



Post-exposure cortisol administration does not augment the success of exposure therapy: A randomized placebo-controlled study

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ARTICLE INFO

Keywords:

Anxiety disorders
Spider phobia
Fear extinction
Exposure therapy
Cortisol

ABSTRACT

Cortisol administration *prior* to treatment can promote the efficacy of exposure-based treatments in specific phobia: cortisol has been proposed to reduce fear retrieval at the beginning of exposure and to enhance the acquisition and consolidation of corrective information learned during exposure. Whether cortisol exerts a beneficial therapeutic effect when given *after* exposure, e.g., by targeting the consolidation of new corrective information, has not been addressed so far to date. Here, we examined whether post-exposure cortisol administration promotes fear reduction and reduces return of fear following contextual change in specific phobia. Furthermore, the effect of cortisol on return of fear following contextual change (i.e., contextual renewal) was assessed. Patients with spider phobia ($N = 43$) were treated with a single session of in-vivo exposure, followed by cortisol administration (20 mg hydrocortisone) in a double-blind, placebo-controlled study design. Return of fear was assessed with behavioral approach tests (BATs) in the familiar therapy context (versus a novel unfamiliar context) at one-month and seven-month follow-up assessment. Exposure was effective in reducing fear from pre-treatment to post-treatment (i.e., 24 h after exposure) on fear-related behavioral (approach behavior during the BAT), psychophysiological (heart rate during the BAT) and subjective (fear during the BAT, spider-fear related questionnaires) measures of therapeutic outcome, with no add-on benefit of cortisol administration. Cortisol had no effect on contextual renewal at one-month follow-up. However, in a subsample ($N = 21$) that returned to the seven-month follow-up, an adverse effect of cortisol on fear renewal was found, with cortisol-treated patients showing an increase in subjective fear at the final approach distance of the BAT from post-treatment to seven-month follow-up. These and previous findings underline the importance of considering the exact timing of cortisol application when used as an add-on treatment for extinction-based psychotherapy: post-exposure cortisol administration does not seem to be effective, but might promote fear renewal at the subjective level.

1. Introduction

Although exposure constitutes a very powerful treatment for anxiety and stressor-related disorders (Hofmann and Smits, 2008; Norton and Price, 2007; Otte, 2011; Ruhmland and Margraf, 2001a,b,c), treatment success varies widely among patients and relapse constitutes a frequent problem (Craske et al., 2006; Durham et al., 2012). Consequently, the identification of novel strategies that can enhance exposure therapy seems to represent a useful avenue of research to yield more enduring and stable treatment benefits.

Pharmacological administration of the stress hormone cortisol, the primary glucocorticoid in humans, has emerged as a promising

approach to augment the efficacy of exposure-based treatments (for a review, see de Quervain et al., 2017). Precisely, cortisol has previously been shown to reduce pathological symptoms in specific phobia () and post-traumatic stress disorder (Aerni et al., 2004; Suris et al., 2010). Most importantly, cortisol application prior to exposure has been found to enhance therapeutic outcome in spider phobia (, 2014), social phobia () and height phobia (de Quervain et al., 2011).

Although various mechanisms can account for exposure-induced fear reduction and symptom improvement, fear extinction has emerged as one central candidate responsible for exposure-induced symptom relief (Craske et al., 2008, 2014). Research on the behavioral and neurobiological underpinnings of fear extinction has received great

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interest in the last few decades. Much of these data suggest that fear extinction does not erase the original fear memory but encompasses the formation of a new inhibitory memory trace that competes with the previously established fear memory trace (Bouton, 2004). Within that model, the memory-modulating characteristics of cortisol are ideally suited to facilitate exposure (de Quervain et al., 2017). Thus far, the evidence from exposure therapy studies suggests that cortisol facilitates therapeutic outcome by suppressing fear memory retrieval and by facilitating the consolidation of the corrective information (i.e., extinction) acquired during exposure at the same time (for reviews, see Bentz et al., 2010; de Quervain and Margraf, 2008; de Quervain et al., 2017). However, the putative mechanisms of action are hard to dissect because the (timing-dependent) effects of cortisol on the different memory stages (i.e., encoding, consolidation, retrieval) of the fear and extinction memory trace have not been assessed systematically in translational studies. In fact, previous studies administered cortisol *prior* to exposure (de Quervain et al., 2011; , 2014), which can potentially affect fear retrieval, encoding of the corrective information learned during exposure, as well as the consolidation of both the corrective and the fear memory. To our knowledge, no translational study has been conducted which examined the effects of cortisol application *after* exposure to specifically target consolidation processes. Apart from a mechanistic understanding, such an investigation might be especially relevant from a clinical perspective. If effective, cortisol may be selectively utilized *after* exposure to enhance only positive mastery experiences.

Another important issue which has been mainly neglected in previous translational studies relates to the role of cortisol in modulating relapse phenomena. Relapse prevention after successful exposure represents a major challenge in clinical settings. Again, the fear extinction model offers a plausible mechanism to understand relapse phenomena. Fear extinction is known for its context-specificity (Bouton, 2004). Hence, in the clinical context, extinguished fear can return when patients encounter their feared object in contexts different to the treatment context, a phenomenon termed fear renewal (Bouton, 2004). Pre-clinical human studies have shown that stress hormones both enhance or attenuate the generalization of extinction across contexts, depending on their timing (Hamacher-Dang et al., 2013, 2015; Meir Drexler et al., 2017; Merz et al., 2014, 2018). Despite the clinical relevance of transferring treatment-induced fear reduction to contexts beyond the therapeutic setting, translational studies investigating the effects of cortisol on fear renewal are lacking so far.

