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# Multiple extinction contexts modulate the neural correlates of context-dependent extinction learning and retrieval

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ABSTRACT

Exposure therapy is a successful treatment for patients with anxiety and fear-related disorders. Extinction of conditioned fear comprises one important mechanism underlying the effects of exposure therapy. Yet, relapses frequently occur in the long-term, probably related to difficulties in generalizing the extinction of conditioned fear to new contexts, leading to renewal of conditioned fear. Extinction training in multiple extinction contexts depicts a promising opportunity to reduce this renewal of conditioned fear. However, the underlying neural correlates are unknown yet. In this functional magnetic resonance imaging study, 49 healthy men participated in a fear conditioning paradigm with fear acquisition training in context A on a first day, extinction training in a single context (B1) or in four different contexts (B1-B4) one day later, and fear and extinction recall and reinstatement in context B1 and a novel context C on a third day one week later. Multiple extinction contexts led to a stronger differential activation decrease in the hippocampus during extinction learning compared to a single extinction context. One week later, the multiple context group compared with the single context group showed reduced differential amygdala activation during fear renewal in the novel context C compared with the extinction context B1. Furthermore, multiple extinction contexts diminished amygdala activation during a subsequent reinstatement test in context B1. However, there were no significant differences in differential conditioned SCRs. These results indicate that the use of multiple extinction contexts during extinction training leads to reduced conditioned responses in the amygdala-hippocampus complex.

## 1. Introduction

Return of fear (ROF) after successful exposure therapy represents one of the major challenges in the treatment of anxiety disorders (McNally, 2007; Yonkers, Bruce, Dyck, & Keller, 2003). Besides other mechanisms of action, exposure therapy is thought to be mediated by the extinction of conditioned fear (Craske, Hermans, & Vervliet, 2018; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). Research in animals and humans has characterized several phenomena leading to the reoccurrence of fear in response to conditioned stimuli (CS) following successful extinction: In addition to a mere passage of time (spontaneous recovery) and the un-signaled presentation of the unconditioned stimulus (UCS; reinstatement), contextual changes (renewal) and psychopathology have been found to reduce extinction memory retrieval (Bouton, 2002; Quirk & Mueller, 2008). These findings suggest extinction training to lead to the development of a new inhibitory memory trace (CS-NoUCS) in addition to the CS-UCS memory arising from fear acquisition, rather than erasing the original CS-UCS association (Bouton, 2004; Quirk & Mueller, 2008; Vervliet, Baeyens, van den Bergh, & Hermans, 2013). In consequence, a CS can activate both memory traces, the fear memory trace as well as the extinction memory trace. The amount of conditioned fear expression therefore depends on the amount each of these memory traces is activated relatively to the other.

On the neural level, the amygdala seems to be related to both the acquisition and storage of fear as well as extinction memories (Quirk & Mueller, 2008). The ventromedial prefrontal cortex (vmPFC) is thought to reduce and the dorsal anterior cingulate cortex (dACC) to enhance

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conditioned fear expression by modulating fear output from the amygdala during delayed recall (Milad & Quirk, 2012). Alterations in this neural circuit have been shown to underlie dysfunctional extinction recall in anxiety and fear-related disorders (Graham & Milad, 2011; Milad et al., 2009). Difficulties in the transfer of therapy effects into new situations and contexts might be related to ROF after successful exposure therapy. Basic experimental research suggests that returning to the acquisition context or entering a new context leads to enhanced conditioned fear expression (e.g. indicated by increased skin conductance responses, SCRs), the so-called 'renewal' effect (Bouton, 2004; Vervliet et al., 2013). Animal research suggests that this contextual gating of conditioned fear and extinction recall relies on the hippocampus (Maren, Phan, & Liberzon, 2013). Also, human neuroimaging studies show hippocampal activation in the 'safe' extinction context (Hermann, Stark, Milad, & Merz, 2016; Kalisch et al., 2006; Milad et al., 2007) as well as in the acquisition context or a novel context (Hermann et al., 2016; Kalisch et al., 2006). Additionally, functional and structural connectivity of the hippocampus with other important brain regions of the fear and extinction network is related to renewal in a novel context (Hermann et al., 2016; Hermann, Stark, Blecker, Milad, & Merz, 2017).

One opportunity to reduce ROF is to carry out exposure therapy or extinction training in several different contexts and situations. Multiple extinction contexts compared with a single extinction context have been shown to result in reduced fear renewal when tested within the acquisition context (Chelonis, Calton, Hart, & Schachtman, 1999; Neumann, 2006; but see Bouton, García-Gutiérrez, Zilski, & Moody, 2006; Neumann, Lipp, & Cory, 2007), or a novel context (Balooch, Neumann, & Boschen, 2012; Gunther, Denniston, & Miller, 1998; but see Bouton et al., 2006). Clinical studies also indicate a beneficial effect of exposure therapy carried out in multiple contexts in spider anxious and phobic individuals (Bandarian-Balooch, Neumann, & Boschen, 2015; Shiban, Pauli, & Mühlberger, 2013; Vansteenwegen et al., 2007). One study further demonstrated a positive effect of multiple extinction contexts on extinction memory recall during reinstatement in a novel context (Dunsmoor, Ahs, Zielinski, & LaBar, 2014). However, to date there are no studies investigating the effects of multiple extinction contexts on the neural circuit underlying the modulation of extinction learning, extinction recall and renewal in a novel context as well as reinstatement.

In the current study, 49 healthy men participated in a three-day differential fear conditioning paradigm during functional magnetic resonance imaging (fMRI) with parallel assessment of SCRs. Fear acquisition training was conducted in context A on a first day, followed by extinction training in context B1 (single context group) or contexts B1, B2, B3 and B4 (multiple context group) approximately 24 h later. Extinction recall in context B1 and in a novel context C took place before and after application of four reinstatement shocks one week after extinction training. Multiple extinction contexts were particularly expected to attenuate fear renewal as reflected in reduced conditioned SCRs, amygdala, insula and dACC as well as enhanced vmPFC activation in response to the novel (compared with the extinction) context. Furthermore, hippocampal activation was hypothesized to be altered during extinction learning, recall, renewal and reinstatement test.

