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Systematically investigating the role of context on effect replicability in reinstatement of fear in humans

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Highlights

1. RoF when extinction and reinstatement context are identical (AAAB)
2. RoF when reinstatement and test context are identical (AABB)
3. No RoF in physiology but in ratings when reinstatement context is different (AABA)
4. Unexpected physiological response enhancement in no-reinstatement control groups
5. Future work should focus on context not cue-contexts compounds

Abstract

Context is crucial in guiding behavior in an ever-changing world and contextual information plays a crucial role in associative learning processes. For instance, the return of fear (RoF) after successful extinction, which is used to study the mechanisms underlying relapse phenomena in fear- and stress-related disorders in an experimental model, is known to be context dependent as evident from phenomena such as renewal (contextual change) and reinstatement (re-exposure to an aversive event).

Human adaptations of reinstatement paradigms have resulted in mixed findings: CS specific as well as unspecific RoF or unexpected “reinstated” conditioned responding in no reinstatement US control groups. Here, we systematically investigate the role of context (i.e., cue-context compound) on reinstatement-induced RoF in a human differential fear conditioning paradigm using subjective and psychophysiological measures in a large sample (N=212) including reinstatement and control groups.

Overall, response patterns in reinstatement-groups mirrored results from single-cue rodent work. Yet, only generalized, not differential RoF was observed. Remarkably, depending on outcome measure RoF was also observed under identical experimental context conditions without US-re-exposure, underlining effects of contextual change beyond the reinstatement-US and challenging reinstatement research in human subjects and highlight that future reinstatement work should focus on the operationalization of context.

Keywords: *skin conductance, startle, ratings, human fear conditioning, return of fear, context*

1. Introduction

Contextual information guides our behavior and is inherently present during every situation where learning is involved. Context helps to retrieve memories - both fearful and safe ones in animal (Bouton, 1988; Maren et al., 2013) and humans (Effting & Kindt, 2007; Milad et al., 2005).

The 2020/21 pandemic, for example, has caused individuals to avoid social interaction in order to minimize chances of getting infected and spreading the COVID-19 virus. This response pattern is adaptive and appropriate in the context of a global pandemic. Yet, in a different, non-threatening context such when global immunity has been reached, the same behavioral pattern becomes maladaptive. Individuals who persist in experiencing worrisome thoughts despite the change in context, may keep avoiding social interaction, and experiencing persistent distress. As a consequence, their daily life functioning may become disrupted and diagnostic criteria for an anxiety and/or stress-related disorder may be met.

While exposure-based treatments are effective in treating anxiety and stress-related disorders, relapse rates remain relatively high, and achieving long-term remission remains a challenge (Vervliet, Craske, et al., 2013). For instance, negative experiences encountered after successful treatment may reinstate the original fear and trigger relapse (Boschen et al., 2009)– such as experiencing anxiety for viral infection after having experienced allergy induced breathing problems. Thus, identifying the circumstances that promote relapse and identifying their underlying mechanisms is critically needed. This can be investigated experimentally in fear conditioning models.

Fear conditioning models are used to study the mechanisms underlying fear acquisition, fear inhibition, and return of fear across species (for example reviewed in (Delgado et al., 2006; Goode & Maren, 2014; Haaker et al., 2019)). During differential fear acquisition training, an initially neutral, to be conditioned stimulus (CS+) is typically paired with an aversive unconditioned stimulus (US), while a second stimulus is never paired with an aversive event (CS-). In contrast, single cue paradigms, which are often used in rodents but rarely in humans, do only employ a CS+ but no CS- cue. During subsequent fear extinction training both CSs are presented without the US, leading to a waning of the conditioned response (CR). Importantly, fear and safety memory traces acquired during fear acquisition and extinction training respectively, are considered to coexist (Bouton, 2002). Consequentially, both memory traces can be re-expressed at a later point in time which is referred to as return of fear (RoF, i.e. expression of the CR) or retention of extinction memory (i.e., no expression of the CR). Return of fear (RoF) can be triggered in the laboratory through different manipulations including contextual change (i.e., renewal) and the unexpected

presentation of an aversive stimulus such as the US after extinction training (i.e., reinstatement) which reinstates conditioned responding to the CS(s) in a subsequent test phase (Haaker et al., 2014a).

More precisely, renewal describes RoF induced by a contextual change between extinction training and the subsequent RoF test (see (Vervliet et al., 2013) for a comprehensive review of clinical implications, and methodological considerations). For instance, a conditioned fear response, which is acquired in Context A, and extinguished in Context B, returns when a later test occurs in the original context (A) (ABA renewal; (Bouton & Bolles, 1979; Vervliet et al., 2013)). Furthermore, renewal can also be induced by a change from the extinction context to a new context (ABC renewal; (Bouton & Bolles, 1979; Hermann et al., 2016); AAB renewal: (Bouton & Ricker, 1994)).

Reinstatement was first established in the rodent field (Bouton & Bolles, 1979; Rescorla & Heth, 1975), decades before human research adopted this manipulation to induce RoF (Haaker et al., 2014b). Interestingly, the different RoF phenomena do not necessarily occur in isolation. Reinstatement manipulations are often applied in paradigms that also involve training and/or test in different contexts, that without the reinstatement-US could be regarded as a renewal condition. Hence, both reinstatement and renewal processes may contribute to responding in these occasions. A systematic investigation of the translatability of reinstatement from the rodent to the human field is, however, lacking (LaBar & Phelps, 2005; Sjouwerman & Lonsdorf, 2020). Already a decade ago, (Sokol & Lovibond, 2012) asked “What are the driving mechanisms behind reinstatement [in humans] and what are the conditions essential for its emergence?” (Sokol & Lovibond, 2012). Today, we still do not have the answers to these questions. Clarifying the circumstances under which (experimental) reinstatement occurs or is facilitated may offer a first step towards understanding the mechanisms underlying clinical relapse phenomena and open up new avenues for their prevention.

Reinstatement studies in human participants have, with few exceptions (LaBar & Phelps, 2005; Schiller et al., 2008), relied on differential fear conditioning paradigms which have revealed generally heterogeneous results (Haaker et al., 2014b): More pronounced responding to the CS+ after reinstatement has been reported (‘differential reinstatement’ (Dirikx et al., 2004, 2009) but also equally increased responding to both CSs (‘generalized reinstatement’, e.g. (Dirikx et al., 2007; Hermans et al., 2005; Kull et al., 2012). Particularly puzzling is the occasional observation of enhanced responding towards both CSs (i.e., CS+ and CS-) in control groups not exposed to any reinstatement USs ((Dirikx, 2006; Kull et al., 2012), (Haaker et al., 2014b) (Haaker et al., 2014a)). While the underlying mechanisms remain unclear, this may suggest that additional mechanisms beyond the intended reinstatement induced RoF may be at play. This

has, however, not yet been investigated systematically, as control groups not exposed to reinstatement USs but undergoing otherwise identical procedures are only rarely included in experiments that use reinstatement as an outcome measure for fear or extinction memory manipulations. As reinstatement often serves as an outcome measure rather than a construct of primary interest in itself, responding is typically compared between an experimental group (e.g., drug administration, behavioral intervention) and its respective control group (e.g., placebo group, no or sham behavioral intervention).

In human reinstatement research, procedural heterogeneity is excessive and it is currently unknown if and to what extent procedural and experimental specifications contribute to these divergent findings (as outlined in (Haaker et al., 2014a)) or if heterogeneous results merely reflect random variation in effects (Lakens, 2017).

