Neuropsychopharmacology (2015) 40, 3036–3043

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Effects of Cortisol on Reconsolidation of Reactivated Fear Memories

Shira Meir Drexler[1,2], Christian J Merz[1], Tanja C Hamacher-Dang[1], Martin Tegenthoff[3] and Oliver T Wolf*[,1,2]

[1]Department of Cognitive Psychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum, Bochum, Germany; [2]International Graduate School of Neuroscience, Ruhr-University Bochum, Bochum, Germany; [3]Department of Neurology, Ruhr-University Bochum, BG-Kliniken Bergmannsheil, Bochum, Germany

The return of conditioned fear after successful extinction (eg, following exposure therapy) is a significant problem in the treatment of anxiety disorders and posttraumatic stress disorder (PTSD). Targeting the reconsolidation of fear memories may allow a more lasting effect as it intervenes with the original memory trace. Indeed, several pharmacological agents and behavioral interventions have been shown to alter (enhance, impair, or otherwise update) the reconsolidation of reactivated memories of different types. Cortisol is a stress hormone and a potent modulator of learning and memory, yet its effects on fear memory reconsolidation are unclear. To investigate whether cortisol intervenes with the reconsolidation of fear memories in healthy males and how specific this effect might be, we built a 3-day reconsolidation design with skin conductance response (SCR) as a measure of conditioned fear: Fear acquisition on day 1; reactivation/no-reactivation of one conditioned stimulus and pharmacological intervention on day 2; extinction learning followed by reinstatement and reinstatement test on day 3. The groups differed only in the experimental manipulation on day 2: Reactivation+Cortisol Group, Reactivation+Placebo Group, or No-reactivation+Cortisol Group. Our results revealed an enhancing effect of cortisol on reconsolidation of the reactivated memory. The effect was highly specific, strengthening only the memory of the reactivated conditioned stimulus and not the non-reactivated one. Our findings are in line with previous findings showing an enhancing effect of behavioral stress on the reconsolidation of other types of memories. These results have implications for the understanding and treatment of anxiety disorders and PTSD.
Neuropsychopharmacology (2015) **40,** 3036–3043; doi:10.1038/npp.2015.160; published online 1 July 2015

INTRODUCTION

Glucocorticoid hormones (GCs; cortisol in humans, corticosterone in rodents) are secreted following the activation of the hypothalamus–pituitary–adrenal (HPA) axis in response to stress. Their activity in the basolateral amygdala has a significant role in modulating memory consolidation (Atsak *et al*, 2015; McGaugh and Roozendaal, 2002), allowing enhanced memory consolidation for emotional events. Strong memories following an emotionally aversive experience are a primary adaptive mechanism. Indeed, intrusive thoughts are common reactions in most individuals following an aversive event, but they tend to decline over time. However, in individuals who develop anxiety disorders (eg, phobias) or posttraumatic stress disorder (PTSD), the memory trace remains strong, leading to clinical symptoms such as re-experiencing and fear (de Quervain *et al*, 2009). Although a new, safe memory can be acquired in extinction learning (eg, in exposure therapy), the original aversive memory is not affected (Bouton, 2002), as evidenced by the high proportion of relapse after treatment (Craske, 1999). If the original emotional memory itself could be weakened, the return of fear after successful treatment might be prevented.

A new memory is initially fragile and susceptible to interruption until its initial consolidation is completed (McGaugh, 1966). According to the traditional view on memory, once consolidation occurs the memory is safe from further interruption. However, already in the late 1960s Misanin *et al* (1968) showed that consolidated memories can be reactivated upon retrieval, brought once again to a temporary fragile state. More than three decades later, the opportunity to alter already-consolidated memories had regained interest, when Nader *et al* (2000) convincingly demonstrated the sensitivity of reactivated fear memories to protein synthesis inhibitors, establishing the need of protein synthesis for reconsolidation of memories after retrieval. Other studies followed, demonstrating the effects of pharmacological (eg, Kindt *et al*, 2009) or behavioral (Monfils *et al*, 2009; Schiller *et al*, 2010) interventions on the reconsolidation of reactivated memories.

