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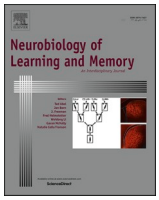

Cortisol decreases activation in extinction related brain areas resulting in an impaired recall of context-dependent extinction memory

Alina Nostadt [a,*], Christian J. Merz [b], Oliver T. Wolf [b], Martin Tegenthoff [a], Silke Lissek [a]

[a] BG University Hospital Bergmannsheil, Department of Neurology, Ruhr University Bochum, Germany
[b] Department of Cognitive Psychology, Faculty of Psychology, Ruhr University Bochum, Germany

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ABSTRACT

Conditioned responding gradually stops during successful extinction learning. The renewal effect is defined as the recovery of a extinguished conditioned response when the context of extinction is different from acquisition. The stress hormone cortisol is known to have an influence on extinction memory and associative learning. Different effects of cortisol on behaviour and brain activity have been observed with respect to stress timing, duration, and intensity. However, the influence of cortisol prior to the initial encoding of stimulus-outcome associations on extinction learning, renewal and its behavioural and neurobiological correlates is still largely unknown. In our study, 60 human participants received 20 mg cortisol or placebo and then learned, extinguished, and recalled the associations between food stimuli presented in distinct contexts and different outcomes in three subsequent task phases. Learning performance during acquisition and extinction phases was equally good for both treatment groups. In the cortisol group, significantly more participants showed renewal compared to placebo. In the subgroup of participants with renewal, cortisol treated participants showed significantly better extinction learning performance compared to placebo. Participants showing renewal had in general difficulties with recalling extinction memory, but in contrast to placebo, the cortisol group exhibited a context-dependent impairment of extinction memory recall. Imaging analyses revealed that cortisol decreased activation in the hippocampus during acquisition. The cortisol group also showed reduced dorsolateral prefrontal cortex activation when extinction learning took place in a different context, but enhanced activation in inferior frontal gyrus during extinction learning without context change. During recall, cortisol decreased ventromedial prefrontal cortex activation. Taken together, our findings illustrate cortisol as a potent modulator of extinction learning and recall of extinction memory which also promotes renewal.

1. Introduction

Extinction learning is described as a process in operant and classical conditioning theories that results in decrease of a conditioned response over time when it is non-reinforced. During this process an organism learns that previously acquired information is no longer valid (Myers & Davis, 2007). However, the recall of extinction memory can fail and the initial learned response recovers. One type of recovery of an extinguished response is called the renewal effect. Renewal occurs when extinction learning is performed in a context that differs from recall (Bouton & Bolles, 1979). Typical renewal paradigms consist of three different phases: acquisition, extinction, and recall. During acquisition, associations between cue and behavioural response are learned. In the extinction learning phase, these associations are extinguished while cues are presented either in the same (AAA condition) or a different context (ABA condition). During recall, cues are presented again in the context of acquisition (context A). When extinction occurred in the different context B, associations formed during both learning phases are presumably competing to produce the behavioural response. It is assumed that the processing of context information plays a crucial role regarding which previously learned association is retrieved during recall (Lissek et al., 2016).

The return of an extinguished response supports the notion that extinction learning is not an irreversible process that causes an erasure of previously learned associations. In fact, extinction learning can be specified as a second learning phase that includes a new associative

* Corresponding author at: BG University Hospital Bergmannsheil, Department of Neurology, Ruhr University Bochum, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany.
E-mail address: alina.nostadt@rub.de (A. Nostadt).

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learning process linking stimulus and consequence. Instead of forgetting the previously acquired association between stimulus and response a second, competing memory trace is formed (Bouton, 1993; Delamater, 2004; Myers & Davis, 2002). Previous studies using a predictive learning task without a fear component have indicated that the hippocampus (HC), ventromedial prefrontal cortex (vmPFC) and inferior frontal gyrus (iFG) are predominantly activated in contextual extinction learning paradigms. It is assumed, that HC and vmPFC display increased co-activation, especially during tasks that require memory consolidation, due to the functional and structural connectivity between these brain regions (Rolls, 2022; E.T. Rolls, 2023a). Also, studies have demonstrated that HC and vmPFC are assumed to mediate renewal during extinction recall (Kinner et al., 2016; Lissek et al., 2013). Greater HC activation during extinction learning and a prominent vmPFC activation during recall was observed for participants who showed renewal (Lissek et al., 2013). Accordingly, the vmPFC and HC are functionally involved in processing context information (Kalisch et al., 2006; Milad et al., 2007; Smith & Mizumori, 2006) and recalling context-dependent memory (Kennedy & Shapiro, 2004). The iFG and its connection with orbitofrontal cortex is shown to be involved during behavioural control and non-reward related learning tasks that require behavioural correction (E.T. Rolls, 2023a; E.T. Rolls, 2023b). Also, iFG activation is repeatedly found during extinction learning and recall (Lissek et al., 2017, 2019, 2020). IFG is generally known to support response inhibition as well as to process conflicting response options (Konishi, 1999). Activation in the dorsolateral prefrontal cortex (dlPFC) was repeatedly found during extinction learning (Lissek et al., 2015, Lissek et al., 2017), but its functional role in extinction and renewal remains unknown.

Context processing during extinction learning is assumed to be evoked by the surprising change in stimulus-outcome associations, and thus plays an important role for renewal (Bouton, 1988, 2004; Lissek et al., 2016). Also, context processing during the initial acquisition phase can influence the recall of extinction memory and is thus associated with renewal (Lissek et al., 2016). It is well-known that learning and memory processes such as extinction and associative learning, are modulated by stress hormones (Meir Drexler et al., 2019). Glucocorticoids (GC), such as cortisol, are released during stressful situations and GC receptors are predominantly located in brain structures that are functionally involved in learning and memory processes in general (Joëls & Baram, 2009; Wolf, 2009) and in extinction learning (e.g., PFC, HC, and amygdala; de Kloet, 2004; de Kloet et al., 2005). Stress can have varying effects on cognitive functions depending on the exact timing and the implications of stress for extinction-based therapy are of great interest (Meir Drexler et al., 2019; Merz & Wolf, 2017; Wolf, 2009; de Quervain et al., 2017; Stockhorst & Antov, 2016). Findings suggest that cortisol can cause impaired recall of extinguished associations and reduced context differentiation as seen in disrupted vmPFC connectivity (Kinner et al., 2016).

So far, there are only few studies that investigate context processing during the acquisition phase. While the context does not provide information that is necessarily relevant to solve the task during this learning phase, context information may nevertheless provide essential support for task solving strategies. In a previous study, participants who showed renewal had greater hippocampal BOLD activation during acquisition compared to participants not showing the renewal effect, pointing towards context processing already during this phase (Lissek et al., 2016). However, participants with renewal who received noradrenergic stimulation prior to acquisition exhibited reduced overall-context dependent renewal (Lissek et al., 2019).

In our present study we aimed to understand the effects of cortisol prior to acquisition on associative learning, extinction and renewal in a non-fear related context. Participants received 20 mg cortisol or placebo before performing a predictive learning task. In the task, they learned, extinguished, and recalled associations of different cues and outcomes in distinct contexts. This study contributes new insights regarding the influence of stress hormones on acquisition and learning of associations between cue and consequence. We assumed, that cortisol administered prior to acquisition will impair the processing of context information throughout the experiment and therefore modulate extinction learning and result in higher renewal rates. Also, cortisol should decrease HC and prefrontal activity, associated with impaired extinction memory recall and higher renewal rates.

