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Cortisol promotes the cognitive regulation of high intensive emotions independent of timing

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Abstract

Failures to cognitively downregulate negative emotions are a crucial risk factor for mental disorders. Previous studies provide evidence for a stress-induced improvement of cognitive emotion regulation possibly mediated via glucocorticoid actions. Cortisol can initialize immediate non-genomic as well as delayed genomic effects on cognitive control functioning, but its distinct effects on emotion regulation processes remain to be shown. Here, we sought to characterize time-dependent effects of oral cortisol administration on cognitive emotion regulation outcomes. We expected cortisol to improve emotion regulation success. Possible interactions with the delay between cortisol treatment and emotion regulation, strategy use and intensity of the emotional stimuli were examined. Eighty-five healthy men received either 10 mg hydrocortisone or a placebo in a double-blind, randomized design 30 or 90 min prior to an emotion regulation paradigm, in which they were asked to downregulate their emotional responses towards low and high intensive negative pictures via reappraisal or distraction. Affective ratings and pupil dilation served as outcome measures. Reduced arousal, enhanced valence ratings as well as increases in pupil dilations indexing the cognitive regulatory effort indicated successful downregulation of negative emotions evoked by high intensive but not low intensive negative pictures. Cortisol significantly reduced arousal ratings when downregulating high intensive negative emotions via distraction and (at a trend level) via reappraisal, independent of timing, demonstrating a beneficial effect of cortisol on subjective regulatory outcomes. Taken together, this study provides initial evidence suggesting that cortisol promotes the cognitive control of high intensive negative emotions both, 30 and 90 min after treatment.

KEYWORDS

cognitive emotion regulation, emotional intensity, genomic cortisol effects, non-genomic cortisol effects, pupil dilation, stress hormones

Abbreviations: DAS, differential affective scale; dmPFC, dorsomedial prefrontal cortex; ER, emotion regulation; GC, glucocorticoids; GR, glucocorticoid receptor; HI, high intensive; HPA axis, hypothalamus-pituitary-adrenal axis; LI, low intensive; MR, mineralocorticoid receptor; PFC, prefrontal cortex; sAA, salivary alpha-amylase.

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1 | INTRODUCTION

Stress is omnipresent nowadays and has frequently been shown to modulate cognitive and affective processes in the human brain (e.g. McEwen et al., 2015). Exposure to acute stress not only activates the sympathetic nervous system leading to the release of catecholamines, but also the hypothalamus-pituitary-adrenal (HPA) axis, which finally causes the secretion of glucocorticoids (GCs; cortisol in humans). Whereas catecholamines rapidly shift the brain to a hypervigilant state preparing the individual for a fight or flight response (Cannon, 1932), GCs crucially contribute to the regulation of the initial stress response and promote the return to homeostasis in the aftermath of stress (Hermans et al., 2014; Joëls & Baram, 2009). Cortisol can induce rapid, non-genomic and slow, genomic effects by binding to mineralocorticoid (MR) and glucocorticoid receptors (GR), that are located in the cell membranes and in the cytoplasm, respectively (Groeneweg et al., 2012; Joëls et al., 2012). Non-genomic effects act as long as cortisol levels are elevated, while genomic effects take at least 60 min to initiate and continue for several hours (Hermans et al., 2014). Cortisol primarily acts on prefrontal and limbic structures (McEwen et al., 2016), which are also critically relevant for cognitive emotion regulation (Etkin et al., 2015).

Emotion regulation comprises all implicit as well as deliberate attempts to modulate emotional responding (Braunstein et al., 2017). Cognitive strategies to regulate upcoming emotions differ in their effectiveness (Webb et al., 2012), long-term adaptivity (McRae, 2016), time point of deployment during the emergence of an emotional response (Gross, 2015; Schönfelder et al., 2013) and the specific brain structures involved (Etkin et al., 2015; Ma et al., 2017). Reappraisal and distraction are two of the most effective and frequently investigated cognitive emotion regulation strategies, which can be applied to deliberately downregulate negative emotions (Webb et al., 2012). Whereas distraction prompts an attentional shift away from the emotional stimulus, reappraisal aims to reframe the given situation in order to change its emotional meaning, therefore requiring more cognitive effort (Gross, 2015). Given its long-lasting beneficial effects (McRae, 2016), reappraisal often represents a crucial part of cognitive psychotherapies (Beck & Dozois, 2011). Accumulating evidence demonstrates that deficits in cognitive emotion regulation constitute a risk factor for various forms of psychopathology (e.g. Berking & Wupperman, 2012; Sheppes et al., 2015). In turn, the ability to downregulate negative emotions can protect individuals from the onset and maintenance of mental disorders (Gross & Munoz, 1995; Hopp et al., 2011). Therefore, it is highly relevant to determine factors, which influence the ability to adaptively cope with challenging emotions.

Initial studies showed that acute stress modulates emotion regulation outcomes (Kinner et al., 2014; Langer et al., 2020; Raio & Phelps, 2015). In particular, the stress-induced increase in cortisol has been linked to improved downregulation of negative emotions via reappraisal (Langer et al., 2020). Importantly, pupillary data further suggested that these rapid beneficial effects of stress were accompanied by an increase in cognitive regulatory effort. Supporting the critical role of cortisol mediating stress effects on emotional responding, there is evidence showing that oral cortisol administration buffers increases of negative affect in response to psychosocial stress (Het et al., 2012; Het & Wolf, 2007; Reuter, 2002) and reduces phobic fear (Nakataki et al., 2017; Soravia et al., 2006). Together, these findings suggest that cortisol protects an individual from high intensive negative affective states possibly mediated via improved capacities to downregulate negative emotions. Consistent with this idea, fMRI data from our lab revealed that a single administration of hydrocortisone increased prefrontal regulatory activity and reduced emotion-related amygdala responsivity during cognitive emotion regulation (Jentsch et al., 2019). Notably, in another study cortisol also interacted with sex, resulting in increased activation in the dorsomedial prefrontal cortex (dmPFC) during emotion regulation in male participants only (Ma et al., 2017). Together, these findings suggest that the stress hormone cortisol may promote the cognitive control of negative emotions. Several lines of evidence furthermore indicate time-dependent differences in the effects of exogenous cortisol on cognitive functioning and affective processing in men (Cornelisse et al., 2014; Henckens et al., 2010, 2012). For instance, rapid effects of cortisol have been shown to strengthen PFC-amygdala connectivity (Henckens et al., 2012; Quaedflieg et al., 2015), probably resulting in improved cognitive reappraisal success in the aftermath of acute stress (Langer et al., 2020). By contrast, delayed cortisol effects decreased cuneus activity which was associated with reduced stimulus-driven attentional processing (Henckens et al., 2012). Accordingly, we found cortisol to facilitate the attentional shift away from an emotional stimulus 90 min after stress (Langer et al., 2021). These results imply that rapid, non-genomic and slow, genomic cortisol actions might improve regulatory success in a strategy-specific manner by modulating central nodes of the emotion regulatory neural network.

However, to the best of our knowledge, no study to date has directly compared rapid and slow cortisol effects on regulatory outcomes of two different emotion regulation strategies in a single design. Likewise, the role of emotional intensity of the stimuli used has received little attention so far. To address these issues, here 85 healthy men received either 10 mg hydrocortisone or a placebo 30 or 90 min prior to the start of an emotion regulation paradigm. In this task, participants were required to downregulate their emotions evoked by low and high intensive

negative pictures or simply view neutral and negative pictures. Affective ratings of arousal, valence and regulatory success were assessed to determine subjective regulatory outcomes. Recordings of pupil diameter served as an additional physiological index of emotion regulation processes. Changes in pupil dilation are typically thought to reflect changes in emotional arousal (Bradley et al., 2008). However, there are several studies showing that the pupil also dilates as a function of prefrontal control and emotion regulatory effort (Kinner et al., 2017; Langer et al., 2020; Urry, 2006). Pupil dilation may thus reflect both, emotional arousal and the cognitive effort required to regulate upcoming emotions.

