Imaging the up's and down's of emotion regulation in lifetime depression

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Abstract

Reappraisal is a particularly effective strategy for influencing emotional experiences, specifically for reducing the impact of negative stimuli. Although depression has repeatedly been linked to dysfunctional behavioral and neural emotion regulation, prefrontal and amygdala engagement seems to vary with clinical characteristics and the specific regulation strategy used. Whereas previous neuroimaging research has focused on down-regulating reactions to emotionally evocative scenes, the current study compared up- and down-regulation in response to angry facial expressions in patients with depression and healthy individuals. During the initial viewing of faces, patients with depression showed hypoactivation particularly in areas implicated in emotion generation, i.e., amygdala, insula and putamen. In contrast, up-regulating negative emotions yielded stronger recruitment of core face processing areas and posterior medial frontal cortex in patients than in controls. However, group differences did not extend to resting-state functional connectivity. Recurrent depression was inversely associated with amygdala activation specifically during down-regulation, but differences in medication status may limit the current findings. Despite a pattern of reduced neural emotional reactivity in mainly medicated patients, their 'successful' recruitment of the regulation network for up-regulation might point toward an effective use of reappraisal when increasing negative emotions. Future studies need to address how patients might benefit from transferring this ability to adaptive goals, such as improving interpersonal emotion regulation.

Keywords: depression; emotion regulation; facial expression; fMRI; reappraisal

Introduction

For influencing our emotional experiences, reappraisal is particularly adaptive with favorable outcomes such as decreased subjective and behavioral reactions to negative emotions (Gross 2015, 1998). Changing one's interpretation of affective stimuli is also a key intervention in cognitive-behavioral therapy of depression, targeting the 'negative cognitive triad' of negative appraisals of the self, the future and the world (Beck et al. 1979). As depression is characterized by emotion dysregulation (Gotlib and Joormann 2010; Aldao et al. 2010), impairments in flexible emotion regulation might stem from a failure to activate or deactivate key regions in a contextually appropriate manner or from alterations in the connectivity between functional brain networks.

Recent meta-analyses of neuroimaging studies in healthy individuals show that reappraisal engages ventrolateral and dorsolateral prefrontal cortices, parietal and temporal regions as well as the cingulate cortex, supplemental motor area (SMA) and pre-SMA (Kohn et al. 2014; Buhle et al. 2014; Frank et al. 2014). Additionally, successful emotion regulation often implies prefrontal control over emotional reactivity associated with amygdala responses (e.g., Frank et al. 2014).

Within this framework, findings on functional alterations in patients with depression remain mixed. For prefrontal control regions, hypoactivation was found in non-medicated, remitted patients (Smoski et al. 2015; Smoski et al. 2013) as well as in medicated, acute inpatients (Erk et al. 2010). Other studies report no differences between non-medicated patients with acute depression and healthy individuals (Greening et al. 2014; Dillon and Pizzagalli 2013). In Greening *et al.* (2014), however, baseline activation of bilateral ventrolateral prefrontal cortex to sad scenes was reduced in depression. In contrast, Kanske et al. (2012) observed prefrontal hyperactivation in remitted patients (9 out of 23 taking antidepressant medication) along with impaired amygdala down-regulation. Such a failure to decrease amygdala responses was also evident in the sample of Greening et al. (2014; acute, non-medicated patients), whereas the acute, medicated patients of Erk et al. (2010) showed successful down-regulation. Thus, activation changes in depression are likely not solely due to medication or clinical state. Although antidepressant medication affects prefrontal and amygdala activation during emotional processing (e.g., Fales et al. 2009; Norbury et al. 2009), for emotion regulation, there is only partial support that medication exerts bottom-up effects in restoring activation of limbic regions (Goldapple et al. 2004). Interestingly, amygdala activation during emotion regulation seems rather influenced by clinical characteristics, e.g., depression severity (Erk et al. 2010; Dillon and Pizzagalli 2013).

These depression-related functional activation patterns appear to persist during resting-state. A recent meta-analysis of seed-based resting-state functional connectivity studies (Kaiser et al. 2015) links depression to reduced connectivity within the frontoparietal system subserving cognitive control and to imbalanced connectivity among emotion regulation networks. Moreover, hyperconnectivity within the default mode network might indicate depressive biases toward internal, ruminative thoughts at the expense of engaging with the external world (Schilbach et al. 2014). Not attending and adapting to external, social stimuli may amplify the negative interpersonal effects of maladaptive emotion regulation (Gross 2015; Gross and John 2003), thereby contributing to impairments in social interactions and psychosocial functioning.

Intriguingly, however, despite prominent social interaction difficulties in depression, neuroimaging studies have not investigated emotion regulation in interpersonal contexts. Instead, negative emotions are commonly evoked by complex aversive scenes from the International Affective Picture System (IAPS; Lang et al. 2008). Yet, emotional facial expressions are not only processed more automatically, but also communicate inherently social and self-relevant information (Britton et al. 2006). Especially the combination of anger and direct gaze prompts for reactions (Adams and Kleck 2005; cf. Radke et al. 2013). Therefore, frequently probed regulation strategies like distraction, i.e., solving an arithmetic task (Kanske et al. 2012), or distancing, i.e., becoming a detached observer (Rive et al. 2015; Erk et al. 2010; Dillon and Pizzagalli 2013), might work best for emotionally evocative scenes, but not fully apply when faced directly with an angry interaction partner. Instead, facing anger may rather require self-focused reappraisals which change its personal relevance (Ochsner et al. 2004) and facilitate contextualized social responding (Blechert et al. 2012). Increased self-referential processing in depression (Northoff 2007; Schilbach et al. 2014) might render this strategy relatively feasible for these patients, particularly for increasing negative emotions (Ochsner et al. 2004), which might be congruent with their negative mood states. Conversely, the relation between amygdala down-regulation and depression severity (Erk et al. 2010; Dillon and Pizzagalli 2013) might point toward stronger impairments for decreasing negative emotions and thus reduced regulation flexibility. Understanding patients' abilities and shortcomings when regulating negative interpersonal affect can provide insights into the neurobiological systems underlying emotion regulation as well as leverage points for the development of interventions.