2. Method

2.1. Participants

We recruited sixty volunteers to participate in our study. We applied standard exclusion criteria for MRI measurements and excluded participants with a history of self-reported neurological disorders, intake of medicine, a body mass index outside the range of 18–27 kg/m^2, age outside the range of 18–40 years, drug use and smoking. Women using hormonal contraceptives were excluded from the study due to an influence on learning behaviour after cortisol intake (Jentsch et al., 2022; Merz & Wolf, 2017). We only included non-pregnant and free-cycling women tested outside the menstrual bleeding phase. Participants were randomly assigned to the cortisol (CORT) and placebo (PLAC) group. We excluded 8 participants (CORT: $n = 7$, PLAC $n = 1$) from all analyses due to excessive head movement or incomplete data sets. In total, the data sets of fifty-two right-handed volunteers (29 females, 23 males) mean age 26.04 (±3.65 SD; range 19–35) years were included. Mean age within the CORT group (n = 23, 13 women; range 23–31) was 26.17 (±2.53 SD) years and 25.93 (±4.37 SD) years in the PLAC group ($n = 29$, 16 women; range 19–35).

All participants provided written informed consent and received a monetary compensation for their participation in the amount of 60€. The protocol was approved by the Ethics Committee of the Ruhr University Bochum (Registration No. 16–5738) and conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Experimental procedure and cortisol administration

Prior to the experiment all participants received detailed information about the experimental procedure and the applied methods. 40 min before the start of the predictive learning task, we administered orally either 20 mg hydrocortisone (JENAPHARM) or an identical looking placebo in a randomized and double-blind design. The three phases of the predictive learning task (acquisition, extinction learning and recall) were performed in succession. To assess the cortisol concentrations of each participant, we collected saliva samples with Salivette sampling devices (Sarstedt, Nümbrecht, Germany) before tablet intake (baseline) as well as 30 min (before acquisition) and 120 min after tablet intake (after recall). Saliva samples were stored at −20 °C until assayed (commercial enzyme-linked immunosorbent assay; IBL International, Hamburg, Germany). Inter- and intra-assay coefficients of variations were below 10 %.

2.3. Predictive learning task

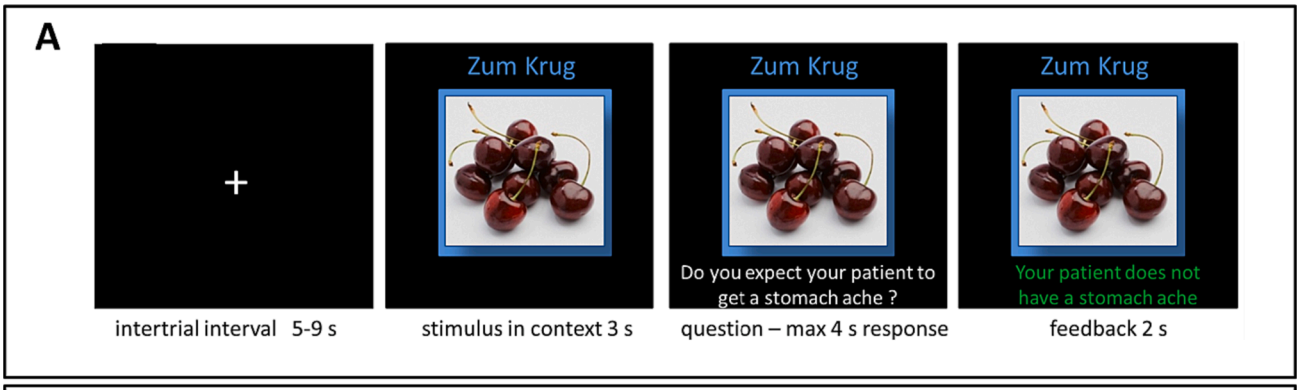
The predictive learning task (Üngör & Lachnit, 2006) used in this study is a task for context-related extinction learning without a fear component, suited to reliably evoke a renewal effect. Previous studies already used this task in a version adapted for fMRI experiments (e.g., Lissek et al., 2013, 2018, 2019; Kinner et al., 2016; Klass et al., 2021). In this task, participants are asked to put themselves in the position of a physician and predict whether various food items served in different restaurants will lead to the aversive consequence of a stomachache in their patient.

During the initial acquisition phase, participants learned to associate a food item with a consequence. In each trial a stimulus (photo of a vegetable or fruit) was presented to the participant in one of two different contexts, which consist of the restaurant names “Zum Krug”

(The Mug; context A) and "Altes Stiftshaus" (The Dome; context B) and a frame in either blue or red color. The stimulus in its context was first presented for 3 s, then a question asking whether the patient will develop a stomachache was superimposed, together with the response options "Yes" or "No". Participants had a maximum response time of 4 s and responded by pressing the respective button with the right hand. After the response, else after expiration of the response time, a feedback with the correct answer was displayed for 2 s underneath the food stimulus ("The patient has a stomachache" or "The patient does not have a stomachache") (see Fig. 1A). The food stimuli were presented in randomized order. The acquisition phase contained 16 different stimuli, 8 stimuli per context. Each stimulus was presented eight times, amounting to a total of 128 trials. Half of the stimuli predicted stomachache, the others predicted no stomachache. The consequence of stomachache was counterbalanced to appear equally often in both contexts.

During the extinction phase, half of the stimuli from the acquisition phase (eight) were presented again. Of these, one half (four) was presented again in context A, as during acquisition and the other half (four) in a different context B (condition ABA – context change) in randomized order. Within these groups of stimuli, a further distinction was made between actual extinction stimuli (i.e., stimuli for which the consequence of stomachache changes and retrieval stimuli (for which the consequence of stomachache does not change), resulting in each two extinction stimuli and two retrieval stimuli per context (see Fig. 1B). In addition, four new stimuli were introduced during the extinction phase, to balance the design to contain equal numbers of stimuli predicting stomachache in both contexts. Therefore, the extinction phase contained a total of 12 different stimuli, 6 per context, with each stimulus being presented eight times, amounting to a total of 96 trials. Again, half of the stimuli predicted stomachache, the other half predicted no stomachache, and the consequence of stomachache was counterbalanced to appear equally often in both contexts. In all other respects, trial design was identical to acquisition.

During the recall phase, extinction and retrieval stimuli were presented once again in the context of acquisition (five presentations per stimulus), resulting in a total of 40 trials. With the exception that during



B

experimental condition		Acquisition		Extinction		Recall	
		context 1	context 2	context 1	context 2	context 1	context 2
AAA	Extinction	A+	B+	A-	B-	A?	B?
	Retrieval	C+	D-	C+	D-	C?	D?
ABA	Extinction	E+	F+	F-	E-	E?	F?
	Retrieval	G+	H-	H-	G+	G?	H?

20 mg hydrocortisone / placebo

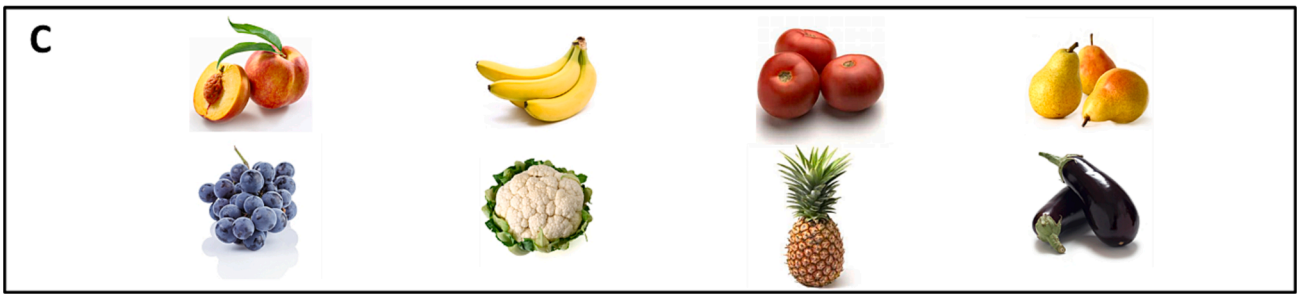


Fig. 1. Predictive learning task. (A) Example of a trial during acquisition of the task. Participants learned to predict whether certain kinds of food, eaten in a certain restaurant, would cause a stomachache or not. After an intertrial interval of 5–9 s the stimulus was presented in its context for 3 s, then a question was superimposed on the screen "Do you expect your patient to get a stomachache?" for a maximum of 4 s response time. Feedback was shown for 2 s, providing the correct answer, "The patient does not have a stomachache." or "The patient has a stomachache.". **(B)** Experimental design of the predictive learning task for extinction and retrieval conditions. Plus and minus indicates if the stimulus predicts stomachache or not ('+': stimulus predicts stomachachse; '-': stimulus predicts no stomachache). In the extinction condition AAA, the stimulus occurs in the same context as acquisition. In the extinction condition ABA, the stimulus occurs in a context different from that during acquisition. In both conditions, the final test (recall) for the renewal effect is performed in the context of acquisition. **(C)** Selection of food images used as stimuli.

the recall phase participants received no feedback at all, trials are identical to those during acquisition. See Fig. 1 for an overview of the task design.

