaction, $F(2.64, 184.57) = 4.11$, $p = .010$, $\eta_p^2 = .06$, and a significant Context × Block interaction, $F(3.43, 239.96) = 11.12$, $p < .001$, $\eta_p^2 = .14$, suggesting that the shock expectancy increased for the CS+ (vs. CS–) and risk context (vs. Safe Context 1 and Safe Context 2) across the acquisition phase (see Table S3). Context- and cue-related shock-expectancy ratings, however, were comparable in the stress and control groups (all $F$s < 2.88, all $p$s > .093).

## *Extinction phase*

Cue-dependent fear extinction differed significantly between the stress and control groups, CS Type × Block × Group: $F(2, 140) = 3.28$, $p = .041$, $\eta_p^2 = .05$. As shown in Figures 4a and 4b, the control group showed a gradual extinction of cue-dependent fear, CS Type × Block: $F(2, 70) = 5.02$, $p = .009$, $\eta_p^2 = .13$, with still stronger SCRs to the CS+ than to the CS– in the first block of extinction ($p_{corr} = .003$) but comparable SCRs to both stimuli in the second block of extinction ($p_{corr} = .205$) and third block of extinction ($p = .584$). In stressed participants, however, the SCRs to the CS+ did not

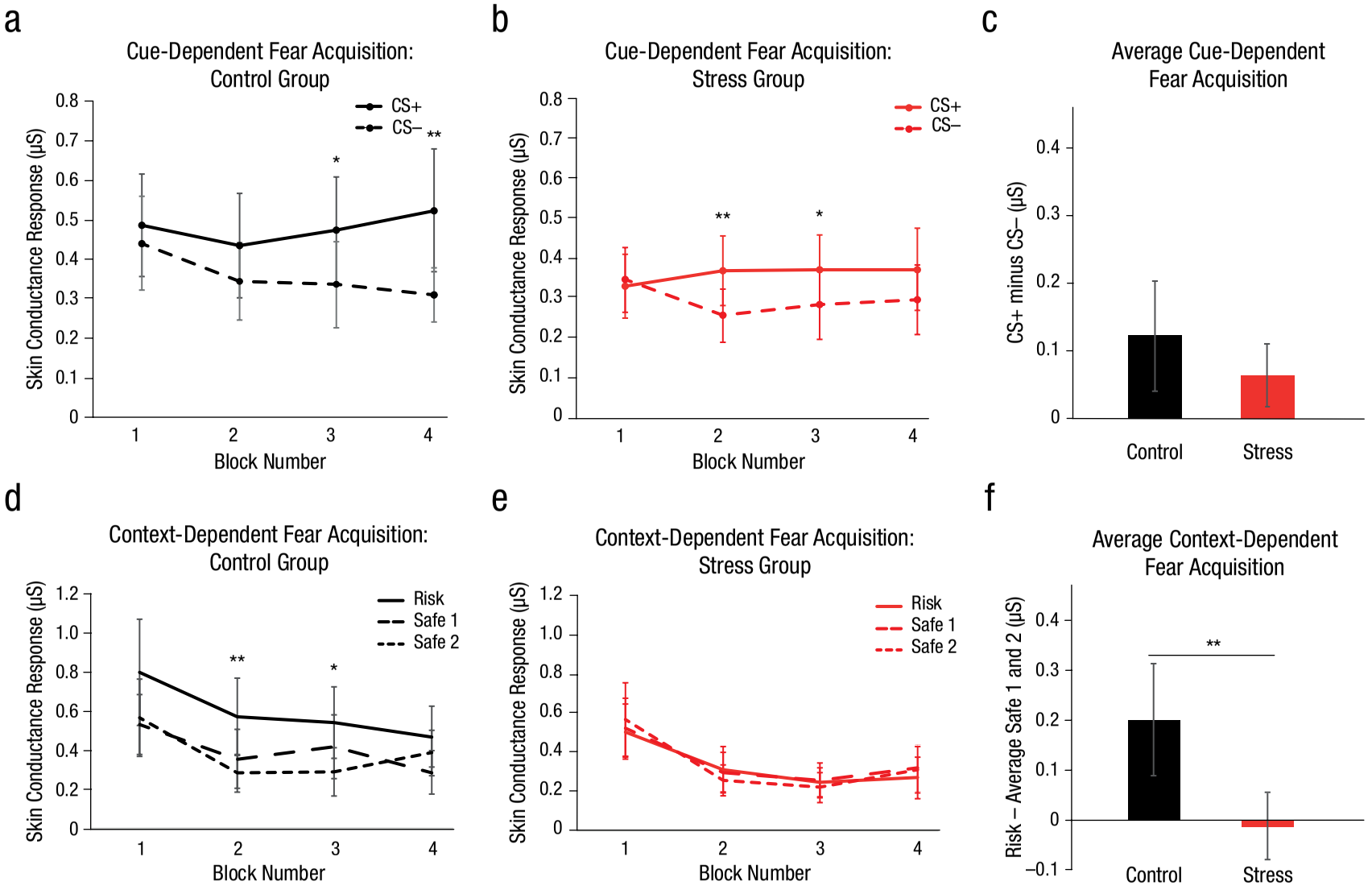


**Fig. 3.** Cue-dependent and context-dependent fear acquisition. In the top row, mean skin conductance response (SCR) in each block is shown for participants exposed to the positive conditioned stimulus (CS+) and the negative conditioned stimulus (CS–) in both the (a) control group and (b) stress group. The difference in SCRs to the CS+ and CS– (c) is shown for each group collapsed across blocks. In the bottom row, mean SCR in each block is shown when participants in (d) the control group and (e) the stress group entered the risk context, Safe Context 1, and Safe Context 2. The difference between SCR in the risk context and average SCRs in the two safe contexts (f) is shown for each group collapsed across blocks. Asterisks indicate significant differences between groups (*$p < .05$, **$p < .01$). Error bars indicate 95% confidence intervals.