In the current study, spider-phobic individuals underwent a single session of in-vivo exposure, followed by cortisol or placebo administration in a randomized, double-blind study design. Precisely, we administered 20 mg hydrocortisone, a dosage that was effective in promoting therapeutic outcome in previous studies (de Quervain et al., 2011; Soravia et al., 2014). The aims of the present study were twofold: First, we examined whether cortisol augments exposure therapy outcome when administered *after* exposure. Since enhanced consolidation of new corrective learning (e.g., extinction learning) construes one potential explanatory mechanism for the beneficial effects of cortisol on exposure, post-session cortisol administration was expected to augment therapeutic success from pre- to post-treatment: the beneficial effects of cortisol (versus placebo) were presumed to be displayed either on the level of spider-fear related questionnaires and/or decreased avoidance, subjective fear and heart rate during a standardized behavioral approach test (see de Quervain et al., 2011). Second, by employing one-month and seven-month follow-ups, we assessed whether cortisol administration affects exposure-induced long-term fear reduction as well as the susceptibility to context-dependent fear renewal as a readout for the generalization of treatment effects. Based on preclinical studies in humans that have shown that stress application *after* fear extinction, the laboratory analog of exposure, can render the extinction memory context-dependent (Hamacher-Dang et al., 2015), we expected cortisol administration to reduce the generalization of exposure effects across contexts. Since the latter has not been assessed in the exposure setting,

we propose that a stronger fear renewal at one-month and seven-month follow-up in participants treated with cortisol is dependent upon which fear indices are being considered during the behavioral approach tests, i.e., subjective fear ratings, changes in heart rate and phobic cognitions (see Mystkowski et al., 2002; Rodriguez et al., 1999).

2. Materials and methods

2.1. Participants

Participants were recruited by newspaper advertisements, postings in social media networks and bulletin board notices at the campus of the Ruhr University Bochum. Participation was restricted to patients with spider phobia (according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition) with an age between 18 and 65 years. Diagnosis was ascertained with the short version of the diagnostic interview for mental disorders (Mini-DIPS; Margraf, 1994). Exclusion criteria comprised any current psychiatric disorder that was considered more severe than spider phobia (as rated by the trained experimenter conducting the Mini-DIPS) as well as any factor which influences basal cortisol concentrations, such as acute or chronic medical diseases, especially endocrine diseases, pregnancy, current drug or alcohol abuse, smoking > 5 cigarettes per month, a body mass index (BMI) < 19 or > 27 kg/m², as well as current pharmacological, neurological, or psychiatric treatment.

169 participants completed a telephone screening, with 53 being eligible for participation. Of these, six participants were unable to attend the sessions and four participants (placebo: $n = 1$, cortisol: $n = 3$) were excluded from data analysis due to procedural errors during the experimental period. Comorbid diagnoses were another specific phobia in 10 patients (placebo: $n = 3$, cortisol: $n = 7$). Furthermore, one participant had a posttraumatic stress disorder (cortisol: $n = 1$) and two an adjustment disorder (placebo: $n = 1$, cortisol: $n = 1$) in the past, with all three patients being fully-remitted. Our analytic sample ($N = 43$ from pre-treatment through one-month follow-up) comprised 9 males, 10 free-cycling (FC) women with a regular menstrual cycle as well as 24 women using oral contraceptives (OC) for at least three months. Due to participant drop-out, the sample comprised $N = 21$ (7 males, 3 FC and 11 OC women) participants at seven-month follow-up.

OC women were tested during the pill intake phase. To reduce the variance associated with circulating sex hormones in FC women, they were tested during the follicular phase of the menstrual cycle (3rd to 9th day after onset of menstruation), which is comparable to the sex hormone status in OC women regarding low sex hormone availability (cf. Merz, 2017; Merz et al., 2012). Participants were instructed that they should not attend the session with an empty stomach and should refrain from eating, smoking, drinking (except for water) and intensive exercise for 90 min prior to each session. All experimental procedures were approved by the ethics committee of the medical faculty (Ruhr University Bochum; Protocol. No: 5100-14) and carried out in accordance with the Declaration of Helsinki. Participants provided written informed consent and received 100€ as compensation.

2.2. Stimuli and apparatus

The phobic stimulus was a non-poisonous house spider (*tegenaria domestica*). Four different rooms were used for the study. There was one instruction room, where the ambulatory monitoring devices were fitted, resting heart rate recorded, saliva samples collected and questionnaires completed. The other three rooms served as experimental contexts A–C. These differed not only in size, decoration, furniture and illumination of the room, color and size of the terrarium used for the Behavioral Approach Tests (BATs), and exposure tools (e.g., brush, gloves) but also in the experimenter being present (gender and clothes).

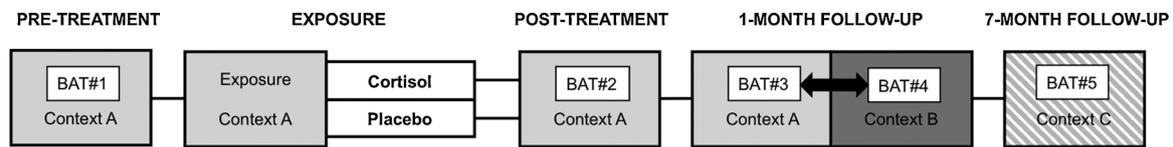


Fig. 1. Outline of the experimental design. Three different rooms were used as experimental contexts: which of these three rooms served as context A (= familiar, treatment context) or context B/C (= novel contexts) was counterbalanced across participants. Patients with spider phobia underwent a standardized in-vivo exposure, after which either cortisol (20 mg) or placebo was administered in a randomized, double-blind study design. Exposure was conducted in context A. Behavioral approach tests (BATs) were employed at different times to assess exposure-induced reduction in fear and avoidance of a house spider. These BATs were conducted in context A at pre-treatment and post-treatment. To assess the effects of contextual components, two BATs were conducted at one-month follow-up: either in context A (BAT#3) or in context B (= novel context; BAT#4), with a counterbalanced order (indicated by double arrow) across participants. All participants completed BAT#5 in context C (= novel context) at seven-month follow-up. Sample size was $N = 43$ (placebo: $n = 23$; cortisol: $n = 20$) from pre-treatment through one-month follow-up and $N = 21$ (placebo: $n = 11$; cortisol: $n = 10$) at seven-month follow-up.

