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Research report

# Restoring emotional stability: Cortisol effects on the neural network of cognitive emotion regulation

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ABSTRACT

Effective emotion regulation in stressful contexts is a key feature of mental health. Acute stress, however, impairs prefrontal top-down control, probably leading to a decline of emotion regulatory capacities. By contrast, the delayed cortisol increase in response to a stressor or after a pharmacological manipulation has been linked to mood-protecting effects and emotion regulation success. In this functional magnetic resonance imaging study, healthy men and women received either 30 mg cortisol or placebo 90 min before they were exposed to an emotion regulation paradigm involving neutral and negative pictures. As expected, behavioural and brain imaging data indicated successful induction and downregulation of negative emotions via cognitive reappraisal and distraction. Cortisol enhanced regulatory activity in the ventrolateral prefrontal cortex when participants used distraction and reduced emotion-related activation in the amygdala when regulating emotions via cognitive reappraisal. Together, these findings provide first evidence for a delayed glucocorticoid-induced facilitation of cognitive emotion regulation processes that might be beneficial for restoring emotional stability in the aftermath of stressful events.

## 1. Introduction

The capability to regulate emotions is a major prerequisite to healthy psychosocial functioning, especially during and after the encounter with a stressor. Deficient emotion regulation constitutes a risk factor and treatment target for stress-associated psychopathologies [1,2]. Imaging data revealed that emotion regulation relies on a cognitive control system involving inhibition-related prefrontal regions to dampen activation in emotion-associated structures, such as the amygdala, insula and anterior cingulate cortex [ACC; 3,4,5]. Importantly, stress hormones are known to impair prefrontal top-down regulation but strengthen emotional responses of the amygdala [6,7]. In line with this notion, executive functions such as cognitive inhibition or cognitive flexibility have been repeatedly shown to deteriorate under stressful conditions [8], while emotional memory consolidation [9] is usually boosted.

Acute stress leads to a concurrent activation of the sympathetic nervous system and the hypothalamus-pituitary-adrenocortical axis, leading to the release of (nor)adrenaline and glucocorticoids [GCs; cortisol in humans; 10]. GCs exert their effects by binding to receptors expressed in the prefrontal cortex (PFC), hippocampus and amygdala [11,12]. Given their crucial role for emotion regulatory processes [4,5] along with the stress-induced deficits in top-down control [6,7], it appears likely that GCs also rapidly impair the cognitive regulation of emotions. Consistent with this hypothesis, acute stress has been shown to undermine newly acquired emotion regulation skills during fear conditioning [13]. In contrast, a recent neuroimaging study reported that stressed participants performed equally well when compared to controls in a regulation task using cognitive reappraisal [14]. Evidence from our laboratory further suggests that the impact of stress may differ depending on the applied strategy [15]. In particular, we found that distraction was impaired, whereas the ability to reappraise negative emotional responses was facilitated after stress exposure, yet only in women. This lines up with work demonstrating that elevated cortisol levels are associated with dispositional emotion regulation capacities [16] and reduced negative affect in response to a psychosocial stressor [17,18]. Congruently, using cognitive reappraisal to downregulate negative emotional responses in a social stress paradigm has been shown to increase cortisol concentrations [19].

Besides rapid effects, GCs also act via slow genomic pathways that take at least an hour to initiate and continue for several hours [20,21]. Crucially, these genomic effects enhance rather than impair prefrontal activity and facilitate higher-order cognitive functioning [22]. Thereby, slow genomic GC actions are proposed to provide a mechanism actively

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reversing the rapid effects of acute stress and thus contributing to the return to homeostasis [7]. In terms of cognitive emotion regulation, this model would predict a GC-induced delayed improvement of emotion regulatory skills mediated by these slow genomic effects.

Taken together, this time-related specificity of stress hormone effects but also interactions between emotion regulation processes and stress hormones may account for the distinct regulatory outcomes observed in previous studies. So far, emotion regulation has been exclusively tested 20–30 minutes after acute stress manipulations [13–15], that is when cortisol concentrations usually peak [23]. In the present study, we therefore sought to characterize the delayed effects of cortisol on the neural networks of cognitive emotion regulation in order to cover the time window in which genomic GC actions come into play. Male and female participants received either an oral dose of cortisol or placebo 90 min before they were asked to downregulate emotional responses to aversive pictures using cognitive reappraisal or distraction. Different emotion regulation strategies activate a common network of prefrontal regions [3,24], but also specifically recruit different parts within this core network. For instance, cognitive reappraisal has been shown to predominantly activate ventrolateral (vlPFC) and dorsolateral (dlPFC) prefrontal regions, usually implicated in cognitive control functions, whereas attention-focused strategies such as distraction seems to additionally recruit specific clusters in the right insula [3,24,25], according to its role in attentional control processes [26–28]. Yet, the insula is also known to be crucially involved in representing emotional states [29,30] and has been associated with interoception [31], self-reported [32] and autonomic arousal [33]. Due to this functional heterogeneity, the insula might therefore show either increased or decreased activity during emotion regulation, probably depending on the strategy applied.

