Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression

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Abstract

Functional magnetic resonance imaging (fMRI) was used to examine cognitive regulation of negative emotion in 12 unmedicated patients with major depressive disorder (MDD) and 24 controls. The participants used reappraisal to increase (real condition) and reduce (photo condition) the personal relevance of negative and neutral pictures during fMRI as valence ratings were collected; passive viewing (look condition) served as a baseline. Reappraisal was not strongly affected by MDD. Ratings indicated that both groups successfully reappraised negative emotional experience. Both groups also showed better memory for negative vs. neutral pictures 2 weeks later. Across groups, increased brain activation was observed on negative/real vs. negative/look and negative/photo trials in left dorsolateral prefrontal cortex (DLPFC), rostral anterior cingulate, left parietal cortex, caudate, and right amygdala. Depressive severity was inversely correlated with activation modulation in the left DLPFC, right amygdala, and right cerebellum during negative reappraisal. The lack of group differences suggests that depressed adults can modulate the brain activation and subjective experience elicited by negative pictures when given clear instructions. However, the negative relationship between depression severity and effects of reappraisal on brain activation indicates that group differences may be detectable in larger samples of more severely depressed participants.

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1. Introduction

Anhedonia and excessive sadness are cardinal symptoms of major depressive disorder (MDD) (American Psychiatric Association, 2000). Emotional context insensitivity research demonstrates that these symptoms flatten the emotional landscape (Rottenberg, 2005; Rottenberg et al., 2005). In one study, healthy controls and depressed adults viewed amusing, sad, and neutral films (Rottenberg et al., 2005). Controls showed predictable changes in self-reported sadness and happiness, but the depressed group showed heightened sadness regardless of which film was presented. While blunted reactivity to positive stimuli in depression is widely known, it is noteworthy that depressed participants did not show increased sadness when viewing sad films (Rottenberg et al., 2005), a result linked to more severe depression and worse psychosocial function (Rottenberg et al., 2002). This finding indicates that depression truncates the range of negative emotional experience, which has clinical implications.

Emotional context insensitivity may have consequences for emotion regulation. Reappraisal—re-interpreting stimuli to modify their meaning—can modulate negative emotional experience (Ochsner et al., 2004) and supports successful interpersonal functioning (Gross and John, 2003). Furthermore, reappraisal does not impair explicit memory and may improve it, in contrast to the negative effects on memory associated with expressive suppression (Dillon et al., 2007; Hayes et al., 2010; Richards and Gross, 2000). Thus, reappraisal is widely considered an effective emotion-regulation technique. Because depression restricts the range of emotional reactions, it may also limit the ability to reappraise emotional responses once they arise.

Behavioral support for this hypothesis is mixed. Studies in remitted depression (Ehring et al., 2010; Kanske et al., 2012) reported found that instructed reappraisal reduced negative emotional experience. However, the use of remitted samples may have decreased the likelihood of detecting depression effects. Indeed, compared to controls, an unmedicated MDD sample reported greater difficulty in cognitively reducing sadness, and the level of difficulty was correlated with depressive severity (Beauregard et al., 2006). Thus, reappraisal of negative emotional experience may be impaired in acute, unmedicated depression.
The neuroimaging literature is also mixed. One functional magnetic resonance imaging (fMRI) study found that medicated depressed adults could cognitively reduce amygdala activation elicited by negative pictures, although the degree of amygdala modulation was negatively correlated with depressive severity (Erf et al., 2010a). This contrasts with reports of blunted reappraisal effects on amygdala activation in both remitted (Kanske et al., 2012) and unmedicated depressed samples (Beauregard et al., 2006). Another study found no amygdala modulation during reappraisal in controls or unmedicated depressed adults (Johnstone et al., 2007), but observed right prefrontal cortex (PFC) hyperactivation in the depressed group. This is difficult to interpret, because another study reported right dorsolateral prefrontal cortex (DLPFC) hypoactivation during reappraisal in medicated depression (Erf et al., 2010a). Overall, effects of depression on reappraisal are not well understood.

In light of this mixed evidence, we conducted an fMRI study of reappraisal in MDD. To maximize sensitivity to depression effects, we recruited an unmedicated sample experiencing a current major depressive episode and compared them to healthy controls. Participants reappraised their responses to negative and neutral pictures and provided trial-by-trial valence ratings to permit investigation of subjective experience. The primary hypothesis was that depressed participants would not be able to cognitively increase or reduce their negative emotional responses, as measured by valence ratings and brain activation.

The alternative hypothesis was that depression would have minimal effects on reappraisal because of the use of detailed instructions and cues. This prediction was motivated by a prior study in remitted students, which found no effects of depression on instructed reappraisal (Ehring et al., 2010). Importantly, this study also reported that the remitted group spontaneously engaged in an ineffective emotion-regulation strategy (expressive suppression). This suggests that the remitted participants were able to reappraise effectively because they were given clear instructions and cues, and may not have done so otherwise.