2.4. Data acquisition

Functional and structural brain scans were acquired using a whole-body 3T scanner (Philips Achieva 3.0 T X-Series, Philips, The Netherlands) with a 32-channel SENSE head coil. Blood-oxygen level dependent (BOLD) contrast images were obtained with a dynamic T2* weighted gradient echo EPI sequence using SENSE (TR 3200 ms, TE 35 ms, flip angle 90°, field of view 224 mm, slice thickness 3.0 mm, voxel size 2.0 × 2.0 × 3.0 mm^3). We acquired 45 transaxial slices parallel to the anterior commissure-posterior commissure (AC-PC) line which covered the whole brain. High resolution structural brain scans of each participant were acquired using an isotropic T1 TFE sequence (field of view 240 mm, slice thickness 1.0 mm, voxel size 1 × 1 × 1 mm^3) with 220 transversally oriented slices covering the whole brain.

The task was presented to the participants via fMRI-ready LCD-goggles (Visuastim Digital, Resonance Technology Inc., Northridge, CA, USA) connected to a laptop which ran specific software programmed in MATLAB (V.2019b, The Math Works, USA). Responses were recorded by an fMRI-ready keyboard (Lumitouch response pad, Photon Control Inc., Canada).

2.5. Behavioural data analysis

For all three learning phases, log files were recorded that contained information on response type, and correctness of response, from which we calculated error rates during acquisition and extinction learning, overall rates as well as specific error rates for the different stimulus types (extinction, retrieval, and new learning stimuli). Errors in acquisition and extinction learning were defined as responses stating the incorrect association between the context-cue-compound and the consequence. During the recall phase, a response that referred to the association which was correct during acquisition constituted an error in the AAA condition and a renewal response in the ABA condition.

For calculation of the renewal effect, during the recall phase only responses to stimuli with consequence change (extinction stimuli) were analysed. The behavioural renewal effect in the predictive learning task is supposed to occur only in the condition ABA, due to the context change introduced during extinction learning. In case of renewal, associations learned during acquisition in context A will reappear in the recall phase, which is again performed in context A, while extinction was performed in context B. In contrast, the AAA condition constitutes a control condition for extinction learning, since here all learning phases are performed in an identical context. If extinction learning is successful, responses during the recall phase will reflect the associations learned during extinction.

Statistical analyses were performed using MATLAB (V.2019b, The Math Works, USA). All results are quoted as mean ± standard error of means (SEM), unless stated otherwise. For the behavioural analyses in which we compared participants who showed or did not show renewal, CORT and PLAC participants were assigned to their respective REN subgroup if they showed at least 10% ABA renewal responses during recall. Participants with < 10% ABA renewal responses were assigned to the NoREN group.

Basic behavioural performance in the three learning phases was analysed by means of analysis of variance (ANOVA) including the between-subjects factors treatment (CORT/PLAC) and renewal propensity (REN/NoREN) and within-subjects factors for the learning phases, unless stated otherwise. For significant main effects resulting from the ANOVA, we calculated planned contrasts comparing all subgroups (CORT/PLAC, and REN/NoREN) to determine which of the groups differed in their performance. If applicable, for our planned contrasts we applied a modified Bonferroni correction (Keppel, 1991).

2.6. Imaging data analysis

For preprocessing and statistical analysis of fMRI data we used the software Statistical Parametric Mapping (SPM), Version 12 (Wellcome Department of Cognitive Neurology, London, United Kingdom), implemented in MATLAB (V.2019b, The Math Works, USA). Three dummy scans, during which the BOLD signal reached steady state, preceded the actual data acquisition of each session, thus preprocessing started with the first acquired volume. Preprocessing on single subject level consisted of the following steps: slice timing correction to account for time differences due to multislice image acquisition; realignment of all volumes to the first volume for motion correction; spatial normalization into standard stereotactic coordinates with 2 × 2 × 2 mm^3 using an EPI template of the Montreal Neurological Institute (MNI) provided by SPM, smoothing with a 6 mm full-width half-maximum (FWHM) kernel, in accordance with the standard SPM procedure. The acceptable limit for head motion was 2 mm for translational movements and 0.5° for rotational movements. If these limits were exceeded in a single volume or across the whole scanning session, the data of the respective participant were excluded from further analysis.

In a first level analysis we calculated activation during acquisition, extinction, and recall phases. For extinction and recall phases, activation was additionally calculated for the respective experimental conditions, i.e., ABA and AAA. We modelled regressors for the onset of each context-cue compound. All regressors were modelled using distinct stick functions convolved with the canonical hemodynamic response function in the general linear model implemented in SPM, in an event-related design (duration = 0). The contrasts were calculated in a second-level analyses and based on the onset of the image of the context-cue compound at the beginning of a trial, compared to baseline. The contrast images from the single subject analyses were entered into second-level random-effects analyses to compare BOLD activation in the treatment and control groups for acquisition, extinction learning, and recall phases in the experimental (ABA) and control (AAA) conditions. We entered the data into a flexible factorial design containing the factors treatment (CORT and PLAC), renewal propensity (REN and NoREN) and calculated contrast images for different learning conditions (ABA and AAA) and trial types (extinction and retrieval). We used “percent errors” (in acquisition and extinction) as a covariate of interest in the SPM flexible factorial design to further investigate learning-related activation during acquisition and extinction.

We restricted our analyses to our regions of interest (ROI) (i.e., bilateral medial, ventral and orbital PFC, bilateral iFG and bilateral HC) based on previous studies which demonstrated their significant contribution to extinction and renewal by processing context features, response selection/inhibition, and decision making (e.g., Kalisch et al., 2006; Lissek et al., 2013, 2018, 2020; Milad et al., 2007). For these regions we constructed anatomical ROIs based on the corresponding anatomical regions defined in the WFU pickAtlas Toolbox implemented in SPM 12, using AAL atlas regions (Tzourio-Mazoyer et al., 2002). In general, imaging results are reported in terms of significance on the whole-brain level with FWE-correction, thresholded at $p < 0.05$ peak level. For results marked with an asterisk (*), small volume correction was applied with FWE-correction, thresholded at $p < 0.05$ peak level. In these cases, the respective small volume always consisted of the complete anatomical ROI.

3. Results

3.1. Salivary cortisol

An ANOVA of salivary cortisol concentrations revealed a significant main effect of time ($F_{(2,146)} = 11.2$; $p < 0.001$), treatment ($F_{(1,146)} = 18.85$; $p < 0.001$), as well as a significant time*treatment interaction ($F_{(2,146)} = 11.25$; $p < 0.001$). At baseline, PLAC had slightly higher cortisol levels compared to CORT ($t(50) = 2.86$, $p = 0.006$). 30 min after

intake of 20 mg hydrocortisone, cortisol levels were significantly higher in the CORT group compared to PLAC ($t(50) = 3.65$, $p < 0.001$). After the experiment (120 min after cortisol intake), cortisol was still elevated in CORT ($t(50) = 7.73$, $p < 0.001$; see Table 1). No significant main and interaction effects with sex occurred.