## 2. Methods and materials

### 2.1. Participants

A sample of 63 healthy male participants (mainly students), recruited with mailing lists at the local university, participated in this fMRI study at the Justus Liebig University Giessen (Germany). MRI contraindications, self-reported chronic or acute illnesses or psychiatric disorders, color blindness, regular intake of medicine, current medical or psychological treatment, drug use, or age younger than 18 or older than 35 years comprised exclusion criteria for this study. Additionally, all participants had to be right-handed as assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971), and had normal or corrected-to-normal vision.

A total of 14 participants were excluded due to the following problems/exclusion criteria: technical problems during scanning ($n = 5$), missing contingency awareness regarding the observed associations between CS and UCS during fear acquisition training (see below; $n = 6$), and early termination of the experiment ($n = 3$), leaving a final sample of 49 participants (age: $M = 24.14$ years, $SD = 2.4$ years), with 25 participants in the single context group and 24 participants in the multiple context group. For reimbursement, participants obtained 10€/h for their participation. All procedures were in accordance with the Declaration of Helsinki and approved by the local ethical review board of the Faculty of Psychology and Sports Science at the Justus Liebig University Giessen.

### 2.2. Stimulus material

Stimuli and procedure were adopted from previous studies (Hermann et al., 2016; Milad et al., 2007). Three additional context pictures were prepared for the investigation of extinction training in multiple contexts. Altogether, pictures of six different rooms served as contexts: an office room, a room with a shelf, a conference room, a library room, a room with a reception desk, and a printer room. Each of the contexts contained a desk lamp for CS presentation. The lamp in the context pictures, lighting up either in red, blue or yellow, served as the three CS. Stimuli were shown on a 32″ LCD monitor (NordicNeuroLab Inc. Milwaukee, WI, USA) behind the scanner (visual field = 28°) and viewed via a mirror mounted to the head coil during the experimental phases.

Electrical stimulation (1 ms pulses with 50 Hz for a duration of 500 ms) was applied as the UCS and administered by a transcutaneous aversive finger stimulator (Model E13-22 Coulbourn Inc) via electrodes (surface size: 1 $cm^2$) attached to the fingertips of the second and third fingers of the right hand. Using a gradually increasing rating procedure the intensity of the electrical stimulation was set individually to be 'unpleasant but not painful'. The intensity of electrical stimulation was on average set to $M = 1.896$ mA ($SD = 0.669$, range = 0.8–4.0 mA). Unpleasantness ratings (1 = 'not unpleasant' to 9 = 'very unpleasant') during the shock workup procedure resulted in a mean value of 7.8 ($SD = 0.79$, range = 6–9). Groups did not differ in the intensity of electrical stimulation or unpleasantness ratings (both $T < 1.2$, both $p > 0.25$).

### 2.3. Procedure

On the first day, participants gave written informed consent, filled out questionnaires on demographic variables, and were tested for red-green color blindness using five Ishihara plates (selected from Ishihara, 1990). Before the start of the fear conditioning experiment, participants were instructed to attentively watch the presentation of pictures and try to figure out any possible regularity in the occurrence of lamplight colors and electrical stimulation. Furthermore, they were informed that if they should discover such an association, this relationship remains stable in all experimental phases: if a lamplight color was safe, it would always be safe; if a lamplight color was followed by electrical stimulation, this might or might not occur again. The instruction was given in order to facilitate learning of contingencies between CS and UCS/No-UCS (contingency awareness; a prerequisite for studying extinction learning and recall), and to avoid participants to expect a complete reversal of contingencies during extinction training. The participants have not been informed about the actual CS-UCS contingencies.

The following trial sequence was identical for all CS types during all experimental phases (except for trials with UCS presentation, which were only present during fear acquisition training; see Fig. 1). After the presentation of a black screen with a white fixation cross (jittered

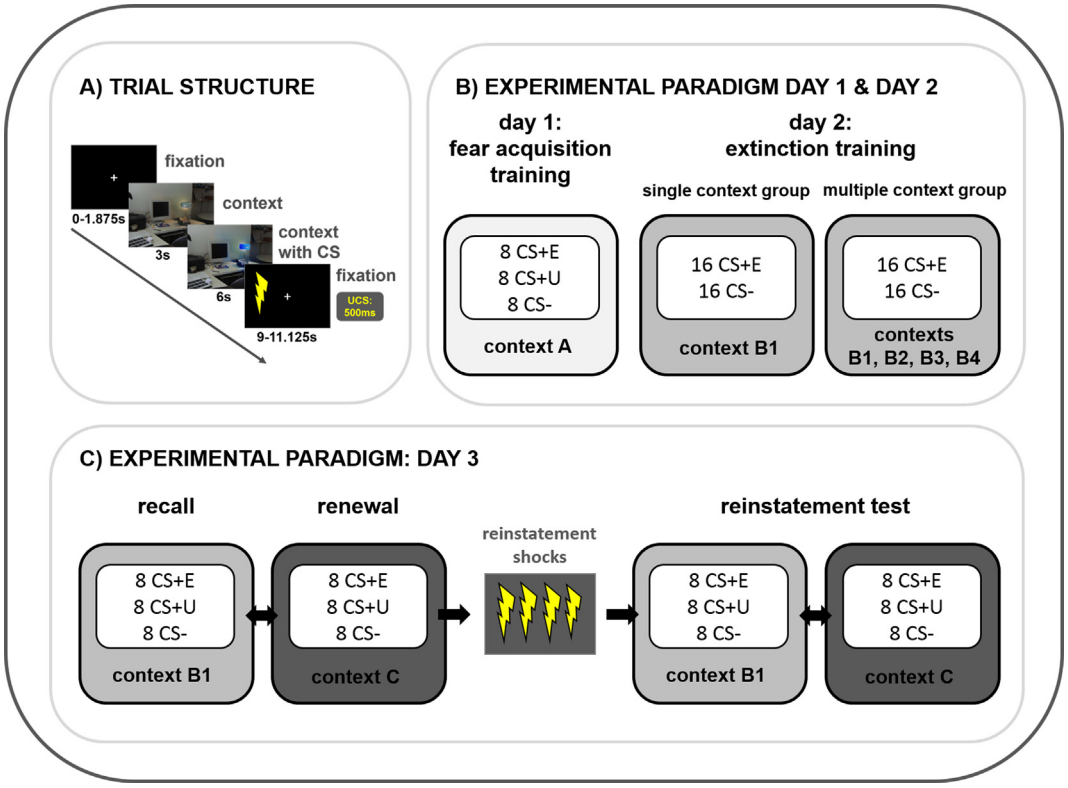


**Fig. 1.** Experimental procedure of the context-dependent fear conditioning task. (A) Trial structure and trial timing. (B) Experimental paradigm day 1 (fear acquisition training) and day 2 (extinction training). (C) Experimental paradigm day 3 (extinction recall, renewal, reinstatement test). For details see methods section.

