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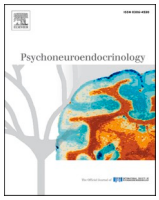

Delayed effects of acute stress on cognitive emotion regulation

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ABSTRACT

Acute stress has been shown to modulate cognitive emotion regulation. Besides interactions with strategy use or sex, another critical modulating factor appears to be stress timing. Exposure to acute stress initiates immediate and delayed glucocorticoid effects on cognitive control functions. Previous studies indicated a delayed increase in prefrontal activity after stress and cortisol elevations, which might also improve the ability to cognitively regulate emotions when the acute stress state has subsided. In this study, we investigated the delayed impact of acute stress on the two emotion regulation strategies reappraisal and distraction. Eighty-one healthy males and free-cycling females were exposed to the Trier Social Stress Test or a control condition 90 min before they were tested in an emotion regulation paradigm, which required them to up- and downregulate their emotional responses towards negative pictures. Affective ratings served to measure emotion regulation success, whereas pupil dilation was included to additionally assess the cognitive effort required to deliberately regulate emotions. Stress affected neither arousal, valence or success ratings nor pupil dilation. However, cortisol increases were significantly associated with reduced arousal and enhanced valence ratings when regulating negative emotions via distraction. Exploratory mediation analyses revealed an indirect effect of stress on arousal and valence ratings for distraction that was mediated by cortisol increase. Our findings thereby provide further evidence that cortisol is positively related to emotion regulation success, which might be driven by a glucocorticoid-mediated mechanism facilitating attentional shifting.

1. Introduction

The ability to cognitively regulate emotions is crucial for psychological functioning and associated with mental health (Kashdan and Rottenberg, 2010). Difficulties to deliberately downregulate negative emotions on the other hand, are mediated by an insufficient recruitment of prefrontal control networks (Zilverstand et al., 2017) and increase the risk for the onset and maintenance of mental disorders (Berking and Wupperman, 2012).

Cognitive emotion regulation can be defined as a set of cognitive processes, with which individuals seek to redirect the spontaneous flow of emotions causing changes in experiential, behavioral and physiological responding (Koole, 2009). Reappraisal and distraction are considered to be amongst the most effective strategies for downregulating negative emotions (Webb et al., 2012). While reappraisal aims to either reduce or intensify emotional experiences by generating an altered interpretation of the emotional situation, distraction enables an individual to focus away from the emotional stimulus (Gross, 2015). Cognitive emotion regulation relies on a neural network composed of prefrontal, inferior parietal and cingulate cortex regions inhibiting emotion-related activation in limbic areas (Etkin et al., 2015; Kanske et al., 2011). Given the clinical relevance of insufficient or maladaptive emotion regulation, it is important to identify factors, which potentially modulate emotion regulation success.

Stress causes an activation of the fast-acting sympathetic nervous system (SNS) leading to the release of the catecholamines epinephrine and norepinephrine and the somewhat slower-acting hypothalamus-pituitary adrenocortical (HPA) axis resulting in the secretion of glucocorticoids (GCs, cortisol in humans; Joëls and Baram, 2009). Cortisol binds to mineralocorticoid (MR) and glucocorticoid receptors (GR) located in the cytoplasm as well as in cell membranes of the brain (Joëls et al., 2012) that affect cognitive and emotional processes in a time-dependent manner (Hermans et al., 2014). Cortisol binding to membrane-bound receptors induces rapid, non-genomic effects (Joëls et al., 2013), which peak 20–30 min after stress onset and continue as long as cortisol concentrations are elevated (Karst et al., 2005). By contrast, cortisol binding to cytoplasmatic receptors triggers delayed genomic effects, which take at least 60 min to initiate and continue for

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several hours (Hermans et al., 2014), leading to changes in gene transcription and translation (Groeneweg et al., 2012; Joëls et al., 2012). Cortisol primarily acts on prefrontal and limbic structures (Dedovic et al., 2009), which are also essential for cognitive emotion regulation.

Initial studies exploring the impact of acute stress on emotion regulatory processes provided mixed evidence for either relatively rapid impairments (Raio et al., 2013; Raio and Phelps, 2015) or improvements of emotion regulatory abilities after acute stress (Kinner et al., 2014; Langer et al., 2020). Stress for instance caused an impairment of cognitive fear regulation (Raio et al., 2013), which was positively correlated with elevated alpha-amylase levels (an index of SNS activity; Nater and Rohleder, 2009). In contrast, research from our lab showed that stress also rapidly improves the effectivity to downregulate negative emotions via cognitive reappraisal (Kinner et al., 2014; Langer et al., 2020), which was positively related to cortisol increases. Consistently, oral administration of cortisol has been shown to enhance prefrontal regulatory activity and reduced emotion-related activity in the amygdala, resulting in a facilitated cognitive downregulation of negative emotions (Jentsch et al., 2019). These findings corroborate with the idea that stress rapidly sensitizes the amygdala at the cost of prefrontal control processes mainly through catecholaminergic actions (Hermans et al., 2014). Yet, as soon as acute stress subsides, GCs actively reverse rapid impairing effects of stress on cognitive functioning thereby supporting prefrontal control activity and contributing to the return of homeostasis. Contradictory findings regarding the effects of stress on cognitive emotion regulation performance might therefore be explained by the opposing effects of catecholamines and GCs acting on the cognitive control of emotions. Several lines of evidence suggest that slow genomic GC actions may promote cognitive control functioning (Henckens et al., 2011) by an increase in prefrontal (Yuen et al., 2009) and a decrease in amygdala activity (Henckens et al., 2010) which might also facilitate cognitive emotion regulation. However, to the best of our knowledge there is no study to date, which investigates the delayed impact of stress on the ability to cognitively downregulate negative emotions.

A growing body of research demonstrates sex differences in stress effects on cognitive and emotional processes (McEwen et al., 2016; Merz and Wolf, 2017; Shields et al., 2016), presumably mediated via complex interactions between GCs and sex hormones, including estrogens, gestagens and androgens (Schoofs and Wolf, 2009; ter Horst et al., 2012). Previous studies from our lab revealed sex-specific effects of stress on emotion regulatory success (Kinner et al., 2014; Langer et al., 2020). Acute stress immediately improved cognitive reappraisal success in men, but neither in free-cycling women nor in women taking oral contraceptives (Langer et al., 2020). Correspondingly, diminished subjective emotional responses were observed 90 min after cortisol administration in men, but not in women (Jentsch et al., 2019).

Taken together, previous work provide support for stress-sex interactions on cognitive emotion regulation. Yet, it remains unclear whether and how stress initiates delayed genomic GC effects on emotion regulatory processes and which factors might be critical in mediating these effects. To address these issues, the present study aimed at investigating the delayed effects of acute stress on the effectivity to regulate negative emotions. An increase in cortisol as a marker of HPA axis activity, alpha-amylase indirectly assessing noradrenergic arousal (Nater and Rohleder, 2009) as well as subjective negative affect scores served to check successful stress induction. Affective ratings of arousal, valence and regulatory success were assessed to index subjective regulation outcome. Recordings of changes in pupil diameter were included as an additional physiological proxy of emotion regulation processes (Kinner et al., 2017; Langer et al., 2020). Although changes in pupil dilation are typically considered as a measure of emotional arousal, there are several studies demonstrating that the pupil also dilates as a function of cognitive effort required to regulate upcoming emotions (Kinner et al., 2017; Langer et al., 2020; Urry, 2006; van Reekum et al., 2007). An increase in pupil size can therefore reflect both, an increase in emotional arousal or cognitive effort.