Based on previous studies showing stress to promote the ability to downregulate negative emotions (Jentsch et al., 2019; Kinner et al., 2014; Langer et al., 2020) together with the affect-protective function of cortisol (Het et al., 2012; Reuter, 2002), we expected cortisol to improve cognitive emotion regulatory outcomes. In particular, we hypothesized reduced arousal, enhanced valence and success ratings as well as increases in pupil dilations (as an index of enhanced regulatory effort) after hydrocortisone compared to placebo administration. Furthermore, we expected cortisol to exert time- and strategy-dependent effects on emotion regulation success (Jentsch et al., 2019; Langer et al., 2020, 2021).

2 | MATERIALS AND METHODS

2.1 | Participants

For an a priori sample size calculation with G*Power 3.1 (Faul et al., 2009), parameter estimations were based on previous literature assuming a small-to-medium-sized effect (d = 0.31) of stress on cognitive emotion regulation in men (Langer et al., 2020). To detect a significant interaction between treatment, delay, emotion regulation condition and emotional intensity with a power of 1-$\beta \geq 0.90$, an alpha error probability of 0.05 and an assumed correlation of $r = 0.4$ for repeated measurements, 84 participants were required. Thus, 85 healthy males aged between 18 and 38 years ($M = 25.22$, $SD = 3.69$) and a mean Body Mass Index (BMI) between 18 and 28 ($M = 23.14$ kg/m^2; $SD = 2.44$ kg/m^2) were tested. Volunteers were recruited via online advertisements in social media networks, mailing lists and advertisements on notice boards throughout Ruhr University Bochum and surroundings. In a telephone interview, we checked the predefined exclusion criteria restricting study inclusion to participants without any chronic and acute illnesses, history or current medical or psychological treatment, drug use including smoking and previous experiences with the current emotion regulation paradigm. To ensure adequate tracking of pupillary responses, we excluded volunteers with corrected-to-normal vision > +1.5 or < −1.5 diopters. Since previous studies reported sex differences in cortisol effects on cognitive and affective processes after hydrocortisone administration (Kinner et al., 2016; Merz et al., 2012), we restricted participation to men only. Participants were asked to refrain from alcohol consumption and physical activity 24h before the start of the experiment, from caffeinated drinks in the morning as well as from eating and drinking anything except water 2h prior to testing. Participants were randomly assigned to the cortisol ($N = 42$) or placebo treatment ($N = 43$). Half of the participants of each treatment were randomly assigned to the immediate (cortisol: $N = 20$, placebo: $N = 21$) or delayed emotion regulation group (cortisol: $N = 24$, placebo: $N = 20$). Some triggers needed for pupillometric analyses could not be saved appropriately and therefore pupillary data of 19 participants could not be analysed (cortisol, immediate: $N = 5$; cortisol, delayed: $N = 5$; placebo, immediate: $N = 3$; placebo, delayed: $N = 6$). The treatment and delay groups neither differed in age (both ps ≥ 0.777), BMI (both ps ≥ 0.616) nor in the habitual use of reappraisal (both ps ≥ 0.355) and distraction (both ps ≥ 0.553), as assessed with the emotion regulation inventory (ERI; König, 2011). The study procedures were conducted in agreement with the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty at the Ruhr University Bochum.

2.2 | Experimental procedure

To control for the circadian rhythm of cortisol secretion (Guilliams & Edwards, 2010), all testing took place between 12.30 p.m. and 6.30 p.m. At first, all participants were informed about the general procedure and possible hydrocortisone administration. After providing written informed consent and answering some questionnaires, participants received either 10 mg hydrocortisone or a placebo and then waited for either 30 or 90 min. To bridge the waiting time between pharmacological treatment and emotion regulation task, five neutral 11 min documentary (nature or technical production) videos accompanied by quiet music without any voices (arousal [9-point visual analog scale ranging between 1 = emotionally calm to 9 = emotionally aroused]: $M = 2.48$, $SD = 1.38$; valence [9-point visual analog scale ranging between 1 = negative to 9 = positive]: $M = 6.51$, $SD = 1.44$) were used. After video 1, participants of the immediate group were prepared for pupillary recordings, instructed and familiarized with the emotion regulation paradigm, which started 30 min after pharmacological administration (see Figure 1a). Subsequently, the immediate group watched video 2–5. The delayed group watched all five videos before being instructed and familiarized with the emotion regulation paradigm, which started 90 min after tablet intake (see Figure 1b). At the end of the experimental session, participants were debriefed and reimbursed with 30€.