Based on the GC-induced genomically mediated augmentation of prefrontal cognitive functions [7,22] and the affect-protective effect associated with cortisol [16,17,19], we expected cortisol to improve cognitive emotion regulation. This facilitation should be reflected in subjectively reduced negative emotional responses. On the neural level, we further expected cortisol to enhance activation of prefrontal regulatory regions, including the ventrolateral and dorsolateral PFC [3,4,25], but reduced activation in emotion-related structures, such as the amygdala, insula and ACC for reappraisal. A cortisol-induced upregulation of prefrontal activity and a downregulation of amygdala activity should also occur for distraction. Yet, due to its specific role in attention-focused emotion regulation [3], we further hypothesized that activity in the insula would rather increase when participants regulate their emotions via distraction, and this effect should be more pronounced in the cortisol as compared to the placebo group. As acute stress has been shown to rapidly impair distraction but enhance reappraisal [15], it is however also probable that the delayed effect of cortisol may differ depending on the applied strategy. We therefore sought to directly compare the effects of cortisol on both strategies. Since initial evidence for sex-dependent effects of stress and cortisol on emotional processing and emotion regulation exist [15,34], we additionally examined the potential interplay between cortisol and sex on behavioral and neural emotion regulation measures in an explorative manner.

## 2. Materials and methods

### 2.1. Participants

It is well established that effective emotion regulation requires intact executive functioning, including working memory capacity [4,35,36], which has been also shown to modulate brain activation during emotion regulation [37]. The required sample size was thus determined using G*Power 3.1 [38], assuming a small-sized effect of cortisol administration on behavioral measures of working memory, as reported in a meta-analysis by Shields, Bonner and Moons [39]; average effect size of $g^{+} = 0.315$. Accordingly, the estimation of the sample size for a small effect size of $f = 0.16$ [40], an assumed correlation of $r = 0.70$ for repeated measurements and a given significance level of $\alpha = .05$, revealed a required sample size of 52 participants in order to achieve a power of $1\text{-}\beta \geq .95$ to detect a significant treatment × condition interaction. Since we additionally aimed to explore the potential interplay between cortisol and sex on emotion regulation processes, we also calculated the required sample size for detecting a significant interaction comprising two between-subject factors (i.e. treatment and sex) and one within-subject factor (i.e. condition). This analysis showed that a sample size of 64 participants is required to detect a three-way interaction between treatment, condition and sex with a probability of at least $1\text{-}\beta \geq .90$.

Sixty-four healthy students (32 females) were thus recruited at the Ruhr University Bochum for study participation. Exclusion criteria were checked in a standardized telephone screening and covered chronic or acute illnesses, history of psychiatric or neurological treatment, standard MRI contraindications, drug use including smoking, regular medication, age < 18 or > 40 years, body mass index (BMI) < 18 or > 27 $kg/m^2$, working night shifts, and vaccination, blood donation or traveling to a country with a time difference in the last month. All participants were right-handed, had normal or corrected-to-normal vision and were not familiar with the used paradigm. Women were required to have been taking oral contraceptives (only monophasic preparations with an ethinylestradiol and a gestagenic component) for at least three months and were tested during the active pill phase to reduce potential influences of circulating sex hormones across the menstrual cycle [41–43]. In addition, all participants were instructed to refrain from physical exercise and consumption of food and drinks except water two hours prior to testing. Two women in the placebo group were excluded from analysis due to technical failure during data recording.

### 2.2. General procedure

Experimental sessions were conducted between 1 and 6 pm to control for diurnal variations in endogenous cortisol concentrations [10]. Upon arrival, participants were informed about the general procedure, pharmacological agents and the fMRI protocol. After providing written informed consent, they completed questionnaires regarding demographic data and were familiarized with the experimental paradigm by written instructions. Participants were then prepared for the scanning session. At the end of the experimental session, participants were reimbursed with 45€ and debriefed. All procedures were in accordance to the Declaration of Helsinki and approved by the ethic committee of the Medical Faculty of the Ruhr University Bochum. The present study was part of a larger project investigating cortisol effects on the neural basis of emotional processes, in which all current participants took part. These results are reported elsewhere [44].

### 2.3. Emotion regulation paradigm

A modified version of the emotion regulation paradigm [15] developed by Kanske et al. [45] was applied. In this task, participants were asked to view negative and neutral pictures (described below) or to downregulate their upcoming emotional response towards negative pictures by using two different emotion regulation strategies. In the distract condition, participants were asked to think about a neutral situation that was unrelated to the negative picture presented (e.g. preparing breakfast or going to the supermarket) without averting their gaze from the displayed scene [46]. In the reappraisal condition, they were instructed to reduce the intensity of their emotional response by reinterpreting the displayed negative situation to happen either in a pleasant context or with a pleasant ending [positive reappraisal, 15,46]. In the view negative condition, participants attended to the content of negative pictures and responded naturally, allowing themselves to have

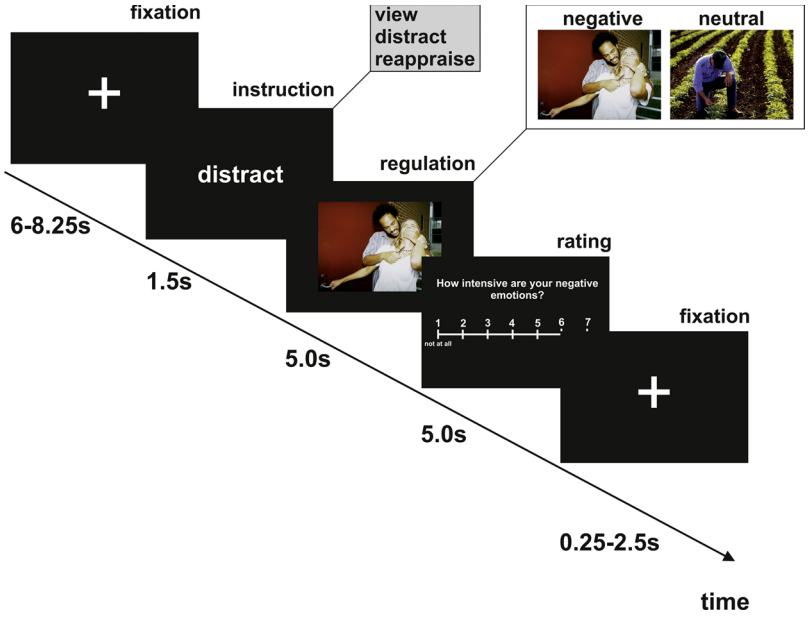


**Fig. 1.** Sequence of events in a trial of the emotion regulation paradigm. Participants were asked to view and respond naturally to neutral or negative pictures (view condition) or to regulate their upcoming emotional response towards negative pictures by means of two different emotion regulation strategies (distract, reappraise). Intensity ratings of experienced negative emotions were assessed directly after each picture presentation.