We also examined explicit memory. Two weeks after the fMRI session, participants completed a recognition memory test for the negative and neutral pictures presented in the scanner. In controls, high confidence memory responses are typically more accurate for arousing vs. neutral material, an effect linked to amygdala activation at encoding (Canli et al., 2000; Dolcos et al., 2004). A prior study in a mostly medicated sample suggested that this mechanism is hyperactive in depression (Hamilton and Gotlib, 2008). Thus, we performed a subsequent memory analysis to test whether the MDD group showed stronger amygdala activation than controls during successful encoding of negative pictures. We also investigated whether memory was sensitive to reappraisal.

2. Methods

2.1. Procedures

2.1.1. Participants

Participants comprised 27 controls and 14 depressed individuals. Data from three controls and one depressed participant were excluded due to excessive head motion (> 4 mm or degrees incremental). A depressed participant with amygdala activation 5 SDs below the MDD mean was removed, leaving 24 controls and 12 depressed participants. Valence ratings were not recorded for one depressed participant. Twenty-two controls and all depressed participants completed a memory test 2 weeks later. Consent was obtained, consistent with an IRB-approved protocol. Participants were paid (MRI: $25/h; memory: $10/h) and debriefed.

2.1.2. Stimulus selection

Three sets of 144 pictures (72 negative, 72 neutral) were used in the MRI session, as distracters in the memory test, and in an electroencephalography session following the memory test (data not presented). Assignment of picture sets to sessions was counterbalanced. Negative pictures included images from the International Affective Picture System (IAPS) (Lang et al., 2005) and the Internet depicting threatening animals, violence, drug use, accidents, painful medical procedures, poverty, and old age. Neutral pictures depicted people engaged in mundane activities.

2.1.3. Stimulus validation

Nine laboratory members (5 females) rated the pictures for valence (1=negative, 9=positive) and arousal (1=calm, 9=excited). Gender ¥ Set ¥ Picture Type analyses of variance (ANOVAs) revealed only effects of Picture Type for valence (negative: 2.62 ± 0.60; neutral: 5.55 ± 0.47; F(1,3) = 171.58, p = 0.001) and arousal (negative: 6.96 ± 0.31; neutral: 4.14 ± 0.80; F(1,3) = 47.55, p = 0.006). Thus, the pictures elicited the intended emotional responses in both genders.

2.1.4. Diagnostic interview

Eligibility was established using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (First et al., 2002). Depressed participants were unmedicated, met criteria for MDD, and had no history of psychosis. Comorbidity was mainly confined to anxiety disorders (see Results). Past psychotropic medication was allowed (no use in the preceding 2 weeks for benzodiazepines, 6 weeks for selective serotonin reuptake inhibitors, 6 months for dopaminergic drugs). Two depressed participants were attending psychotherapy sessions once or twice monthly; the other depressed participants were not in therapy. Five depressed participants reported past psychotherapy of varying duration (1 month or less, n=2; 2 years or less, n=2; unclear, n=1). Controls reported no current or past Axis I diagnosis. Participants were 19–63 years old and right-handed. None presented with neurological conditions or significant medical history, or met criteria for lifetime substance dependence or substance abuse in the last year.

2.1.5. Reappraisal task

The task was designed to modulate emotional experience and minimize demand characteristics. Trials included a cue word (“REAL”, “LOOK”, or “PHOTO”; duration: 1 s), a jittered inter-stimulus interval (ISI: 3–5 s), a negative or neutral picture (6 s), a second ISI (1.5–3 s), and a rating screen (3 s). The rating screen displayed self-assessment manikins (Lang et al., 2005) corresponding to five levels on a valence scale (1=positive, 3=neutral, 5=negative). Participants pressed a button to rate their emotional state at trial end. A fixation cross was presented during the ISIs and inter-trial interval (2–11 s). Participants completed 12 practice trials after the interview and in the scanner to ensure comprehension. During scanning, they completed six blocks of 24 trials. Optimal trial sequences were determined with optseq (Dale, 1999).

The cues were explained after the interview and at the outset of the MRI session. To maximize experimental control, we constrained the reappraisal technique by emphasizing self-focused reappraisal rather than situation-focused reappraisal, in which participants reinterpret negative situations in order to envision more positive outcomes (Ochsner et al., 2004). Specifically, in response to the real cue, participants were asked to mentally place themselves in scenes as though they were happening now, and vividly imagine all the sensations that would be experienced. This was intended to intensify negative emotional experience. By contrast, the photo cue was designed to dampen responses to negative pictures by increasing the sense of psychological distance (Kross and Ayduk, 2008). Thus, in response to the photo cue, participants were told to imagine that scenes were old, posed photographs being viewed from a distance. In response to the look cue, participants viewed pictures without controlling their responses. The instructions emphasized imagery rather than emotion regulation to limit demand characteristics.