GCs are potent modulators of learning and memory processes (Wolf, 2008), yet their effects on the reconsolidation of fear memory in humans are not clear. Although several animal studies suggest an impairing effect of behavioral stress or GCs on reactivated memories, others

*Correspondence: Professor OT Wolf, Department of Cognitive Psychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum, Universitätsstraße 150, Bochum 44801, Germany, Tel: +49 234 32 22670, Fax: +49 234 32 14308,
E-mail: Oliver.T.Wolf@ruhr-uni-bochum.de
Received 28 April 2015; revised 21 May 2015; accepted 3 June 2015; accepted article preview online 10 June 2015

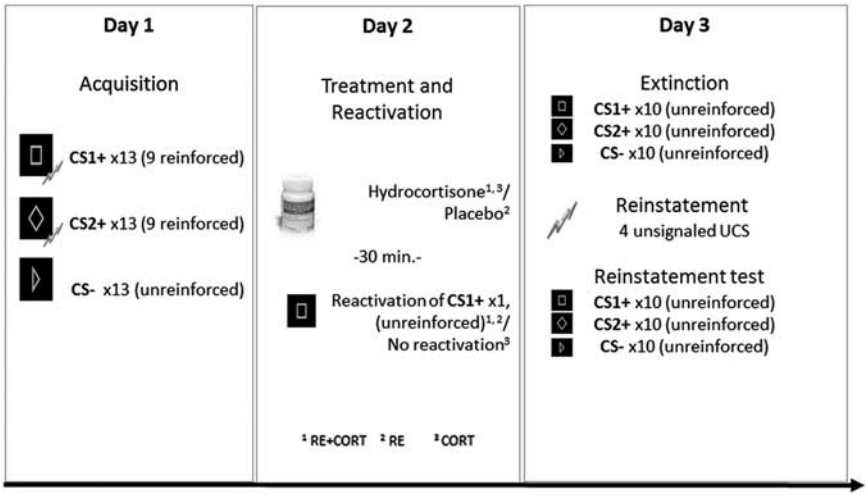

Figure 1 Experimental timeline. The experiment was conducted on three consecutive sessions, separated by 24 h intervals: fear acquisition on day 1; fear memory reactivation and pharmacological intervention on day 2; and extinction, reinstatement, and reinstatement test on day 3. The groups differed only on day 2, in which the memory for the previously acquired CS1+ was reactivated or not reactivated following hydrocortisone or placebo intake. CS, conditioned stimuli; UCS, unconditioned stimuli.

suggest an enhancing effect, as both GC receptor agonists (Abrari *et al*, 2008; Cai *et al*, 2006) or antagonists (Pitman *et al*, 2011) were shown to impair reactivated memories of different types (for a thorough review, see Akirav and Maroun, 2013). The human literature have mainly examined the effects of psychosocial stress on declarative memories and reached mixed results as well, with either an impairment (Schwabe and Wolf, 2010; Zhao *et al*, 2009) or enhancement (Bos *et al*, 2014; Coccoz *et al*, 2011) of reactivated memories by stress induction. Stress leads to secretion of cortisol, (nor)epinephrine, and other hormones. The possible influences of cortisol itself on the reconsolidation of fear memories in humans have not been investigated as of today. Recently, cortisol treatment has been shown to boost exposure-based therapy (de Quervain and Margraf, 2008), whereas noradrenergic β-blockers prevented the return of conditioned fear in a reconsolidation-based paradigm (Kindt *et al*, 2009). Considering the dissociation between memory reconsolidation and extinction (Merlo *et al*, 2014), an understanding of the impact of cortisol on fear memory reconsolidation appears warranted. This is, therefore, the focus of the current study.

To investigate how cortisol affects the reconsolidation of fear memories in humans, and how specific the effect might be, we used a 3-day reconsolidation design (Kindt *et al*, 2009; Schiller *et al*, 2010) with skin conductance response (SCR) as a measure of conditioned fear (Schiller *et al*, 2010). After creating conditioned fear for two (out of three) stimuli on the first day, the memory of one conditioned stimulus was reactivated on the second day following cortisol administration. On the third day, the return of extinguished fear following reinstatement was assessed. Studies using the β-blocker propranolol have observed highly similar effects on consolidation (Cahill *et al*, 1994) and reconsolidation (Kindt *et al*, 2009). As cortisol has been shown to enhance emotional memory consolidation (Roozendaal, 2002; Wolf, 2008), we expected it to enhance reconsolidation as well. Indeed, animal studies have previously shown that a GC antagonist blocks fear memory reconsolidation (Pitman *et al*, 2011). In addition, similar to Schiller *et al* (2010), we expected the reconsolidation effect to be specific to the reactivated memory trace.