In rodents, boundary conditions, such as the role of the context in different experimental phases have been delineated systematically (Bouton & Bolles, 1979; Pavlov, 1927; Rescorla & Heth, 1975; Westbrook, Iordanova, McNally, et al., 2002). Initially, it was proposed, that reinstatement induced RoF is only observed when reinstatement and test context are identical but not if they are distinct (Bouton & Bolles, 1979). In these early experiments, acquisition and extinction context were distinct (conditioning in context A and extinction in context B) and test took place in the extinction context B (A_{acquisition}B_{extinction}B_{reinstatement}B_{test} design). Later studies confirmed this, but also showed that reinstatement is observed when reinstatement and test occur in the same context (AAAA, AABB, ABAA, ABCC) and also when extinction and reinstatement occur in the same context and test in a novel context (ABBC, AAAB) (Westbrook, Iordanova, McNally, et al., 2002) – but not when extinction and test context are identical but distinct from the reinstatement context (AABA) (Westbrook, Iordanova, McNally, et al., 2002). These results suggested a two-fold role of the context in reinstatement. In the first case (reinstatement and test context are identical), reinstatement originates from context conditioning retrieving the CS-US memory (unmasking of old fear) and in the latter case (extinction and reinstatement occur in the same context, test in a different one) through mediated conditioning, as CS and US are linked by their common context associate (new learned fear).

Despite of the well documented contextual influences on reinstatement of fear in rodents (Bouton & Bolles, 1979; Rescorla & Heth, 1975; Westbrook, Iordanova, McNally, et al., 2002), only two human single-cue studies compared reinstatement between participants receiving reinstatement USs in the same (AAAA) or a different (AABA) spatial context than the test phase (LaBar & Phelps, 2005; Schiller et al., 2008). As expected from rodent work, participants undergoing no spatial contextual change (AAAA)

showed pronounced and significant reinstatement in both studies, while the AABA group, in which the reinstatement context was different from both the extinction and the test context, exhibited less pronounced (Schiller et al., 2008) or no reinstatement effects (LaBar & Phelps, 2005). In further support of a contribution of the experimental context to reinstatement in humans, reinstatement effects were more pronounced towards contextual as compared to the cued CSs (Haaker et al., 2014a).

Despite the crucial role of ‘context’ as known from rodent work, the context presented during reinstatement-US administration in human work has largely been neglected to an extent that experimental specifications and timings are often not even reported (for a summary see (Haaker et al., 2014a)). As the ITI background, the cue background or a novel background served as reinstatement context in human work (as summarized in (Haaker et al., 2014a)), it can be speculated that this heterogeneity in reinstatement context in human work may contribute to heterogeneous findings. In fact, the operationalization of context, which can be defined spatially, temporally, interoceptively or as a cognitive context, in human work is challenging (e.g., Maren et al., 2013).

Here, we provide a systematic investigation on the role of context during the reinstatement phase in human differential fear conditioning by studying four different experimental reinstatement groups differing in contextual sequences (rAAAB, rAABB, rAABA, rAAAA) and their respective control groups not exposed to reinstatement USs (i.e., cAAAB, cAABB, cAABA, cAAAA) but undergoing otherwise identical experimental procedures. Of note, most human reinstatement work has not employed contexts as “multisensory, diffuse and continuously present” (cf. Maren et al., 2013) but has employed for instance the ITI or a novel background as reinstatement context (for a detailed review see Haaker et al., 2014b). Here, context (i.e., background colour) and cue (i.e., CS, geometric figure) occurred simultaneously during fear acquisition and extinction training as well as during the return of fear test and the context alone was presented during the reinstatement phase.

First, we compare reinstatement-induced RoF only between the four reinstatement groups and expect, based on rodent work, RoF in groups rAABB, rAAAB and rAAAA but not rAABA. We further speculate that RoF might be differential (i.e., CS+ specific) in rAABB when the US during reinstatement triggers the CS-specific fear acquisition memory though their common US-associate (i.e., context conditioning) and leads to unmasking of old fear. In turn, we speculate that RoF is generalized in rAAAB as both stimuli (i.e., CS+ and CS-) are linked to the US by their common context-associate (i.e. mediated conditioning) leading to new fear.

Second, we compare RoF between the four no-reinstatement control groups. As control groups are not systematically included in the reinstatement literature, we have no clear hypotheses on conditioned responding in these groups and the analyses are of explorative nature. Theoretically, we would not expect response enhancement in control groups. Yet, we speculate that conditioned responding at test might be enhanced in control groups when extinction and test context are not identical (i.e., in **cAAAB** and **cAABB**) due to (unintended) renewal processes (see Haaker 2014 for a discussion) but absent when extinction and test context are identical (**cAABA**, **cAAAA**).

Third, we directly compare responding in the reinstatement groups with their corresponding control groups, which will allow to potentially identify under which conditions the reinstatement-US might impact on responding at test differently as compared to the control groups.

2. Methods

2.1 Participants

Two-hundred-thirty-two right-handed healthy volunteers participated in this study (172 females), with a mean age of 25 ± 4 (SD) years. Twenty participants had to be excluded from all analyses due to aborting the experiment, overwritten log files, or programming error, leaving $N = 212$ for analyses. Participants were not included when self-reporting any current or past clinical diagnoses in a pre-experimental telephone screening. Participants were reimbursed with €10 per hour for their participation. All gave written informed consent. The Ethical Review Board of the German Psychological Association approved this study, which was conducted in accordance with the Declaration of Helsinki.

Part of this sample overlaps with previous publications focusing on individual differences and methodological aspects and effects of context in experimental phases preceding the reinstatement and test phases that are of main interest here, and one study also focusses on RoF – however, not on contextual manipulations (for details see **Fehler! Verweisquelle konnte nicht gefunden werden.**).

2.2. Experimental design

The experimental design has been previously described in detail (Sjouwerman & Lonsdorf, 2020). In brief, the experiment started with a startle habituation phase (5 startle probe presentations) and a CS habituation phase (2 CS+, 2 CS- presentations). Next, during the fear acquisition training phase each CS+ was reinforced with the US (100% reinforcement rate), while the CS- was never followed by the US (9 CS+, 9 CS- presentations). During immediate fear extinction training, none of the CSs was reinforced with the US (9 CS+, 9 CS- presentations). In the subsequent reinstatement phase no CSs were shown, and experimental groups (i.e., reinstatement groups) were re-exposed to a single US whereas control groups (i.e., no-reinstatement-US groups) were not exposed to the US. Finally, responding to both CSs was tested in the return of fear test phase (4 unreinforced CS+, 4 CS- presentations, first CS+/CS- was counterbalanced). During the reinstatement phase, no visual stimuli were presented except for the background color, which differed between groups, for 54s. Reinstatement groups were re-exposed to one US presentation 19.5s after onset of the reinstatement background. Thus, the test phase started 34.5s (= 54 – 19.5) after this reinstatement-US. Control groups underwent an identical procedure but were not exposed to the reinstatement US.

All participants underwent fear acquisition training and fear extinction training in context A. Participants were randomly assigned to one of three contextual sequences (AAAB, AABB, AABA). Note that groups with context sequence AAAA were acquired at a later point in time. For each contextual sequence,

we employed a reinstatement group (r) exposed to a reinstatement US during the reinstatement phase and a control group (c) not exposed to reinstatement USs but otherwise identical procedure. This adds up to eight experimental groups as illustrated in **Figure 1** (see **Table 1** for descriptive information).

Table 1. Descriptive information of the sample and the eight different groups.

Experimental group	N Total	N females	Aware/ Unaware/Missing	Mean age (years)	SD age (years)	Mean US intensity (mA)	SD US intensity (mA)
cAAAB	32	23	20 / 11 / 1	24.7	3.9	5.3	6.8
rAAAB	27	20	20 / 7 / 0	25.2	4.5	3.9	4.4
cAABA	28	21	23 / 4 / 1	24.4	3.4	3.9	2.8
rAABA	27	19	22 / 5 / 0	25.5	3.6	3.8	3.6
cAABB	27	19	18 / 8 / 0	25.0	3.4	4.6	3.9
rAABB	30	22	22 / 8 / 0	25.6	4.6	4.7	4.4
cAAAA	21	13	18 / 3 / 0	24.2	3.5	9.9	14.6
rAAAA	20	18	13 / 6 / 1	23.7	4.0	4.9	3.4

Note that groups with contextual sequence AAAA were not initially tested but were included later as additional exploratory control condition for reinstatement and control groups (highlighted by light grey text). Also note that US intensities were on average significantly (post hoc pairwise t-test with $p_{\text{bonf}} = .031$) higher in individuals that underwent the context sequence AAAA compared to US intensities in

2.3 Stimuli

Stimulus presentation was controlled by the software Presentation (NeuroBehavioral Systems, Albany, CA). Black geometrical shapes (i.e., ellipse and rectangle) were utilized as CSs and presented on a colored background (i.e., blue, purple, green, or yellow). The color of the screen served as context and the sequence of these contexts during the different experimental phases differed between groups **Figure 1**. Experimental phases were run without interruption without signaling of any transition to the next experimental phase except directly after the habituation phase when the actual start of the experiment was indicated by displaying the text “the experiment starts now” on the screen (see also section 2.6.3 Ratings). Allocation of shapes and contexts was counterbalanced between participants. CSs were presented for 6s together with the respective context, resulting in compound of CS and context. During fear acquisition training, the CS+ co-terminated with the US. Trials were separated by inter trial intervals (ITIs) of 11.5 ± 1.5 s consisting of a white fixation cross presented on a black background screen. The context change between experimental phases was initiated together with the CS after the presentation of an ITI.