The task was programmed in E-Prime (Psychology Software Tools, Inc; Sharpsburg, PA). Behavioral data were analyzed with SPSS version 19.0.0 software (IBM; Armonk, NY).

2.1.6. Questionnaires

To assess depressive and anxious symptoms, habitual use of emotion-regulation strategies, and mental imagery, the following self-report measures were administered after scanning: the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), Emotion Regulation Questionnaire (ERQ: Gross and John, 2003), Mood and Anxiety Symptom Questionnaire (MASQ: Watson et al., 1995), Ruminative Responses Scale (RRS: Nolen-Hoeksema and Morrow, 1991; Treynor et al., 2003), and Vividness of Visual Imagery Questionnaire (VVIQ: Marks, 1973). The Wechsler Test of Adult Reading (WTAR: Green et al., 2008; Psychological Corporation, 2001) provided an IQ estimate.

See Supplementary Material for verbatim instructions.
2.1.7. MRI acquisition

MRI data were collected on a 3 T magnet (Siemens, USA; 12-channel head coil). Sessions included an auto-align localizer (van der Kouwe et al., 2005), a T1-weighted MPRAGE structural image (1.2 mm3 voxels; 144 slices; TR=2.2 s; TE/1/2/3/4=1.5/4.3/6.5/18.7/01 ms; flip angle =7°), and T2-weighted images sensitive to both group-level dependency, Group Reappraisal Condition contrast, acquired during the reappraisal task (3.0 mm3 voxels; 46 slices; TR=3 s; TE=30 ms; flip angle =85°; transverse acquisition).

2.1.8. Recognition memory test

The 144 “old” pictures from the MRI session plus 144 “new” distractors were presented. Participants indicated whether pictures were old or new, and rated their confidence (high, medium, low) in each decision. There was no time limit for either response. The picture sequence was random, and the BDI-II was re-administered.

2.2. Data analysis

2.2.1. Questionnaires

Scale scores were computed for the MASQ [General Distress: Depression (MASQ-GD)], Anhedonic Depression (MASQ-AD), General Distress: Anxiety (MASQ-GA), and Anxious Arousal (MASQ-AA). The RRS (RRS-Broiding, RRS-Reflection, RRS-Depression), and the ERQ (habitual use of reappraisal [ERQ-R] and expressive suppression [ERQ-S]). Total scores were computed for the BDI-II, VVIQ, and WTAR. WTAR scores were age-normed. Group differences were assessed by two-tailed t-test.

2.2.2. Valence ratings

Ratings were entered into a Group x Gender x Cue x Picture Type ANOVA. For all ANOVAs, Greenhouse-Geisser corrected p-values are reported when sphericity was violated. Exploratory analyses investigated whether reappraisal efficacy, assessed with [negative/real – negative/photo] valence rating difference scores, was correlated with BDI-II, RRS-Broiding, RRS-Reflection, or ERQ-R scores.

2.2.3. Recognition memory: emotion analysis

A Group x Gender x Valence (hit, miss) x Picture Type ANOVA was conducted on [hit rate–false alarm rate] scores for old items. False alarm rates were subtracted from hit rates because emotion tends to increase both; thus, considering only hit rates can inflate estimates of improved memory (Sharot et al., 2004; Dougall and Rotello, 2007). To avoid spurious results, only data from participants with at least 10 high confidence negative hits and 10 negative misses were analyzed (controls: n=17; MDD: n=11). Repeating this analysis with all participants yielded identical results (Supplementary Material).

2.2.4. Recognition memory: reappraisal analysis

A Group x Cue x Gender x Picture Type ANOVA was conducted on hit rates. False alarms were not subtracted as there is no independent measure of false alarms for the cue conditions within each picture type.

2.2.5. fMRI pre-processing

Pre-processing involved the following procedures: discarding five volumes collected at the onset of each run to ensure stable longitudinal magnetization; slice-time and motion-correction using the FSL tools slicetimer and mcflirt (Jenkinson et al., 2002); normalization to MNI152 templates; re-sampling to 2 mm (Jenkinson et al., 2002); segmentation of brain tissue (Smith, 2002); coregistration; normalization to MN152 templates; re-sampling to 2 mm3 voxels; and spatial smoothing (6 mm FWHM).

2.2.6. fMRI: reappraisal and subsequent memory analyses

The general linear model (GLM) implemented in SPM8 (Wellcome Department of Cognitive Neurology, London, UK) was used for statistical analysis. Onset times and durations for the cues, pictures, and rating screen were convolved with a canonical hemodynamic response function, and nuisance regressors accounted for run-to-run fluctuations in mean image intensity. The data were high-pass filtered (cut-off period: 128 s). The GLM returns least squares parameter estimates (‘‘beta weights’’) for conditions of interest, which were used in separate reappraisal and subsequent memory analyses.

