Neural correlates of immediate and prolonged effects of cognitive reappraisal and distraction on emotional experience

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Abstract

Cognitive emotion regulation strategies are important components of cognitive-behavioral therapy (CBT). Additionally, up-regulation and difficulties in the down-regulation of negative feelings are associated with mental disorders. However, little is known about the lasting effects of cognitive emotion regulation strategies on emotional experience and associated neural activation. Therefore, this study investigated immediate and prolonged effects of emotion regulation using cognitive reappraisal and distraction on subjective report and its neural correlates. Twenty-seven healthy females took part in a 2-day functional magnetic resonance imaging study. They were instructed to either up-regulate or down-regulate their negative feelings using a situation-focused cognitive reappraisal strategy, to distract themselves by imagining a specific neutral situation, or to passively look at repeatedly presented aversive and neutral pictures. Re-exposure to the same stimuli without a regulation instruction was conducted one day later. Self-reported negative feelings and blood-oxygen-level-dependent responses served as main outcome variables. As expected, the results show successful immediate up- or down-regulation of negative feelings by cognitive reappraisal and down-regulation of negative feelings by distraction. Furthermore, these changes in negative feelings were correlated with amygdala activation. A lasting effect on emotional experience associated with stronger ventromedial prefrontal cortex activation was found for down-regulation of negative feelings via cognitive reappraisal. Compared to distraction, down-regulation via cognitive reappraisal led to reduced negative feelings and stronger dorso- and ventrolateral prefrontal cortex responses one day later. While cognitive reappraisal and distraction are both effective strategies during active regulation, only cognitive reappraisal had a lasting effect. These findings might have implications for CBT.

Introduction

Cognitive emotion regulation plays a crucial role in cognitive behavioral therapy (CBT) (Beck 1976) and is supposed to influence relapse after successful CBT (Craske et al. 2008). The most prominent strategy, cognitive reappraisal, is defined as reinterpreting a potentially emotion-eliciting stimulus in a way that changes its emotional impact. Distraction as one form of attentional deployment is characterized by restricting attention to external stimuli by focusing on internal information maintained in working memory (Gross and John 2003; Ochsner, Silvers and Buhle 2012).

Several neuroimaging studies investigating the neural correlates of cognitive emotion regulation found an interaction of regulatory lateral and medial prefrontal and anterior cingulate cortex areas with brain regions important for emotional bottom-up processing (e.g. amygdala) (Ochsner, Silvers and Buhle 2012). Neuroimaging studies directly comparing cognitive reappraisal and distraction showed a reduction of amygdala activation using these strategies (compared with looking at aversive pictures), with a stronger reduction for distraction as compared to reappraisal (Dörfel et al. 2014; Kanske et al. 2011; McRae et al. 2010). These studies also found overlapping as well as distinct enhanced activation of prefrontal, anterior cingulate, and parietal cortex areas. Findings in patients with mental disorders indicate reduced top-down control of emotional responses with altered activation of the underlying neural circuits (Hermann et al. 2009; Kanske et al. 2012; Goldin et al. 2009; New et al. 2009). Additionally, up-regulation of negative emotions by cognitive strategies such as worrying or rumination is a characteristic of mental disorders (American Psychiatric Association 2000).

Despite many findings on the immediate effects of cognitive emotion regulation on emotional experience and neural activation, considerably less is known about its prolonged effects (Ochsner, Silvers and Buhle 2012). However, the interaction of cognitive emotion regulation strategies with emotional learning and memory is a key mechanism underlying CBT (Beck 1976; Craske et al. 2008), and might also be involved in the development and maintenance of mental disorders.

In general, explicit memory is enhanced for emotional compared to neutral stimuli or events (Bennion et al. 2013; LaBar and Cabeza 2006). Studies investigating the regulation of emotions by cognitive reappraisal found lasting effects on emotional experience (Ahn et al. 2015; Ayduk and Kross 2009; Kross and Ayduk 2008; Macnamara, Ochsner and Hajcak 2011). Concerning explicit memory, subsequent recognition of the stimuli (Kim and Hamann 2012; Knight and Ponzio 2013; but see Erk, von Kalckreuth and Walter 2010) and the memory for the previously applied regulation strategy was improved with cognitive reappraisal (Knight and Ponzio 2013). Free recall of emotional stimuli was enhanced with up-regulation (Ahn et al. 2015; Knight and Ponzio 2013; but see Kim and Hamann 2012), but reduced with down-regulation of emotions (Ahn et al. 2015; Knight and Ponzio 2013) using cognitive reappraisal. These findings indicate that cognitive reappraisal has a lasting effect on emotional experience and leads to enhanced explicit memory for the stimuli (except free recall) and the previously applied regulation strategy.

More clinically relevant studies indicate that cognitive reappraisal but not distraction leads to less negative emotional memory for stressful situations (Levine et al. 2012). A positive effect on exposure-based treatment outcome in specific phobia (Kamphuis and Telch 2000) and reduced recall of depressive experiences in depressive patients (Kross and Ayduk 2008) was furthermore found for cognitive reappraisal compared with distraction. These findings indicate beneficial lasting effects of cognitive reappraisal, while distraction leads to an enhanced reoccurrence of negative emotions.

Investigating neural correlates might help to understand the mechanisms underlying differential prolonged effects of distinct cognitive emotion regulation strategies. An EEG-study investigating the effects of cognitive reappraisal, found a reduced late positive potential (LPP) during delayed re-exposure to previously reappraised stimuli (Macnamara, Ochsner and Hajcak 2011). In contrast, distraction resulted in enhanced lasting LPP-responses (Thiruchselvam et al. 2011).

Functional magnetic resonance imaging studies found reduced amygdala activation during immediate re-exposure to previously reappraised stimuli in healthy subjects (Walter et al. 2009), but not in patients with major depressive disorder (Erk et al. 2010). This effect also appeared during re-exposure after one week, but only when emotions were repeatedly (four times) regulated in response to the same stimuli the week before (Denny et al. 2015).

Other studies focused on the interaction of cognitive emotion regulation strategies with fear conditioning and extinction processes. These found an effect of instructed cognitive reappraisal (Blechert et al. 2015), as well as trait-reappraisal (Hermann, Keck and Stark 2014) on socially relevant fear learning, extinction and extinction recall. Here, a stronger habitual use of cognitive reappraisal was associated with enhanced ventromedial prefrontal cortex (vmPFC) activation during extinction recall (Hermann, Keck and Stark 2014). The vmPFC is a prominent region for regulating negative emotions through cognitive strategies as well as during extinction (Diekhof et al. 2011) and might be crucial for the interaction of cognitive reappraisal with emotional memory processes.

