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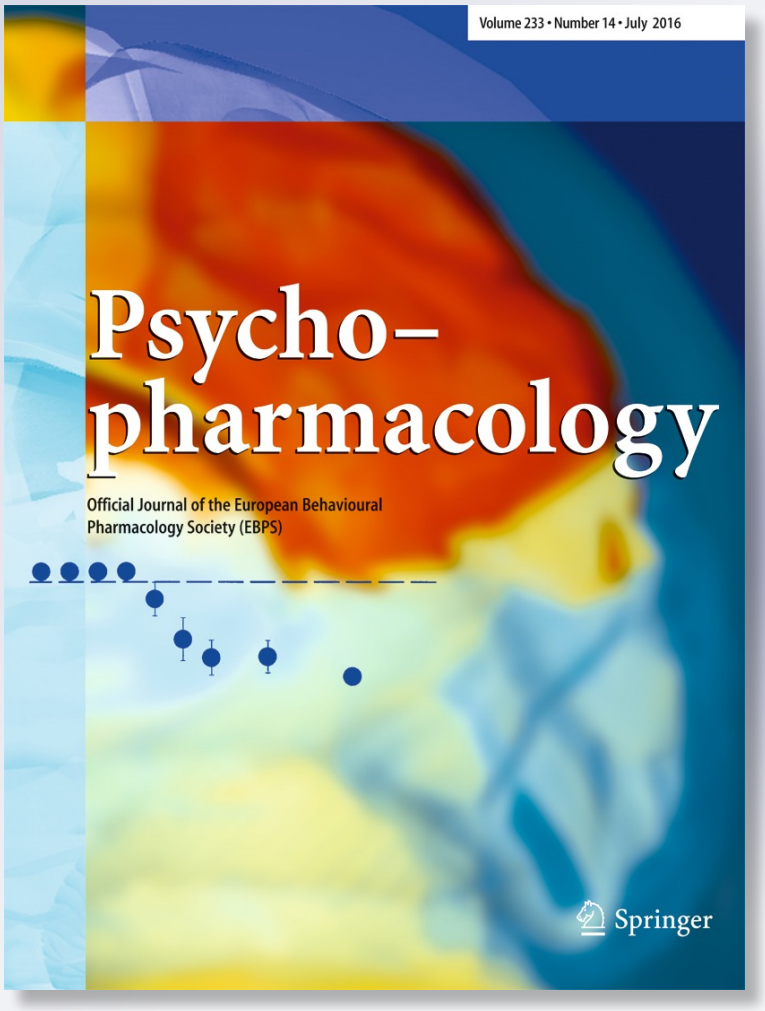

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ORIGINAL INVESTIGATION

Cortisol effects on fear memory reconsolidation in women

Shira Meir Drexler[1,2] · **Christian J. Merz**[1] · **Tanja C. Hamacher-Dang**[1] · **Oliver T. Wolf**[1,2]

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Abstract
Rationale Previous work from our group has shown that cortisol enhances fear reconsolidation in men. Whether similar effects can be observed in women remains an open question.
Objectives The effects of cortisol on the reconsolidation of fear memories were investigated in women. Based on results in men, we expected a specific enhancing effect of cortisol administration on the reactivated fear memory. In addition, possible interactions with oral contraceptive use were tested.
Methods We incorporated a differential fear conditioning paradigm in a 3-day reconsolidation design. A fear memory, which was created on the first day, was reactivated on the second day following cortisol administration in the target group. One control group was given cortisol without reactivation, and the other participated in the reactivation session following placebo intake. On the third day, the return of fear for all stimuli following reinstatement was tested. Skin conductance response served as measure of conditioned response.
Results In contrast to the hypothesis, cortisol in combination with reactivation did not enhance fear reconsolidation. No differences between the three experimental groups were apparent. In addition, hormonal contraceptive use had no effect on any of the learning phases and did not interact with the cortisol manipulation.
Conclusions The lack of an effect in women might be the result of alternating concentrations of sex hormones during different phases of the menstrual cycle or following oral contraceptive use. Considering the higher vulnerability of women to stress-related mental disorders, further investigations in women are of great importance for both theory and treatment.

Keywords Fear conditioning · Return of fear · Reinstatement · Glucocorticoids · Skin conductance response · Memory reactivation · Sex differences

Abbreviations

BMI	Body mass index
CR	Conditioned response
CS	Conditioned stimulus/stimuli
FC	Free cycling
GCs	Glucocorticoids
HPA	Hypothalamus-pituitary-adrenal
ITI	Intertrial interval
OC	Oral contraceptives
PTSD	Post-traumatic stress disorder
SCR	Skin conductance response
UCS	Unconditioned stimulus

Introduction

Glucocorticoids (GCs; the main GCs are cortisol in humans and corticosterone in rodents) are the end-products of the hypothalamus-pituitary-adrenal (HPA) axis. GCs are secreted in a circadian fashion and in a large burst following stress exposure (Joels and Baram 2009; Kirschbaum and Hellhammer 1994). Apart from their major role in the physiological and behavioral response to stress, GCs are potent modulators of learning and memory. Their effects, differing in direction and strength, are highly timing dependent. When

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secreted following a learning task or shortly prior to it, they tend to enhance the memory for the associated event, i.e., enhance its consolidation (de Kloet et al. 1999; Roozendaal 2002). When secreted after the conclusion of the learning task, they tend to lead to the opposite effect, i.e., impair memory retrieval (de Quervain et al. 2009). The enhanced consolidation of emotional (compared with neutral) events, resulting from GC activation (together with noradrenergic activity) is a highly adaptive mechanism, yet in most cases even emotional memories tend to subside and weaken over time. In several psychiatric disorders, such as post-traumatic stress disorder (PTSD) and anxiety disorders (such as phobias), in contrast, fear memories remain robust even months and years after the experience had taken place. This leads to clinical symptoms, such as intrusions, re-experiencing and fear (de Quervain et al. 2009; Pitman 1989; Rombold et al. 2015; Yehuda 2002; Yehuda and LeDoux 2007). Relapse (also termed "return of fear") is substantial following traditional extinction-based therapies (e.g., exposure therapy) used for treating anxiety disorders and PTSD (Craske 1999). It might occur either spontaneously (spontaneous recovery) (Rescorla 2004), following contextual change (renewal) (Bouton and King 1983) or after exposure to the original (or different) stressor (Rescorla and Heth 1975).

