Sex Differences in Cognitive Regulation of Psychosocial Achievement Stress: Brain and Behavior

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Abstract: Although cognitive regulation of emotion has been extensively examined, there is a lack of studies assessing cognitive regulation in stressful achievement situations. This study used functional magnetic resonance imaging in 23 females and 20 males to investigate cognitive downregulation of negative, stressful sensations during a frequently used psychosocial stress task. Additionally, subjective responses, cognitive regulation strategies, salivary cortisol, and skin conductance response were assessed. Subjective response supported the experimental manipulation by showing higher anger and negative affect ratings after stress regulation than after the mere exposure to stress. On a neural level, right middle frontal gyrus (MFG) and right superior temporal gyrus (STG) were more strongly activated during regulation than nonregulation, whereas the hippocampus was less activated during regulation. Sex differences were evident: after regulation females expressed higher subjective stress ratings than males, and these ratings were associated with right hippocampal activation. In the nonregulation block, females showed greater activation of the left amygdala and the right STG during stress than males while males recruited the putamen more robustly in this condition. Thus, cognitive regulation of stressful achievement situations seems to induce additional stress, to recruit regions implicated in attention integration and working memory and to deactivate memory retrieval. Stress itself is associated with greater activation of limbic as well as attention areas in females than males. Additionally, activation of the memory system during cognitive regulation of stress is associated with greater perceived stress in females. Sex differences in cognitive regulation strategies merit further investigation that can guide sex sensitive interventions for stress-associated disorders. *Hum Brain Mapp* 36:1028–1042, 2015. © 2014 Wiley Periodicals, Inc.

Key words: gender; emotion regulation; amygdala; putamen; hippocampus; fMRI; skin conductance response; cortisol

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INTRODUCTION

In everyday life, stress is triggered when situational demands exceed one's resources, especially in situations that are characterized by high achievement, social evaluation, or diminished controllability. Such situations elicit modulatory behavioral, hormonal, and psychophysiological reactions [Dickerson and Kemeny, 2004; Duchesne et al., 2012; Kirschbaum et al., 1993]. On a neural level, deactivations in limbic and striatal structures including amygdala, hippocampus, hypothalamus, putamen, and medial prefrontal cortex were reported during psychosocial achievement stress [e.g., Pruessner et al., 2008]. Only one previous neuroimaging study investigated sex differences in neural stress responses [Wang et al., 2007] and showed stronger activations in the prefrontal cortex and deactivation in the orbitofrontal cortex in males in the stress condition. In females, activations of limbic structures including insula, putamen, and ventral striatum were associated with subjective stress. Thus, it seems that stress differentially affects females and males and distinctly engages brain regions involved in cognitive control and modulation of emotional processing and neuroendocrine responses in females and males [Herman et al., 2005; Kim and Hamann, 2012; Pruessner et al., 2008].

The experience of stress can be altered by recruitment of cognitive regulation strategies such as decreasing or suppressing negative subjective experiences or changing the attentional focus [Gross, 1998; Kim and Hamann, 2007; Ochsner et al., 2002; Ochsner et al., 2004]. The neural network underlying cognitive emotion regulation comprises prefrontal, cingulate, and limbic areas such as the hippocampus, the amygdala, and the insula [Eippert et al., 2007; Kim and Hamann, 2007; McRae et al., 2010; Ochsner et al., 2002; Ochsner et al., 2004]. Although superior, middle, and inferior frontal and dorsal anterior cingulate areas show an activation increase, temporal regions and the insula are characterized by deactivation during cognitive regulation [McRae et al., 2010]. Sex differences in cognitive regulation have been reported for usage of cognitive regulation strategies [Nolen-Hoeksema, 2012; Tamres et al., 2002] and in neural activation [e.g., Domes et al., 2010]. McRae et al. [2008] observed stronger activation decreases in the amygdala in males and stronger activation increases in the ventral striatum, the anterior cingulate gyrus, and frontal regions in females during cognitive decrease of negative emotions. These data suggest that females and males rely on different neural strategies when trying to cognitively regulate their emotions. Males seem to deactivate emotion processing regions while females activate areas associated with motivational and emotional domains. Importantly, cognitive regulation of emotion is required in multiple stressful settings including social evaluation in achievement situations. Differences in cognitive regulation strategies and stress reaction between females and males are of special interest for understanding psychiatric illnesses that are associated with stress reactions and whose prevalence

show sex differences [World Health Organization, 2004]. Notably, the subjective stress response can be decreased by external reassuring feedback [Rohrmann et al., 1999], but there is a lack of studies examining cognitive regulation strategies during psychosocial achievement stress. Furthermore, the neural correlates of cognitive stress regulation in females and males have not been investigated. To address this gap, we applied cognitive regulation strategies for modulating negative sensations in stressful situations [Gross, 2002; Ochsner et al., 2002]. The cognitive regulation strategies incorporated elements of reappraisal and suppression based on the individual's attempts to regulate a stressful situation to draw from subjective abilities on cognitive regulation in healthy adults. Cognitive reappraisal is a strategy to contemplatively change a situation's emotional meaning, whereas suppression is the inhibition of behavioral and expressional reactions to emotional situations [Gross and John, 2003].

Based on previous findings on sex differences in stress response and cognitive emotion regulation cited above [e.g., McRae et al., 2008], we hypothesized that the application of a cognitive regulation strategy leads to less subjective stress experience in both sexes. Using cognitive regulation during stress will affect the psychophysiological responses differently in females and males and furthermore prompt sex differences in neural activation. Most prominent effects were expected in activation of temporal (e.g., hippocampus, amygdala), medial frontal, and striatal (putamen, caudate nucleus) regions. In more detail, a stronger decrease in activation was expected in the amygdala in males and a stronger increase in the striatum in females.