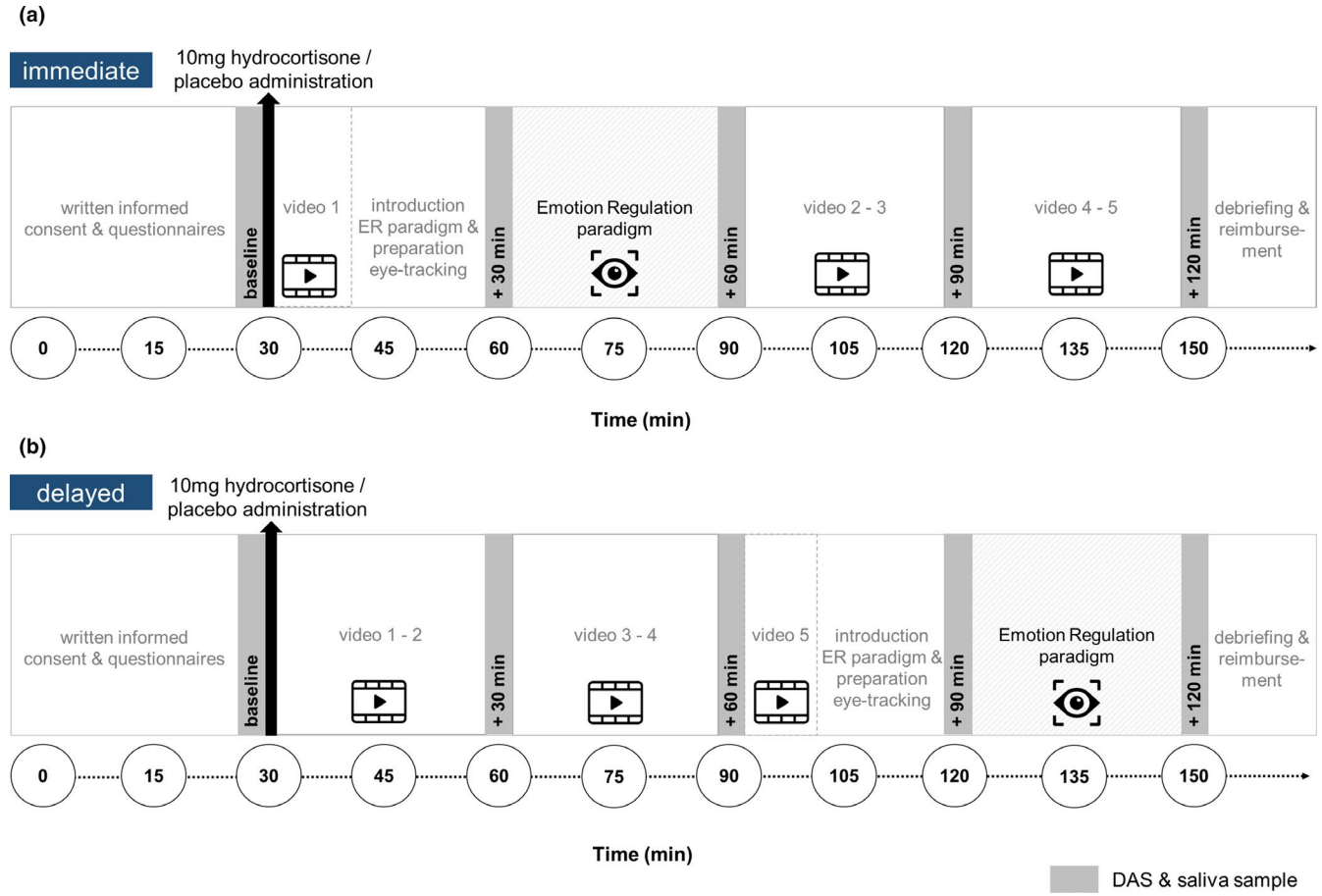

FIGURE 1 Experimental timeline of the immediate (a) and the delayed (b) group. All participants provided five saliva samples together with affective state ratings via the Differential Affective Scale (DAS) over the course of the testing procedure. Sampling time points are marked by shaded areas: baseline, +30, +60, +90 and +120 min after hydrocortisone or placebo administration (time point of pharmacological treatment highlighted by black arrows). The emotion regulation (ER) paradigm started 30 min after the pharmacological treatment for the immediate and 90 min afterwards for the delayed group. Neutral videos were used to bridge the time window between tablet intake and start of the ER paradigm

2.3 | Cortisol administration, saliva sampling and analysis

In a double blind, randomized, placebo-controlled design, 44 participants received 10 mg cortisol (hydrocortisone; Hoechst) either 30 or 90 min prior to the start of the emotion regulation paradigm. Visually identical placebos were given to the remaining 41 participants. To validate the effectiveness of the pharmacological treatment and to check for differences in alpha-amylase concentrations indexing sympathetic nervous system activity, saliva samples were collected via Salivette sampling devices (Sarstedt, Nümbrecht, Germany) directly before (baseline), as well as 30, 60, 90 and 120 min after tablet intake. Saliva samples were stored at −20°C until assayed. Commercial enzyme-linked immunosorbent assays (ELISAs; Demeditec, Germany) served to measure free salivary cortisol concentrations analysed on a Synergy2 plate reader (Biotek, USA) according to the manufacturer's instructions. To measure salivary alpha-amylase (sAA) concentrations, a colorimetric test using 2-chloro-4-nitrophenyl-α-maltrotriosoide (CNP-G3) as a substrate reagent was applied (Lorentz et al., 1999). Intra- and inter-assay coefficients of variations of all salivary analyses were below 10%. To check whether groups differed in the experienced affective state, the Differential Affective Scale (DAS; negative affect factors: *sadness, anger, disgust, contempt, fear, shame, guilt*; positive affect factors: *joy, surprise, interest*) was answered concurrent with each saliva sample (see Figure 1). Negative and positive affect scores were calculated as the mean of the associated factor values for each time point of measurement.

2.4 | Emotion regulation paradigm

A slightly modified version of the emotion regulation paradigm used in previous research of our lab was applied (Kinner et al., 2017; Langer et al., 2020). Participants were instructed

to either view negative and neutral pictures or to downregulate their upcoming emotional responses towards negative pictures via two different emotion regulation strategies. In the *reappraisal* condition, they were asked to decrease any emotional response by reinterpreting the meaning of the displayed situation to either happen in a positive context or with a positive ending. The *distraction* condition required participants to shift the attention away from the emotional stimulus by thinking about a neutral situation not related to the presented situation on the picture. The *view* condition served as a control condition for emotional responses and emotion regulation outcomes, requesting participants to simply watch negative (view negative) and neutral pictures (view neutral) without intending to downregulate the upcoming emotions. The emotion regulation paradigm thus consisted of four different conditions (view neutral, view negative, reappraisal, distraction), which were randomly presented in sets of 15 trials.

After having received the instructions for the emotion regulation conditions, the experimenter practiced the different strategies together with the participant showing sample pictures and asking for an alternative interpretation (reappraisal) or a neutral situation, which the participant could think of (distraction), giving corrective feedback whenever necessary. Prior to the start of the actual emotion regulation paradigm, participants were then familiarized with the procedure using six computer-based practice trials (two of each regulation condition, one for the view negative and one for the view neutral condition). Stimulus presentation and behavioral recordings were controlled by MATLAB R2018a (MathWorks Inc. Natick, MA) on a PC running on Windows 10.

Overall, the paradigm consisted of 60 trials with 45 negative and 15 neutral pictures each presented only once for a participant. At the beginning of each trial, a 750 ms instructional cue (view, reappraisal, distraction) appeared on the screen, which was followed by a luminance-matched white fixation cross on a grey background for ,500 ms. Subsequently, the picture was presented for 5000 ms, which served both as the emotion induction and emotion regulation phase. After each picture presentation, participants were asked to rate their emotional response on a 9-point visual analogue scale regarding arousal (ranging between 1 = emotionally quiet to 9 = emotionally active) and valence (ranging between 1 = unpleasant to 9 = pleasant). A third scale (5-point scale ranging from 1 = not successful at all to 5 = very good) requested the participants to estimate the success in applying the respective emotion regulation strategy. Every scale was presented for 5000 ms. The trial ended with an inter-trial interval of 2000 ms.

A set of 25 low intensive negative (valence: $M = 3.21$, $SD = 0.69$; arousal: $M = 6.5$, $SD = 0.64$), 20 high intensive negative (valence: $M = 2.09$, $SD = 0.39$; arousal: $M = 7.40$, $SD = 0.22$) and 15 neutral pictures (valence: $M = 5.00$, $SD = 0.44$; arousal: $M = 4.26$, $SD = 0.36$) were selected from the Nencki Affective Picture System (NAPS; Marchewka et al., 2014). Based on normative ratings, negative pictures were rated as significantly more arousing ($t(58) = -14.68$, $p < 0.001$) and less pleasant ($t(58) = 10.56$, $p < 0.001$) than neutral pictures. Additionally, high intensive negative pictures were significantly more arousing ($t(43) = -5.91$, $p < 0.001$) and less pleasant ($t(43) = 6.30$, $p < 0.001$) than low intensive negative pictures. We created three clusters of 15 negative pictures with an equal distribution of low and high intensive negative pictures, which were then randomly assigned to the *view*, *reappraisal* and *distraction* condition. Pictures within one cluster were presented in a random order. All pictures were matched for content, complexity and mean luminosity using the MATLAB R2016a SHINE toolbox (MathWorks Inc.). A white fixation cross displayed on a grey luminance-matched background (2500 ms) was presented prior to each picture presentation to control for the level of illumination. The stimuli were landscape in orientation (1024 × 768 pixels) and displayed in greyscale.

2.5 | Pupillometry

To record changes in pupil diameter, iView eye-tracking glasses (iViewETG 2.0, SensoMotoric Instruments, Germany) connected to a SMI-ETG recording device (Lenovo X230-Notebook) were used. An infrared-sensitive eye camera detected retinal and corneal reflections providing pupil diameter data of both eyes. Prior to recording, a one-point calibration procedure was conducted to ensure correct tracking of the pupil. The viewing distance was set to 60 cm while the position of the participant´s head was stabilized in a chin rest. Pupil data were continuously recorded at a binocular sampling rate of 30 Hz during the emotion regulation paradigm. Constant moderate illumination without daylight luminance in the testing room reduced the influence of different light conditions.

