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Stress disrupts the reconsolidation of fear memories in men

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ABSTRACT

Reconsolidation is a post-retrieval process of restabilization of the memory trace. Previous findings from our group suggest that cortisol, a glucocorticoid hormone secreted in response to stress, enhances the reconsolidation of fear memories in healthy men. Cortisol effect was found to be very specific, enhancing only the fear memory that was reactivated (i.e. retrieved), but not the non-reactivated memory. In the current study we aimed to investigate the effects of psychosocial stress, a more ecologically valid intervention, on fear memory reconsolidation in men. Using a similar design, we expected stress induction to have comparable effects to those of cortisol intake. During the three testing days, the participants went through (1) fear acquisition, (2) stress induction and memory reactivation (or the corresponding control conditions), (3) fear extinction, reinstatement and reinstatement test. Salivary cortisol, blood pressure measures and subjective ratings confirmed the success of the stress induction. Skin conductance response, serving as a measure of conditioned fear, confirmed acquisition, fear retrieval, and extinction in all groups. In the three control groups (where either reactivation, stress, or both components were missing) reinstatement effects were seen as expected. Yet in contrast to the hypothesis, the target group (i.e. combining reactivation and stress) showed no reinstatement to any of the stimuli. Stress induction is thus suggested to have a general impairing effect on the reconsolidation of fear memories. The unique characteristic of the stress response and experience compared to a pharmacological intervention are proposed as possible explanations to the findings. This disruptive effect of stress on fear memory reconsolidation may have potential therapeutic implications.

1. Introduction

A stressor is a physical or psychological challenge that exceeds the natural regulatory capacity of the animal. The resulting 'stress response', that involves a variety of modulators (neurotransmitters, peptides and steroid hormones), promotes the physiological and behavioral adaptation to the challenge (Joels and Baram, 2009; Koolhaas et al., 2011). The sympathetic nervous system (SNS), a division of the autonomic nervous system, is fast to response. Leading to the secretion of (nor)adrenaline and additional monoamines from the adrenal medulla, it induces rapid but mostly short-lasting changes in neuronal excitability. SNS activity promotes physiological and behavioral responses (e.g. enhanced metabolism, increased arousal) that are critical at the initial phase of the stressful event (Joels and Baram, 2009). The hypothalamus-pituitary-adrenal (HPA) axis is slower to response, yet its effects may be more long-lasting. Glucocorticoids (GCs, mainly cortisol in humans and corticosterone in rodents) are the end-products of the HPA axis. In the brain, they bind to mineralocorticoids (MR) and glucocorticoids (GR) receptors (de Kloet et al., 1998). While the high affinity MR mediate the initial GCs response to stress, such as appraisal of information and response selection (Lupien and McEwen, 1997), the lower affinity GR contribute to terminating the stress response in a negative feedback loop (de Kloet et al., 1998). The membrane-bound variants of MR and GR can alter neuronal function within minutes via non-genomic pathways, while the nuclear variants can lead to changes through gene expression with a delay of more than one hour (Joels and Karst, 2012; Joels et al., 2008).

The timing of stress is a key factor in determining the modulation of memory by stress. Stress in close proximity to the initial learning episode might enhance the consolidation of memory,

Abbreviations: ASI, Anxiety Sensitivity Index; BMI, body mass index; CS, conditioned stimulus/stimuli; GCs, glucocorticoids; GR, glucocorticoid receptors; HPA, hypothalamus pituitary-adrenal; ITI, inter-trial interval; MR, mineralocorticoid receptors; NEO-FFI, NEO-Five Factor Inventory; PTSD, post-traumatic stress disorder; SCR, skin conductance response; SECPT, Socially Evaluated Cold-Pressor Test; SNS, sympathetic nervous system; STAI-T, State and Trait Anxiety Inventory; TICS, Trier Inventory of Chronic Stress; UCS, unconditioned stimulus.

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especially for emotional stimuli or in an arousing new context (e.g. an encounter with an aggressive dog in a new neighborhood) (Buchanan and Lovallo, 2001; Maroun and Akirav, 2008; Roozendaal, 2000; Smeets et al., 2008). In contrast, stress exposure prior to a retrieval task (e.g. during an exam) would most likely impair the retrieval of information that had been previously consolidated (Atsak et al., 2016; Buchanan et al., 2006; de Quervain et al., 2009; Roozendaal, 2002; Smeets et al., 2008; Wolf, 2009). Stress intensity, duration and source are additional factors that affect both the direction and magnitude of the stress-dependent memory modulation (Sandi and Pinelo-Nava, 2007). For instance, while moderate stress tends to enhance the consolidation of spatial memory, too low or too high levels of stress will impair it (Sandi et al., 1997).

Reconsolidation is a post-retrieval process of restabilization of the memory trace. Following retrieval ('reactivation'), the memory can be brought to a susceptible state for a period of several hours (Kindt et al., 2009; Schiller and Delgado, 2010). Introducing pharmacological or behavioral manipulations during this fragile period was found to affect (enhance or impair) the reconsolidation process, thereby revealing the mechanisms of post-retrieval memory modulation. For instance, the reconsolidation of emotional memory, much like its initial consolidation, was found to depend on protein synthesis (Nader et al., 2000) and noradrenergic activity (Kindt et al., 2009).

While the (mostly enhancing) effects of stress on memory consolidation are well-documented, less is known about its potential effects on memory reconsolidation. Animal studies have demonstrated memory impairment when either stress, GCs agonists or antagonists were given after the reactivation of aversive memories (Abrari et al., 2008; Pitman et al., 2011; Yang et al., 2013). The human literature, focusing mainly on declarative memories, have demonstrated either an enhancing (Bos et al., 2014; Coccoz et al., 2011, 2013) or impairing (Schwabe and Wolf, 2010; Zhao et al., 2009) effect of a mild stressor on memory reconsolidation, with conflicting findings with regard to the susceptibility of strong emotional memories. Recent work from our group was the first to investigate the effects of cortisol administration on the reconsolidation of fear memories in healthy men (Meir Drexler et al., 2015) using the fear conditioning paradigm, a model for stress- and trauma-related disorders (Pull, 2007). By enhancing the reconsolidation of reactivated memories, cortisol was suggested to play a major role in emotional memory persistence, e.g. in anxiety disorders and post-traumatic stress disorder (PTSD).