whatever reaction the picture would normally evoke in them. Similar to previous studies [47–49], we used an event-related design in which 30 negative pictures were randomly assigned to the two emotion regulation conditions and the view negative condition (10 negative pictures each) for each participant individually and with each picture presented only once for a given participant. This design was realized in order to avoid multiple repetitions of the same stimuli and/or same experimental conditions and ensuing habituation effects. To provide a neutral baseline condition, 10 neutral pictures were additionally presented in the view neutral condition. Thus, in total, four experimental conditions were defined: view neutral, view negative, distract, and reappraise.

In each trial, an instructional cue was first presented for 1.5 s (view, distract, reappraise) indicating which strategy to apply, followed by 5 s of picture presentation serving both to induce emotions and to initiate the emotion regulation phase. Subsequently, a rating screen appeared for 5 s that requested participants to indicate the intensity of the experienced negative emotions on a 7-point Likert scale (ranging from *'not at all'* to *'very strong'*). Inter-trial intervals depicting a white fixation cross on a black screen were randomly jittered before presentation of the instructional cue (total trial duration: 20 s). Fig. 1 illustrates the sequence of events in a trial. Trial order was pseudorandomized with no more than two equal conditions in succession, arranged in two blocks of twenty trials with five trials of each condition in each block and matched between the cortisol and placebo group. To ensure that participants were able to apply the instructed emotion regulation strategies properly, practice trials were carried out together with the experimenter prior to the scanning session. To get further familiarized with the task, participants performed additional computer-based practice trials within the scanner (8 trials, 2 min) before the experimental run started (13 min). Stimulus presentation and behavioral recordings were controlled by MATLAB R2012a (MathWorks Inc., Sherborn, MA) on an IBM compatible PC running Windows 7 and presented to the participants via fMRI-ready goggles (VisuaStim Digital; Resonance Technology Inc., Northridge, CA, USA). Responses were given on an fMRI-ready keyboard (LUMItouch™ response pad; Photon Control Inc., BC, Canada).

### 2.4. Stimuli

Pictures were selected from the International Affective Picture System (IAPS) based on normative ratings [50]. Sets of 30 negative pictures (valence: $M = 2.41$, $SD = 0.55$; arousal: $M = 5.58$, $SD = 0.83$) and 10 neutral pictures (valence: $M = 5.03$, $SD = 0.32$; arousal: $M = 3.20$, $SD = 0.46$) were created[1] . Arousal and valence ratings differed significantly between the sets (both $ps < .001$). All pictures were landscape (1024 × 768 pixels) in orientation and matched for content and complexity.

### 2.5. Cortisol administration, saliva sampling and analysis

In a double-blind, randomized design 16 men and 16 women received three 10 mg tablets of cortisol (hydrocortisone; Hoechst) 90 min before the start of the functional scans for the emotion regulation paradigm. This dosage was chosen based on previous studies from our laboratory and other groups reporting a clear modulation of behavioral and brain responses with similar dosages [51–54]. Visually identical placebos were given to the remaining 16 men and 14 women. Saliva samples for the assessment of cortisol concentrations were collected via Salivette sampling devices (Sarstedt, Nümbrecht, Germany) directly before tablet intake (baseline), as well as 35 min, 90 min (before the emotion regulation paradigm) and 120 min after tablet intake (after the emotion regulation paradigm) and stored at −20 °C until assayed. Commercially available enzyme-linked immunosorbent assays (Demeditec, Kiel, Germany) subserved to measure free cortisol concentrations. Inter- and intra-assay coefficients of variation were below 10%.

### 2.6. Statistics

Statistical analyses were performed using IBM SPSS 22 Statistics for Windows with the significance level set to $\alpha = 0.05$. For the analyses of cortisol concentrations and intensity ratings, ANOVA with the repeated measurement factor time (baseline, +35 min, +90 min, +120 min) or condition (view neutral, view negative, distract, reappraise) was conducted, respectively. Greenhouse-Geisser corrected $p$-values were reported if the assumption of sphericity was violated and partial $\eta^2$ were reported as estimations of effect sizes. The between-subjects factors treatment (cortisol vs. placebo) and sex (men vs. women) were included in all analyses.

[1] The library numbers for IAPS pictures [50] used in this study are: negative: 2120, 2205, 2278, 2312, 2455, 2490, 2683, 2691, 2703, 2710, 2800, 2900, 3180, 3181, 3230, 3500, 3530, 6212, 6242, 6312, 6313, 6570, 9040, 9041, 9250, 9253, 9433, 9435, 9911, 9921; neutral: 1670, 2190, 2191, 2214, 2383, 2393, 2396, 2749, 2840, 7036; practice: 2102, 3022, 6560, 9423, 9920, 9495.