The reappraisal analysis consisted of a Group x Reappraisal Condition (negative/real, negative/look, negative/photo) ANOVA (Urry et al., 2009). The main effect of Reappraisal Condition was expected to reveal increased activation on negative/real vs. negative/look trials in regions implicated in emotional arousal (amygdala; Ochsner et al., 2004), self-referential processing (medial PFC; Mitchell et al., 2005), and mental imagery (parietal cortex; Farah, 1984), with negative/look trials eliciting intermediate activation. No predictions were made regarding the main effect of Group. However, Group x Reappraisal Condition interactions were expected in prefrontal areas thought to implement reappraisal, as well as in sub-cortical regions whose activation is affected by reappraisal, namely the amygdala. Weaker modulation of brain activation by reappraisal was expected in the MDD group.

Given the link between amygdala activation and subsequent memory for emotional stimuli in controls, as well as evidence of amygdala hyperactivation during negative picture encoding in depressed adults (Hamilton and Gotlib, 2008), the subsequent memory analysis focused on negative pictures. Encoding responses were binned according to eventual memory status, and a [high confidence negative hits – negative misses] contrast identified brain regions whose activation was linked to accurate memory. This contrast was computed in each group separately, and a between-groups t-test investigated whether amygdala activation was stronger in the MDD group.

2.2.7. fMRI: whole-brain comparisons

Activation in a [negative/real – negative/photo] contrast was regressed against BDI scores in the MDD group to identify brain regions where the range of activation modulation during reappraisal was negatively correlated with depression severity. The [negative/real – negative/photo] contrast was used to maximize the likelihood of identifying effects of depression on emotional flexibility. Negative correlations were expected in the amygdala and DLPFC (Erk et al., 2013a; Siegle et al., 2002, 2007). To identify regions that tracked shifts in subjective experience, this contrast was also regressed against [negative/photo – negative/real] valence difference scores. In this analysis, stronger effects of reappraisal on subjective experience (bigger valence drops from the photo to real trials) are positively correlated with larger effects in the [negative/real – negative/photo] contrast.

2.2.8. fMRI: multiple comparisons correction

The voxelwise p-value was 0.005. Inferences were made after multiple comparisons correction using Gaussian Random Fields. Only clusters significant at p < 0.05 (corrected) are reported unless otherwise noted. Given a priori interest, contrasts in the amygdala were corrected for multiple comparisons over the amygdala mask in the Wake Forest University PickAtlas (Maldjian et al., 2003). MarsBar was used to extract beta weights for additional analysis (Brett et al., 2002).

3. Results

3.1. Clinical data

Data on the number and timing of major depressive episodes (MDE) are provided in Table 1. Four depressed participants had co-morbid anxiety (two had social anxiety disorder; one had social anxiety and panic disorder; one had social anxiety, panic

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Depressed</th>
<th>t</th>
<th>t</th>
<th>\chi^2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MDEs</td>
<td>–</td>
<td>2.33 (1.56)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age at first MDE</td>
<td>18.58 (7.65)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gender</td>
<td>12 f, 12 m</td>
<td>7 f, 5 m</td>
<td>0.22</td>
<td>0.637</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.42 (14.93)</td>
<td>31.00 (8.20)</td>
<td>0.89</td>
<td>0.382</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.88 (1.51)</td>
<td>15.33 (2.06)</td>
<td>0.90</td>
<td>0.376</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BDI-II (fMRI session)</td>
<td>16.32 (2.34)</td>
<td>25.83 (10.94)</td>
<td>7.58</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BDI-II (memory session)</td>
<td>1.18 (2.65)</td>
<td>21.42 (10.10)</td>
<td>6.81</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MASQ-GD</td>
<td>13.29 (2.05)</td>
<td>37.33 (10.24)</td>
<td>8.06</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MASQ-AD</td>
<td>47.38 (12.24)</td>
<td>83.08 (8.97)</td>
<td>8.95</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MASQ-GA</td>
<td>13.17 (2.06)</td>
<td>25.00 (5.31)</td>
<td>7.45</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MASQ-AA</td>
<td>18.38 (1.58)</td>
<td>27.33 (10.88)</td>
<td>2.84</td>
<td>0.016</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RRS-Broiding</td>
<td>7.42 (2.08)</td>
<td>12.58 (3.53)</td>
<td>5.54</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RRS-Depression</td>
<td>17.67 (5.06)</td>
<td>32.25 (6.52)</td>
<td>7.40</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RRS-Reflection</td>
<td>9.46 (4.01)</td>
<td>11.33 (3.60)</td>
<td>1.37</td>
<td>0.181</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ERQ-Reappraisal</td>
<td>30.96 (4.36)</td>
<td>27.83 (8.74)</td>
<td>1.17</td>
<td>0.262</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ERQ-Suppression</td>
<td>12.13 (4.03)</td>
<td>14.67 (4.58)</td>
<td>1.71</td>
<td>0.097</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>VVIQ</td>
<td>29.25 (9.86)</td>
<td>33.50 (9.89)</td>
<td>1.22</td>
<td>0.232</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>WTAR-standardized score</td>
<td>117.00 (7.17)</td>
<td>102.30 (13.83)</td>
<td>2.54</td>
<td>0.028</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Note. f= female; m= male; BDI= Beck Depression Inventory II; MASQ= Mood and Anxiety Symptoms Questionnaire (GDD= General Distress: Depressive symptoms, AD= Anhedonic Depression, GD= General Distress: Anxious Symptoms, AA= Anxious Arousal); RRS= Rumination Responses Scale; ERQ= Emotion Regulation Questionnaire; VVIQ= Vividness of Visual Imagery Questionnaire; WTAR= Wechsler Test of Adult Reading.