In the current study, we examined the effects of stress on the reconsolidation of fear memories in healthy men. While a pharmacological intervention can isolate the effects of cortisol and control for dose-dependent effects (Meir Drexler et al., 2015), an exposure to a psychosocial stressor, as used in this work, is more ecologically valid, leading to secretion of cortisol, (nor)epinephrine and additional stress modulators that constitute the complex stress response. Due to the similarity between initial consolidation an reconsolidation (Nader et al., 2000; Kindt et al., 2009) and the enhancing effect of stress and cortisol on memory consolidation (Wolf, 2009), we expected stress to have comparable effects to those of cortisol on memory reconsolidation (i.e. a specific enhancement of the reconsolidation of the reactivated fear memories). As reconsolidation modulation by stress hormones might be affected by sex and sex hormones (Meir Drexler et al., 2016), in the current study we tested only men.

2. Materials and methods

The design of the current study is an adaptation of our previous reconsolidation studies, which investigated cortisol modulation of fear memory reconsolidation in men and women (Meir Drexler et al., 2015, 2016).

2.1. Participants

Seventy-two healthy men, aged 18–34 years with body mass index (BMI) between 18 and 28, participated in this study. The following were used as exclusion criteria: smoking, somatic or endocrine disease, current or past psychiatric/neurological disorders, and regular medication intake. The participants were recruited via announcements on the campus of the Ruhr-University Bochum, Germany, and received either a financial reimbursement or credit points for participation. The study was approved by the local ethics committee. All participants signed an informed consent.

The participants were randomly assigned to one of four groups: reactivation + stress (RE + STR), reactivation + no stress (RE), no reactivation + stress (STR), no reactivation + no stress (CONTROL).

2.1.1. Exclusion criteria

To test the effects of stress on the reconsolidation of fear memories, only stress responders and control non-responders were included in the analyses, a common practice in studies using a mild psychosocial stress (Buchanan et al., 2006; Miller et al., 2013). The literature has no standardized criterion for distinguishing cortisol responders from non-responders. However, several criteria were suggested, with a conservative cutoff set at 2.5 nmol/l or 1.5 nmol/l (Miller et al., 2013) and a more liberal cutoff set at 0 nmol/l baseline-to-peak increase (Buchanan et al., 2006). While the more conservative cutoffs might create a clearer separation between experimental groups in terms of cortisol response, the liberal criterion minimizes the threat to external validity and preserves statistical power. As the desired patterns of cortisol, SNS activity and subjective ratings in response to stress were seen in our dataset already when using the liberal cutoff (see Section 3.2. and Tables 1 and 2), we adopted this criterion for all analyses. Thus, in line with the criterion set by Buchanan et al. (2006), response was defined as a rise > 0 nm/l, 30 min after the stress induction compared to the baseline (i.e. beginning of the same testing day). Twenty-two participants were excluded: stress non-responders (N = 13), control responders (N = 7), and participants with missing cortisol values (N = 2).

In this study, a differential fear conditioning paradigm was used with two reinforced stimuli (CS1+ and CS2 +) and one unreinforced stimulus (CS-). Thus, an additional exclusion criterion was implemented to ensure equivalent acquisition to the two reinforced stimuli (Schiller et al., 2013) prior to the reactivation of one of them on the second testing day. A differential SCR for CS1+ and CS2+ (d = | (CS1 +) − (CS2 +) |) was calculated based on mean acquisition values (the lower the differential value, the more equivalent the acquisition of the two stimuli). Five participants that showed a differential SCR higher than 1.5 interquartile ranges above the higher quartile were excluded.

The following analyses thus include 45 participants in four experimental groups: RE + STR (N = 10), RE (N = 11), STR (N = 11), CONTROL (N = 13).

2.2. Experimental timeline

The experimental procedure consisted of three experimental days, separated by 24 h intervals. The three testing days were as follows: (1) fear acquisition; (2) memory reactivation (or no reactivation) following exposure to stress (or the control condition); (3) extinction, reinstatement, and reinstatement test. To minimize contextual effects as much as possible, all procedures were conducted in the same experimental room by the same experimenter. The experimental procedure was identical for the participants of

all four groups on experimental days 1 and 3, and differed only on day 2.

Skin conductance responses (SCR) were used as a measure of conditioned fear, and were recorded during acquisition, extinction and reinstatement test. Saliva samples were used to assess salivary cortisol concentrations, and were collected at seven time points during the three experimental days. The experimental timeline is presented in Fig. 1.

2.2.1. Day 1: Fear acquisition training

After SCR and shock electrodes attachment, the participants were generally instructed to look for possible stimuli contingencies (i.e. between shape/s and shocks) but were not told which shapes would be paired with a shock and which wouldn't. For the acquisition phase, two geometrical shapes (the conditioned stimuli CS1+ and CS2 +) were followed by an electric shock (unconditioned stimulus, or UCS) in 9 out of 13 presentations i.e. a partial reinforcement rate of approx. 70%. A third shape (CS−) was never followed by a shock. The entire phase consisted of 13 presentations of each of the three stimuli (for 4 s each) in a pseudo-randomized order with an intertrial interval (ITI) of 10–12s. This phase lasted 10 min.

2.2.2. Day 2: Stress/control and reactivation/no reactivation

The experimental procedure was different for each of the groups only on this day. Shortly after arrival, the participants were either exposed to stress (RE + STR and STR groups) or to the control condition (RE and CONTROL groups) (see Section 2.3.2.) and were given a 30 min break. The break was inserted to allow the expected stress-related cortisol peak (Buchanan et al., 2006; Guenzel et al., 2014; Hamacher-Dang et al., 2013). By pairing this peak with the reactivation of memory we aimed to create a direct comparison to our previous pharmacological study (Meir Drexler et al., 2015) that used similar timeline. During the break, the participants remained in the experimental room and were given reading material. The reactivation session for participants from the reactivation groups (RE + STR and RE) was then performed as follows: the participants were attached to the SCR and shock electrodes and were instructed that the CS-UCS contingencies would remain unchanged from the previous day. To reactivate the specific memory of a previously reinforced stimulus, CS1+ was then presented (in a single trial that lasted 4s) and was not followed by a shock. Following this single presentation, the electrodes were immediately disconnected and the participants resumed the break until the end of the testing day. The single unreinforced presentation is thus similar but not identical to the original acquisition, and the lack of UCS is thought to serve as a 'prediction error' that triggers the reconsolidation process (Sevenster et al., 2012) as demonstrated in our previous study (Meir Drexler et al., 2015). Participants in the no-reactivation groups (STR and CONTROL) received no intervention apart from stress/control induction but remained in the testing room for approx. 45 min, the same amount of time as the participants from the reactivation groups.