**Table 1**
**(A)** Mean ( ± SEM) salivary cortisol concentrations before, 35 min, 90 min and 120 min after the administration of cortisol (hydrocortisone; 30 mg) or placebo. **(B)** Mean ( ± SEM) intensity ratings of experienced negative emotions for the different conditions of the emotion regulation task (view neutral, view negative, distract, and reappraise). Data is shown separately for men and women in the cortisol and placebo group, respectively. The statistics are described in detail in the text.

| | cortisol | | placebo | |
|---|---|---|---|---|
| | men | women | men | women |
| **(A) salivary cortisol (nmol/l)** | | | | |
| before treatment | 8.28 ± 1.46 | 7.13 ± 0.57 | 8.50 ± 1.05 | 7.35 ± 0.73 |
| 35 min after treatment | 265.15 ± 85.46 | 450.21 ± 72.35 | 7.98 ± 1.12 | 6.99 ± 0.61 |
| 90 min after treatment | 166.62 ± 38.44 | 364.54 ± 30.65 | 7.66 ± 1.01 | 6.34 ± 0.60 |
| 120 min after treatment | 131.24 ± 22.43 | 244.97 ± 17.86 | 6.44 ± 0.67 | 5.83 ± 0.60 |
| **(B) Intensity ratings (1-7)** | | | | |
| view neutral | 1.13 ± 0.56 | 1.20 ± 0.46 | 1.45 ± 0.80 | 1.15 ± 0.04 |
| view negative | 3.90 ± 0.30 | 4.84 ± 0.30 | 4.60 ± 0.27 | 4.56 ± 0.36 |
| distract | 3.26 ± 0.23 | 3.51 ± 0.24 | 3.72 ± 0.19 | 3.02 ± 0.14 |
| reappraise | 2.76 ± 0.29 | 3.26 ± 0.21 | 3.11 ± 0.12 | 2.87 ± 0.48 |

***Note.*** Intensity ratings: 1 = not at all, 7 = very strong.

### 2.7. fMRI data acquisition and analyses

Functional and structural brain scans were acquired using a whole-body 3 T scanner (Philips Achieva 3.0 T X-Series, Philips, Netherlands) with a 32-channel SENSE head coil. Structural images were obtained with an isotropic T1 TFE sequence (field of view = 240 mm × 240 mm; voxel size = 1 mm × 1 mm × 1 mm) and comprised 220 transversally orientated slices covering the whole brain. For functional imaging, 335 volumes were registered using a T2*-weighted gradient echoplanar imaging sequence with 40 transaxial slices parallel to the orbitofrontal cortex-bone transition (TR = 2.5 s; TE = 30 ms; flip angle = 67°; field of view = 192 mm × 192 mm; gap = 0.75 mm; ascending slice order; voxel size = 2 mm × 2 mm × 3 mm). Three dummy scans preceded data acquisition during which magnetization could reach steady state (in addition, the first three volumes of the functional data were discarded). For preprocessing and statistical analyses we used the software Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK), implemented in MatLab R2012a (Mathworks Inc., Sherborn, MA). Preprocessing encompassed unwarping and realignment, slice time correction, co-registration of functional data to each participant's anatomical image, segmentation into gray and white matter, normalization to the standard space of Montreal Neurological Institute (MNI) brain, and spatial smoothing with a 6 mm full-width half-maximum kernel.

The statistical model for each participant included the following regressors: view neutral, view negative, distract, reappraise, button presses, cues and ratings. All regressors were modeled by a stick function convolved with the canonical hemodynamic response function in the general linear model, without specifically modeling the duration of the different events (i.e. event-related design). The six movement parameters from the realignment step served as covariates in the analysis. A high pass filter with a time constant of 128 s was used to remove slow signal drifts and serial correlations were accounted for using an auto-regressive (AR(1)) model. Similar to previous emotion regulation studies [14,25,45,55], random effect group analyses were conducted and focused on the contrasts [view NEG – view NEU], [view NEG – distract], and [view NEG – reappraise]. ANOVA was conducted with the group factors treatment and sex in the full factorial model implemented in SPM8. Results regarding the contrast [distract – reappraise] served to identify regions that were specifically engaged in one of the regulation strategies and can be found in the supplementary material.

For all statistical analyses, we used region of interest (ROI) analyses targeting brain regions identified in previous meta-analyses examining emotion regulation processes [3,25]: amygdala, insula, anterior cingulate cortex (ACC), dorsolateral PFC (dlPFC) and ventrolateral PFC (vlPFC; maximum probability masks; probability threshold set to 0.25, Harvard-Oxford Cortical and Subcortical Structural Atlases, Harvard Center for Morphometric Analysis; http://www.cma.mgh.harvar.edu/fsl_atals.html). Bilateral masks for the dlPFC and vlPFC were created with the MARINA software package [56]. Correction for multiple comparisons at a significance level of $p \leq .05$ was restricted to the predefined ROIs and used the small volume correction (SVC) based on the Gaussian random field theory [family-wise error (FWE) rate method; [57]. Results of complementary exploratory whole brain analyses are provided in the supplementary material (see Supplementary Table 1).

## 3. Results

### 3.1. Sample description and salivary cortisol

Participants were aged between 18 and 36 years ($M = 23.81$, $SD = 3.28$) and had a mean BMI of $M = 22.43\ kg/m^2$ ($SD = 2.38$). Men and women differed significantly regarding their BMI (main effect of sex: $F_{(1,59)} = 21.63$, $p < .001$, $\eta_p^2 = .27$), with men (M = 23.62, SD = 2.44) having a higher BMI as compared to women (M = 21.16, SD = 1.52).