In the current functional magnetic resonance imaging (fMRI) study, negative interpersonal affect was conveyed by pictures of angry faces and needed to be not only down-, but also up-regulated. Using self-focused reappraisal as the regulation strategy, we expected dysfunctional interpersonal emotion regulation in patients with depression on the behavioral level. Given the divergence of previous studies regarding prefrontal and amygdala activation mentioned above, we refrained from directional hypotheses on task-related neural alterations associated with depression, and tested for group differences in both baseline and differential activation. Nonetheless, we speculated to observe reduced connectivity in the emotion regulation network in patients with depression in task-independent resting-state. Including an up-regulation condition with matched cognitive effort allowed us to examine the specificity of alterations and their modulation by clinical characteristics in depression.

Method

Sample

Twenty-two patients meeting the DSM-IV criteria for current (n = 4) or past (n = 18) major depressive disorder (MDD) and 22 healthy controls (HC) matched for age, sex and education were investigated (see Table 1).

Patients were recruited from the Department of Psychiatry, Psychotherapy, and Psychosomatics of the RWTH Aachen University. Diagnoses were confirmed by a trained psychologist via the German version of the Structured Clinical Interview (SCID; Wittchen et al. 1997). Exclusion criteria for patients were psychotic and (hypo-)manic symptoms as well as Axis I comorbidities (except for dysthymia) during the last five years. Potential comorbid disorders were assessed with the SCID-I and, if the clinical record indicated a suspected or diagnosed personality disorder, also the SCID-II. One patient fulfilled the criteria for dysthymia, and two other patients fulfilled the criteria for a personality disorder (one with dependent personality disorder, one with combined personality disorder). In the course of the screening interview with a trained psychologist, HC completed the screening questions of the SCID-I to exclude a presence/history of DSM-IV Axis I disorders and psychiatric/psychotherapeutic treatment. Exclusion criteria for both groups were age <18 or >60, neurological disorders, illicit substance use during the last six months, current substance dependency, left-handedness, and contraindications for MRI, e.g., metal in the body. At the time of testing, 15 patients received antidepressant medication (see Table 1).

The study was approved by the ethics committee of the Medical Faculty of the RWTH Aachen University. All participants received written information about the purpose of the study and provided written informed consent.

Questionnaires

Participants completed trait measures assessing habitual emotion regulation (Emotion Regulation Questionnaire; ERQ; Gross and John 2003) and anxiety (State Trait Anxiety Inventory; Spielberger et al. 1983). Severity of affective symptoms was assessed with the BDI-II (German version by Hautzinger et al. 2006).

Moreover, all participants completed neuropsychological tests tapping executive functions (TMT-A/-B; Reitan 1956), crystallized verbal intelligence (Wortschatztest; Schmidt and Metzler 1992), and working memory (digit span, WAIS III; Von Aster et al. 2006). Notably, HC and MDD did not differ significantly in their performance (see Table 1).

Experimental paradigm and procedure (Task)

We selected 120 angry and 20 neutral Caucasian faces (balanced for age and sex) from the FACES database (Ebner et al. 2010). In a behavioral pilot study, these were rated in terms of valence and arousal by an independent group (n = 31 with *mean age* = 31 years, *SD* = 14.4; 15 males/16 females). Angry faces were rated as more negative,$t(30) = 19.80$, $p < .001$, and more arousing, $t(30) = 15.75$, $p < .001$, than neutral faces.

In the current paradigm, each face was presented for 3s, followed by a rating scale for 4s, and an inter-stimulus interval of 5-9s. Participants rated their emotional state with regard to the preceding face, with “very uncomfortable” and “very comfortable” provided as verbal labels at the scale’s endpoints (range 1-8; see Figure 1a) by pressing the corresponding button on the respective response pad (in the left or right hand).

Extending previous emotion regulation studies (Blechert et al. 2012; Ziv et al. 2013; Morawetz et al. 2016), the paradigm consisted of three conditions, implemented as three blocks: view, increase, decrease, i.e., one block was presented for each condition. Strategy implementation was trained prior to scanning by providing examples of reappraisal and probing participants for own regulation situations to ensure full comprehension. In the *view* condition, no regulation should be applied, but faces should be attended to and rated. For *increasing* their emotional experience, participants were

instructed to imagine that the presented face belonged to a close person (e.g., sibling, friend) who was really angry at them because they did something wrong. During the *decrease* condition, participants should imagine that the presented face belonged to a stranger who might actually be a nice person, but had a bad day. Thus, reappraisal instructions predominantly emphasized changing the personal relevance of the stimuli.

Using a mixed block/event-related design, 40 angry faces were randomly presented in each block. The view block, always presented first, additionally included 20 neutral faces to obtain an estimate of emotional reactivity (view-angry vs. view-neutral). The order of increase and decrease blocks was counterbalanced between participants. Before each block, participants were reminded of the specific strategy to use via headphones. The paradigm took approximately 35 minutes.