Given that slow GC effects have been shown to facilitate executive control functions (Hermans et al., 2014), we expected an improved effectivity to regulate negative emotions in the aftermath of stress. As such, we hypothesized reduced arousal, enhanced valence and success ratings as well as increases in pupil dilations reflecting enhanced regulatory engagement 90 min after stress relative to the control condition. Since cortisol has been positively related to reappraisal success (Langer et al., 2020) and increases in prefrontal control of emotions (Jentsch et al., 2019) we further expected cortisol, but not alpha-amylase, to be significantly associated with the beneficial effects of stress on emotion regulation outcomes. Stress has been shown to affect cognitive and emotional processes primarily in men (Shields et al., 2016). Thus, we hypothesized that the delayed effects of stress on regulatory success are more pronounced in men than in women.

2. Materials and methods

2.1. Participants

The required sample size was determined using G*Power 3.1 (Faul et al., 2009) assuming a medium-sized sex-dependent effect (d = 0.41) of stress on cognitive emotion regulation as reported in a recent study by Langer et al. (2020). With $\alpha = 0.05$ and an assumed correlation of $r = 0.4$ for repeated measurements, 80 participants were required in order to detect a significant interaction between stress, sex and emotion regulation condition with a power of $1\text{-}\beta \geq 0.95$. Therefore, 81 healthy adults (41 males and 40 females) aged between 18 and 38 years ($M = 24.25$, $SD = 4.29$) and a mean Body Mass Index (BMI) between 18 and 28 ($M = 22.12$ kg/m^2; $SD = 2.38$ kg/m^2) participated in this study. Volunteers were recruited via online advertisements in social media networks, mailing lists and advertisements on notice boards throughout Ruhr University Bochum and surroundings. We restricted study inclusion to participants without any chronic and acute illnesses, history or current medical or psychological treatment, drug use including smoking, previous experiences with the current stress protocol or emotion regulation paradigm. To ensure adequate tracking of pupillary responses, we included only participants with normal and corrected-to-normal vision between + 1.5 and − 1.5 diopters. Since sex hormones can alter the stress-induced secretion of stress hormones (Kirschbaum et al., 1999), emotional reactivity (Bradley et al., 2001) and emotion regulatory processes (McRae et al., 2008), we included men as well as free-cycling women. To reduce alterations in sex hormones over the menstrual cycle, females were exclusively tested in their luteal phase, defined as nine to three days prior to the next menses (Schoofs and Wolf, 2009) with cycle phase assessed via self-report. Participants were randomly assigned to the stress and control group, which did not differ in age ($p = .951$) or BMI ($p = .649$). Moreover, the groups showed an equal distribution of the habitual use of reappraisal ($p = .371$) and distraction ($p = .475$), as assessed with the emotion regulation inventory (ERI). The present study was not pre-registered. All study procedures were conducted in agreement with the Declaration of Helsinki and written informed consent was obtained in accordance with procedures approved by the ethics committee of the Medical Faculty at the Ruhr University Bochum.

2.2. Experimental procedure

Participants were asked to refrain from sports, drugs and alcohol 24 h prior to the start of the experiment and the consumption of food and drinks except water two hours prior to testing. Due to the circadian rhythm of cortisol secretion (Guilliams and Edwards, 2010), all testing were scheduled between 12.30 p.m. and 6.30 p.m. At the beginning of the testing procedure, participants rested for 25 min, during which they read study information, gave written informed consent and answered questionnaires (demographic data, Brief Symptom Inventory (BSI; Derogatis and Melisaratos, 1983) assessing trait anxiety). Participants

provided six saliva samples and affect ratings at several time points across the experiment (for a detailed illustration of the procedure, see Fig. 1). Following baseline collection of a saliva sample and current affective state, participant underwent the stress or control procedure. They then watched four neutral documentary videos (arousal [9-point visual analog scale ranging between 1 = emotionally calm to 9 = emotionally aroused]: $M = 2.59$, $SD = 1.58$; valence [9-point visual analog scale ranging between 1 = negative to 9 = positive]: $M = 6.39$, $SD = 1.62$) providing a standardized waiting period between stressor and emotion regulation task. Subsequently, they were prepared for pupillary recordings, instructed and familiarized with the emotion regulation paradigm, which started 90 min after stress onset. Finally, participants were debriefed and reimbursed with 30€.

2.3. Stress and control manipulation

Half of the participants were exposed to a short version of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) as implemented and described in more detail in Langer et al. (2020). In short, participants in the stress condition underwent a 2 min preparation period, a 5 min free speech in front of a reserved panel (one male/one female) and a 3 min mental arithmetic task, which reliably activates both the SNS as well as the HPA axis. Participants of the control condition were subjected to a placebo version of the Trier Social Stress Test (Het et al., 2009), which is comparable to the TSST in terms of timing and components excluding any stress-inducing factors. It required participants to give a speech about their last holiday, a book or a movie without being observed and to solve an easy mental arithmetic task.

To validate the effectiveness of the TSST in eliciting physiological and psychological stress responses, subjective affect ratings as well as saliva samples were collected using Salivette sampling devices (Sarstedt, Nümbrecht, Germany) at multiple time points (see Fig. 1) that were stored at − 20 °C until assayed. Salivary cortisol was analyzed on a Synergy2 plate reader (Biotek, Winooski, USA) using commercial enzyme-linked immunosorbent assays (ELISAs; free cortisol in saliva; Demeditec, Kiel, Germany) according to the manufacturer's instructions. Intra- and interassay variability were less than CV 9.79%. A colorimetric test was applied, using 2-chloro-4-nitrophenyl-α-maltrotriosoide (CNP-G3) as a substrate reagent to measure salivary alpha-amylase (sAA) concentrations (Lorentz et al., 1999). Intra- and inter-assay variabilities were below CV 5.28%. The affective stress response was assessed using the Differential Affect Scale (DAS; negative affect factors: *sadness, anger, disgust, contempt, anxiety, shame, guilt*; positive affect factors: *joy, surprise, interest*) on a 5-point likert scale ranging from 1 (not at all) to 5 (very strong). A total negative affect and positive affect score was calculated as the mean of the associated factor values.

2.4. Emotion regulation paradigm

A slightly modified version of the emotion regulation paradigm developed by Kanske et al. (2011) was applied (Kinner et al., 2017; Langer et al., 2020). In this task, participants were asked to view negative and neutral pictures or to up- and downregulate their emotional responses towards negative pictures using three different emotion regulation strategies. In the *reappraisal* condition, participants were instructed to reframe the meaning of the presented situation on the picture by imagining it to happen either in a positive context or with a positive ending. The *distraction* condition requested participants to shift the attention away from the emotional stimulus while thinking about a neutral situation, which was not related to the presented situation. In the *intensify* condition, participants were asked to increase their upcoming emotional response by putting themselves in the situation presented on the picture and imagining all negative consequences of it. The *view* conditions required participants to watch and respond naturally to negative (*view negative*) or neutral pictures (*view neutral*) without deliberately regulating upcoming emotions and thus served as control conditions for emotional and regulated emotional responses. The emotion regulation paradigm therefore consisted of five different conditions (view neutral, view negative, intensify, reappraisal, distraction), presented randomly in sets of five trails per condition, once in the first and once in the second half of the paradigm.