MATERIALS AND METHODS

Participants and General Procedure

To avoid the possible influence of altering concentrations of sex hormones on emotional learning (Milad *et al*, 2009) and their modulation through cortisol (Merz *et al*, 2012a, b), this study included male participants only. Forty-two healthy males, aged 18–35 (25.45 ± 0.57) years, with a body mass index (weight (kg)/height (m^2)) of 18–28 participated in this study. Smoking, regular medication intake, somatic/endocrine disease, or a history of psychiatric/neurological disorders were set as the exclusion criteria. The participants were recruited via announcements on bulletin boards on the campus of the Ruhr-University Bochum, Germany, and received financial reimbursement for participation. The study was approved by the local ethics committee. All participants signed an informed consent.

In line with previous work (Kindt *et al*, 2009), the participants were randomly assigned to one of three groups: Reactivation+Cortisol (RE+CORT), Reactivation+Placebo (RE), or No-reactivation+Cortisol (CORT). The procedure differed only in the experimental manipulation on day 2.

Conditioning Procedure

The experimental procedure consisted of three testing days, separated by 24 h intervals: fear acquisition on day 1; reactivation/no-reactivation and pharmacological intervention on day 2; and extinction learning followed by reinstatement and reinstatement test on day 3 (Figure 1). The 24 h breaks were used to allow memory consolidation after the learning phase (Dudai, 2004). SCRs were recorded during the acquisition, extinction, and reinstatement test phases.

Day 1: Acquisition. All participants were attached to the SCR and shock electrodes during the acquisition phase. The participants were instructed to pay attention to possible contingencies between stimuli and shocks, and were told that the contingences would not change in the next experimental days. For fear acquisition, two conditioned stimuli (CS1+, CS2+) were partially reinforced (reinforcement rate: about 70%, 9 out of 13 presentations) with an unconditioned stimulus (UCS, an electric shock) and one CS (CS−) was never reinforced. All three CSs were presented 13 times each in a pseudorandomized order (starting with either CS1+, CS2+, or CS−, counterbalanced between participants). The intertrial interval (ITI) was 10–12 s.

Day 2: Pharmacological treatment and reactivation. On the following day, the participants received either cortisol (RE+CORT, CORT groups) or placebo (RE group). Participants from the reactivation groups (RE+CORT, RE groups) were instructed to wait for 30 min. The break was inserted to allow a peak in cortisol plasma concentrations. The participants were attached to both SCR and shock electrodes (Sevenster *et al*, 2012) and were told that the same CS-UCS contingency from day 1 would apply on that day as well. Then, to reactivate one of the previously reinforced stimuli, CS1+ was presented without reinforcement for 4 s. This single unreinforced presentation of the CS1+ concluded the learning procedure on this experimental day. The participants from the no-reactivation group (CORT) had no further intervention on day 2 apart from pill intake, but they remained in the experimental room for the same amount of time (~45 min) as did the participants from the two reactivation groups.

Day 3: Extinction, Reinstatement, and Reinstatement test. All participants were attached to the SCR and shock electrodes during all learning phases of this testing day and were told that the same CS-UCS contingency from day 1 would apply on that day as well. In extinction, all three stimuli (CS1+, CS2+, CS−) were presented, unreinforced, and in a pseudorandomized order, 10 times each, with an ITI of 10–12 s. To reinstate the conditioned fear, four unsignaled UCS (ITI: 10–12 s) were presented immediately after the completion of the extinction phase. Afterwards, all three stimuli were again presented, unreinforced, and in a pseudorandomized order, 10 times each, with an ITI of 10–12 s. This reinstatement test concluded the conditioning procedure.

Stimuli

Conditioned stimuli. Three geometrical shapes (a square, a rhombus, and a triangle) in gray color were used as CS for all conditioning phases (Tabbert *et al*, 2011), pseudorandomized between participants as CS1+, CS2+, and CS−. All CS had identical luminance and were presented for 4 s in an 800 × 600 pixel resolution screen against a black background.

Unconditioned stimulus. An electric shock co-terminating with the reinforced CS+ was used as a UCS. A constant voltage stimulator (STM200; BIOPAC Systems) was used to deliver transcutaneous electrical stimulation (100 ms) 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) placed on the left shin. The intensity of the electric shock was individually set for each participant to a level described by the participant as 'uncomfortable but not painful'.

Skin Conductance Responses

SCRs were sampled (sampling rate: 1000 Hz) using a commercial SCR coupler and amplifying system (MP150 +GSR100C; BIOPAC Systems; software: AcqKnowledge 4.2) 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 on the hypothenar of the non-dominant hand. Data were transformed with the natural logarithm to attain a normal distribution. In acquisition, extinction, and reinstatement test, the maximal base-to-peak difference in SCR during the 1–4.5 s after CS onset served as a measure of the conditioned response.