MATERIAL AND METHODS

Sample

Initially, 44 healthy volunteers (23 females; 21 males) participated in the experiment. One male participant interrupted the experiment due to the stress experience. Hence, the final sample consisted of 20 males (mean age: 24.85 ± 3.3) and 23 females (mean age: 24.30 ± 2.3). All participants were right handed [Oldfield, 1971] and reported no history of neurological or psychiatric disorders based on the German version of the Structured Clinical Interview [SCID; Wittchen et al., 1997]. To control for potential group differences based on neurocognitive abilities, participants were administered neuropsychological tests tapping verbal intelligence [Wortschatztest; Schmidt and Metzler, 1992], executive functions [Trail-Making Test, TMT-A/B; Reitan, 1956], and working memory [digit span; WIE, Aster et al., 2006]. Moreover, questionnaires assessing stress coping [German version of the coping inventory for stressful situations (CISS); Kälén, 1995], emotion regulation strategies [German version of the emotion regulation questionnaire (ERQ); Abler and Kessler, 2009; three male

TABLE I. Sample description

	Females <i>n</i> = 23 mean (SD)	Males <i>n</i> = 20 mean (SD)	<i>P</i> -value
Age (years)	24.30 (2.3)	24.85 (3.3)	0.531
Working memory (raw score)	16.77 (4.2) ^a	17.30 (4.1)	0.682
Verbal intelligence (raw score)	32.87 (2.7)	32.63 (2.7) ^b	0.775
Processing speed (sec)	32.74 (25.8)	28.54 (10.7)	0.502
BDI 2	3.78 (4.9)	3.40 (4.9)	0.799
Trait anxiety	37.63 (6.8) ^a	35.16 (6.5) ^b	0.239
State suppression (post-scan)	4.75 (1.3)	5.00 (1.6) ^c	0.581
State reappraisal (post-scan)	4.59 (1.9)	4.48 (1.6) ^c	0.841
ERQ - suppression	3.70 (1.1)	4.34 (1.2) ^b	0.077
ERQ - reappraisal	4.38 (1.3)	4.32 (1.3) ^b	0.881
With/without hormonal contraceptive intake	11/12		

^a*n* = 22.^b*n* = 19.^c*n* = 17.

(SD = standard deviation): working memory: digit span (raw scores; WIE, Aster, 2006); verbal intelligence (raw scores; Wortschatztest, WST; Schmidt and Metzler, 1992); processing speed (sec; Trail-Making Test, TMT-B; Reitan, 1956); BDI-II (Hautzinger et al., 2006); trait anxiety (STAI; Laux et al., 1981); suppression, reappraisal (ERQ, Abler and Kessler, 2009)

participants did not complete the ERQ], personality characteristics [FPI-R; Fahrenberg et al., 1984; results are not reported here as they are not of interest for this research question], depression [BDI 2; Hautzinger et al., 2006], and anxiety ratings [STAI; Laux et al., 1981] were administered. Details on sample characteristics for female and male participants are listed in Table I. Written informed consent was obtained from each participant prior to the experimental procedure and the study was approved by the ethics committee of the RWTH Aachen University. Participants were financially reimbursed after completion (€ 10/h).

fMRI Stress Task

We applied the “Montreal Imaging Stress Test” [Dedovic et al., 2005], which has frequently been used in neuroimaging studies [e.g., Dedovic et al., 2009; Lederbogen et al., 2011; Pruessner et al., 2008]. The task consists of three conditions (rest, control, stress): During the rest condition participants watch the screen and in the control condition they perform mental arithmetic tasks. In the stress condition, additionally, a time limit is enforced for each task, depending on the participant's previous performance. Importantly, the task has an adaptive design and thus guarantees 45–55% correct responses [see Dedovic et al., 2005; for detailed description]. Participants received training on mental arithmetic tasks prior to the fMRI session to familiarize them with the task. In the fMRI-scanner, the three conditions were arranged in a block design with 15 sec rest, 70 sec control, and 70 sec stress condition (see Fig. 1). Between conditions a jittered fixation cross of 6–8 sec was presented. One run consisted of two rest, two control, and two stress conditions, and

two runs were presented per regulation block (nonregulation, regulation). Between the runs the investigator gave individual feedback on the performance, told participants about the necessity of the specific performance level and asked them to improve their performance. Two regulation blocks (nonregulation, regulation) were presented in a randomized order: In a preexperimental cognitive training session participants were familiarized with the regulation strategies. The investigator explained that stressful situations can be perceived in different manners and

Figure 1.

Time-line of the paradigm including timeline of one run: Block A and B were presented randomized. Block A was either the non-regulation block or the regulation block and vice versa block B. Each block consisted of two runs. In each run between conditions, a jittered fixation cross (~6–8 sec) was presented. Participants received negative, verbal feedback between the two runs. For guaranteeing comparable arousal preconditions, participants received a resting-state scan prior to block A and an anatomical scan prior to block B. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

participants were asked to think about the way they felt during the training on mental arithmetic tasks. For one block (nonregulation), participants should simply perform the task in a normal manner and were told that their performance level is important for subsequent data analysis. For the second block (regulation), participants were instructed to regulate their negative sensations in a top-down attentional manner. They were trained to modify their negative sensations (suppression) and put less emphasize on the time limit and the negative performance feedback (reappraisal) and to focus instead on their intrinsic motivations to improve their performance as this was still important for subsequent data analysis. Thus, we asked them to avoid the stressful components of the task, which trigger negative sensations in stressful situations while maintaining motivational involvement in the task. Time pressure and negative social comparison of performance are important external factors that trigger stress reactions [Dickerson and Kemeny, 2004]. Thereby, participants were instructed to modify their negative sensations on those external factors of the paradigm in a way that those factors were no longer experienced as stressful. To draw from subjective abilities on cognitive regulation in healthy adults, the training was not meant to last for several hours or weeks. Instead, we wanted to familiarize and sensitize participants for the application of either one or both cognitive strategies (reappraisal or suppression) in stressful situations. Participants were debriefed after the cognitive regulation training and all participants confirmed that they understood and could apply the cognitive regulation strategies when told to do so. The applied regulation strategies were assessed immediately after the scanner-session (see Table I – post-scan state suppression and state reappraisal): Participants had to respond on a 7-point scale to 10 items which were adapted from the ERQ for in-scanner-use [Abler and Kessler, 2009] (such as “I changed the way I thought about the situation to control my emotions” [reappraisal] or “I did not express my negative emotions” [suppression]).

The comparison of activation during stress versus control in the nonregulation block allowed us to assess sex differences in stress reactivity. Comparing females and males on performance and activation during stress conditions between the regulation blocks allowed us to test for neural correlates of sex differences in cognitive regulation ability.

To assess subjective stress and affect participants provided self-ratings on subjective stress and anger as well as positive and negative affect ratings by means of the Positive and Negative Affect Scale on a 5-point scale [PANAS; Watson et al., 1988] before and after each block (see Fig. 1).

Skin Conductance Response

Skin conductance data as measure of peripheral arousal were assessed during imaging. Measurement and analysis of skin conductance response (SCR) were performed based on publication recommendations [Boucsein et al., 2012].