In total, the paradigm consisted of 50 trials with each picture presented only once for a given participant. Forty negative pictures were randomly assigned to the three emotion regulation conditions and the *view negative* condition. In addition, 10 neutral pictures were presented in the *view neutral* condition. Each trial started with a 750 ms instructional cue (*view, intensify, reappraisal, distraction*) followed by a white fixation cross displayed on a grey luminance-matched background for 2500 ms. Afterwards, the picture was presented for 5000 ms initializing either automatic emotional responses or the volitional emotion regulation phase according to the respective condition. After picture offset, participants rated their emotional response on a 9-point visual analog scale with regard to arousal (ranging between 1 = emotionally quiet to 9 = emotionally active) and valence (ranging between 1 = unpleasant to 9 = pleasant). Additionally, they were requested to specify how successful they were in applying the respective emotion regulation strategy on a 5-point scale ranging from 1 = not successful at all to 5 = very good. Every rating scale was displayed for 5000 ms. A 2000 ms inter-trial interval depicting a black screen was presented before the start of the next trial.

In order to check whether participants understood the task and were able to apply the different emotion regulation strategies correctly, the experimenter went through all instructions once again together with the participants and then practiced the different strategies with sample pictures (e.g. showing the participants a negative picture and asking

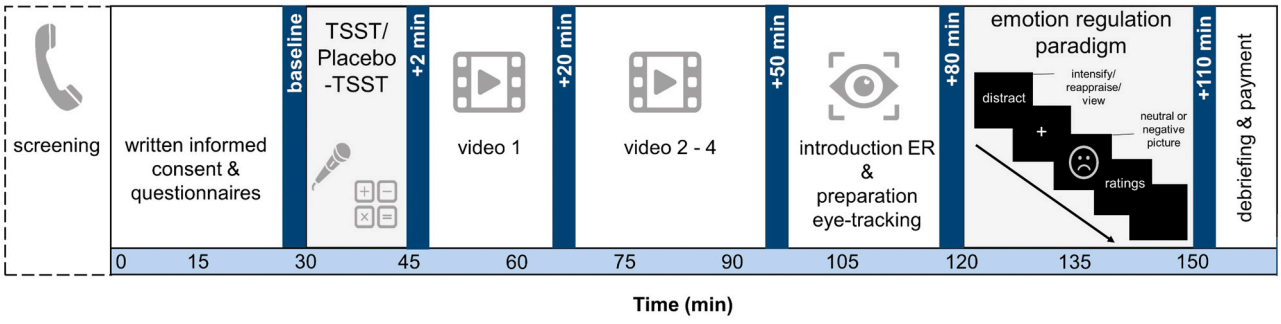

Fig. 1. I Experimental timeline. Participants provided six saliva samples concurrent to affective state ratings via the Differential Affective Scale (DAS) over the course of the experiment (sampling time points for saliva and DAS are highlighted with blue boxes: baseline, +2, +20, +50, +80 and +110 min after the offset of the Trier Social Stress Test (TSST) or Placebo-TSST. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

them which alternative interpretation they could imagine for this specific situation) giving corrective feedback if necessary. Moreover, eight computer-based practice trials (two trials for each regulation condition and one for each view condition) were conducted to familiarize participants with the trial structure and timing of the paradigm. Stimulus presentation and behavioral recordings were controlled by MATLAB R2016a (MathWorks Inc. Natick, MA) on an IBM compatible PC running on Windows 10.

All pictures were selected from the Nencki Affective Picture System (NAPS; Marchewka et al., 2014). A set of 40 negative pictures (valence: $M = 3.55$, $SD = 0.71$; arousal: $M = 4.35$, $SD = 1.53$) and 10 neutral pictures (valence: $M = 5.38$, $SD = 0.68$; arousal: $M = 2.23$, $SD = 0.94$) was chosen (cf. Langer et al., 2020). Based on normative ratings, negative pictures were significantly more arousing ($t_{(47.84)} = 25.15$, $p < .001$) and negative ($t_{(48)} = -13.84$, $p < .001$) than neutral pictures. All pictures were landscape in orientation (1024 × 768 pixels), matched for content and complexity and displayed in greyscale. Mean luminosity of the selected pictures was matched using the MATLAB R2016a SHINE toolbox (MathWorks Inc.) in order to ensure that mean luminosity did not vary between the pictures. To control the level of illumination prior to picture onset, a white fixation cross on a grey background (2500 ms) with the mean luminosity across all pictures was presented prior to each picture presentation.

2.5. Pupillometry

Pupil diameter was tracked using iView eye-tracking glasses (iViewETG 2.0, SensoMotoric Instruments, Germany) connected to an SMI-ETG recording device (Lenovo X230-Notebook) compatible to the iViewETG software. A high-definition scene camera equipped with an infrared-sensitive eye camera for dark pupil detection assessed retinal and corneal reflections obtaining the participants' pupil diameter of both eyes. A one-point calibration procedure ensured correct tracking of the pupil. During the emotion regulation paradigm, data were continuously recorded at a binocular sampling rate of 30 Hz and a viewing distance of 60 cm from the screen while the position of the participant's head was permanently stabilized via a chin rest (Bardeen and Daniel, 2017). All testing took place in a moderately lit room without daylight luminance in order to control for variance in light influences. Due to technical failure, pupillary data of 14 participants (10 males, 4 females) had to be excluded from further analyses.

2.5.1. Analysis of pupillary data

Pupillary data were preprocessed according to routines reported in previous studies from our lab (Kinner et al., 2017; Langer et al., 2020). After averaging pupil diameter across both eyes, recorded data was smoothed with a finite impulse response filter at 6 Hz and onsets of event-locked segments (instructional cue, fixation cross, picture presentation) were marked for each trial. Trials with a pupil size outside a feasible range, i.e. smaller than 1.5 mm and greater than 9 mm, were discarded (Kret et al., 2014). Outliers in dilation speed were removed with a cutoff threshold of 6 median absolute deviations at most (MAD; Kret and Sjak-Shie, 2018). Gabs resulting from eye blinks were detected in order to prevent pupil size underestimation due to eyelid occlusion. We used a MATLAB-based algorithm to discard trials with major eye blinks (> 100 ms) and to correct trials with smaller gabs with linear interpolation. For each participant and each trial, baseline pupil size was defined as the average pupil diameter recorded during the 300 ms prior to picture onset. To correct for individual differences in pupil diameter, baseline pupil size was subtracted from the mean pupil dilation during picture presentation for each individual trial. 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 2 s to 5 s after picture onset (Langer et al., 2020). Pupil dilations were averaged across 10 trials of each emotion regulation condition.

2.6. Statistical analysis

In order to investigate the delayed effects of stress and sex on cognitive emotion regulation, we used a 2 × 2 between-subjects design with the factors *stress* (stress vs. control) and *sex* (males vs. females). All statistical analyses were performed with IBM SPSS Statistics 20 (Armonk, USA) for Windows with the significance level set to $\alpha = 0.05$. Data was checked for normality using Kolmogorov-Smirnov tests and log-transformed if necessary. Given that cortisol data did not meet the assumption of normality, all statistical analyses were conducted with log-transformed cortisol data. In addition, all dependent variables were checked for homogeneity of variance using Levene-tests. Greenhouse-Geisser corrected *p*-values and degrees of freedom were reported if the assumption of sphericity was violated. Partial eta square (η^2) were reported as estimations of effect sizes.