The fate of a memory trace is more flexible than once thought. While the traditional view on memory suggested that memory consolidation is a one-time event, completed shortly after acquisition (McGaugh 1966), Misanin et al. (1968) demonstrated that memory reactivation (i.e., retrieval) can cause the memory to re-enter a transient labile state until its re-stabilization (reconsolidation) is completed. The reactivation-dependent lability period, lasting from several minutes until approximately 6 h post-retrieval (Kindt et al. 2009; Schiller and Delgado 2010), was later suggested to serve as an adaptive update mechanism allowing weakening, modification, or strengthening of memories (Alberini 2011; Alberini and LeDoux 2013; Forcato et al. 2014). In contrast to traditional extinction methods, in which a new "safe" memory is created leaving the original memory unaffected (Bouton 2002, 2004), reconsolidation-based manipulations target the original memory and might thus be able to prevent relapse (Nader et al. 2000; Schiller et al. 2010; Soeter and Kindt 2015). Various pharmacological agents were found to affect memory reconsolidation, by doing so revealing the processes involved in memory formation and modulation after retrieval. To name but a few, Nader et al. (2000) demonstrated that reconsolidation is a protein-synthesis-dependent process by using post-retrieval protein synthesis inbibitors, while Kindt et al. (2009) and Soeter and Kindt (2015), using noradrenergic β-blockers, showed that noradrenergic activity is crucial for the reconsolidation of emotional memories. Reconsolidation enhancement might be a mechanism underlying the persistence of emotional memories. Recently (Meir Drexler et al. 2015), this process was suggested to be modulated by cortisol.

The possible influence of GCs on memory reconsolidation has been investigated only in the last few years. Akirav and Maroun (2013) have recently provided a review of the different, sometimes conflicting, effects of stress and GCs on memory reconsolidation. Several animal studies suggest an impairing effect of either behavioral stress (leading to the secretion of GCs, noradrenaline and other stress modulators) or GC administration on the reconsolidation of reactivated memories (Abrari et al. 2008; Amiri et al. 2015; Yang et al. 2013). However, both GC receptor agonists (Abrari et al. 2008; Cai et al. 2006) and antagonists (Nikzad et al. 2011; Pitman et al. 2011) were shown to impair reactivated memories. The human literature have mainly focused on the effects of psychosocial stress, as opposed to cortisol administration, on reactivated declarative memories. The studies demonstrated either an impairing (Zhao et al. 2009) or enhancing (Bos et al. 2014; Coccoz et al. 2011) effect of stress on memory reconsolidation. Therefore, they could not offer a clear conclusion as well. In a recent study (Meir Drexler et al. 2015), we demonstrated an enhancing effect of cortisol administration on the reconsolidation of reactivated fear memories in men. Using the fear conditioning paradigm in a 3-day reconsolidation design, we could show a specific enhancement of the return of fear (i.e., more robust reinstatement) of a memory that was reactivated under high cortisol concentrations. The effect was highly specific, enhancing the reconsolidation of the reactivated (but not the non-reactivated) memory. This is in line with previous studies that could show an enhancing effect of naturalistic stress on reactivated declarative memories (Coccoz et al. 2011; Coccoz et al. 2013). These results indicate a similarity in mechanism between reconsolidation after retrieval and initial consolidation, which is also enhanced by GC administration or stress exposure (de Kloet et al. 1999; Roozendaal 2002). In addition, these findings suggest a mechanism for emotional memory persistence. Repeated spontaneous reactivations occurring in the presence of elevated cortisol concentrations could lead to reconsolidation enhancement, keeping the fear memories lasting and robust, as seen in anxiety disorders and PTSD. The study, however, was conducted only in men. The results can therefore not be generalized to women.

Vulnerability and resistance to PTSD and anxiety disorders are highly dependent on individual differences (Yehuda 2004; Yehuda and LeDoux 2007), such as life history, personality traits, and sex. Sex differences are apparent in the higher prevalence of anxiety disorders and PTSD in women compared with men (Kessler et al. 2005) as well as in emotional learning patterns in healthy participants (Cahill et al. 2003). They may become hard wired during early brain development, but they

apparently also depend on sex hormones and their alternation during the female's menstrual cycle (Ferree et al. 2011; Milad et al. 2009, 2010; Zeidan et al. 2011) or following the intake of hormonal contraceptives (Ferree et al. 2012; Merz et al. 2012). Even though males and females may respond differently to emotional or stressful tasks (Otte et al. 2005), the majority of subjects are male animals (Beery and Zucker 2011) and human males (Soldin and Mattison 2009). Indeed, the hormonal state of the female requires multiplying the number of participants per experiment and so males are often chosen for pragmatic reasons. Nonetheless, a better understanding of the biological significance of sex hormones for mental health and disease is crucial (ter Horst et al. 2012). Of particular interest are the possible influences of the oral contraceptives (OC). With almost 200 million world-wide female users from the time of the first clinical trials until present day, OC are one of the most widely consumed classes of drugs in the world (Chadwick et al. 2012), yet their long-term consequences on human cognition remain largely unknown. Recent evidence has shown that OC use might alter the effects of cortisol on fear learning (Merz et al. 2012) and memory retrieval (Kuhlmann and Wolf 2005). This suggests an interaction between OC use and cortisol treatment on fear conditioning, which is a model for anxiety disorders and PTSD (Cordero et al. 2002; Yehuda and Antelman 1993). Considering the higher vulnerability of women to stress-related disorders, investigating the effects of cortisol on fear memory reconsolidation in females is of great importance for both theory and treatment.

In the current study, the effects of cortisol on the reconsolidation of fear memories were investigated in females. To examine the potential influences of OC use, both free cycling and OC users were tested. Based on our previous results in men (Meir Drexler et al. 2015), we expected a specific enhancing effect of cortisol administration on the reactivated fear memory. As the knowledge on sex differences and OC use effects on memory reconsolidation is lacking, OC use within the female sample was taken as an additional factor and examined in an exploratory manner.

Materials and methods

The study was based on the design of Meir Drexler et al. (2015). A fear memory, which was created on the first day, was reactivated on the second day following systemic cortisol administration in the target group. One control group was given the cortisol treatment without reactivation, while the other control group participated in the reactivation session following placebo intake. On the third day, the return of fear following reinstatement was tested. Skin conductance response (SCR), serving as a measure of conditioned response (CR), was sampled during acquisition, extinction, and return of fear (i.e., reinstatement) test. Saliva samples were collected during the three experimental days for cortisol analysis.

Participants

Seventy-two healthy females, aged 18–34 with body mass index (BMI; weight (kg)/height^2 (m^2)) of 18–28 participated in this study. The following conditions comprised the exclusion criteria: smoking, somatic or endocrine disease, history of psychiatric/neurological disorders, and regular medication intake other than hormonal contraceptives. An additional, SCR-based, exclusion criterion was used following acquisition (see below). The participants were recruited via announcements on the campus of the Ruhr-University Bochum, Germany. The participants 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.

Experimental groups

The participants were randomly assigned to one of three groups: reactivation + cortisol (RE + CORT), reactivation + placebo (RE), or no reactivation + cortisol (CORT). The experimental procedure differed only on day 2.