2.3. Materials and measures

2.3.1. Control variables

The German versions of the Beck's Depression Inventory-II (BDI-II; Hautzinger et al., 2006) and the State-Trait Anxiety Inventory – Trait version (STAI-T; Laux et al., 1981) served to control for differences in depression and anxiety across participants. Self-efficacy levels and emotion regulation were assessed with German versions of the General Self-efficacy Scale (GSE; Jerusalem et al., 1999) and the Emotion Regulation Questionnaire (ERQ; Abler and Kessler, 2009), respectively. All questionnaires were given in paper- and pencil- format.

2.3.2. Spider-fear related questionnaires

Except for the exposure session, German versions of paper-and-pencil spider-fear related questionnaires were completed at each appointment. These comprised the Spider Phobia Questionnaire (SPQ; Hamm, 2006), the Fear of Spiders Questionnaire (FSQ; Rinck et al., 2002) and the Spider Beliefs Questionnaire (SBQ; Pössel and Hautzinger, 2003).

2.3.3. Subjective fear

During the BATs and exposure, subjective fear, which was reported verbally, was assessed using the Subjective Unit of Distress Scale (SUDs; Wolpe, 1973), with scores from 0 (= no fear) to 100 (= excessive fear).

2.3.4. Behavioral approach test (BAT)

We used the BAT as described in detail in Lass-Hennemann and Michael (2014). Briefly, participants were asked to enter the room and approach a spider, which was placed in a plastic container at the far end of the room. No time limit for BAT completion was imposed but participants were instructed to undertake the BAT as fast as possible and continue approaching the spider until fear becomes intolerable. The BAT was terminated when participants indicated that they could not proceed any further or when they had successfully (i.e., BAT score of 12, see below) completed the BAT.

BATs were scored behaviorally, i.e., approach distance, which ranges from 0 (= did not enter the room) to 12 (= holds the spider for 20 s), and subjectively, i.e., verbally-reported fear using the SUDs at the closest distance to the spider attained by the participant. At post-treatment and both follow-ups, exposure-induced fear reduction was assessed by having participants report their fear (SUDs) at the same approach distance accomplished during pre-treatment (= initial approach distance) in addition to their fear at the closest distance at the current assessment (= final approach distance).

2.3.5. Heart rate

Resting heart rate (3 min), measured five minutes after BAT completion at each of the five sessions, and heart rate during the BAT were measured with the Polar RS800CX ambulatory monitoring system. To this end, participants were fitted with an electrode belt strapped around their chest, which measured heart rate in 5 s intervals, and a wristwatch receiver unit, which stored the data.

2.3.6. Cortisol administration and salivary cortisol

Participants were randomly assigned to receive either two tablets of 10 mg hydrocortisone or two tablets of placebo. Drug administration was blinded for both the patient and experimenter. Salivary cortisol was collected with saliva sampling tubes (Sarstedt, Nümbrecht, Germany). Four saliva samples were collected: prior to exposure, 25 min after exposure onset, at the end of exposure (immediately before tablet intake), and 25 min after cortisol/placebo administration. All saliva samples were stored at -20°C until assayed. Free cortisol concentrations were measured via commercially available enzyme-linked immunosorbent assays (ELISA; Demeditec, Kiel, Germany) with inter- and intra-assay variations below 7% and 4%, respectively.

2.4. Experimental design and procedure

Participation comprised five appointments, which were conducted in the afternoon (1pm-5pm) at the Mental Health Research and Treatment Center of the Ruhr University Bochum: pre-treatment, exposure (conducted either 24 h or 48 h after pre-treatment), after which cortisol or placebo was administered in a double-blind study design, post-treatment (conducted 24 h after exposure), one-month and seven-month follow-up. An outline of the experimental design and the contextual renewal procedure is depicted in Fig. 1.

2.4.1. Pre-treatment

Written informed consent was obtained, the diagnostic interview conducted and different questionnaires (BDI-II, STAI-T, ERQ, and GSE) completed. Thereafter, participants engaged in the BAT#1, filled in the spider-fear related questionnaires#1, and received psychoeducation about spider phobia and information about exposure.

2.4.2. Exposure

Exposure was based on a fourteen-steps standardized fear hierarchy with increasing difficulty, ranging from watching the spider in a glass to letting the spider walk on the arm (for details, see Mystkowski et al., 2002). The experimenter first modeled each step, after which the participant performed the step herself/himself. Fear levels (SUDs) were collected at the beginning of each step and collected continuously. The next step of the hierarchy was only initiated if fear had decreased to a SUDs of 25 or below. Exposure was terminated when all steps had been successfully completed or 2.5 h had expired, whichever occurred first (in 4 out of 43 cases exposure was terminated due to expiry of the time limit). Immediately after exposure, cortisol/placebo was administered. At the end of the session, i.e., 25 min after drug administration, blinding treatment guess was assessed by a questionnaire, which asked participants to indicate whether they believed they had received cortisol or placebo (including a “don't know” option) and to report any side effects.

2.4.3. Post-treatment and follow-ups

At post-treatment, participants engaged in the BAT#2 and completed the spider-fear related questionnaires#2. At one-month follow-

up, participants performed BAT#3 in the treatment context and BAT#4 in a novel context, completed the spider-fear related questionnaires#3, and were fully debriefed about the study purpose (but not about the received medication). Seven month later, participants were invited to participate in another session, in which BAT#5 was conducted in another novel context and the spider-fear related questionnaires#4 were completed.

2.5. Statistical analyses

Data were analyzed with SPSS, Version 24 (IBM SPSS, Armonk, NY, USA). Our final analytic sample comprised $N = 43$ participants (placebo: $n = 23$; cortisol: $n = 20$) from pre-treatment through one-month follow-up and $N = 21$ (placebo: $n = 11$; cortisol: $n = 10$) at seven-month follow-up. Heart rate change scores during the BAT at each appointment were calculated by subtracting mean resting heart rate from the mean heart rate during the respective BAT. Due to technical failures, only $N = 35$ participants (placebo: $n = 16$; cortisol: $n = 19$) could be included in analyzing heart rate data (as well as $N = 15$: placebo: $n = 6$; cortisol: $n = 9$ in the reduced sample at seven-month follow-up).