However, up to date there are no neuroimaging studies investigating the neural correlates of prolonged effects of distraction and up-regulation of negative emotions via cognitive reappraisal. It is conceivable that distraction leads to the reoccurrence of negative emotions because stimuli are not processed very deeply. This might result in enhanced amygdala activation during re-exposure because of enhanced stimulus novelty. Up- or down-regulation of negative emotions by reinterpreting the specific story or content of a picture via cognitive reappraisal rather provokes a more intense processing of each specific stimulus. Compared to distraction, the stimulus-specific processing during cognitive reappraisal might furthermore lead to a stimulus-dependent and probably more sustained memory effect.

Therefore, the goal of this study was to investigate immediate and prolonged effects of cognitive reappraisal and distraction on subjective and related neural responses toward aversive pictures. Twenty-seven females took part in a 2-day functional magnetic resonance imaging (fMRI) study with an active regulation task on the first day and re-exposure to the same pictures without regulation instructions one day later. The following hypotheses were tested:

1) Active Regulation on Day 1: An immediate reduction of negative feelings was expected for both, distraction as well as down-regulation of negative emotions by cognitive reappraisal, whereas up-regulation was expected to augment negative feelings. These changes in emotional experience are especially assumed to correlate with activation changes in the amygdala in the respective direction.

2) Re-exposure on Day 2: One day later, pictures previously presented in the down-regulation compared with the control condition (i.e., passively looking at aversive pictures) and the distraction condition should evoke reduced negative feelings, associated with reduced amygdala activation, indicating reduced emotional responsiveness. Furthermore, enhanced vmPFC activation, probably indicating inhibitory memory processes, as well as active-regulation-related lateral prefrontal cortex responses were expected. Distraction

and up-regulation using cognitive reappraisal each compared with passively looking at aversive pictures should furthermore lead to stronger negative feelings on the second day, associated with enhanced amygdala activation.

Methods and Materials

Subjects

Thirty-four healthy female students recruited at the Justus Liebig University Giessen participated in this functional magnetic resonance imaging (fMRI) study. Exclusion criteria consisted of self-reported neurological disorders, mental disorders, and severe medical diseases, MRI contraindications, and the use of psychoactive or other potentially confounding substances. All participants were right-handed as assessed by the Edinburgh Inventory of Handedness (Oldfield 1971), between 18 and 35 years old, and had normal or corrected-to-normal vision. Participants were reimbursed with course credits or 10€/h for participation. Seven participants were excluded because of falling asleep during the scanning session (n=1), insufficient MRI data quality (n=3), or excessive head movement during scanning (n=3), leaving a final sample of 27 women (age: M=21.59 years; SD=2.58 years; range=18-27). All participants gave written informed consent according to the guidelines of the ethical standards of the Declaration of Helsinki and were told that they could end the experiment at any time. All procedures were approved by the local ethical review board of the Faculty of Psychology and Sports Science at the Justus Liebig University Giessen, Germany.

Stimuli

Twenty aversive pictures (16 on day 1 and an additional 4 on day 2) and eight neutral pictures (4 on day 1 and an additional 4 on day 2) served as stimuli. Moreover, eight unpleasant and two neutral pictures were used for regulation training. Aversive pictures showed one or more people suffering (four subcategories containing five pictures each: homeless person, domestic violence, ill persons in hospital, and accident scenes), while neutral images displayed everyday scenes (e.g. two people in a conversation). At least one person was depicted in every picture. Stimuli were selected from the International Affective Picture System (IAPS) (Lang, Bradley and Cuthbert 2008) and the Internet. Valence and arousal ratings (of the pictures used in the main experiment) assessed in a pre-study (n=16 women; age: M=23.8 years, SD=3.13 years, range: 19-32 years) indicated aversive pictures to be less pleasant (M=2.38, SD=2.03) and more arousing (M=5.94, SD=2.11) than neutral pictures (valence: M=5.50, SD=1.41; arousal: M=3.25, SD=1.44). During the experiment, stimuli were presented on a 32" LCD monitor (NordicNeuroLab Inc., Milwaukee, WI, USA) at the end of the scanner (visual field=28°). The monitor was viewed through a mirror mounted to the head coil.

Experimental procedure

Emotion regulation was performed on day 1 and re-exposure to the same stimuli took place approximately 24 hours later. Subjects received written instruction that they would take part in a study examining the neural correlates of emotion regulation. Before the emotion regulation phase started, they were informed that they would see unpleasant and neutral pictures and would have four different tasks during picture viewing. Participants were instructed to watch all stimuli attentively and either increase their negative feelings by imagining the displayed situation to have a bad ending or being worse than expected (condition: *up-regulation*) or decrease their negative feelings by imagining the displayed situation to have a happy ending or being better than expected (condition: *down-regulation*), in order to regulate negative feelings by reinterpreting the meaning of the picture using cognitive reappraisal. Furthermore, they were instructed to distract themselves from the content of the picture by thinking about a specific neutral situation that had taken place before the scanning session (condition: *distraction*). This neutral situation consisted of completing questionnaires in another room at the beginning of the study. Regarding the remaining conditions, participants were instructed to look at aversive and neutral pictures, respectively, to respond naturally and to permit all upcoming feelings and thoughts without actively changing them (condition: *look aversive* and condition: *look neutral*).

After reading the written instruction, the experimenter went through the complete instruction together with the participant, whereby the correct understanding of the strategies was ensured and practiced with sample pictures. Next, participants underwent a training phase outside the scanner consisting of 20 trials with different stimuli (8 aversive and 2 neutral pictures each shown twice). Each condition (*up-regulation, down-regulation*, *distraction*, *look aversive*, *look neutral*) was performed four times. After that, the correct implementation of the strategies was checked and all resulting questions and problems were resolved. The same training session was repeated inside the scanner during a functional run.

The emotion regulation phase on day 1 consisted of 80 trials, 16 trials for each of the experimental conditions (*up-regulation*, *down-regulation*, *distraction*, *look aversive*, *look neutral*). For aversive pictures, one picture of each subcategory (homeless person, domestic violence, ill person in hospital and accident scenes) was assigned to each condition in order to have comparable stimuli over conditions. The assignment of the specific pictures of each subcategory to the conditions was randomized across subjects.