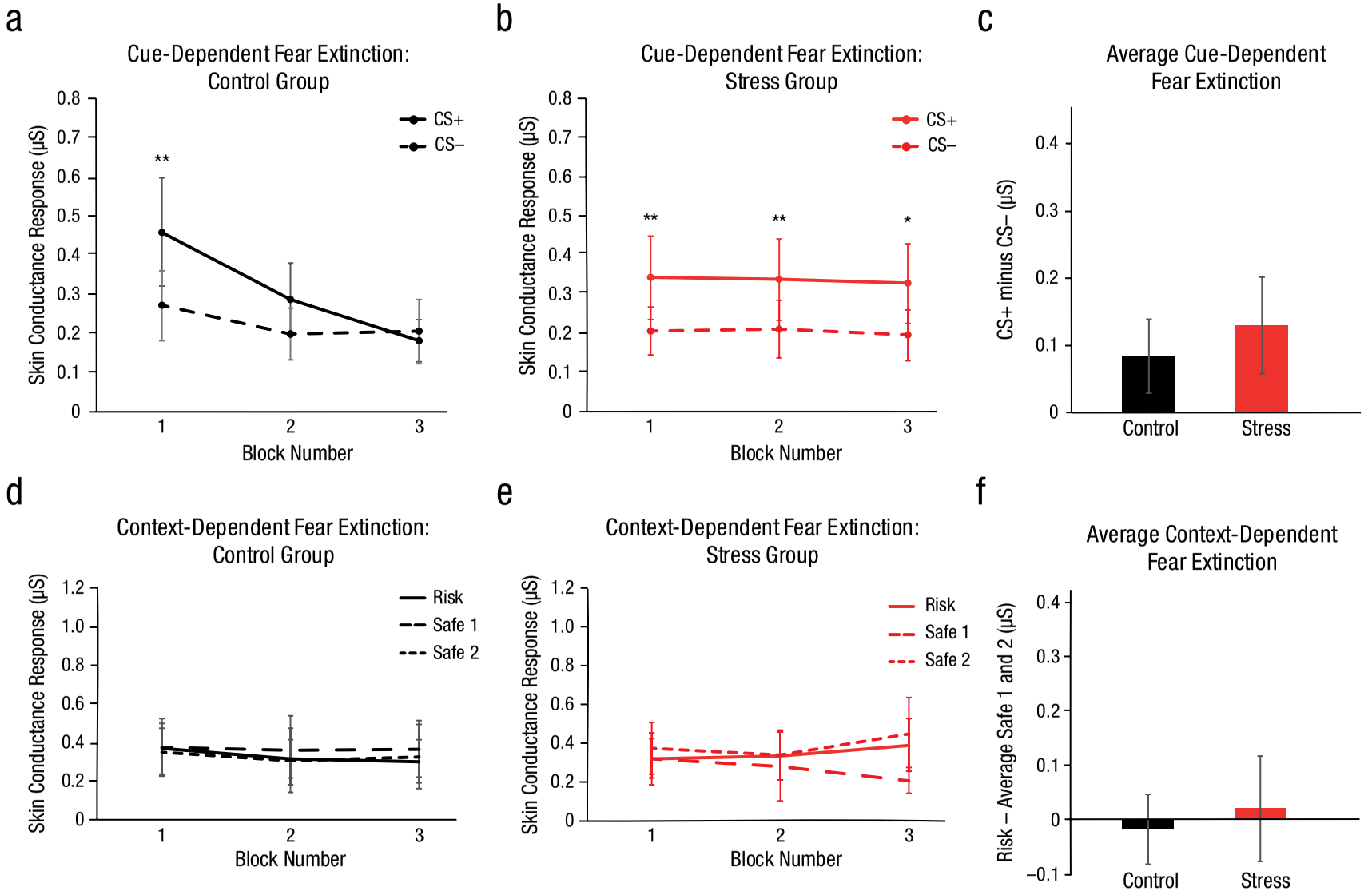


**Fig. 4.** Cue-dependent and context-dependent fear extinction. In the top row, mean skin conductance response (SCR) in each block is shown for participants exposed to the positive conditioned stimulus (CS+) and the negative conditioned stimulus (CS–) in both the (a) control group and (b) stress group. The difference in SCRs to the CS+ and CS– (c) is shown for each group collapsed across blocks. In the bottom row, mean SCR in each block is shown when participants in (d) the control group and (e) the stress group entered the risk context, Safe Context 1, and Safe Context 2. The difference between SCR in the risk context and average SCRs in the two safe contexts (f) is shown for each group collapsed across blocks. Asterisks indicate significant differences between groups (*$p < .05$, **$p < .01$). Error bars indicate 95% confidence intervals.

decrease significantly across the extinction session, $F(1.68, 58.95) = 0.01$, $p = .976$, $\eta_p^2 < .01$. In the first block ($p_{corr} = .003$) and second block ($p_{corr} = .009$), participants showed significantly stronger SCRs to the CS+ relative to the CS–; even in the third block, there was a trend (after Bonferroni correction) for stronger SCRs to the CS+ ($p_{corr} = .090$). Not surprisingly, the SCRs to the CS+ (vs. CS–) during extinction were significantly correlated with those during acquisition ($r = .26$, $p = .026$).

Context-related SCRs across blocks of extinction were overall rather low, in line with the habituation observed already at the end of acquisition, and did not reveal any significant differences between contexts or groups (all main and interaction effects: $F$s < 2.50, $p$s > .085). We reasoned that this absence of a context effect during conditioning might further be due to the fact that extinction was analyzed in blocks of two trials each and that context-dependent conditioning might have extinguished very quickly. Therefore, we focused in an additional, exploratory