Two silver–silver chloride (Ag–AgCl) electrodes were placed at the middle phalanges of the index and middle finger of the left hand. The electrodes were filled with electrode gel (Biopac Systems, Goleta). SCR data were recorded at a sampling rate of 5000 Hz in DC mode using a bipolar BrainAmp ExG MR amplifier (Brain Products, Gilching, Germany). Data were analyzed offline, including downsampling to 2 Hz, artifact reduction using spline interpolation, and extraction of phasic components from tonic activity based on continuous decomposition analysis [Benedek and Kaernbach, 2010] implemented in Ledalab© software (Leipzig, Germany). Phasic SCR responses were defined as deflections above $0.02 \mu\text{S}$ and were analyzed with respect to the parameter “nSCR” (number of SCRs) in a time window of 1–72 sec after stimulus onset. Data were normalized using a log transformation ($y = \log_{10}(x + 1)$) prior to statistical analysis as done in previous studies [Boucsein et al., 2012; Moessnang et al., 2013]. Individual SCR data were analyzed with a $2 \times 2 \times 2$ repeated-measures analysis of variances (rmANOVA) with “regulation” (nonregulation, regulation) and “condition” (control, stress) as repeated-measures factors and “sex” as the between-subjects factor.

Salivary Cortisol Samples

Saliva samples were taken at six time points (see Fig. 1) using salivettes that participants placed in their mouth. Cortisol was analyzed in the clinical trial center (University Hospital, RWTH Aachen; “ECLIA,” electrochemiluminescence immunoassay; functional sensitivity $< 8.5 \text{ nml/l}$). Data were normalized using a log transformation ($y = \log_{10}(x + 1)$) prior to statistical analysis [King and Liberzon, 2009]. Difference-scores (post-task vs. pre-task) and area-under-the-curve (AUC) were calculated [Pruessner et al., 2003]. For comparison between nonregulation and regulation, difference scores between pre- and post-task were analyzed. Measurements were controlled for time of last meal, smoking, and circadian rhythm (samples were only taken in the afternoon). In females, the day of the menstrual cycle and the intake of hormonal contraceptives were assessed (see Table I). Exploratory analysis with the intake of hormonal contraceptives can be found in the Supporting Information.

Data and Statistical Analysis of Behavioral and Psychophysiological Data

Statistical analysis was conducted using IBM SPSS statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). Behavioral (percent of correct trials in the stress condition) and psychophysiological (nSCR, cortisol levels) data were analyzed using rmANOVAs. The level of significance was set at $P < 0.05$ for all tests. Degrees of freedom were adjusted using Greenhouse-Geisser-correction, if necessary. Significant effects were examined with planned contrasts and Bonferroni-corrected t -tests. Partial eta-squared (η_p^2) is

reported to indicate effect sizes for rmANOVAs in case of significant results. Values of $\eta_p^2 = 0.01, 0.06$, and 0.14 represent small, medium, and large effects [Kirk, 1996]. Additional sex-specific analyses are listed in the Supporting Information.

FMRI Data Acquisition, Preprocessing, and Analysis

The fMRI data were acquired using a 3T Siemens Trio Scanner (Siemens Medical Systems, Erlangen, Germany) located at the Department of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen University. A standard head coil and foam paddings to reduce head motion were used. T2* weighted echo-planar image sequences (34 slices, TR = 2000 ms, TE = 28 ms; gap 10%, field of view (FoV) = 260 mm; flip angle = 77° , voxel: $3.6 \times 3.6 \times 3.3$ mm) were acquired in an axial plane. Additionally, T1 anatomical images were acquired (3-D Magnetization Prepared Rapid Gradient Echo; TR = 1900; TE = 2.52; TI = 900 ms; flip angle = 9° ; 256 matrix; FoV = 250; 176 slices per slab, voxel: $1 \times 1 \times 1$ mm) for 9 min 50 sec. The fMRI data were analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB (Mathworks, Sherborn, MA). Five dummy scans at the beginning of the experiment were discarded. Functional images were realigned to correct for head movement [Ashburner and Friston, 2005]. Each participant's T1-scan was coregistered to the mean image of the realigned functional images which were further coregistered to an anatomical template (SPM8). The mean functional image was subsequently normalized to the Montreal Neurological Institute (MNI) single-subject template [Evans et al., 1992] using linear proportions and a nonlinear sampling as derived from a segmentation algorithm [Ashburner and Friston, 2005]. Normalization parameters were then applied to the functional images and coregistered to the T1-image. Images were resampled at a $1.5 \times 1.5 \times 1.5$ mm voxel size and spatially smoothed using 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Functional data were analyzed using a General Linear Model. Each condition (rest, control, stress for both the nonregulation and the regulation block) was separately modeled by a boxcar reference vector convolved with a canonical hemodynamic response function and its first-order temporal derivative. Between-scan movement parameters as estimated during spatial realignment were included as covariates of no interest. Simple main effects for each of the conditions were computed for every participant and then fed into a second-level group analysis using a mixed-effects model (factor: condition, subject). The block-design resulted in six experimental conditions (nonregulation: rest, control, stress; regulation: rest, control, stress) and two groups (females, males). Hypothesis-driven [Dedovic et al., 2009; Kanske et al., 2011; McRae et al., 2008] a-priori defined comparisons of "regulation block (stress and control) versus nonregulation block (stress and control)" and "stress condition in the regulation block versus stress condition in the nonregulation

block" were performed by whole-brain *t*-contrasts. These analyses identified regions showing modified activation in the regulation block compared to the nonregulation block for both control and stress condition, as well as specifically for the stress condition. We relied on Monte-Carlo simulations with AlphaSim [Cox, 1996], a cluster-defining threshold of $P(\text{unc}) < 0.001$, 1000 simulations, and the spatial properties of the residual image. An extent threshold of 124 contiguous voxels corresponds to a corrected threshold of $P < 0.05$. All results are reported at this cluster-level corrected threshold.

Region-of-interest analysis

Based on previous findings of sex differences and our a-priori hypotheses we performed region-of-interest (ROI) analyses for the amygdala, the hippocampus, and the putamen. For the amygdala, males show a stronger increase when naturally viewing compared to downregulating emotional scenes [McRae et al., 2008]. In females, subjective stress was positively associated with putamen activity [Wang et al., 2007]. Moreover, these three regions represent important nodes in both cognitive regulation and stress reactivity [McRae et al., 2010; Ochsner et al., 2004, 2002; Pruessner et al., 2008]. We examined these regions based on an anatomical ROI analysis (small volume correction). Anatomical ROIs for amygdala and hippocampus were defined using AnatomyToolbox v1.8 [Eickhoff et al., 2005] implemented in SPM8. Putamen activation was extracted based on MNI coordinates of a previous manuscript [Dedovic et al., 2009]. The mean values of the functional maxima (Amygdala: left [$-22.5, -8.5, -12.5$], right [$22.5, 5.5, -12.5$]; Hippocampus: left [$-24, -11.5, -14$], right [$36, -25, -8$]; Putamen: left [$-27, 14, -0.5$], right [$24, 8, -9.5$]) within a sphere of 10 mm were extracted for each participant with SPM8.