Analysis of pupillary data. Preprocessing of pupillary data was conducted according to routines reported in previous studies from our laboratory (Kinner et al., 2017; Langer et al., 2020). Pupil diameter was averaged across both eyes and subsequently smoothed with a finite impulse response filter at 6 Hz. For each trial, onsets of event-locked segments (instructional cue, fixation cross, picture presentation) were marked. Trials with a pupil size outside a feasible range between 1.5 and 9 mm (Kret et al., 2014) were discarded and outliers in dilation speed with a maximum cutoff threshold of 6 median absolute deviations removed (MAD; Kret & Sjak-Shie, 2018). We used a MATLAB-based algorithm to discard trials with major eye blinks (>100 ms) and to correct trials with smaller gabs due to eyelid occlusions with linear interpolation. For each participant and each trial, baseline pupil size was defined

as the mean pupil diameter recorded during the 300 ms prior to picture onset. Baseline pupil size was then subtracted from the mean pupil diameter during picture presentation for each trial to correct for individual differences in pupil size. As a measure of total pupillary increase in response to emotional picture presentation, we calculated the area under the curve with respect to ground (AUCg) from 2s to 5s after picture onset (Langer et al., 2020, 2021). Pupil dilations were averaged across each emotion regulation condition for low and high intensive negative pictures, respectively.

2.6 | Statistical analysis

To investigate time-dependent effects of cortisol on cognitive emotion regulatory outcomes, a 2 × 2 between-subjects design with the factors *treatment* (hydrocortisone vs. placebo) and *delay* (immediate vs. delayed) was realized. Statistical analyses were conducted using IBM SPSS Statistics 20 (Armonk, USA) for Windows. The significance level was set to $\alpha = 0.05$. After checking for normality using Kolmogorov-Smirnov tests, data were log-transformed if necessary. In addition, all dependent variables were checked for homogeneity of variance using Levene-tests. In case of violation of the sphericity assumption, *p*-values and degrees of freedom were Greenhouse-Geisser corrected. Partial eta square (η^2) served as estimations of effect sizes.

All analyses of variance (ANOVAs) included the between-subjects factors *treatment* (hydrocortisone vs. placebo) and *delay* (immediate vs. delayed). For the analyses of cortisol, alpha amylase and negative affect ratings, ANOVAs with the repeated measures factor *time* (baseline vs. +30 min vs. +60 min vs. +90 min vs. +120 min) were conducted. To verify successful emotion induction and regulation as well as to test whether cortisol had a time-dependent influence on emotion regulatory outcomes, mixed-design ANOVAs with the repeated measures factor *condition* (view neutral vs. view negative vs. reappraisal vs. distraction) and *intensity* (low intensive negative pictures vs. high intensive negative pictures) for subjective ratings (arousal, valence, success) and pupil dilations (AUCg) were applied. Significant interactions were solved using appropriate (Bonferroni-corrected) *post-hoc* tests.

3 | RESULTS

3.1 | Salivary cortisol, alpha amylase and negative affect ratings

Five participants displayed extremely high cortisol values (increases larger than 350 nmol/l), most likely due to some micro hydrocortisone residue of the uncoated tablet in the mouth of the participants (cf. Merz et al., 2010), which thus were excluded from hormonal analyses. Due to insufficient amount of saliva, data of one additional participant was missing. Salivary cortisol levels increased after hydrocortisone compared to placebo administration (main effect of time: $F(2.56,189.45) = 64.75$, $p < 0.001$; $\eta^2 = 0.467$; main effect of treatment: $F(1,74) = 122.94$, $p < 0.001$; $\eta^2 = 0.624$; time × treatment interaction: $F(2.56,189.45) = 108.31$, $p < 0.001$; $\eta^2 = 0.594$), indicating successful pharmacological treatment. Bonferroni-corrected *post-hoc* t-tests showed that cortisol was significantly elevated 30, 60, 90 and 120 min compared to baseline after hydrocortisone (all *p*s < 0.001; Figure 2a), but not after placebo administration (all *p*s < 0.001; Figure 2a). There were no main or interaction effects with the delay, suggesting that the immediate and delayed group did not differ in cortisol increases (all *p*s ≥ 0.495). No differences in negative affect ratings (Figure 2b) or alpha-amylase levels, indexing sympathetic nervous activity, between cortisol and placebo treated participants were found (no main effect of treatment: both *p*s ≥ 0.533; no time × treatment interaction: both *p*s ≥ 0.070).

3.2 | Emotion induction and regulation

3.2.1 | Affective ratings

For arousal, valence and success ratings, ANOVAs revealed significant differences between the four emotion regulation conditions (main effects of condition, arousal: $F(2.74,231.19) = 107.32$, $p < 0.001$; $\eta^2 = 0.573$; valence: $F(2.42,220.76) = 136.17$, $p < 0.001$; $\eta^2 = 0.630$; success: $F(2.38,223.56) = 107.22$, $p < 0.001$; $\eta^2 = 0.570$). *Post-hoc* pairwise comparisons showed that participants rated negative pictures as significantly more arousing and less pleasant than neutral pictures (both *p*s < 0.001), verifying successful induction of negative emotions. Negative pictures were rated as significantly less arousing ($p = 0.012$) and more pleasant ($p < 0.001$) when applying reappraisal and more pleasant when applying distraction ($p < 0.001$) compared to just viewing them. As expected, high intensive negative pictures were rated as significantly more arousing and less pleasant than low intensive negative pictures (main effects of intensity, arousal: $F(1,80) = 120.69$, $p < 0.001$; $\eta^2 = 0.601$; valence: $F(1,80) = 246.32$, $p < 0.001$; $\eta^2 = 0.755$). Further, significant condition × intensity interactions (arousal: $F(2.89,231.19) = 49.88$, $p < 0.001$; $\eta^2 = 0.384$; valence: $F(2.80,220.76) = 85.83$, $p < 0.001$; $\eta^2 = 0.518$; success: $F(2.76,223.56) = 31.19$, $p < 0.001$; $\eta^2 = 0.279$) revealed that participants successfully downregulated negative emotions evoked by high intensive negative pictures but not by low