Each trial started with the presentation of a white fixation cross on a black background jittered between 1125 and 3000ms. This was followed by an instruction word (in German; white letters on a black background) indicating the different tasks ('increase' for *up-regulation*, 'decrease' *for down-regulation*, 'distract' for *distraction*, 'look' for *look aversive* or *look neutral*) for a duration of 2000ms and the presentation of a picture for 6000ms during which participants should perform the instructed task. Next, the question 'How strong are you experiencing negative feelings right now?' was displayed above a seven-point Likert scale (ranging from 1= 'not at all' to 7= 'very strong') for a maximum of 4000ms. Participants rated their negative feelings with a keyboard. Each trial ended with the presentation of a white fixation cross on a black background (2500-4375ms). The total trial duration was 17.5s. The active emotion regulation phase on the first day consisted of 4 blocks: In the first block, 4 different pictures were shown in each of the 5 conditions, resulting in 20 trials. This was repeated for the second, third and fourth block. Each picture was again shown with the same regulation instruction in each block. Thus, every picture was presented four times in total (once in each block). Within and across blocks, the trials were presented in pseudo-randomized order (no more than twice the same instruction in succession). For the 5 conditions, the 4 different pictures per condition, and the 4 blocks, this resulted in altogether 80 trials. After the emotion regulation phase on day 1, participants rated their success and effort for the three regulation conditions on 9-point Likert scales outside the scanner.

During the re-exposure phase on day 2, participants were instructed to attentively look at the pictures without any specific regulation task. Therefore, in contrast to day 1, there was no presentation of instruction words. The 20 pictures of the emotion regulation phase on day 1 (16 aversive and 4 neutral) were presented again, in addition to four new aversive and four new neutral pictures. This resulted in 7 conditions: aversive pictures with down-regulation on day 1 (*previous down-regulation*), aversive pictures with up-regulation on day 1 (*previous up-regulation*), aversive pictures with distraction on day 1 (*previous distraction*), aversive pictures passively looked at on day 1 (*previous look aversive),* neutral pictures passively looked at on day 1 (*previous look neutral*), new aversive pictures (*new aversive*) and new neutral pictures (*new neutral*). All 28 pictures were presented in each of two blocks resulting in 56 trials altogether. During each block all 28 pictures were presented in pseudo-randomized order (maximum of two presentations of the same condition in succession). Trials started with the presentation of a white fixation cross on a black background jittered between 1125 and 3000ms followed by an aversive or a neutral picture for 6000ms, followed by the same rating screen as on day 1 for a maximum of 4000ms, and a subsequent presentation of a fixation cross for 4500-6375ms. The total trial duration was 17.5s.

After the re-exposure phase on day 2, pictures were rated on eight dimensions: valence and arousal with the Self-Assessment Manikin (SAM) (Bradley and Lang 1994) as well as negative and positive feelings, fear, empathy, sadness, and anger on 9-point Likert scales (results for these post-hoc ratings are not reported in the current manuscript). Furthermore, recognition of pictures and strategy-awareness were assessed for each picture with the questions ‘Did you see this picture during the experiment yesterday?’ (‘yes’, ‘no’), ‘Which instruction did you receive for this picture yesterday?’ (‘look’, ‘increase’, ‘decrease’, ‘distract’, ‘I don´t know’), and ‘Did you use this strategy again today?’ (‘yes, ‘no’).

Magnetic resonance imaging

A 3-T whole-body scanner (Siemens Prisma) with a 64-channel head/neck coil was used for the acquisition of brain images. In total 992 volumes were registered (emotion regulation phase on day 1: 580 volumes, re-exposure phase on day 2: 412 volumes) using a T2*-weighted gradient echo-planar imaging sequence (EPI) with 40 slices covering the whole brain (slice thickness=3mm; 0.75mm gap; descending slice order; TE=30ms; TR=2.5s; flip angle=85°; field of view=220x220mm; matrix size=110x110; PAT mode GRAPPA, acceleration factor PE 2). The first three volumes were discarded as the steady state of magnetization was incomplete. An anatomical scan (MPRAGE; 0.94mm slice thickness) was conducted before the functional runs on day 1 in order to get highly resolved structural information for the normalization procedure. In order to get information for unwarping B0 distortions a gradient echo field map sequence was acquired. Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK; 2009) implemented in Matlab R2007b (Mathworks Inc., Sherborn, MA, USA) was utilized for data analysis. After unwarping and realignment (b-Spline interpolation), slice time correction, co-registration of functional data to each participant's anatomical image, segmentation into gray and white matter, and normalization to the standard space of the Montreal Neurological Institute brain (MNI brain) was carried out. Smoothing was executed with an isotropic three-dimensional Gaussian filter with a full-width at half maximum (FWHM) of 9mm.

The following regressors were included in the first-level model separately for each block (day 1: 4 blocks; day 2: 2 blocks): down-regulation, up-regulation, distraction, look aversive, look neutral (regressors for data of day 1; duration: 6s), previous up-regulation, previous down-regulation, previous distraction, previous look aversive, previous look neutral, new aversive, new neutral (regressors for data of day2; duration: 6s). One regressor for the instruction on day 1 (duration: 2s), as well as two for the ratings (day 1 and day 2), and six movement parameters of the realignment procedure for each day (regressors of no interest) were implemented in one first-level model with two sessions (day 1 and day 2).

These regressors were each modelled by a boxcar function convolved with the canonical hemodynamic response function (hrf) in the general linear model. A high-pass filter of 128s was used to filter voxel-based time series. Contrasts between the different conditions were calculated on an individual level (all 4 blocks on day 1, first block on day 2) and analyzed in one-sample *t*-tests during second-level analyses as implemented in SPM8. Contrasts for the conditions “look new aversive” and “look new neutral” from day 2 were not analyzed for the question of this study. Moreover, simple regression analyses were conducted for each phase to evaluate the association of neural responses and ratings of negative feelings. Mean values of negative feelings for the contrasts *look aversive* minus *look neutral, up-regulation* minus *look aversive*, *look aversive* minus *down-regulation*, *look aversive* minus *distraction*, *previous up-regulation* minus *previous look aversive*, *previous look aversive* minus *previous down-regulation*, *previous look aversive* minus *previous distraction*, served as regressors.