First of all, we compared the placebo and cortisol group in terms of pre-exposure participant characteristics and the progress made during exposure using unpaired t -tests and chi-square tests. Cortisol concentrations were analyzed with a mixed ANOVA with time (pre-exposure, 25 min after exposure onset, at the end of exposure/prior to tablet intake, 25 min after tablet intake) as within-subjects factor and group (placebo, cortisol) as between-subjects factor. Finally, we compared the two study groups in their treatment guess (i.e., whether they believed they had received cortisol or placebo) using Fisher's exact test.

Measures of therapeutic outcome included scores on the spider-fear related questionnaires as well as the BAT, with the latter encompassing the behavioral score (i.e., approach distance), subjective fear at the initial and final approach distance as well as heart rate. These dependent variables were analyzed in mixed ANOVAs with time (2 or 3 levels, see below) as within-subjects factor and group (placebo, cortisol) as between-subjects factor. Power analysis (G*Power, version 3.1.9.2) revealed that our sample ($N = 43$), which is comparable to previous studies on cortisol-augmented exposure (e.g., Soravia et al., 2014), exceeds the required sample size of 28–34 (for 2 or 3 levels of the factor time) to detect a medium effect ($f = .25$) with sufficient power (.8) at $p < .05$ for the within-between interaction in a mixed ANOVA.

First, we assessed the effects of cortisol vs. placebo administration on the immediate change in each outcome measure from pre- to post-treatment (within-subjects factor time: pre-treatment, post-treatment). Second, return of fear was assessed with a 2×2 mixed MANOVA for the spider-fear related questionnaires (within-subjects factor time: pre-treatment, post-treatment) and with a 3×2 mixed ANOVA for BAT-related outcome measures (time: post-treatment, one-month follow-up in context A, one-month follow-up in context B) which allowed to assess the context-dependent return of fear. Third, a 2×2 mixed ANOVA (within-subjects factor time: post-treatment in context A, seven month-follow-up in context C) was utilized to compare the cortisol and placebo group in the context-dependent return of fear from post-treatment to seven-month follow in the reduced sample ($N = 21$). In each analysis, support for study hypotheses was derived from a significant time \times group interaction. Where appropriate, degrees of freedom were Greenhouse-Geisser corrected. Results were considered significant at $p < .05$.

3. Results

3.1. Pre-exposure participant characteristics

As shown in Table 1, the cortisol group was not different from the placebo group in each control variable (i.e., age, BMI, BDI-II, STAI-T,

Table 1
Participant characteristics at pre-treatment and salivary cortisol levels during exposure.

Variable	Placebo ($n = 23$)		Cortisol ($n = 20$)		p -value
	M	SD	M	SD	
Age (years)	22.57	3.78	22.70	4.21	.91
Sex hormone status (n)					.75
OC women	14		10		
FC women	4		5		
Men	5		5		
BMI	22.73	2.73	22.27	2.37	.56
STAI-T	33.88	7.81	34.25	7.15	.87
BDI-II	3.04	3.32	4.75	4.76	.18
GSE	29.04	4.50	30.97	4.11	.15
ERQ					
Reappraisal	4.93	1.11	5.13	0.69	.51
Suppression	2.91	0.91	3.48	1.34	.11
Salivary cortisol					
Prior to exposure onset	9.05	7.20	8.06	4.32	.61
Exposure onset + 25 min	7.01	5.79	6.49	2.77	.73
Immediately after exposure and prior to tablet intake	4.34	3.74	4.40	2.04	.96
Tablet intake + 25 min	3.81	3.05	185.51	163.40	< .001

Notes. OC women = women using oral contraceptives; FC women = free-cycling women; BMI = Body Mass Index; STAI-T = State-Trait Anxiety Inventory - Trait version; BDI-II = Beck's Depression Inventory - II; GSE = General Self-efficacy Scale; ERQ = Emotion Regulation Questionnaire; Salivary cortisol is presented as means and based on $n = 23$ in the placebo and $n = 18$ in the cortisol group.

ERQ, GSE) and the proportion of males, OC women, and FC women. Importantly, both groups were comparable in their pre-treatment scores on the spider-fear related questionnaires (cf. Table 1), score on the BAT (BAT#1; placebo: $M = 6.61$, $SD = 1.95$; cortisol: $M = 7.35$, $SD = 1.31$; $t_{(38.70)} = 1.48$, $p = .15$), subjective fear at the initial approach distance (placebo: $M = 73.26$, $SD = 8.61$; cortisol: $M = 69.75$, $SD = 10.06$; $t_{(41)} = 1.23$, $p = .22$), as well as heart range change scores during the BAT#1 (placebo: $M = 18.69$, $SD = 7.38$; cortisol: $M = 19.47$, $SD = 9.16$; $t_{(33)} = 0.28$, $p = .78$).

3.2. Exposure

3.2.1. Progress during exposure

The number of exposure steps completed (placebo: $M = 13.91$, $SD = 0.29$; cortisol: $M = 13.90$, $SD = 0.31$; $t_{(41)} = .143$, $p = .89$) as well as the individual duration needed to accomplish all steps of the hierarchy (placebo: $M = 101.17$ min, $SD = 30.43$ min; cortisol: $M = 87.20$ min, $SD = 29.34$ min; $t_{(41)} = 1.53$, $p = .13$) did not differ across groups.

3.2.2. Cortisol measurements

Cortisol concentrations are shown in Table 1. Data from two participants of the cortisol group were discarded from analysis due to unrealistically high cortisol concentrations (i.e., > 1200 nmol/l) after drug administration. As indicated by a significant time \times group interaction ($F_{(1.0,39.1)} = 28.75$, $p < .001$; main effects: time $F_{(1.0,39.1)} = 26.93$, $p < .001$; group: $F_{(1,39)} = 27.61$, $p < .001$), the change in cortisol concentrations over time differed across groups. Simple effects analysis revealed elevated cortisol concentrations in the cortisol compared to the placebo group in the fourth sample only (i.e., 25 min after tablet intake; $p < .001$; first, second and third sample: all $p \geq .61$), indicating successful pharmacological manipulation.