The US consisted of a train of three electrotactile square waves of 2ms with an inter stimulus interval of 50ms delivered to the dorsal part of the right hand. The electrotactile stimulus (i.e., US) was generated by a DS7A electrical stimulator (Digitimer, Welwyn Garden City, UK) and delivered through a platinum pin surfaced electrode (Specialty Developments, Bexley, UK). US intensity was individually calibrated reaching a level that was unpleasant but tolerable.

Stimuli were paired with an auditory startle probe (95dB(A), a 50ms burst of white noise with a rise time < 1 ms) to elicit a startle reflex. The startle probe was delivered binaurally through headphones (Sennheiser, Wedemark, Germany). For CSs the probe was presented 4 or 5s post CS onset, for ITIs 5 or 7s post ITI onset. Startle probes were presented in 1/2 of the CS habituation trials, 2/3th of the CS acquisition and extinction training trials with a startle probe always presented on the first and last trials per stimulus type. In addition, one startle probe was presented 6s before offset of the reinstatement phase in experimental and control groups (note that the probe was presented after re-exposure to the US in experimental groups), and startle probes were included during all CS trials during the return of fear test. Participants were explicitly informed that startle probes were necessary for physiological recording only and unrelated to the task.

2.4 Procedure

Participants filled in a batch of questionnaires that included questions on demographic information, the State-Trait Anxiety Inventory (Spielberger et al., 1983) to measure trait anxiety, the NEO-FFI (Gerhard, 1999) to measure the five domains of personality, the IPC (Krampen, 1981) to measure locus of control, and the IUS (Gerlach et al., 2008) to measure intolerance of uncertainty. These questionnaires are not of relevance to the research question of the present manuscript but were included for other research questions focusing on experimental phases prior to reinstatement (Lonsdorf, Klingelhöfer-Jens, Andreatta, Beckers, Chalkia, Gerlicher, Jentsch, Drexler, Mertens, Richter, et al., 2019; Sjouwerman et al., 2020), see also **Fehler! Verweisquelle konnte nicht gefunden werden.**). After completing the batch of questionnaires, the electrodes to acquire the skin conductance data and electrodes to deliver electrotactile stimulation were attached. US intensity was calibrated (see section on stimuli), the rating procedure (see section on ratings) was demonstrated and practiced, and the computerized experiment was started.

2.5 Contingency awareness

After the experiment, participants filled in a brief CS-US awareness questionnaire in which they reported if they had observed any systematics in stimulus presentations and the number of perceived US presentations, the answers were orally confirmed with the experimenter. 156 participants were classified as aware, 52 as unaware. Subjects uncertain of CS-US contingencies but reporting a tendency towards the correct CS-US contingency (e.g., “I think the electrical stimulation always occurred after the rectangle, but I’m not sure”) were classified as aware (see **Table 1**). Information on awareness was missing for three participants.

2.6 Outcome measures

Methods for physiological data acquisition and ratings have been previously described in detail (Sjouwerman & Lonsdorf, 2020). In brief, skin conductance responses (SCR) and startle (EMG) data were recorded with a Biopac MP100 amplifier (Biopac Systems, Goleta, CA, USA) and fed into the software Acqknowledge 3.9.2 (Biopac Systems, Goleta, CA, USA). Three participants had to be excluded from physiological analyses due to missing physiological data files (i.e., SCR and startle) but were included for rating analyses.

2.6.1 Skin conductance responses (SCR)

Participants cleaned their hands with lukewarm water. Two disposable hydrogel Ag/AgCl electrodes (ø 55 mm, Covidien, Germany) were placed at the distal and proximal palmar surface of the left

hand. Data were recorded continuously at 1000 Hz with a gain of 5 $\mu\Omega$. Data were down sampled offline to 10 Hz. Responses were scored manually but computer-assisted from foot to peak with onsets within .9-4 s after stimulus onset (Boucsein et al., 2012) using a custom made program. Responses smaller than .02 μS were set to zero and trials with recording artifacts were set to missing values.

Participants with more than 2/3th missing or zero responses towards the US were excluded as non-responder from skin conductance analyses ($n = 7$) as suggested by (Lonsdorf, Klingelhöfer-Jens, Andreatta, Beckers, Chalkia, Gerlicher, Jentsch, Drexler, Mertens, Sjouwerman, et al., 2019). Raw skin conductance responses X were log transformed (with base 10) and range corrected per individual for their maximum response to any stimulus (i.e., CS+, CS- or US) within the full experiment, see Formula 1.

$$(1) SCR_{trial_i} = \log_{10}(1 + X) / \log_{10}(1 + \max(all\ X))$$

2.6.2 Startle

Electromyography (EMG) was used to record muscular activity of the orbicularis oculi muscle underneath the right eye. After the respective skin areas were cleaned with alcohol and scrubbed with NuPrep gel (Weaver and company, Colorado), two Ag/AgCl electrodes ($\varnothing$ 5 mm, BIOPAC) filled with conductive electrode cream (SYNAPSE, GVG-geliMED KG, Bad Segeberg) were placed on this muscle, one reference electrode was placed on the forehead. Electrodes were attached to a EMG100C (BIOPAC) amplifier. Data were recorded using a gain of 5000 at 1000 Hz and were band-pass filtered with 28-500 Hz. Data were rectified and integrated in real-time using build-in functions from the AcqKnowledge software. Startle responses were scored manually but computer-assisted from foot to peak with response onsets within 20-150ms post startle probe onset (Blumenthal et al., 2005) using a custom made program.

Participants with more than 1/3th missing or zero responses towards the startle probes were excluded from startle analyses ($n = 14$). Raw startle responses were T-transformed across all experimental phases per individual, see formula 2 and 3 with Z referring to the z score defined in formula 3. X refers to the raw startle amplitude on trial i , μ refers to mean of all raw startle amplitudes per subject, and σ refers to the corresponding standard deviation.

$$(2) T = (Z \times 10) + 50$$

$$(3) Z = \frac{X - \mu}{\sigma}$$

2.6.3 Ratings

Participants rated their level of fear, anxiety, and distress towards the CS+ and the CS- on a computerized visual analog scale ranging from none to extensive (0-100). Ratings were presented in white text on a black background that was different from all the context backgrounds. As described in (Sjouwerman et al., 2020) participants were asked: “How much stress, fear or anxiety did you experience the last time you saw symbol X?”, with the “X” referring to an inserted small graphical representation of one of the CS types at a time. Participants used their right hand to operate left and right arrow keys on the keyboard to move along the scale. The return key needed to be pressed to confirm the rating. Nine rating blocks were presented intermittently during the experiment. Rating blocks did not mark transitions between experimental phases. One rating block was presented after CS habituation, three during fear acquisition training (after at least 4 CS presentations), three during fear extinction training (after at least 4 CS presentations), and two during return of fear testing (consistently after 2 CS+ and 2 CS- presentations, and after the last CS presentation in the experiment).

Participants failing to confirm their rating in more than 1/3th of all ratings, or participants showing no variance in ratings (i.e., consistently rated 100 on all trials) were excluded from rating analyses ($n = 1$). To standardize rating responses and to remove inter-individual differences in rating responses, raw rating data were centered per individual around zero with a standard deviation of one (z-transformation).