a Memory session data are from 22 controls (11 f, 11 m) and 12 depressed participants (7 f, 5 m).

b WTAR data from two non-native English speaking participants in the MDD group were not analyzed. Data are frequency counts or mean (SD).
3.2. Demographics and questionnaires

There were no group differences in age, education, or gender (Table 1). The MDD group reported more brooding and anxious/depressive symptoms than controls, but there were no differences in VVIQ, reflection, or habitual use of reappraisal or expressive suppression. Controls had higher WTAR scores.

3.3. Valence ratings

Reappraisal affected responses to negative pictures while having weak effects on responses to neutral pictures, but this was not influenced by MDD (Fig. 1A; see caption for statistics). Valence was lowest on negative/real trials, intermediate on negative/look trials, and highest on negative/photo trials. There were no significant correlations between BDI-II, RRS-Brooding, RRS-Reflection, or ERQ-Reappraisal scores and [negative/real—negative/photo] rating difference scores.

3.4. Recognition memory: emotion analysis

A beneficial effect of emotion on high confidence responses was observed, but was not affected by depression (Fig. 1B). Accuracy was higher for negative vs. neutral pictures remembered with high confidence. No effects involving Group were significant.

3.5. Recognition memory: reappraisal analysis

No effects of reappraisal on memory were found.

3.6. fMRI: reappraisal model

As shown in Fig. 2 and Table 2, the main effect of Reappraisal Condition revealed activation in the left DLPC, left parietal cortex, rostral anterior cingulate cortex (rACC) extending into medial PFC, caudate, and the right amygdala, with a trend in the right cerebellum. To decompose these results, beta weights were extracted from spherical ROIs (8-mm radius) centered on the peak voxel in each region and submitted to Group × Reappraisal Condition ANOVAs. For the right amygdala, activation was simply extracted from the 5 significant voxels.

The main effect of the Reappraisal Condition was significant in each region ($F(2, 68)$ values > 5.77, $p < 0.01$). As depicted in Fig. 2 (bar graphs), in every ROI activation was stronger on negative/real vs. negative/look trials ($t(35)$ values > 2.31, $p < 0.03$) and negative/photo trials ($t(35)$ values > 4.20, $p < 0.001$). Activation did not differ between negative/look and negative/photo trials in any region ($t(35)$ values < 1.52, $p > 0.13$). Thus, reappraisal effects were observed in expected regions and driven by increased activation on negative/real trials.

Contrary to the primary hypothesis, and in favor of the alternative hypothesis, no brain region showed a significant Group × Reappraisal Condition interaction or main effect of Group (Table 2). To protect against Type II error, an exploratory amygdala ROI analysis looked for any voxels showing a Group × Reappraisal Condition interaction, but none were found. Next, psychophysiological interaction analyses were conducted to determine if functional connectivity of the right amygdala, left DLPC, or rACC differed across the negative/real and negative/photo conditions, but no group differences emerged [Supplementary Material]. Thus, effects of reappraisal on brain activation were similar across groups.

3.7. fMRI: correlations with BDI-II

Regressing the [negative/real—negative/photo] contrast against BDI-II scores in the MDD group revealed negative correlations in the left DLPC, right amygdala, and right cerebellum (Fig. 3). Increased depressive severity was associated with weaker effects of reappraisal on brain activation in these regions. To test the specificity of these relationships, identical analyses were performed with MASQ-GDA and MASQ-AA scores; no significant findings emerged, providing evidence that these correlations were specific to depressive symptoms rather than general psychological distress.

3.8. fMRI: correlation with valence ratings

Regressing the [negative/photo—negative/photo] contrast against [negative/photo—negative/real] valence rating scores revealed a correlation in the left cerebellum (Fig. 4).
3.9. fMRI: subsequent memory model

No significant clusters were seen when the [high confidence negative hits – negative misses] contrast was computed separately in each group, and no significant group differences emerged. When the data were collapsed across groups, the peak activation was just dorsal to the right amygdala (peak: 20, 2, 12; Z=4.14; 106-voxel cluster). A structural ROI analysis confirmed right amygdala activation (peak: 20, –6, –20; Z=3.92; 40 voxels; cluster p=0.01).