duration between 625 and 2500 ms), the context was presented without CS for a duration of 3000 ms. Afterwards, the CS (lamp within the context picture shining either in red, blue, or yellow for the three CS types) was presented for a duration of 6000 ms. The UCS (electrical stimulation) was delivered at the end of the CS presentation for a duration of 500 ms during reinforced CS+ trials. From CS offset until the start of the next context presentation, a white fixation cross on a black background was shown for a duration of 9125–11,000 ms (total trial duration: 20 s).

All participants underwent fear acquisition training in context A on day 1 and extinction training in a single context B1 (single context group) or four different contexts (B1, B2, B3, B4; multiple context group) on day 2 approximately 24 h later. Extinction recall and renewal before and after reinstatement (including four un-signaled UCS presentations) were tested in the extinction context B1 and in a novel context C on day 3 (6–8 days after day 2; $M_{days}$ = 6.98, $SD_{days}$ = 0.25). During all phases of the experiment, the electrodes for delivery of the electrical stimulation were kept attached to the fingers.

During fear acquisition training in context A, two separate CS+ (CS+E and CS+U (see below); e.g. red and yellow light) were shown eight times each, and both CS+ were paired with the UCS in five out of eight trials (62.5% partial reinforcement rate). The CS− (e.g. blue light) was never paired with the UCS and shown eight times. The first three and the last three trials consisted of presentations of the CS+E (reinforced), CS+U (reinforced), and CS−, respectively. The order of the first three CS presentations was counterbalanced across participants and kept equal between groups, while the last three CS presentations were presented randomly. The remaining six trials per condition (18 trials altogether) were arranged in three blocks of six trials each (one CS+E with UCS, one CS+E without UCS, one CS+U with UCS, one CS+U without UCS, and two CS− per block), resulting in an even distribution of the (reinforced) CS types over fear acquisition training. The trials were presented in pseudo-randomized order, with no more than two CS+E/CS+U/CS− or three CS+ in succession. After the scanning session on the first day, participants were asked to indicate if and how often the electrical stimulation followed the yellow/blue/red lamplight ('never', 'sometimes', 'always' or 'I do not know'). All individuals not showing behavioral evidence of learning in terms of contingency awareness were excluded from the study after the scanning session on day 1. Six participants were excluded from the study, since they were not aware of the CS-UCS contingencies, i.e. they could not report that the CS− was never followed by the UCS and that both CS+ were sometimes (or always) followed by the UCS.

On the second day (approximately 24 h later), extinction training took place either in context B1 (single context group) or four different contexts (B1, B2, B3, B4; multiple context group). One of the CS+ was shown 16 times without subsequent UCS presentation, in order to extinguish the conditioned fear response (CS+E, extinguished). Intermixed with the 16 CS+E trials, 16 CS-trials were presented. The CS+U was not shown during extinction training (CS+U, unextinguished). In the multiple context group, both CS were presented four times within each of the four contexts (B1-B4), also resulting in 16 trials for the CS+E and the CS−, respectively. Context B1 was presented during the first presentation of both CS (first two trials of the extinction training phase) in both groups. The order of the first two CS presentations (CS+E vs. CS− first) was counterbalanced across participants and kept equal between groups. Extinction training was subdivided into four blocks: within each block, four trials of both CS (in each of the four contexts) were presented randomly, resulting in an even distribution of CS and contexts over extinction training. The trials were presented in a pseudo-randomized order, with no more than two CS+E or CS− trials and no more than two identical contexts in succession.

During the recall phase on day 3 (6–8 days after extinction training), all three CS (CS+E, CS+U, CS−) were presented in context B1 (first context presented during extinction training in the multiple context group), and in a new context C for each participant (within-subjects design). The recall phase (altogether 48 trials) was subdivided into a

first and a second half, comprising four of the altogether eight CS trials in each context, respectively. Each CS type × context combination (altogether six combinations) was presented equally often during the first trial of the recall phase (across participants) and kept equal between groups. Afterwards, during the reinstatement phase, four unsignaled presentations of the UCS were given: after the last trial (including the fixation cross presentation) of the recall phase, a gray background was presented for 20 s, with four UCS presentations 5 s apart (starting 2 s after presentation of the gray background), and a following fixation cross presentation on a black background for 20 s. Afterwards, the recall phase was repeated, using exactly the same sequence of CS and context presentations as before (altogether eight trials per CS and context). The trials during recall and reinstatement test were presented in pseudo-randomized order, with no more than two CS + E/CS + U/CS −, or three CS +, or three identical contexts in succession.

The assignment of specific context pictures to contexts A, B and C and lamplights to CS types was counterbalanced across participants and kept equal between groups. After the experiment on day 3, participants retrospectively indicated arousal, valence, fear and UCS expectancy outside the scanner for each of the context-CS combinations and the contexts alone (without CS, i.e. lamplight turned off). These post-hoc rating results are not presented in the current manuscript.