For exploratory whole brain analyses, the intensity and significance thresholds were set to $p<.05$ on voxel-level corrected for multiple testing (family-wise error (FWE) correction); the minimal cluster size (k) was 10 voxels. ROI-analyses were conducted for the left and right amygdala on the first and second day. During re-exposure on the second day, additional ROI analyses for the vmPFC, left and right ventrolateral prefrontal cortex (vlPFC) and left and right dorsolateral prefrontal cortex (dlPFC) were done for *previous down-regulation* compared with *previous look aversive* and compared with *previous distraction*. ROI analyses were performed using the small volume correction option of SPM8. The significance threshold was set to α=0.05 on voxel level, corrected for multiple testing (family wise error (FWE) correction). Probability masks taken from the current ´Harvard-Oxford Cortical and Subcortical Structural Atlases` provided by the Harvard Center for Morphometric Analysis (http://www.cma.mgh.harvard.edu/) with a probability threshold of 0.50 included in the FSL software package (http://www.fmrib.ox.ac.uk/fsl/) were used for amygdala ROI analyses. The vmPFC mask was constructed by adding a sphere (radius: 9mm) around the peak voxel (x=0, y=40, z=-18) of regulation-related vmPFC activation, as identified in a recent meta-analysis (Diekhof et al. 2011). The MARINA software package (Walter et al. 2003) was employed to create masks for vlPFC and dlPFC.

Results

Emotional reactivity (look aversive minus look neutral day 1)

Looking at aversive pictures led to significantly higher ratings of negative feelings compared to looking at neutral stimuli ($T_{(26)}$=16.363, p<.001), indicating successful induction of negative feelings (Figure 1). Results for ROI analysis for the amygdala and exploratory whole brain analyses can be found in the Supplementary Table 1. Individual differences in ratings of negative feelings (*look aversive* minus *look neutral*) were positively associated with enhanced left and right amygdala activation (see Table 1).

- *insert Figure 1 and Table 1 about here -*

Immediate effects of emotion regulation (day 1)

ROI analyses for the amygdala and exploratory whole brain analyses for general effects of emotion regulation (comparisons between each of the different strategies and looking at aversive pictures and between down-regulation and distraction) can be found in the Supplementary Table 1). Below are the results for subjective responses and the correlations with amygdala activation (ROI).

Down-regulation vs. *look aversive*

The ratings show successful down-regulation of negative feelings using cognitive reappraisal compared with looking at aversive pictures ($T_{(26)}$=5.899, p<.001) (Figure 1). As expected, a stronger down-regulation of negative feelings by cognitive reappraisal (difference of negative feelings: *look aversive* minus *down-regulation*) was furthermore positively correlated with a stronger reduction of right amygdala activation (ROI analysis, see Table 1).

Up-regulation vs. *look aversive*

The ratings show successful up-regulation of negative feeling using cognitive reappraisal compared with looking at aversive pictures ($T_{(26)}$=4.424, p<.001) (Figure 1). Furthermore, up-regulation of negative feelings (difference of negative feelings: *up-regulation* minus *look aversive*) was related to significantly enhanced temporal pole (whole brain), cuneal cortex (whole brain) as well as bilateral amygdala (ROI) responses for the contrast *up-regulation* compared with *look aversive* (see Table 1).

Distraction vs. *look aversive*

There was a significant reduction of negative feelings during distraction compared to looking at aversive pictures ($T_{(26)}$=4.495, p<.001) (Figure 1). Moreover, the reduction of negative feelings by distraction (difference of negative feelings: *look aversive* minus *distraction*) was correlated with a stronger reduction of left brain stem (whole brain analysis) and as a trend with right amygdala activation (*look aversive* minus *distraction*) (ROI analysis, see Table 1).

Down-regulation vs. *distraction*

Additionally, down-regulation via cognitive reappraisal led to a stronger reduction of negative feelings as compared to distraction ($T_{(26)}$=3.686, p=.001) (Figure 1). Moreover, down-regulation via cognitive reappraisal compared to distraction was associated with enhanced regulation success ($T_{(26)}$=2.263, p=.032) as well as reduced regulation effort ($T_{(26)}$=2.595, p=.015). There were no significant differences in amygdala activation (ROI) or for exploratory whole brain analyses.

Re-exposure (day2): prolonged effects of emotion regulation

Previous down-regulation vs. *previous look aversive*

Ratings of negative feelings on the second day show that *previous down-regulation* by cognitive reappraisal led to a significantly stronger reduction of negative feelings compared to *previous look aversive* ($T_{(26)}$=2.560, p=.017), indicating a prolonged effect on emotional experience (see Figure 2). Post hoc ratings show that there was no significant difference in the number of recognized pictures (p>.16). Awareness for the previously applied strategy/instruction was significantly higher for *previous down-regulation* as compared to *previous look aversive* ($T_{(26)}$=6.802, p<.001). There were no significant activation differences between these two conditions (see Table 2). As hypothesized, lasting effects of down-regulation of negative feelings by cognitive reappraisal (difference of negative feelings: *previous look aversive* minus *previous down-regulation*) were associated with enhanced vmPFC activation for *previous down-regulation* as compared to *previous look aversive* (ROI analysis; MNI: x=0, y=32, z=-20; T=3.27, p=.044) (see Figure 3A and Table 3). However, there were no significant associations with amygdala or lateral prefrontal cortex activation (ROI analyses) nor significant exploratory whole brain results.

- *insert Figure 2 and 3 about here -*
- *insert Table 2 and 3 about here -*

Previous up-regulation vs. *previous look aversive*

There was no significant difference in ratings of negative feelings for *previous up-regulation* compared with *previous look aversive* (p>.90) (Figure 2). *Previous up-regulation* showed a trend for reduced recognition memory compared to *previous look aversive* ($T_{(26)}$=1.803, p=.083). Furthermore, awareness for the previously applied strategy/instruction was significantly enhanced for up-regulation compared with looking at aversive pictures ($T_{(26)}$=4.087, p<.001). There were no significant activation differences between *previous up-regulation* and *previous look aversive*, or correlations of brain activation with ratings of enhanced? negative feelings (difference of negative feelings:

previous up-regulation minus *previous look aversive*) for amygdala ROI analysis or exploratory whole brain analysis (see Table 2 and 3).

<u>*Previous distraction* vs. *previous look aversive*</u>

Ratings of negative feelings (see Figure 2) for *previous distraction* compared with *previous look aversive* on day 2 showed no significant differences (p>.25). Additionally, distraction led to reduced recognition memory for the emotional pictures compared to looking at aversive pictures ($T_{(26)}$=2.126, p=.043), but there was no difference in strategy awareness for *previous distraction* compared with *previous look aversive* (p>.22). Furthermore, there were no activation differences for the comparison of these two conditions (see Table 2). However, stronger prolonged reduction of negative feelings (difference of negative feelings: *previous look aversive* minus *previous distraction*) was related to a reduced activation of the amygdala (trend) for the same contrast during re-exposure (see Figure 3B and Table 3). There were no further significant results for exploratory whole brain analyses.