3.2. ABA renewal level

We analysed the percentage of participants who showed ABA renewal and no renewal for each treatment group separately. As described in section 2.5 participants were assigned to their respective REN and NoREN subgroups. Mean percent renewal responses ranged from 40−100 % in both treatment groups. For PLAC, we found a significantly higher percentage of participants who showed no renewal (REN: $n = 7$, NoREN: $n = 22$; $\chi^2 = 15.51$, $p < 0.001$; Fig. 2A). Within CORT, REN and NoREN subgroups were almost equally distributed (REN: $n = 12$, NoREN: $n = 11$; $\chi^2 = 0.08$, $p = 0.76$; Fig. 2A). In comparison, the CORT group had a significantly greater percentage of ABA renewal participants than PLAC ($\chi^2 = 4.34$, $p = 0.03$; Fig. 3A). The ABA renewal levels differed significantly between REN participants of both treatment groups: we observed higher renewal rates in CORT compared to PLAC ($t(16.5) = 1.7$, $p = 0.04$; Fig. 2B). Also, there we no significant differences of salivary cortisol levels of REN and NoREN subgroups (within CORT and PLAC) at three different time points (*t*-test, $p > 0.3$) (see Table 2).

In the renewal condition (during recall of extinction stimuli in the ABA condition), we observed differences in BOLD activation between treatment groups regardless of their renewal level: CORT had a reduced activation in left vmPFC compared to PLAC (see Table 5 and Fig. 3C).

3.3. Recall phase performance

In both groups, participants with renewal had difficulties recalling AAA extinction memory and made more recall errors compared to participants who showed no renewal (CORT: $t(21) = 1.8$, $p = 0.08$; PLAC: $t(27) = 2.5$, $p = 0.01$) but CORT and PLAC did not differ significantly in recall performance of the AAA extinction condition. We compared ABA renewal rates and AAA extinction recall errors within the subgroup of participants showing renewal of both treatment groups and observed a significant difference between CORT and PLAC (CORT: $t(22) = 5.1$, $p < 0.001$; PLAC: $t(12) = 2.9$, $p = 0.01$; Fig. 3B). There was no difference in recall error rates between the CORRT REN and PLAC REN subgroups.

3.4. Renewal ratio

To determine whether ABA renewal behaviour in the REN participants of both groups was based on processing of context, we calculated the proportion of renewal responses in the condition with context-change (ABA) compared to the condition without context-change (AAA; for further details, see Lissek et al., 2017, 2019). The renewal ratio describes to what degree renewal responses were associated with impaired extinction learning or recall, or context-driven. The renewal ratio was calculated between acquisition responses in the recall conditions ABA and AAA (ABA - AAA / ABA + AAA). Here, a renewal ratio of 1 (context-driven response) shows that renewal responses occurred during ABA recall and not during AAA. A renewal value of 0 indicates that participants had the same proportion of ABA renewal responses and AAA errors, and therefore an impaired extinction memory recall is suggested (Lissek et al., 2017, 2019). The mean renewal ratio was significantly higher in CORT REN compared to PLAC REN ($t(17) = 2.05$, $p = 0.05$; Fig. 3C). This result indicates that recall behaviour of CORT REN was more context-driven while PLAC REN exhibited less context-consideration during recall.

Table 1
Salivary cortisol (mean ± SEM) in CORT and PLAC groups at baseline (before tablet intake), before acquisition and after the experiment (30 min and 120 min after tablet intake).

Salivary Cortisol (nmol/l)	Cortisol		Placebo	
	Men	Women	Men	Women
Baseline	4.32 ± 1.01	6.27 ± 1.55	9.48 ± 1.76	11.84 ± 2.27
Before Acquisition	224.96 ± 107.14	199.96 ± 75.16	9.34 ± 1.91	8.23 ± 1.33
After Experiment	44.27 ± 10.63	57.80 ± 8.74	6.61 ± 0.96	4.10 ± 0.38

3.5. Learning performance and imaging results

3.5.1. Acquisition

In the first learning phase, all participants successfully learned stimulus-outcome associations. Error rates did not differ significantly between subgroups, indicating that neither the administration of hydrocortisone before the start of the learning task nor the individual propensity for renewal affected acquisition of associations between stimulus and outcome (main effect treatment: $F_{(1,48)} = 0.73$, $p = 0.39$, main effect renewal propensity: $F_{(1,48)} = 0.33$, $p = 0.56$, interaction effect treatment*renewal: $F_{(1,48)} = 0.22$, $p = 0.64$; Table 3).

The contrast CORT vs. PLAC showed a trend towards a higher BOLD activation in right posterior HC in PLAC compared to CORT (see Table 5 and Fig. 3A).

3.5.2. Extinction learning phase

During extinction, participants of all subgroups successfully extinguished stimulus-outcome associations, subgroups did not differ in error rates for all extinction conditions (ABA and AAA) (main effect renewal propensity: $F_{(1,48)} = 0.08$, $p = 0.77$; main effect treatment: $F_{(1,48)} = 0.68$, $p = 0.41$, interaction effect renewal propensity*treatment $F_{(1,48)} = 1.41$, $p = 0.24$; Table 4).

3.5.3. ABA extinction learning

ANOVA showed a significant interaction effect (treatment*renewal: $F_{(1,48)} = 4.6$; $p = 0.03$) but no main effect of treatment and renewal (treatment: $F_{(1,48)} = 4.6$; $p = 0.4$; renewal: $F_{(1,48)} = 4.6$; $p = 0.9$). Participants with renewal had lower error rates during ABA extinction learning in the CORT group compared to PLAC ($t(17) = 2.07$, $p = 0.05$; Table 4).

During ABA extinction learning, contrasts showed significant differences in activation between the treatment groups. During extinction learning in a novel context, activation in the CORT group was reduced in the right middle frontal gyrus / dlPFC and the left paracentral lobule (see Table 5 and Fig. 3).

3.5.4. AAA extinction learning

During extinction learning in the context of acquisition, learning performance did not differ between groups (main effect renewal propensity: $F_{(1,48)} = 0.24$, $p = 0.62$; main effect treatment: $F_{(1,48)} = 0.17$, $p = 0.68$, interaction effect renewal propensity*treatment $F_{(1,48)} = 0.17$, $p = 0.68$; Table 4).

Despite a lack of differences in learning performance, the CORT group exhibited increased activation in left iFG (triangular/opercular/orbital part) and right temporal pole / inferior frontal gyrus (orbital part) (see Table 6 and Fig. 3B) compared to PLAC (see Table 6 and Fig. 3B) who showed reduced activation in these brain regions (see Table 5 and Fig. 3B).