Stimuli were presented via goggles (VisuaStimDigital, Resonance Technology,Inc., Los Angeles,CA). Stimulus presentation and response acquisition were controlled via Presentation software (Neurobehavioral Systems,Inc., Albany,CA).

FMRI data acquisition

On a 3T Siemens scanner at the Department of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen University equipped with a standard 12-channel head coil, fMRI images were obtained with a gradient-echo EPI sequence (TR: 2200ms, TE: 30ms, FoV: 200mm, 36 slices oriented parallel to the anterior and posterior commissure at an in-plane resolution of 3.2x3.2x3.2mm, flip angle: 77°, distance factor: 20%). Before the experimental paradigm, a resting-state scan with the same parameters acquired 210 volumes (7min). Participants were instructed to keep their eyes closed, letting their mind wander without thinking of anything in particular or falling asleep. Compliance with these instructions was confirmed during debriefing.

Behavioral data analyses

After excluding trials with missed responses (i.e., trials in which no button press occurred; 4%), ratings were averaged per condition and subjected to a mixed-model ANOVA with Condition (view-neutral, view-angry, increase, decrease) as a within-subject and Group (HC, MDD) as a between-subjects factor. Significant effects were followed-up by independent or paired *t*-tests, and sociodemographic and neuropsychological data were compared with independent *t*-tests using an α-level of $p < .05$. For

the ANOVAs, within-subject effects using Greenhouse-Geisser correction are reported with partial eta-squared as an estimate of effect size. Statistical testing was performed with IBM SPSS 20.

Task-based fMRI data processing and analyses

Statistical parametric mapping (SPM8, Wellcome Department of Imaging Neuroscience, London) was used for preprocessing and analyses. To allow for magnetic field saturation, the first six volumes of each block were discarded. Images were realigned to correct for head movement, and slice-timing was applied. Subsequently, the mean functional image was coregistered and normalized to the Montreal Neurological Institute (MNI) single-subject template (Collins et al. 1994) using linear proportions and a nonlinear sampling as derived from a segmentation algorithm (Ashburner and Friston 2005). Images were spatially smoothed using an 8mm full-width-at-half-maximum Gaussian kernel.

For the event-related GLM-analysis, events were isolated by convolving vectors of stimulus onset times and stimulus duration (3s) within each condition with the canonical hemodynamic response function. Female and male stimuli were initially modeled as separate regressors, but then collapsed after exploration had excluded major gender effects, resulting in four task-relevant regressors on the first level: view-neutral, view-angry, increase-angry, decrease-angry. To separate neural effects of cognitive stimulus evaluation and motor response from these regressors of interest, the subsequent regulation phase was modeled as separate regressors each with the duration of median response time per condition. In addition, six head movement parameters from the realignment were included as regressors of no interest in the first-level model. Finally, images were high-pass filtered at 128s, and an autoregressive AR(1) model was used to account for serial correlations.

In addition to the individual statistical maps of task-relevant activation contrasted against baseline (view-neutral, view-angry, increase-angry, decrease-angry), difference contrasts of view-angry>view-neutral, increase>view-angry and decrease>view-angry were computed on the first level. Two types of second-level analyses were performed: 1) To investigate within-subject effects, the four contrast images reflecting task-related activation against baseline were subjected to a flexible factorial design with subject, condition and group as factors. Following Kanske *et al.* (2012), we also considered within-group effects by comparing the two regulation blocks directly within MDD and within HC, i.e., increase vs. decrease. 2) Differences between MDD and HC were assessed by two-sample *t*-

tests on the above mentioned individual contrasts. Following Greening *et al.* (2014), we considered group differences in both baseline and differential contrasts.

In addition to whole brain effects, we assessed these regulation contrasts within the amygdala using an anatomically defined mask of the right and left amygdala derived from the SPM anatomy toolbox (v2.0; Eickhoff et al. 2005).

Based on the previously reported association between amygdala down-regulation and depression severity (Erk et al. 2010; Dillon and Pizzagalli 2013), we performed a correlation analysis within the amygdala for MDD. Parameter estimates (eigenvariates) were extracted for the four task-related conditions from the flexible factorial design and correlated with clinical parameters (age at onset, duration of illness, number of previous episodes) and depression severity (BDI) in SPSS. Clinical parameters were available for 20/20/18 out of 22 MDD, respectively.

Resting-state fMRI data processing and analyses

After discarding the first four volumes, images were realigned to correct for head movement by aligning them to the initial volume and then to the mean of all volumes. Subsequently, the mean image was normalized to the non-linear MNI152 template (Holmes et al. 1998) using unified segmentation (Ashburner and Friston 2005). Images were spatially smoothed using a 5mm full-width-at-half-maximum Gaussian kernel. To minimize spurious correlations, the mot

ion parameters and their first-order derivatives were included as nuisance terms into the model (Satterthwaite et al. 2013). Lastly, a band-pass filter (0.01 and 0.08Hz) was applied to eliminate low-frequency fluctuations. Given spurious effects in between-group comparisons resulting from global signal removal (e.g., Murphy et al. 2009; Saad et al. 2012), global signal regression was not employed. Data were de-noised by the effects of age.