<u>*Previous down-regulation* vs. *previous distraction*</u>

Ratings of negative feelings on the second day show that *previous down-regulation* led to significantly reduced negative feelings compared to *previous distraction* ($T_{(26)}$=2.896, p=.008) (see Figure 2). No difference for the two regulation conditions was found for recognition memory (p>.425). Furthermore, awareness for the previously applied strategy was significantly reduced for *previous distraction* as compared to *previous down-regulation* ($T_{(26)}$=9.347, p<.001). Additionally, *previous down-regulation* compared to *previous distraction* led to enhanced activation of right dlPFC (MNI: x=36, y=59, z=1;

T=4.83, *p*=.017) and left vlPFC (MNI: x=-60, y=14, z=7; *T*=4.26, *p*=.033) (see Figure 4 and Table 2), while no significant differences were found for amygdala and vmPFC ROI as well as exploratory whole brain analyses (see Table 2).

- insert Figure 4 about here -

Discussion

This study is the first to investigate the neural correlates of immediate and prolonged effects (~24 hours) of different cognitive emotion regulation strategies on emotional experience. Increase of amygdala activation during up-regulation and decrease of amygdala activation during down-regulation of negative emotions using cognitive reappraisal was associated with respective changes in negative feelings. Successful down-regulation of emotions was observed for both, distraction and cognitive reappraisal on the first day, while distraction resulted in stronger negative feelings compared with cognitive reappraisal on the second day. For distraction (compared with looking at aversive pictures), stronger negative feelings were related to enhanced amygdala activation during re-exposure. Previous down-regulation using cognitive reappraisal led to less negative feelings during re-exposure compared with stimuli previously presented in the look condition. Notably, this prolonged reduction in negative feelings for previous down-regulation via cognitive reappraisal was also correlated with stronger vmPFC activation. Compared to distraction, down-regulation by cognitive reappraisal was associated with stronger activation of the dlPFC and vlPFC during re-exposure. Up-regulation of negative feelings by cognitive reappraisal on the other hand did not result in prolonged changes in emotional experience and associated neural activation.

The results of this study are in line with previous findings, showing that both cognitive reappraisal and distraction are effective emotion regulation strategies in the short-term (Dörfel et al. 2014; Kanske et al. 2011; McRae et al. 2010). Successful up- or down-regulation of negative feelings was correlated with respective activation changes in the amygdala, supporting the prominent role of this region as an output region for emotion regulation (Ochsner, Silvers and Buhle 2012).

During uninstructed re-exposure to the stimuli one day later, previous down-regulation using cognitive reappraisal compared to distraction (and looking at aversive pictures) led to lower negative feelings as well as enhanced memory for the applied regulation strategy, replicating and extending previous findings (Ahn et al. 2015; Ayduk and Kross 2009; Kross and Ayduk 2008; Macnamara, Ochsner and Hajcak 2011). This result was accompanied by enhanced activation of the right dlPFC and the left vlPFC for cognitive reappraisal compared to distraction. These areas have been shown to be activated during the cognitive regulation of emotions and are thought to influence activation in emotion generating regions as for example the amygdala (Ochsner, Silvers and Buhle 2012). The dlPFC has less direct projections to the amygdala and might therefore exert its influence on the amygdala by projections to other prefrontal cortex regions as for example the vlPFC and the vmPFC, which have stronger direct projections to the amygdala (Ray and Zald 2012). The vmPFC has been found to be involved in different forms of diminishing negative affect (Denkova, Dolcos and Dolcos 2015; Diekhof et al. 2011). Besides explicit cognitive emotion regulation, the (successful) recall of extinction memories depends on vmPFC activation (Hermann et al., 2016; Kalisch et al. 2006; Milad et al. 2007; Phelps et al. 2004). It is assumed that during the extinction of conditioned fear, a new memory trace develops which allows for the inhibition of the original fear memory trace during recall of extinction. However, it is still unknown, how the effect of emotion regulation after reinterpreting the meaning of a stimulus is stored in memory. Similar to extinction learning, it is possible that due to the applied stimulus-specific regulation, a memory trace develops which inhibits the 'natural' emotional response elicited by these stimuli if recalled later. The association of vmPFC activation with reduced negative feelings during re-exposure to previously reappraised stimuli (down-regulation) in our study might therefore point to the involvement of inhibitory learning processes. Previous studies have also demonstrated that a stronger habitual use of cognitive reappraisal is related to enhanced vmPFC activation during extinction recall (Hermann, Keck and Stark 2014), as well as to a reduced habituation of vmPFC activation during symptom provocation in specific phobia (Hermann et al. 2013). The results of the current study further underline the importance of this region for emotion-cognition interactions during emotional learning processes. In contrast, a previous study only found an effect of cognitive reappraisal on attenuated amygdala activation but not on vlPFC responsiveness during re-exposure one week later, while not explicitly investigating vmPFC activation (Denny et al. 2015). The cognitive reappraisal tactic used by Denny and colleagues consisted of detachment, a self-focused and rather stimulus-independent strategy, compared with reinterpretation, which is a more stimulus-specific and situation-focused strategy used in the present study. These different reappraisal tactics and/or the different time-periods (one day vs. one week) between active regulation and re-exposure might be associated with different neural mechanisms. Further differences to our study were that reappraisal was conducted on two days outside and inside the scanner, a shorter picture presentation time (2s) was used during re-exposure, and participants were trained before each active regulation session. These methodological differences might have contributed to the differences in the observed results, and need to be investigated in future studies.

The finding of enhanced negative feelings during re-exposure after previous use of distraction compared with reappraisal and the trend for an association of negative feelings (for distraction vs. look aversive) with enhanced amygdala activation indicate a distinct underlying mechanism for distraction. Distraction as one form of attentional deployment is thought (Gross 1998) and has been shown (Thiruchselvam et al. 2011) to intervene relatively early in the emotion generation process. This might lead to a less deep processing of the emotional stimulus with distraction as compared to cognitive reappraisal. As a consequence, these less deeply processed stimuli might - at re-exposure – be experienced as more novel resulting in enhanced negative affective and amygdala responses. In line with this, distraction compared with looking at aversive pictures was related to less frequent explicit recognition of the stimuli one day later, also indicating a more superficial processing of the stimuli on the first day during the distraction task. Additionally, distraction led to reduced remembrance of the applied strategy compared with cognitive reappraisal.