3.5.5. Retrieval trials

As expected, participants successfully retrieved stimulus-outcome associations learned in acquisition indicating no substantial learning difficulties occurred in all subgroups. Total learning errors across

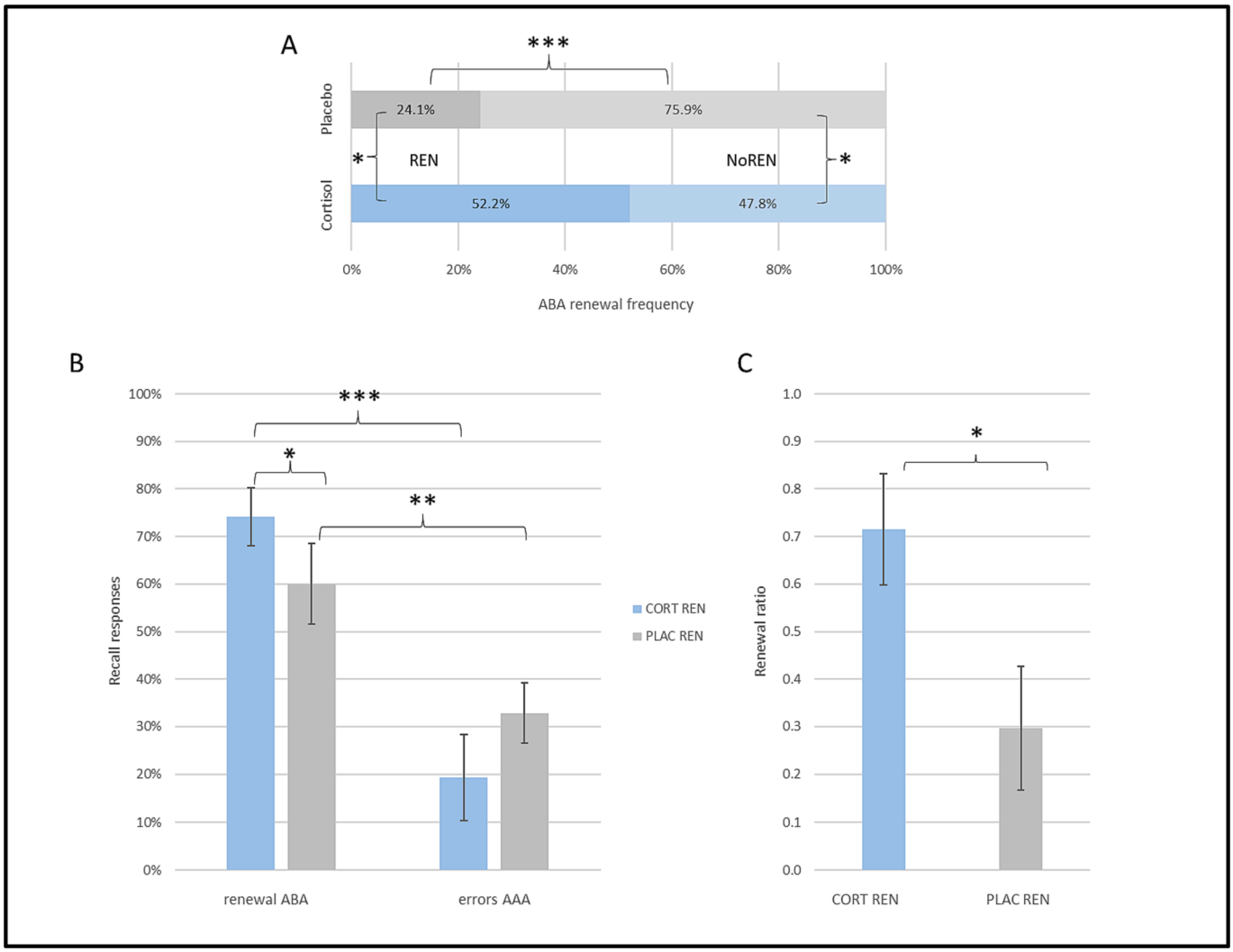


Fig. 2. Recall performance. (A) Frequency of REN and NoREN in both treatment groups. In PLAC, we observed significantly less participants showing renewal and in comparison, we found an increased frequency of participants who showed renewal in CORT. Within the CORT group, REN and NoREN subgroups were distributed similar. **(B)** Mean percent of ABA renewal responses and AAA errors for participants showing renewal in both treatment groups. In both groups, we observed significantly higher ABA renewal rates compared to recall errors of AAA extinction stimuli. CORT had higher levels of ABA renewal responses compared to PLAC. Both groups had similar AAA extinction recall errors. **(C)** Significant difference of the renewal ratio between CORT REN and PLAC REN showing higher renewal ratio for CORT REN. According to the renewal ratio, recall behaviour of CORT REN reflects a more context-dependent renewal effect and not a general impairment of recalling extinction memory.

retrieval conditions (no consequence change) were equally good for all subgroups, but the CORT REN group revealed significantly fewer retrieval errors for participants with renewal compared to CORT NoREN ($t(21) = 2.4$, $p = 0.02$; Table 4). Except for this finding, learning performance did not significantly.

4. Discussion

The administration of cortisol prior to acquisition affected behavioural and neural correlates during acquisition, extinction and recall of stimulus-outcome associations in a predictive learning task. Cortisol reduced vmPFC activation during recall of ABA extinction memory, which was accompanied by higher renewal rates in this group, compared to PLAC. In addition, in the CORT group more participants showed renewal than in the PLAC group. We also observed differences in BOLD activation of extinction-related brain areas between treatment groups during acquisition and extinction learning. In the following, results of all three predictive learning task phases will be discussed, starting with the most prominent finding.

4.1. Cortisol reduces BOLD activation in task-relevant brain areas during ABA extinction learning and ABA recall

Left vmPFC activation was significantly reduced in the CORT group during recall of ABA extinction memory. ABA renewal rates were higher in the CORT group, in addition more participants in this group showed renewal behaviour. The renewal ratio war higher for CORT, suggesting that ABA renewal in this group was more context-dependent than in PLAC. Our results reflect findings of previous studies, which showed that the vmPFC is functionally involved in recall of contextual information and extinction memory (Kinner et al., 2016; Lissek et al., 2019). Previous studies found that extinction learning depends on integrated functioning of vmPFC and HC (Milad & Quirk, 2012). This prefrontal-hippocampal network is assumed to mediate the recall of extinction memory and regulate exchange of contextual information (Kalisch et al., 2006; Milad et al., 2007; Milad & Quirk, 2012). Cortisol can block this functional crosstalk by reducing prefrontal activation, resulting in impaired extinction memory retrieval associated with stronger return of initially acquired responses (Kinner et al., 2016).