Analyses of variance (ANOVAs) always included the between-subjects factors *stress* (stress vs. control) and *sex* (males vs. females). To verify successful stress induction, cortisol, alpha-amylase as well as subjective negative affect ratings were analyzed using mixed-design ANOVAs with the repeated measurement factor *time* ($t_{baseline}$,t_{+2},t_{+20}, t_{+50},t_{+80},t_{+110}). For subjective ratings (arousal, valence, success) and pupil dilations (AUCg), mixed-design ANOVAs with the repeated measures factor *condition* (view neutral vs. view negative vs. intensify vs. reappraisal vs. distraction) were conducted in order to verify successful emotion induction and regulation and to test for the impact of stress on emotion regulation outcomes. In case of significant interactions, Bonferroni-corrected post-hoc tests were applied. Furthermore, we examined the link between stress-induced increases in cortisol levels and emotion regulation outcomes. Therefore, we calculated delta cortisol by subtracting the baseline sample from the + 20 min sample and correlated this score with mean subjective ratings and pupil data for every emotion regulation condition using Pearson product-moment correlations. To explore whether cortisol mediated the effect of stress on emotion regulation performance, we subsequently ran explorative mediation analyses using the PROCESS 3.2 macro for SPSS (Hayes, 2013) with stress as the predictor X (stress = 1, control = 0), arousal, valence and success ratings as the outcome variables Y and delta cortisol as the mediator M for those emotion regulation conditions, for which we found a significant correlation between delta cortisol and affective ratings. For evidence that cortisol mediates stress effects on emotion regulatory success, three conditions should turn out to be significant. First, stress should predict cortisol responses (path *a*). Second, cortisol should be associated with affective ratings (path *b*) and finally, cortisol should mediate the relationship between stress and affective ratings (path *a* x *b*; Zhao et al., 2010). To test the significance of *a*, *b*, and *a* x *b* effects, bootstrap tests were used. Indirect effects were tested via calculation of 5000 bias-corrected and accelerated (BCa) bootstrap 95% confidence intervals (CI). *P*-values for each pathway as well as the BCa CI for significance of the indirect effect were given.

3. Results

3.1. Physiological and subjective response to stress

3.1.1. Physiological stress response

Stress led to an increase in salivary cortisol (main effect of time: $F_{(2.53,186.97)} = 56.75$, $p < .001$; $\eta^2 = .434$; main effect of stress: $F_{(1,74)} = 5.76$, $p = .019$; $\eta^2 = .072$; stress x time interaction: $F_{(2.53,186.97)} = 7.58$ $p < .001$; $\eta^2 = .093$, Fig. 2a) and alpha-amylase concentrations (main effect of time: $F_{(3.05,222.94)} = 14.04$, $p < .001$; $\eta^2 = .161$; stress x time interaction: $F_{(3.05,222.94)} = 6.03$, $p = .001$; $\eta^2 = .076$, Fig. 2b) compared to the control manipulation, indicating successful stress induction by the TSST. Post-hoc *t*-tests confirmed that the groups did not differ in cortisol and alpha-amylase levels at baseline (both $ps \geq .567$). However, immediately after the TSST, stressed participants exhibited higher cortisol ($t_{(78)} = -2.20$, $p = .031$) and alpha-amylase concentrations

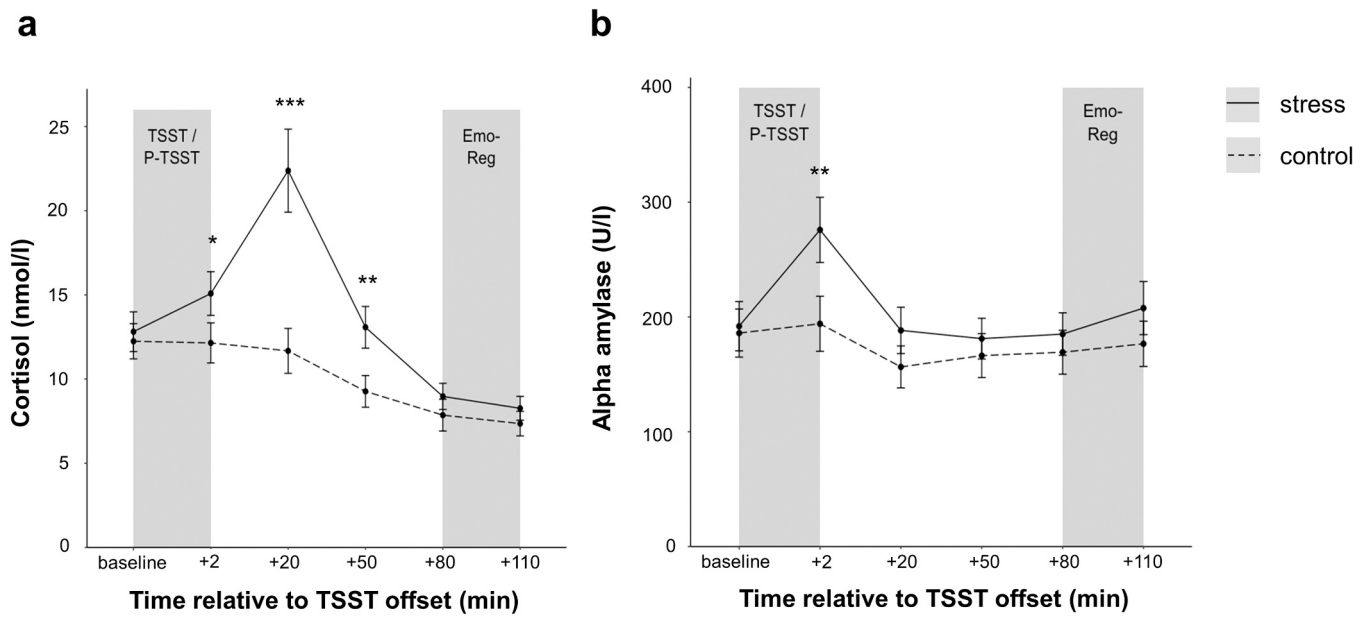

Fig. 2. I Physiological stress response. Mean (± SEM) salivary cortisol (**a**) and mean (± SEM) salivary alpha-amylase concentrations (**b**) for participants in the stress (TSST) and the control (P-TSST) group. Exposure to the TSST led to significant increases in salivary cortisol and alpha-amylase concentrations. However, with the beginning of the emotion regulation paradigm, groups did not differ in salivary cortisol and alpha-amylase anymore. For illustration purposes, raw data is displayed. Time point of the stress manipulation (TSST/P-TSST) and the emotion regulation paradigm (EmoReg) are represented by shaded areas. Significant effects after Bonferroni-corrected post-hoc *t*-tests are marked as follows: ***$p < .001$; **$p < .01$; *$p < .05$.

($t_{(78)} = -2.82$, $p = .006$) than controls. Cortisol levels were also significantly elevated 20 min ($t_{(78)} = -3.96$, $p < .001$) and 50 min ($t_{(78)} = -2.70$, $p = .008$) after stress offset. Critically however, at the beginning of the emotion regulation paradigm, groups did not differ in cortisol (both $ps \geq .125$) or alpha-amylase (both $ps \geq .320$) levels anymore. There were no significant differences in the physiological stress response between males and females ($p = .214$, Table 1).