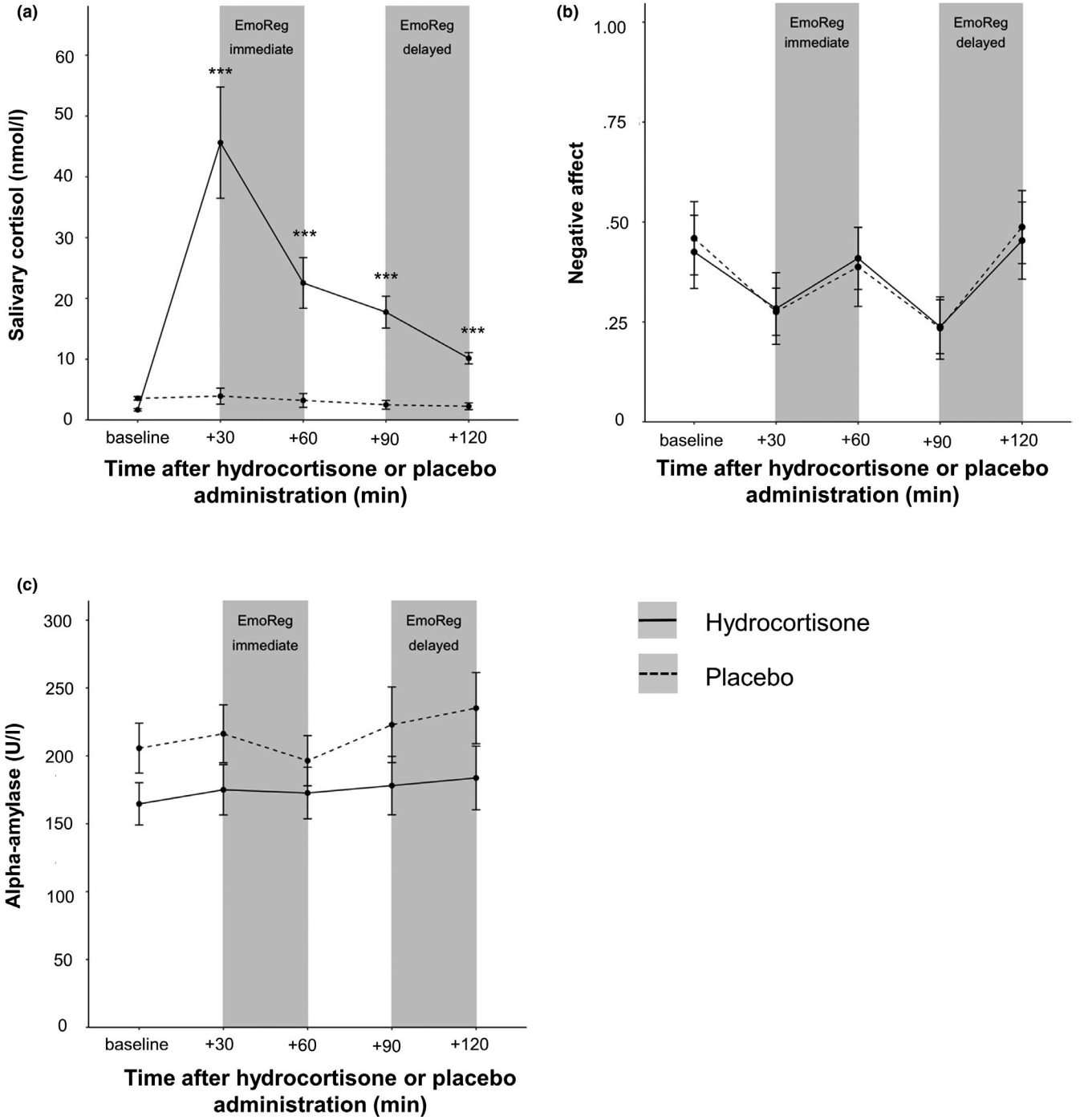

FIGURE 2 Mean (± *SEM*) salivary cortisol concentrations (a), mean (± *SEM*) negative affect ratings (b) and mean (± *SEM*) alpha-amylase concentrations (c) before, 30, 60, 90 and 120 min after administration of 10 mg hydrocortisone or placebo. Hydrocortisone administration led to significant elevations of cortisol concentrations 30, 60, 90 min as well as 120 min after tablet intake, whereas participants neither differed in subjective negative affect nor in alpha-amylase concentrations. For illustration purposes, raw data are displayed. Time points of the emotion regulation paradigm in the immediate and the delayed group are represented by shaded areas. Significantly elevated cortisol levels in the hydrocortisone compared to the placebo treatment as a result of Bonferroni-corrected *post hoc* tests are marked as follows: ***$p < 0.001$

intensive negative pictures (main effects of condition, arousal: $F(2.85,231.09) = 107.06$, $p < 0.001$; $\eta^2 = 0.569$, Figure 3a; valence: $F(2.71,219.50) = 173.65$, $p < 0.001$; $\eta^2 = 0.682$, Figure 3b). In contrast to low intensive negative pictures, high intensive negative pictures were rated as significantly less arousing and more pleasant after downregulating negative emotions via reappraisal (both ps < 0.001) and distraction (both ps ≤ 0.033) compared to just viewing them. There was no modulation of arousal and valence ratings by reappraisal and distraction after presentation of low intensive negative

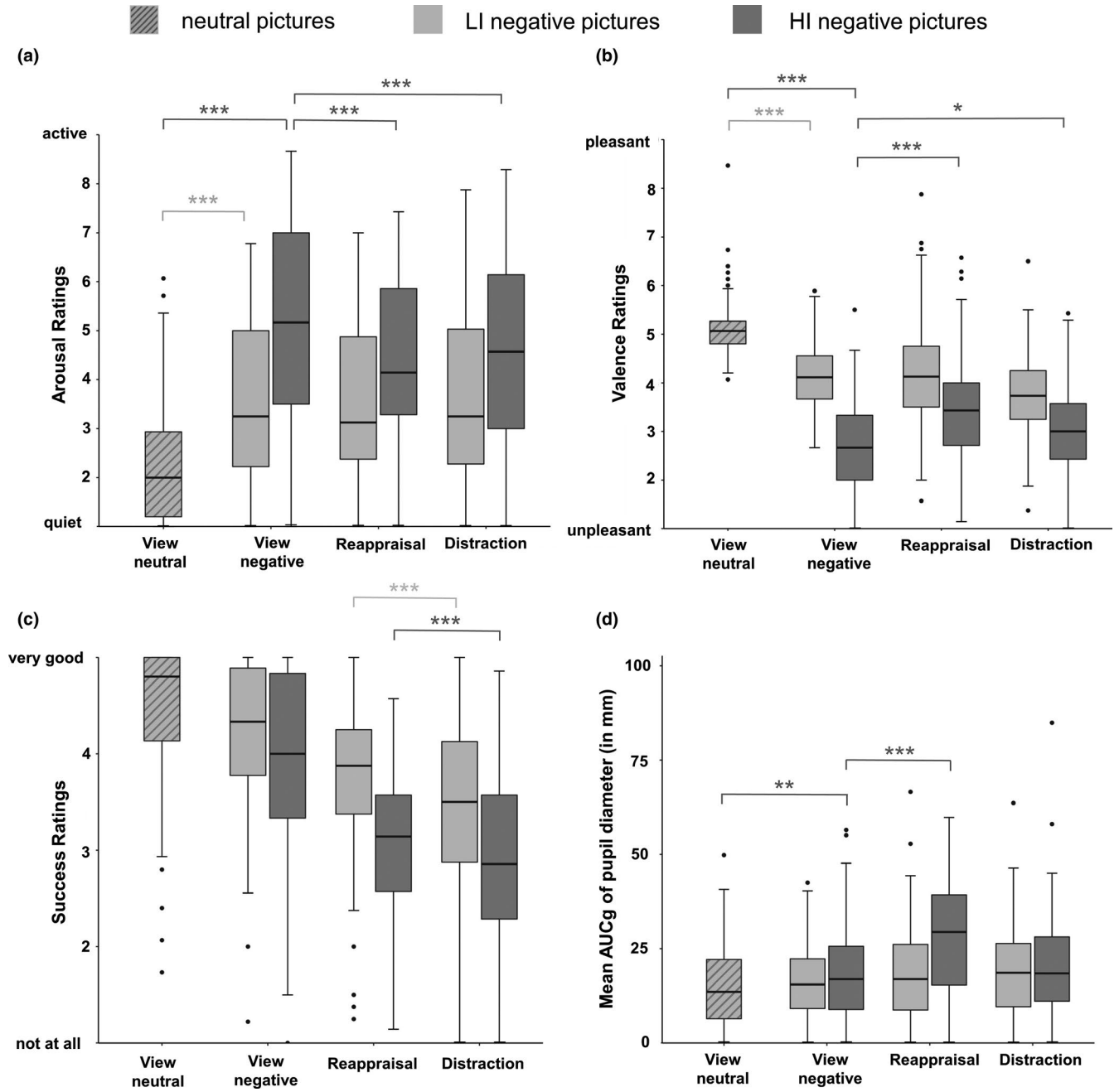

FIGURE 3 Box plots showing subjective arousal (a), valence (b) and success ratings (c) as well as pupil diameter (d) indexed by the area under the curve with respect to ground (AUCg) for neutral, low intensive (LI) and high intensive (HI) negative pictures with respect to each emotion regulation condition (view, reappraisal, distraction). Medians are represented by horizontal lines within the boxes ranging from the first (bottom: Q1) to third quartile (top: Q3). The minimum and maximum are indicated by whiskers extending from the boxes. Black dots display outliers defined as >1.5 interquartile range (Q3 – Q1) below Q1 or above Q3. For both, low intensive and high intensive negative pictures, successful emotion induction was indicated by increased arousal (a) and reduced valence ratings (b) as well as increased pupil dilations (d; for HI negative pictures only) compared to neutral pictures. Whereas application of reappraisal and distraction after presentation of low intensive negative pictures neither modulated affective ratings nor pupil diameter, downregulation of emotions evoked by high intensive negative pictures via reappraisal and distraction led to reduced arousal (a), enhanced valence ratings (b) as well as increased pupil sizes (d) compared to the view condition. Significant effects after Bonferroni-corrected pairwise comparisons are marked as follows: ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$

pictures (all *p*s = 1.0; Figure 3a and b). Irrespective of emotional intensity, participants reported to be more successful in downregulating negative emotions by reappraising the presented situation than distracting themselves from the emotional content of the picture (main effects of condition, success: low intensive: $F(2.40,194.17) = 56.44$, $p < 0.001$; $\eta^2 = 0.411$; high intensive: $F(2.59,209.71) = 117.09$, $p < 0.001$; $\eta^2 = 0.591$, *post-hoc* comparisons: both *p*s < 0.001; Figure 3c).