We applied a seed-region approach (Biswal et al. 1995) to analyze functional connectivity and defined two seed regions based on the fMRI results: For emotional reactivity, we based the amygdala seed on the effect of Group for view-angry [HC>MDD; two-sample *t*-test], and masked activation with the bilateral amygdala mask from the SPM anatomy toolbox (v2.0; Eickhoff et al. 2005), yielding inclusion of only the voxels within the amygdala in the seed. For emotion regulation, we used a pMFC seed based on the effect of Group for increase > view-angry [MDD>HC; two-sample t-test]. Resting-state functional connectivity was quantified by computing linear correlation coefficients between the time series of the seed regions and all other gray matter voxels of the brain. After transforming these

voxel-wise correlation coefficients of each seed into Fisher's *Z*-scores, they were subjected to the second-level analyses, including an appropriate non-sphericity correction as implemented in SPM8. First, in two separate ANOVAs with the factor Group (HC, MDD), we tested for group differences in functional connectivity of each of these seeds. Second, due to the correlation between the number of previous episodes and amygdala activation during down-regulation (see Results), we tested for correlations between the number of previous episodes and connectivity of the bilateral amygdala for MDD only.

All effects were thresholded at p <.05 at cluster-level, family-wise-error-corrected for multiple comparisons (p_{FWE} <.05), with an underlying voxel-level threshold of p <.001, uncorrected. For whole-brain effects, the SPM anatomy toolbox (v2.0; Eickhoff et al. 2005) was used for anatomical localization.

Results

Habitual emotion regulation

HC and MDD significantly differed in self-report measures of emotion regulation (ERQ, see Table 1). As hypothesized, HC reported more frequent reappraisal use, $t(42)$ = 3.73, p =.001, and less frequent suppression use than MDD, $t(42)$ = -2.08, p =.043.

Behavioral ratings

The Condition x Group ANOVA on the emotional state ratings showed a significant main effect of Condition, $F(3,126)$= 125.6, p <.001, η_p^2= .75, and a main effect of Group, $F(1,42)$ = 4.19, p =.047, η_p^2= .09. There was also a trend for a Condition x Group interaction, $F(3,126)$= 2.82, p =.053, η_p^2= .06.

Follow-up analyses of the main effect of Condition revealed significant differences between all conditions, with most positive ratings for viewing neutral faces (M = 5.4 ±0.9), followed by the decrease condition (M = 4.5 ±1.0), followed by viewing angry faces (M = 3.5 ±0.9) and increase (M = 2.8 ±0.9; all $t(43)$s >|5.9|, all ps <.001). The main effect of Group was due to overall higher ratings in HC (M = 4.3 ±0.7) than in MDD (M = 3.9 ±0.7).

The trend for the Condition x Group interaction was due to i) more positive ratings for neutral faces in HC compared to MDD (M = 5.8 ±0.6 and M = 5.1 ±1.0, respectively; $t(42)$ = 2.94 p =.005), and ii) more positive ratings in the decrease condition in HC compared to MDD (M = 4.9 ±0.9 and M = 4.2 ±1.0, respectively; $t(42)$ = 2.4, p =.021; see Figure 1a), i.e., less efficient down-regulation in MDD.

FMRI data

Within-subject effects

Across the whole sample, viewing angry, compared to neutral stimuli, elicited increased activation in the right precentral gyrus, right rolandic operculum, left cerebellum, right superior temporal gyrus and left inferior temporal gyrus (for details see Table 2). The opposite contrast [view-neutral>view-angry] revealed a stronger recruitment of the left postcentral gyrus, right cerebellum, right angular gyrus, right mid-orbital gyrus, the left thalamus and the right anterior cingulate cortex (see Table 2).

The increase compared to the decrease condition led to stronger engagement of a number of regions including the mid-cingulate cortex, bilateral rolandic operculum, including maxima in the insulae, and clusters within the occipital and frontal lobe (see Table 2). The reverse comparison [decrease>increase] yielded increased activation in the right superior parietal lobule, right cerebellum and right pallidum. Supplementary Table S1 reports results from additional contrasts involving the view condition.

Within-group effects (see Table 3)

In HC, contrasting increase>decrease revealed heightened engagement of the left rolandic operculum and right precuneus. Testing for the opposite [decrease>increase] yielded no suprathreshold activation.

In MDD, comparing increase>decrease resulted in stronger activation of the left superior temporal gyrus, left superior parietal lobule and left superior frontal gyrus. Additional clusters peaked in the right supramarginal gyrus, right precentral gyrus right precuneus and left cuneus. The reverse comparison [decrease>increase] yielded no suprathreshold activation.

Between-group effects: baseline contrasts

For neutral stimuli, compared to MDD, HC showed stronger activation of a wide-spread network, such as the right precuneus, the left mid-cingulate cortex and a cluster peaking in the left insula which extended to the left inferior frontal gyrus. There were additional clusters within the occipital, temporal and frontal lobes, for a complete list see Table 4.

When viewing angry faces, compared to MDD, HC showed, again, increased activation of the left insula, the left mid-cingulate cortex, and additional areas in the occipital, temporal and frontal lobes

(see Table 4 and Figure 1b). There was no group difference in the two regulation conditions (increase, decrease).

Between-group effects: differential contrasts

Contrasting increase against view-angry, MDD showed stronger activation in the right posterior medial frontal cortex, left fusiform gyrus, left supramarginal gyrus and left superior temporal gyrus, compared to HC [MDD > HC: Increase > view-angry; see Table 4 and Figure 1c]. No other group comparison yielded suprathreshold activation.

Amygdala effects (see Table 5)

Across the whole group, viewing angry faces elicited stronger amygdala activation than viewing neutral faces. Compared to MDD, in HC, increased amygdala activation was evident when viewing neutral and angry faces. No other comparisons yielded suprathreshold activation.