2.2.3. Day 3: Fear extinction training, reinstatement, and reinstatement test

After SCR and shock electrodes attachments, the participants were generally instructed that the CS-UCS contingencies would remain unchanged as in the previous days. For the extinction phase, all three stimuli (CS1+, CS2+, and CS-) were presented (4s, 10 times each) in a pseudo-randomized order with an ITI of 10–12s. None of the stimuli were followed by a shock. The extinction phase lasted approx. 8 min. After the conclusion of the extinction phase, four unsignaled UCS presentations (ITI: 10–12s) were given in order to reinstate the extinguished fear. This phase lasted 1 min. The reinstatement test that followed was identical to the extinction test (i.e. 10 unreinforced presentations of each of the three stimuli) and concluded the conditioning procedure.

2.3. Materials

2.3.1. Fear conditioning and assessment

2.3.1.1. Conditioned stimuli. Three geometrical shapes (a square, a rhombus, and a triangle) were pseudorandomized between participants as CS1+, CS2+, and CS−. All were gray-colored and identical in luminance. The CS were presented (4s) in an 800×600 pixel resolution against black background.

2.3.1.2. Unconditioned stimulus. An electric shock co-terminating with the CS+ on the reinforced trials served as UCS. The transcutaneous electrical stimulation (10 ms) was produced by a constant voltage stimulator (STM200; BIOPAC Systems) and was delivered to the left shin through two Ag/AgCl electrodes (0.5 cm^2 surface) filled with isotonic (0.05 m NaCl) electrolyte medium (Synapse Conductive Electrode Cream; Kustomer Kinetics, Arcadia, CA). The UCS was individually adjusted for each of the participants before acquisition and reinstatement, to ensure a 'subjectively uncomfortable but not painful' level.

2.3.1.3. Skin conductance response. SCR were sampled using Ag/AgCl electrodes (0.5 cm^2 surface) filled with isotonic (0.05 m NaCl) electrolyte medium (Synapse Conductive Electrode Cream; Kustomer Kinetics, Arcadia, CA) placed at the hypothenar of the non-dominant hand. A commercial SCR coupler and amplifying system (MP150 + GSR100C; BIOPAC Systems; software: AcqKnowledge 4.2) sampled the SCR with a sampling rate of 1000 Hz. The maximal base-to-peak difference in SCR during 1–4.5 s after CS onset were used as a measure of conditioned response in acquisition, extinction and reinstatement test. The data was transformed with the natural logarithm to attain a normal distribution.

2.3.2. Stress induction and assessment

2.3.2.1. Stress induction. On day 2, the participants were either exposed to stress (RE + STR and STR groups) or to the control procedure (RE and CONTROL groups). Participants in the stress groups went through the socially evaluated cold-pressor test (SECPT) procedure (Schwabe et al., 2008). The stress induction protocol involved the immersion of the right hand and wrist into ice-cold water (0–3 °C) for 3 min while being observed and videotaped by a reserved experimenter. The experimenter was unknown to the participant and was involved in the stress procedure only (i.e. did not take part in any of the phases during the three testing days). Participants in the control groups were instructed to immerse the right hand and wrist into warm water (36–37 °C) for 3 min and were neither videotaped nor watched by an experimenter. No unknown experimenter was present in the room during the control procedure.

2.3.2.2. Salivary cortisol. Free salivary cortisol concentrations served to validate the cortisol stress response. Salivette collection devices (Saarstedt, Nuembrecht, Germany) were used for saliva collection at 7 time points during the three experimental days. On day 2, samples were collected before stress/control procedure, 30 min (immediately before memory reactivation) and 45 min after procedure. On days 1 and 3, samples were collected at the beginning and end of the testing session. The samples were kept at −18 °C until biochemical analysis. Free salivary cortisol concentrations were then determined by commercial chemiluminescence immunoassays (CALIA; IBL International, Hamburg, Germany). Inter- and intra-assay variations were below 10%.

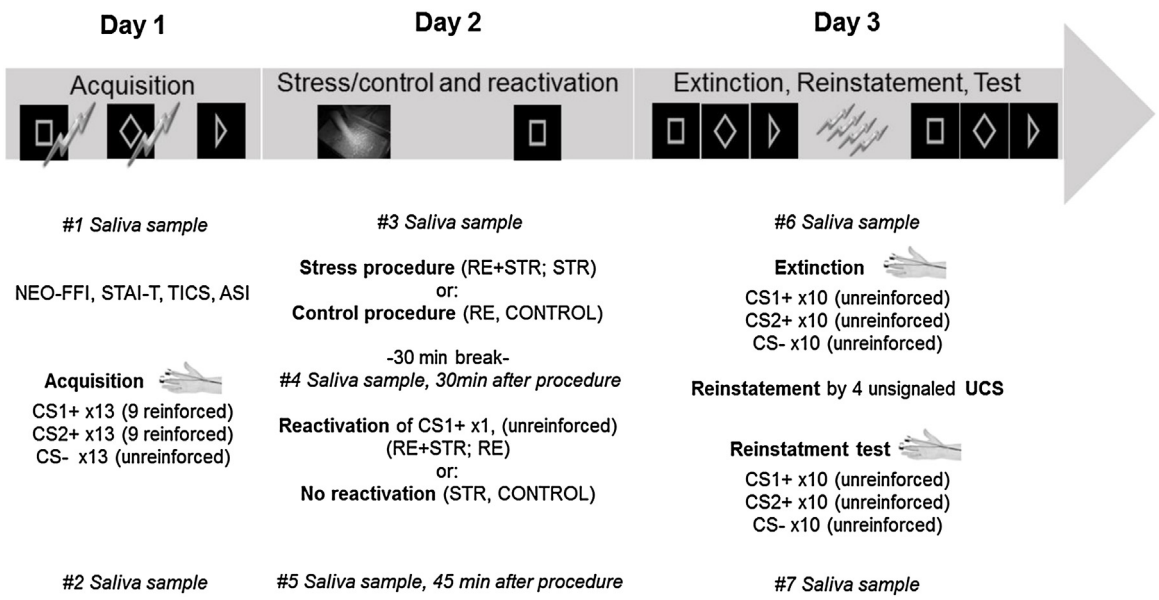

Fig. 1. *Experimental timeline.* The testing was conducted in three consecutive days separated by 24 h intervals: fear acquisition on day 1; stress/control procedure and memory reactivation/no reactivation on day 2; extinction, reinstatement, and reinstatement test on day 3. The procedure was identical for the groups on day 1 and 3 and differed only on day 2. Skin conductance response (SCR; here illustrated by the palm) served as a measure of conditioned fear, and were recorded during the acquisition, extinction and reinstatement test phases. Seven saliva samples were used to assess salivary cortisol, and were collected during the three experimental days. CS, conditioned stimuli. UCS, unconditioned stimuli. NEO-FFI, NEO Five Factor Inventory. STAI-T, State and Trait Anxiety Inventory. TICS, Trier Inventory of Chronic Stress. ASI, Anxiety Sensitivity Index.