### 2.4. Skin conductance responses and analyses

Skin conductance responses (SCRs) were sampled continuously throughout the fMRI-experiment. Ag/AgCl electrodes filled with isotonic (0.05 M NaCl) electrolyte medium were placed on the hypothenar of the left hand. Before SCR analyses, the electrodermal signal was smoothed in a first step in order to remove noise from the data. The raw data were sampled at 1000 Hz and filtered by down sampling to 100 Hz and smoothing with a Gaussian kernel with a FWHM of 32 samples. SCR data were analyzed from all CS + trials, including reinforced and non-reinforced CS + trials during fear acquisition training. After pre-processing, the data were analyzed by means of a "trough-to-peak" analysis. The largest difference between a minimum value, which had to occur within a 0.8–6.8 s time window after CS onset, and a maximum directly following the minimum was defined as the entire interval response (Pineles, Orr, & Orr, 2009). Conditioned responses were defined as larger response magnitudes in reaction to the CS + than to the CS −. SCRs were transformed logarithmically to render the data in the direction of normal distribution.

Statistical comparisons of mean SCRs were conducted separately for each phase via analysis of variance (ANOVA). For fear acquisition training, the within-subjects factor CS type (CS + (i.e. average of CS + E and CS + U), CS −) was entered; additionally, the factors time (first vs. second half; each comprising eight trials for CS + E and CS −) and group (multiple context vs. single context group) were introduced for extinction training. For the recall phase, the within-subjects factors CS type (CS + E and CS −) as well as context (B, C) and the between-subjects factor group were entered, in order to test for differences in conditioned responding between groups. Analysis of fear and extinction recall on day 3 was restricted to the first half of the recall and reinstatement test phase, respectively, in order to capture fear and extinction recall rather than re-extinction processes probably occurring over the long run (first and second half combined) of the recall phase. Additionally, early recall was compared to late extinction training as well as early reinstatement test to late recall. Additionally, we analyzed fear recall (CS + U vs. CS −) during early recall and reinstatement test. Therefore, ANOVAs with the within-subjects factors CS type (CS + U and CS −) as well as context (B, C) and the between-subjects factor group were entered, in order to test for differences between groups. The results for these additional analyses are presented in the supplementary material.

All statistical analyses were performed in IBM SPSS Statistics for Windows 22.0 with Greenhouse-Geisser correction if needed, and the statistical significance level was set to $p \leq 0.05$. Significant main or interaction effects were followed by appropriate post-hoc tests. Data of seven participants had to be excluded from SCR analyses due to non-responding (less than two SCRs > 0.05 μS in reaction to the UCS during fear acquisition training (multiple context group: $n = 1$; single context group: $n = 1$); these participants were not excluded from fMRI analysis) or artifacts (multiple context group: $n = 4$; single context group: $n = 1$), leaving 19 participants in the multiple context group and 23 participants in the single context group for final SCR analyses.

### 2.5. FMRI data acquisition and analyses

Brain images were acquired with a 3 T whole-body scanner (Siemens Prisma) with a 64-channel head/neck coil. In total 1308 volumes were registered (fear acquisition training on day 1: 212 volumes, extinction training on day 2: 280 volumes; recall and reinstatement test on day 3: 816 volumes) using a T2*-weighted gradient echo-planar imaging sequence (EPI) with 40 slices covering the whole brain (voxel size: 2 mm × 2 mm × 3 mm; slice thickness = 3 mm; 0.75 mm gap; descending slice order; TE = 30 ms; TR = 2.5 s; flip angle = 85°; field of view = 220 mm × 220 mm; matrix size = 110 × 110; PAT mode GRAPPA, acceleration factor PE 2). The first three volumes were discarded due to an incomplete steady state of magnetization. An anatomical scan (MPRAGE; 0.9 mm isovoxel) was acquired before fear acquisition training on day 1 in order to get highly resolved structural information for the normalization procedure. A gradient echo field map sequence was acquired before each functional run to get information for unwarping B0 distortions.

The Statistical Parametric Mapping software (SPM12, V6685, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab R2012 (Mathworks Inc., Sherborn, MA, USA) was used for data analyses. After unwarping and realignment (2nd degree b-Spline interpolation), slice time correction, co-registration of functional data to each participant's anatomical image, registration of the anatomical image to the MNI space using the unified model (SPM12), and resampling of the functional images to MNI space using the above-mentioned registration with a voxel size of 2 mm × 2 mm × 2 mm were carried out. Smoothing was executed with an isotropic three-dimensional Gaussian filter with a full-width at half maximum (FWHM) of 6 mm.

Fear acquisition training, extinction training, and recall/reinstatement test were integrated as three separate sessions in one first level model in SPM12 with the following experimental conditions (for the respective phase when applicable), as done before (Hermann et al., 2016; Merz, Hamacher-Dang, Stark, Wolf, & Hermann, 2017): context alone (separately for each context A, B and C and each of the four experimental phases), blocks of four trials for CS + E, CS + U, and CS − (separately for each context during recall/reinstatement test), UCS, UCS omission (after CS + presentation), and non-UCS (after CS − presentation). All regressors were modeled by a stick function convolved with the canonical hemodynamic response function in the general linear model, without specifically modeling the durations of the different events (i.e. event-related design). Covariates in the model comprised the six movement parameters from the realignment step. Furthermore, a high-pass filter (time constant = 128 s) was implemented. On the second level, random effects group analyses were done in SPM12 (one- and two-sample *t*-tests).

Region of interest (ROI) analyses targeting the main structures of the fear and extinction circuitry (Fullana et al., 2016, 2018) were conducted for the amygdala, hippocampus, and insula (maximum probability masks; probability threshold set to 0.50; Harvard-Oxford Cortical and Subcortical Structural Atlases, Harvard Center for Morphometric Analysis; http://www.cma.mgh.harvard.edu/fsl_atlas.html). Additionally, dACC and vmPFC masks were created with the MARINA software package (Walter, 2002). We conducted ROI analyses for confirmatory hypothesis testing. The significance threshold was set to

**Table 1**
Neural activation during fear acquisition (CS + E minus CS −) in context A in both groups combined.

| Structure | H | x | y | z | $Z_{max}$ | $p_{FWE}$ |
|---|---|---|---|---|---|---|
| *Both groups: CS + E minus CS − during fear acquisition training* | | | | | | |
| insula | L | −30 | 22 | 8 | 4.61 | .001 |
| insula | R | 32 | 26 | 0 | 4.00 | .010 |
| dACC | R | 6 | 12 | 44 | 3.61 | .046 |
| *Both groups: CS − minus CS + E during fear acquisition training* | | | | | | |
| vmPFC | L | 0 | 46 | −18 | 3.69 | .036 |
| vmPFC | R | 2 | 50 | −16 | 3.68 | .038 |

The significance threshold was set to $p = .05$ (FWE-corrected). All coordinates (*x, y, z*) are given in MNI space. L = left, R = right.