Correlation with clinical characteristics

The number of previous depressive episodes was negatively correlated with bilateral amygdala activation during the decrease block, left: r= -.495, p =.037 and right: r= -.590, p =.010, respectively. There were no significant correlations with other clinical parameters (age at onset, illness duration), depression severity (BDI) or with activation during the other two blocks (all ps >.113)

Resting-state

There were no group differences in resting-state functional connectivity of any of the two seed regions. For MDD, no significant association emerged with the number of previous depressive episodes for resting-state functional connectivity of the left and right amygdala.

Discussion

The current study identified behavioral and neural alterations in interpersonal emotion regulation associated with depression. Although both patients and healthy individuals were able to change their feelings consistent with the affordances of self-focused reappraisal, patients showed an overall bias of feeling less comfortable than controls in response to all stimuli. Along these lines, patients exhibited decreased neural reactivity when processing and not yet regulating emotional facial expressions, but

also showed differential neural engagement for up-regulation. Moreover, recurrent depression was negatively correlated with amygdala activation during down-regulation. Depression-related neural alterations could not be established regarding resting-state functional connectivity.

Altered neural reactivity in depression

During the initial viewing of (both angry and neutral) faces, patients showed decreased activation in regions associated with rather automatic emotion processing, i.e., amygdala, insula and putamen. Although these regions have been linked to altered emotion processing in depression, the alteration usually manifests as a hyper-responsiveness to negative facial expressions along with hypoactivation to positive expressions (see e.g., Stuhrmann et al. 2011). Importantly, antidepressant medication has been shown to decrease amygdala activation during emotional processing (Norbury et al. 2009). The fact that the majority of our patients received antidepressant medication at the time of testing precludes testing for 'pure' depression-effects. However, if this medication was crucial and effective, one would not have expected hypoactivation in patients, but restored activity (i.e., equivalent to healthy controls). Also other studies with varying percentages of medicated patients do not reveal a consistent pattern with regard to medication effects (e.g., compare Smoski et al. 2015; Smoski et al. 2013; with Erk et al. 2010). This makes it at least less likely that hypoactivation was a result of medication or that inconsistencies between studies are attributable to medication effects. Moreover, our correlation of amygdala activation with the number of previous episodes suggests this activation to be rather related to depression instead of medication, in accordance with previous studies showing that amygdala activation during emotion regulation is influenced by clinical characteristics, e.g., depression severity (Erk et al. 2010; Dillon and Pizzagalli 2013).

The impact of clinical characteristics

Along these lines, clinical characteristics need to be considered when interpreting findings from heterogeneous samples. Investigating patients in remission might reveal vulnerability markers for the recurrence of depression (Alloy et al. 1999), such as deficits in habitual and spontaneous emotion regulation (Ehring et al. 2008; Ehring et al. 2010). This converges with maladaptive habitual emotion regulation, assessed by the ERQ, in our current sample where depression went in hand with self-reported reduced use of reappraisal, and with increased use of suppression. In particular, when instructed to down-regulate their emotional response, patients were less successful than healthy

participants. Although this difference emerged only post-hoc, requiring cautious interpretation, it might indicate patients' limited benefit from applying self-focused reappraisal to decrease their emotional reaction. The negative correlation between amygdala activation during down-regulation and the number of prior depressive episodes complements similar previous associations regarding depression severity (Erk et al. 2010; Dillon and Pizzagalli 2013). Our results extend these and other findings on the link between recurrent depression and maladaptive habitual emotion regulation (Ehring et al. 2008; Aker et al. 2014), to reappraisal use in an experimental context, which might have further implications for cognitive-behavioral interventions.

Up-regulation vs. down-regulation

Up-regulating negative emotions differentially engaged core areas of visual face processing (e.g., fusiform gyrus) as well as posterior medial frontal cortex in patients compared to controls. Along with patients' differential neural responses to up-regulation vs. down-regulation, this may suggest more pronounced impairments for decreasing rather than increasing negative emotional reactions. Behavioral ratings indicate successful up-regulation, and corresponding activation in parietal and frontal areas involved in emotion regulation, e.g., supramarginal gyrus and superior frontal gyrus, hint at patients' ability to use reappraisal for increasing negative emotions. Enhanced self-referential processing and biases toward internal thoughts might facilitate such maladaptive up-regulation of negative emotion. In fact, up-regulation might be similar to depressive catastrophizing, thereby matching the putative dominant direction of emotion modulation in depression. These negative biases being triggered by task demands might explain why seed-based analyses could not provide evidence for altered connectivity during resting-state in our depressed sample. Based on this first study differentiating between reappraisal goals in depression, future research should include both valences to investigate in how far patients' intensification of emotion extends to positive stimuli or whether it is limited to the domain of negative emotions (cf. Ochsner et al. 2004).

Our findings in healthy controls broaden previous emotion regulation research regarding stimulus material and regulation strategies. Social affordances in emotional processing were incorporated by facial expressions, and their reappraisal engaged several regions associated with cognitive control over emotion (e.g., superior frontal gyrus, parietal and mid-cingulate cortex as in (Kohn et al. 2014; Buhle et al. 2014; Frank et al. 2014). This network has recently been implicated in the regulation of other stimuli, i.e., film clips (Morawetz et al. 2015) and emotional faces (Nelson et al.