2.7 Statistical analyses

For all statistical analyses, one Bayesian mixed model approach was used for each outcome measure and for the experimental manipulation check and the RoF of interest separately (see sections 2.7.1 and 2.7.2 for details), which has a number of relevant advantages over traditional repeated measure ANOVA models (as discussed for example in (Bürkner, 2017)), with one advantage being avoiding a multiple comparison problem (Gelman et al., 2012). Two main analyses were performed which will be described in more detail in the next sections: First, successful acquisition and extinction training was checked in the full sample (i.e, pooled across all eight groups) by investigating CS+ and CS- responses at the last trial or rating of both phases using one Bayesian mixed model for each outcome measure (for details see section 2.7.1). These analyses were not of main interest and will only be reported in brief as a manipulation check for successful fear acquisition and extinction.

Second, our main hypotheses were tested in another Bayesian mixed model for each outcome measure separately by comparing reinstatement-induced RoF depending on context: conditioned responding at test (first trial/rating; as the reinstatement effect extinguishes rapidly, see also section 2.7.2)

was evaluated with respect to conditioned responding at the end of extinction (last trial/rating) between i) the four reinstatement groups, ii) between the four control groups and iii) between reinstatement and control group of each contextual sequence respectively (i.e., AAAB, AABB, AABA, AAAA). In all analyses, potential generalized RoF effects were evaluated first and differential RoF effects were evaluating second. Further details are provided in section 2.7.2.

For all analyses, the optimal random effect structure was selected by comparing five different random structures ranging from minimal to maximal random structure for the within subject variables before interpreting the fixed effect structure. Minimal models included only random intercepts for subjects, maximal models included additional random slopes for the highest order within factors interaction (i.e., phase * stimulus type interaction). The model including all fixed variables and maximum random effect structure is shown in Formula 4. Note that this formula is applied for all analyses. For the experimental manipulation check phase refers to acquisition and extinction and for the RoF test of interest, phase refers to extinction and test. Model fits were compared, and the model with the lowest WAIC (widely applicable information criterion, (Watanabe, 2010)) index was selected for subsequent analyses on the fixed effect structure. Model comparisons for each of the outcome measures and for each research question are available at <https://osf.io/rhzev/>.

$$(4) \text{ response} = \text{phase} \times \text{stimulus type} \times \text{context group} \times \text{reinstatement group} + (1 + \text{phase} \times \text{stimulus type} \mid \text{subject})$$

Contrasts of interest were extracted from the best fitting model to compare point estimates (the median of the estimated values; displayed as symbols in the results **Figure 2** and **Figure 3**) and highest density intervals (HDI; displayed as horizontal bars in the results **Figure 2** and **Figure 3**) for pairwise comparisons to answer the specific research questions. In the following, the term *point* estimate will thus be used to refer to the median value of all estimated values from the posterior distribution, which will be used as an index of centrality (Makowski et al., 2019). When using the term *estimates*, this refers to the 95% of values falling within the posterior range of estimated values, i.e., values within the 95% HDI. Contrasts, which will be explicitly specified in the respective sections, test for or illustrate effects for CS types (e.g. CS+ versus CS- estimates) i) within one experimental phase or ii) across experimental phases (e.g. acquisition vs. extinction, and extinction vs. test). Uncertainty was restrained by extracting 95% HDIs, indicating that 95% of the predicted data, in other words 95% of the posterior estimates, lie within this interval.

If the HDI includes zero, this indicates that the difference between the estimates of the contrast, for instance CS+ versus CS- at the end of extinction, is estimated as zero, and responding in both conditions of the contrast (in this example CS+ and CS-) can be interpreted to be comparable. In case the HDI does not include zero, and 95% of the estimates is thus positive or negative, it can be assumed that there is a signal that represents a positive or negative effect. Note that in **Fehler! Verweisquelle konnte nicht gefunden werden.**, which is purely exploratory in nature, the full (i.e., 100%) posterior distributions are plotted for the RoF-effect for the stimulus types separately to facilitate future hypothesis generation.

Data were analyzed and visualized in R version 3.6.0 (2019-04-26) using packages ggplot2 (Wickham, 2016) for plotting, dplyr (Wickham et al., 2019) for data manipulation, brms (Bürkner, 2017, 2018) for Bayesian mixed model analyses, emmeans (Lenth, 2019) for extracting estimates, cowplot (Wilke, 2019) and patchwork (Pedersen, 2020) for arranging plots.

2.7.1 Contrasts investigating successful fear acquisition and extinction

Successful fear acquisition and fear extinction was tested separately for each dependent measure (i.e., ratings, SCR, and startle). A Bayesian mixed model was used to investigate differences in responding to the CS+ and CS- during the last trial/rating (i.e., end-point performance) of fear acquisition training and extinction training phases respectively and to investigate the change in CS specific responding from acquisition to extinction. Note that we were interested in group averages of fear acquisition and extinction performance to illustrate general responding during the task across experimental groups as these did not differ in procedures during acquisition and extinction training.

The Bayesian mixed model for each outcome measure included fixed factors *context group* [AAAB, AABB, AABA, AAAA] and *group type* [reinstatement vs. control group] even though experimental procedures were identical for both fear acquisition and extinction training and these groups were not established until after the extinction training phase. Hence, these were fixed factors of no interest and differences between groups in acquisition and extinction learning performance were not expected. Therefore results are reported across all participants irrespective of group. Details on fear acquisition learning and fear extinction learning within these subgroups is provided separately for the three outcome measures and can be found for completeness in **Fehler! Verweisquelle konnte nicht gefunden werden.**, **Fehler! Verweisquelle konnte nicht gefunden werden.**, and **Fehler! Verweisquelle konnte nicht gefunden werden.**

Fixed factors of interest included *phase* [last acquisition trial/rating, last extinction trial/rating] and *stimulus type* [CS+, CS-]. Four contrasts of interest were defined: (i) CS discrimination [CS+ response minus CS- response] at the last acquisition trial (for SCR and startle) or rating; (ii) CS discrimination [CS+ response minus CS- response] at the last extinction trial (for SCR and startle) or rating; (iii) change in CS+ responding from acquisition to extinction [CS+ acquisition minus CS+ extinction]; and (iv) change in CS- responding from acquisition to extinction [CS- acquisition minus CS- extinction].

Models were fitted using four Markov chains. Each chain included either 2000 or 8000 iterations depending on the random effect structure. The larger number of iterations were applied for the random effect structure that included random slopes for stimulus type and phase within subject for ratings and startle, and for the random effect structure that included random slopes for ratings. The first half of the iterations of each chain were warmup iterations. Adapt delta was set to .99 for ratings, and the default value .8 was used for SCR and startle.

2.7.2 Return of fear test of interest

Again, a Bayesian mixed model was constructed separately for each dependent measure (i.e., ratings, SCR, and startle). These models included four fixed factors of interest: *context group* [AAAB, AABB, AABA, AAAA], *group type* [reinstatement group, control group], *phase* [last extinction trial/rating, first test trial/rating], and *stimulus type* [CS+, CS-, (for startle also ITI)].

For all eight groups separately (i.e., rAAAB, rAABB, rAABA, rAAAA, cAAAB, cAABB, cAABA, and cAAAA) generalized (i.e., CS unspecific) RoF responding as well as differential (i.e., CS specific) RoF responding was examined. Generalized RoF was examined with the following contrast: Change in responding irrespective of stimulus type from extinction to test [CS+ and CS- responding at last extinction trial/rating minus CS+ and CS- responding at first test trial/rating]. Note that in contrast to our previous publication on RoF after reinstatement (Sjouwerman & Lonsdorf, 2020) where we used averaged two trial data within each phase to overcome loss of data due to missing data points in repeated measures ANOVAs, here we used single trial data as mixed models can handle missing data without case deletion and potentially are more susceptible to subtle short-lasting effects (for a discussion see (Haaker et al., 2014a)). Differential RoF was examined through the stimulus type x phase interaction for all outcome measures: the difference between stimulus types [e.g. CS+ vs CS-] was compared between phases [extinction vs test]. For startle, two additional contrasts including the ITI were included [CS+ vs ITI; CS- vs ITI] derived from a model that also included the ITI data. Note that for startle responding, generalized RoF was tested

including CS+ and CS- only to maintain consistency to SCR and ratings, and for differential RoF startle responding during the ITI is also displayed.