Regression analysis

We performed correlation analyses between mean parameter estimates of the a-priori defined ROIs and psychophysiological responses (cortisol, nSCR) as well as ratings of subjective affect, stress ratings, and cognitive regulation strategies. Correlations were corrected for multiple comparisons where appropriate.

ROI analyses and correlation analyses were performed using IBM SPSS statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY).

RESULTS

Behavioral Results

Performance

A 2×2 rmANOVA with the within-subject factors "regulation" (nonregulation/regulation) and the between-

subjects factor “sex” for percent of correct trials in the stress condition showed no significant main effect for “regulation” ($F_{1,41} = 0.826$, $P = 0.369$, $\eta_p^2 = 0.020$) or “sex” ($F_{1,41} = 2.2461$, $P = 0.124$, $\eta_p^2 = 0.057$) nor an interaction ($F_{1,41} = 1.373$, $P = 0.248$, $\eta_p^2 = 0.032$).

Subjective Ratings of Stress, Affect, and Cognitive Regulation

Subjective data were analyzed using $2 \times 2 \times 2$ rmANOVAs with the within-subject factors “regulation” (nonregulation/regulation) and “time” (pre-stress/post-stress) and the between-subjects factor “sex.” Only significant effects are listed.

Subjective stress

Subjective stress ratings revealed a significant main effect of “time” ($F_{1,37} = 63.886$, $P < 0.001$, $\eta_p^2 = 0.633$) with higher stress ratings post-stress than pre-stress and a significant 3-way interaction “regulation-by-time-by-sex” ($F_{1,37} = 4.296$, $P = 0.045$, $\eta_p^2 = 0.104$). No other main effect or interaction was significant (all P s > 0.084). Disentangling the significant 3-way interaction we performed rmANOVAs with the within-subject factors “regulation” (nonregulation/regulation) and the between-subjects factor “sex” for pre- and post-stress separately. No significant effect occurred (all P s > 0.644) for prior to the stress task but after the stress task a significant interaction “regulation-by-sex” ($F_{1,38} = 5.622$, $P = 0.023$, $\eta_p^2 = 0.129$) emerged. Post hoc analysis revealed higher post-stress ratings in the regulation block than in the nonregulation block for females ($t_{22} = 2.517$, $P = 0.020$) but no difference in males ($t_{16} = 0.899$, $P = 0.382$; see Fig. 2).

Positive affect

Positive affect revealed a significant main effect of “time” ($F_{1,37} = 16.216$, $P < 0.001$, $\eta_p^2 = 0.305$) with higher positive affect post-stress than pre-stress. In addition, a significant “time-by-sex” interaction occurred ($F_{1,37} = 4.401$, $P = 0.043$, $\eta_p^2 = 0.106$). Post hoc analysis showed differences in positive affect in males with higher ratings post-stress than prior to stress ($t_{17} = 4.255$, $P = 0.001$) but no significant difference in females ($t_{21} = 1.386$, $P = 0.180$). No other main effect or interaction was significant (all P s > 0.076). Higher positive affect ratings after the stress task were unexpected, hence additional exploratory analyses for single items of the positive affect scale that might indicate greater alertness ratings after than prior to stress (items: excited, attentive, determined, active) are listed in the Supporting Information.

Negative affect

Negative affect revealed a significant main effect of “regulation” ($F_{1,37} = 4.677$, $P = 0.037$, $\eta_p^2 = 0.112$), with

Figure 2.

Subjective stress ratings for females and males after the nonregulation and the regulation block. (Abbreviations: NR = nonregulation block; R = regulation block.) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

higher negative affect in the regulation condition versus the nonregulation condition, a significant main effect of “time” ($F_{1,37} = 31.575$, $P < 0.001$, $\eta_p^2 = 0.460$), with higher negative affect after stress induction and a significant interaction “regulation-by-time” ($F_{1,37} = 6.068$, $P = 0.019$, $\eta_p^2 = 0.141$). Post hoc analysis showed higher negative affect ratings after the regulation block than after the nonregulation block ($t_{39} = 2.760$, $P = 0.009$). No significant sex difference ($P = 0.794$) nor any other significant interaction (all P s > 0.396) occurred.

Anger

Subjective anger ratings revealed a significant main effect of “regulation” ($F_{1,39} = 5.035$, $P = 0.031$, $\eta_p^2 = 0.114$) with higher ratings after the regulation block and a significant main effect of “time” ($F_{1,39} = 45.768$, $P < 0.001$, $\eta_p^2 = 0.540$) with higher ratings post-stress but no significant sex difference ($P = 0.763$). Additionally, a significant interaction “regulation-by-time” ($F_{1,39} = 20.358$, $P < 0.001$, $\eta_p^2 = 0.343$) occurred, showing higher anger ratings post-stress for the regulation block than post-stress in the nonregulation block ($t_{41} = 4.121$, $P < 0.001$).

Cognitive regulation

Application of state suppression and state reappraisal did not differ either between or within groups ($P = 0.581$ and $P = 0.841$, respectively; see Table I). Additionally, males and females differed in CISS-scales “emotion oriented stress coping” ($t_{41} = 2.219$, $P = 0.032$) and “coping by

TABLE II. Whole brain fMRI contrasts

Contrasts	MNI					Region
	X	Y	Z	k	t-value	
Regulation > nonregulation	33	47	19	571	$T = 4.55$	Right middle frontal gyrus
	54	-25	10	144	$T = 4.22$	Right superior temporal gyrus
Stress regulation > stress nonregulation	53	-27	12	150	$T = 3.93$	Right superior temporal gyrus
Nonregulation stress > control	42	-66	9	102093	$T = 11.07$	Right middle temporal gyrus
	-36	16	4	997	$T = 4.84$	Left insula lobe
Nonregulation control > stress	56	-12	6	640	$T = 5.35$	Right superior temporal gyrus
	51	-64	33	408	$T = 4.86$	Right angular gyrus
	-51	-67	30	297	$T = 4.96$	Left angular gyrus
Regulation stress > control	42	-66	12	67897	$T = 8.20$	Right middle temporal gyrus
	38	-19	-11	1218	$T = 5.12$	Right hippocampus
	-11	-31	-23	652	$T = 4.17$	Left brainstem
	-30	19	9	551	$T = 4.51$	Left insula lobe
	8	-39	22	250	$T = 4.35$	Right posterior cingulate
	-2	-31	-4	161	$T = 3.93$	Left brainstem
Nonregulation stress females > males	50	-72	15	179	$T = 4.14$	Right middle temporal gyrus
Nonregulation stress > control females > males	51	-40	16	289	$T = 4.53$	Right superior temporal gyrus

social distraction" ($t_{41} = 2.378$, $P = 0.022$), with higher values in females than males for both scales.