2015). In addition, evaluating the meaning and significance of stimuli likely involves inner speech, subserved by the inferior frontal gyrus and temporal regions (Geva et al. 2011; cf. Morawetz et al. 2015). Interestingly, this system is not only involved in the representation of reappraisal goals in healthy individuals (Morawetz et al. 2015), but also in negatively biased self-referential attribution in depression (Hao et al. 2015), thereby supporting the connection between self-focused reappraisal and attribution. Consistent with the idea of a 'negative cognitive triad' (Beck et al. 1979), attributional biases are likely to limit patients' flexibility in emotion regulation.

By including a different reappraisal goal with matched cognitive effort, i.e., up-regulation, we show that activation differences between patients and healthy controls emerged only for up-regulation, not for down-regulation. Given that the behavioral ratings show the opposite pattern, i.e. effects for down-regulation, but not up-regulation, the current findings may therefore suggest a dissociation between neural and behavioral indices of regulation success. This is crucial as most fMRI studies in depression focus on down-regulation by applying situation-focused strategies, i.e., reinterpretation (Smoski et al. 2015; Smoski et al. 2013; Kanske et al. 2012; Greening et al. 2014) or distancing (Rive et al. 2015; Erk et al. 2010; Dillon and Pizzagalli 2013), yet others include distraction (Kanske et al. 2012). Particularly for patient populations with more severe impairments, distancing appears more feasible than using a cognitively challenging strategy as reappraisal (Rive et al. 2015), and might be implicitly used in everyday life (e.g., when watching horrifying scenes on the news). Thus, there is clearly a need for developing both practical and effective regulation strategies.

Limitations and future directions

Methodological limitations might have contributed to the scarceness of neural reappraisal effects when contrasting regulation against the initial viewing of faces. Namely, the latter always preceded regulation in order to capture participants' 'natural' response, i.e., emotional reactivity, before becoming familiar with applying reappraisal. However, particularly in combination with the block design, this might have induced habituation, resulting in a suboptimal neural baseline condition, especially for the amygdala. Due to their complexity, IAPS scenes might be less affected by habituation than facial expressions (Britton et al. 2006), yet potentially more susceptible to implicit regulation strategies, such as distancing, not targeted by the experimental design. Similarly, the social stimulus material may account for the absence of reappraisal-associated engagement regarding prefrontal control regions (see also Morawetz et al. 2016). Along these lines, a clear-cut temporal

separation of the viewing and the rating period might further help in disentangling effects of emotional and cognitive processing. As the patients in our study were only mildly depressed, with the majority of them being in remission, the applicability to severe depression remains to be tested, e.g., by directly comparing remitted and acute patients in future studies. With a larger sample, further subsampling into non-medicated and medicated patients might tackle the issue in how far medication normalizes amygdala activity during reappraisal. Most importantly, it should be addressed how patients might benefit from transferring their ability to 'successfully' up-regulate negative emotions to an adaptive goal, i.e., up-regulating positive emotions.

Conclusions

Taken together, our findings underscore the notion that maladaptive emotion regulation constitutes a vulnerability marker for depression. Implementing self-focused reappraisal in an interpersonal context revealed initial emotional hyporeactivity in patients, compared to healthy individuals, with amygdala activation during down-regulation being inversely associated with recurrent depression. Despite a stronger increase in well-being in healthy participants than in patients during down-regulation, within-group patterns indicate subjective regulation success even within the patient group. It remains open in how far the divergence between behavioral and neural alterations reflects compensatory or facilitatory mechanisms, particularly when using reappraisal to increase negative emotions. Further research is needed to determine how interventions can build upon this potential resource in order to improve patients' regulatory abilities and psychosocial functioning in an adaptive manner.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional 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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Conflict of interest

All authors declare no conflict of interest.

Table 1. Sociodemographic and clinical characteristics of study participants (presented as n or Mean [SD], otherwise indicated).

	HC (n = 22)	MDD (n = 22)	*p*-value
Age (in years)	32.6 (10.9)	34.5 (9.9)	.556
Sex (M/F)	13/9	13/9	
Education (in years)	14.6 (3.2)	13.1 (2.8)	.091
ERQ Reappraisal	30.1 (4.9)	23.1 (7.4)	**.001**
ERQ Suppression	12.9 (4.5)	16.1 (5.6)	**.043**
TMT-A (in secs)	21.4 (8.7)	19.1 (5.0)	.277
TMT-B (in secs)	40.1 (13.3)	38.8 (16.7)	.781
WST	32.5 (2.2)	31.1 (7.7)	.399
WM digit span forward	8.3 (1.8)	7.6 (2.3)	.280
WM digit span backward	8.0 (1.4)	8.0 (2.5)	1
BDI-II	2.7 (3.4)	13.8 (9.5)	**<.001**
Clinical state (acute/remitted)		4/18	
Onset of illness (in years)		27.3 (10.1)	
		Range: 17-48	
Duration of illness (in years)		6.0 (5.8)	
		Range: 0-20	
Number of previous episodes		2.8 (2.0)	
		Range: 1-8	
Time since last episode (in months;		19.5 (17.2)	
for remitted patients)		Range: 2-72	
Patients with 1+ previous episode		13	
SSNRI only		4	
SSRI only		3	
SSNRI & atypical antipsychotic		2	
SSRI & atypical antipsychotic		1	
SSNRI & anticonvulsant		1	
SSRI & NaSSA		1	

SSRI & lithium	1
NaSSA & atypical antipsychotic	1
Agomelatine	1

Note: HC = healthy controls, MDD = patients with depression, M = male, F = female, ERQ = Emotion Regulation Questionnaire, TMT = Trail Making Test, WST = Wortschatztest [German], WM = Working Memory, BDI = Beck Depression Inventory, SSNRI = serotonin–norepinephrine reuptake inhibitor, SSRI = selective serotonin re-uptake inhibitor, NaSSA = noradrenergic and specific serotonergic antidepressant. Significant differences ($p < .05$) between HC and MDD are depicted in bold.