Pharmacological Intervention

On day 2, the participants were given an oral dose of 30 mg cortisol (3 pills of hydrocortisone 10 mg; Jenapharm) or visually identical placebos (3 pills of P Tabletten Weiss 7 mm, Winthrop). The dose of cortisol was chosen based on our previous studies on cortisol effects on fear learning (Merz *et al*, 2012a, b; Merz *et al*, 2014).

Saliva Sampling

Free salivary cortisol concentrations were used to validate the success of the pharmacological intervention. Saliva samples were collected using Salivette (Saarstedt, Nuembrecht, Germany) collection devices at seven time points during the three experimental days. On days 1 and 3, samples were taken at the beginning and end of the session. On day 2, samples were taken at the beginning of the session (immediately before pill intake), 30 min after the pharmacological treatment (before memory reactivation), and at the end of the session (45 min after the pharmacological treatment). The samples were kept at − 18 °C until biochemical analysis. Free salivary cortisol concentrations were then determined by commercial chemiluminescence immunoassays (CLIA; IBL International, Hamburg, Germany). Inter- and intra-assay variations were below 10%.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows 22.0. The statistical significance level was set to $\alpha = 0.05$. Greenhouse–Geisser corrected *P*-values were used if assumptions of sphericity were violated.

SCR Exclusion Criterion

Successful acquisition is a prerequisite for studying reconsolidation effects. To exclude participants who did not acquire differential responding to both CS+ as compared with the CS−, we defined an exclusion criterion based on the differential SCR (mean SCR to the CS− subtracted from mean SCR to each of the CS+). Two participants showing a

Table 1 Cortisol Concentrations

Cortisol (nmol/l)	Before pill intake	After 30 min	After 45 min
RE+CORT	15.39 ± 1.82	250.821 ± 35.16	176.35 ± 20.84
RE	14.13 ± 2.34	12.41 ± 1.24	9.58 ± 11.11
CORT	13.14 ± 2.71	322.22 ± 43.37	222.98 ± 125.20

Mean (SEM) cortisol concentrations (in nmol/l) on day 2 in the three groups (RE+CORT, RE, CORT) before pill intake, 30 and 45 min after pill intake.

differential SCR lower than 1.5 interquartile ranges below the lower quartile to either CS1+ or CS2+ were excluded.

The following analyses, therefore, includes 40 participants in three groups: RE+CORT ($N=13$), RE ($N=13$), and CORT ($N=14$).

RESULTS

Cortisol Concentrations

To confirm a rise in free salivary cortisol concentrations after hydrocortisone intake on day 2 (in the cortisol groups RE +CORT, CORT compared with the placebo group RE), we conducted an ANOVA with the within-subjects factor Time (baseline, 30 min, and 45 min after pill intake) and the Between-Subjects Factor Group (RE+CORT, RE, and CORT). The analysis revealed a significant Time × Group interaction ($F_{2.54,\ 43.28}=17.16$, $P\leqslant.001$). *Post hoc* *t*-tests revealed that cortisol concentrations were significantly higher at 30 and 45 min after treatment compared with baseline in the cortisol groups RE+CORT (($t_{12}=6.54$, $P\leqslant.001$) for 30 min, ($t_{12}=7.57$, $P\leqslant.001$) for 45 min) and CORT (($t_{13}=7.18$, $P\leqslant.001$) for 30 min, ($t_{13}=8.40$, $P\leqslant.001$) for 45 min). The placebo group RE showed no significant difference between baseline and 30 min ($P>0.05$) and significantly lower cortisol concentrations ($t_9=3.17$, $P\leqslant.05$) at 45 min compared with baseline (Table 1). No significant Time × Group interactions were found on day 1 or day 3 (all $P>0.05$). These results show a temporary rise in cortisol concentrations upon hydrocortisone (but not placebo) intake in the RE+CORT and CORT groups, but not in the RE group.

SCR

Acquisition. To examine whether fear was successfully acquired, we compared the SCR response to the three CS in 13 trials of acquisition (mean). ANOVA with the within-subjects factor CS (CS1+, CS2+, CS−) and the between-subjects factor Group (RE+CORT, RE, CORT) showed a significant effect of CS ($F_{1.67,62.02}=5.21$, $P\leqslant.05$). *Post hoc* *t*-tests revealed that the response to the CS− was significantly lower compared with both the CS1+ ($t_{39}=2.61$, $P\leqslant.05$) and the CS2+ ($t_{39}=2.61$, $P\leqslant.05$). No significant difference between CS1+ and CS2+ was found. In addition, the factor CS had no significant interaction with Group (all $P>0.05$). These results indicate a successful acquisition, with higher SCR to both CS+ compared with the CS− in all groups (see Figure 2).