3.1.2. Subjective stress response

Stressed participants rated their affective state as significantly more negative than controls (main effect of time: $F_{(3.15,242.26)} = 26.74$, $p < .001$; $\eta^2 = .258$; main effect of stress: $F_{(1,77)} = 0.98$, $p = .015$; $\eta^2 = .074$; stress x time interaction: $F_{(3.15,242.26)} = 7.50$, $p < .001$; $\eta^2 = .089$, Table 1) 2 min ($t_{(58.61)} = -3.86$, $p < .001$) as well as 20 min ($t_{(54.11)} = -2.33$, $p = .023$) and 50 min ($t_{(46.97)} = -2.39$, $p = .021$) after TSST offset. No differences in negative affect between the groups occurred at baseline ($p = .328$), immediately before (+80 min; $p = .094$) or after the emotion regulation paradigm (+110 min; $p = .764$). Likewise, subjective stress responses did not significantly differ between males and females ($p = .460$, Table 1).

3.2. Emotion induction and regulation

3.2.1. Affective ratings

For affective ratings, ANOVAs revealed significant differences in arousal, valence and regulatory success between the emotion regulation conditions (main effect of condition, arousal: $F_{(3.24,249.82)} = 107.12$, $p < .001$; $\eta^2 = .582$, Fig. 3a; main effect of condition, valence: $F_{(2.99,230.27)} = 113.42$, $p < .001$; $\eta^2 = .596$, Fig. 3b; main effect of condition, success: $F_{(3.21,247.03)} = 44.19$, $p < .001$; $\eta^2 = .365$, Fig. 3c). Post-hoc comparisons showed that participants rated negative pictures as significantly more arousing and less pleasant than neutral pictures (both $ps < .001$) indicating successful induction of negative emotions. Affective ratings moreover confirmed successful modulation of valence and arousal via the three different emotion regulation strategies. Participants rated negative pictures as significantly more arousing and less pleasant (both $ps < .001$) when upregulating negative emotions via intensify and less arousing and more pleasant (both $ps \leq .019$) when downregulating negative emotions via distraction compared to just viewing them. Likewise, negative pictures were rated as more pleasant when reappraisal was applied to downregulate negative emotions relative to simply viewing them ($p < .001$). However, reappraisal did not

Table 1
I Mean (± SEM) baseline to peak differences (Δ) in salivary cortisol, alpha-amylase and subjective negative affective ratings (DAS) of the stress and the control group in men and women.

	Men		Women	
	Stress	Control	Stress	Control
Δ Cortisol (nmol/l)	9.26 ± 12.51*	1.52 ± 8.29	9.89 ± 14.95**	−2.34 ± 2.78
Δ Alpha-amylase (U/l)	75.14 ± 93.97***	6.37 ± 62.48	93.14 ± 121.96***	12.06 ± 60.54
Δ Negative affect	0.33 ± 0.75*	−0.01 ± 0.39	0.38 ± 0.71*	0.12 ± 0.32

Significance of pairwise comparisons between stressed men/women and the respective controls are marked as follows: ***p<.001, **p<.01, *p<.05.

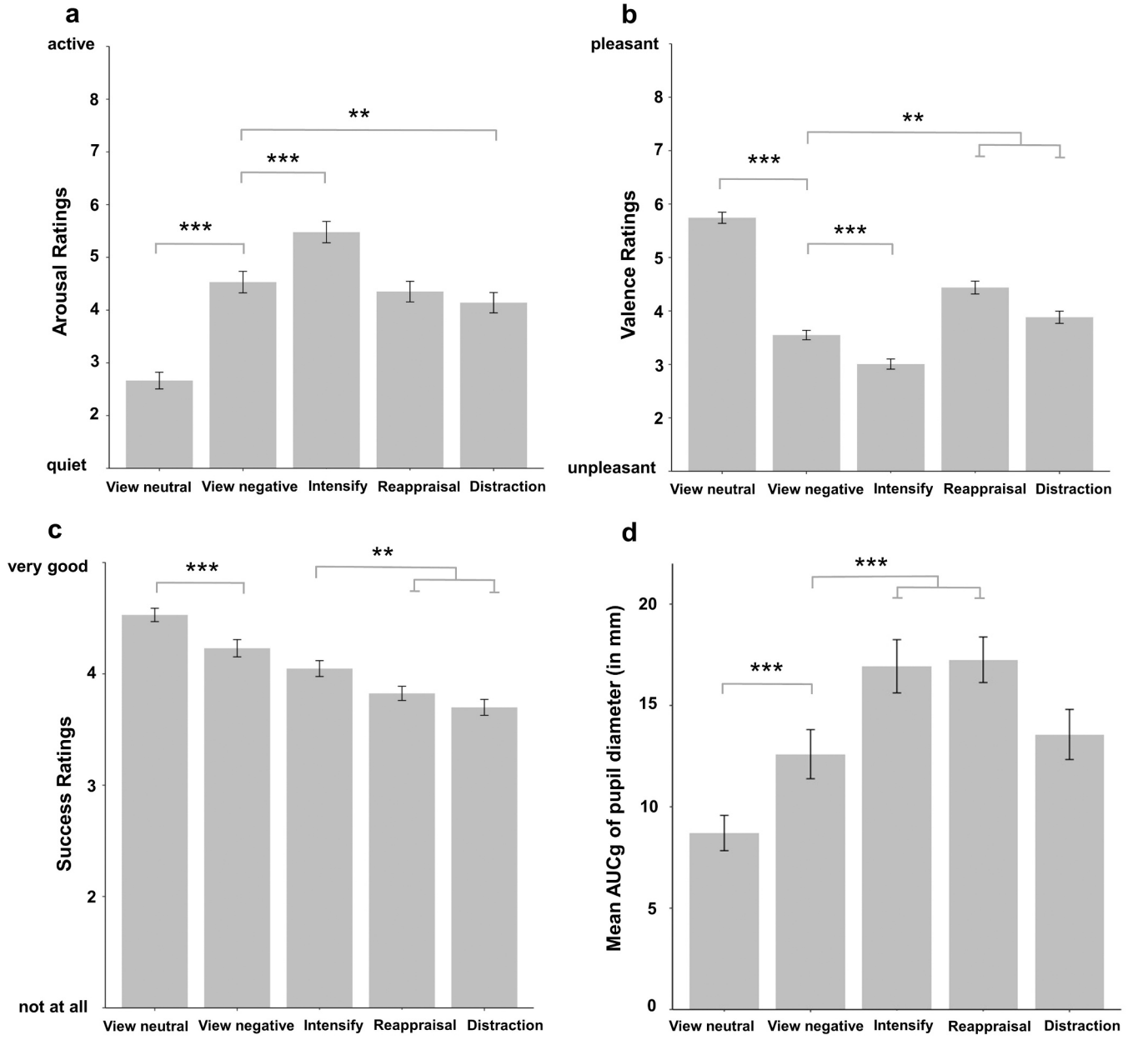

Fig. 3. I Affective ratings and pupil diameter with respect to the different emotion regulation conditions. Mean (± SEM) subjective arousal (**a**), valence (**b**) and success ratings (**c**) as well as mean (± SEM) pupil diameter (**d**) indexed by the area under the curve with respect to ground (AUCg) are displayed for the different emotion regulation conditions. Successful emotion induction was indicated by increased arousal (**a**), reduced valence ratings (**b**) and increased pupil sizes (**d**) after viewing negative relative to neutral pictures. Participants rated negative pictures as significantly less arousing and more pleasant when downregulating negative emotions with *distraction,* but more arousing and less pleasant when they were instructed to upregulate negative emotions via *intensify* (**c**) when compared to just viewing them. Moreover, downregulation via *reappraisal* led participants to rate negative pictures significantly more pleasant (**b**). Application of *reappraisal* and *intensify* led to increased pupil sizes as compared to the view negative condition (**d**). Significant effects after Bonferroni-corrected post-hoc *t*-tests are marked as follows: ***$p < .001$; **$p < .01$; *$p < .05$.

lead to a significant reduction in emotional arousal compared to just viewing negative pictures. Participants reported to be more successful in intensifying upcoming emotions than downregulating them with distraction or reappraisal (both *ps* $\leq .007$).