3.2.3. Treatment guess

Most of the participants indicated they 'did not know' (placebo: 19 of 23; cortisol: 12 of 20) which tablet they had received. Importantly,

Table 2
Scores on the spider-fear related questionnaires at pre- and post-treatment, one-month follow-up and seven-month follow-up.

	Placebo		Cortisol		p-value
	M	SD	M	SD	
FSQ					
Pre-treatment	83.00	11.37	75.10	19.31	.12
Post-treatment	32.17	19.72	26.05	14.35	.26
One-month follow-up	25.17	15.95	26.25	15.11	.82
Seven-month follow-up	27.73	25.57	23.90	20.48	.71
SPQ					
Pre-treatment	23.00	3.40	21.75	3.77	.26
Post-treatment	13.09	4.83	11.30	3.76	.19
One-month follow-up	12.65	5.28	10.50	4.52	.16
Seven-month follow-up	12.82	6.13	11.20	6.36	.56
SBQ					
Pre-treatment	66.51	12.47	66.05	11.14	.90
Post-treatment	25.95	16.16	17.72	12.21	.07
One-month follow-up	21.89	16.33	18.07	12.69	.40
Seven-month follow-up	23.09	20.43	19.10	15.49	.62

Notes. FSQ = Fear of Spiders Questionnaire; SPQ = Spider Phobia Questionnaire; SBQ = Spider Beliefs Questionnaire. Sample size was $n = 23$ in the placebo group and $n = 20$ in the cortisol group from pre-treatment through one-month follow-up. At seven-month follow up, sample size was $n = 11$ in the placebo and $n = 10$ in the cortisol group. See text for exposure-induced changes in scores on these questionnaires over time.

groups did not differ in their guesstimates of whether they had received cortisol or placebo ($p = .22$, Fisher's exact test; ignoring 'don't know' responses).

3.3. Exposure effectiveness and effects of cortisol

3.3.1. Pre- to post-treatment

Exposure was highly effective in reducing fear of spiders from pre- to post-treatment on complementary fear-related measures. Scores on the FSQ, SBQ, and SPQ decreased significantly over time (main effect for time, $F_{(3,39)} = 149.13$, $p < .001$, $\eta_p^2 = .92$, Wilk's $\Lambda = 0.08$; all univariate analyses $p < .001$, $\eta_p^2 > .82$; see Table 2 for descriptive statistics). As depicted in Fig. 2 and indicated by main effects for time, participants significantly increased their proximity to the spider from BAT#1 to BAT#2 ($F_{(1,41)} = 247.88$, $p < .001$, $\eta_p^2 = .86$) and reported significantly less subjective fear at the initial ($F_{(1,41)} = 379.53$, $p < .001$, $\eta_p^2 = .90$) and final approach distance ($F_{(1,41)} = 70.05$, $p < .001$, $\eta_p^2 = .63$) after exposure. Similarly, heart rate change scores showed a significant decline over time ($F_{(1,33)} = 10.88$, $p = .002$, $\eta_p^2 = .25$). Importantly, no differences between the cortisol and placebo group emerged in these analyses (all main and interaction effects, $p \geq .09$, $\eta_p^2 < .16$).

3.4. Return of fear and effects of cortisol

3.4.1. Post-treatment to one-month follow-up

Participants' scores on the spider-fear related questionnaires at one-month follow-up were comparable to post-treatment (main effect for time, $F_{(3,39)} = 1.23$, $p = .31$, $\eta_p^2 = .09$, Wilk's $\Lambda = .91$; cf. Table 2). In a similar vein, as indicated by non-significant main effects for time, participants' scores on the BAT ($F_{(2,82)} = 2.35$, $p = .10$, $\eta_p^2 = .05$) as well as their subjective fear at the initial approach distance ($F_{(1.6,65.47)} = 1.47$, $p = .24$, $\eta_p^2 = .04$) was comparable across the repeated BATs (i.e., BAT#2, #3, #4). At the final approach distance, the main effect for time was significant ($F_{(2,82)} = 8.74$, $p < .001$, $\eta_p^2 = .18$). Bonferroni-corrected post-hoc tests revealed that participants showed a further decline in fear levels from post-treatment (#2) to the follow-up in the treatment context (#3, $p = .001$), and showed more fear in the novel (#4) as compared to the treatment context (#3)

at follow-up ($p = .002$, cf. Fig. 3). Heart rate change scores during the BATs at one-month follow-up in the treatment context and the novel context were comparable to post-treatment (main effect for time; $F_{(1.49,49.06)} = 0.06$, $p = .89$, $\eta_p^2 = .002$). Importantly, none of these analyses yielded any group differences (all main effects and interactions, all $p > .07$, $\eta_p^2 < .17$).

3.4.2. Post-treatment to seven-month follow-up

Data was only available for 21 participants (placebo: $n = 11$; cortisol: $n = 10$) due to drop-outs. Decision for participation in the seven-month follow-up was not associated with the respective drug received ($\chi^2 = .02$, $df = 1$, $p = .89$). Participants who engaged in the seven-month follow-up were comparable to those who refrained from participation in each control variable (i.e., age, BMI, STAI-T, BDI-II, GSE, ERQ, all $p > .06$), scores on the spider-fear related questionnaires (#1; $F_{(3,39)} = 2.09$, $p = .188$, Wilk's $\Lambda = 0.86$), scores on the BAT#1 ($t_{(41)} = 0.36$, $p = .72$), as well as fear at the initial approach distance ($t_{(41)} = 0.35$, $p = .73$), and heart rate change scores during the BAT#1 at pre-treatment ($t_{(33)} = 1.26$, $p = .22$).