4. Discussion

MDD is characterized by truncated emotional reactions (Rottenberg, 2005; Rottenberg et al., 2005), and we hypothesized that this lack of emotional flexibility would limit reappraisal. Prior studies have reported mixed findings, but some evaluated medicated (Erk et al., 2010a) or remitted (Ehring et al., 2010; Kanske et al., 2012) samples, possibly underestimating depression effects. Thus, we tested an unmedicated MDD group. Contrary to expectations, reappraisal reliably affected valence ratings and brain...
activation in the MDD group. This supports the alternative hypothesis that depressed participants can reappraise negative emotions if given detailed instructions and cues. The findings echo studies indicating that, although depressed individuals often perform poorly on unstructured tasks, they can exhibit normative performance if supported (Ehring et al., 2010; Hertel and Rude, 1991).

However, this conclusion is tempered by negative correlations between BDI-II scores and reappraisal effects in the left DLPFC, right amygdala, and right cerebellum (Fig. 3). These data are consistent with work implicating the cerebellum in emotion regulation (Schutter and van Honk, 2009) and linking DLPFC and amygdala dysfunction to depression (Siegle et al., 2002, 2007). Moreover, they dovetail with previously reported negative relationships between depressive severity and right amygdala modulation during reappraisal (Erk et al., 2010a), as well as between depressive severity and difficulty regulating sadness (Beauregard et al., 2006). These correlations suggest that despite the use of detailed instructions, more severe depression had a negative effect on brain systems implicated in reappraisal, although it was not large enough to support a group difference. Future studies should recruit larger samples of more severely depressed individuals, and investigators may wish to take additional steps to maximize the paradigm’s sensitivity to depression (see Section 4.4).

4.2. Effects of reappraisal on brain activation and the default mode network

Across groups, reappraisal modulated activation in the left DLPCF, left parietal cortex, rACC/medial PFC, and right amygdala. Left DLPCF activation may reflect the generation and maintenance of reappraisal plans in working memory (Curtis and D’Esposito, 2003). Neurological data link generation of visual images to left posterior parietal cortex (Farah, 1984); thus, left parietal activation may index the use of imagery to achieve reappraisal goals. Modulation of rACC/medial PFC activation during self-focused reappraisal is consistent with the established role of these regions in self-referential processing (Mitchell et al., 2005; Phan et al., 2004), and reappraisal-based shifts in amygdala activation may reflect changes in subjective experience.

At a systems level—and with the exception of the left DLPCF—the brain regions activated by reappraisal strongly resemble the default mode network (DMN; Buckner et al., 2008; Habas et al., 2009; Raichle et al., 2001). Indeed, inspection of the [negative/real—negative/photo] contrast collapsed across the groups (data not shown) reveals the regions in Fig. 3 plus right parietal cortex and precuneus, yielding considerable overlap with the DMN (Buckner et al., 2008). Although the DMN is the focus of intense interest, its role in emotion regulation has not been emphasized. We propose that self-focused reappraisal should reliably activate the DMN, because the DMN supports self-relevant mental simulations (Buckner et al., 2008) and self-focused reappraisal entails mentally reframing events to modify their personal relevance and emotional impact. Furthermore, reappraisal often requires two processes—envisioning future scenarios and deploying theory of mind—that robustly activate the DMN (Buckner et al., 2008).

Table 2

Effects of reappraisal and group on fMRI activation elicited by negative pictures.

<table>
<thead>
<tr>
<th>Region</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Voxels</th>
<th>Z-score</th>
<th>FWE-corrected p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main effect of reappraisal condition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>−26</td>
<td>26</td>
<td>46</td>
<td>821</td>
<td>5.71</td>
<td>0.001</td>
</tr>
<tr>
<td>Left lateral occipital cortex (superior division)</td>
<td>−36</td>
<td>−84</td>
<td>36</td>
<td>1742</td>
<td>5.42</td>
<td>0.004</td>
</tr>
<tr>
<td>Rostral anterior cingulate</td>
<td>−12</td>
<td>38</td>
<td>0</td>
<td>2220</td>
<td>5.34</td>
<td>0.005</td>
</tr>
<tr>
<td>Caudate (anteroventral)</td>
<td>−7</td>
<td>4</td>
<td>4</td>
<td>856</td>
<td>5.33</td>
<td>0.005</td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>10</td>
<td>−52</td>
<td>−54</td>
<td>545</td>
<td>4.78</td>
<td>0.067</td>
</tr>
<tr>
<td>Right amygdala</td>
<td>24</td>
<td>−8</td>
<td>−22</td>
<td>5</td>
<td>3.36</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>Main effect of group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No significant activations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group × Reappraisal Condition Interaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No significant activations</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

* The p-value for this cluster reflects multiple comparison correction using the structurally defined bilateral amygdala mask from the Wake University PickAtlas.

For all other regions, p-values are given for the peak voxel and reflect multiple comparison correction over the whole brain.