For salivary cortisol, ANOVA revealed a significant main effect of time ($F_{(3,174)} = 31.81$; $p < .001$; $\eta_p^2 = .35$), treatment ($F_{(1,58)} = 76.32$; $p < .001$; $\eta_p^2 = .60$) and a time × treatment interaction ($F_{(3,174)} = 32.02$; $p < .001$; $\eta_p^2 = .36$). Whereas groups did not differ at baseline ($p > .10$), cortisol was elevated 35, 90 and 120 min after cortisol compared to placebo administration (all $ps < .001$; Table 1A), indicating a successful pharmacological treatment. In addition, a significant main effect of sex ($F_{(1,58)} = 8.88$; $p < .01$; $\eta_p^2 = .13$) and a treatment × sex interaction ($F_{(1,58)} = 9.14$; $p < .01$; $\eta_p^2 = .14$) occurred. While men and women did not differ at baseline ($t_{(30)} = 0.73$; $p > 0.5$) or 35min ($t_{(30)} = 1.66$; $p > 0.5$) after cortisol intake, women showed significantly higher cortisol levels 90 ($t_{(30)} = 4.03$; $p < .001$) and 120 min ($t_{(30)} = 5.58$; $p < .001$) after cortisol administration when compared to men[2] . No sex differences occurred in the placebo group (all $ps > .05$).

### 3.2. Emotion regulation

#### 3.2.1. Intensity ratings

Intensity ratings of negative emotions differed significantly between the different conditions (main effect of condition: $F_{(3,174)} = 212.63$;

[2] Due to this sex difference in the cortisol group, we ran additional ANCOVAs for the intensity ratings, including either delta cortisol (calculated as the increase in cortisol from baseline to +90 min after pill intake) or mean cortisol (calculated as the mean of the samples +90 min and +120 min) as a covariate. Results for the reported main effect of condition and treatment by sex interaction were highly similar to the original analyses.

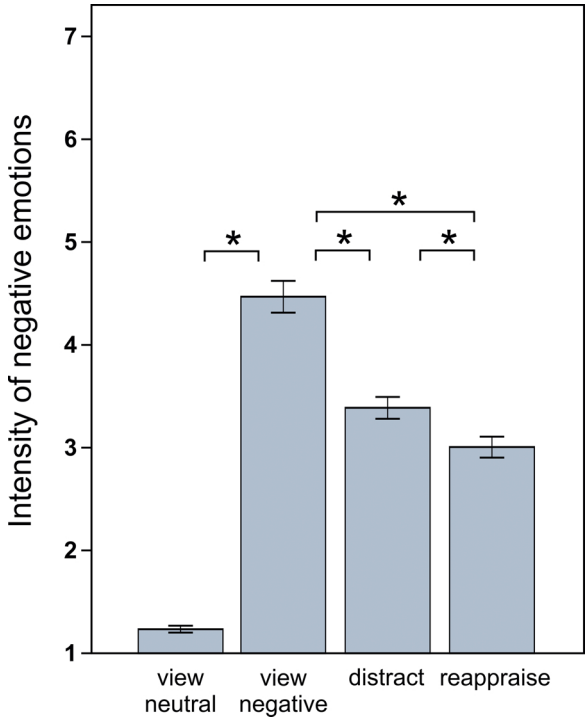


**Fig. 2.** Mean ( ± SEM) ratings of the intensity of negative emotions (1 = *not at all* to 7 = *very strong*) in the view condition (neutral, negative) and the two emotion regulation conditions (distract, reappraise). *$p < .001$, Bonferroni-corrected *post hoc t*-tests.

$p < .001$; $\eta_p^2 = .79$; Fig. 2, Table 1B). Bonferroni-corrected *post hoc t*-tests revealed that viewing negative pictures led to significantly higher ratings of negative feelings compared to viewing neutral pictures ($p < .001$), indicating a successful induction of negative emotions. Furthermore, distraction and reappraisal both significantly reduced negative emotions relative to the view negative condition ($ps < .001$), indicative of subjective emotion regulation success. Reappraisal was more effective in reducing negative emotions than distraction ($p < .001$). In addition, a significant treatment × sex interaction ($F_{(1,58)} = 7.43$; $p < .01$; $\eta_p^2 = .11$) occurred. Follow-up ANOVAs separately for men and women revealed that cortisol treated men reported less intense negative emotions relative to men receiving placebo (main effect of treatment: $F_{(1,30)} = 4.93$; $p < .05$; $\eta_p^2 = .14$; Table 1B) across all conditions, whereas no treatment effect occurred in women ($p > .05$). Yet, the condition × treatment × sex ($F_{(3,174)} = 0.55$; $p > .05$; $\eta_p^2 = .01$) interaction did not reach significance and no other main or interaction effects with treatment occurred (all $ps > .05$).

### 3.2.2. Neural responses

*3.2.2.1. Effects of emotion induction.* To identify brain regions involved in emotional processing, we first contrasted negative and neutral pictures in the view condition. ROI analyses indicated that the ACC, left insula, right dlPFC, as well as the bilateral vlPFC were significantly activated when viewing negative as compared to neutral pictures (see Table 2). No modulations by treatment or sex were found.

*3.2.2.2. Effect of emotion regulation*

*3.2.2.2.1. Effects of distraction.* Downregulating negative emotions via distraction led to a significantly reduced activity in the left amygdala relative to viewing negative pictures, while increasing neural responses in the right insula and bilaterally in the dlPFC and vlPFC (Table 2).

Cortisol administration significantly enhanced regulatory activity in the left vlPFC during distraction when compared to the view negative condition (see Fig. 3A). No other main or interaction effects with treatment or sex occurred.

*3.2.2.2.2. Effects of reappraisal.* Similarly to distraction, downregulation via reappraisal recruited prefrontal cortex regions such as the left vlPFC and bilateral dlPFC (Table 2).