Subsequently, effects of context and group type were investigated by comparing the results from the described contrasts between these groups. Models were fitted using four Markov chains each with 2000 iterations. The first 1000 iterations of each chain were warmup iterations.

2.7.3 Replication framework

To evaluate the results, a replicability framework, adapted from recommendations for evaluating statistical aspects of replication results (Lebel et al., 2018) was employed. This was applied to answer our research question whether the RoF effects observed in the different groups can be considered replications. The effect between two groups were interpreted as a replication based on whether i) a signal was detected (yes/no), and ii) whether this signal was consistent. According to this framework (Lebel et al., 2018), a signal was considered present for one group, when its HDIs do not include zero as estimate. The signal between a pair of two groups was considered consistent when the point estimate of one group falls within the HDI of the other group (and vice versa). A signal thus refers to CS discrimination in the experimental manipulation checks, or to the presence of generalized RoF or differential RoF in the RoF analyses of interest.

3. Results

The raw single trial data of all experimental phases (i.e., habituation, acquisition, extinction, and test) for all three outcome measures (i.e., ratings, SCR, and startle) is displayed in **Fehler! Verweisquelle konnte nicht gefunden werden.-3**, for ratings, skin conductance and startle respectively. In addition, supplementary frequentist analyses are provided for the experimental manipulation checks as well as for the RoF tests of interest (Supplementary section 5) to enable comparisons with previous literature. Below, results from Bayesian mixed model analyses are reported. In sum, results are at large convergent across both approaches.

3.1 Fear acquisition and extinction

Successful fear acquisition and extinction training, which both occurred prior to the experimental context and reinstatement manipulations of interest, were observed across all participants in skin conductance, startle, and ratings (Information on model evaluation and graphical illustrations for all eight subgroups can be found in the supplementary material section 1.1 as well as **Fehler! Verweisquelle konnte nicht gefunden werden.-6**).

3.1.1 End of acquisition training

More precisely, successful differential fear acquisition was established in ratings (**Figure 2A**), SCR (**Figure 2B**), and startle (**Figure 2C**). At the end of fear acquisition training, the CS+ was i) rated as more fear-inducing than the CS-, ii) elicited stronger skin conductance responses than the CS- and iii) facilitated stronger startle responses in response to startle probes as compared to probes during the CS-, as indicated by positive point estimates for the CS+ minus CS- contrast with HDIs not including zero (**Figure 2A,B,C** (diamond shape in) black bars).

3.1.2. End of extinction training

At the end of extinction training (i.e., last trial or rating), the point estimates for CS+ versus CS- responding are positive (**Figure 2A,B,C** diamond shape in light grey bar) indicating larger responding to the CS+ as compared to the CS- across all outcome measures. However, HDIs for SCR (**Figure 2B**) and startle (**Figure 2C**) overlap with zero, which signifies no evidence for differences in CS+ and CS- responding at the end of extinction training and thus successful and complete extinction. For ratings, however, the HDI (**Figure 2A**) does *not* overlap with zero and hence, there is evidence for sustained CS discrimination at the end of fear extinction training for ratings only.

3.1.3. Change in responding from acquisition to extinction

Importantly, the difference between CS+ and CS- responding (i.e., point estimates as well as the HDIs; CS+ versus CS-) for all three outcome measures **Figure 2A,B,C**), is smaller at the end of extinction (light grey) than at the end of acquisition training (black) and the HDIs at both time points do not overlap within each outcome measure. This indicates that CS discrimination at the end of extinction training is estimated to be reduced as compared to CS discrimination values at the end of acquisition training for all three outcome measures, which supports successful experimental manipulation during extinction.

In addition, for all three outcome measures (**Figure 2A,B,C**), the reduction in responding from the end of acquisition to the end of extinction is larger for the CS+ (in red) than for the CS- (in blue), evident from estimates for the CS+ > CS-. For all three outcome measures, the corresponding HDIs for both CS types do not overlap supporting genuine differences.

Figure 2. Graphical illustration of successful fear acquisition and extinction training across all participants for (A) z-transformed ratings (B) log transformed and range-corrected SCR and (C) T-transformed startle. Point estimates are displayed as symbols (CS+: circle, CS-: triangle; CS discrimination: diamonds) together with 95% highest density intervals (HDI's) for CS+ versus CS- contrasts at the end of fear acquisition training (last trial/rating, black) and at the end of extinction training (last trial/rating, light grey). Note that larger estimates indicate larger responding to the CS+ than to the CS-. HDI's not overlapping with zero indicate a meaningful effect.

The difference in responding to the last acquisition trial versus the last extinction trial are displayed for CS+ (red, point estimate as circle) and CS- (blue, point estimate as triangle) with larger estimates indicating larger responding during acquisition relative to extinction. HDI's not overlapping with zero indicate a meaningful effect.

Note that the scale of the estimates for the different outcome measures in A, B, and C differs, because the outcome measures are measured on different scales (ratings are z-transformed, SCR are log transformed and range corrected, and startle is T-transformed).

3.2 Reinstatement test

While all eight groups underwent an identical procedure during fear acquisition and extinction training, groups differed in contextual assignment during reinstatement administration (i.e., either in context A: rAAAB, rAAAA or context B: rAABB, rAABA) and test (i.e., in context B: rAAAB, rAABB or in context A: rAABA, rAAAA). The same applied for control groups with the exception of not being exposed to the reinstatement US. In the following, reinstatement-related responding is compared i) within the four reinstatement groups (section 2.1), ii) within the four control groups (section 2.2.) and iii) finally between the reinstatement and control groups within one contextual sequence (section 2.3).

Stronger responding at test (first trial) as compared to extinction (last trial) is indicated by *negative* estimates (thus including point estimates) derived from the Bayesian mixed model. As described in the methods, we apply a replicability framework (Lebel et al., 2018) to evaluate reinstatement-responding (i.e., is a signal present? Is the signal consistent across groups?, see 2.7.3). We refer to the supplementary material for information on model evaluation (Supplementary material section 2.1) and graphical illustration of the original (raw) individual data points (**Fehler! Verweisquelle konnte nicht gefunden werden.-9**).

3.2.1 Effects of context on RoF in the reinstatement groups

First, responding in the four groups exposed to a reinstatement US was compared separately for (1) generalized (i.e., CS unspecific, section 2.1.1.) and (2) differential (i.e., CS+ specific, section 2.1.2.) RoF based on contrasts *without* and *with* the factor stimulus type, respectively (see methods section 2.7.2. for details). Based on results from rodent work and single-cue studies in humans (see introduction for details), RoF was expected to be observed only in groups rAAAB (**Figure 3**: blue) and rAABB (**Figure 3**: pink), as well as in rAAAA (**Figure 3**: yellow) but not in rAABA (**Figure 3**: orange).

3.2.1.1 Generalized RoF in reinstatement groups

As expected, **generalized RoF**, that is response enhancement to both the CS+ and the CS-, was observed in all outcome measures (ratings, SCR, startle) in groups rAAAB and rAABB (**Figure 3A**, C and E in dark blue and dark pink respectively). This is indicated by negative point estimates (i.e., vertical black lines in **Figure 3** indicating responding at test > extinction) and their corresponding highest density intervals (HDI, 95%, colored horizontal bars in **Figure 3**) not including zero. Hence, a signal (i.e., generalized RoF) is detected in both groups.

Contrary to our hypotheses, however, no generalized RoF was observed in group rAAAA in any of the outcome measures (dark yellow bars in **Figure 3A**, C, and E). Even though point estimates were also

negative for ratings and startle, HDIs also included the zero estimate, which suggests the absence of RoF despite this descriptive tendency for stronger responding at test as compared to extinction. For SCRs, point estimates were close to zero indicating no change in responding between extinction and test. In sum, no signal (i.e., generalized RoF) was observed in group rAAAA.