Extinction. We tested for group differences in CS retrieval on the first trial of extinction. ANOVA with the within-subjects factor CS and the between-subjects factor Group did not find an effect of CS or interaction with Group ($P>0.1$ for all). To test whether the CS were extinguished following 10 unreinforced trials of extinction on day 3, we compared the SCR to the three CS in the early phase (mean of trials 1–5) to the late phase (mean of trials 6–10) of extinction. Using ANOVA with the within-subjects factors CS, Time (early, late phase) and the between-subjects factor Group, we found a significant effect of Time ($F_{1,37}=16.99$, $P\leqslant.001$) with no main effect of CS or interaction with Group ($P>0.05$ for all; see Figure 3). This reduction in SCR indicates a successful extinction of the CS in all groups.

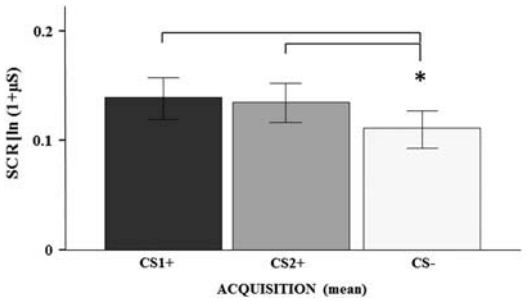

Figure 2 Day 1: Fear acquisition. The mean skin conductance response (SCR) (of 13 trials) to the unreinforced CS− is significantly lower than the response to the reinforced CS1+ and CS2+, demonstrating successful acquisition. As no interaction with group was found, the graph presents all groups combined. Error bars represent SEM. *$P\leqslant.05$. CS, conditioned stimuli.

Reinstatement test. To test the return of conditioned fear after reinstatement, we calculated a Reinstatement index by subtracting SCR in the last extinction trial from SCR in the first trial after reinstatement (Reinstatement index = 1st reinstatement trial − 10th extinction trial; Schiller *et al*, 2010). ANOVA with the within-subjects factor CS and the between-subjects factor Group revealed a significant CS × Group interaction ($F_{4,\ 74}=2.84$, $P\leqslant.05$). No main effect of CS or Group (all $P>0.05$) was found. As illustrated in Figure 4, *t*-tests revealed that in the RE+CORT group ($t_{12}=3.43$, $P\leqslant.005$), the Reinstatement index for the CS1+, the reactivated stimulus, was significantly higher compared with that for the CS2+, the not-reactivated stimulus. In addition, in this group the differences between CS1+ and CS− showed a trend ($t_{12}=-2.10$, $P=0.057$). No significant differences between the CS were found in the RE or CORT groups (all $P>0.05$). These findings demonstrate that reactivation in the presence of cortisol (RE+CORT group only) led to a specific higher reinstatement for the reactivated CS1+.

DISCUSSION

When reactivated, already-consolidated memories go back to a fragile state for a limited period of time needed for their reconsolidation. During this period, the reactivated memory can be enhanced, impaired, or otherwise updated by various pharmacological (Soeter and Kindt, 2011) or behavioral (Schiller *et al*, 2010) interventions. Our study aimed to investigate the effects of cortisol on fear memory reconsolidation in humans. We tested three groups on a 3-day experimental design. The fear conditioning on the first day was followed by cortisol/placebo treatment and memory