There was no overall lasting effect of up-regulation of negative feelings by cognitive reappraisal in the present study and the hypothesized associated amygdala activation. This might probably indicate that prolonged effects of up-regulation of negative emotions are not very important in healthy people, but might nevertheless be of relevance for individuals more prone to use up-regulation of negative emotions, as frequently observed in patients with mental disorders.

Furthermore, some limitations of this study need to be mentioned: Because of sex differences in the processing of emotional stimuli and in the cognitive regulation of emotions as previously demonstrated, only women have been investigated in the actual study; therefore, the findings cannot be generalized to men. Additionally, we did not acquire data on the hormonal status/the menstrual cycle of the participating females, which might also have influenced the results.

In conclusion, this study shows for the first time that the beneficial prolonged effect of down-regulating negative emotions via cognitive reappraisal is associated with vmPFC activation during re-exposure one day later. Distraction appears to be less stable in lowering negative affect during re-exposure one day later, despite its beneficial short-term consequences. In the long-term, these findings might help to better understand emotion regulation deficits in mental disorders and to further improve intervention strategies in CBT.

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Compliance with Ethical Standards:

Conflict of Interest: All authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figure Captions

Figure 1: Ratings of the intensity of negative feelings during the active regulation task on day 1 for the different conditions. All conditions differed significantly from each other (all $p \leq .001$). Error bars depict standard errors of the mean.

Figure 2: Ratings of the intensity of negative feelings during re-exposure to the stimuli on day 2 previously presented with different instructions on day 1.

Significant differences for the planned comparisons (previous down-regulation vs. previous look aversive; previous up-regulation vs. previous look aversive; previous distraction vs. previous look aversive; previous down-regulation vs. previous distraction) are marked with * ($p < .05$) and ** ($p < .01$).

Figure 3: A) Correlation of negative feelings (difference for previous look aversive minus previous down-regulation) with enhanced activation in the ventromedial prefrontal cortex (vmPFC) for previous down-regulation minus previous look aversive during re-exposure on day 2. **B)** Correlation of negative feelings (difference for previous look aversive minus previous distraction) with activation in the right amygdala (trend) for previous distraction minus previous look aversive during re-exposure on day 2.

The intensity threshold was set to p=.005 (uncorrected) for illustration purposes; activations were superimposed on the MNI305 T1 template. All coordinates (*x, y, z*) are given in MNI space. The color bar depicts T-values. L = left, R = right, A = anterior, P = posterior.

Figure 4: Enhanced activation during re-exposure on day 2 for previous down-regulation via cognitive reappraisal compared to previous distraction in the left ventrolateral prefrontal cortex (vlPFC) and the right dorsolateral prefrontal cortex (dlPFC).

The intensity threshold was set to *p*=.0025 (uncorrected) for illustration purposes; activations were superimposed on the MNI305 T1 template. All coordinates (*x, y, z*) are given in MNI space. The color bar depicts T-values. L = left, R = right, A = anterior, P = posterior.

Tables

Table 1: Correlation of neural activation and the intensity of negative feelings for the respective contrast during the active emotion regulation phase on day 1 (each of the different regulation conditions compared to looking at aversive pictures; looking at aversive pictures compared to looking at neutral pictures).

Brain structure	**H**	**x**	**y**	**z**	T_{max}	p_{corr}
Look aversive vs. look neutral						
Positive correlation with negative feelings (look aversive minus look neutral)						
amygdala (ROI)	left	-27	-10	-14	4.16	.006
amygdala (ROI)	right	30	-1	-20	4.30	.005
Negative correlation with negative feelings (look aversive minus look neutral)						
no significant results						
Down-regulation vs. look aversive						
Positive correlation with negative feelings (down-regulation minus look aversive)						
amygdala (ROI)	right	18	-1	-20	3.51	.020
Negative correlation with negative feelings (down-regulation minus look aversive)						
no significant results						
Distraction vs. look aversive						
Positive correlation with negative feelings (distraction minus look aversive)						
brain stem (WB)	left	-3	-31	-11	6.73	.008
amygdala (ROI)	*right*	*15*	*-1*	*-20*	*3.00*	*.057*
Negative correlation with negative feelings (distraction minus look aversive)						
no significant results						
Up-regulation vs. look aversive						
Positive correlation with negative feelings (up-regulation minus look aversive)						
temporal pole (WB)	left	-30	11	-23	6.78	.007
cuneal cortex (WB)	left	-15	-79	19	6.23	.022
amygdala (ROI)	left	-18	-1	-17	4.54	.002
amygdala (ROI)	right	21	-1	-17	4.67	.002
Negative correlation with negative feelings (up-regulation minus look aversive)						
no significant results						

The significance threshold was set to p=.05 (FWE-corrected). Trends up to p_{corr}<.10 are reported in italics. Exploratory whole brain results are labeled with (WB), results from region of interest analysis with (ROI). All coordinates (*x, y, z*) are given in MNI space. L = left, R = right.

Table 2: Neural activation during the re-exposure phase on day 2.

Brain structure	H	x	y	z	T_{max}	p_{corr}
Previous down-regulation vs. previous look aversive						
no significant results						
Previous distraction vs. previous look aversive						
no significant results						
Previous up-regulation vs. previous look aversive						
no significant results						
Previous down-regulation minus previous distraction						
dlPFC (ROI)	right	36	59	1	4.83	.017
vlPFC (ROI)	left	-60	14	7	4.26	.033
Previous distraction minus previous down-regulation						
no significant results						

The significance threshold was set to p=.05 (FWE-corrected). Trends up to p_{corr}<.10 are reported in italics. Exploratory whole brain results are labeled with (WB), results from region of interest analysis with (ROI). All coordinates (*x, y, z*) are given in MNI space. L = left, R = right.

Table 3: Correlation of neural activation and the intensity of negative feelings for the respective contrast during the re-exposure phase on day 2 (each of the different regulation conditions compared to looking at aversive pictures).