Alternation in sex hormone concentrations following the intake of oral contraceptives was shown to influence emotional learning (Milad et al. 2009) and its cortisol-dependent modulation (Merz et al. 2012). Therefore, we collected data on OC intake. 58.3 % of the participants were free cycling (based on self-report on the last menstruation, 27.8 % were in the luteal phase and 30.6 % in the follicular phase) and 41.7 % were regularly taking hormonal contraceptives. The factor "OC use" (OC for oral contraceptive users, FC for free cycling females) was used as an additional factor for all the following analyses. Despite possible influence of the menstrual phase on emotional learning (Ferree et al. 2011; Milad et al. 2010), the FC females were not further divided (i.e., to luteal and follicular phases) due to the limited participants number.

Conditioning procedure

The experimental procedure consisted of three testing days. A 24-h intervals were inserted between the testing days to allow the memory to consolidate following the learning phases (Dudai 2004). This typical 3-day reconsolidation design was used in our previous study in men (Meir Drexler et al. 2015) as an adaptation to other reconsolidation studies that used pharmacological manipulations (Kindt et al. 2009). On the first day, the participants were conditioned to two (out of three) stimuli. On the second day, a pharmacological manipulation (cortisol/placebo administration) was followed by reactivation (or no reactivation) of one conditioned stimulus. On the third day, the return of extinguished fear following reinstatement

was tested for all stimuli. The procedure was identical for the groups on days 1 and 3 and differed only on day 2 (reactivation/no reactivation following cortisol/placebo intake). The experimental timeline is displayed in Fig. 1.

Day 1: acquisition The participants were instructed to pay attention to possible CS-UCS contingencies and memorize them. For acquisition, two conditioned stimuli (CS1+, CS2+) were reinforced in 9 out of 13 presentations (partial reinforcement rate of approximately 70 %) with an unconditioned stimulus (UCS; electric shock). One CS (CS−) was never reinforced. The partial reinforcement rate was used to prevent rapid extinction on day 3 (Schiller et al. 2010). Each of the three CS was presented (for 4 s each) 13 times in a pseudorandomized order with an intertrial interval (ITI) of 10–12 s.

Day 2: pharmacological treatment and memory reactivation The participants received either cortisol (i.e., hydrocortisone; RE + CORT, CORT groups) or placebo (RE group) and were given a 30-min break to allow a peak in cortisol plasma concentrations. During the break, they remained in the experimental room and were given reading material. To induce the prediction error needed for triggering reconsolidation processes (Sevenster et al. 2012), the participants from the reactivation groups (RE + CORT, RE groups) were then 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 the previously reinforced stimulus, CS1+ was then presented once (4 s, unreinforced). This concluded the learning phase for that day. Participants from the no-reactivation condition (CORT group) received no intervention other than pill intake but remained in the experimental room for the same amount of time (approximately 45 min) as the participants from the reactivation groups.

Day 3: extinction, reinstatement, and reinstatement test For extinction, all three stimuli (CS1+, CS2+, CS−) were presented (4 s, 10 times each, ITI: 10–12 s), unreinforced, starting either with CS1+, CS2+, or CS− (pseudorandomized). After the conclusion of extinction, reinstatement was triggered by four unsignaled UCS presentations (ITI: 10–12 s). The reinstatement test, consisting of unreinforced presentations of each of the three stimuli (4 s, 10 times each, pseudorandomized order; ITI: 10–12 s) concluded the conditioning procedure.

Stimuli

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

Unconditioned stimulus An electric shock co-terminating with the CS+ on reinforced trials served as UCS. The transcutaneous electrical stimulation (100 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). UCS adjustment was performed individually for each participant to ensure a subjectively "uncomfortable but not painful" shock level.

Pharmacological intervention

On day 2, the participants received an oral dose of either 30 mg cortisol (3 pills of hydrocortisone 10 mg; Jenepharm)

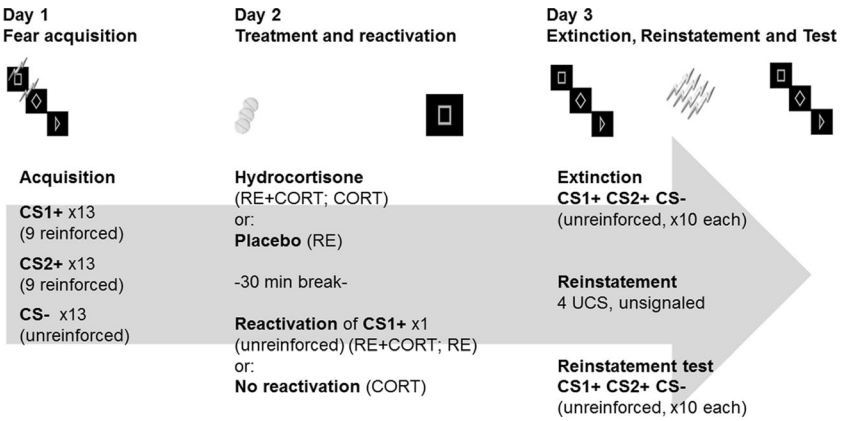

Fig. 1 Experimental timeline. Three testing days (separated by 24-h intervals) comprised the experimental procedure: fear acquisition on day 1; pharmacological treatment and memory reactivation on day 2; and extinction, reinstatement, and reinstatement test on day 3. The procedure was identical for the groups on days 1 and 3 and differed only on day 2 (reactivation/no reactivation following hydrocortisone/placebo intake). Skin conductance response (*SCR*) were recorded during the acquisition, extinction, and reinstatement test phases. *CS* conditioned stimulus, *UCS* unconditioned stimulus

or a visually identical placebo (3 pills of P Tabletten Weiss 7 mm, Winthrop). This dosage was chosen based on previous studies on the effects of cortisol on affective and cognitive processes (Kukolja et al. 2008; Merz et al. 2012).

Saliva sampling

Free salivary cortisol concentrations served to validate the pharmacological treatment. Saliva samples were taken at 7 time points during the three experimental days. On days 1 and 3, samples were collected at the beginning and end of the testing session. On day 2, samples were collected before pill intake, 30 min (immediately before memory reactivation) and 45 min after pill intake. Salivette collection devices (Sarstedt, Nuembrecht, Germany) were used for saliva collection. 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 %.

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). The electrodes were 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 (sampling rate, 1000 Hz). The maximal base-to-peak difference in SCR during 1–4.5 s after CS onset was taken as a measure of CR in acquisition, extinction, and reinstatement test. The data were transformed with the natural logarithm to attain a natural distribution.

Statistical analyses

All statistical analyses (apart from power analysis) were performed using IBM SPSS Statistics for Windows 22.0. The statistical significance level was set to $\alpha = .05$. Greenhouse-Geisser corrected P values were used if assumptions of sphericity were violated. Power analysis was performed using G*Power for Windows 3.1.9.2.