Again in line with what was expected, no generalized RoF was observed in group rAABA for psychophysiological outcome measures (SCR and startle, dark orange bars including zero in **Figure 3C** and **E**) while in ratings RoF was observed (**Figure 3A**, dark orange). More precisely, point estimates for all outcome measures were negative in rAABA, indicating higher responding at test as compared to the end of extinction. Yet, a signal (i.e., generalized RoF) was only detected for ratings, as only HDIs for ratings did not include zero while HDIs for SCR included zero.

In sum, in line with our hypotheses, generalized RoF was observed in group rAAAB and rAABB in all three outcome measures, but not in physiological measures (SCR, startle) in group rAABA. Contrary to our hypotheses, RoF was observed in ratings in group rAABA and also contrary to our hypotheses, RoF was not observed in any outcome measure for the smaller group rAAAA.

Finally, we compared responding between the four reinstatement groups with respect to signal (i.e., generalized RoF) consistency. Accordingly, effects across groups are considered consistent (i.e., replications) when the point estimate of one group falls within the HDI of a second group (see 2.7.3). Following these criteria, we conclude that the generalized RoF effects in groups rAAAB and rAABB are consistent across all outcome measures. Furthermore, responding can also be interpreted as being consistent between groups rAAAA and rAABA across outcome measures.

Furthermore, when focusing on the physiological outcome measures only, the point estimates of the context groups in which *no* RoF signal was observed (rAABA and rAAAA) fall – with one exception – outside the HDIs of the context groups in which RoF was observed (rAAAB and rAABB). The one exception applies to SCR responding in group rAABA where the point estimate falls outside the HDI of group rAAAB. For ratings, generalized RoF has to be interpreted as being consistent between all four groups, despite no support for RoF in group rAAAA (i.e., HDI includes zero but point estimate falls within other groups HDIs).

3.2.1.2 Differential RoF in reinstatement groups

Differential RoF, that is CS specific response enhancement (i.e., $CS+ > CS-$) is not evident in any of the four reinstatement groups in any of the outcome measures (**Figure 3B,D,F**) More precisely, CS discrimination is comparable at the end of extinction and after reinstatement as indicated by the HDIs of

all groups for all outcome measures overlapping with zero, indicating the absence of a differential RoF signal.

The absence of differential RoF in all reinstatement groups can be interpreted as consistent across outcome measures indicated by the point estimates of one group falling within the HDIs of all other groups – with one exception: For startle, the point estimate for group rAABA has to be interpreted as inconsistent (i.e., smaller) as compared to group rAAAB and rAAAA but not group rAABB. More precisely, the point estimate was positive in group rAABA, indicating stronger discrimination at the end of extinction as compared to test. In contrast, the estimates were negative for group rAAAB and rAAAA indicating stronger CS discrimination after reinstatement. In sum, despite the absence of a differential RoF signal in any of the reinstatement groups, startle CS discrimination changed differently from the end of extinction to test in group rAABA as compared to groups rAAAB and rAAAA.

For startle, an interesting additional and explorative observation is, that only in group rAABB response enhancement (extinction to test) was larger for both the CS+ and the CS- as compared to responding to the ITI (**Figure 3G**, dark pink bars denoted with x and *) – as indicated by negative estimates for both contrasts and HDIs not overlapping with zero (CS+ vs. ITI and CS- vs. ITI). The absence of such a pattern in all other groups (rAAAB, rAABA, rAAAA) indicates that response enhancement to the ITI in these other groups is comparable to response enhancement to the conditioned stimuli (CS+ and CS-, see dark blue, dark orange and dark yellow bars in Figure 3G).

For the interested reader, Fehler! Verweisquelle konnte nicht gefunden werden. shows the posterior distributions and the respective stimulus specific HDIs separately for CS+, CS- (and for startle also ITI) which provide more details on overlap between stimulus types. These descriptive patterns that are purely exploratory in nature might be helpful for future hypothesis generation in delineating the mechanisms underlying reinstatement induced return of fear.

3.2.2. Effects of context on return of fear in control groups

Previous research in human participants has rarely employed control groups (Haaker et al., 2014b) and puzzlingly, unexpected response enhancement following reinstatement was reported in such no-reinstatement US control groups (Dirikx et al., 2007, 2009; Kull et al., 2012). Yet, this observation has never been systematically investigated even though this has the potential to shed light on the mechanisms underlying reinstatement induced RoF in humans. In particular, as response enhancement in the reinstatement groups was generalized (i.e., comparable for both the CS+ and CS-), it remains a matter of debate whether this can be attributed to genuine associative processes including generalization processes

or merely attributable to non-associative processes such as orienting responding, sensitization (i.e., a general increase in physiological responding after exposure to an intense stimulus (Dworkin & Dworkin, 1990; Perusini et al., 2016)) or a general sense of “uncertainty” ((Haaker et al., 2014b; Scharfenort & Lonsdorf, 2016).

Furthermore, if response enhancement is observed in control groups (Dirikx et al., 2007, 2009; Kull et al., 2012), this points to the involvement of processes independent from the administration of reinstatement USs, which would likely affect both reinstatement and control groups. It has previously been speculated that unintended renewal effects might be at play (i.e., unintended RoF after contextual change) (Haaker et al., 2014b). Here, we provide for the first time a systematic exploration of control groups undergoing an identical paradigm as the reinstatement groups – except for reinstatement US exposure. In the following, results will be presented separately for generalized RoF (2.2.1) and differential RoF (2.2.2.) and results are based on contrasts *without* and *with* the factor stimulus type, respectively (see methods section 2.7.2. for details).

3.2.2.1 Generalized RoF in control groups

Similarly to what was observed in the reinstatement groups, **generalized RoF** was – at large – consistently present in all three outcome measures in control groups cAAAB (light blue in **Figure 3A**, C and F) and cAABB (light pink in **Figure 3A**, C and F) – with the exception of ratings in group cAAAB (i.e., HDI overlapping with zero indicating the absence of a significant effect). In contrast, and also similar to what was observe in the reinstatement groups, generalized RoF was – at large – absent in groups cAAAA (light yellow in **Figure 3A**, C, and F) and cAABA (light orange in **Figure 3A**, C and F) in all three outcome measures (i.e., estimates centering around zero) – with the exception of evidence for generalized RoF in startle in group cAABA (i.e., negative point estimate and HDI not overlapping with zero).

Furthermore, the generalized RoF signal in the groups showing – at large - generalized reinstatement (i.e., cAAAB and cAABB) was consistent across all outcome measures, as indicated by the point estimates of one group falling within the HDIs of the other group. Responding between the groups showing –at large – no generalized RoF (cAABA and cAAAA) was also consistent for ratings and SCRs but for startle, the signal was inconsistent. In line with a generalized RoF signal in group cAABA but not cAAAA, point estimates of one group were not included in the HDI of the other group, indicating inconsistency of the signals. Consistency between the two clusters of groups (RoF vs. no RoF) was complex. Generally, response enhancement was inconsistent and smaller in group cAAAA (in ratings and SCRs) and cAABA

(ratings) than compared to group cAABB. All other comparisons yielded consistent response pattern, irrespective of one group showing a signal or not.

3.2.2.2 Differential RoF in control groups

No evidence for **differential RoF** was observed in any of the control groups (i.e., cAAAB, cAABB, cAABA, cAAAA) for any of the outcome measures (i.e., ratings, SCR, startle) (see **Figure 3B,D,F**). Again, for the interested reader posterior distributions including respective HDIs for CS+, CS- (and for startle also ITI) separately are shown in **Fehler! Verweisquelle konnte nicht gefunden werden..**

3.2.3 Generalized RoF compared within the four contextual sequences between reinstatement and control groups

It is noteworthy that irrespective of reinstatement or control group, a signal (i.e., RoF) is detected across all three outcome measures (i.e., HDIs not overlapping with zero) in groups AAAB and AABB - with the exception of ratings in group cAAAB. Most strikingly, however, is that the signal for all three outcome measures was consistent in strength between control and reinstatement groups within one contextual sequence (i.e., between rAAAB and cAAAB as well as between rAABB and cAABB) as indicated by the point estimate of the reinstatement groups falling within the HDIs of their respective control groups (and vice versa). In sum, the observed response enhancement was comparable irrespective of administration of a reinstatement US. This forcefully raises the question if and to what extent different mechanisms other than those triggered by administration of the reinstatement US are at play here. It is, in principle, conceivable that different mechanisms underlie the response enhancement in control and reinstatement groups – although we consider this rather unlikely given the similarity of response patterns.