Brain structure	**H**	**x**	**y**	**z**	T_{max}	p_{corr}
Previous down-regulation vs. previous look aversive						
Positive correlation with negative feelings (previous down-regulation minus previous look aversive)						
no significant results						
Negative correlation with negative feelings (previous down-regulation minus previous look aversive)						
vmPFC (ROI)		0	32	-20	3.27	.044
Previous Distraction vs. previous look aversive						
Positive correlation with negative feelings (previous distraction minus previous look aversive)						
amygdala (ROI)	*left*	*-24*	*-1*	*-17*	*2.83*	*.089*
amygdala (ROI)	*right*	*27*	*2*	*-26*	*3.08*	*.061*
Negative correlation with negative feelings (previous distraction minus previous look aversive)						
no significant results						
Previous Up-regulation vs. previous look aversive						
Positive correlation with negative feelings (previous up-regulation minus previous look aversive)						
no significant results						
Negative correlation with negative feelings (previous up-regulation minus previous look aversive)						
no significant results						

The significance threshold was set to p=.05 (FWE-corrected). Trends up to p_{corr}<.10 are reported in italics. Exploratory whole brain results are labeled with (WB), results from region of interest analysis with (ROI). All coordinates (*x, y, z*) are given in MNI space. L = left, R = right.

Figure 1

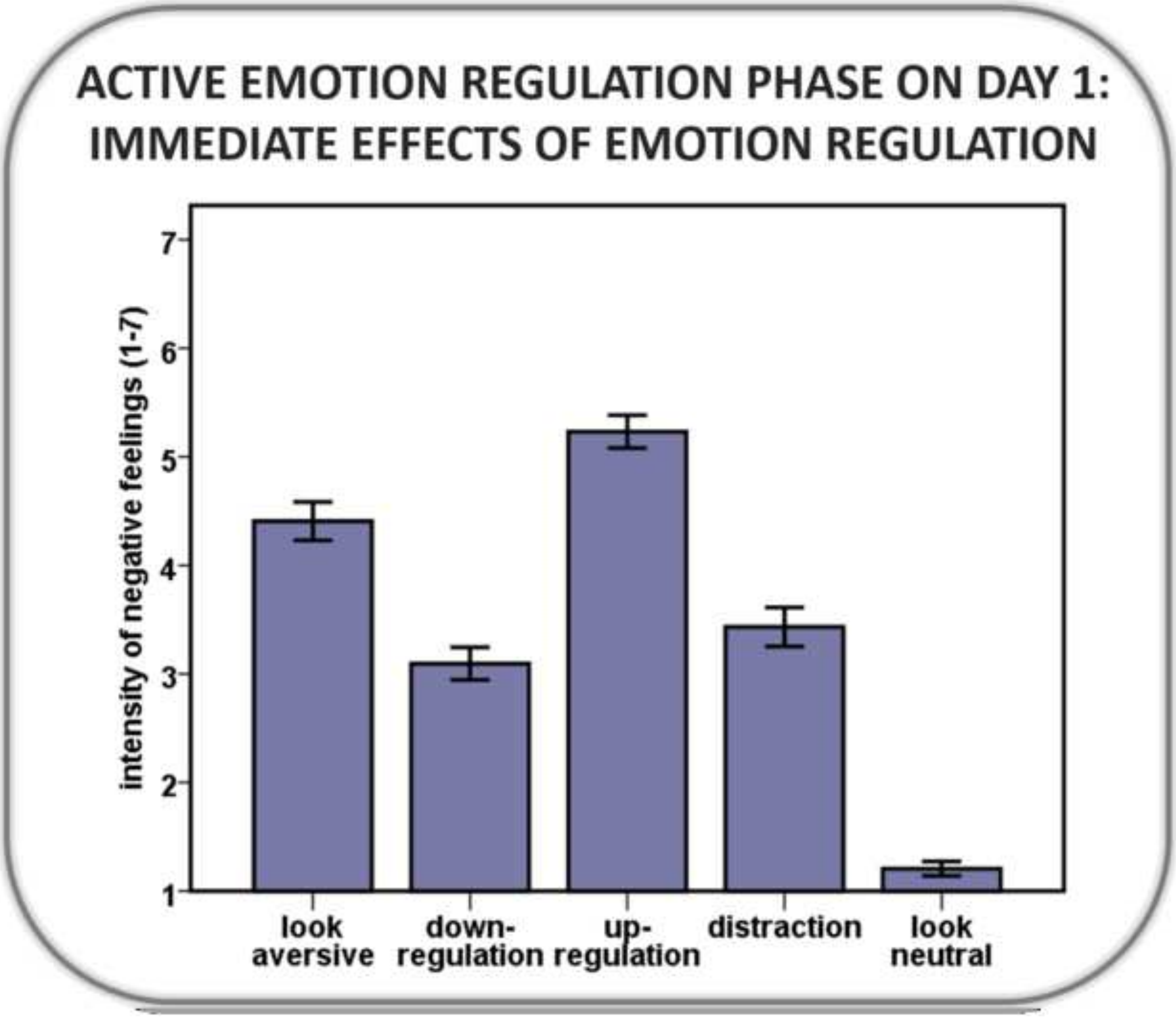
ACTIVE EMOTION REGULATION PHASE ON DAY 1:
IMMEDIATE EFFECTS OF EMOTION REGULATION
intensity of negative feelings (1-7)
7
6
5
4
3
2
1
look aversive
down-regulation
up-regulation
distraction
look neutral