Table 2

Whole-brain condition effects, all with p < .05 (FWE-corrected at the cluster level), with cluster size (k), side, MNI coordinates and t-values. For each cluster, only the maximum peak in gray matter is reported.

Contrast	k	Side	MNI			t-value
Region			x	y	z	
View-Angry > View-Neutral						
Precentral Gyrus	17051	R	39	-26	56	15.83
Rolandic Operculum	1471	R	42	-20	17	8.04
Cerebellum	1053	L	-21	-51	-23	7.22
Superior Temporal Gyrus	974	R	57	-18	-6	4.73
Inferior Temporal Gyrus	434	L	-44	-30	-18	4.64
View-Neutral > View-Angry						
Postcentral Gyrus	11306	L	-39	-30	63	17.21
Cerebellum	2603	R	23	-51	-26	9.80
Angular Gyrus	1836	R	50	-71	32	5.65
Postcentral Gyrus	1764	L	-50	-18	17	9.25
Mid-orbital Gyrus	1732	R	6	36	-12	5.96
Thalamus	1694	L	-17	-18	0	6.29
Anterior Cingulate Cortex	627	R	11	42	8	4.56
Increase > Decrease						
Mid-cingulate Cortex	5642	L	-11	-15	47	5.31
Rolandic Operculum	5167	L	-44	-29	18	7.00
Superior Frontal Gyrus	965	L	-14	66	15	5.28
Rolandic Operculum	958	R	41	-17	17	5.20
Superior Occipital Gyrus	711	L	-15	-83	32	5.31
Postcentral Gyrus	420	L	-26	-35	69	4.21
Superior Temporal Gyrus	401	R	48	-24	-5	5.14
Decrease > Increase						
Superior Parietal Lobule	693	R	8	-80	54	4.74

Cerebellum	376	R	36	-81	-21	4.44
Pallidium	361	R	24	2	-3	4.51

Table 3

Within-group whole-brain effects, all with p < .05 (FWE-corrected at the cluster level), with cluster size (k), side, MNI coordinates and t-values. Only significant effects are listed. For each cluster, only the maximum peak in gray matter is reported.

Contrast	k	Side	MNI			t-value
Region			x	y	z	
HC						
Increase > Decrease						
Rolandic Operculum	600	L	-39	-32	18	4.56
Precuneus	426	R	2	-54	48	3.87
MDD						
Increase > Decrease						
Superior Temporal Gyrus	8028	L	-48	-29	17	7.25
Superior Parietal Lobule	4151	L	-23	-45	60	5.10
Supramarginal Gyrus	1323	R	63	-27	36	5.04
Supramarginal Gyrus	1322	R	54	-39	24	5.14
Precuneus	1184	R	9	-50	57	5.74
Precentral Gyrus	586	R	54	0	23	5.20
Cuneus	569	L	-15	-83	33	4.97
Superior Frontal Gyrus	490	L	-14	66	15	5.69

Note: HC = healthy controls, MDD = patients with depression

Table 4

Whole-brain group differences, all with p < .05 (FWE-corrected at the cluster level), with cluster size (k), side, MNI coordinates and t-values. For each cluster, only the maximum peak in gray matter is reported.

Contrast	k	Side	MNI			t-value
Region			x	y	z	
Differences in baseline contrasts						
HC > MDD: Neutral						
Calcarine Gyrus	3797	L	-20	-57	5	6.09
Precuneus	2401	R	8	-60	54	4.70
Postcentral Gyrus	1809	R	33	-32	41	4.85
Insula	1808	L	-27	21	5	5.09
Fusiform Gyrus	1702	R	29	-60	-17	5.88
Superior Frontal Gyrus	1160	R	27	-6	63	4.75
Superior Parietal Lobule	1067	L	-24	-56	68	4.37
Rolandic Operculum	630	L	-50	2	9	4.22
Mid-cingulate Cortex	594	L	-11	3	42	4.51
Thalamus	550	R	17	-14	2	4.46
Hippocampus	493	L	-24	-24	-8	4.67
Postcentral Gyrus	456	L	-60	-20	24	4.22
HC > MDD: Angry						
Calcarine Gyrus	8394	L	-14	-59	5	6.16
Inferior Parietal Lobule	8150	R	38	-41	45	5.97
Insula	6319	L	-27	21	5	6.13
Mid-cingulate Cortex	2658	L	-11	5	42	5.57
Putamen	2463	R	32	8	6	5.22
Superior Temporal Gyrus	670	L	-50	-42	20	4.82
Supramarginal Gyrus	546	L	-51	-26	29	4.71
HC > MDD: Increase						
No suprathreshold activation						

HC> MDD: Decrease						
		No suprathreshold activation				
MDD > HC (any of the above)						
		No suprathreshold activation				
Differences in differential contrasts						
MDD > HC: Increase > View-Angry						
Fusiform Gyrus	1005	L	-24	-78	-6	4.43
Posterior Medial Frontal Cortex	856	R	12	2	48	5.06
Supramarginal Gyrus	511	L	-56	-27	29	4.77
Superior Temporal Gyrus	391	L	-38	-11	-9	5.08

Note: HC = healthy controls, MDD = patients with depression

Table 5

Regional effects within the amygdala, all with p < .05 (FWE-corrected at the voxel level), with cluster size (k), side, MNI coordinates and t-values. Only significant effects are listed.