Furthermore, it is striking that the additional group AAAA, which was acquired at a later time point for means of completeness, a signal (i.e., RoF) was consistently absent across outcome measures for both the control and reinstatement groups. This absence of a signal was also consistent for all three outcome measures (i.e., point estimate of the reinstatement groups falling within the HDIs of their respective control groups, and vice versa) between groups rAAAA and cAAAA.

Of note, responding in the control and reinstatement group of contextual sequence AABA was complex across outcome measures and difficult to reconcile. For SCRs a signal (i.e., RoF) was absent in both groups and responding was consistent. For ratings, there was a signal only in the reinstatement but not the control group and responding was also inconsistent between both groups. For startle in turn, there was a signal only in the control but not the reinstatement group and responding between both groups was inconsistent.

is shown on the right side of the figure (B, E, F, G). In each subpanel the upper rows (dark shades) refer to reinstatement (r) groups, lower rows (lighter shades) refer to control (c) groups. The vertical line refers to the median estimate independent of stimulus type in A, C, and E. The plus symbol refers to CS+ vs CS- contrast over extinction vs test in B, D, F, additionally the cross refers to CS- vs ITI and the star symbol to CS+ vs ITI in G.

4. Discussion

Already a decade ago, (Sokol & Lovibond, 2012) asked “What are the driving mechanisms behind reinstatement [in humans] and what are the conditions essential for its emergence?” (Sokol & Lovibond, 2012). The current study aimed to answer this question and to systematically investigate the role of context during reinstatement as an experimental boundary condition in reinstatement induced RoF in human participants. In doing so, we aimed to i) evaluate the translatability of results derived from rodent work to human participants, ii) provide insights into the mechanisms driving reinstatement induced response enhancement and iii) address puzzling findings from prior work in humans such as (seemingly) unexpected response enhancement in no-reinstatement control groups.

We tested a total of 212 participants in a total of four groups differing in contextual assignment during acquisition, extinction, reinstatement administration and test (i.e., AAAB, AABB, AABA, AAAA). Each context group was divided into a group exposed to a reinstatement US (i.e., rAAAB, rAABB, rAABA, rAAAA) and a respective no-reinstatement control group (i.e., cAAAB, cAABB, cAABA, cAAAA) undergoing otherwise identical procedures, thus summing up to eight groups in total. Conditioned responding was investigated across multiple outcome measures (ratings, SCR, startle). As different outcome measures tap into slightly different processes, a multi-methods approach holds promise to provide a comprehensive view on underlying mechanisms (Lonsdorf et al., 2017).

The results of the reinstatement groups appear largely in line with our hypotheses which we derived from previous single-cue work in rodents (Westbrook, Iordanova, McNally, et al., 2002) and humans: We observed response enhancement after a reinstatement-US in ratings, SCR and startle in groups rAAAB and rAABB. In group rAABA, RoF was only absent in physiological outcome measures but present in ratings. Surprisingly, and contrary to previous work and our hypotheses, no evidence for generalized RoF was observed in group rAAAA. It should be noted, however, that this group was included later in time as an additional exploratory control condition and was somewhat smaller than the other groups. Of note, response enhancement was always generalized and no evidence for differential (i.e. CS-specific) RoF was observed in any of the groups.

This pattern of results can be taken to support the previous conclusions from rodents and humans that reinstatement is observed when reinstatement USs are administered in a context identical to the extinction context (i.e., rAAAB) or the test context (i.e., rAABB) but not when these are administered in a context different from both extinction and test context (i.e., rAABA).

As our hypotheses were derived primarily from rodent work (Westbrook, Iordanova, McNally, et al., 2002) the dissociation between physiological and verbal outcome measures in group rAABA is particularly striking. More precisely, verbal reports of fear cannot be obtained from rodents, which limits translatability of findings from rodents to human work using verbal reports of feelings. In fact, it has been discussed widely in the past decade that processes that give rise to conscious feelings of fear and nonconscious processes underlying defensive responding to threat are distinct (Ledoux, 2014). It is noteworthy, however, that also studies in human participants employing an rAABA group found no evidence for RoF (LaBar & Phelps, 2005) or less pronounced RoF (as compared to an rAAAA group; (Schiller et al., 2008). Importantly, both studies in humans employed a single-cue paradigm (i.e., CS+ only) and relied exclusively on a physiological outcome measure (i.e., SCRs) without recording verbal reports. At first glance, the fact that Schiller et al. (2008) reported significant response enhancement from the last extinction trial to the first test trial in a rAABA group may seem inconsistent with rodent work and work by LaBar & Phelps (2005). Yet, in the study by Schiller et al. (2008) the reinstatement administration took place 24h prior to test and SCRs were the only outcome measure for which the last extinction training trial was compared to the first test trial. Therefore, it is likely that response enhancement observed in this study does not reflect genuine reinstatement induced RoF but rather orienting responding at a new experimental day or spontaneous recovery. More precisely, SCR is a measure of autonomic arousal (Boucsein et al., 2012; Lonsdorf et al., 2017) and subject to substantial habituation processes. SCRs to the first test trial (i.e., the first trial on that experimental day) will necessarily be higher than to the last trial of the extinction training phase on a previous day. This is a common caveat when including SCRs as the outcome measure, which we have discussed in detail (Lonsdorf, Merz, & Fullana, 2019).

One of the aims of this study was to elucidate potentially different mechanisms leading to RoF in groups differing in contextual sequences during reinstatement administration. To this end, we used a differential protocol with a reinforced CS+ and a non-reinforced CS- cue while previous work in rodents and humans had relied on single-cue protocols. As such, based on rodent work we had speculated that mediated conditioning (new fear) may be at play in group rAAAB which may manifest as generalized RoF (to the CS+ and CS-), while context conditioning (unmasking of old fear) was expected to be at play in group rAABB which in turn may manifest as CS+ specific reinstatement in a differential conditioning paradigm (Westbrook, Iordanova, McNally, et al., 2002). However, as we did only observe generalized and not differential RoF across outcome measures, we cannot distinguish between potentially different mechanisms underlying RoF in groups rAAAB and rAABB. Generalized response enhancement to both CSs

may i) indicate generalization of fear from the CS+ to the CS- or ii) may also result from non-associative processes that impact on both stimulus types similarly such as sensitization or orienting responding.

Yet, there is some evidence from our results hinting towards potentially different mechanisms underlying reinstatement induced response enhancement in both groups: In group rAAAB but not rAABB, response enhancement also generalized to ITI startle responses (note that neither SCRs nor ratings are recorded for responding during the ITI). This may hint to response enhancement in group rAABB being driven by associative processes (i.e., confined to the conditioned stimuli) and enhanced responding to the CS- might indeed reflect generalization processes. In group rAAAB, however, associative processes seem less likely and it can be speculated that a sense of general unsafety may underlie response enhancement to the CSs as well as the ITI. Yet, a similar pattern for ITI responding – albeit weaker and only descriptive in nature – emerges for the control groups. It should also be noted, that it cannot be excluded that these results may be specific to the operationalization of a compound presentation of context and cue stimuli during all experimental phases (except for reinstatement administration) as context is typically operationalized as a continuous, multisensory and diffuse (Maren et al., 2013), which was also the case in two studies in humans (LaBar & Phelps, 2005; Schiller et al., 2008).

Theoretically, response enhancement following the “reinstatement” phase is not expected in control groups, as they do not undergo a reinstatement manipulation. These control groups undergo an identical procedure as the reinstatement groups except for not being exposed to the reinstatement US, but depending on the condition are subject to contextual change. Strikingly, however, despite not being exposed to a reinstatement US in the first place, we observed a similar pattern in control groups as in their respective reinstatement groups: Rather consistent response enhancement in groups cAAAB and cAABB and generally no response enhancement in groups cAABA and cAAAA (with the exception of no response enhancement in ratings in cAAAB and response enhancement in startle in cAABA). Such at the first glance unexpected response enhancement in no-reinstatement control groups has also been described and critically discussed in the literature previously (Haaker et al., 2014b).