Cortisol significantly attenuated emotion-related activity in the right amygdala during reappraisal (see Fig. 3B). No other main or interaction effects with treatment or sex occurred.

Results of the direct comparison between reappraisal and distraction and their modulation by cortisol can be found in Supplementary Table 2.

## 4. Discussion

In the current study, we investigated the delayed effects of the stress hormone cortisol on the behavioral and neural correlates of cognitive emotion regulation.

**Table 2**
ROI analyses for the effects of emotion induction and emotion regulation. Localization and statistics of the peak voxel are displayed for the contrasts [view NEG – view NEU], [view NEG – distract], and [view NEG – reappraise], referring to the main effects of condition. Significant treatment × condition interactions are inserted below the respective main effects of condition and labeled as (cortisol - placebo) and (placebo - cortisol), respectively.

| Contrast | Brain structure | *x* | *y* | *z* | $T_{max}$ | $P_{corr}$ |
|---|---|---|---|---|---|---|
| **[view NEG – view NEU]** | anterior cingulate cortex | −6 | 30 | 28 | 5.76 | < .001 |
| | L insula | −42 | 18 | −6 | 4.62 | .006 |
| | R dorsolateral PFC | 36 | 14 | 60 | 5.56 | .001 |
| | L ventrolateral PFC | −46 | 28 | 30 | 5.01 | .004 |
| | R ventrolateral PFC | 54 | 18 | 4 | 4.95 | .004 |
| **[view NEG – distract]** | L amygdala | −22 | −4 | −16 | 4.39 | .003 |
| **[distract – view NEG]** | L dorsolateral PFC | −36 | 58 | 16 | 5.62 | .001 |
| | R dorsolateral PFC | 48 | 18 | 42 | 5.22 | .003 |
| | L ventrolateral PFC | −46 | 48 | 6 | 4.78 | .008 |
| | R ventrolateral PFC | 48 | 16 | 38 | 4.24 | .036 |
| | R insula | 46 | 16 | −6 | 4.35 | .015 |
| cortisol - placebo | L ventrolateral PFC | −52 | 22 | 8 | 4.31 | .030 |
| **[view NEG – reappraise]** | no significant activations | | | | | |
| **[reappraise – view NEG]** | L dorsolateral PFC | −38 | 60 | −4 | 6.97 | < .001 |
| | R dorsolateral PFC | 34 | 62 | 10 | 4.66 | .017 |
| | L ventrolateral PFC | −46 | 48 | 4 | 4.13 | .049 |
| placebo - cortisol | R amygdala | 26 | −2 | −26 | 3.60 | .032 |

The significance threshold was $p_{corr.} \leq .05$ (FWE-corrected for small volume correction). All coordinates (*x, y, z*) are given in MNI space. L = left, R = right.

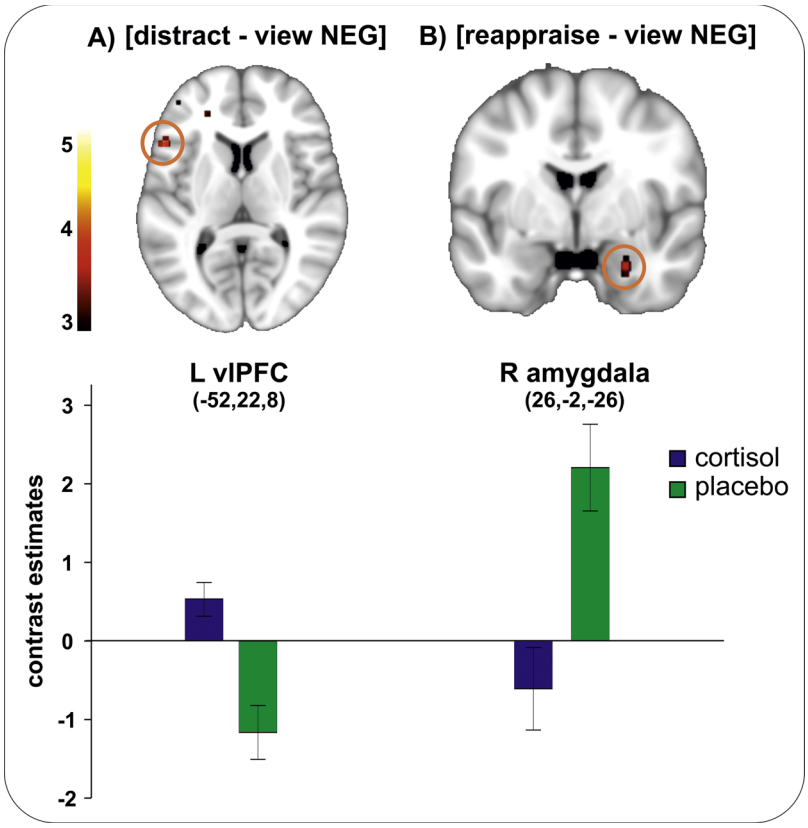


**Fig. 3.** Neural activations for the treatment × condition interactions are shown for the contrasts **A)** [distract – view NEG] and **B)** [reappraise – view NEG]. The depicted transverse and coronal slices were selected according to the reported activation in the left ventrolateral prefrontal cortex (vlPFC) and right amygdala. For demonstration purposes, data were thresholded with $T \geq 3.0$ (see color bar for exact *T*-values). In the bar graphs, mean ( ± SEM) differential contrast estimates are additionally given for the cortisol and placebo group in the respective peak voxel. Cortisol significantly enhanced activity in the left vlPFC during distraction **A)**, while reducing activation in the right amygdala during reappraisal **B)**.