SCR exclusion criteria

SCR was the main dependent variable used in this study. Therefore, only participants who showed a measureable SCR to the two CS+ during the acquisition phase were included. Three participants with a maximal SCR response lower <0.01 (ln 1 + μS) to either CS1+ or CS2+ were excluded. In addition, to ensure equivalent acquisition for both CS+, only participants who showed differential SCR response to each of the CS+ compared with the CS− were included. The exclusion criterion was based on the differential SCR (mean SCR to the CS− subtracted from mean SCR to each of the CS+). Two participants who showed a differential SCR lower than 1.5 interquartile ranges below the lower quartile to either CS1+ or CS2+ in either the beginning (trials 1–6) or end (trials 7–13) of acquisition were excluded.

The following analyses thus include 67 participants (39 FC females, 28 OC females) in three experimental groups: RE + CORT ($N = 22$; of which FC = 13, OC = 9), RE ($N = 22$; of which FC = 12, OC = 10), and CORT ($N = 23$; of which FC = 14, OC = 9).

Results

Cortisol concentrations

The cortisol analyses confirmed a successful pharmacological treatment. Analysis of variance (ANOVA) with the within-subject factor Time (baseline, 30 min, 45 min after treatment) and the between-subject factors group (RE + CORT, RE, CORT) and OC use (FC, OC) was conducted to confirm a higher free salivary cortisol concentrations on day 2 following the intake of hydrocortisone in the cortisol groups (RE + CORT and CORT) compared with the placebo group (RE). The analysis revealed a time × group interaction ($F_{2.65,\ 79.53} = 23.61$, $P \leq .001$). Bonferroni post hoc comparisons revealed that the cortisol concentrations were significantly higher 30 and 45 min after treatment compared with baseline in both cortisol groups. In the placebo group, cortisol concentrations were significantly lower at 30 and 45 min after pill intake. No significant interactions with group were found on either day 1 or 3; no interaction with OC use was found in any of the 3 days (all $P > .05$). These results confirm a temporary rise in cortisol concentrations following hydrocortisone (and not placebo) intake and indicate no influence of OC use on the pharmacological treatment. Table 1 presents the cortisol concentration values for the three testing days.

SCR

Acquisition The SCR results revealed higher SCR to both CS+ compared with the CS−. ANOVA with the within-subject factor CS (CS1+, CS2+, CS−) and the between-subject factor group and OC use revealed a significant main effect of CS ($F_{2,\ 122} = 17.39$, $P \leq .001$) for acquisition (mean 13 trials). Bonferroni post hoc comparisons showed a significantly lower SCR to CS− compared with both CS1+ and CS2+ and no significant difference between CS1+ and CS2+. No significant interactions with either group or OC use were

Table 1 Cortisol concentrations

Cortisol (nmol/l)	RE + CORT	RE	CORT	*P* values
Day 1 (before testing)	18.00 ± 8.70	23.47 ± 13.24	19.94 ± 13.19	.317
Day 1 (after testing)	13.85 ± 6.61	18.60 ± 11.76	16.27 ± 10.49	.358
Day 2 (baseline)	18.10 ± 8.51	21.55 ± 12.46	17.79 ± 10.60	.305
Day 2 (30 min post-treatment)	271.00 ± 173.01	18.05 ± 8.07 **	308.91 ± 171.43	≤.001
Day 2 (45 min post-treatment)	225.89 ± 139.09	16.01 ± 7.03 **	247.79 ± 173.80	≤.001
Day 3 (before testing)	13.35 ± 8.35	19.73 ± 10.65	15.39 ± 8.84	.080
Day 3 (after testing)	12.14 ± 8.29	16.14 ± 8.35	12.63 ± 7.20	.222

Data represents mean ± standard deviation (*SD*). *P* values of ANOVAs regarding potential differences between the groups are given. ** Significant difference ($p \leq .001$) between the placebo (RE) and the cortisol groups RE + CORT and CORT

found (all $P > .05$). The results confirm a successful fear acquisition for the reinforced CS+ in all groups (see Fig. 2).

Extinction The higher response to the two previously reinforced stimuli, seen in the first block of extinction, subsided following unreinforced extinction trials and by the last block of extinction no significant differences between the stimuli were seen. To confirm fear retrieval at the first block of extinction (mean trials 1–2), SCR to the three CS were tested using ANOVA with the within-subject factor CS and the between-subject factor group and OC use. A significant effect of CS ($F_{2,\ 122} = 12.26$, $P \leq .001$) with no interaction with group or OC use was found. Bonferroni post hoc comparisons revealed significant differences between each of the reinforced stimuli and CS− and no difference between CS1+ and CS2+, indicating a successful retrieval of the fear memory in all groups. To confirm extinction, the SCR to each of the three CS in the first extinction block was compared with the last extinction block (mean trials 9–10). ANOVA with the within-subject factor CS and time (first block, last block) and the between-subject factors group and OC use revealed a main effect of CS ($F_{2,\ 122} = 8.06$, $P \leq .001$). Bonferroni post hoc comparisons revealed a significantly lower SCR to CS− compared with both CS1+ and CS2+ and no significant difference between CS1+ and CS2+. However, a main effect of time ($F_{1,\ 61} = 26.19$, $P \leq .001$) was found, demonstrating an overall reduction in the SCR response to all CS, with no significant interactions with either group or OC use. Indeed, using ANOVA with the within-subjects factor CS and the between-subject factors group and OC use to compare the response to the different CS on the last block, a main effect of CS was found ($F_{2,\ 122} = 3.18$, $P = .045$) but no significant differences between the CS could be seen using Bonferroni post hoc comparisons. No interactions with group or OC use were found (all $P > .05$) at this phase as well. The results, displayed in Fig. 3, indicate a successful extinction of the CS+ in all groups.

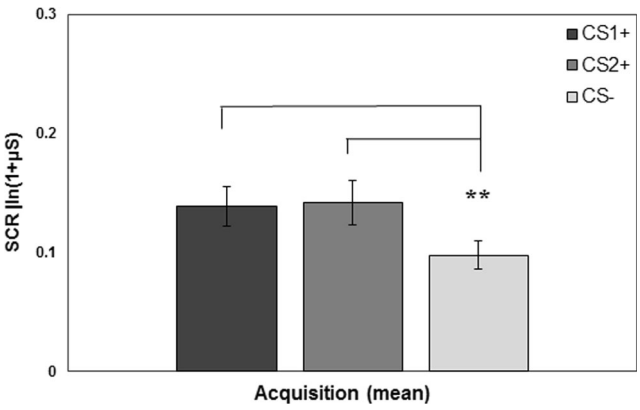

Fig. 2 Day 1: fear acquisition. The skin conductance response (*SCR*; mean 13 trials) to the reinforced CS1+ and CS2+ is significantly higher than the SCR to the unreinforced CS− (with no difference between the two reinforced stimuli) demonstrating a successful fear acquisition. As no interaction with group was found, the graph presents all three groups combined. *Error bars* represent SEM. $^{**}P \leq .001$. *CS* conditioned stimulus