This pattern of results (i.e., comparable generalized response enhancement in reinstatement and control groups) may cast substantial doubt on any associative processes related to the reinstatement US in the current study - even though it remains a possibility that different mechanisms drive responding in control and reinstatement groups which all share enhanced responding across outcome measures as final common pathway. Still, the possibility of non-associative processes such as sensitization (Dworkin & Dworkin, 1990; Perusini et al., 2016) or orienting responding (to novelty) needs to be considered, in

particular as no such response enhancement in either reinstatement or control group was observed in contextual sequence AAAA. Strikingly, the AAAA groups do not undergo any change in context. Even though results should be interpreted with caution due to the later inclusion of group AAAA and the smaller sample size, it is obvious that unintended contextual changes (switch from ITI to the context/cue compound) and the corresponding orienting responses to novelty are strong candidates for the observed response enhancement particular in groups rAAAB, rAABB. As the operationalization of context as a compound of CS and context makes it impossible to disentangle their respective effects in our experimental design – at least for SCRs, future studies should circumvent this limitation of our work and explicitly aim to operationalize the context such that it is more clearly differentiated from the cues (e.g., CSs), possibly multisensory, and continuously present during the full experimental paradigm (Bouton, 1988; Maren et al., 2013). The focus of our work was to investigate different operationalizations of context (intended and unintended) as employed in the reinstatement literature (for a review see Haaker et al., 2014b) and future work should specifically focus on context conditioning and hence use tailored experimental designs.

Hence, our work highlights the challenges of cross-species translation of experimental paradigms and measures (for evaluative conditioning see Luck & Lipp, 2020). As we have discussed earlier (Haaker et al., 2019; Sjouwerman & Lonsdorf, 2020), procedures established in one species (here: rodents) cannot simply and “literally” be adapted to other species (here: humans), without testing for (experimental) boundary conditions potentially inherent to research in different species – including different outcome measures (e.g., physiological responding vs. subjective ratings as discussed above). This also extends to the operationalizing of “context” between species (see Haaker et al., 2019 for a discussion). In humans, context is typically operationalized as “what is presented on a computer screen” (with few exceptions such as (LaBar & Phelps, 2005) and in rodents typically as “being placed in an experimental cage”. It is noteworthy that, in humans, even a blank screen (i.e., showing “nothing” on the screen) during reinstatement-US administration may serve as contextual information and may hence signal a context different from the context during CS presentations and the ITI. Accordingly, studies that employ reinstatement manipulations may apply (unintended) contextual changes in their experimental design beyond the explicitly intended reinstatement manipulation. Importantly, such contextual changes between extinction learning and a subsequent test phase are also known to induce return of fear– a phenomenon termed “renewal” (Bouton & King, 1983; Bouton & Ricker, 1994; Vervliet, Baeyens, et al., 2013). In humans, the role of context in reinstatement has largely been neglected to an extent that the precise procedural details (e.g., timing, visual input) are often not even reported (Haaker et al., 2014b). In

particular, in group AAAB, it cannot be excluded that (unintended) renewal processes may contribute to response enhancement in both the reinstatement and the control group. As such, also the fact that we unexpectedly observed the complete absence of response enhancement in control and reinstatement group with the AAAA sequence across outcome measures may support that the contextual changes and the choice of a compound cue-context operationalization – particularly in groups AAAB and AABB – may underlie the observed response enhancement in both control and reinstatement groups.

We have also previously highlighted the role of apparently subtle procedural changes with potentially large consequences in fear conditioning research (Lonsdorf et al., 2017; Lonsdorf, Klingelhöfer-Jens, Andreatta, Beckers, Chalkia, Gerlicher, Jentsch, Drexler, Mertens, Richter, et al., 2019; Lonsdorf, Merz, & Fullana, 2019)). Hence, investigating under which experimental conditions a phenomenon under study manifests will contribute substantially to and improve our understanding of these phenomena, help to refine our theories, and will likely also contribute to enhanced replicability in general (Larson & Moser, 2017). The focus of the present investigation was the role of context in reinstatement-induced RoF in humans. Yet, despite the possibility of experimental boundary conditions contributing to heterogeneous findings, also a rather unattractive interpretation may explain heterogeneous findings in the literature: random variation. It has been highlighted previously, that it is often tempting to explain away heterogeneous findings with procedural and methodological differences, while random variation of effects sizes is often neglected as a possibility (Lakens, 2017).

Relatedly, despite the large overall sample size ($N > 212$), the highest density intervals (HDIs) which reflect 95% of the by the model predicted data falling within that interval, were rather wide for all subgroups in the present study. These wide HDIs indicate low precision of the estimates in subgroups that included 27 to 36 participants (AAAB, AABB and AABA groups) - and only 21-25 participants for the later included AAAA subgroups. More precisely, the HDIs of different groups – both contextual sequences as well reinstatement and control groups – overlap largely which can partly be attributed to their imprecision. Generally, this low precision for the subgroups points towards suboptimal statistical power to detect reinstatement effects in samples < 40 participants. Yet, sample sizes between 27 and 36 as employed here are not particularly small and match the typical sample sizes in reinstatement research (see Haaker et al., 2015, Table 3).

Importantly, the width or in other words the imprecision or uncertainty of the estimates has implications for the application of a replicability framework as employed here. Our data suggest that most of the response patterns observed – in particular between groups AAAB and AABB as well as between

AABA and AAAA, can be considered replications with respect to the effect of response enhancement between the end of extinction and the early test phase. This interpretation is based on an adopted framework by LeBel (LeBel et al., 2018) which considers the effects in two groups as consistent (i.e., replicated) when their respective point estimates fall within each other's HDIs. It follows that when the estimations in both groups are imprecise (i.e., wide HDIs), we may easily conclude consistency (i.e., replication) while more precise estimates in (for instance) larger samples or by using more reliable measures would tell a different story. It is, however, noteworthy that despite the generally wide HDIs, some clear pattern of non-consistency in effects emerged – more strikingly the different strength of response change between groups AAAB/AABB and AABA/AAAA, which clearly suggest that different mechanisms are at play in these two clusters of contextual sequences.

In closing, we aimed to shed light on the driving mechanisms behind reinstatement-induced RoF in humans and the modulatory role of context presentation during in a study employing a systematic small-scale design-multiverse approach (Harder, 2020). Our results are generally in line with previous work and our hypotheses illustrating generalized response enhancement when either test and reinstatement context or test and extinction context were identical (AAAB, AABB) but not when reinstatement context differed from extinction and test context (i.e. AABA). Yet, this was only true for physiological outcome measures but not subjective ratings of fear. Furthermore, we observed comparable response enhancement following reinstatement in groups exposed and not exposed to the reinstatement manipulation. Consequently, our results may suggest, that what we have considered as RoF induced by reinstatement in the past, may in fact either derive from other associative processes than reinstatement (e.g., renewal by unintended contextual change) or may even represent non associative effects (Sjouwerman & Lonsdorf, 2020) such as sensitization or orienting responding—at least in some cases such as in our design and previous work that involved a switch from ITI to a context or a context/cue compound. Additional studies are clearly needed to improve our understanding of the experimental boundary conditions in return of fear research in human participants and to make translation from rodent work successful in humans (Haaker et al., 2019) – in particular as return of fear phenomena have a potentially high clinical value.

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Data sharing statement

Data and code are available at <https://zenodo.org/badge/latestdoi/397299678>.

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Author contributions (CRediT statement)

Rachel Sjouwerman: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project Administration, Visualization, Software, Writing: Original draft

Tina B. Lonsdorf: Conceptualization, Funding acquisition, Methodology, Project Administration, Resources, Supervision, Writing: Original draft

Conflict of interest

The authors declare no conflict of interest. The authors received no funding from an external source.

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