Contrast	k	Side	MNI			t-value
Region			x	y	z	
Baseline contrasts						
View-Angry > View-Neutral						
Amygdala	148	L	-26	-5	-24	4.45
Group differences						
HC > MDD: View-Neutral						
Amygdala	55	R	17	-3	-21	5.33
Amygdala	31	L	-23	-2	-20	4.05
HC > MDD: View-Angry						
Amygdala	114	R	17	-3	-21	5.14
Amygdala	178	L	-24	-2	-21	5.01

Note: HC = healthy controls, MDD = patients with depression

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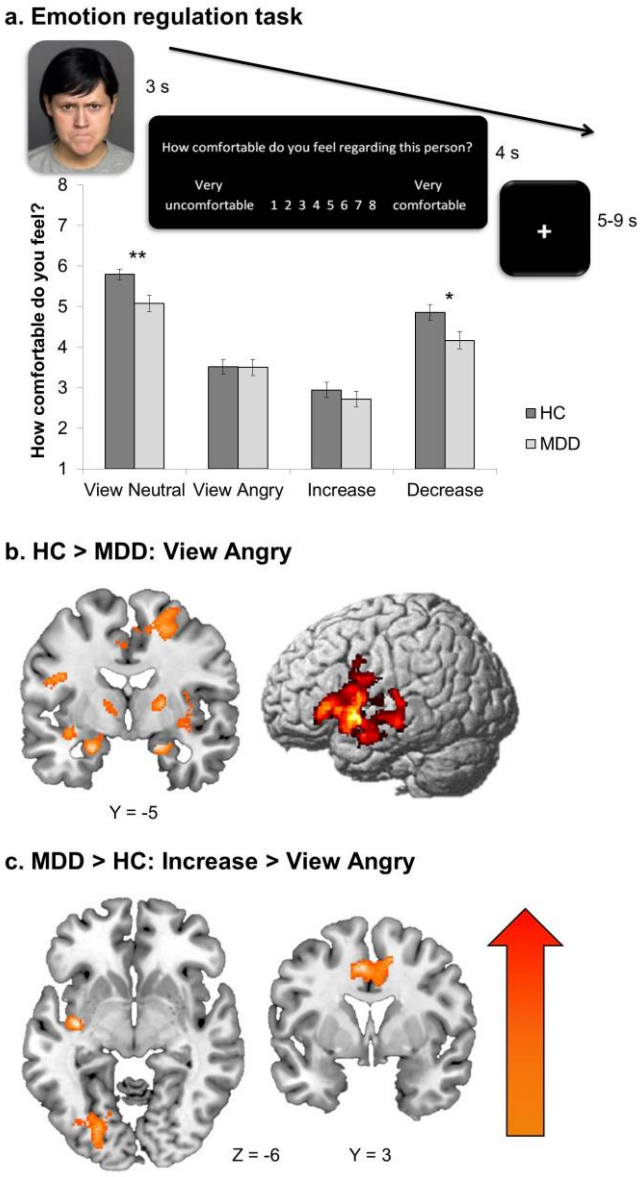

Fig. 1 Illustration of the emotion regulation task (a) and group differences in brain activation for viewing angry faces (b) and up-regulation (compared to view-angry) (c). **a:** mean ratings per condition (with standard errors). Only significant group differences are marked, * $p < .05$ (follow-up *t*-test) and ** $p < .01$. **b:** Coronal slice from a representative template brain showing clusters in bilateral amygdala, mid-cingulate cortex, precentral gyrus, putamen and remainders of clusters peaking in the insula lobe (left), and overlay of the left insular cluster extending to the inferior frontal gyrus (right). **c:** Axial and coronal slices from a representative template brain showing clusters in left fusiform gyrus and left superior temporal gyrus (left), and posterior medial frontal cortex (right). Images are thresholded at $p_{FWE} < .05$ at the cluster level, with an underlying voxel-level threshold of $p < .001$, uncorrected. HC = healthy controls (n = 22), MDD = patients with depression (n = 22)

Supplementary Material

Supplementary Table S1

Whole-group whole-brain effects involving the view-angry condition, all with p < .05 (FWE-corrected at the cluster level), with cluster size (k), side, MNI coordinates and t-values. For each cluster, only the maximum peak in gray matter is reported.

Contrast	k	Side	MNI			t-value
Region			x	y	z	
View-Angry > Decrease						
Superior Parietal Lobule	30617	R	18	-62	56	6.68
Middle Frontal Gyrus	941	L	-26	53	18	5.30
Insula	709	L	-35	-6	14	4.99
Inferior Temporal Gyrus	648	L	-51	-54	-6	4.39
Superior Medial Gyrus	472	R	14	54	5	5.38
Superior Orbital Gyrus	457	L	-26	50	-2	4.02
View-Angry > Increase						
Superior Frontal Gyrus	800	R	23	-3	53	4.74
Postcentral Gyrus	790	R	32	-35	41	4.32
Precuneus	742	L	-14	-71	56	4.70
Decrease > View-Angry						
Cerebellum	1032	L	-44	-68	-33	5.03
Cerebellum	718	L	-14	-87	-23	4.81
Cerebellum	536	R	51	-65	-30	5.52
Increase > View-Angry						
No suprathreshold activation						