3.2.2. Pupil diameter

Analyses of pupillary data indicated that pupil diameter differed significantly between the emotion regulation conditions (main effect of condition: $F_{(3.44,216.84)} = 26.54$, $p < .001$; $\eta^2 = .296$; Fig. 3d). Follow-up comparisons revealed that participants exhibited significant greater pupil dilations when viewing negative pictures relative to neutral pictures ($p = .001$). Downregulation of negative emotions via reappraisal or upregulation of negative emotions via intensify led to a further increase in pupil diameter when compared to simply viewing negative pictures (both *ps* $\leq .003$), suggesting a further modulation through the cognitive effort that is required to reframe a negative picture with a more positive (reappraisal) or negative (intensify) meaning.

3.3. Stress effects on emotion regulation

3.3.1. Affective ratings

Neither a significant main effect of stress (all *ps* $\geq .327$) nor a significant stress x condition interaction (all *ps* $\geq .471$) was found, indicating that stressed participants did not differ in arousal, valence or

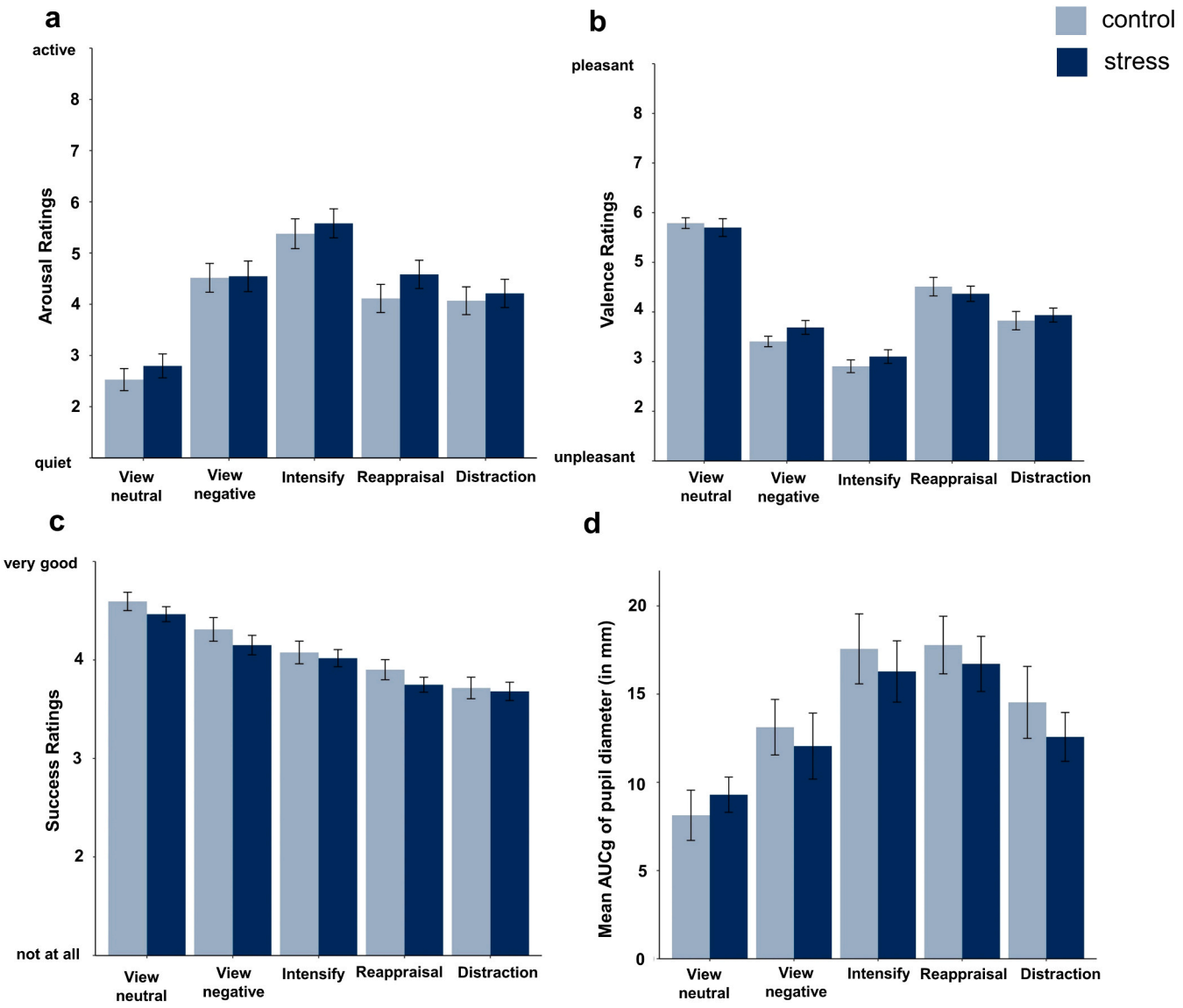

Fig. 4. I Affective ratings and pupil diameter for each emotion regulation condition in the stress and control group. Mean (± SEM) subjective arousal (**a**), valence (**b**) as well as success ratings (**c**) and mean (± SEM) pupil diameter (**d**) indexed by the area under the curve with respect to ground (AUCg) are displayed for each emotion regulation condition in the stress (TSST) and control (Placebo-TSST) group. Groups did not differ in arousal, valence and success ratings or pupil dilation for any of the emotion regulation conditions.

success ratings from control participants for any of the emotion regulation conditions (Fig. 4a–c). Likewise, no significant main or interaction effects with the factor sex occurred (all *ps* ≥ .478).

3.3.2. *Pupil diameter*

Analysis of pupillary responses revealed no significant differences in pupil dilations between the stress and control group for any of the emotion regulation conditions (main effect of stress: $p = .362$, stress x condition interaction: $p = .481$, Fig. 4d). Likewise, no modulations by sex were found (all *ps* > .367).

3.4. *The relationship between cortisol and emotion regulation outcome*

Correlation analyses showed that cortisol increases, but not alpha-amylase increases (both *ps* ≥ .244), were positively associated with arousal ratings ($r = -0.234$, $p = .038$; Fig. 5a) and negatively correlated with valence ratings ($r = 0.251$, $p = .025$; Fig. 5b) for the *distraction* condition in the whole sample (for figures showing log-transformed cortisol data, see Supplementary Information A). No significant correlations regarding other strategies were found (all *ps* ≥ .141). Given that cortisol was positively related to subjective emotion regulatory performance in the *distraction* condition, we further explored whether cortisol played a mediating role between stress (X) and emotion regulation outcomes (Y) specifically for this strategy. Mediation analyses confirmed that stress did relate to delta cortisol (path $a = 9.876$, $p < .001$), and cortisol was also directly related to arousal (path $b = -0.046$, $p < .013$) and valence ratings (path $b = 0.024$, $p < .031$). Importantly, cortisol significantly mediated the effects of stress on arousal ($a \times b = -0.451$, BCa CI [− 0.871,− 0.089]) and valence ratings ($a \times b = 0.2353$, BCa CI [− 0.051, − 0.531]) for *distraction*. However, no direct effects of stress on emotion regulatory outcomes were found (arousal: path $c = 0.612$, $p = .152$, valence: path $c = -0.088$, $p = .732$). The different paths and respective statistics are illustrated in Fig. 5c and d. No significant indirect effects were found for success ratings or pupil dilation. Further moderated mediation analyses revealed that the mediation effect for arousal and valence ratings was neither influenced by sex nor trait or state anxiety (for details: see Supplementary Information B & C).