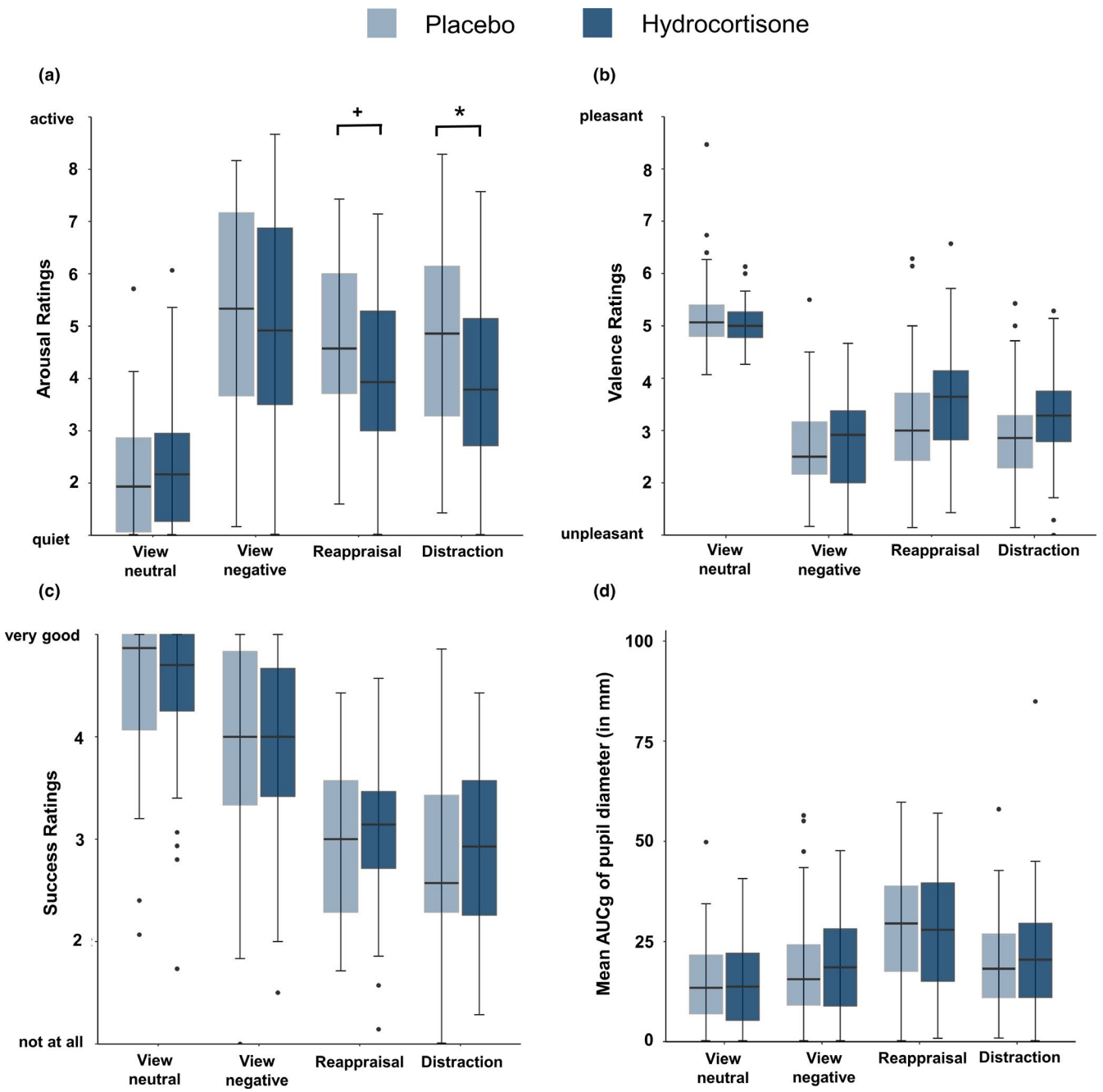

FIGURE 4 Box plots showing subjective arousal (a), valence (b) and success ratings (c) as well as pupil diameter (d) indexed by the area under the curve with respect to ground (AUCg) for neutral and high intensive negative pictures after cortisol and placebo administration with respect to each emotion regulation condition (view, reappraisal, distraction). Medians are represented by horizontal lines within the boxes ranging from the first (bottom: Q1) to third quartile (top: Q3). The minimum and maximum are indicated by whiskers extending from the boxes. Black dots display outliers defined as >1.5 interquartile range (Q3 – Q1) below Q1 or above Q3. Cortisol treated participants showed reduced arousal and descriptively enhanced valence ratings after distraction and reappraisal (a) compared to participants receiving placebo. (Trend-) significant effects after Bonferroni-corrected pairwise comparisons are marked as follows: $^{*}p < 0.05$; $^{+}p = 0.088$

3.2.2 | Pupil diameter

Analyses of pupillary data revealed that pupil diameter differed significantly between the emotion regulation conditions (main effect of condition: $F(2.60,135.80) = 18.56$, $p < 0.001$; $\eta^2 = 0.236$; Figure 3d). *Post-hoc* pairwise comparisons revealed significantly larger pupil dilations after viewing negative compared to neutral pictures ($p = 0.007$), indicating greater pupil sizes with increasing emotional arousal. Downregulation of negative emotions

via reappraisal was followed by a further increase in pupil diameter compared to just viewing negative pictures ($p < 0.001$) indicating that the pupil is further modulated by the increase in cognitive effort to reappraise the presented situation on the picture. High intensive negative pictures caused stronger pupil size enlargements than low intensive negative pictures (main effect of intensity: $F(1,60) = 185.86$, $p < 0.001$; $\eta^2 = 0.756$). A significant condition × intensity interaction ($F(2.26,135.80) = 12.14$, $p < 0.001$; $\eta^2 = 0.168$) showed that pupil diameter was only increased by the emotional content and further enlarged applying reappraisal after viewing high intensive (both ps ≤ 0.003; Figure 3d) but not after low intensive negative pictures (all ps ≥ 0.369; Figure 3d).