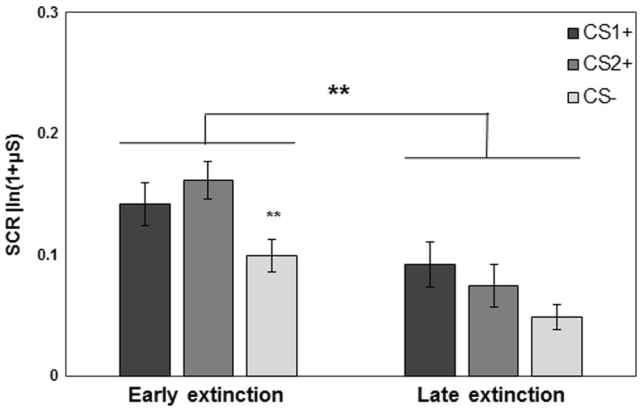

Fig. 3 Day 3: fear extinction. This graph presents the skin conductance response (*SCR*) to each conditioned stimulus (*CS*) at early extinction (trials 1–2) vs. late extinction (trials 9–10) in all groups (combined). The significant effect of CS in early extinction indicates that fear for the conditioned stimuli CS1+ and CS2+ was retrieved. The significant effect of time with no group interaction and the lack of significant difference between the stimuli at late extinction confirm that extinction was successful in all groups. *Error bars* represent SEM. $^{**}P \leq .001$

Reinstatement test The reinstatement test showed no differences in reinstatement of the stimuli in the target group. The return of conditioned fear after reinstatement was tested using a reinstatement index which was modified from Meir Drexler et al. (2015). The reinstatement index was calculated for each of the CS by subtracting SCR in the last block of extinction (mean trials 9–10) from SCR in the first block (mean trials 1–2) after reinstatement (reinstatement index = first reinstatement test block − last extinction block). A one-sample *t* test confirmed that the reinstatement index was significantly larger than 0 for CS1+ (t_{66} = 2.06, $P \leq .005$; M = 0.04, SD = 0.17), CS2+ (t_{66} = 2.78, $P \leq .005$; M = 0.05, SD = 0.14), and CS− (t_{66} = 2.02, $P \leq .005$; M = 0.03, SD = 0.13), indicating a general reinstatement for all stimuli. ANOVA with the within-subject factor CS and the between-subject factor group and OC use showed no significant effects of CS or interactions with group or OC use on the reinstatement index (all $P > .05$). Thus, in contrast to the hypothesis, the results could not show an effect of cortisol on the strength of the reactivated fear memory. The results are presented in Fig. 4.

Power analysis In our previous study in men (Meir Drexler et al. 2015), the interaction CS × group revealed a significant higher reinstatement for the reactivated stimulus CS1+ in the target group RE + CORT. The interaction effect was found to be medium (CS × group interaction in the male sample corresponded to an effect size *f* of 0.39). We calculated the power to find a similar interaction effect in the entire female sample and in the two female groups (FC, OC) separately. The power of the entire female sample ($N = 67$) to detect a medium interaction effect was larger than 99 %. When separated into subgroups, the power of the FC sample ($N = 39$) was found to be larger than 90 % while the power of the OC sample ($N = 28$) was approximately 80 %.

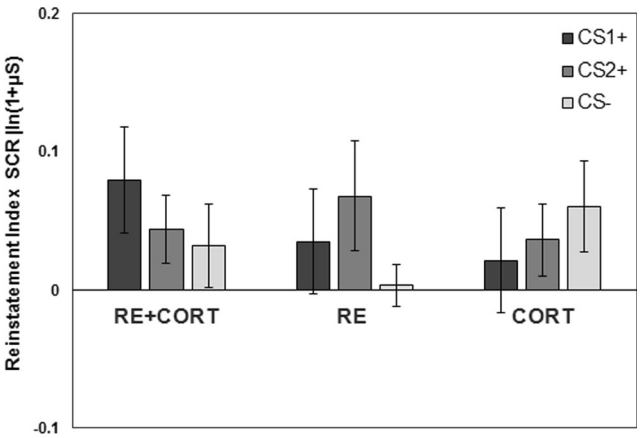

Fig. 4 Day 3: reinstatement. Reinstatement index (=first reinstatement test block − last extinction block) was calculated for each CS. No effects of CS or interaction with group were found (all $P > .05$). Therefore, no effect of cortisol on the strength of the reactivated fear memory could be demonstrated. *CS* conditioned stimulus, *SCR* skin conductance response

Discussion

This study aimed to investigate the effects of cortisol on the reconsolidation of fear memories in women. Using a 3-day reconsolidation design, acquired fear memories were reactivated following the intake of cortisol, extinguished and tested for reinstatement. Based on previous findings in men (Meir Drexler et al. 2015), we predicted an enhancing effect of cortisol (i.e., a more robust reinstatement) specifically on the reactivated memory. Potential effects of OC use were tested in an exploratory manner.

Acquisition, reactivation, and extinction

The results confirmed that fear was successfully acquired and extinguished in all groups with no effect of OC use. As the paradigm included three stimuli, an SCR exclusion criteria was employed to ensure an equivalent fear conditioning to the two reinforced stimuli prior to the reactivation and manipulation of one of them (Meir Drexler et al. 2015; Schiller et al. 2010). Indeed, the fear acquisition results showed a successful fear conditioning to the two reinforced stimuli compared with the unreinforced stimulus with no baseline difference between the experimental groups. On the second day, the memory was reactivated. The induction of a memory reconsolidation effect depends on a prior destabilization of the memory. To trigger reconsolidation processes, a prediction error (Sevenster et al. 2012; Sevenster et al. 2013) was evoked using a single unreinforced presentation of the stimulus (Merlo et al. 2014). To investigate the specificity of the reconsolidation effect, for the reactivation session we presented a single unreinforced CS1+. On the third day, SCR results indicated a reduction in the conditioned fear to the previously reinforced stimuli following the unreinforced extinction trials in all groups. The lack of group differences in extinction is in line with previous findings (Meir Drexler et al. 2015). In addition, the results showed no effect of OC use on either acquisition or extinction. Even though differences in emotional learning are expected between OC and FC females, in extinction in particular (Ferree et al. 2011; Milad et al. 2009; Milad et al. 2010), the lack of effect might be related to paradigm differences as extinction learning here was conducted after the reactivation manipulation.

Return of fear

The main hypothesis predicted an enhancing effect of cortisol on the reconsolidation of the reactivated fear memory. More specifically, a higher reinstatement test index was predicted for the target stimulus CS1+ (reactivated following cortisol intake) compared with the other two stimuli in the target group RE + CORT. The results showed no group differences or interactions in the reinstatement of the three CS in any of the groups. In addition, OC use showed no significant effect.