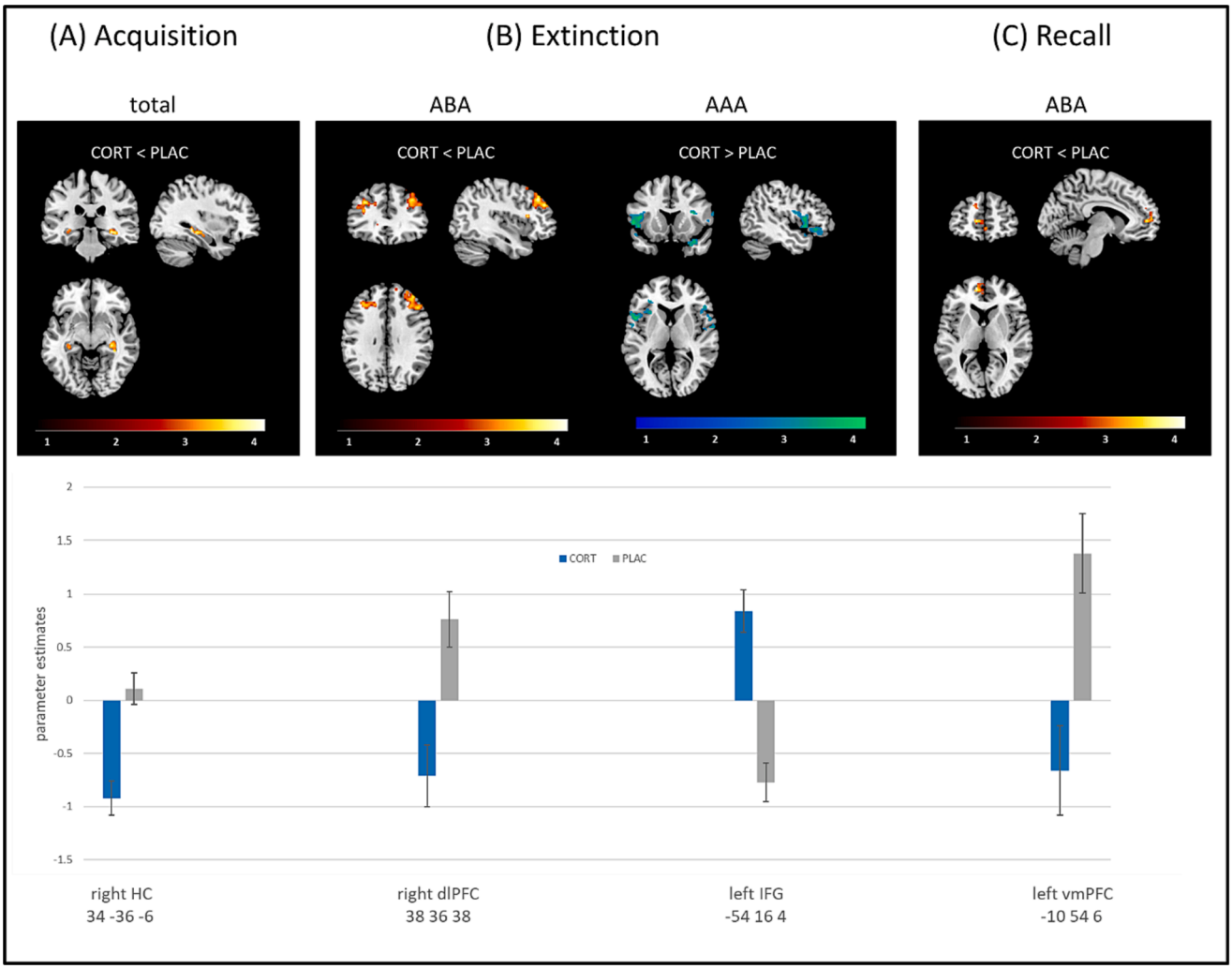


Fig. 3. Imaging results. Parameter estimates were extracted from single subject data at peak MNI coordinates of second level analysis. **(A)** Reduced activation in right posterior HC for CORT compared to PLAC during the acquisition phase, SVC on peak-level and FWE-corrected at $p < 0.05$. **(B)** For extinction in the ABA condition, the CORT group showed reduced activation in right dlPFC compared to PLAC, SVC on cluster-level and FWE-corrected at $p < 0.05$. During extinction trials of the AAA condition, the CORT group had higher left iFG activation compared to PLAC, FWE-corrected $p < 0.05$, k = 10, on cluster level. **(C)** Reduced vmPFC activation was observed for CORT compared to PLAC during ABA extinction recall, SVC on peak-level and FWE-corrected at $p < 0.05$.

Table 2
Salivary cortisol levels (mean ± SEM) of REN and NoREN subgroups (in CORT and PLAC) at three different time points.

	CORT		PLAC	
Mean nmol/l	***REN***	***NoREN***	***REN***	***NoREN***
L1 (baseline)	6.22 ± 1.72	4.55 ± 0.85	10.64 ± 2.74	10.86 ± 1.77
L2 (before acquisition)	267.01 ± 112.59	149.55 ± 38.77	9.48 ± 2.7	8.49 ± 1.22
L3 (after experiment)	59.56 ± 10.80	43.58 ± 7.55	4.99 ± 0.6	5.3 ± 0.67

Table 3
Percent acquisition error rates in REN and NoREN subgroups of CORT and PLAC (± SEM). **Acquisition.**

	CORT	PLAC
REN	16.54 % ± 1.58	16.7 ± 3.54
NoREN	20.6 % ± 3.45	17.52 ± 1.79

differ between REN and NoREN subgroups in all retrieval conditions (ABA and AAA) (see Table 4).

After cortisol administration, reduced right dlPFC activation during ABA extinction learning was observed for CORT compared to PLAC. It is assumed that the dlPFC is part of a frontal-lobe network that is recruited while solving cognitive problems (Duncan & Owen, 2000). Studies have shown that dlPFC activity and its functional connectivity to the HC is directly linked to successful updating of previously learned associations (Kluen et al., 2019). This ability is important for cognitive flexibility and essential in successful extinction learning and retrieval. Accordingly, higher activation in this brain area was found associated with a lack of renewal (Lissek et al., 2013). There is evidence that dlPFC activation is sensitive to stress hormones, which can affect cognitive functions such as working memory (Qin et al., 2009). Despite this reduced activation in right dlPFC during ABA extinction learning, overall extinction learning performance in the CORT group was unaffected. However, in comparison to PLAC, more participants in the CORT group showed renewal, and successfully recalled stimulus-outcome associations of ABA extinction stimuli while integrating contextual information.

4.2. Cortisol increases BOLD activation in iFG during AAA extinction learning

In the CORT group, left (opercular) iFG showed increased activation

Table 4
Percent error rates during the extinction learning phase of all subgroups (±SEM), in the trial types of extinction and retrieval for both context change (ABA) and non-context change (AAA). **Extinction learning phase.**

	Extinction			Retrieval		
	total	ABA	AAA	total	ABA	AAA
CORT REN	17.19 % ± 2.57	14.06 % ± .28 *	20.31 % ± 2.57	5.99 % ± 1.65**	6.77 % ± 2.49	5.12 % ± 1.86
CORT NoREN	17.33 % ± 2.32	18.18 % ± 3.62	16.48 % ± 3.89	12.22 % ± 1.91**	12.50 % ± 2.80	11.93 % ± 2.97
PLAC REN	20.98 % ± 2.23	24.11 % ± 2.87*	17.86 % ± 5.36	10.27 % ± 2.01	9.82 % ± 2.86	10.71 % ± 3.79
PLAC NoREN	19.60 % ± 1.54	18.75 % ± 2.1	20.45 % ± 1.44	10.23 % ± 2.82	8.81 % ± 3.04	10.23 % ± 2.93

*Significant difference of ABA extinction learning between CORT REN and PLAC REN ($p = 0.05$).
**Significant difference of total learning errors in retrieval condition between CORT REN and CORT NoREN ($p = 0.02$).

Table 5
CORT < PLAC. Contrasts between treatment groups show higher activation in PLAC compared to CORT groups in extinction related brain areas during acquisition, extinction (ABA), and recall of extinction memory (ABA). [Two-sample test, FWE-corrected $p < 0.05$, $k = 10$, on cluster level (* SVC on peak level)].

	Area	BA	HEM	MNI Coordinates			Voxel	*t*	*p*
Acquisition	Hippocampus*		R	34	36	-6	115	4.00	0.059
Extinction ABA	Middle frontal gyrus/ dlPFC	9	R	38	36	38	618	3.90	<0.001
	Paracentral Lobule	6	L	−8	16	72	305	3.84	0.003
Recall ABA	Ventromedial PFC*	10	L	10	54	6	104	4.24	0.040

Table 6
CORT > PLAC. Contrasts between treatment groups show higher activation in CORT compared to PLAC groups in extinction related brain areas during extinction learning (AAA). [Two-sample test, FWE-corrected $p < 0.05$, $k = 10$, on cluster level].

	Area	BA	HEM	MNI Coordinates			Voxel	*t*	*p*
Extinction AAA	Inferior frontal gyrus (triangular/opercular/orbital part)	45/44/47	L	−54	16	4	660	4.35	<0.001
	Temporal pole / Inferior frontal gyrus (orbital part)	38 47	R	36	16	24	377	3.92	0.011

during AAA extinction learning, i.e., in the condition in which the stimulus-outcome association changed while the contextual information remained constant during acquisition and extinction learning. The iFG is assumed to play a fundamental role during operant and instrumental extinction learning (Bouton et al., 2016) and in mediating response inhibition (Konishi, 1999). Our previous studies provided evidence that iFG is functionally involved in extinction learning and associated with renewal (Lissek et al., 2017, 2019), by making an essential contribution to the selection of context-tied responses that result in renewal (Lissek et al., 2020). Presumably, the left iFG is more relevant for extinction learning and processing of conflicting response options, since it is involved in conflict resolution such as detecting and resolving internal representational conflicts (Novick et al., 2005). Accordingly, a previous study showed higher left opercular iFG activation during extinction learning when participants showed renewal (Lissek et al., 2020). Our present findings of increased activation in left opercular iFG during AAA extinction learning in the CORT group are in line with these results. While we found no differences of learning performance between CORT and PLAC groups in AAA extinction learning, the recall of AAA extinction memory differed between the REN and NoREN subgroups.