analysis on the first extinction trial only. For the first trial of extinction, stressed participants ($M = 0.326$, $SD = 0.429$) showed a reduced SCR to the risk context compared with control participants ($M = 0.505$, $SD = 0.541$). Yet because this difference did not reach statistical significance, $t(70) = 1.56$, $p = .062$, one tailed, $d = 0.37$, and SCR analysis for a single trial is generally not very reliable, this exploratory finding is to be interpreted with caution. SCR measures of cued and contextual fear during extinction were not correlated with the cortisol response to the experimental treatment (all $r$s < .08, all $p$s > .514).

Subjective arousal during the extinction session tended to be higher for the CS+ than for the CS–, $F(1, 70) = 3.27$, $p = .075$, $\eta_p^2 = .05$, without differences between groups (all $F$s < 1.98, all $p$s > .163; see Table S4 in the Supplemental Material). The arousal provoked by the risk context (vs. Safe Context 1 and Safe Context 2) was high overall in the first extinction block (both $p_{corr}$s < .001) and decreased over the second block (both $p_{corr}$s < .022) and third block (both $p_{corr}$s > .395), Context × Block: $F(2.99, 209.06) = 6.25$, $p < .001$, $\eta_p^2 = .08$. However, the context-related arousal also did not differ between groups in the extinction phase (all $F$s < 1.04, all $p$s > .37). For cue-related shock-expectancy ratings, there was an overall decrease across blocks, $F(1.58, 111.14) = 117.15$, $p < .001$, $\eta_p^2 = .63$, without differences between CS types or groups (all $F$s < 1.74, all $p$s > .191). The expectation of receiving a shock in the risk context (vs. Safe Context 1 and Safe Context 2), however, was still high in the first extinction block ($p_{corr} < .001$) but not high any longer in the second and third blocks (both $p$s > .357). Again, there were no group differences in context-related shock-expectancy ratings (all $F$s < 1.11, all $p$s > .33, all $\eta_p^2$s < .02).