Repeating the aforementioned analyses with regard to changes in fear and avoidance on complementary fear-related measures from a) pre- to post-treatment and b) post-treatment to one-month follow-up with participants who participated in the seven-month follow-up only did not change the pattern of results attained (see Tables S1 – S3 for descriptive statistics and results of the mixed ANOVAs).

Scores on the spider-fear related questionnaires at seven-month follow-up were comparable to post-treatment (cf. Table 2), with no difference between the cortisol and placebo group (main and interaction effects, all $F_{(3,17)} < 0.65$, $p > .59$, $\eta_p^2 < .11$, Wilk's $\Lambda > 0.89$). However, participants showed an increase in avoidance from post-treatment to seven-month follow-up as indicated by scores on the BAT (BAT#2 vs. BAT#5; main effect for time, $F_{(1,19)} = 16.83$, $p = .001$, $\eta_p^2 = .47$), which did not differ by group (main effect for group and interaction, all $p > .14$). At the initial approach distance, main effects for time and group (all $p \geq .28$, $\eta_p^2 < .07$) were non-significant, whereas the time x group interaction ($F_{(1,19)} = 4.03$, $p = .059$, $\eta_p^2 = .18$) was significant at trend-level. The same interaction attained statistical significance at the final approach distance ($F_{(1,19)} = 4.66$, $p = .044$, $\eta_p^2 = .20$); both main effects: $p > .07$). Simple effects analysis on this interaction indicated that the cortisol group ($p = .012$), but not the placebo group ($p = .85$), showed a return of fear from post-treatment to the seven-month follow-up (cf. Fig. 3). No effects for heart rate change scores were evident (all main and interaction effects, $p > .24$, $\eta_p^2 < .11$).

4. Discussion

In the current study, we investigated whether cortisol promotes exposure therapy outcome when given after exposure. Furthermore, we tested the effects of post-exposure cortisol administration on long-term fear reduction and fear renewal. Exposure treatment was highly effective in reducing fear of spiders on the behavioral (BAT), subjective (spider fear-related questionnaires, fear at the initial and final approach distance), and physiological level (heart rate). However, compared to placebo, post-exposure cortisol administration did not further promote fear reduction at post-treatment and did not affect the magnitude of fear renewal at one-month follow-up. Instead, in the reduced sample that returned to the seven-month follow-up, cortisol-treated participants showed fear renewal from post-treatment to the seven-month follow-up as indicated by an increase in self-reported fear at the final approach distance of the BAT (but not on other subjective, behavioral and psychophysiological read-out measures).

Whilst several potential mechanisms may underlie cortisol-augmented exposure, the fear extinction model has been put forward as a potentially useful mechanism to understand the effects of cortisol administration on exposure-based treatment benefit. In the following, we

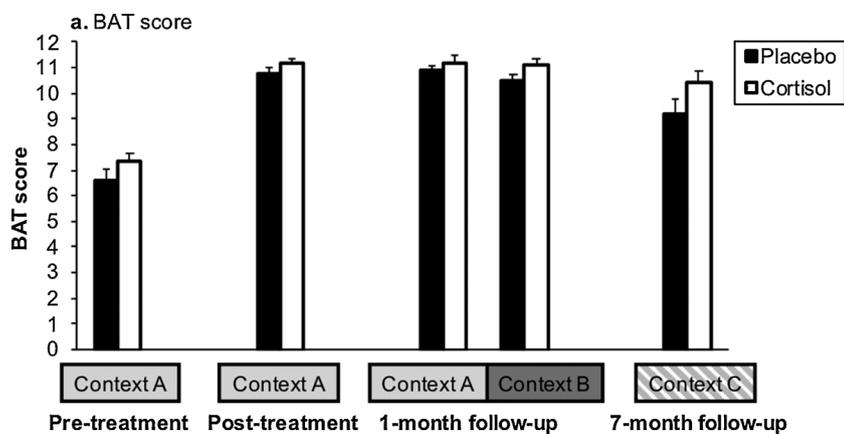


Fig. 2. Mean BAT score (top; a) and heart rate (expressed as change scores) during the BAT (bottom; b) from pre-treatment to seven-month follow-up for the placebo and the cortisol group. Data ($n = 23$ in the placebo and $n = 20$ in the cortisol group from pre-treatment through one-month follow-up; $n = 11$ in the placebo and $n = 10$ in the cortisol group at seven-month follow-up) is represented as means \pm SEM.