2.3.2.3. Blood pressure measurement. Blood pressure during the stress and control procedures was used as a measure of SNS activity. The blood pressure was measured using a Dinamap vital signs monitor (Critikon, Tampa, FL) before, during and after the stress or control procedure (three measurements at each phase). The cuff was placed on the left upper arm.

2.3.2.4. Subjective ratings. Immediately after the stress/control condition the participants were asked to rate the difficulty, discomfort, stress and pain of the procedure on a scale ranging from 0 (*not at all*) to 100 (*very much*). The rating method was adapted from Schwabe et al. (2008).

2.3.3. Assessment tools

The following assessment tools were used: The Five Factor Inventory (NEO-FFI) (Mccrae and Costa, 2004) to assess the five personality factors; the trait section of the State and Trait Anxiety Inventory (STAI-T) (Spielberger et al., 1970) to measure trait anxiety; the Trier Inventory of Chronic Stress (TICS) (Schulz and Schlotz, 1999) for assessment of chronic stress; the Anxiety Sensitivity Index (ASI) (Peterson and Reiss, 1992) to assess the tendency towards a fearful response to anxiety-related symptoms.

2.3.4. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows 22.0. The statistical significance level was set to α=0.05. Greenhouse-Geisser corrected *P*-values were used if assumptions of sphericity were violated. Significant ANOVAs were followed by Bonferroni *post-hoc* tests. Effect size was calculated by using G*Power for Windows 3.1.9.2.

3. Results

3.1. Participant characteristics and assessment

There were no significant differences between the groups in age and BMI. In addition, no significant differences were found in NEO-FFI, STAI-T, TICS and ASI scores. In all ANOVAs regarding potential differences between the groups, $P > 0.05$ (not presented).

3.2. Day 2: Stress assessment

3.2.1. Salivary cortisol

Following the exclusion of stress non-responders and control responders (see Section 2.1.1.), the salivary cortisol analysis confirmed that the stress (but not control) procedure activated the HPA axis, leading to elevated cortisol concentrations. A repeated measures ANOVA with the within-subjects factor Time (before procedure, 30 and 45 min after procedure) and the between-subjects factor Group (RE + STR, RE, STR, CONTROL) revealed a significant Time x Group interaction ($F_{3.63,49.64} = 11.18$, $P \leq 0.001$). Bonferroni *post-hoc* analysis confirmed that salivary cortisol concentrations were significantly ($P \leq 0.05$) higher 30 min after stress induction (i.e. immediately before reactivation) compared to baseline in both stress groups (RE + STR, STR). Forty-five minutes after the stress induction, however, the cortisol concentrations were not significantly different from baseline ($P > 0.05$). In the two no-stress group (RE, CONTROL), in contrast, salivary cortisol concentrations were lower both 30 and 45 min after the control procedure compared to baseline ($P < 0.05$) (see Table 1). As expected, no differences between the groups were seen on either day 1 or day 3. On both days, a significant Time effect (Day 1: $F_{1,40} = 12.85$, $P \leq 0.001$; Day 3: $F_{1,40} = 5.44$, $P \leq 0.005$) revealed lower cortisol concentrations at the end of the testing day compared to its beginning (not presented).

3.2.2. Blood pressure measurements

Systolic and diastolic blood pressure (mmHg), mean arterial pressure (mmHg) and pulse were measured three times (45 s apart) during each of the three phases (before, during and after the stress/control induction) to create a mean value for each phase.

Significant group differences were found in the following measures: systolic ($F_{3,39} = 12.56$, $P \leq 0.001$) and diastolic ($F_{3,39} = 14.82$, $P \leq 0.001$) blood pressure and mean arterial pressure ($F_{3,39} = 17.41$, $P \leq 0.005$) during the procedure, revealing higher values in the stress compared to the control groups. No significant difference

Table 1
Cortisol concentrations.

Cortisol (nmol/l)	Baseline (Before stress/control procedure)	After 30 min (Immediately before reactivation)	After 45 min
RE + STR	10.34 ± 5.61	20.39 ± 13.59 (S)	15.39 ± 12.59
RE	15.16 ± 10.13	11.79 ± 6.90 (C*)	9.99 ± 5.76 (C*)
STR	11.17 ± 5.10	20.15 ± 11.51 (S)	13.63 ± 6.56
CONTROL	13.40 ± 6.68	8.47 ± 3.95 (C**)	7.46 ± 3.20 (C**)

Note. Data represents mean ± standard deviation (SD).
(S) Significantly higher cortisol concentrations ($P \leq 0.05$) in post-procedure value compared to baseline value.
(C) Significantly lower cortisol concentrations (*$P \leq 0.05$, **$P \leq 0.001$) in post-procedure value compared to baseline value.

Table 2
Blood pressure responses and subjective ratings.

	RE + STR	RE	STR	CONTROL	*p* values
Blood pressure responses					
Systolic blood pressure (mmHg)					
Baseline	112.50 ± 13.26	117.27 ± 9.11	120.45 ± 11.34	110.00 ± 5.75	0.067
During procedure	144.60 ± 18.68	119.94 ± 10.63	141.93 ± 16.97	116.23 ± 7.22	≤0.001**
After procedure	120.67 ± 14.79	117.30 ± 10.39	121.17 ± 11.03	111.18 ± 6.44	0.109
Diastolic blood pressure (mmHg)					
Baseline	62.27 ± 12.33	62.30 ± 5.97	66.21 ± 6.88	61.28 ± 2.97	0.419
During procedure	87.27 ± 12.13	66.39 ± 6.55	85.81 ± 14.22	67.38 ± 4.40	≤0.001**
After procedure	63.60 ± 10.49	61.48 ± 6.15	66.80 ± 6.44	61.85 ± 5.80	0.336
Mean arterial pressure (mmHg)					
Baseline	81.50 ± 12.25	84.18 ± 7.89	86.88 ± 5.88	79.64 ± 4.43	0.150
During procedure	109.80 ± 12.45	87.09 ± 7.74	108.00 ± 14.89	85.72 ± 4.98	≤0.001**
After procedure	83.67 ± 11.31	82.61 ± 6.96	87.67 ± 7.30	80.31 ± 6.20	0.199
Pulse (bpm)					
Baseline	66.03 ± 8.35	64.73 ± 13.38	73.48 ± 11.42	69.21 ± 10.13	0.265
During procedure	74.97 ± 10.56	65.64 ± 13.25	76.52 ± 9.43	69.95 ± 10.38	0.121
After procedure	64.90 ± 8.66	65.27 ± 13.00	69.17 ± 12.15	68.95 ± 10.71	0.717
Subjective ratings					
Difficulty	57.00 ± 32.68	0.91 ± 3.02	52.73 ± 29.36	3.33 ± 6.51	≤0.001**
Discomfrt	64.00 ± 25.91	9.09 ± 27.00	51.82 ± 29.94	3.08 ± 4.80	≤0.001**
Stress	57.00 ± 29.46	1.82 ± 4.05	38.18 ± 27.50	3.08 ± 6.30	≤0.001**
Pain	55.00 ± 25.93	0.00 ± 0.00	60.91 ± 27.73	0.00 ± 0.00	≤0.001**