α = 0.05 on voxel-level, corrected for multiple testing (family-wise error (FWE) correction) for the respective region of interest (using the small volume correction option of SPM12).

## 3. Results

Results for fear recall and reinstatement test regarding the comparison between CS + U and CS − are presented in the supplementary material.

### 3.1. Fear acquisition training

On the neural level, fear acquisition (CS + E vs. CS −) was reflected in enhanced differential activation of the bilateral insula and right dACC, structures of the fear network (see Table 1). Additionally, we found reduced differential activation of the vmPFC. Consistent with previous studies, enhanced SCRs to the CS + (average of CS + U and CS + E) compared with the CS − were found during fear acquisition training (main effect CS type: $F_{(1,40)} = 36.025$, $p < .001$, $\eta_p^2 = 0.474$; see Fig. 2; all effects with factor group: $p > .15$).

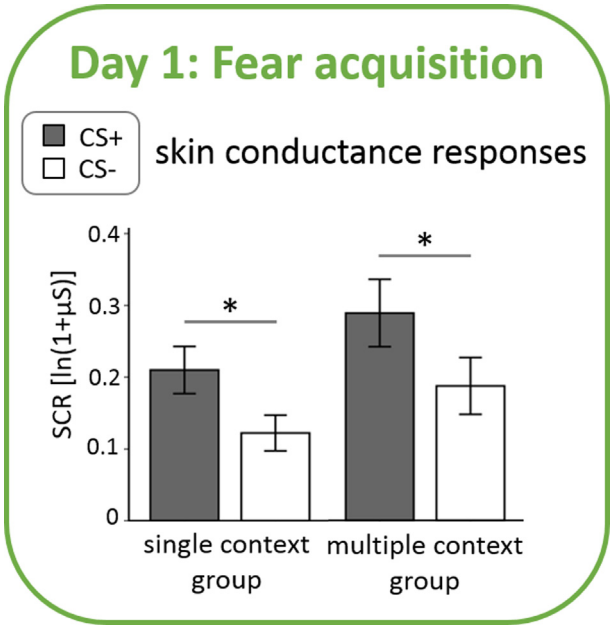


**Fig. 2.** Skin conductance responses (SCR [ln(1 + µS)]) towards the CS + (combined CS + E and CS + U) and the CS − in the single context group (left) and the multiple context group (right) during fear acquisition training in context A on day 1. Error bars depict standard errors of the mean.

**Table 2**
Neural correlates of extinction training in the extinction context B1 (single context group) or in extinction contexts B1, B2, B3, and B4 (multiple context group) on day 2.

| Structure | H | x | y | z | $Z_{max}$ | $p_{FWE}$ |
|---|---|---|---|---|---|---|
| *Multiple minus single context group: CS + E minus CS − during early minus late extinction training* | | | | | | |
| hippocampus | R | 22 | −20 | −18 | 3.41 | .044 |
| *Single minus multiple context group: CS + E minus CS − during early minus late extinction training* | | | | | | |
| no significant results | | | | | | |
| *Both groups: CS + E minus CS − during early minus late extinction training* | | | | | | |
| insula | L | −42 | 0 | −6 | 3.95 | .012 |
| hippocampus | L | −18 | −16 | −22 | 3.58 | .026 |
| dACC | L | −8 | −6 | 50 | 3.70 | .029 |
| *Both groups: CS + E minus CS − during late minus early extinction training* | | | | | | |
| vmPFC | L | −4 | 42 | −24 | 4.12 | .008 |

The significance threshold was set to $p = .05$ (FWE-corrected). All coordinates (*x, y, z*) are given in MNI space. L = left, R = right.

### 3.2. Extinction training

On the neural level, extinction training in four different contexts B1, B2, B3, and B4 (multiple context group) compared with extinction training in a single context B1 (single context group) led to a stronger reduction of differential right hippocampal activation from early to late extinction (see Table 2 and Fig. 3), while no significant activation differences between groups could be observed in further brain regions. Overall, both groups showed a significant activation decrease in the left insula, hippocampus and dACC, as well as an activation increase in the left vmPFC from early to late extinction (see Table 2).

Extinction training in multiple contexts compared with extinction training in a single context did not result in significantly different SCRs (all effects with factor group: $p > .14$). Extinction learning was reflected in a general reduction of conditioned responding (CS + E minus CS −) from the first to the second half of extinction training (interaction effect CS type × time: $F_{(1,40)} = 21.595$; $p < .001$; $\eta_p^2 = .351$), with a stronger reduction of SCRs towards the CS + E compared to the CS −. Additionally, higher responses for the CS + E compared with the CS − (main effect CS type: $F_{(1,40)} = 23.401$; $p < .001$; $\eta_p^2 = .369$), and a general reduction of SCRs over time (main effect time: $F_{(1,40)} = 39.594$; $p < .001$; $\eta_p^2 = .497$) were observed. Analyzing the last four trials of extinction training (late extinction) revealed that extinction learning was successful in both groups, with no significant differences between the CS + E and CS − and between groups (all $p > .25$).

### 3.3. Extinction recall in the extinction context

Extinction recall (CS + E vs. CS −) in extinction context B1 one week later did not result in significant differences between groups on the neural level, while both groups combined (main effect CS type) showed reduced responding in the left hippocampus for CS + E minus CS − in context B1 (see Table 3).

Extinction recall (CS + E vs. CS −) in extinction context B1 did also not result in significant differences in conditioned SCRs between the two groups (all effects with factor group: $p > .23$). Presentation of CS + E and CS − in context B1 did not lead to spontaneous recovery of conditioned SCRs neither tested during early recall ($p = .149$), nor tested during early recall compared with late extinction training ($p = .241$), indicating successful extinction recall in the safe extinction context B1. For this latter analysis (comparison of early extinction recall in context B1 with late extinction training), there were also neither significant interactions with the factor group, nor significant main effects of group and time (all $p > .07$).