Lack of effect

Replication failures or lack of reconsolidation effects following either behavioral (Golkar et al. 2012; Kindt and Soeter 2013; Meir Drexler et al. 2014) or pharmacological (Tollenaar et al. 2009) manipulations are not rare. With regard to GC effects, two studies in the recent years have reported no effect of either cortisol (Tollenaar et al. 2009) or the GC antagonist mifepristone (Wood et al. 2015) on the reconsolidation of reactivated emotional memories. Memory reconsolidation does not occur each and every time when a memory trace is retrieved. Triggering memory reconsolidation is thought to be dependent on specific parameters, collectively termed boundary conditions. Among the boundary conditions are memory-related factors (e.g., memory type, age, and strength) and reactivation-related factors (i.e., the various factors affecting the degree of memory destabilization) (Akirav and Maroun 2013; Debiec et al. 2002; Sevenster et al. 2013; Suzuki et al. 2004). Any of these factors could have led to lack of reconsolidation effect in the above studies. Moreover, an independent marker for a successful memory reactivation is not available. Often, the appropriate conditions under which a retrieved memory becomes labile can only be inferred in retrospect once a reconsolidation effect had been found. This further demonstrates the sensitivity of post-reactivation manipulations to methodological alternations. However, as the current study was identical in methodology and design to our previous study in men (Meir Drexler et al. 2015), and in contrast showed no effect, sex differences, as opposed to methodological factors, could provide a possible explanation.

Sex differences

The literature on sex difference in learning and its modulation through cortisol is often mixed. For instance, Zorawski et al. (2005) reported no sex differences in fear conditioning; Guimaraes et al. (1991) reported elevated conditioned response in women compared with men while Milad et al. (2006) reported the opposite finding (i.e., higher response in men). Sex differences are also seen in non-aversive tasks. Wiemers and Wolf (2015) demonstrated a cortisol-dependent broadening of memory of a non-aversive episode in males but not females. These conflicting results can be explained by the lack of control for the menstrual cycle phase and the inclusion of unknown number of OC users in the same sample together with free cycling women (Ferree et al. 2011, 2012; Milad et al. 2010). In the current study, even though OC use was controlled for, the sample was not further divided according to menstrual phases. Our power analysis showed that the power of the entire female sample was sufficient to detect a medium interaction effect similar to the one seen in males, but dividing the female group into two subgroups (39 FC females, 28 OC females, each divided into three experimental groups) lowers the statistical power in each subgroup. Thus, even though a potential lack of power appears not to be a major concern for the entire sample, the division to subgroups based on hormonal status slightly lowers the statistical power, for the smaller OC group in particular. In addition, the lack of control for the cycle phase could be a possible confound in the design. Considering the effects of alternating levels of sex hormones on emotional learning during the menstrual cycle, such a division could be necessary. Some studies that controlled the menstrual cycle phase have indeed demonstrated sex differences in emotional learning (Ferree et al. 2011; Hwang et al. 2015; Maeng and Milad 2015; Zeidan et al. 2011; for a recent review, see, Merz and Wolf 2015).

During the early follicular phase, estrogen and progesterone concentrations are at their lowest levels. At the late follicular phase, estrogen concentrations rise, while progesterone concentrations remain relatively low (Milad et al. 2006). Hormonal contraceptives, which inhibit ovulation, lead to low levels of natural estradiol and progesterone (Likis 2002). Milad et al. (2010) have demonstrated an association between the natural fluctuations of sex hormones (estradiol in particular) and emotional learning. Elevated estradiol concentrations enhance extinction recall in humans (Milad et al. 2010) and enhance the formation of extinction memory in rodents (Milad et al. 2009). Progesterone was found to have similar anxiolytic effect in rodents (Milad et al. 2009) but not in humans (Milad et al. 2010). In addition to differences in emotional learning, the menstrual cycle influences HPA reactivity. While women in the luteal phase have comparable cortisol stress response to men, women in the follicular phase and women using OC show a lower increase. Elevated levels of corticosteroid-binding globulin may account for the blunted cortisol response in OC women or during the follicular phase (Kirschbaum et al. 1999). The menstrual cycle is also related to alternations in the negative feedback regulation of the HPA, with reduced feedback sensitivity during high estradiol and progesterone levels (Altemus et al. 1997). Cortisol-dependent modulation of learning and memory can thus differ during the menstrual cycle and following OC intake. For instance, Merz et al. (2012) demonstrated that while cortisol reduces fear learning in males and FC females, it enhanced the learning in OC users. Due to reduced sensitivity of the brain to acute cortisol elevations, OC females show no effects of cortisol on memory retrieval (Kuhlmann and Wolf 2005).

Practical reasons such as group size are one argument for the preference of males as subjects in neuroscience studies. Yet the complex interactions between sex, sex hormones, and emotional learning, which make these studies so challenging, are themselves the reason for their necessity. A better understanding of the role of sex hormones and OC use in mental health and disease is crucial and will allow the development of personalized and more efficient pharmacological and behavioral treatments (Cahill 2012; Ferree et al. 2011, 2012).

Implications

Memory reconsolidation shares similar mechanisms with initial memory consolidation. Protein synthesis inhibitors impair both reconsolidation (Nader et al. 2000) and initial memory consolidation (Kandel 2001), demonstrating that both processes depend on protein synthesis. Blocking noradrenergic β-receptors have the same impairing effect on both reconsolidation (Kindt et al. 2009) and consolidation (Cahill et al. 1994), thus revealing the key role of noradrenergic activity in the formation and maintenance of strong emotional memories. In a previous study (Meir Drexler et al. 2015), we demonstrated that high cortisol concentrations following a pharmacological treatment enhance the reconsolidation of reactivated fear memories in healthy human males. The cortisol-dependent reconsolidation enhancement resembles the enhancing effect of cortisol on initial consolidation (Joels 2006; Roozendaal 2002). The effect was suggested as a potential mechanism underlying the persistence of fear memories. The initial robustness of aversive memories results from the activity of stress hormones, including cortisol, following a highly stressful event (Pitman 1989), leading to enhanced consolidation. Spontaneous retrievals (e.g., intrusive thoughts, nightmares, flashbacks) are common in stress-related disorders (de Quervain et al. 2009; de Quervain and Margraf 2008) following the event. Repeated memory reactivations, occurring during elevated cortisol levels, may thus lead to an enhanced reconsolidation and to further strengthening of the fear memory in PTSD and anxiety disorders. Whether this suggested mechanism exists in women and its possible interactions with sex hormones are yet to be investigated. As women are more vulnerable than men to anxiety disorders and PTSD (Ferree et al. 2011, 2012; Kessler et al. 2005), further studies are needed.

Conclusion

In this study, we investigated the effects of cortisol on the reconsolidation of reactivated fear memories in women. In contrast to our previous study which was conducted in men and revealed a specific enhancing effect of cortisol on fear memory reconsolidation, no significant difference in reinstatement of the three CS was found following the reactivation manipulation. In addition, no significant effect or interactions with any of the learning phases were related to either hormonal contraceptive use or free cycling. The lack of a reconsolidation effect might be a result of sex differences, e.g., due to alternating concentrations of sex hormones during the menstrual cycle or following OC use. Future studies could examine this by testing women of different hormonal status (luteal, follicular phases, or users of various OC types) using groups of sufficient sizes. Considering the higher vulnerability of women to anxiety disorders and PTSD, further investigations of the effects of cortisol on fear memory reconsolidation in females are of great importance for both theory and treatment.