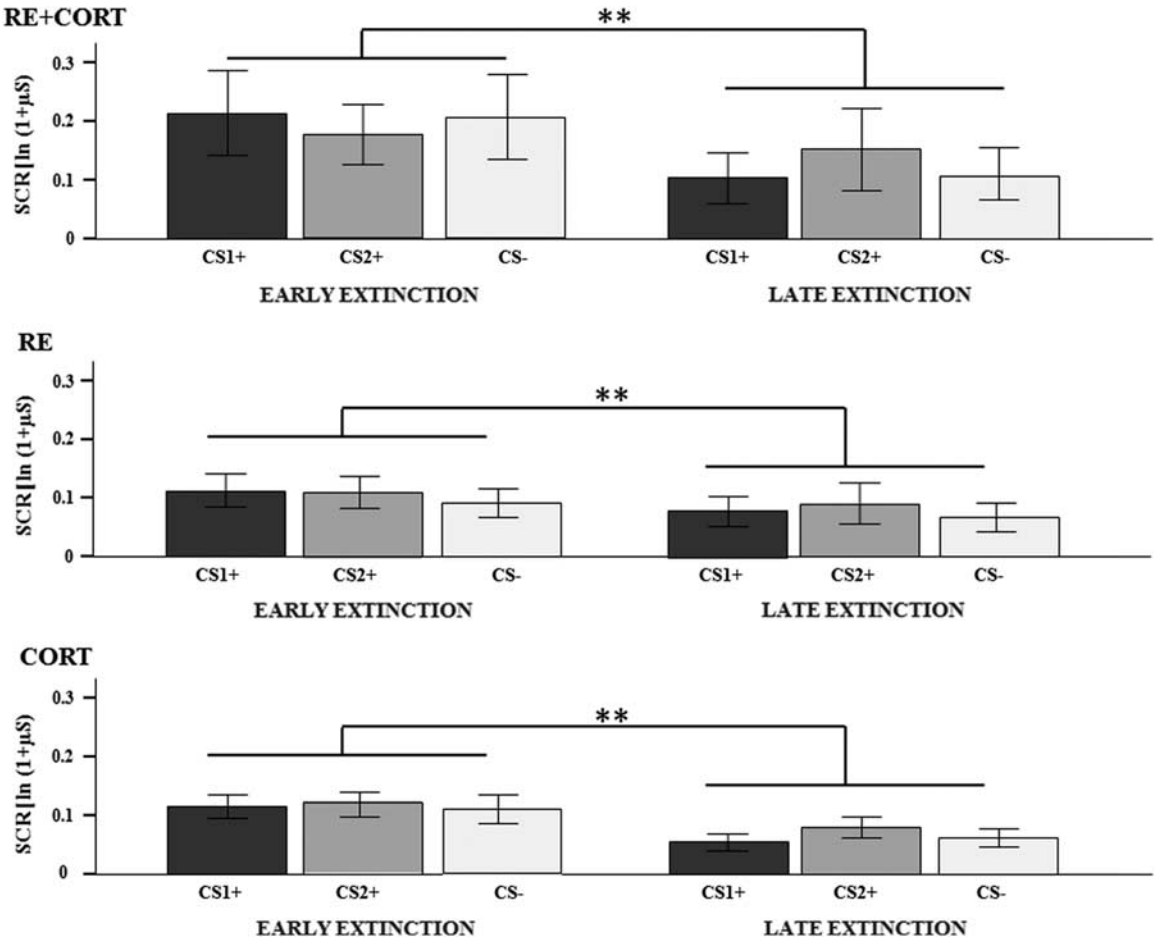

Figure 3 Day 3: Fear extinction. This graph presents the skin conductance response (SCR) to each conditioned stimuli (CS) at the early phase (trials 1–5) *vs* the late phase (trials 6–10) of extinction in each of the three groups. The significant effect of Time (**$P \leqslant .001$) with no interactions with CS or Group confirms a successful extinction of the CS in all groups. Error bars represent SEM.

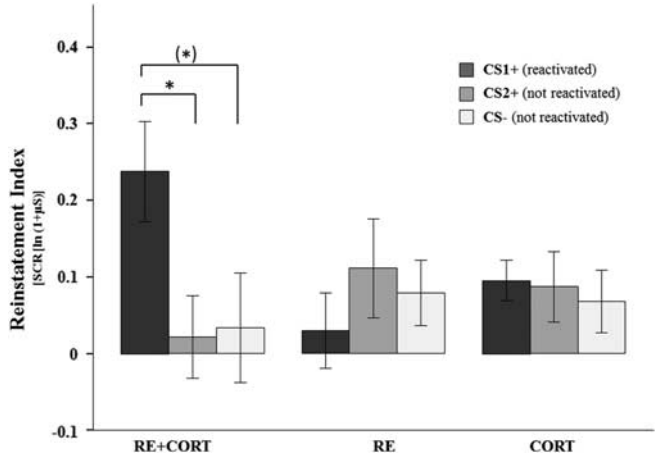

Figure 4 Day 3: Reinstatement index. (Reinstatement index = 1st reinstatement trial − 10th extinction trial). A significant interaction CS × Group was found ($P \leqslant .05$). CS1+, reactivated on day 2 following hydrocortisone intake in the RE+CORT group, showed a significantly higher reinstatement compared with the non-reactivated CS2+ (*$P \leqslant .05$). The differences between CS1+ and CS− revealed a trend (*$P = 0.057$). No differences between the stimuli were found in the other two groups (RE and CORT). These results demonstrate an enhancing effect of cortisol on the reconsolidation of reactivated fear memories. CS, conditioned stimuli; SCR, skin conductance response.

reactivation of one of the CS on the second day. On the third day, we examined the reinstatement of fear. Based on the similarity between memory reconsolidation and initial consolidation, we predicted a specific enhancement in the reconsolidation of the memory that was reactivated following cortisol intake. The results support this hypothesis.