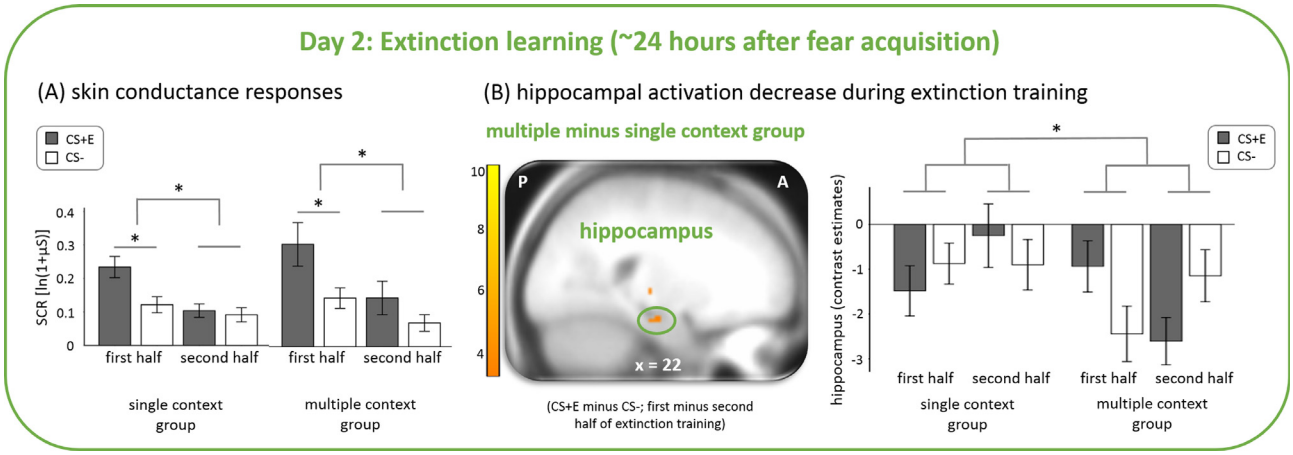


**Fig. 3.** (A) Skin conductance responses (SCR [ln(1 + µS)]) towards the CS + E and the CS − during the first and second half of extinction training in context B1 on day 2 in the single context group (left) and in contexts B1-B4 in the multiple context group (right). (B) Hippocampal activation decrease towards the CS + E compared with the CS − from the first to the second half of extinction training in the multiple compared with the single context group. Error bars depict standard errors of the mean, P = posterior; A = anterior.

**Table 3**
Neural correlates of extinction recall in the extinction context B1 and renewal in the novel context C on day 3.

| Structure | *H* | *x* | *y* | *z* | $Z_{max}$ | $p_{FWE}$ |
|---|---|---|---|---|---|---|
| *Multiple minus single context group: CS + E minus CS − in context C vs. B1* | | | | | | |
| no significant results | | | | | | |
| *Single minus multiple context group: CS + E minus CS − in context C vs. B1* | | | | | | |
| amygdala | L | −20 | 0 | −24 | 3.33 | 0.026 |
| *Multiple vs. single context group: CS + E minus CS − in context B1* | | | | | | |
| no significant results | | | | | | |
| *Both groups: CS + E vs. CS − in context C vs. B1* | | | | | | |
| no significant results | | | | | | |
| *Both groups: CS + E minus CS − in context B1* | | | | | | |
| no significant results | | | | | | |
| *Both groups: CS − minus CS + E in context B1* | | | | | | |
| hippocampus | L | −28 | −18 | −18 | 3.58 | 0.025 |

The significance threshold was set to $p = .05$ (FWE-corrected). All coordinates (*x, y, z*) are given in MNI space. L = left, R = right.

### 3.4. Renewal test in the novel context

Importantly, the multiple compared with the single context group showed reduced differential activation in the left amygdala during renewal in the novel compared with recall in the extinction context (see Table 3 and Fig. 4). Overall (both groups combined) there were no significant differences in conditioned responding in context C vs. B1 on the neural level.

A direct comparison of conditioned SCRs (CS + E vs. CS − ) in context B1 with context C during early recall did neither result in significant differences between groups (all effects with factor group: $p > .33$), nor in significant differences between contexts (all $p > .41$; see Fig. 4). In general, stronger SCRs were found towards the CS + E compared with the CS − (main effect CS type: $F_{(1,40)} = 6.907$; $p = .012$; $\eta^2 = 0.147$). Additionally, differential conditioned responses during early recall in context C differed from late extinction training (interaction effect time × CS type: $F_{(1,40)} = 4.496$; $p = .040$; $\eta^2 = 0.101$), also indicating a renewal of conditioned SCRs in the novel context. There were no significant interactions with the factor group for the comparison of early recall in context C with late extinction training in context B (all effects with factor group: $p > .14$). Furthermore, no main effect of time ($p = .981$), but significantly enhanced SCRs towards the CS + E compared with the CS − (main effect CS type: $F_{(1,40)} = 7.274$; $p = .010$; $\eta^2 = 0.154$) could be found.

### 3.5. Reinstatement test in the extinction context

On the neural level, the multiple compared with the single extinction context group showed attenuated activation of the left amygdala during extinction recall in the extinction context B1 after reinstatement shock administration (see Table 4 and Fig. 5).

Extinction recall in the safe extinction context B1 (CS + E vs. CS − ) after reinstatement was not significantly different between the two groups concerning SCRs (all effects with factor group: $p > .53$; see Fig. 5). Presentation of CS + E and CS − in context B1 led to enhanced conditioned responding after reinstatement (main effect CS type: $F_{(1,40)} = 4.306$; $p = .044$; $\eta^2 = 0.097$), indicating recovery of conditioned fear after reinstatement. However, compared with late recall in context B1 (trials 5–8), there were no significant interaction or main effects (all $p > .13$).