For exploratory analyses of differences between men and women in the impact of stress on cued and contextual fear acquisition and extinction, see the Supplemental Material.

### *Control variables*

Overall, participants' levels of chronic stress, depressive mood, and state or trait anxiety were relatively low, and the stress and control groups did not differ in these measures (all $p$s > .443; see Table S5 in the Supplemental Material). Furthermore, there were no differences between groups with respect to gaming experience or years of education, nor did groups differ in the number of shocks received during acquisition or the individual shock intensity (all $p$s > .382; see Table S5). Finally, the questionnaire after the extinction session suggested that groups were comparable in their explicit knowledge about the task (all $p$s > .077; see Table S6 in the Supplemental Material).

## Discussion

Here, we showed for the first time that acute stress biases the balance of cued and contextual fear learning toward cue-dependent responding and does so at the expense of context-dependent fear conditioning. Specifically, stressed participants showed, in sharp contrast to nonstressed control participants, no contextual fear acquisition in a task that allowed both cue- and context-dependent fear learning. At the same time, stress led to enhanced cue-dependent fear conditioning as reflected in increased resistance to extinction. The stress-induced reduction in extinction of cue-dependent fear was observed even though the cue was relocated to another context during extinction, which further underlines the decontextualized fear response after stress.

The current study extends earlier studies on stress and fear conditioning in several important ways. First, whereas there is evidence from rodents that stress or stress hormones may affect context-dependent fear conditioning (Cordero et al., 2002; Cordero et al., 1998; Toledo-Rodriguez & Sandi, 2007; Zhou et al., 2010), the present study is, to the best of our knowledge, the first to show a stress-induced impairment of contextual fear acquisition in healthy humans. This stress-induced impairment in contextual fear learning dovetails with findings from episodic memory suggesting that stress before learning reduces the incorporation of context information into the episodic memory trace (Schwabe et al., 2009; van Ast, Cornelisse, Meeter, Joëls, & Kindt, 2013). Moreover, our results are generally in line with rodent data suggesting that prolonged stress specifically interferes with contextual fear conditioning but leaves cue-dependent conditioning intact (Diamond et al.,

2007; for mechanistic insights into how stress primarily affects hippocampal memory, see Zoladz et al., 2012).

Second and even more importantly, we here tested cued and contextual fear learning in a single task, which is a prerequisite to probe the balance of these two forms of fear conditioning. Our data demonstrated that whereas cue- and context-dependent fear acquisition were equally strong in nonstressed control participants, cue-dependent fear acquisition was significantly stronger than context-dependent fear acquisition in stressed participants. The stress-induced strengthening of cue-dependent fear learning became further apparent in its increased resistance to extinction. Contextual fear conditioning, however, was virtually absent after stress. It is well known that contextual fear conditioning relies heavily on the hippocampus (Maren, 2001; Phillips & LeDoux, 1992), which in turn is highly sensitive to the stress hormone cortisol (de Quervain et al., 2003; Kim & Diamond, 2002). The interpretation that cortisol may have been a driving force in the stress-induced modulation of the balance of contextual and cued fear conditioning is further supported by the negative correlation between the cortisol response to the treatment and the degree of context-dependent fear conditioning that we observed here. Further support for a critical role of cortisol in the impairment of contextual fear comes from research indicating that testing rats at a time of increased glucocorticoid concentrations impairs contextual fear conditioning, whereas testing at a time when adrenergic activation prevails but glucocorticoid levels have not reached peak levels may even facilitate contextual fear learning (Diamond et al., 2007). Overall, the present findings are in line with evidence that stress induces a shift from flexible but cognitively demanding forms of learning toward simpler, more reflexive forms of learning (Goodman et al., 2012; Schwabe, 2017; Vogel et al., 2016), but our findings show this modulation of multiple memory systems for the first time in the domain of fear learning.