3.3 | Effects of cortisol on cognitive emotion regulation

3.3.1 | Affective ratings

Analyses of arousal ratings revealed significant differences between cortisol and placebo treated participants depending on the emotion regulation condition (treatment × condition interaction: $F(2.74,231.19) = 3.04$, $p = 0.034$; $\eta^2 = 0.037$). *Post-hoc* pairwise comparisons of each emotion regulation condition turned out to be non-significant (all ps ≥ 0.327). However, analyses revealed a trend for a treatment × condition × intensity interaction ($F(2.89,231.19) = 2.13$, $p = 0.098$; $\eta^2 = 0.026$). Exploratory *post-hoc* ANOVAs separately for both negative emotional intensities resulted in a significant treatment × condition interaction for high intensive negative pictures ($F(2.85,231.09) = 3.62$, $p = 0.015$; $\eta^2 = 0.043$; Figure 4a). Subsequent t-tests indicated that cortisol treated participants rated high intensive negative pictures as significantly less arousing than participants receiving placebo when applying distraction ($t(83) = 2.01$, $p = 0.048$) and on a trend level when applying reappraisal ($t(83) = 1.73$, $p = 0.088$). No such treatment effect was found for low intensive negative pictures (treatment × condition interaction: $p = 0.216$). With respect to valence ratings, the three-way interaction between treatment, condition and intensity neither reached significance nor was it apparent as a trend ($p = 0.161$). Due to a significant treatment × intensity interaction ($F(1,220.76) = 4.60$, $p = 0.035$; $\eta^2 = 0.054$), separate mixed-design ANOVAs for each intensity were conducted. Whereas the main effect of treatment did not reach significance for low or high intensive negative pictures (both ps ≥ 0.270), a marginally significant treatment × condition interaction for high intensive negative pictures was found ($F(2.71,219.50) = 3.07$, $p = 0.078$; $\eta^2 = 0.028$). Exploratory *post-hoc* pairwise comparisons for each emotion regulation condition revealed no significant differences between the cortisol and placebo group (all ps ≥ 0.130). However, on a descriptive level, cortisol treated participants rated high intensive negative pictures as more pleasant than participants receiving placebo after applying reappraisal and distraction (Figure 4b). There were no differences between cortisol and placebo treated participants in regulatory success ratings (no main effect of treatment: $p = 0.974$; no treatment × condition interaction: $p = 0.683$; no treatment × condition × intensity interaction: $p = 0.690$; Figure 4c). For arousal, valence and success ratings, no significant interaction with the factor *delay* (immediate vs. delayed) was found (all ps ≥ 0.195, Table 1; for additional descriptive statistics of arousal and valence ratings with respect to delay, pharmacological treatment, emotion regulation condition regarding low and high intensive pictures separately, see Supplementary Information A).

3.3.2 | Pupil diameter

No significant differences in pupil dilations between cortisol and placebo treated participants for any of the emotion regulation conditions were found (no main effect of treatment:

	Immediate		Delayed	
Arousal	Hydrocortisone	Placebo	Hydrocortisone	Placebo
View neutral	2.44 (± 0.28)	2.03 (± 0.27)	2.30 (± 0.26)	2.24 (± 0.28)
View negative	3.99 (± 0.38)	4.20 (± 0.37)	4.55 (± 0.36)	4.58 (± 0.38)
Reappraisal	3.79 (± 0.35)	4.04 (± 0.34)	3.80 (± 0.33)	4.28 (± 0.35)
Distraction	3.86 (± 0.38)	4.21 (± 0.37)	3.80 (± 0.35)	4.43 (± 0.38)
Valence				
View neutral	5.11 (± 0.14)	5.21 (± 0.13)	5.00 (± 0.13)	5.30 (± 0.14)
View negative	3.72 (± 0.16)	3.53 (± 0.15)	3.21 (± 0.15)	3.23 (± 0.16)
Reappraisal	3.99 (± 0.24)	3.50 (± 0.24)	3.87 (± 0.22)	3.93 (± 0.24)
Distraction	3.68 (± 0.18)	3.28 (± 0.18)	3.33 (± 0.17)	3.34 (± 0.18)

TABLE 1 Mean (± *SEM*) subjective arousal and valence ratings in the immediate and delayed group after hydrocortisone and placebo administration with respect to each emotion regulation condition

$p = 0.934$, no treatment × condition interaction: $p = 0.847$, no treatment × condition × intensity interaction: $p = 0.887$). In addition, no significant modulations by *delay* occurred (all ps ≥ 0.587).

4 | DISCUSSION

To the best of our knowledge, the present study is the first experiment systematically comparing immediate and delayed effects of oral cortisol administration on the effectiveness to downregulate negative emotions via reappraisal and distraction and further explored the role of emotional intensity for these effects. Reduced arousal, enhanced valence ratings and increases in pupil dilations indicated successful emotion induction and regulation after presentation of high intensive but not low intensive negative pictures. Independent of the timing of pharmacological treatment, cortisol further improved the effectiveness of distraction and (at a trend level) reappraisal to downregulate subjective emotional arousal evoked by high intensive negative pictures. By contrast, application of reappraisal and distraction in response to low intensive negative pictures neither reduced arousal nor enhanced valence ratings or pupil dilations and was not further modulated by cortisol.

This study indicates that cortisol may exert beneficial effects on the cognitive downregulation of high intensive negative emotions, resulting in reduced subjective emotional arousal within a rapid (30 min) and delayed (90 min) post-treatment time window. Although we found less strong cortisol effects than expected, the results are in accordance with findings showing that cortisol promotes the cognitive downregulation of negative emotions (Jentsch et al., 2019) probably mediated by increases in prefrontal functioning (Jentsch et al., 2019; Urry, 2006) and inhibitory effects on emotion-related amygdala responsivity (Henckens et al., 2010). Several lines of evidence demonstrated a cortisol-induced reduction of negative affect in response to psychosocial stress (Het et al., 2012; Het & Wolf, 2007; Reuter, 2002), phobic fear (Nakataki et al., 2017; Soravia et al., 2006) and anxiety-driven selective attention to threat (Putman et al., 2007). Together with this work, our findings might indicate that cortisol protects an individual from high intensive negative affective states via boosted emotion regulation capacities. Consistent with this speculation, recent studies from our lab showed acute stress to promote reappraisal (Langer et al., 2020) and distraction success (Langer et al., 2021) 30 and 90 min after stress exposure, respectively. Importantly, in both studies the regulatory improvements were linked to cortisol increases in response to the stressor, implying that the beneficial effects of stress on cognitive emotion regulation may be primarily mediated via GC mechanisms. However, contrary to these findings, acute stress has been also shown to impair emotion regulation of conditioned fear (Raio & Phelps, 2015), the effectiveness to be distracted from emotional material (Kinner et al., 2014) and cognitive flexibility (Fournier et al., 2017). It has to be noted though, that stress does not only trigger the secretion of cortisol but also of monoamines, such as catecholamines, and neuropeptides (Joëls & Baram, 2009). Importantly, stress-induced impairments of fear regulation (Raio & Phelps, 2015) have been positively associated with increases in alpha-amylase (an index of sympathetic nervous system activity; Nater & Rohleder, 2009). In a similar vein, β-adrenergic receptor blockade but not the inhibition of cortisol synthesis has been shown to diminish stress-induced increases in functional connectivity between the amygdala and other salience network regions (Hermans et al., 2011). It might thus be speculated that stress-induced impairments of cognitive emotion regulation are primarily driven by noradrenergic excitatory effects on amygdala activity and inhibitory effects on prefrontal activation (Arnsten, 2009), ultimately leading to stronger emotional responding. By contrast, data of the present study might imply that rapid, non-genomic and delayed, genomic cortisol actions both contribute to better cognitive emotional control functioning. Future studies using pharmacological agents to block or activate glucocorticoid and noradrenergic receptors are needed to determine the specific effects mediated by each system.

Cortisol affected neither subjective success ratings nor pupil dilations in response to cognitive emotion regulation. Pupil size increases have been positively related to prefrontal activity (Urry, 2006). This finding corroborates with studies demonstrating that pupil dilations not only reflect emotional arousal but also critically index the cognitive effort during deliberate attempts to cognitively downregulate negative emotions (Kinner et al., 2017; Langer et al., 2020). Here, cortisol did not lead to a further increase in pupil size or enhanced success ratings during emotion regulation trials. One might therefore speculate that cortisol may improve regulatory outcomes (reflected in reduced emotional arousal) without additional cognitive engagement and awareness of the regulatory improvement. In line with this interpretation, imaging data (Henckens et al., 2010) revealed that cortisol suppresses amygdala responsivity in response to emotional stimuli 75 min after administration of 10 mg hydrocortisone, while PFC-amygdala connectivity did not differ between the cortisol and placebo group. In addition, there are several stress studies demonstrating that cortisol secretion actively contributes to the gradual downregulation of the salience network, thereby fostering prefrontal control functioning (for a review, see Hermans et al., 2014). Data of the present study may thus contribute to this line of evidence, suggesting that cortisol supports the downregulation of emotional responsivity in the first place, thereby facilitating deliberate attempts to cognitively regulate negative emotions. However, future studies including additional valence-specific physiological

measurements of emotional responsivity and regulatory outcome are clearly needed to examine the effect of cortisol on objective regulatory outcome markers.