Fear Acquisition, Reactivation, and Extinction

Our fear acquisition results showed successful fear conditioning to the two stimuli paired with a shock compared with the 'safe' stimulus that was never paired. As expected, there were no baseline differences in acquisition between the experimental groups. To test how specific the reconsolidation effect is, we reactivated only the memory for one conditioned stimulus (as performed by Schiller *et al*, 2010) after administering the pharmacological intervention. On the next day, the participants went through the extinction procedure. In some studies in which a reconsolidation effect was found, the effect emerged already in extinction (for instance, Kindt *et al*, 2009). We, however, could not find any significant differences between the groups during the extinction phase.

The Return of Fear After Reinstatement

Similar to Schiller *et al* (2010), we used reinstatement by UCS as a method of triggering the return of conditioned fear. The response to the CS after reinstatement was used to examine both the direction and specificity of possible cortisol effects on the reactivated fear memory.

Cortisol enhances reactivated fear memories. In the group which had received cortisol before reactivation, the reinstatement of the reactivated CS1+ was significantly higher compared with the non-reactivated CS2+. Memory reactivation alone or cortisol administration without reactivation had no effect on the strength of the memory.

The effects of GCs on memory reconsolidation may depend on the memory task tested (Akirav and Maroun, 2013). Different tasks require the activation of different brain regions, which might explain the mixed results seen in the human literature, with some studies showing an impairing effect of behavioral stress on declarative memory reconsolidation (Schwabe and Wolf, 2010; Zhao *et al*, 2009), whereas others observed an enhancing effect (Bos *et al*, 2014; Coccoz *et al*, 2011). Behavioral stress leads to secretion of cortisol, (nor)epinephrine, and other stress hormones. Using it as a postreactivation manipulation does not allow to isolate the specific contribution of glucocorticoids to memory reconsolidation. Several animal studies, however, have suggested an enhancing effect of glucocorticoids on reactivated fear memories. Pitman *et al* (2011), for instance, demonstrated that a postreactivation GC antagonist blocks the reconsolidation of fear memory, preventing the return of fear. Our study is the first human study to isolate the effects of cortisol and examine its influence on the reconsolidation of amygdala-dependent fear memories. By exhibiting a more pronounced reinstatement of fear to the stimulus that was reactivated under elevated cortisol concentrations, we demonstrate the enhancing effect of cortisol on fear memory reconsolidation in healthy human males.

The reconsolidation effect is highly specific. The reconsolidation effect demonstrated here was of a very specific nature. The reinstatement of the reactivated stimulus was more pronounced by cortisol, significantly differing from the non-reactivated stimulus. In a similar way, Schiller *et al* (2010) had previously demonstrated the specificity of the reconsolidation effect. After fear conditioning with three stimuli (two reinforced stimuli, one safe stimulus), one reinforced stimulus was reminded and followed by a behavioral intervention (postretrieval extinction learning) during the reconsolidation window. The return of fear following reinstatement was prevented specifically for the reactivated target stimulus.

Implications

An exposure to a conditioned cue can lead to two distinct consequences: reconsolidation or extinction (Pedreira and Maldonado, 2003; Suzuki *et al*, 2004). Repeated or prolonged unreinforced retrievals can lead to extinction learning (Merlo *et al*, 2014; but see Cai *et al* (2006) for single-trial extinction). GCs and stress have been shown to enhance exposure-based psychotherapy (de Quervain *et al*, 2011; Soravia *et al*, 2006; Soravia *et al*, 2014) and extinction learning (Hamacher-Dang *et al*, 2013), presumably by enhancing the consolidation of the newly acquired extinction memory (de Quervain and Margraf, 2008). In their rodents fear conditioning study, Cai *et al* (2006) demonstrated that postreactivation corticosterone can impair recall of established contextual fear memory, presumably through enhancement of extinction learning, even after a single trial. These findings illustrate the potential benefits of using GCs as an adjuvant to exposure-based treatments. However, as this intervention augments the consolidation of extinction memory and does not change the original fear memory, the effects may be transient and the fear may return, as shown by Cai *et al* (2006).