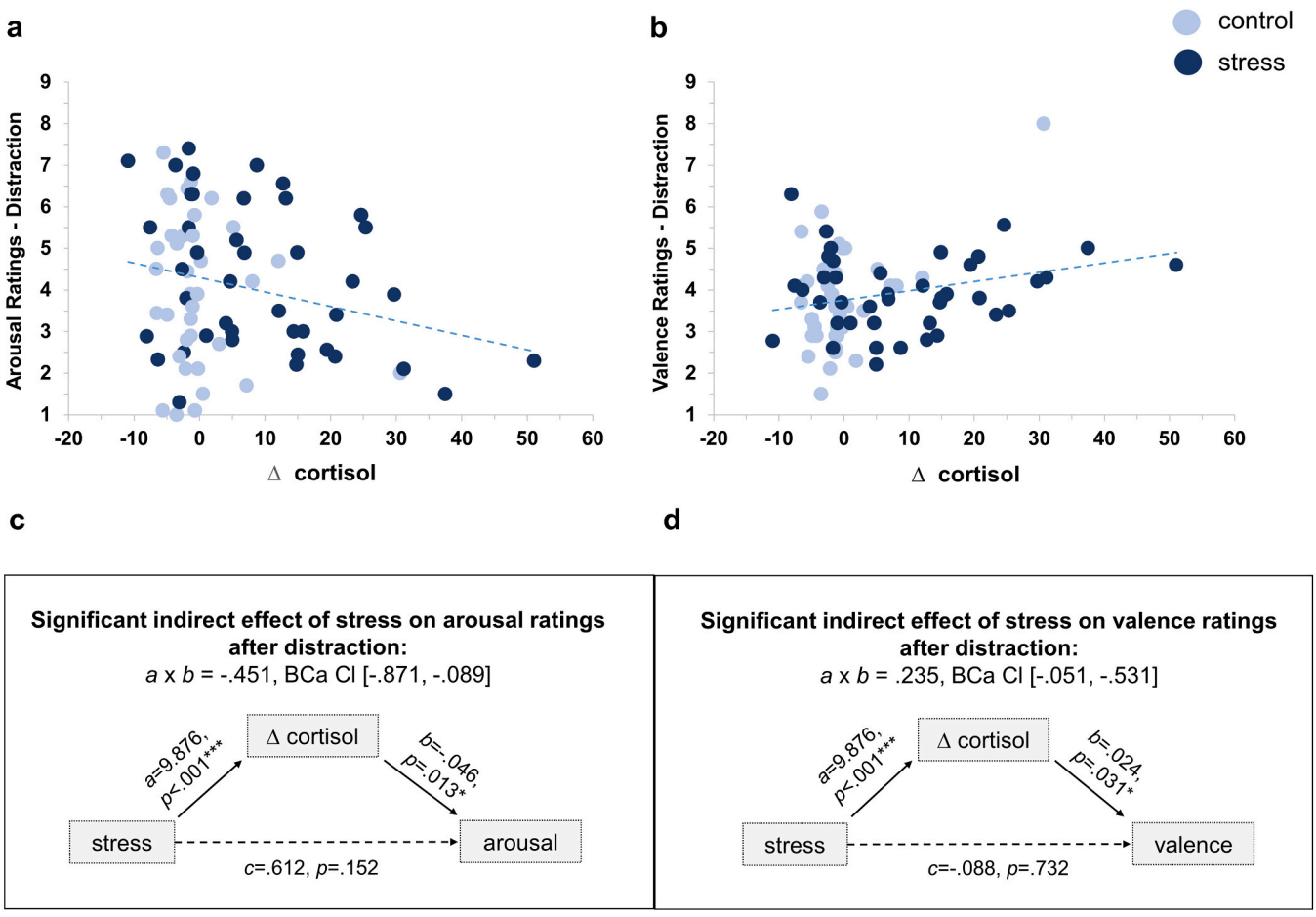

Fig. 5. I Relationship between stress, cortisol increases and distraction outcome. Scatterplots depict the relationship between cortisol increase (Δ cortisol) and arousal (**a**) and valence ratings (**b**) after distraction in the whole sample. Delta cortisol values were negatively correlated with arousal and positively correlated with valence ratings for distraction. Mediation graphs depict the relationships between stress (predictor: X), cortisol (mediator: M) and arousal (**c**) as well as valence ratings (**d**) (outcomes: Y) for distraction. Stress resulted in significant increases in cortisol (significant path *a* effect) and cortisol was positively related to valence and negatively related to arousal ratings in the *distraction* condition (significant path *b* effect). Even though the direct effect of stress on arousal and valence ratings was not significant (path *c*), cortisol significantly mediated the effects of stress on experienced valence and arousal for *distraction* (path *a* x *b*). Significant effects are marked as follows: ***$p < .001$, *$p < .05$.

4. Discussion

The present study investigated delayed effects of acute stress on the effectivity to downregulate negative emotions in men and free-cycling women. Stress overall neither affected arousal, valence and success ratings nor changes in pupil dilations. However, an increase in cortisol secretion was positively associated with distraction performance. Cortisol further mediated the effects of stress on subjective arousal and valence when participants applied distraction to downregulate their negative emotions, indicating an association between cortisol increases and enhanced subjective emotion regulatory performance. However, we did not find a direct effect of stress on emotion regulation performance.

Our results are consistent with an *indirect-only* mediation model (Zhao et al., 2010), suggesting cortisol to be a specific mediator of stress affecting emotion regulatory performance. More precisely, cortisol has been shown to mediate stress effects on the ability to deliberately distract oneself from negative emotions, while other mediators such as alpha-amylase appear to have less influence. This corroborates with previous studies showing that GCs are associated with delayed beneficial effects on cognitive control functioning (Henckens et al., 2011; Shields et al., 2016). For instance, administration of hydrocortisone resulted in an increase in prefrontal activity improving working memory performance (Henckens et al., 2011) when cortisol levels had already returned to baseline. These studies support the idea that cortisol is causally related to a delayed improvement of core executive functions (Shields et al., 2016), which is probably mediated via slow genomic modulations of neural activity in the prefrontal-hippocampal-amygdala complex (Joëls et al., 2012). Consistently, we found cortisol increases to be positively associated with subjective success of downregulating negative emotions via distraction in a typical time window of genomic GC actions (i.e. 90 min after stress exposure, when cortisol levels of stressed participants were no longer elevated). Unexpectedly however, we did not find an association between cortisol increase and reappraisal success. Reappraisal and distraction both rely on a common cognitive control network (Etkin et al., 2015; Kanske et al., 2011), but also selectively recruit different brain regions within this core network. The ability to flexibly distract oneself from a negative stimulus particularly engages neural systems that are relevant for conscious top-down control of attention (Kanske et al., 2011). Our findings may therefore indicate a specific association between cortisol increase and delayed improvements of attentional processes. Imaging data demonstrated that delayed GC effects decreased activity in the cuneus (Henckens et al., 2012), thereby hampering stimulus-driven, bottom-up attentional processing (Hahn et al., 2006). Given that the neuroanatomical substrates of top-down and bottom-up processes have been shown to be dissociated (Hahn et al., 2006), delayed GC effects might thus facilitate top-down control of emotions via reduced attentional interference.