Although we assume that stress biased the balance of cue-dependent and contextual fear learning during acquisition, it might also be argued that stress solely affected contextual fear acquisition and left cue-dependent acquisition unchanged but then impaired cue-dependent extinction. We consider this latter interpretation rather unlikely. First, there was a significant correlation between cue-dependent fear responses during acquisition and extinction. Although not at all surprising, this correlation underlines that responding during extinction was closely linked to what was learned during acquisition. Moreover, the acquisition phase was timed to begin when stress-induced cortisol levels peaked in order to maximize the impact on fear acquisition. At the time of extinction, cortisol levels in the stress group were already comparable with those in the control group; autonomic and subjective stress responses were most likely back to baseline (Kirschbaum et al., 1993; Kudielka et al., 2007). However, there is evidence that, in addition to rapid, nongenomic effects of cortisol, there are also genomic cortisol actions that are delayed but may last significantly longer than the acute rise in cortisol (Joëls et al., 2011). Thus, although it remains unclear whether genomic cortisol actions had already developed at the time of extinction testing and we obtained some evidence to suggest a stress effect primarily on fear acquisition, we cannot definitely separate stress effects on acquisition and extinction in our study. However, no matter whether the present pattern of results is attributed to stress-induced changes during acquisition or extinction, it does show a stress-induced bias toward cue-dependent fear-learning processes at the expense of context-dependent fear-learning processes.

It is important to note that the effects of stress on cue-dependent and context-dependent fear learning were reflected in SCRs but less or not at all in ratings of subjective arousal or shock expectancy. Such discrepancies have been observed in previous studies as well (Cornelisse, van Ast, Joëls, & Kindt, 2014; Lonsdorf & Merz, 2017) and are thought to indicate that those measures reflect different aspects of fear learning. In particular, an evolved fear-learning module has been proposed that is automatic and relatively independent from cognitive learning of stimulus relationships (Öhman & Mineka, 2001). Thus, physiological measures such as SCRs may be better suited to capture this fear-learning module. In addition, a distinction between physiological, automatic fear responses on the one hand and cognitive assessments on the other hand is also very common in fear-related psychopathologies such as phobias (Öhman & Mineka, 2001).

Finally, it should be noted that contextual fear conditioning was rather low, even in the control group, at the end of acquisition and extinguished quickly, suggesting that contextual conditioning was weaker than cue-dependent conditioning, even in control participants. Although our trial procedure ensured that contextual and cued fear responses could be distinguished, the finding that cue-dependent fear responses in the control group were strongest at the end of the acquisition phase and still present in the first block of extinction, whereas contextual fear responses were strongest in the second and third blocks of acquisition, might suggest that cue-dependent and context-dependent fear learning may have interacted in some way. In particular, the development of strong cue-related fear learning might have diminished the fear response to the context. Although we did not find direct evidence for this idea in our study, understanding the dynamic interplay of

contextual and cued fear learning, after stress as well as without stress, remains an important challenge for future research.

In sum, our study shows that acute stress may shape the nature of fear learning by enhancing responses to discrete cues preceding an aversive event but impairing the contextual embedding of the aversive encounter. These findings may have critical implications for understanding fear-related disorders, such as PTSD, in which fear is decontextualized but triggered by single cues (e.g., odors, tones) and in which stress is a major factor.

## Action Editor

Ian H. Gotlib served as action editor for this article.

## Author Contributions

L. Schwabe designed the experiment and supervised the project. C. Hiller programmed the task. K. Simon-Kutscher collected the data. L. Schwabe, K. Simon-Kutscher, and N. Wanke analyzed the data. L. Schwabe drafted the manuscript; all other authors provided critical revisions. All the authors approved the final manuscript for submission.

## ORCID iD

Lars Schwabe https://orcid.org/0000-0003-4429-4373

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## Supplemental Material

Additional supporting information can be found at http://journals.sagepub.com/doi/suppl/10.1177/0956797619852027

## Open Practices

All data have been made publicly available and can be accessed at https://osf.io/dxvrq. All materials and scripts will be provided by the corresponding author on request. This project was preregistered on the Open Science Framework and can be accessed at https://osf.io/vutr9/. The complete Open Practices Disclosure for this article can be found at http://journals.sagepub.com/doi/suppl/10.1177/0956797619852027. This article has received the badges for Open Data and Preregistration. More information about the Open Practices badges can be found at http://www.psychologicalscience.org/publications/badges.

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