### *4.1. Cortisol effects on the neural correlates of emotion regulation*

As expected, cortisol increased regulatory activity in the vlPFC during distraction and attenuated emotion-related activation in the amygdala when regulating negative emotions via cognitive reappraisal as compared to the view condition. These results support the idea that cortisol foster emotion regulatory processes [16,19] and exert affect-buffering effects in stressful contexts [17,18]. Consistently, clinical studies and neuroimaging data demonstrate that cortisol reduces phobic fear [58] and amygdala responsiveness [59], pointing towards a role for cortisol in preventing an emotional *overshoot*. In contrast, acute stress was shown to impair the regulation of conditioned fear [13] and the ability to distract from negative images in an emotion regulation task [15]. Moreover, a large body of research suggests that stress impairs prefrontal control but promotes activity in emotion-processing systems [6,7]. Yet, most of this work was based on acute stress manipulations [60,61], which trigger both noradrenergic activity and glucocorticoid release. In line with this notion, β-adrenergic receptor blockade, but not cortisol synthesis inhibition diminished the stress-induced increase in salience-network activity that usually promotes fear and vigilance [62]. Together, these studies indicate that noradrenergic activity in the early stress phase drives the neuromodulatory enhancement of amygdala responsiveness. It is therefore reasonable that catecholamines also play an important role in mediating the immediate emotion regulatory impairments after stress. However, the different contributions of SNS and HPA axis related stress mediators on these effects have yet to be disentangled, for example by using pharmacological agents to either activate or block GC and (nor)adrenergic receptors.

By contrast, GCs also exert slow genomic effects that typically commence after about an hour and continue for at least several hours [20,21]. The crucial factor might therefore be the timing between cortisol treatment and task performance. In previous studies, emotion regulation was typically tested shortly after stress onset [13–15]. Here, we administered cortisol 90 min prior to the emotion regulation paradigm: thus, the observed cortisol effects may be mainly driven by slow genomic actions. Consistent with this idea, the model by Hermans, Henckens, Joels and Fernandez [7] suggests that stress-related hormones strengthen salience-network activity during the acute stress phase, but reverse this allocation of neural resources in favor of executive control functions in the aftermath of stress. Ultimately, this time-dependent reallocation normalizes emotional reactivity and enhances higher-order cognitive processes. Congruently, amygdala activity has been found to be reduced in response to emotional faces 285 min after cortisol administration [59]. By contrast, prefrontal activity was enhanced when cortisol was given 120 min before an implicit emotion processing task [63]. In a similar vein, cortisol impairs working memory at shorter delays but enhance it at longer delays [39], pointing towards a GC-mediated recovery of higher-order cognitive functioning. For the current results, it is therefore reasonable that cortisol facilitates (via slow genomic effects) cognitive control systems that aid to cope with negative emotions and thereby promotes emotional recovery and restore affect stability when acute stress subsides. Together with the beneficial effects of cortisol in reducing stress-induced negative affect [17,18] and its positive association with emotion regulatory engagement [16,19], these findings raise the intriguing question, whether reducing an acute cortisol stress response is favorable in the long run. Our results rather support the idea of a highly adaptive physiological stress response, which orchestrates optimal responses to diverse challenges by its rapid and delayed hormonal and neuronal modulations [10,64]. However, due to the relatively high dose of 30 mg hydrocortisone, cortisol concentrations were still substantially elevated after 90 min and thus non-genomic effects could have been still active at the time when emotion regulation was tested. Since we have not directly compared immediate and delayed effects of cortisol on emotion regulatory processes in the current study, we cannot rule out that the

observed effects may also be driven by a combination of both non-genomic and genomic GC actions. Future studies could help to delineate such time-dependent GC effects by comparing varying delays between stress or cortisol administration relative to the onset of the emotion regulation paradigm, including even longer delays that allow cortisol concentrations to return to baseline levels before testing [22,59].

Moreover, it remains open whether the observed effects are specific to the dosage of 30 mg cortisol. Given the well-established inverted-U-shaped dose-response curve between GCs and learning and memory [65–68], it could be speculated that lower or higher cortisol dosages might lead to different result patterns in emotion regulation as well. However, whether such a U-shaped dose-response function also exist between GCs and emotion regulation remains to be determined in future experiments. In addition, it would be of interest how chronically elevated or reduced cortisol levels, as evident in patients with Morbus Cushing or Morbus Addison for instance, would affect the ability to regulate emotional responses.

### 4.2. Cortisol effects on the behavioral correlates of emotion regulation

On the behavioral level, cortisol overall diminished subjective emotional responses in men, whereas ratings remained unaffected in women. These results corroborate again with previous work showing elevated cortisol levels to be linked with reduced negative affect [17,18] and emotion regulatory engagement in aversive contexts [16,19]. Moreover, sex-dependent stress hormone effects on cognition and emotion in general [41,42,69] as well as on emotion regulatory processes in particular [15] have been previously reported. Our data extend these findings by providing further evidence for a sex-specific cortisol effect on both regulated and non-regulated subjective emotional experience. However, since we only tested women taking oral contraceptives (OC) it remains open whether these findings can be extended to free-cycling women. For emotional learning and memory processes though, it has been repeatedly shown that the effects of stress and cortisol administration converge for men and free-cycling women, whereas OC women often demonstrate opposite result patterns [41,42]. These findings indicate that OC usage and not necessarily sex per se might interfere with stress hormone actions. Nevertheless, although the sex-specific cortisol effect is consistent with prior work, it has to be noted that the statistical power for detecting such an interaction was not optimal with the given sample size and should thus be treated with caution. Future studies are warranted including both free-cycling women and OC users to allow for a comprehensive comparison with males.