Previous research provided evidence for immediate impairing effects

of stress on top-down control of attention in favor of stimulus-driven processing (Sänger et al., 2014). In line with this finding, rapid GC actions have been shown to enhance the functional connectivity between the amygdala and the executive control network, leading to impaired top-down control of attention (Henckens et al., 2012). These relatively rapid neural GC effects may shift the brain in an automated response-mode strengthening attention to negative emotional stimuli. Consistently, data from our lab demonstrated that stressed participants were less effectively distracted from emotional pictures than controls when testing took place 25 min after stress exposure (Kinner et al., 2014), while activity in the ventrolateral PFC was enhanced during emotional distraction 90 min after cortisol administration (Jentsch et al. 2019). Together with these findings, the present results suggest that delayed GC effects may reverse immediate impairments of attentional shifting (Oei et al., 2012), thereby facilitating distraction from negative emotional stimuli and adaptively contributing to the return of homeostasis in the aftermath of stress (Henckens et al., 2012; Hermans et al., 2014). Pharmacological studies administrating hydrocortisone are warranted to directly compare immediate and delayed GC effects on cognitive emotion regulation via distraction in comparison to reappraisal.

As opposed to previous findings, the present study did not reveal sex differences in the influence of stress on emotion regulatory outcomes. Likewise, we did not find a sex-specific association between cortisol increase and emotion regulation success. There is a growing body of literature showing that stress effects on emotional and cognitive processes are more pronounced in men than in women (Merz and Wolf, 2017; Shields et al., 2016). Accordingly, previous work from our lab also demonstrated sex-dependent stress effects on cognitive emotion regulation (Kinner et al., 2014; Langer et al., 2020). Of note however, in these studies significantly stronger stress-induced cortisol increases were also found in men compared to free-cycling women. It might therefore be reasonable that sex-specific stress effects on cognitive emotion regulation are driven by larger cortisol increases in men. Here, we neither found sex differences in baseline cortisol levels nor in stress-induced cortisol increases, possibly explaining similar emotion regulation outcomes in men and women. Hence, our results appear to support the idea that emotion regulation success may covary with the amount of cortisol secretion.

The present study did not provide evidence for direct delayed effects of stress on cognitive emotion regulation performance. Typically two thirds of participants respond with cortisol increases above 1.5 nmol/l to the TSST (Goodman et al., 2017). In the present study, the TSST initiated a significant cortisol response in 64% of the stressed participants, whereas the Placebo-TSST led to a significant cortisol response in 17.5% of the controls. The missing overall stress effect might therefore be explained by similar cortisol increases in some of the control participants (see Fig. 5a and b). Research on the impact of stress on cognitive emotion regulation is scarce. Yet, there are studies revealing enhanced activity of the executive control network through slow genomic GC actions (Henckens et al., 2011; Hermans et al., 2014; Yuen et al., 2009), resulting in an improvement of cognitive control performance in the aftermath of stress. However, stress does not only initiate the secretion of corticosteroids but also of catecholamines (Joëls and Baram, 2009). Previous research provide evidence for rapid impairing stress effects on cognitive emotion regulation (Raio et al., 2013; Raio and Phelps, 2015) which were associated with the release of catecholamines (Raio et al., 2013). Furthermore, blocking β-adrenergic activity but not GC synthesis resulted in diminished stress-induced increases in functional connectivity between the amygdala and other salience network regions (Hermans et al., 2011). Given its excitatory effects on the interconnectivity within the salience network, SNS activation might thus impede emotional downregulation and thereby counteract the beneficial effects of GCs. However, contrary to this hypothesis, emotion regulatory outcomes were not related to increases in alpha-amylase concentrations - one potential marker of SNS activation (Nater and Rohleder, 2009). Nevertheless, stress also initiates the secretion of other monoamines including dopamine and serotonin as well as neuropeptides, such as vasopressin, orexin and dynorphin (Joëls and Baram, 2009), with each of these stress mediators having its own spatial and temporal domains of release and action. Given that previous studies primarily reported delayed effects of hydrocortisone administration on cognitive functioning (Henckens et al., 2012, 2011; Henckens et al., 2010; Shields et al., 2015), the missing direct stress effect in the present study might still be attributed to complex interactions between different stress mediators possibly opposing beneficial effects of cortisol on emotion regulatory outcomes. In view of the well-established inverted U-shaped dose-response curve between GCs and cognitive performance (Joëls, 2006), one might also speculate that delayed stress effects on cognitive emotion regulation rely on a certain magnitude of cortisol secretion. In the present study, we found a positive association between cortisol increase and delayed distraction success. The non-significant group difference in emotion regulation outcomes between stress and control participants might therefore be due to insufficient cortisol increases on average. Future work is needed systematically investigating the delayed impact of different dosages of hydrocortisone on emotion regulation outcomes. Furthermore, in the present study the emotion regulation paradigm started 90 min after TSST/Placebo-TSST onset. Since genomic GC actions typically take some time to exert their effects, it might be possible that the delay was too short for GCs to fully unfold its genomic stress effects on emotion regulation, explaining why we did not find any group differences between stressed and control participants. In order to determine the specific time window of genomic GC effects on cognitive emotion regulation, future studies should include different delays between stress exposure and cognitive testing.

There are some limitations that should be noted. First, reappraisal did not lead to a significant reduction in emotional arousal when compared to simply viewing negative pictures. However, ratings of emotional arousal are not specific for valence (Zaehringer et al., 2020). Together with the significantly enhanced valence for reappraised pictures, it is thus reasonable that the instruction to positively reappraise negative pictures might have changed emotional arousal in a positive direction. To overcome this interpretation ambiguity, future studies would benefit from an additional valence-specific physiological emotion regulation outcome measure such as the startle reflex (Zaehringer et al., 2020). Secondly, the assessment of emotion regulation success ratings cover the risk of a performance bias. A comparison between pre- and post-regulation arousal and valence ratings might have reduced the extent of this bias, possibly representing a more robust measurement of regulatory success. However, on the other hand, pre-to-post comparisons would have required emotional stimuli to be presented twice, thereby bearing the risk of habituation effects (i.e. negative pictures could be perceived as less negative when presented a second time) interfering with true emotion regulation effects. Moreover, one cannot rule out automatic implicit emotion regulation during the initial picture presentation, which also would have interfered with the instructed regulation phase. We therefore decided to assess post-regulation success, valence and arousal ratings in addition to pupil dilation recordings representing an objective regulatory performance index.

In conclusion, this study revealed that cortisol increase is positively associated with emotion regulatory success using distraction 90 min after stress exposure. This finding support the crucial role of glucocorticoids initializing beneficial effects on the cognitive control of emotions possibly mediated via slow, genomic actions on attentive processes. The present study contributes to a better understanding of the adaptive nature of stress reactivity and its importance explaining differences in the vulnerability to the development and maintenance of stress- and emotion-related mental disorders.

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CRediT authorship contribution statement

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

Declaration of Competing Interest

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

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2020.105101.

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