Note. Difficulty, discomfort, stress and pain were rated on a scale from 0 (*not at all*) to 100 (*very much*). Data represents mean ± standard deviation (SD). *P* values of ANOVAs regarding potential differences between the groups are given. ** Significant difference ($P \leq 0.001$) between the stress (RE + STR, STR) and control (RE, CONTROL) groups.

in pulse during the procedure was found between the groups. For all other comparisons, $P > 0.05$. This confirms that the stress procedure was successful in activating the SNS system. The values are presented in Table 2.

3.2.3. Subjective ratings

The subjective ratings confirmed that the stress procedure was more aversive than the control procedure. ANOVAs followed by Bonferroni *post-hoc* analyses confirmed that difficulty ($F_{3,40} = 21.63$, $P \leq 0.001$), discomfort ($F_{3,41} = 18.78$, $P \leq 0.001$), stress ($F_{3,41} = 20.64$, $P \leq 0.001$) and pain ($F_{3,41} = 37.78$, $P \leq 0.001$) levels were significantly higher in the stress groups compared to the control groups. The ratings are presented in Table 2.

3.3. SCR during the learning phases

SCR during acquisition, extinction and reinstatement test were used as a measure of conditioned response.

3.3.1. Day 1: Acquisition

Fig. 2 illustrates the higher SCR for the reinforced stimuli (CS1+ and CS2+) compared with the safe stimulus (CS−) during acquisition (mean 13 trials) in all groups combined. ANOVA with the within-subjects factor CS and the between subjects factor Group was found to be significant for CS ($F_{2,82} = 5.72$, $P \leq 0.05$), demonstrating lower response to CS- compared to both CS1+ and CS2+ without significant Group interaction. For all other comparisons, $P > 0.05$.

3.3.2. Day 3: Extinction

Fig. 3 depicts the SCR at the two extreme ends of the extinction process (trials 1–2 vs. trials 9–10) that took place on day 3. The results demonstrate fear retrieval at the early phase of extinction followed by successful extinction (i.e. reduction in SCR to all stimuli that results in no significant difference between them at the late phase). As no group differences were seen during extinction, all groups are combined. Early extinction: repeated measures ANOVA (factors: CS, Group) was significant for CS ($F_{2,82} = 5.54$, $P \leq 0.05$); *post-hoc* tests revealed that CS- was significantly lower than CS1+ and CS2+. Early vs. late extinction: Repeated measures ANOVA (factors: CS, Time, Group) was found significant for Time ($F_{1,41} = 13.41$, $P \leq 0.001$) with lower SCR at the late extinction phase compared with the early phase; significant effect of CS ($F_{1.39,57.22} = 3.68$, $P \leq 0.05$) was also found but no significant difference between the CS emerged in *post-hoc* analysis. Late extinction: repeated measures ANOVA (factors: CS, Group) found no significant differences (all $P > 0.05$).

3.3.3. Day 3: Reinstatement test

The SCR on trials 6–10 of extinction, representing the end of extinction, were compared to the first trial after reinstatement (i.e. immediately after the unsignaled UCS) to explore for different patterns of reinstatement to the three CS across the groups. The first trial is a preferred measure in reinstatement paradigms (Agren et al., 2012; Kindt et al., 2009; Schiller et al., 2010), as it captures the most robust reinstatement response, which is then compared to the weak response previously seen at the late phase of extinction. Repeated measures ANOVA (factors: CS, Time, Group) revealed a significant CS x Time X Group interaction ($F_{6,82} = 2.21$,

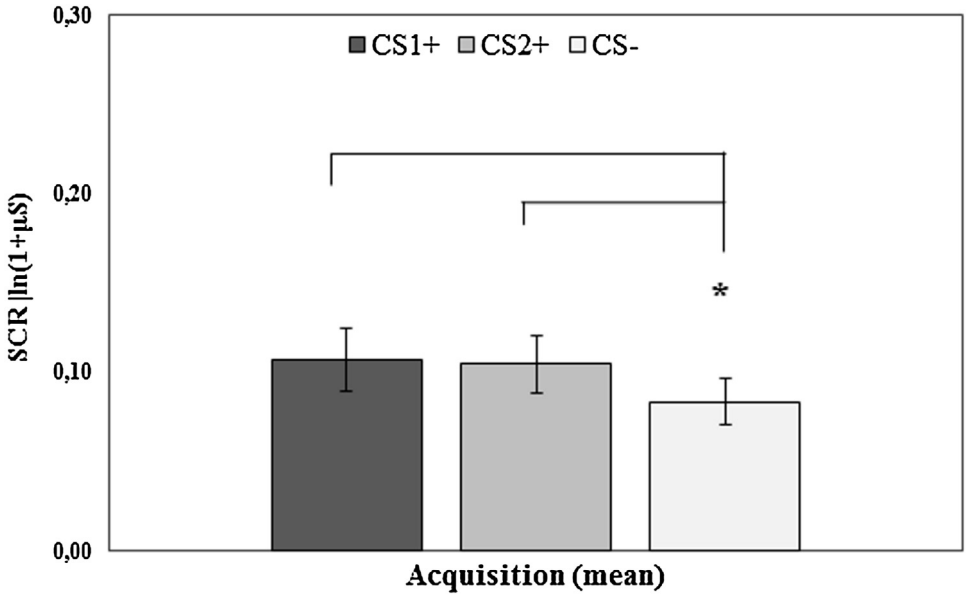

Fig. 2. *Day 1: Fear acquisition.* The skin conductance response (SCR) (mean of 13 trials) to the unreinforced CS—was significantly lower than the SCR to the reinforced CS1+ and CS2+ (with no difference between the two reinforced stimuli) demonstrating a successful fear acquisition. No interaction with Group was found, therefore the graph presents all four groups combined. Error bars represent SEM and thus between-subject variance. $^{*}P \leq 0.05$. CS, conditioned stimulus.