Figure 2

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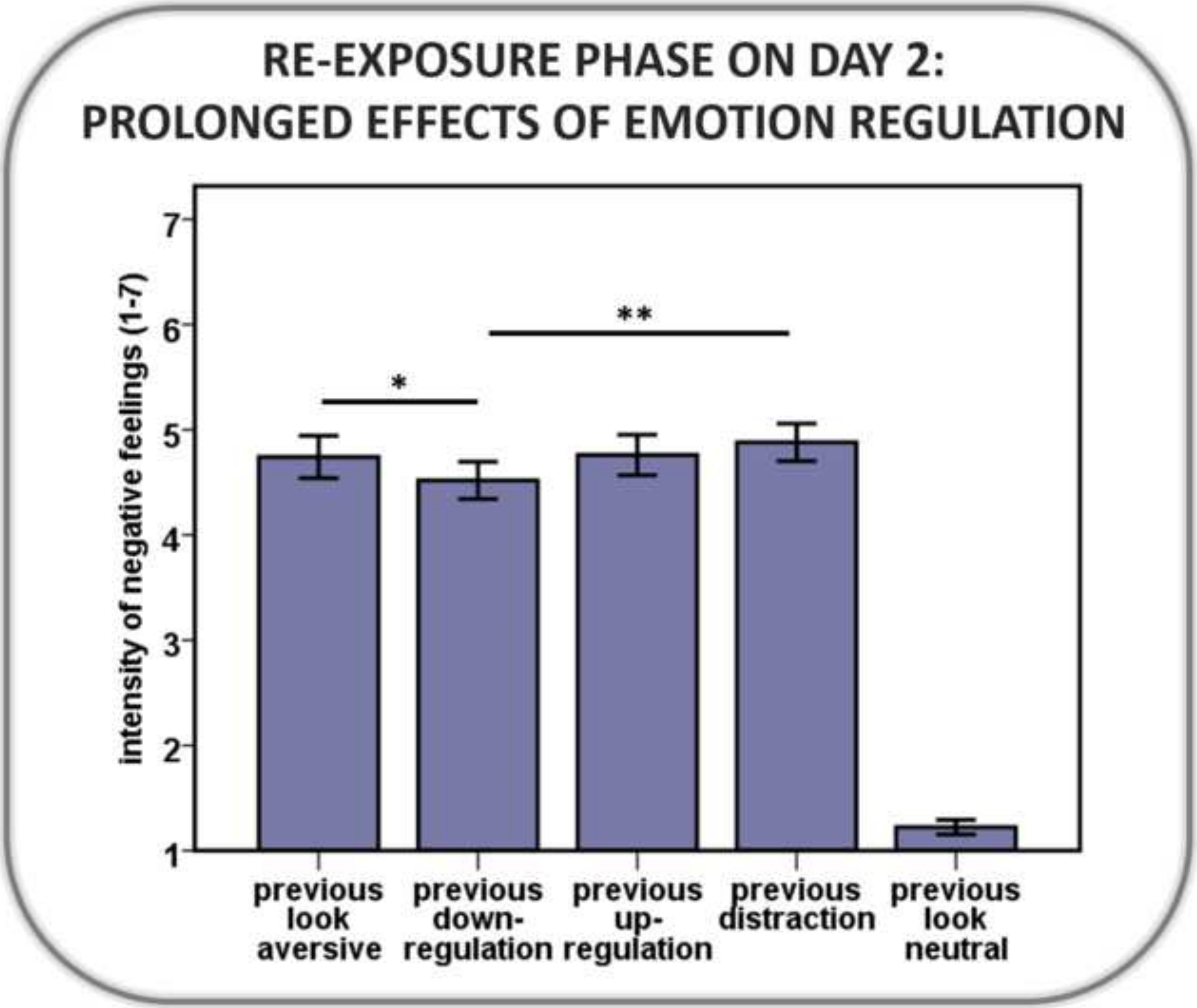

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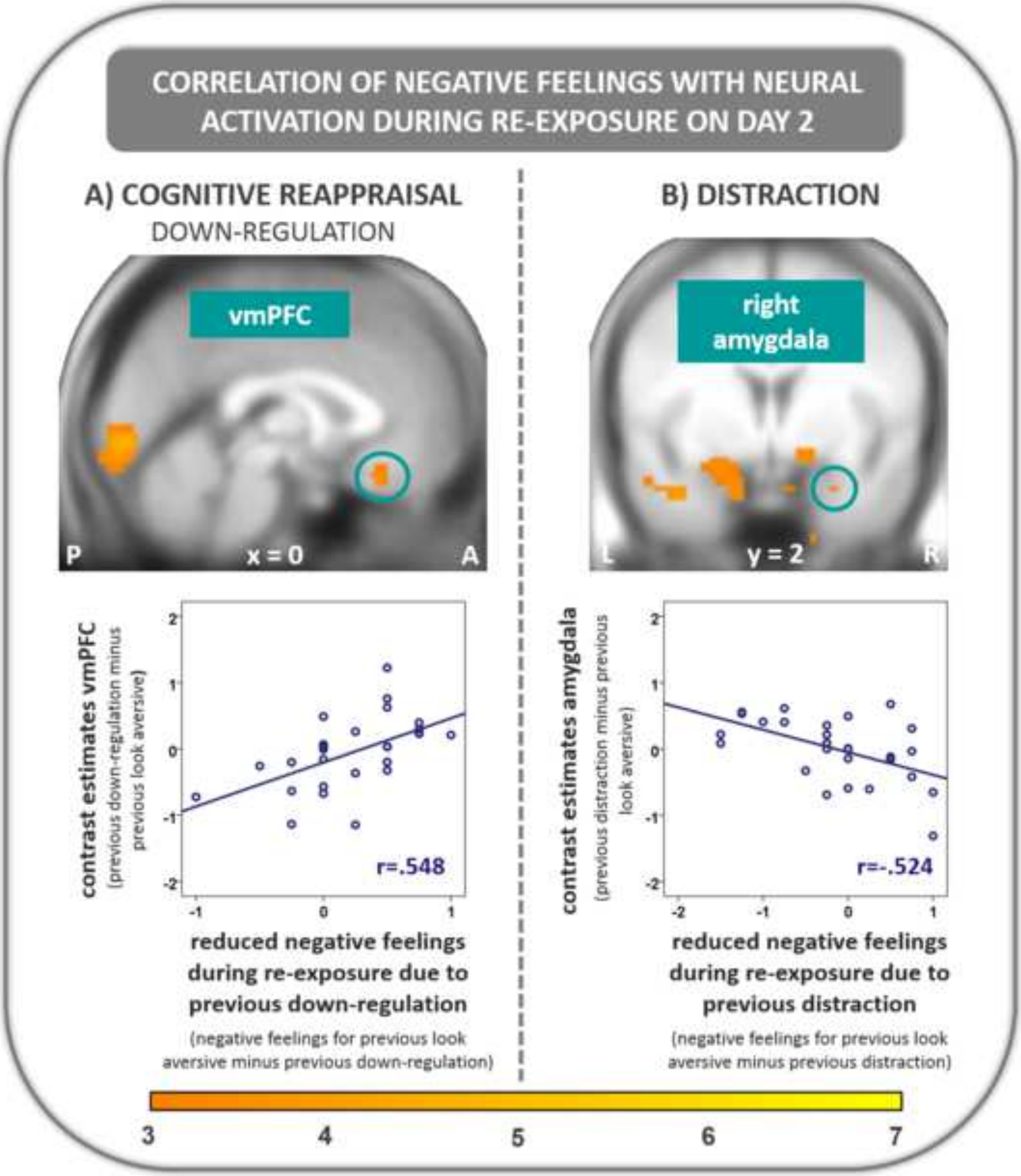

Figure 4

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