### 3.6. Reinstatement test in the novel context

On the neural level, there were neither significant differences between groups during early renewal after reinstatement shocks in context C compared with context B1 nor in both groups combined (interaction CS type × context).

Regarding SCRs, a direct comparison of conditioned responding (CS + E vs. CS − ) in context C with context B1 after reinstatement did also not lead to significant results (all $p > .10$; see Fig. 5). Compared with late recall on day 3 (context C), there was a significant increase in SCRs independent of CS type and group for context C (main effect time: $F_{(1,40)} = 8.311$; $p = .006$; $\eta^2 = 0.172$), indicating a generally enhanced responding towards both CS after reinstatement (all other $p > .278$).

## 4. Discussion

The main results of this study show that extinction training in multiple contexts compared with a single context was associated with a stronger decrease of right hippocampal activation during extinction learning. Additionally, multiple extinction contexts compared with a single extinction context during extinction training led to attenuated fear renewal in a novel context as well as diminished reinstatement in the extinction context one week later, as indicated by reduced left amygdala activation, respectively.

Fear acquisition was successful as reflected in enhanced conditioned SCRs and activation of the insula and dACC, as well as reduced vmPFC

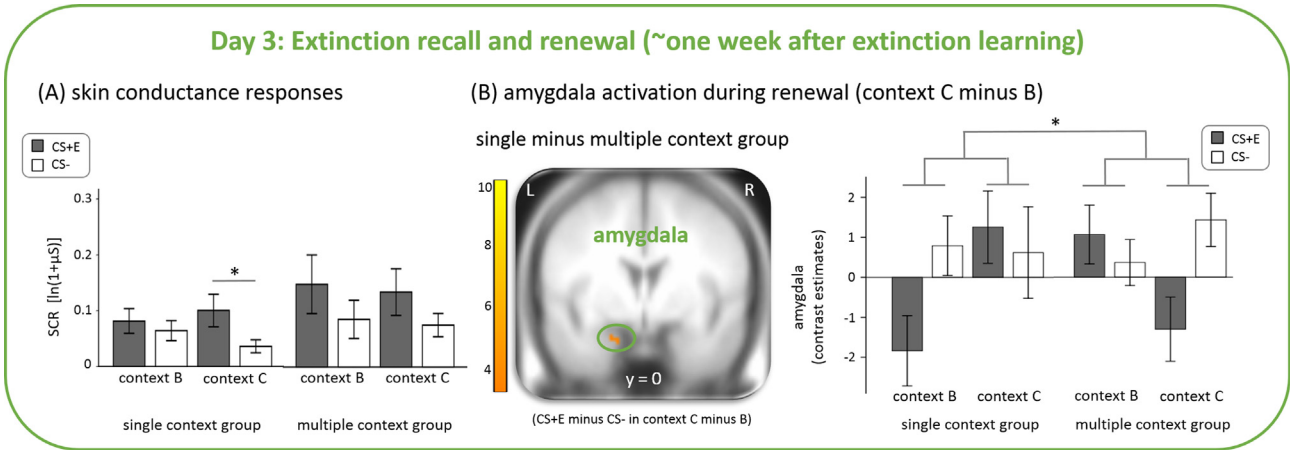


**Fig. 4.** (A) Skin conductance responses (SCR [ln(1 + µS)]) towards the CS + E and the CS − during extinction recall in context B1 and renewal in context C on day 3 in the single context group (left) and the multiple context group (right). (B) Amygdala activation towards the CS + E compared with the CS − during early renewal (context C minus B1) in the single compared with the multiple context group. Error bars depict standard errors of the mean; L = left; R = right.

**Table 4**
Neural correlates of reinstatement in the extinction context B1 and in the novel context C on day 3.

| Structure | *H* | *x* | *y* | *z* | $Z_{max}$ | $p_{FWE}$ |
|---|---|---|---|---|---|---|
| *Multiple vs. single context group: CS + E minus CS − in context C1 vs. B1* | | | | | | |
| no significant results | | | | | | |
| *Multiple minus single context group: CS + E minus CS − in context B1* | | | | | | |
| no significant results | | | | | | |
| *Single minus multiple context group: CS + E minus CS − in context B1* | | | | | | |
| amygdala | L | −18 | −4 | −12 | 3.12 | 0.047 |
| *Both groups: CS + E vs. CS − in context C vs. B1* | | | | | | |
| no significant results | | | | | | |
| *Both groups: CS + E vs. CS − in context B1* | | | | | | |
| no significant results | | | | | | |

The significance threshold was set to $p = .05$ (FWE-corrected). All coordinates (*x, y, z*) are given in MNI space. L = left, R = right.

activation, important structures of the fear circuit (Fullana et al., 2016). Extinction training in multiple contexts compared with a single context resulted in a stronger hippocampal activation decrease from early to late extinction, which was, however, not directly reflected in SCRs. The hippocampus as an important region for contextual processing (Maren et al., 2013) influences the recall of conditioned responses, probably by modulating activation in the dACC, vmPFC and amygdala (Hermann et al., 2016), further important structures of the fear and extinction network. A stronger reduction of hippocampal activation during extinction learning might thus indicate less hippocampus-mediated contextualization of the extinction memory in the multiple context group. If the extinction memory is less contextualized, reduced renewal of conditioned fear should occur in a novel context, as the extinction memory is not very strongly tied to one specific context. This hypothesis is very well in accordance with the results of the present study: extinction training in multiple contexts led to reduced activation of the left amygdala during renewal (CS + E vs. CS − in context C vs. B1) one week later. This finding likely reflects diminished fear renewal and corresponds well to a previous study showing that fear renewal is indeed reflected in enhanced amygdala activation (Agren et al., 2012). However, a reduced renewal effect for multiple extinction contexts was not found for conditioned SCRs in the current study, limiting the explanatory power of reduced amygdala responding during fear renewal.