4.1. Depression and modulation of subjective experience by reappraisal

Trial-by-trial valence ratings indicated that all participants could reappraise negative emotional experience. Across groups, valence ratings were lowest on negative/real trials, intermediate on negative/look trials, and highest on negative/photo trials (Fig. 1a). These results are consistent with prior studies (Beauregard et al., 2006; Sheline et al., 2009) and confirm reliable effects of reappraisal on negative emotional experience in acute, unmedicated depression. Similar effects have been reported in remitted samples (Ehring et al., 2010; Kanske et al., 2012). Thus, depression does not appear to strongly affect reappraisal-based modulation of self-reported negative experience.

This evidence of effective reappraisal in the MDD group is encouraging and reminiscent of the efficacy of cognitive therapy for depression (Beck et al., 1979; Gloaguen et al., 1998). However, this study was not designed with clinical practice in mind, and the “distancing” technique used in the photo condition differs substantially from the methods used to challenge automatic negative thinking in cognitive therapy (e.g., hypothesis-testing). Building strong links between research on reappraisal and clinical practice thus remains an important goal.
This implies that stronger deactivation from baseline should be seen when reappraisal is used to de-emphasize self-referential processing. This hypothesis was not confirmed, as rACC deactivation was not stronger in the negative/photo vs. the negative/look condition. This reflects the limitations of the photo condition rather than a problem with conceptualization of DMN function, as no region showed differential activation on negative/look vs. negative/photo trials. These results raise an important caveat: although the real and photo cues modulated valence ratings, only the real cue reliably influenced brain activation. Thus, the fMRI
This pattern of reappraisal results—stronger effects in the “increase” vs. the “decrease” condition—has been observed in studies using fMRI (Urry et al., 2006) and eyeblink startle responses (Dillon and LaBar, 2005), but it may appear to contrast with reports of increased lateral PFC activation and reduced amygdala activation when reappraisal is used to decrease negative emotional experience (e.g., Ochsner et al., 2004). However, even these studies suggest that the “distancing” technique used in the photo condition does not powerfully affect brain activation. For example, Ochsner et al. (2004) reported that bilateral PFC regions (along with many other regions) were more strongly activated during situation-focused vs. self-focused reappraisal when decreasing negative emotion. By contrast, only small sectors in the cingulate and left parietal cortex showed stronger activation during self-focused reappraisal. Similarly, Kross et al. (2009) elicited negative emotion in healthy volunteers and instructed them to feel the negative emotion as normal or reduce it, either by analyzing its causes or using a mindfulness-based accept ance strategy. Both the “analyze” and “accept” strategies reduced activation in any brain region than the “feel” condition. The current study found the same pattern: the negative/photo condition reduced negative emotional experience, but the negative/real condition had a stronger effect on brain activity.

Intriguingly, cerebellum activation emerged as positively correlated with shifts in subjective experience (Fig. 4), consistent with a growing appreciation of cerebellar contributions to emotional responses. Although effects of cerebellar lesions on emotional responding are often subtle, they can lead to disinhibition and flat affect (Levisohn et al., 2000; Schmahmann and Sherman, 1998). Moreover, a transcranial magnetic stimulation study linked cerebellar inhibition to increased negative mood after a reappraisal task (Schutter and van Honk, 2009). The present study extends these findings by indicating that cerebellar activation is related to modulation of subjective experience during reappraisal.

4.4. Limitations and considerations for future studies

This study is limited by the small MDD sample and by the fact that the photo cue did not reliably modulate brain activation, restricting inferences about neural systems involved in the reduction of negative emotion. Future studies should consider taking four steps to address these limitations. First, larger samples of more severely depressed participants are needed. Second, it would be valuable to replace the broadly negative stimulus set used here with depressogenic stimuli organized around themes of sadness and hopelessness (Watkins et al., 1992). Third, it may be useful to induce negative mood prior to the reappraisal task, as this impairs emotion regulation in healthy volunteers (Berna et al., 2010) and may be especially potent in depressed adults. Similarly, presenting reappraisal cues mid-way through emotional stimulus presentation, rather than before, may increase task difficulty for depressed participants. Fourth, situation-focused reappraisal may be better suited for probing emotion regulation in depression than self-focused reappraisal. As noted earlier, situation-focused reappraisal more consistently activates lateral PFC regions that may be hypofunctional in depression. Moreover, situation-focused reappraisal likely requires greater suppression of DMN activity, which may be impaired in depression (Anticevic et al., 2012). Indeed, one study of situation-focused reappraisal already reported weak DMN suppression in depressed adults (Sheline et al., 2009).

4.5. Conclusion

This study suggests that unmedicated, depressed adults can reappraise negative emotions if provided with clear instructions. However, severe depression was associated with weak reappraisal effects in the DLPFC, amygdala, and cerebellum, suggesting that group differences in these regions may be evident with larger, more severely depressed samples.

Acknowledgments

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pnsy.2013.01.001.