Skin Conductance Response

Four participants were excluded from SCR analysis (3 due to a broken wire and 1 due to severe artifacts), leaving 39 participants for the analysis (20 female; 19 males). nSCR revealed a significant main effect of "condition" ($F_{1,37} = 10.664$, $P = 0.002$, $\eta_p^2 = 0.224$) with a higher number of SCR in the stress condition than in the control condition. No significant sex difference, main effect "regulation" or interaction occurred (all P s > 0.136).

Cortisol Response

Cortisol data of 40 participants (23 females; 17 males) were analyzed. Three participants were excluded due to technical problems of data analysis in the clinical trial center. With independent t -tests no sex differences were observed for difference scores (post-stress vs. pre-stress) either in the nonregulation block ($t_{38} = 0.024$, $P = 0.981$) or in the regulation block ($t_{38} = 0.445$, $P = 0.656$; Further analyses on cortisol can be found in the Supporting Information).

fMRI Data

Regulation versus nonregulation

The whole sample contrast of the regulation block (control and stress) versus the nonregulation block (control and stress) revealed stronger activation in the right middle frontal gyrus (MFG) and the right superior temporal gyrus (STG) gyri. We did not find stronger activation in the non-

regulation block than in the regulation block. Directly comparing the stress conditions in the regulation and the nonregulation block revealed a significant cluster in the right STG during the regulation block (see Table II).

Stress versus control condition

In the nonregulation block, we observed stronger activations during the stress than the control condition in a large cluster extending from bilateral middle temporal gyrus (MTG) to middle occipital gyri and right MFG as well as in the right precentral gyrus. A second cluster extended from left insula to inferior frontal gyrus. In contrast, during the control condition participants showed greater activations than during the stress condition in the right STG and angular gyrus bilaterally (see Table II).

In the regulation block during the stress relative to the control condition, significantly stronger activations emerged in one cluster in the right MTG extending to precentral, superior frontal, and left middle occipital gyri, right precuneus as well as the cerebellum. A second cluster in the right hippocampus extended to the pallidum and a third cluster centered in the left insula. No stronger activations appeared for the contrast control versus stress in the regulation block.

Sex-specific analysis

To compare neural activation in females and males we conducted the contrast stress versus control in the nonregulation and the regulation block for males versus females. Separate sex-specific analysis per regulation block can be found in the Supporting Information. Directly comparing the stress condition in the nonregulation block revealed stronger activation in females than in males in the right

Figure 3.

Whole-brain contrast showing stronger activations in the right superior temporal gyrus in females than in males in the stress condition compared to the control condition in the nonregulation block. (Abbreviations: C = control condition; S = stress condition; F = female; M = male.) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

MTG. Additionally, for the stress compared to the control condition stronger activation emerged in females than in males in the right STG extending to the angular gyrus (see Table II and Fig. 3). There were no stronger activations for males in this contrast, nor any significant sex differences in the regulation block applying the corrected threshold.

ROI Analysis

Amygdala

A $2 \times 2 \times 2 \times 2$ rmANOVA with the within-subject factors "laterality" (left/right), "regulation" (nonregulation/regulation) "condition" (control/stress), and the between-subjects factor "sex" revealed a significant main effect for "condition" ($F_{1,41} = 14.547$, $P < 0.001$, $\eta_p^2 = 0.262$), with stronger activation during stress than during control, and a significant interaction effect for "regulation-by-condition-by-sex" ($F_{1,41} = 6.782$, $P = 0.013$, $\eta_p^2 = 0.142$). No other main effect or interaction emerged (all P s > 0.147). Disentangling the significant 3-way interaction, we performed two 2×2 rmANOVAs with the within-subject factors "condition" (control/stress) and the between-subjects factor "sex" for the nonregulation and the regulation block separately. In the non-regulation block, a significant main effect for "condition" ($F_{1,41} = 21.009$, $P < 0.001$, $\eta_p^2 = 0.339$) with stronger activation of the amygdala during stress than during control and a significant "condition-by-sex" interaction ($F_{1,41} = 4.891$, $P = 0.033$, $\eta_p^2 = 0.107$) was revealed. The amygdala showed stronger activations during stress in the nonregulation block in females than in males ($t_{41} = 2.071$, $P = 0.045$; see Fig. 4A). No significant effects emerged for the regulation block (all P s > 0.103).

Hippocampus

A $2 \times 2 \times 2 \times 2$ rmANOVA with the within-subject factors "laterality" (left/right), "regulation" (nonregulation/

regulation) and "condition" (control/stress), and the between-subjects factor "sex" revealed significant main effects for "laterality" ($F_{1,41} = 123.507$, $P < 0.001$, $\eta_p^2 = 0.751$), with stronger activation of the right than of the left hippocampus and for "condition" ($F_{1,41} = 12.376$, $P = 0.001$, $\eta_p^2 = 0.232$), with stronger activation during the stress than the control condition. Additionally, the "laterality-by-regulation" interaction ($F_{1,41} = 11.111$, $P = 0.002$, $\eta_p^2 = 0.213$) and "laterality-by-regulation-by-condition" interaction ($F_{1,41} = 7.988$, $P = 0.007$, $\eta_p^2 = 0.163$) were significant. No other main effect or interaction was significant (all P s > 0.05). Disentangling the 3-way interaction, we performed two separate 2×2 rmANOVAs for the left and the right hippocampus separately with the within-subject factors "regulation" (nonregulation/regulation) and "condition" (control/stress).