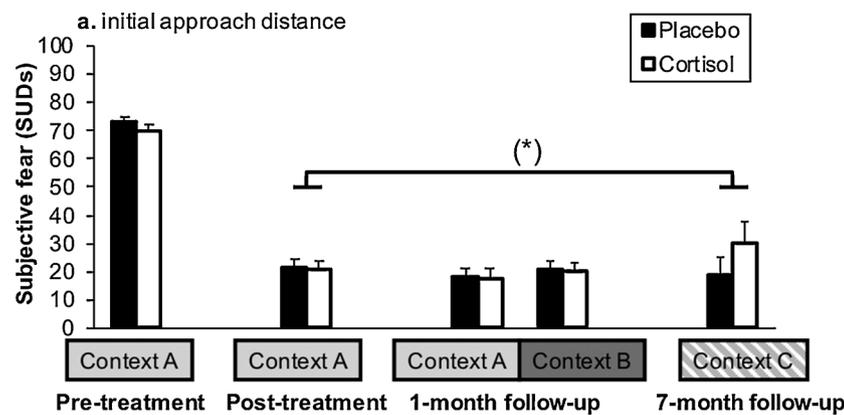
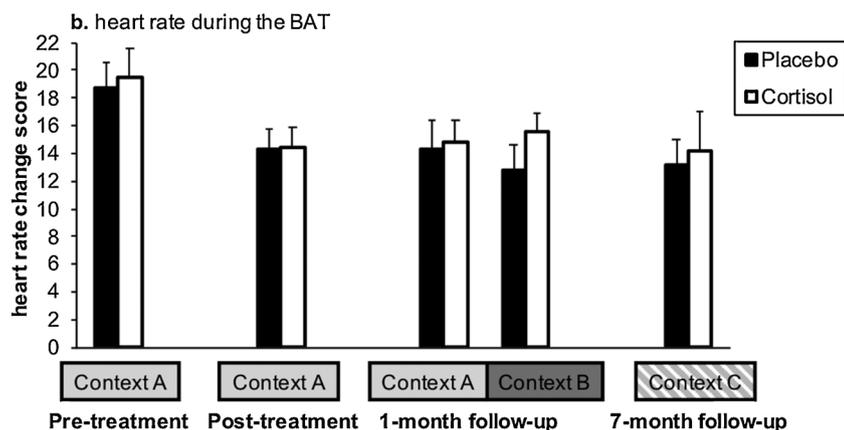
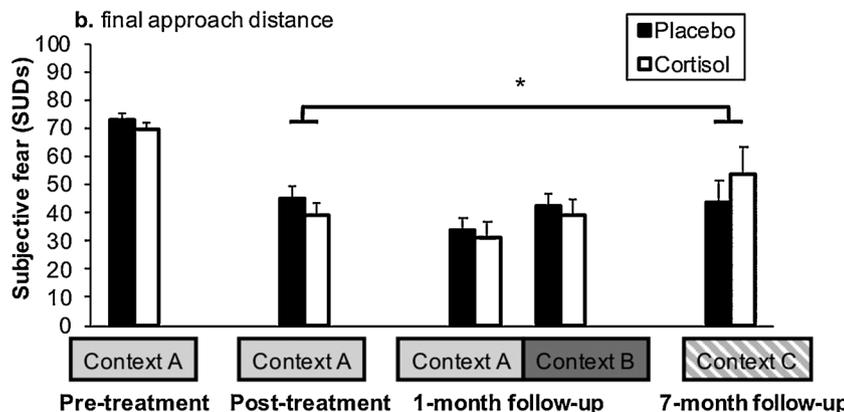


Fig. 3. Mean self-reported fear at the initial (top; a) and final (bottom; b) approach distance of the BAT from pre-treatment to seven-month follow-up for the placebo and the cortisol group. Data ($n = 23$ in the placebo and $n = 20$ in the cortisol group from pre-treatment through one-month follow-up; $n = 11$ in the placebo and $n = 10$ in the cortisol group at seven-month follow-up) is represented as means \pm 1 SEM. * denotes the significant group x time interaction with $p < .05$. (*) denotes a trend for a significant interaction, with $p < .06$.



will discuss our and previous findings against that background although we are aware that exposure encompasses more than the mere modulation of fear and extinction memories. Previous studies in clinical samples have typically found that cortisol prior to exposure enhanced therapeutic outcome (de Quervain et al., 2011; Soravia et al., 2006, 2014). From a mechanistic point of view to account for these findings, cortisol has been proposed to affect therapeutic outcome by inhibiting aversive memory retrieval associated with the fear stimulus and by strengthening the consolidation of new corrective learning (i.e., extinction learning) acquired during exposure (for reviews, see Bentz et al., 2010; de Quervain and Margraf, 2008). Yet, our findings do not accord with and at least raise doubts about the latter mechanism: post-exposure cortisol administration in the present study did not augment treatment outcome and/or the generalization of treatment effects across different contexts. Thus, although this was not directly tested in our approach and needs to be tested with elaborated experimental designs, one might speculate that the sole influence on the consolidation of corrective learning with post-exposure cortisol is not effective in augmenting therapeutic success, at least in the current design. Rather, as shown previously (de Quervain et al., 2011; Soravia et al., 2014), cortisol might only work as an adjunct for exposure therapy when given *before* exposure, presumably targeting fear retrieval (at the beginning of exposure) as well as encoding and consolidation of the corrective information acquired during exposure at the same time (Bentz et al., 2010; de Quervain and Margraf, 2008). In fact, very recent experimental research in patients with spider phobia underscores this assumption by showing that acute cortisol administration *prior* to the presentation of phobia-relevant pictures was associated with reduced amygdala activity and suppressed connectivity between the amygdala and the fusiform gyrus (Nakatani et al., 2017), which, in turn, might be related to reduced aversive memory retrieval and enhanced encoding of the corrective experience.

Collectively, our and previous findings on cortisol-augmented exposure suggest that depending on the specific timing of cortisol administration, cortisol can generate diverse long-term treatment effects. This corroborates with other studies focusing on the role of acute stress application on exposure and fear extinction as its laboratory proxy. Post-exposure stress induced by the cold pressor test (CPT) (primarily leading to an increase in activation of the sympathetic nervous system, but not necessarily to an increase in cortisol secretion) did not enhance therapeutic outcome in spider-fearful individuals (Schmidt et al., 2010). This result might be driven by the supposedly absent cortisol response (which was not measured in this study). Likewise, a number of human studies investigated the effects of stress during the phases of extinction acquisition, consolidation and extinction retrieval. Stress (CPT) *prior* to extinction (Antov et al., 2015), but not *after* extinction (Hamacher-Dang et al., 2015), was suitable to enhance the retrieval of extinction memories. And finally, stress (CPT and the socially evaluated CPT) has been shown to facilitate extinction retrieval in healthy men when applied *prior* to extinction (Bentz et al., 2013) or *prior* to retrieval (Merz et al., 2014). In addition to exposure to stress, *pre*-extinction cortisol administration was related to reduced fear retrieval at the beginning of extinction (conveyed by a amygdala-hippocampal network) and facilitated extinction memory consolidation as seen in an inhibitory activation pattern one week later (Merz et al., 2018). Together, these findings support the conclusion that stress, which, amongst others, induces higher cortisol levels, can promote or impair extinction memories depending on the exact timing of the stress application.