As far as we know, the study reported here is the first experiment to show that beneficial effects of cortisol on the cognitive regulation of subjective emotional arousal are more pronounced when dealing with high intensive compared to low intensive negative emotions. Previous studies already indicated that the effectiveness of an emotion regulation strategy depends on the intensity of the emotional stimuli (Shafir et al., 2016). Our data extend these findings by demonstrating that the beneficial effects of cortisol on cognitive emotion regulation may also vary as a function of intensity of the emotional material used. In particular, we found cortisol to support the downregulation of subjective emotional arousal for trials evoking high intensive but not low intensive negative emotions. This finding supports the idea of cortisol having an adaptive function (Hermans et al., 2014; Smeets et al., 2018; Vogel et al., 2016) that might reduce the risk of an affective overload in response to highly emotionally challenging situations (Het et al., 2012; Het & Wolf, 2007). It has to be noted though that independent of pharmacological treatment, participants were generally successful in downregulating high intensive emotions, whereas they failed to effectively regulate emotions evoked by low intensive negative pictures. Given that low intensive negative pictures triggered less strong emotional responses in the first place, the better regulatory outcomes for high intensive negative emotions appear somewhat counterintuitive. However, lower negative emotional experiences may also cause a lower need to regulate (Barrett et al., 2001). It might thus be speculated, that participants were less motivated to put effort in downregulating low intensive emotions. In line with this idea, we found pupil size increases (reflecting cognitive effort) in regulatory trials using high but not low intensive negative pictures. Following up on this hypothesis, it could be reasonable that a certain degree of cognitive regulatory engagement is necessary for cortisol to exert its modulatory effects on emotion regulation processes. Future work directly inducing a variation in the cognitive regulatory engagement to determine its role for cortisol effects on emotion regulatory outcomes might be promising.

Contrary to previous expectations, we did not find significant time-dependent or strategy-specific effects of cortisol on cognitive emotion regulation. More precisely, the assumed interaction effect of cortisol on cognitive regulatory outcomes in dependence of the delay, strategy use and emotional intensity turned out to be somewhat smaller than expected based on previous findings (assumed: $d = 0.31$, actually achieved: $d = 0.024$). However, research on the impact of cortisol on cognitive emotion regulation is scarce and results are highly heterogeneous. Hence, our hypotheses and assumed effect sizes for this study were mainly derived from existing literature regarding the effects of acute stress manipulations on cognitive emotion regulation (Kinner et al., 2014; Langer et al., 2020, 2021). Yet, stress does not only trigger the release of cortisol, but also of other monoamines, neuropeptides and steroids (Joëls & Baram, 2009), possibly interacting with cortisol to alter cognitive control functioning. This might explain smaller effects when focusing on cortisol solely. Beyond, it is worth mentioning that cortisol levels were still elevated 90 min after hydrocortisone administration (i.e. the starting point of the emotion regulation paradigm for the delayed group) and thus, non-genomic GC actions could have affected emotion regulatory outcomes for both, the immediate and delayed cortisol group. This in turn might explain why we did not find any time-dependent effects. Alternatively, the improving effects of cortisol on cognitive emotion regulation might also be driven by a combination of non-genomic and genomic cortisol effects. Given that we could not effectively isolate fast and slow cortisol effects with the timing implemented in the current study, one cannot exclude possible opposing GC actions in the delayed group that might have reduced present effect sizes. In view of evidence suggesting strategy-dependent improvements of cognitive emotion regulation capacities after stress as a function of timing (Langer et al., 2020, 2021), the failure to separate cortisol actions might also account for absent differences in reappraisal and distraction. Furthermore, to the best of our knowledge, the present study is the first varying the intensity of the negative emotional material when investigating cortisol effects on regulatory outcomes. Besides neutral and low intensive negative pictures, the current emotion regulation paradigm included 14 trials of high intensive negative pictures (7 trials for each strategy). In fact, only those high intensive negative pictures were experienced as significantly more arousing and unpleasant than neutral pictures and hence elicited a sufficiently strong emotional response that could be further modulated by deliberate emotion regulatory attempts. The relatively small number of trials evoking pronounced emotional responses might therefore additionally account for the limited statistical power compared with previous studies probably also contributing to the smallish effect of cortisol on regulatory outcomes in subjective emotion arousal. Future work increasing the number of trials focusing on high intensive negative emotional stimuli only might contribute to more robust effects. In order to clearly separate non-genomic from genomic cortisol effects on cognitive emotion regulation strategies, future studies should extend the delay between hydrocortisone administration and the emotion regulation paradigm (see e.g. Henckens et al., 2012).

Some limitations have to be mentioned. First, beneficial cortisol effects on the ability to downregulate high intensive negative emotions were only evidenced by subjective

emotional arousal and were based on a marginally significant three-way interaction. Interpretations of (trend-) significant *post-hoc* effects are therefore limited. Second, the sample consisted of male participants only. Given complex interactions between GCs and sex hormones (Kirschbaum et al., 1999; Merz & Wolf, 2017; Toufexis et al., 2014), our findings thus cannot be generalized to women. Previous studies from our lab reported sex differences in the influence of stress-induced cortisol increases on cognitive emotion regulation (Kinner et al., 2014; Langer et al., 2020). Consistently, administration of hydrocortisone frequently resulted in distinct effects on cognitive functioning and regulatory brain activation in men and women (Andreano & Cahill, 2006; Jentsch et al., 2019; Merz et al., 2010). Since most of the studies investigating the time-dependent impact of hydrocortisone administration on cognitive and affective processes are conducted in men only (Cornelisse et al., 2014; Henckens et al., 2010, 2012), our results are easy comparable to them. However, in future studies it will be of utmost importance to examine sex-specific effects of exogenous cortisol administration on cognitive emotion regulation. Third, pupil dilation has been shown to index both, emotional arousal and cognitive emotion regulatory effort (e.g. Kinner et al., 2017). Since pupil dilation is not specific for valence (Zaehringer et al., 2020), future studies including additional physiological measurements such as the startle reflex (as an index of valence; Zaehringer et al., 2020), skin conductance response, changes in heart rate variability (as an additional marker for emotional arousal; Appelhans & Luecken, 2006; Matejka et al., 2013) or corrugator electromyography (as an index of both, valence and arousal; Heller et al., 2014; Tan et al., 2016) may help to reduce this ambiguity.

5 | CONCLUSION

In sum, the present study provides further evidence that cortisol may improve the ability to cognitively downregulate high intensive negative emotions both, 30 and 90 min after pharmacological treatment with 10 mg hydrocortisone. Our findings therefore support and extend existing data from experimental stress studies, suggesting cortisol to be an important mediator of the beneficial effects of stress on cognitive emotion regulation processes that might aid the adaptive recovery from acute emotionally challenging stress states.

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CONFLICTS OF INTEREST

The DFG had no role in study design, collection, analysis and interpretation of data, writing of the manuscript or in the decision to submit the paper for publication. All authors reported no biomedical financial interests or potential conflicts of interest.

AUTHOR CONTRIBUTIONS

KL acquired, analyzed and interpreted data, drafted the manuscript and prepared figures. VLJ and OTW designed the work, interpreted data, edited and revised the manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available at the Open Science Framework (OSF) under https://osf.io/vpdgm/.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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