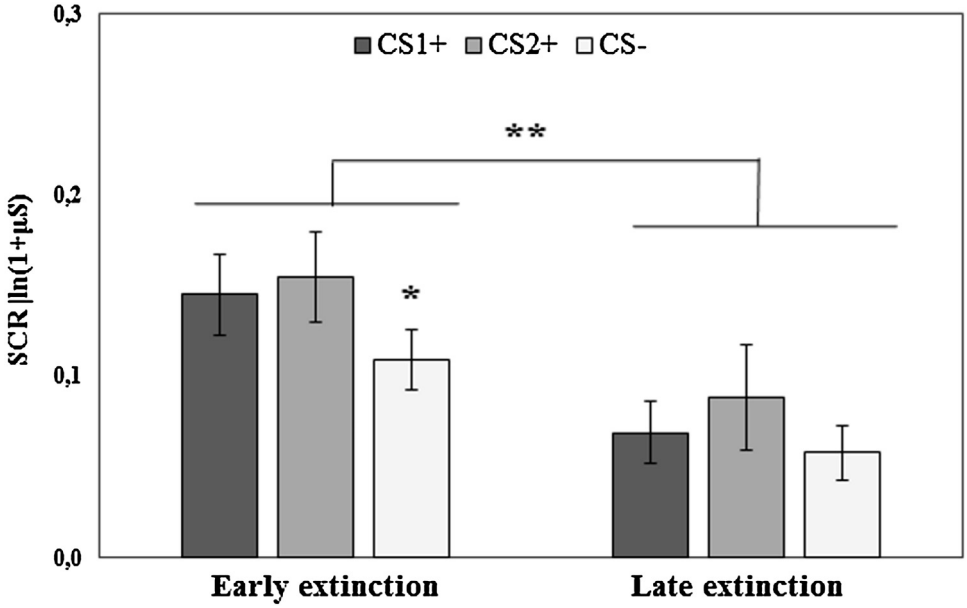

Fig. 3. *Day 3: Fear extinction.* This graph presents the skin conductance response (SCR) to each conditioned stimulus (CS) at early extinction (trials 1–2) vs. late extinction (trials 9–10). The significant difference between CS- and the previously reinforced CS1+ and CS2+ in early extinction ($^{*}P \leq 0.05$) confirms fear retrieval. The significant difference between the early and late phases ($^{**}P \leq 0.001$) indicates extinction. No differences between the previously reinforced stimuli CS1+ and CS2+ and the safe stimulus CS- were found in late extinction, confirming that extinction was successful. As no interaction with Group was found, all four groups are combined. Error bars represent SEM and thus between-subject variance.

$P \leq 0.05$). The interaction effect was found to be medium (effect size *f* of 0.40). Fig. 4 illustrates the lack of significant reinstatement in the target group (RE + STR) and the different reinstatement patterns in the control groups. In the RE + STR group, no significant reinstatement was found (Time, CS x Time: all $P > 0.05$). An effect of CS ($F_{2,18} = 6.89$, $P \leq 0.05$) was found, with higher response to CS2+ (the non-reactivated stimulus) compared with CS-. In contrast, generalized reinstatement (i.e. main effect of Time) was found in the RE ($F_{1,10} = 4.97$, $P \leq 0.05$) and the CONTROL ($F_{1,12} = 5.07$, $P \leq 0.05$) groups. A differential reinstatement (i.e. CS x Time interaction) was found in the STR group ($F_{2,20} = 6.26$, $P \leq 0.05$), revealing reinstatement only for the previously reinforced stimuli CS1+ and CS2+. For all other main effects and interactions, $P > 0.05$.

4. Discussion

This study aimed to investigate the effects of stress on the reconsolidation of fear memories in healthy men. Our previous work demonstrated an enhancing effect of cortisol administration on the reconsolidation of reactivated fear memories (Meir Drexler et al., 2015). Using similar design but with a psychosocial stress as manipulation, we expected stress to lead to effects similar to those of

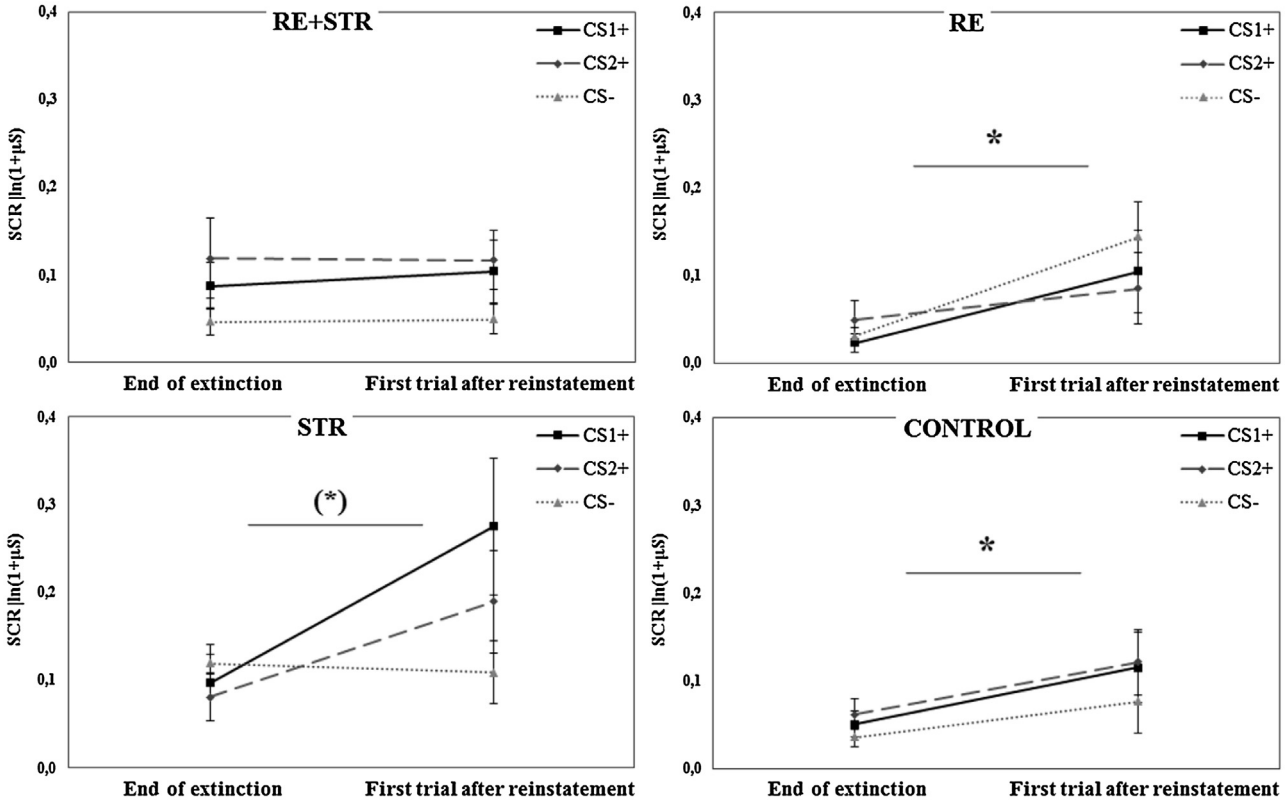

Fig. 4. *Day 3: Reinstatement test*. This graph demonstrates the lack of a significant reinstatement effect in the target group (RE + STR) and the reinstatement patterns on the control groups. Skin conductance response (SCR) at the end of extinction (trials 6–10) were compared to the first trial after reinstatement for each of the conditioned stimuli (CS). In the RE + STR group, no significant reinstatement was found. Generalized reinstatement (to all stimuli) was found in the RE and the CONTROL groups ($^{*}P \leq 0.05$). Differential reinstatement (i.e. only to CS1+ and CS2+, the previously reinforced stimuli) was found in the STR group ($(^{*})P \leq 0.05$). Error bars represent SEM and thus between-subject variance.