We assume that participants who showed renewal had general impairments in recalling extinguished stimulus-outcome associations regardless of context change. Our findings support the role of left iFG in mediating response options in extinction learning, and additionally suggest that the cortisol-induced increase in left iFG activation is associated with the observed higher ABA renewal rates.

4.3. Cortisol reduces activity in right hippocampus during initial acquisition of associations

While cortisol had no effects upon initial acquisition of associations in terms of error rates, it was associated with reduced BOLD activation in the right HC during the acquisition phase. Our result suggests that cortisol prior to acquisition of our predictive learning task reduced HC functioning, consequently impairing its communication with brain areas supporting associative learning and processing context-related information, such as the prefrontal cortex. There is evidence that the HC plays an essential role in context processing (Smith & Mizumori, 2006) likewise in learning of cue-outcome relations in specific contexts (Maren, 2011). Especially the right HC is associated with acquisition and extinction of aversive and neutral stimulus-outcome associations (Lissek et al., 2013; Maren, 2011; Milad & Quirk, 2012; Orsini et al., 2011). It is known that stress hormones have effects on neural functioning especially in the HC, due to a high density of glucocorticoid receptors in this brain area (de Kloet, 2004). High levels of glucocorticoids, such as cortisol, can affect HC dependent learning and memory processes (Hamacher-Dang et al., 2013; Roozendaal, 2002). In line with our findings, multiple studies have shown reduced hippocampal functioning after administration of high doses of cortisol (de Quervain et al., 2003; Kinner et al., 2016; Pruessner et al., 2008; Schwabe & Wolf, 2012). Our imaging analysis revealed significantly reduced BOLD activation in right HC in the CORT group during associative learning in the acquisition phase. While HC is crucially involved in processing of context information during extinction learning (Kalisch et al., 2006; Milad et al., 2007), its activation is not necessarily required for the acquisition phase of our predictive learning task, since the task can be solved without integrating contextual information. Therefore, the reduction in HC

activation had no discernible effects upon error rates in acquisition. Nevertheless, reduced HC activation might have influenced later recall of contextual information and thus affected behavioural performance during recall.

5. Conclusion

In this study, we investigated the effects of cortisol prior to the acquisition of stimulus-outcome associations on extinction learning, renewal, and its behavioural and neurobiological correlates. Our findings demonstrate that cortisol administration resulted in a reduced HC activation during acquisition compared to PLAC. Participants with increased cortisol levels showed a context-dependent impairment of extinction memory recall associated with a higher number of participants who showed renewal and higher renewal rates in this group compared to PLAC. This was presumably resulting from reduced activation of HC and prefrontal areas which mediate context processing as well as encoding and recall of stimulus-outcome associations. Cortisol also affected functioning of dlPFC and vmPFC, regions that are involved in mediating context-dependent extinction learning and recall of extinction memory, thereby likely preventing updating of successfully learned stimulus-outcome associations and recall of context-dependent extinction memory.

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CRediT authorship contribution statement

Alina Nostadt: Investigation, Formal analysis, Writing – original draft, Project administration. **Christian J. Merz:** Funding acquisition. **Oliver T. Wolf:** Funding acquisition. **Martin Tegenthoff:** Funding acquisition, Resources. **Silke Lissek:** Funding acquisition, Conceptualization, Methodology, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

Bouton, M. E. (1988). Context and ambiguity in the extinction of emotional learning: Implications for exposure therapy. *Behaviour Research and Therapy, 26*(2), 137–149. https://doi.org/10.1016/0005-7967(88)90113-1

Bouton, M. E. (1993). Context, time, and memory retrieval in the interference paradigms of pavlovian learning. *Psychological Bulletin, 114*(1), 80–99. https://doi.org/10.1037/0033-2909.114.1.80

Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning and Memory, 11*(5), 485–494. https://doi.org/10.1101/lm.78804

Bouton, M. E., & Bolles, R. C. (1979). Contextual control of the extinction of conditioned fear. *Learning and Motivation, 10*(4), 445–466. https://doi.org/10.1016/0023-9690(79)90057-2

Bouton, M. E., Trask, S., & Carranza-Jasso, R. (2016). Learning to inhibit the response during instrumental (operant) extinction. *Journal of Experimental Psychology. Animal Learning and Cognition, 42*(3), 246–258. https://doi.org/10.1037/XAN0000102

de Kloet, E. R. (2004). Hormones and the stressed brain. *Annals of the New York Academy of Sciences, 1018*, 1–15. https://doi.org/10.1196/ANNALS.1296.001

de Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Reviews. Neuroscience, 6*(6), 463–475. https://doi.org/10.1038/NRN1683

de Quervain, D. J. F., Henke, K., Aerni, A., Treyer, V., McGaugh, J. L., Berthold, T., … Hock, C. (2003). Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. *The European Journal of Neuroscience, 17*(6), 1296–1302. https://doi.org/10.1046/J.1460-9568.2003.02542.X

de Quervain, D., Schwabe, L., & Roozendaal, B. (2017). Stress, glucocorticoids and memory: Implications for treating fear-related disorders. *Nature Reviews. Neuroscience, 18*(1), 7–19. https://doi.org/10.1038/NRN.2016.155

Delamater, A. R. (2004). Experimental extinction in Pavlovian conditioning: Behavioural and neuroscience perspectives. *Quarterly Journal of Experimental Psychology Section B: Comparative and Physiological Psychology, 57*(2), 97–132. https://doi.org/10.1080/02724990344000097

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences, 23*(10), 475–483. https://doi.org/10.1016/S0166-2236(00)01633-7

Hamacher-Dang, T. C., Uengoer, M., & Wolf, O. T. (2013). Stress impairs retrieval of extinguished and unextinguished associations in a predictive learning task. *Neurobiology of Learning and Memory, 104*, 1–8. https://doi.org/10.1016/j.nlm.2013.04.007

Jentsch, V. L., Pötzl, L., Wolf, O. T., & Merz, C. J. (2022). Hormonal contraceptive usage influences stress hormone effects on cognition and emotion. *Frontiers in Neuroendocrinology, 67*, Article 101012. https://doi.org/10.1016/j.yfrne.2022.101012

Joëls, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature Reviews. Neuroscience, 10*(6), 459–466. https://doi.org/10.1038/NRN2632

Kalisch, R., Korenfeld, E., Stephan, K. E., Weiskopf, N., Seymour, B., & Dolan, R. J. (2006). Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. *Journal of Neuroscience, 26*(37), 9503–9511. https://doi.org/10.1523/JNEUROSCI.2021-06.2006

Kennedy, P. J., & Shapiro, M. L. (2004). Retrieving memories via internal context requires the hippocampus. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 24*(31), 6979–6985. https://doi.org/10.1523/JNEUROSCI.1388-04.2004

Keppel, G. (1991). *Design and Analysis: A Researcher's Handbook* (3rd Edition). Englewood Clifts, New York: Prentice Hall.