To our knowledge, this is the first clinical study which investigated the effects of post-exposure cortisol administration on the generalization of treatment effects by assessing context-dependent fear renewal. Cortisol did not lead to changes in avoidance behavior during the BAT in an unfamiliar (relative to the familiar) context at one-month follow-up. However, the cortisol, but not the placebo group, showed an increase in subjective fear (i.e., at the final as well as at trend-level at the initial approach distance of the BAT) in the unfamiliar context from

post-treatment to seven-month follow-up. Although this finding needs to be interpreted with caution (lowered sample size due to drop-outs), it may be suspected that post-exposure cortisol administration favored the consolidation of contextual cues present during exposure. Again, studies investigating the role of cortisol on fear extinction might offer one explanation for this effect. In particular, recent basic research indicates that stress after extinction enhanced the context-dependency of extinction (Hamacher-Dang et al., 2013, 2015), whereas stress prior to extinction rendered the extinction memory less context-dependent (Meir Drexler et al., *in press*; Meir Drexler et al., 2017).

Notably, the observed effect of cortisol on fear renewal was not evident at one-month follow-up, but emerged not until after seven months at the final approach distance (but not on other fear-related indices). The herein observed dissociation of cortisol effects on different fear-related indices is compatible with the often observed desynchrony in fear reduction after exposure. Thus, a contextual change at follow-up can lead to fear renewal, which, however, might not be observed consistently on different fear levels (Mystkowski et al., 2002; Rodriguez et al., 1999). It is reasonable to assume that this desynchrony is dependent upon the degree of contextual overlap between the exposure context and the context used at follow-up. In our study, the degree of contextual overlap was higher during the one-month follow-up, but lower at the seven-month follow-up, i.e., due to the fact that a completely new context (a room containing various new information and a new experimenter) was used at seven-month follow-up. It is known that cortisol interferes with processes related to contextualization of fear associations by its prominent effects on hippocampal and amygdala activity (Lovallo et al., 2010; for reviews, see Kim et al., 2006; Rodrigues et al., 2009). Thus, one might conclude that the effects of cortisol administration on fear renewal after exposure depend on both the time between exposure and follow-up and the degree of contextual overlap between the exposure context and the context in which the follow-up was performed. Of course, this conclusion is speculative. Nevertheless, considering its clinical relevance, especially with regard to long-term symptom relief, our findings certainly warrant further investigations to disentangle cortisol effects on memory contextualization and relapse phenomena.

Our study suffers from some limitations and considerations that deserve mention. First of all, it should be noted that participants were aware of the study purpose at seven-month follow-up. However, they were still unaware of the study drug assignment. While a greater awareness about the study purpose might have influenced overall performance, this effect, however, should have affected both groups equally. Second, both the reduction in sample size and the fact that any cortisol effects were only evident at the level of subjective fear at the final approach distance of the BAT compromises the generalizability and interpretability of our findings related to the contextual fear renewal in the cortisol group at seven-month follow-up. Third, and in line with the former, although a novel context (i.e., context C) was introduced at seven-month follow-up, fearful responding in the familiar therapy context (A) as well as context B was not re-assessed, thus precluding to investigate cortisol effects in different contexts and disentangle the effects on fear renewal from spontaneous recovery.

Most importantly, the interpretation for the absence of beneficial cortisol effects on exposure outcome and comparisons to studies using pre-exposure cortisol administration must be treated with caution. First of all, exposure success was considerably large even in placebo-treated participants, which may render it inherently difficult to evaluate the effects of an additional booster strategy. Based on previous findings (de Quervain et al., 2011), one might suggest that cortisol effects are dependent on the relative efficacy of exposure per se (suboptimal vs optimal exposure-induced fear reduction). Second, our and previous studies differed in the exact treatment protocol (i.e., exposure steps and spiders used) as well as in the number of times exposure sessions were conducted and hence in the frequency of cortisol administration (Lass-Hennemann and Michael, 2014; Soravia et al., 2014). Finally, cortisol

effects on memory might be dose-dependent (Lupien et al., 1999; Schilling et al., 2013). Since only a specific dosage (20 mg) was tested, the possibility for a dose-dependent effect cannot be excluded. For the aforementioned reasons, only experimental designs that rigorously compare pre-exposure vs. post-exposure dosing under the same conditions would allow to rule out some of these alternative explanations as well as to derive tentative conclusions as to whether the absence of beneficial cortisol effects on therapeutic outcome is attributable to post-exposure study drug administration.

Our study investigated the effects of cortisol on the context-dependent return of fear. Yet, poor generalization of exposure effects across stimuli construes another source for the return of fear after therapy completion (Preusser et al., 2017). Accordingly, future studies might investigate whether cortisol modulates the stimulus-based generalization of exposure (cf. Dunsmoor et al., 2017). Finally, since sex hormones have an influence on cortisol effects on emotional memory (Merz and Wolf, 2017), future studies might focus on the interactive effects of sex hormones and cortisol administration on exposure therapy outcome.

Concluding, in contrast to pre-exposure cortisol administration augmenting therapeutic outcome (de Quervain et al., 2011; Soravia et al., 2006, 2014), cortisol administration after exposure did not promote exposure therapy efficacy in our study. However, an adverse effect of cortisol on susceptibility to fear renewal was found in the reduced sample at seven-month follow-up. Along with previous findings on cortisol-augmented exposure (de Quervain et al., 2011; Soravia et al., 2006, 2014), our findings shed new light on the importance of considering the specific timing of cortisol application when used as an add-on treatment for extinction-based psychotherapy: although our initial findings require replication, they advance the field by suggesting that post-exposure cortisol administration does not augment exposure therapy outcome, but may promote fear renewal in the long-term.

Contributors

FR, AZ designed the study. FR conducted the study. FR, CJM, AZ analyzed the data. FR, CJM, OTW, JM, AZ interpreted the data. FR, AZ wrote the manuscript. All authors contributed to and approved the final version of the manuscript.

Role of the funding source

The study was supported by grants from the Deutsche Forschungsgemeinschaft (FOR 1581, project 9 to A.Z. and J.M.; SFB 874, project A1 to M.T.; SFB 1280, project A13 to A.Z. and J.M., project A08 to M.T., project A09 to C.J.M. and O.T.W.). The funders had no role in study design, data collection and analysis, preparation of the manuscript and decision to publish.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: <https://doi.org/10.1016/j.psyneuen.2018.09.015>.

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