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Compliance with ethical standards

Conflict of interests The authors declare no competing financial interests.

References

Abrari K, Rashidy-Pour A, Semnanian S, Fathollahi Y (2008) Administration of corticosterone after memory reactivation disrupts subsequent retrieval of a contextual conditioned fear memory: dependence upon training intensity. Neurobiol Learn Mem 89:178–184

Akirav I, Maroun M (2013) Stress modulation of reconsolidation. Psychopharmacology (Berl) 226:747–761

Alberini CM (2011) The role of reconsolidation and the dynamic process of long-term memory formation and storage. Front Behav Neurosci 5

Alberini CM, LeDoux JE (2013) Memory reconsolidation. Curr Biol 23: R746–R750

Altemus M, Redwine L, Leong YM, Yoshikawa T, Yehuda R, Detera-Wadleigh S et al (1997) Reduced sensitivity to glucocorticoid feedback and reduced glucocorticoid receptor mRNA expression in the luteal phase of the menstrual cycle. Neuropsychopharmacology 17:100–109

Amiri S, Jafarian Z, Vafaei AA, Motaghed-Larijani Z, Samaei SA, Rashidy-Pour A (2015) Glucocorticoids inteact with cholinergic system in impairing memory reconsolidation of an inhibitory avoidance task in mice. Basic Clin Neurosci 6:155–162

Beery AK, Zucker I (2011) Sex bias in neuroscience and biomedical research. Neurosci Biobehav Rev 35:565–572

Bos MGN, Schuijer J, Lodestijn F, Beckers T, Kindt M (2014) Stress enhances reconsolidation of declarative memory. Psychoneuroendocrinology

Bouton ME (2002) Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol Psychiatry 52:976–986

Bouton ME (2004) Context and behavioral processes in extinction. Learn Mem 11:485–494

Bouton ME, King DA (1983) Contextual control of the extinction of conditioned fear—tests for the associative value of the context. J Exp Psychol-Anim Behav Process 9:248–265

Cahill L (2012) A half-truth is a whole lie: on the necessity of investigating sex influences on the brain. Endocrinology 153:2541–2543

Cahill L, Prins B, Weber M, McGaugh JL (1994) Beta-adrenergic activation and memory for emotional events. Nature 371:702–704

Cahill L, Gorski L, Le K (2003) Enhanced human memory consolidation with post-learning stress: interaction with the degree of arousal at encoding. Learn Mem 10:270–274

Cai WH, Blundell J, Han J, Greene RW, Powell CM (2006) Postreactivation glucocorticoids impair recall of established fear memory. J Neurosci 26:9560–9566

Chadwick KD, Burkman RT, Tornesi BM, Mahadevan B (2012) Fifty years of "the pill": risk reduction and discovery of benefits beyond contraception, reflections, and forecast. Toxicol Sci 125:2–9

Coccoz V, Maldonado H, Delorenzi A (2011) The enhancement of reconsolidation with a naturalistic mild stressor improves the expression of a declarative memory in humans. Neuroscience 185:61–72

Coccoz V, Sandoval AV, Stehberg J, Delorenzi A (2013) The temporal dynamics of enhancing a human declarative memory during reconsolidation. Neuroscience 246:397–408

Cordero MI, Kruyt ND, Merino JJ, Sandi C (2002) Glucocorticoid involvement in memory formation in a rat model for traumatic memory. Stress 5:73–79

Craske M (1999) Anxiety disorders: psychological approaches to theory and treatment. Westview Press, Boulder

de Kloet ER, Oitzl MS, Joels M (1999) Stress and cognition: are corticosteroids good or bad guys? Trends Neurosci 22:422–426

de Quervain DJ, Margraf J (2008) Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: a novel therapeutic approach. Eur J Pharmacol 583:365–371

de Quervain DJ, Aerni A, Schelling G, Roozendaal B (2009) Glucocorticoids and the regulation of memory in health and disease. Front Neuroendocrinol 30:358–370

Debiec J, LeDoux JE, Nader K (2002) Cellular and systems reconsolidation in the hippocampus. Neuron 36:527–538

Dudai Y (2004) The neurobiology of consolidations, or, how stable is the engram? Annu Rev Psychol 55:51–86

Ferree NK, Kamat R, Cahill L (2011) Influences of menstrual cycle position and sex hormone levels on spontaneous intrusive recollections following emotional stimuli. Conscious Cogn 20:1154–1162

Ferree NK, Wheeler M, Cahill L (2012) The influence of emergency contraception on post-traumatic stress symptoms following sexual assault. J Forensic Nurs 8:122–130

Forcato C, Fernandez RS, Pedreira ME (2014) Strengthening a consolidated memory: the key role of the reconsolidation process. J Physiol Paris 108:323–333

Golkar A, Bellander M, Olsson A, Ohman A (2012) Are fear memories erasable?-reconsolidation of learned fear with fear-relevant and fear-irrelevant stimuli. Front Behav Neurosci 6:80

Guimaraes FS, Hellewell J, Hensman R, Wang M, Deakin JFW (1991) Characterization of a psychophysiological model of classical fear conditioning in healthy-volunteers—influence of gender, instruction, personality and placebo. Psychopharmacology 104:231–236

Hwang MJ, Zsido RG, Song H, Pace-Schott EF, Miller KK, Lebron-Milad K et al (2015) Contribution of estradiol levels and hormonal contraceptives to sex differences within the fear network during fear conditioning and extinction. BMC Psychiatry 15:295

Joels M (2006) Corticosteroid effects in the brain: U-shape it. Trends Pharmacol Sci 27:244–250

Joels M, Baram TZ (2009) The neuro-symphony of stress. Nat Rev Neurosci 10:459–466

Kandel ER (2001) The molecular biology of memory storage: a dialog between genes and synapses. Biosci Rep 21:565–611

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication (vol 62, pg 593, 2005). Arch Gen Psychiatr 62:768

Kindt M, Soeter M (2013) Reconsolidation in a human fear conditioning study: a test of extinction as updating mechanism. Biol Psychol 92:43–50

Kindt M, Soeter M, Vervliet B (2009) Beyond extinction: erasing human fear responses and preventing the return of fear. Nat Neurosci 12:256–258

Kirschbaum C, Hellhammer DH (1994) Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 19:313–333

Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Hellhammer DH (1999) Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosom Med 61:154–162

Kuhlmann S, Wolf OT (2005) Cortisol and memory retrieval in women: influence of menstrual cycle and oral contraceptives. Psychopharmacology (Berl) 183:65–71