For the left hippocampus, we found a significant main effect "condition" ($F_{1,42} = 4.278$, $P = 0.045$, $\eta_p^2 = 0.092$), with stronger activation during stress than the control condition. Additionally, the "regulation-by-condition" interaction was significant ($F_{1,42} = 4.564$, $P = 0.039$, $\eta_p^2 = 0.098$), showing stronger activation during nonregulation than regulation for the stress condition ($t_{42} = 2.839$, $P = 0.007$), but higher activation during the stress than the control condition was observed in the nonregulation block ($t_{42} = 4.400$, $P < 0.001$; see Fig. 4B). Notably, no difference between control and stress conditions appeared in the regulation block ($P = 0.881$; see Fig. 4B). For the right hippocampus, the 2×2 rmANOVA revealed a significant main effect of "condition" ($F_{1,42} = 46.355$, $P > 0.001$, $\eta_p^2 = 0.525$), with stronger activation during the stress than the control condition (see Fig. 4B). Neither the main effect for "regulation" nor the interaction was significant (all P s > 0.09).

Putamen

A $2 \times 2 \times 2 \times 2$ rmANOVA with the within-subject factors "laterality" (left/right), "regulation" (nonregulation/regulation) and "condition" (control/stress), and the between-subjects factor "sex" revealed a significant main effect for "laterality" ($F_{1,41} = 147.929$, $P < 0.001$, $\eta_p^2 = 0.783$) with higher activation in the left putamen, a significant main effect for "condition" ($F_{1,41} = 14.478$, $P < 0.001$, $\eta_p^2 = 0.261$) with higher activation during the stress condition, and a significant 4-way interaction "laterality-by-regulation-by-condition-by-sex" ($F_{1,41} = 6.439$, $P = 0.015$, $\eta_p^2 = 0.136$). No other main effect or interaction was significant. Disentangling the 4-way interaction, we conducted two $2 \times 2 \times 2$ rmANOVAs for the left and the right putamen separately with the within-subject factors "regulation" (nonregulation/regulation) and "condition" (control/stress) and the between-subjects factor "sex." For the left putamen there was a main effect "condition" ($F_{1,41} = 6.352$, $P = 0.016$, $\eta_p^2 = 0.134$) with higher activation during the stress condition, and a significant interaction "regulation-by-condition-by-sex" ($F_{1,41} = 6.937$, $P = 0.012$, $\eta_p^2 = 0.145$).

Figure 4.

ROI analysis. **A:** Activation strength of the amygdala for control and stress for the nonregulation block. **B:** Activation strength of the left hippocampus (left side) for control and stress for the nonregulation and the regulation block and for the right hippocampus (right side) for control and stress condition for both nonregulation and regulation block. Correlational analysis in the regulation block for subjective stress in females (right side; red

dots). **C:** Activation strength for the left putamen for stress in the nonregulation block (left side) and the right putamen for the nonregulation block (right side). (Abbreviations: F = female; M = male; NR = nonregulation block; R = regulation block; C = control condition; S = stress condition.) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Decomposing the 3-way interaction, we conducted two 2×2 rmANOVAs with the within-subject factor “regulation” and the between-subjects factor “sex” for the control and the stress condition separately. The control condition did not reveal any significant main effects or interactions (all P s > 0.266). The stress condition revealed a significant interaction “regulation-by-sex” ($F_{1,41} = 5.032$, $P = 0.030$, $\eta_p^2 = 0.109$). Males showed higher activation of the left putamen in the nonregulation block in the stress condition than females ($t_{41} = 2.152$; $P = 0.037$; see Fig. 4C). No other main effect or interaction reached significance for both stress and control condition (all P s > 0.263). The right putamen again revealed a significant main effect “condition” ($F_{1,41} = 39.330$, $P > 0.001$, $\eta_p^2 = 0.490$) with

higher activation in the stress condition and a significant “regulation-by-condition” interaction ($F_{1,41} = 13.836$, $P = 0.001$, $\eta_p^2 = 0.252$). For the nonregulation block, the right putamen showed higher activation during stress than the control condition ($t_{42} = 3.066$, $P = 0.004$; see Fig. 4C). No other main effect or interaction reached significance (all P s > 0.069).

Sex Specific Regression Analysis

For exploration of sex specific analysis, only significant and Bonferroni-corrected correlations are listed in the following.

Subjective stress

In females, we found a significant positive correlation between right hippocampus activity in the regulation block and subjective stress after the block ($r_{23} = 0.646$, $P = 0.001$; see Fig. 4B).

No other correlation with amygdala, hippocampus, or putamen activity reached significance (physiological data [nSCR, cortisol]: all P s > 0.050 , Bonferroni-corrected; positive and negative affect: all P s > 0.050 , Bonferroni-corrected; subjective stress: all P s > 0.080 ; state suppression/reappraisal: all P s > 0.05 , Bonferroni-corrected; trait social distraction/emotion-oriented coping: all P s > 0.050 , Bonferroni-corrected).

DISCUSSION

This study investigated sex differences in the neural correlates of cognitive regulation of negative sensations in stressful situations [Gross, 2002; Ochsner et al., 2002]. Based on previous studies showing sex differences in stress reactions as well as in the application of cognitive regulation strategies, we investigated cognitive regulation strategies in stressful situations in females and males on subjective, psychophysiological, and neural levels. Using a psychosocial stress task, we successfully induced stress in females and males, apparent on all measured levels (subjective, physiological and neural). Our results support two main conclusions: first and in contrast to emotion induction paradigms, stress impairs cognitive regulation and recruits regions of working memory, attention, and cognitive regulation. Second, males and females differ in their approach to cognitive stress regulation: in females, the attempt to cognitively regulate stress induces higher stress ratings, whereas this is not seen in males. On a neural level, females engage emotion related areas more strongly in the mere exposure to stress than males while males seem to be more motivationally engaged. In females, this may require more effort to cognitively regulate stress which further probably triggers higher subjective stress in females than in males. Although no quantitative differences in applying cognitive regulation strategies were found, qualitative differences are apparent between females and males.

Subjective Effects of Cognitive Regulation on Stress Response

Both females and males reported higher negative affect and anger ratings after stress regulation than after merely experiencing stress. This was contrary to the expectation that stress regulation would lead to less negative subjective response. Our data rather suggests that asking participants to consciously regulate stress responses, which did not lead to better performance, instead induced further frustration apparent in significantly higher anger and negative affect ratings. Recently, Raio et al. [2013] investigated the effects of cognitive emotion regulation after a stress task on behavioral and psychophysiological fear responses.

They demonstrated a significant regulation effect only in nonstressed participants, whereas stressed participants showed no reduction in emotional response in the subsequent fear experiment. These results suggest that stress markedly impairs cognitive regulation of emotion and also show that this technique has limitations when invoked to control for affective responses under stress.

Neural Effects of Cognitive Regulation on Stress Response

On a neural level, directly comparing the regulation block with the nonregulation block revealed stronger activation in right MFG and right STG. Additionally, focusing on stress induction revealed stronger activation in the right STG during the regulation than the nonregulation block. In contrast, the left hippocampus showed stronger activation during stress in the nonregulation block than in the regulation block.