Kinner, V. L., Merz, C. J., Lissek, S., & Wolf, O. T. (2016). Cortisol disrupts the neural correlates of extinction recall. *NeuroImage, 133*(March), 233–243. https://doi.org/10.1016/j.neuroimage.2016.03.005

Klass, A., Otto, T., Tegenthoff, M., & Lissek, S. (2021). The DA-antagonist Tiapride affects context-related extinction learning in a predictive learning task, but not initial forming of associations, or renewal. *Neurobiol. Learn Mem., 183*(2021), Article 107465. https://doi.org/10.1016/j.nlm.2021.107465

Kluen, L. M., Dandolo, L. C., Jocham, G., & Schwabe, L. (2019). Dorsolateral Prefrontal Cortex Enables Updating of Established Memories. *Cerebral Cortex, 29*(10), 4154–4168. https://doi.org/10.1093/CERCOR/BHY298

Konishi, S. (1999). Contribution of working memory to transient activation in human inferior prefrontal cortex during performance of the Wisconsin Card Sorting Test. *Cerebral Cortex, 9*(7), 745–753. https://doi.org/10.1093/cercor/9.7.745

Lissek, S., Glaubitz, B., Klass, A., & Tegenthoff, M. (2018). The effects of dopaminergic D2-like receptor stimulation upon behavioral and neural correlates of renewal depend on individual context processing propensities. *NeuroImage, 169*(December 2017), 69–79. https://doi.org/10.1016/j.neuroimage.2017.12.022

Lissek, S., Glaubitz, B., Schmidt-Wilcke, T., & Tegenthoff, M. (2016). Hippocampal Context Processing during Acquisition of a Predictive Learning Task Is Associated with Renewal in Extinction Recall. *Journal of Cognitive Neuroscience, 28*(5), 747–762. https://doi.org/10.1162/JOCN_A_00928

Lissek, S., Glaubitz, B., Uengoer, M., & Tegenthoff, M. (2013). Hippocampal activation during extinction learning predicts occurrence of the renewal effect in extinction recall. *NeuroImage, 81*, 131–143. https://doi.org/10.1016/j.neuroimage.2013.05.025

Lissek, S., Glaubitz, B., Wolf, O. T., & Tegenthoff, M. (2015). The DA antagonist tiapride impairs context-related extinction learning in a novel context without affecting renewal. *Frontiers in Behavioral Neuroscience, 9*(september), 1–13. https://doi.org/10.3389/fnbeh.2015.00238

Lissek, S., Golisch, A., Glaubitz, B., & Tegenthoff, M. (2017). The GABAergic system in prefrontal cortex and hippocampus modulates context-related extinction learning and renewal in humans. *Brain Imaging and Behavior, 11*(6), 1885–1900. https://doi.org/10.1007/s11682-016-9662-y

Lissek, S., Klass, A., & Tegenthoff, M. (2019). Effects of noradrenergic stimulation upon context-related extinction learning performance and BOLD activation in

hippocampus and prefrontal cortex differ between participants showing and not showing renewal. *Frontiers in Behavioral Neuroscience, 13*(April). https://doi.org/10.3389/fnbeh.2019.00078

Lissek, S., Klass, A., & Tegenthoff, M. (2020). Left Inferior Frontal Gyrus Participates in Mediating the Renewal Effect Irrespective of Context Salience. *Frontiers in Behavioral Neuroscience, 14*. https://doi.org/10.3389/FNBEH.2020.00043

Maren, S. (2011). Seeking a Spotless Mind: Extinction, Deconsolidation, and Erasure of Fear Memory. *Neuron, 70*(5), 830. https://doi.org/10.1016/J.NEURON.2011.04.023

Meir Drexler, S., Merz, C. J., Jentsch, V. L., & Wolf, O. T. (2019). How stress and glucocorticoids timing-dependently affect extinction and relapse. *Neuroscience and Biobehavioral Reviews, 98*, 145–153. https://doi.org/10.1016/J.NEUBIOREV.2018.12.029

Merz, C. J., & Wolf, O. T. (2017). Sex differences in stress effects on emotional learning. *Journal of Neuroscience Research, 95*(1–2), 93–105. https://doi.org/10.1002/JNR.23811

Milad, M. R., & Quirk, G. J. (2012). Fear Extinction as a Model for Translational Neuroscience: Ten Years of Progress. *Annual Review of Psychology, 63*(1), 129–151. https://doi.org/10.1146/annurev.psych.121208.131631

Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007). Recall of Fear Extinction in Humans Activates the Ventromedial Prefrontal Cortex and Hippocampus in Concert. *Biological Psychiatry, 62*(5), 446–454. https://doi.org/10.1016/j.biopsych.2006.10.011

Myers, K. M., & Davis, M. (2002). Behavioral and neural analysis of extinction. *Neuron, 36*(4), 567–584. https://doi.org/10.1016/S0896-6273(02)01064-4

Myers, K. M., & Davis, M. (2007). Mechanisms of fear extinction. *Molecular Psychiatry, 12*(2), 120–150. https://doi.org/10.1038/sj.mp.4001939

Novick, J. M., Trueswell, J. C., & Thompson-schill, S. L. (2005). *Novick_Trueswell_Thompson-Schill., 5*(3), 263–281.

Orsini, C. A., Kim, J. H., Knapska, E., & Maren, S. (2011). Hippocampal and prefrontal projections to the basal amygdala mediate contextual regulation of fear after extinction. *Journal of Neuroscience, 31*(47), 17269–17277. https://doi.org/10.1523/JNEUROSCI.4095-11.2011

Pruessner, J., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., … Lupien, S. (2008). Deactivation Of The Limbic System During Acute Psychosocial Stress: Evidence From Positron Emission Tomography And Functional Magnetic Resonance Imaging Studies. *Biological Psychiatry, 63*(2), 234–240.

Qin, S., Hermans, E. J., van Marle, H. J. F., Luo, J., & Fernández, G. (2009). Acute psychological stress reduces working memory-related activity in the dorsolateral prefrontal cortex. *Biological Psychiatry, 66*(1), 25–32. https://doi.org/10.1016/J.BIOPSYCH.2009.03.006

Rolls, E. (2023). *Brain computations and connectivity*. https://books.google.com/books?hl=de&lr=&id=WkDHEAAAQBAJ&oi=fnd&pg=PP1&ots=ZcbgnMfHFk&sig=wnmG8TLMpIzs2gBYlxCty9zkPRU.

Rolls, E. T. (2022). The hippocampus, ventromedial prefrontal cortex, and episodic and semantic memory. *Progress in Neurobiology, 217*. https://doi.org/10.1016/J.PNEUROBIO.2022.102334

Rolls, E. T. (2023). Emotion, motivation, decision-making, the orbitofrontal cortex, anterior cingulate cortex, and the amygdala. *Brain Structure and Function 2023 228:5*, *228*(5), 1201–1257. https://doi.org/10.1007/S00429-023-02644-9.

Roozendaal, B. (2002). Stress and memory: Opposing effects of glucocorticoids on memory consolidation and memory retrieval. *Neurobiology of Learning and Memory, 78*(3), 578–595. https://doi.org/10.1006/NLME.2002.4080

Schwabe, L., & Wolf, O. T. (2012). Stress modulates the engagement of multiple memory systems in classification learning. *Journal of Neuroscience, 32*(32), 11042–11049.

Smith, D. M., & Mizumori, S. J. Y. (2006). Learning-related development of context-specific neuronal responses to places and events: The hippocampal role in context processing. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 26*(12), 3154–3163. https://doi.org/10.1523/JNEUROSCI.3234-05.2006

Stockhorst, U., & Antov, M. I. (2016). Modulation of Fear Extinction by Stress, Stress Hormones and Estradiol: A Review. In *Frontiers in Behavioral Neuroscience* (Vol. 9). Frontiers Media S.A. https://doi.org/10.3389/fnbeh.2015.00359.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage, 15*(1), 273–289. https://doi.org/10.1006/nimg.2001.0978

Üngör, M., & Lachnit, H. (2006). Contextual control in discrimination reversal learning. *Journal of Experimental Psychology: Animal Behavior Processes, 32*(4), 441–453. https://doi.org/10.1037/0097-7403.32.4.441

Wolf, O. T. (2009). Stress and memory in humans: Twelve years of progress? *Brain Research, 1293*, 142–154. https://doi.org/10.1016/J.BRAINRES.2009.04.013