### 4.3. General effects of emotion induction

Besides the cortisol effects, behavioral and imaging data indicate that both emotion induction and emotion regulation was successful. As expected, aversive relative to neutral pictures enhanced the negativity ratings as well as activation in the left insula and the ACC. Congruently, both regions are considered to be part of the emotional response network [4,70] and specifically supporting the integration of visceral and affective signals mediating emotional awareness [29,71]. Furthermore, the vlPFC and the right dlPFC were activated for negative versus neutral pictures in the simple viewing condition, indicating that participants might have automatically downregulated their emotional responses also during the view negative trials. This matches data from emotion regulation studies showing enhanced prefrontal activation during emotion processing [14,55,63]. Consistently, accumulating evidence imply the PFC to be involved in both effortful as well as automatic emotion regulation [72].

Contrary to our expectations however, the amygdala was not significantly activated by viewing negative compared to neutral pictures. No effects of emotional reactivity on amygdala signaling have been previously reported in an emotion regulation study [14] and also in a recent meta-analysis of fear conditioning studies [73]. Although the amygdala is generally implicated in the processing of affectively arousing stimuli [74], it is most likely specialized to rapidly and automatically detect cues signaling potential threat in the immediate environment [75,76]. Some evidence moreover suggest that amygdala responsiveness is related specifically to the arousal dimension of emotional experience [77]. Highly arousing pictures depicting mutilations or contaminations might thus have been more effective in evoking amygdala signaling in the view negative compared to the view neutral condition in the present study. However, we decided to choose aversive scenes of medium intensity that more likely offer the possibility to generate alternative interpretations of the depicted scenes and thus being more suitable to investigate emotion regulation processes, in particular cognitive reappraisal [78,79]. Furthermore, it has to be noted that we used an event-related design with 10 pictures per condition, which were presented in a pseudorandomized trial order allowing no more than two equal conditions in succession in order to avoid fatigue and habituation effects. This might have reduced the statistical power to detect robust neural effects of emotion processing. However, studies using a similar number of trials showed that they could reliably track effects of emotion generation [80] and regulation [48] in the amygdala. Beyond that, we chose a stimulus presentation time of 5 s with the instructional cue given shortly before picture presentation, which together should have provided sufficient time for the emotional response to unfold and for implementing the respective emotion regulation strategy [45,47,81,but see 82,83]. Nevertheless, due to the nature of the event-related design, in which conditions switch on a trial-by-trial basis, it cannot be excluded that participants automatically and unintentionally downregulated their emotional responses in the view trials as well, especially when it was directly preceded by a reappraisal or distraction trial. Such an assumed “transfer” effect is also supported by the prefrontal activations found for this contrast.

### 4.4. General effects of emotion regulation

Downregulating negative emotions via distraction and reappraisal subjectively reduced negative emotions relative to the view negative condition and activated a network of prefrontal control areas including the dlPFC, the vlPFC and the right insula particularly for distraction. Consistently, these brain regions have been previously shown to be activated during the cognitive regulation of emotions and are thought to influence emotion generating areas such as the amygdala or insula [4,5]. In line with this notion, we also observed a regulation-induced reduction of amygdala activity, when participants used distraction to downregulate their negative emotions as compared to simply viewing negative images. By contrast, no such decrease in amygdala activation was found for reappraisal as compared to view negative, even though it was more effective in reducing negative emotions on a subjective level. This pattern corroborates with previous findings showing amygdala downregulation to be stronger for distraction than reappraisal, whereas decreases in negative affect were usually more pronounced for reappraisal [45,84,85]. While distraction relies on attentional control to shift the focus away from the emotional stimulus, reappraisal requires attending to the emotional aspects of a stimulus in order to cognitively change their affective meaning. This in turn may initiate a more elaborate processing of the emotional stimulus during reappraisal and potentially leads to a maintained amygdala activation. In accordance with this idea, reappraisal as compared to distraction was related to less negative affect but better explicit recognition, when participants were re-exposed to the same stimuli 24 h later [55]. Furthermore, reinterpreting the meaning of a negative situation as being positive may also maintain some level of emotional arousal, albeit with a different valence. In line with this idea, participants in the placebo group showed increased rather than reduced amygdala activation when reappraising negative pictures relative to simply viewing them. However, this would also implicate that the amygdala reduction observed during reappraisal

in the cortisol group could also be interpreted as a failure to successfully reappraise negative scenes in a positive way. Contrary to this, reappraisal effectively reduced self-reported negative emotions, which was even more pronounced in cortisol treated men. Nevertheless, as we only assessed the subjective intensity of negative emotions without specifically measuring the dimensions of valence and arousal, the cortisol effect on amygdala activity during reappraisal should still be considered with caution. For future studies, it would be therefore desirable to assess emotional responding via multiple dimensions, including both subjective valence and arousal, but also physiological measures, such as pupillary responses, electrodermal activity [86] or heart rate [87] in order to better characterize the effects of cortisol on emotion regulatory outcome for positive reappraisal and other emotion regulation strategies.

## 5. Conclusion

In conclusion, our findings demonstrate that cortisol promotes cognitive emotion regulation processes, characterized by enhanced regulatory activity of the vlPFC during distraction but reduced emotion-related neural signaling in the amygdala when participants used cognitive reappraisal. We thereby provide first evidence for a delayed GC-mediated mechanism on cognitive emotion regulation that might help to restore emotional stability in the aftermath of stressful events. Yet, there are still some unresolved issues, which await further investigations, including the systematic exploration of time- and dose-dependent stress hormone effects on different emotion regulation strategies as well as the potential role of sex in modulating these effects.

## Declarations of interest

None.

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