Regulation versus nonregulation

Regarding activation of the right MFG in the regulation block, an increase in neural activation of this region was reported previously during cognitive regulation of negative emotions [Kim and Hamann, 2007; McRae et al., 2010; Ochsner et al., 2002]. Stronger activation of the MFG has frequently been reported in working-memory tasks and in the integration of stimulus-driven and goal-directed attention [Asplund et al., 2010; Corbetta and Shulman, 2002; Rottschy et al., 2012]. Therefore, our finding might indicate higher vigilance, attention integration, and working memory during cognitive regulation of stressful events in both females and males [Phan et al., 2005]. The recruitment of the right STG was previously associated with emotion processing [Kohn et al., 2014; Wager et al., 2003] and deactivation of the STG with subjectively relaxed states [Wang et al., 2005]. Thus, the activation of the STG may point on regulating emotional experience during cognitive stress regulation. As pointed out by Viviani [2013], cognitive emotion regulation is engaging the bottom-up as well as the top-down attention networks, thus it involves STG but also MFG activation. Additionally, MFG and STG are anatomically connected to each other and both seem to modulate amygdala activation [Müller et al., 2012]. Therefore, our results not only support Viviani's [2013] assumption but also expand it to cognitive regulation during a demanding achievement task.

Nonregulation versus regulation

The left hippocampus showed stronger activation during stress in the nonregulation block than in the regulation block, indicating that cognitive regulation modulated stress reaction on the neural level. Increase in hippocampus activity was associated with decreasing negative affect in cognitive regulation of emotions [Kim and Hamann, 2007] and

additionally may indicate stronger memory processing and retrieval [Cabeza and Jacques, 2007], whereas decreased activity indicate a heightened stress reaction [Pruessner et al., 2008]. Thus, in addition to higher subjective anger and negative affect ratings in the regulation block, deficits in recalling previous experiences when participants have to simultaneously perform a demanding stress task and cognitively regulate their stress sensations may lead to further increase in neural stress processing and negative affect.

For the nonregulation block, the right putamen showed higher activity in the stress than in the control condition. The putamen is engaged during working memory and executive function tasks [Arsalidou et al., 2013], and a similar pattern of activation in the putamen during stress reactions was shown previously. Its activation was associated with perceived anxiety, stress [Wang et al., 2005], and withdrawal [Wager et al., 2003]. However, other studies also reported reduced activity during stress in the basal ganglia [Dedovic et al., 2009; Pruessner et al., 2008] and its association with sensitivity to rewards in stressful situations [Kumar et al., 2014; Porcelli et al., 2012]. Thus, increased putamen activation during stress exposure may indicate reward sensitivity and motivation processing during a challenging achievement task [Dickerson and Kemeny, 2004; Kumar et al., 2014; Pruessner et al., 2008].

To summarize, during cognitive regulation of stressful events brain regions associated with goal-directed behavior, the integration of bottom-up and top-down attention and cognitive regulation show higher activation while brain regions associated with memory and stress processing are less activated. The additional load of cognitive regulation during a demanding achievement task seems to be effortful. It induces more stress instead of adapting subjective stress sensations. Reports on higher stress levels after regulation were contrary to our expectations and to results of previous literature on emotion regulation paradigms [e.g., Ochsner et al., 2004]. In stress regulation, external feedback can increase or decrease the stress response, but however, it modulates the subjective and physiological stress levels in opposite directions [Rohrmann et al., 1999]: Reassuring feedback decreases subjective but increases physiological response, whereas the contrary pattern is seen in feedback indicating arousal. Additionally, a psychoeducational priming prior to stress induction seems to trigger an adapted physiological response but no change in subjective reaction occurs [Jamieson et al., 2012]. Differences in physiological versus subjective reaction may be prompted by a self-related bias and engagement on bodily sensations [Viviani, 2013]. Thus, our findings expand the results on discrepancies in subjective and psychophysiological stress regulation. Stress reactions are modulated differentially on subjective, physiological, and neural levels by regulation approaches [Jamieson et al., 2012; Rohrmann et al., 1999]. Furthermore, the results add a first insight on the neural correlates of cognitive stress regulation during a concurrent cognitive task and are consistent with literature showing that stress impairs the ability for cognitive regulation [Raio et al.,

2013]. This may reflect higher cognitive needs and effort for withholding affective responses in cognitive stress regulation than in emotional stress settings [e.g. McRae et al., 2010; Rohrmann et al., 1999]. In this study, the cognitive regulation training was applied directly before the stress task as it was meant to draw from subjective cognitive regulation abilities. As shown in a previous study on the effects of cognitive emotion regulation on fear conditioning [Raio et al., 2013], training of cognitive stress regulation strategies seems to be mandatory to ensure the effectiveness of the regulation approach by overcoming the additional effort and cognitive load. This seems to be particularly necessary in stressful situations. Together with our results, this points to the importance of a longer lasting and better internalized training of cognitive stress regulation for an effective way of using it in a concurrent, demanding, and stressful situation.

Sex Differences in Subjective Ratings During Regulation of Stress Sensations

For females, cognitive regulation seems to be more stressful as revealed by higher post-stress subjective ratings in the regulation block than in the nonregulation block. Additionally, females show less subjective stress with higher attempts to reappraise their stress sensations whereas no such association appeared in males. Females and males did not differ in their subjective response to unregulated stress, thus it is unlikely that sex differences arose because females initially perceived stress as more unpleasant than males. This divergence between females and males suggests different approaches of benefitting from cognitive regulation, which can be interpreted in the context of neural activation.

Positive affect showed a significant time-by-sex interaction with higher ratings after stress in males but not in females. At a first glance this seems contrary to expectations. Exploratory analysis revealed that ratings of items as “excited,” “attentive,” and “determined” showed higher ratings post-stress than prior to stress induction in both females and males. Additionally, a significant “time-by-sex” interaction was revealed for the rating of “active” showing sex differences with higher ratings prior to stress in females than in males but no sex difference after stress. Thus, higher positive affect after stress induction in males indicates greater alertness and attention after than prior to stress whereas males seem to be less attentive than females prior to the tasks. (Please find all listed exploratory correlation analysis in the Supporting Information.)