cortisol administration, i.e. a more robust reinstatement of the reactivated memory.

4.1. Stress induction

This study aimed to replicate the reconsolidation-enhancing effects of cortisol administration (Meir Drexler et al., 2015) using a behavioral method of a mild stress induction. Participants who failed to demonstrate a cortisol stress response and participants who demonstrated a stress response following the control condition were excluded. This is a common practice in studies using a psychosocial stress (Buchanan et al., 2006; Miller et al., 2013). Using a liberal cutoff criterion of cortisol response (Buchanan et al., 2006), we managed to achieve the desired pattern of stress response while minimizing the threat to external validity and preserving statistical power. Following this exclusion, the stress procedure was found to lead to the desired response in all measures (i.e. cortisol concentrations, SNS activity, and negative subjective ratings) compared with the control procedure.

4.2. Fear acquisition and extinction

As the paradigm included three stimuli, an exclusion criterion was used to confirm an equivalent fear conditioning to the two reinforced stimuli prior to reactivation and manipulation of one of them (Schiller et al., 2010). Following this exclusion, the significantly higher SCR to the two reinforced stimuli compared to the unreinforced stimulus confirmed that fear was successfully acquired with no baseline group differences. On the second testing day, the memory of one previously-reinforced stimulus was reactivated by unreinforced presentation of the CS1+. The reactivation session included the induction of a prediction error (Sevenster et al., 2012, 2013) in a brief stimulus presentation (Merlo et al., 2014), conditions that are thought to trigger the reconsolidation processes as previously shown (Meir Drexler et al., 2015).

On the third day, the results demonstrated a successful fear retrieval that was followed by extinction. Several reconsolidation studies could demonstrate group differences already in the extinction phase (Agren et al., 2012; Kindt et al., 2009; Schiller et al., 2010). In the current study, however, we could not show any group differences in this phase. The lack of group differences might be attributed to the paradigm (e.g. the fear conditioning design or manipulation). Nevertheless, in line with our previous findings (Meir Drexler et al., 2015), a significant difference between the groups emerged in the return of fear test, i.e. following the reinstating exposure to the UCS. While successful extinction is thought to represent the creation of a new safety memory, it does not indicate the fate of the original fear memory. In contrast, the recovery of extinguished fear following a reinstatement test (as well as renewal and spontaneous recovery) suggest that the original memory is still intact (Bouton, 2002, 2014). Thus, the reinstatement effect (or lack thereof) is presented here, as in previous studies (Kindt et al., 2009; Schiller et al., 2010), as an indicator to the successful disruption to the original fear memory.

4.3. Reinstatement test in the target group

Reinstatement is the return of conditioned response after extinction, following an exposure to (either the original or an equivalent) UCS. Reinstatement is often used to assess the strength of the original memory. Previously (Meir Drexler et al., 2015), our findings suggested an enhancing effect of cortisol on the reconsolidation of

fear memories in men, revealing a more robust reinstatement that was specific to the reactivated memory (CS1 +) but did not generalize to the non-reactivated memory (CS2 +). We predicted that the more ecologically valid stress induction would lead to similar consequences, i.e. memory enhancement, as previously demonstrated for declarative memory (Bos et al., 2014; Coccoz et al., 2011, 2013). In contrast, the results of the current work showed a general impairing effect of stress on the reconsolidation of the fear memories (both CS1+ and CS2 +). The results indicate that the combination of reactivation and stress blocked the return of fear for both previously-reinforced stimuli. This impairing effect is in line with previous findings of an impairing effect of stress on declarative memory reconsolidation (Schwabe and Wolf, 2010; Zhao et al., 2009).

4.3.1. Direction of the effect: stress vs. cortisol

While our hypothesis suggested a specific enhancing effect of stress on the reactivated fear memory (in other words, a more robust reinstatement effect for CS1 +), the results showed no reinstatement effect in the target group to any of the stimuli. The proximity in time between the reactivation of memory and the manipulation, and the apparent reinstatement effects in all control groups that lacked either (or both) the reactivation or the stress condition suggest this was indeed a reconsolidation effect (Tronson and Taylor, 2007). Thus, stress (in this study) and cortisol (Meir Drexler et al., 2015) can be seen as having opposite effects on fear memory reconsolidation. Indeed, both stress induction and systemic cortisol administration lead to elevated cortisol concentrations and often to similar effects on memory (Wolf, 2009). However, the two manipulations differ in quantity (resulting cortisol concentrations) and quality (SNS involvement, affective and cognitive factors). These factors might account for the conflicting results.

4.3.1.1. SNS activity. A pharmacological administration of cortisol specifically targets the HPA axis. Stress induction, in contrast, triggers the activation of both SNS and HPA axis. This leads to the secretion of (nor)adrenaline, cortisol, and additional stress modulators (Joels, 2006). The various modulates have a discrete function, but they also interact with one another to promote an adaptive response to the environmental threat. The current study was designed to allow a direct comparison with our previous pharmacological study (Meir Drexler et al., 2015), with the manipulation given 30 min prior to memory reactivation. In pharmacological settings, this timing ensures a peak of cortisol concentrations around the time of reactivation. In behavioral settings, cortisol peak is also expected around this time, while noradrenaline levels are expected to return to baseline levels. Even though no other neuro-endocrine markers (i.e. salivary alpha amylase of SNS activity) were used in this study, the timing suggests that cortisol was probably the main modulator of the reactivated memory, while noradrenaline (and its interactions with cortisol) were not involved in this effect. Thus, the results might vary given a different timing of intervention. When a psychosocial stress is presented immediately before or after memory reactivation (i.e. capturing the SNS activity), the memory trace is impaired in some cases (Schwabe and Wolf, 2010; Zhao et al., 2009) but enhanced in others (Bos et al., 2014; Cheung et al., 2015).