Kukolja J, Schlapfer TE, Keysers C, Klingmuller D, Maier W, Fink GR et al (2008) Modeling a negative response bias in the human amygdala by noradrenergic-glucocorticoid interactions. J Neurosci 28:12868–12876

Likis FE (2002) Contraceptive applications of estrogen. J Midwifery Womens Health 47:139–156

Maeng LY, Milad MR (2015) Sex differences in anxiety disorders: interactions between fear, stress, and gonadal hormones. Horm Behav

McGaugh JL (1966) Time-dependent processes in memory storage. Science 153:1351–1358

Meir Drexler S, Merz CJ, Hamacher-Dang TC, Marquardt V, Fritsch N, Otto T et al (2014) Effects of postretrieval-extinction learning on return of contextually controlled cued fear. Behav Neurosci 128:474–481

Meir Drexler S, Merz CJ, Hamacher-Dang TC, Tegenthoff M, Wolf OT (2015) Effects of cortisol on reconsolidation of reactivated fear memories. Neuropsychopharmacology 40:3036–3043

Merlo E, Milton AL, Goozee ZY, Theobald DE, Everitt BJ (2014) Reconsolidation and extinction are dissociable and mutually exclusive processes: behavioral and molecular evidence. J Neurosci 34:2422–2431

Merz CJ, Wolf OT (2015) Stress and emotional learning in humans: evidence for sex differences. In: Shansky R (ed) Sex differences in the central nervous system. Elsevier, Oxford, pp 149–170

Merz CJ, Tabbert K, Schweckendiek J, Klucken T, Vaitl D, Stark R et al (2012) Oral contraceptive usage alters the effects of cortisol on implicit fear learning. Horm Behav 62:531–538

Milad MR, Goldstein JM, Orr SP, Wedig MM, Klibanski A, Pitman RK et al (2006) Fear conditioning and extinction: influence of sex and menstrual cycle in healthy humans. Biol Psychiatry 59:143S

Milad MR, Igoe SA, Lebron-Milad K, Novales JE (2009) Estrous cycle phase and gonadal hormones influence conditioned fear extinction. Neuroscience 164:887–895

Milad MR, Zeidan MA, Contero A, Pitman RK, Klibanski A, Rauch SL et al (2010) The influence of gonadal hormones on conditioned fear extinction in healthy humans. Neuroscience 168:652–658

Misanin JR, Miller RR, Lewis DJ (1968) Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. Science 160:554–555

Nader K, Schafe GE, LeDoux JE (2000) Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406:722–726

Nikzad S, Vafaei AA, Rashidy-Pour A, Haghighi S (2011) Systemic and intrahippocampal administrations of the glucocorticoid receptor antagonist RU38486 impairs fear memory reconsolidation in rats. Stress Int J Biol Stress 14:459–464

Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC (2005) A meta-analysis of cortisol response to challenge in human aging: importance of gender. Psychoneuroendocrinology 30:80–91

Pitman RK (1989) Post-traumatic stress disorder, hormones, and memory. Biol Psychiatry 26:221–223

Pitman RK, Milad MR, Igoe SA, Vangel MG, Orr SP, Tsareva A et al (2011) Systemic mifepristone blocks reconsolidation of cue-conditioned fear; propranolol prevents this effect. Behav Neurosci 125:632–638

Rescorla RA (2004) Spontaneous recovery. Learn Mem 11:501–509

Rescorla RA, Heth CD (1975) Reinstatement of fear to an extinguished conditioned stimulus. J Exp Psychol 104:88–96

Rombold F, Wingenfeld K, Renneberg B, Hellmann-Regen J, Otte C, Roepke S (2015) Does the noradrenergic system influence intrusive memories? An experimental approach with a trauma film paradigm. Psychoneuroendocrinology 61:24

Roozendaal B (2002) Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval. Neurobiol Learn Mem 78:578–595

Schiller D, Delgado MR (2010) Overlapping neural systems mediating extinction, reversal and regulation of fear. Trends Cogn Sci 14:268–276

Schiller D, Monfils MH, Raio CM, Johnson DC, LeDoux JE, Phelps EA (2010) Preventing the return of fear in humans using reconsolidation update mechanisms. Nature 463:49-U51

Sevenster D, Beckers T, Kindt M (2012) Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. Neurobiol Learn Mem 97:338–345

Sevenster D, Beckers T, Kindt M (2013) Prediction error governs pharmacologically induced amnesia for learned fear. Science 339:830–833

Soeter M, Kindt M (2015) An abrupt transformation of phobic behavior after a post-retrieval amnesic agent. Biol Psychiatry

Soldin OP, Mattison DR (2009) Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 48:143–157

Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S (2004) Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J Neurosci 24:4787–4795

Tabbert K, Merz CJ, Klucken T, Schweckendiek J, Vaitl D, Wolf OT et al (2011) Influence of contingency awareness on neural, electrodermal and evaluative responses during fear conditioning. Soc Cogn Affect Neurosci 6:495–506

ter Horst JP, de Kloet ER, Schachinger H, Oitzl MS (2012) Relevance of stress and female sex hormones for emotion and cognition. Cell Mol Neurobiol 32:725–735

Tollenaar MS, Elzinga BM, Spinhoven P, Everaerd W (2009) Psychophysiological responding to emotional memories in healthy young men after cortisol and propranolol administration. Psychopharmacology 203:793–803

Wiemers US, Wolf OT (2015) Cortisol broadens memory of a non-stressful social interaction. Psychopharmacology (Berl) 232:1727–1733

Wood NE, Rosasco ML, Suris AM, Spring JD, Marin MF, Lasko NB et al (2015) Pharmacological blockade of memory reconsolidation in posttraumatic stress disorder: three negative psychophysiological studies. Psychiatry Res 225:31–39

Yang C, Liu JF, Chai BS, Fang Q, Chai N, Zhao LY et al (2013) Stress within a restricted time window selectively affects the persistence of long-term memory. Plos One 8

Yehuda R (2002) Post-traumatic stress disorder. N Engl J Med 346:108–114

Yehuda R (2004) Risk and resilience in posttraumatic stress disorder. J Clin Psychiatry 65(Suppl 1):29–36

Yehuda R, Antelman SM (1993) Criteria for rationally evaluating animal models of posttraumatic stress disorder. Biol Psychiatry 33:479–486

Yehuda R, LeDoux J (2007) Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron 56:19–32

Zeidan MA, Igoe SA, Linnman C, Vitalo A, Levine JB, Klibanski A et al (2011) Estradiol modulates medial prefrontal cortex and amygdala activity during fear extinction in women and female rats. Biol Psychiatry 70:920–927

Zhao LY, Zhang XL, Shi J, Epstein D, Lu L (2009) Psychosocial stress after reactivation of drug-related memory impairs later recall in abstinent heroin addicts. Psychopharmacology 203:599–608

Zorawski M, Cook CA, Kuhn CM, LaBar KS (2005) Sex, stress, and fear: individual differences in conditioned learning. Cogn Affect Behav Neurosci 5:191–201