Sex Differences in Neural Correlates During Regulation of Stress

Regulation versus nonregulation

In addition to the significant sex difference in the effect of regulation on the subjective stress and affect ratings, we

also observed sex differences in the underlying neural network. Although the amygdala was more strongly activated during mere exposure to stress than during the control condition in females, no such effect was observed in males. This is consistent with previous work showing an association between stress and amygdala activation in females but not in males [Wang et al., 2007] and indicates an upregulated emotional response during mere perception of stress that is more pronounced in females than in males [Ochsner and Gross, 2005]. Thus, we observed a discrepancy between subjective and neural stress processing in females: they showed increased activation of emotion related regions during stress exposure but higher subjective stress ratings after cognitive regulation. These higher stress ratings might be elicited by higher effort during cognitive regulation: areas that were more strongly activated in mere stress exposure in females may have required more effort to downregulate these areas. This probably caused increased subjective stress in females compared to males after regulation.

Stress versus control condition

During the nonregulation block, females showed stronger activation than males in the stress condition compared to the control condition in a more posterior part of the right STG. Activation of the STG is often reported during stress experiences [e.g. Dagher et al., 2009; Pruessner et al., 2008; Wang et al., 2005] and its deactivation has been interpreted as an indicator for a relaxed state [Wang et al., 2005]. Additionally, the STG was considered as an executive node during cognitive regulation [Kohn et al., 2014]. Thus, females recruited a region associated with attention and emotion regulation during stress exposure more strongly than males. We found a negative correlation between right STG activity and “excited” as well as “nervousness” in males in the regulation block and with “anxiousness” in the nonregulation block, supporting the linkage between relaxed states and higher STG activity (see Supporting Information). Notable, in females these associations are absent. In contrast, in females a positive correlation was found between hippocampus activity and subjective stress in the regulation block. Hence, our results suggest that females compared to males put more effort in recruiting regions associated with attention and emotion regulation during stress exposure indicating a stronger emotional processing during stress.

Regarding activation of the putamen, males showed higher activation in the left putamen in the stress condition during the nonregulation block than females, a difference not appearing during regulation. In contrast to a previous study that did not report sex differences in putamen activation during stress perception [Wang et al., 2007], this task included social evaluation and comparison of participants’ performances. Additionally, a meta-analysis on emotion processing showed higher activation in males in the putamen for processing negative emotions

[Stevens and Hamann, 2012]. Social competition or rivalry combined with inferiority in an achievement situation may induce stronger motivation processing and “fight-or-flight” responses in males [Kumar et al., 2014; Stroud et al., 2002; Taylor et al., 2000], which may explain higher activation in the putamen during stress exposure.

Our study supports the findings of McRae et al. [2008] on neural sex differences in emotion regulation and extends them to neural sex differences in cognitive stress regulation during a demanding achievement task. We showed that reported sex differences in brain regions associated with emotion regulation also apply to cognitive stress regulation. On a neural level, significant sex differences appeared in mere stress exposure with females engaging areas related with emotion regulation while males relied more strongly on regions associated with motivation and reward sensitivity. On a subjective level sex differences were apparent during cognitive regulation of stress with females reporting significantly higher stress ratings. Taken together, the observed sex differences might indicate different ways of stress reaction and regulation approaches: males were more motivationally engaged in demanding achievement situations, whereas females were more emotionally involved. Higher emotional involvement may necessitate more effort to regulate emotional sensations. This might have accounted for higher subjective stress after regulation in females. The data indicate that females and males might benefit from stress regulation in distinct ways.

Limitations and future directions

This study has some limitations that could affect interpretation of the results. The sample includes very homogeneous, healthy, young, and highly educated individuals (mostly students). For the purpose of applying cognitive stress regulation in stress-related mental disorders, the assessment of cognitive regulation strategies in stressful situations within patient groups would be necessary. Additionally, we do not know whether participants changed the applied cognitive regulation strategy throughout the task. In general, a stereotypically feminine cognitive regulation strategy is social affiliation [Nolen-Hoeksema, 2012; Tamres et al., 2002; Taylor et al., 2000; Taylor, 2006]. In this study, we did not include the possibility to seek social support under stress. Observed sex differences in the demanding stress task may be guided by the missing feminine cognitive regulation strategy. This issue should be subject to further research. We did not find sex differences on a physiological level. Although some authors reported sex differences in physiological stress reaction [e.g., Kirschbaum et al., 1992], others could not replicate this finding for stress reactions or emotion regulation [e.g., Kim and Hamann, 2012; Wang et al., 2007]. Sex differences that have been found in physiological stress reactions seem to be particularly associated with menstrual cycle phase [Duchesne et al., 2012; Kirschbaum

et al., 1992]. However, in this study, we did not analyze menstrual cycle information in females because splitting the female group would result in too small sample sizes. We hope that this issue will be taken into account in future research. For exploratory reasons to guide future research, we included an analysis of the intake of hormonal contraceptives and cortisol levels in the Supporting Information.

CONCLUSION

Considering the strong association between mental health and stress reports [Keller et al., 2012], the investigation of cognitive stress regulation and its outcomes is important for advancing the knowledge of stress modulation and may have implications for future research. Importantly, and in contrast to our hypotheses, this study showed that the application of cognitive regulation in stressful achievement situations is rather effort than helpful in demanding stress situations. It induces stronger subjective response and implicates brain areas associated with goal-directed behavior, attention integration, and emotion processing and down-regulates regions involved in memory and stress processing. Together with previous reports on emotion regulation in stressful situations [Raio et al., 2013], these results emphasize the importance of a training in cognitive regulation strategies to successfully modulate emotional sensations during stress situations.

The study also showed that sex matters in the application of cognitive regulation. Females and males showed differences on a neural level during mere stress perception, and additionally on a subjective level during cognitive stress regulation. Higher recruitment of emotion related regions during stress may necessitate higher effort during cognitive downregulation. This further may lead to increased subjective stress in females. Contrarily, males seem to be more engaged by achievement tasks. There is evidence that females and males benefit from different forms of interventions [Ogrodniczuk et al., 2001]. As females and males seem to differ in their approach to cognitive modulation of stress responses, they would likely respond to different kinds of cognitive regulation strategies, for example, with a focus on regulating strong emotions in stressful situations for females.

Additionally, it is presumable that dysfunctions in cognitive stress regulation during a demanding achievement task arise in patients suffering from stress-related mental disorders, which are often accompanied by emotion regulation dysfunctions and show sex differences in prevalence (such as depression, borderline personality disorder, or schizophrenia). Such individual differences may influence the efficacy of cognitive stress regulation. In efforts to personalize the efficacy of cognitive stress regulation strategies, our results could be considered for developing sex-specific interventions for patients with mental disorders

with a diminished capacity to cognitively regulate stress sensation.

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