4.3.1.2. Dose-dependent effects. As a result of the activity of different receptor subtypes (each with their own specific affinity, desensitization, feedback system etc.), neurotransmitters and hormones often demonstrate a non-linear dose-dependent activity. The inverted U-shaped curve of cortisol modulation of memory consolidation is well-documented (Joels, 2006), with moderate cortisol concentrations having a beneficial effect while too high or too low concentrations may hinder performance. Dose-dependent effects might also account for the conflicting effects of cortisol and stress on memory reconsolidation. While the very high cortisol concentrations following the pharmacological treatment led to memory enhancement (Meir Drexler et al., 2015), the more moderate cortisol elevation following stress induction in the current study could have led to memory impairment. Interestingly, this explanation suggests a U-shaped curve of cortisol modulation of memory reconsolidation, which is distinct from the inverted U-shaped curve for consolidation. Since memory reconsolidation and consolidation are similar but not identical processes (Maroun and Akirav, 2008), this explanation might be possible. However, these two studies (only one of which directly controlled for doses) are not sufficient to establish a dose-response curve for reconsolidation. Future (mainly pharmacological) studies are required for further support.

4.3.1.3. Affective and cognitive factors. Stress induction and pharmacological administration of cortisol differ in an additional major factor: the learning experience. The stress procedure presents a more complex, possibly emotional, learning experience compared with the benign experience of pill intake. Like other emotional experiences, stressful events are better remembered compared with neutral ones (Wolf, 2008). The stressful episode could thus present a new emotional learning experience that leads to interference (e.g. by rumination, intrusive memories) (Cadle and Zoladz, 2015) to the reactivated fear memory, blocking its reconsolidation. Previous human studies by the research groups of Schiller (Schiller et al., 2010, 2013) and Agren (Agren et al., 2012; Bjorkstrand et al., 2015) had convincingly demonstrated how post-reactivation extinction learning can impair the return of fear of reactivated memories. Whereas a stressful episode is not as relevant to the original fear memory as post-retrieval extinction learning is, it might be potent enough to impair the memory at the fragile reconsolidation state. Less robust post-retrieval manipulations, in contrast, are often not strong enough to impair reactivated emotional memories (Schwabe and Wolf, 2009).

Creating a new aversive memory (of the stressful event) to compete with an established aversive memory (of the fear stimuli), as demonstrated in the current study, is intriguing from a theoretical point of view but is not particularly useful for therapy as it has no advantage over a (successful) pharmacological intervention (Kindt et al., 2009; Soeter and Kindt, 2015). To this limitation adds the exclusion of women from our study. Women are more susceptible to anxiety and stress-related disorders than men (Kessler et al., 2005), and might response differently to similar reconsolidation protocols compared to men (Meir Drexler et al., 2014, 2015, 2016) yet were not tested in our study. Thus, it is yet to be examined whether similar results could be replicated in women as well, while using a less aversive – but still potent – behavioral intervention. Promising results come from the study of James et al. (2015). Using a non-aversive cognitive task (a game of Tetris) after the reactivation of trauma film memories, the authors were able to reduce the amount of aversive intrusions in both men and women. This demonstrates that even a neutral or slightly positive cognitive task might create a potent interference in the reconsolidation of unwanted memories, having a beneficial effect in both women and men.

4.3.2. Generality of effect and clinical implications

In real life situations, traumatic memories can be associated with several cues. Soeter and Kindt (2015) point to the importance of generalization of the reconsolidation disruption to other associated stimuli if it is to be served as a therapeutic tool. In their study, an abrupt exposure to the feared stimulus (tarantula) followed by propranolol intake led to a decrease in avoidance to an associated stimulus (baby tarantula) as well. In our current study, as opposed to our previous cortisol study (Meir Drexler et al.,

2015), the effect of stress on memory reconsolidation was not limited to the reactivated memory but was generalized to the other previously reinforced stimulus. The reasons that lead to a general reconsolidation effect in some cases (Soeter and Kindt, 2015) and a specific effects in others (Hupbach and Dorskind, 2014; Meir Drexler et al., 2015; Schiller et al., 2010) are yet to be investigated. Undoubtedly, a more general effect is therapeutically more desirable for relapse prevention for psychiatric disorders such as anxiety disorders, PTSD and drug addiction. Two recent studies (Liu et al., 2014; Luo et al., 2015) suggest that it might also be achieved using a novel reactivation method, using low intensity UCS presentation instead of the more commonly-used reactivation by CS.

4.4. Reinstatement patterns in the control groups

Unlike the target group that combined memory reactivation and stress and showed no reinstatement, the three control groups lacked either or both of these conditions and, as expected, demonstrated reinstatement of the extinguished fear following the UCS presentation. The RE and CONTROL groups showed a generalized reinstatement (i.e. to both the previously reinforced stimuli as well as to the safe stimulus), while the stress group showed differential reinstatement (i.e. only to the previously reinforced stimuli).

Theoretically, the return of fear phenomena should be specific to the stimuli that were previously associated with fear. This ability to discriminate safety cues is negatively associated with pathological anxiety (Lissek et al., 2005). Yet, even in healthy participants can the return of fear be generalized to the safe stimulus as well (Haaker et al., 2014). Generalized patterns of return of fear were found for reinstatement (Dirikx et al., 2009), renewal (Vervliet et al., 2013) and spontaneous recovery (Norrholm et al., 2008). It remains unclear why some studies demonstrate differential reinstatement while others show generalized reinstatement. Lack of control for personality traits can account for some of the cases (Vervliet et al., 2013). For instance, higher prevalence of high trait anxiety participants in one group might lead this group towards fear generalization (Lissek et al., 2005). This explanation, however, cannot account for the reinstatement patterns in the current study, as no significant differences in trait anxiety (and other trait and state factors) were found between the groups. The difference in the experimental protocol is thus a more likely reason for the different patterns. These results, however, are unpredicted, since the contextual fear (and subsequent generalization) are expected to be higher in the stress group, yet this group demonstrated differential reinstatement.

5. Conclusion

In the current study we aimed to investigate the effects of a psychosocial stress on fear memory reconsolidation in men. Based on our previous findings following pharmacological cortisol administration, we expected stress induction to lead to a specific enhancement of the reactivated fear memory. In contrast, stress induction led to a general impairing effect on the reconsolidation of fear memories, blocking the return of fear following reinstatement shocks for all stimuli. The unique characteristic of the stress response and experience compared to a pharmacological intervention are possible explanations to the conflicting findings between the current study and our previous cortisol findings. This general disruptive effect of stress on reconsolidation has possible therapeutic implications for the prevention of the return of fear in several psychiatric disorders.

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