Our findings also corroborate previous studies demonstrating the prevention of ABC renewal by multiple extinction contexts for conditioned startle responses and UCS expectancy (Balooch et al., 2012) as well as in a predictive learning task (Bustamante, Uengoer, Thorwart, & Lachnit, 2016). However, in another study, the renewal of conditioned startle responses was not reduced by multiple extinction contexts (Dunsmoor et al., 2014); instead, multiple extinction contexts

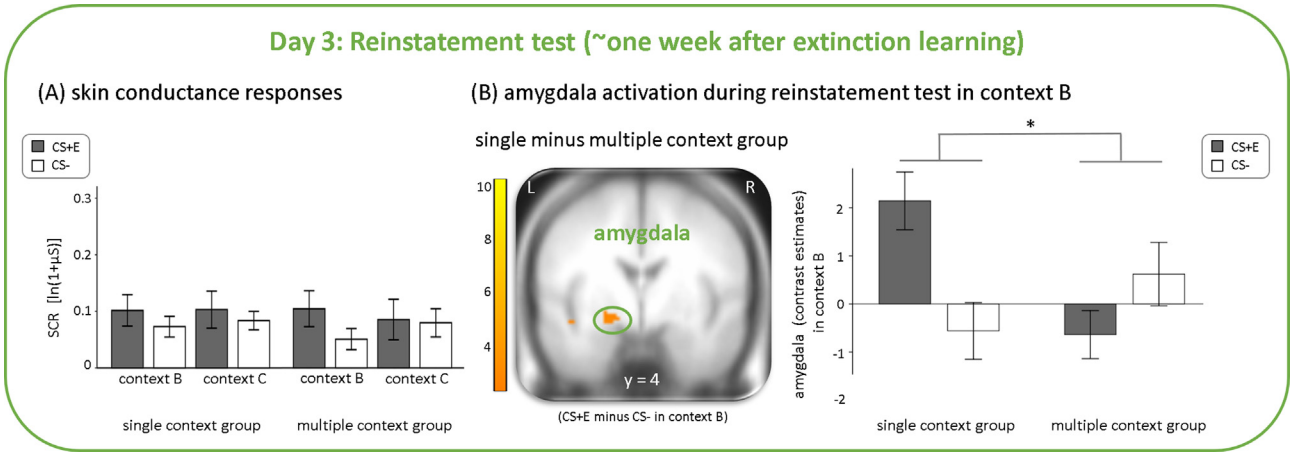


**Fig. 5.** (A) Skin conductance responses (SCR [ln(1 + µS)]) towards the CS + E and the CS − during early reinstatement test in context B1 and context C on day 3 in the single context group (left) and the multiple context group (right). B) Amygdala activation towards the CS + E compared with the CS − during early reinstatement test in context B1 in the single compared with the multiple context group. Error bars depict standard errors of the mean; L = left; R = right.

specifically attenuated fear reinstatement when tested again in the novel context (after the renewal phase), but without specifically investigating extinction recall within the extinction context. In the current study, the reinstatement test was carried out in both the extinction as well as the novel context. This procedure resulted in reduced amygdala activation during the reinstatement test in the extinction context for the multiple relative to the single context group. In conditioned SCRs, fear reinstatement (CS+E vs. CS−) was observed in the extinction context irrespective of group. For the reinstatement test in the novel context, we did not observe differential (CS+E vs. CS−) reinstatement of conditioned fear on the level of SCRs, but rather a generally enhanced responding irrespective of CS type and group compared with late extinction recall. There were, however, no significant activation differences during renewal in the novel compared with the extinction context. Together, these results indicate that multiple extinction contexts prevent fear reinstatement in the known and probably safe extinction context in the amygdala. But it does not interfere with the uncertainty provoked by the novel context during the reinstatement test, as evidenced by generally enhanced SCRs (generalized reinstatement) independent of group, which is in accordance with previous studies (Haaker, Golkar, Hermans, & Lonsdorf, 2014). The usage of a novel context and the extinction context during reinstatement test, as well as different measures (BOLD vs. startle responses) might explain the differing results between the current and a recent (Dunsmoor et al., 2014) study, which showed diminished reinstatement of conditioned startle responses in a novel context.

Some limitations of this study need to be mentioned: as we investigated only male participants, it is unknown if the current findings can be generalized to women, especially regarding the influence of sex hormones on (context-dependent) fear conditioning and extinction processes (Lebron-Milad & Milad, 2012; Merz et al., 2018). Complex sex differences have been observed for extinction learning particularly due to fluctuating sex hormones over the menstrual cycle and the intake of hormonal contraceptives (for reviews see Merz et al., 2018; Velasco, Florido, Milad, & Andero, 2019). We emphasize that future studies need to explore the underlying mechanisms of multiple extinction contexts also in women, taking circulating sex hormone concentrations into account. Additionally, we did not find differential effects of multiple compared with a single extinction context on conditioned SCRs. This might be due to our specific experimental design with extinction learning one day after fear acquisition and extinction recall/renewal taking place one week after extinction learning. There was no return of conditioned SCRs during recall of extinction within the extinction context, probably preventing to find differences in conditioned SCRs between groups. However, the neural level might be a more sensitive measure compared with electrodermal responding, which was reflected in significant differences between groups in this study. Due to restrictions in experimentally manipulating the context presentations in this fMRI study, it needs to be kept in mind that contextual changes in this experimental study might differ from actual real-life contextual changes. Future studies could try to enhance the context representation for example by using virtual reality or by prolonging the context presentation times.

In summary, the findings of this study highlight that extinction training in multiple extinction contexts leads to diminished amygdala activation during extinction recall in a novel context. This might probably be related to reduced fear renewal, which was, however not observed in conditioned SCRs. Additionally, multiple contexts also effected reinstatement during test in the extinction context, which was also reflected in reduced amygdala activation. A stronger activation decrease in the hippocampus during extinction learning might represent the underlying mechanism leading to this diminished amygdala activation. Due to altered hippocampal processing the extinction memory might get less context-dependent and therefore more resistant against contextual changes and fear reinstatement. These basic findings give a first hint that hippocampus-mediated processes might also be relevant for the positive effect of multiple context exposure in the treatment of anxiety disorders (Shiban et al., 2013). Future studies investigating these mechanisms in female samples as well as patients with anxiety disorders might contribute to further improve existing treatment strategies, especially by reducing ROF after successful exposure therapy.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nlm.2019.107150.

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