Reconsolidation processes are triggered by a brief memory reactivation (Merlo *et al*, 2014). The reactivated memory then becomes labile for a limited period of time, and—if not interrupted—reconsolidates and remains intact. Interrupting the reactivated memory at this fragile state might change (impair, enhance, or update) the original memory trace, potentially preventing the return of fear in anxiety disorders and PTSD. Nader *et al* (2000) have demonstrated the need of protein synthesis in the reconsolidation process and Kindt *et al* (2009) established the importance of noradrenergic activity for fear memory reconsolidation. In our study, we demonstrated that GCs enhance the reconsolidation of the original fear memory, leading to a more pronounced reinstatement of fear. This cortisol-dependent enhancement of retrieved memories could, in part, be responsible for the persistence of fear memories in anxiety disorders and PTSD. Spontaneous memory reactivations ('Flashbacks') occurring during elevated cortisol concentrations can further strengthen the original fear memory. Therefore, while protein synthesis inhibitors are not safe for use in humans and GC activity might lead to undesired effect on reactivated fear memories, noradrenergic β-blockers (eg propranolol) appear to be promising candidates for reconsolidation-based therapies (Kindt *et al*, 2009). Having said that, it needs to be acknowledged that a recent study (Wood *et al*, 2015) failed to find a beneficial effect of reactivation followed by propranolol or the glucocorticoid antagonist mifepristone in PTSD patients. The study emphasizes that the translation of laboratory-based findings on reconsolidation into the clinic remains a challenge.

Regardless of the desired direction of the effect, reconsolidation findings also have theoretical implications. The enhancement of memory reconsolidation by cortisol demonstrated here resembles the enhancement of initial memory consolidation by cortisol (Joels *et al*, 2006; Roozendaal, 2002; Wolf, 2008). Comparable to the similar effects of GCs on both memory processes, β-blockers have similar impairing effects on both memory consolidation (Cahill *et al*, 1994) and reconsolidation (Kindt *et al*, 2009), and protein-synthesis inhibitors impair both memory consolidation (Kandel, 2001) and reconsolidation (Nader *et al*, 2000). These results indicate a similarity between some of the neurobiological processes involved in initial memory consolidation and those mediating memory reconsolidation following retrieval.

In this study, we used systemic administration of hydrocortisone to examine the effects of GCs on memory reconsolidation. Cortisol effects the brain via two different nuclear receptors: the low-affinity glucocorticoid receptors (GRs), which are distributed throughout the brain, and the high affinity mineralocorticoid receptor (MRs), which are primarily located in limbic areas. In addition to the intra-

cellular MR, a membrane-bound MR, which mediates rapid non-genomic effects, has been described (Joels *et al*, 2008) and it is involved in fast cognitive effects on memory and executive function (Otte *et al*, 2015; Vogel *et al*, 2015). Future studies can target the activity of specific receptors to investigate their contribution to fear memory reconsolidation during the labile period, and to further understand the similarity between the processes of consolidation and reconsolidation.

Varying concentrations of sex hormones in freely cycling females or their suppression by the use of oral contraceptives can lead to differences in emotional learning (Merz *et al*, 2012a, b; Milad *et al*, 2009). To avoid possible influence of altering sex hormones concentration on fear learning or interactions with the pharmacological intervention, we tested only male participants. Our results are therefore limited to males only.

CONCLUSION

In the current study, we examined the effects of cortisol on reconsolidation of fear memories in human males. Using a 3-day reconsolidation design, we found an enhancing effect of cortisol on the reconsolidation of reactivated fear memories. These results suggest a similarity between the processes mediating memory reconsolidation and initial consolidation, and contribute to the understanding of the mechanisms involved in memory persistence in anxiety disorders and PTSD. Put together with previous studies, our results suggest GCs to be of potential benefit in exposure-based (but not reconsolidation-based) therapies.

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank Tobias Otto for technical support and Christoph Fraenz for his invaluable help in data collection and recruitment. The work of the authors was funded by project P5 (SMD, CJM, TCHD, OTW) and project P6 (MT) of the German Research Foundation (DFG) Research Unit 1581 'Extinction Learning: Neural Mechanisms, Behavioral Manifestations, and Clinical Implications. The DFG had no role in study design, collection, analysis and interpretation of data, writing of the manuscript, or in the decision to submit the paper for publication.

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