References


Craik and Tulving, 1975. When participants use situation-focused reappraisal to reinterpret negative stimuli in more favorable ways, stronger left VLPFC activation is seen than when they use self-focused reappraisal (Ochsner et al., 2004). This is noteworthy because an fMRI study found a positive effect of reappraisal on memory after a 2-week delay that was linked to left VLPFC and hippocampal activation (Hayes et al., 2010). Thus, reappraisal may affect memory via left VLPFC activation, which was not observed here.
Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression

Daniel Gerard Dillon and Diego Andrea Pizzagalli

Supplementary Material

This material supplements but does not replace the content of the peer-reviewed paper published in Psychiatry Research: Neuroimaging.

S1. Verbatim reappraisal cue instructions

S1.1. “Real” cue

When you see a picture after the cue word REAL, your job is to imagine that the scene in the picture is real, that it is happening now, and that you are in the middle of it. Try your best to mentally ‘get into’ the scene. Imagine how things would look if you were in the scene. Imagine things moving as they would in real-life. Imagine what would you hear; try to mentally hear any sounds that would be present in the scene. Imagine what would you touch—or what would touch you—in the scene. Try to mentally feel any touches or sensations you would have. Imagine what would you smell. Try to mentally smell any odors elicited by the scene. To summarize, when you see a picture after the word REAL, your job is to get into the scene by imagining that it is real, that it is happening now, and that you are in it. As you view the scene as though you were in it, imagine that things are moving, making sounds, can touch you or be touched, and are associated with odors as in real-life.

S1.2. “Photo” cue
When you see a picture after the cue word PHOTO, your job is to imagine that the scene is a ‘staged’ or ‘posed’ photograph that you are viewing from a distance, that it happened in the past, and that it does not involve you. Try your best to mentally ‘keep your distance’ from the scene. Imagine that it is an old photograph: you are looking at it from a distance. Imagine that nothing is moving in this old photograph. Because this is an old photograph, imagine that there is nothing to hear: this scene does not make any sound. Imagine that there is nothing to touch and nothing can touch you in the scene. Imagine that this photograph does not have any smell. To summarize, when you see a picture after the word PHOTO, your job is to stay out of the scene by imagining that it is a staged or posed photograph, that it happened in the past, and that it does not involve you. As you imagine viewing the scene from a distanced perspective, imagine that everything is still, nothing makes sound, nothing can touch you or be touched by you, and nothing in the scene has any odor.

S1.3. “Look” cue
When you see a picture after the word LOOK, your job is just to look at the scene and pay attention to it. Let any reactions you have to the picture unfold naturally. To summarize, when you see a picture after the word LOOK, your job is simply to pay attention to the scene as you normally would—in other words, just look at it.

S2. Emotional memory results in all participants
Repeating the emotional memory analysis in all participants with memory data (22 controls, 12 depressed) yielded identical results. There was a Confidence x Picture Type interaction, $F(1, 30) = 8.20, p = 0.008$, that did not vary by Group ($Group \times Confidence \times$ Picture Type interaction).
Picture Type, $F < 1$). Accuracy was better for negative vs. neutral pictures remembered with high confidence, $t(33) = 3.18, p = 0.003$, but not low confidence, $t(33) < 1, p = 0.46$.

S3. Functional connectivity: psychophysiological interaction analyses

In order to determine whether there were group differences in functional connectivity during reappraisal, psychophysiological interaction (PPI) analyses were conducted. The time-course of activation was extracted from 8 mm spheres centered on peak activations in the rostral anterior cingulate (-12, 40, 2; $Z = 5.16$), left DLPFC (-18, 30, 50; $Z = 5.15$), and right amygdala (26, -6, -22; $Z = 3.64$) that emerged when the [negative/real – negative/photo] contrast was computed across groups. This contrast was used for the PPI analysis because it revealed strong activation in all the regions that showed main effects of Reappraisal Condition, and because directly contrasting the negative/real vs. negative/photo conditions should reveal brain regions that show maximal changes in activation as a consequence of reappraisal. Because there were no group differences in this contrast, the data were collapsed across the groups in order to select unbiased ROIs. The time-series data from each ROI were then entered into PPI analyses designed to highlight brain regions whose connectivity with the ROIs differed across the negative/real vs. negative/photo conditions. This analysis did not reveal statistically reliable results, in either group or when between-group comparisons were computed.

We carefully inspected the output of each PPI analysis, and found that the data were highly variable across participants. Depending on the analysis, different participants showed strong activity in different brain regions (including the medial temporal lobes, the ventral visual stream, and the PFC), while others showed weaker activations overall. We could not detect any patterns that reliably differentiated the depressed versus controls participants. We speculate that this variability reflects the fact that, although our version of the reappraisal task is well-
controlled relative to many prior versions (i.e., participants were given a single strategy to use and experimenter demand was limited by emphasizing imagery rather than emotion regulation), the task still permits variation in exactly how reappraisal is achieved. Gaining a stronger understanding of individual differences in the networks that support reappraisal, in terms of both connectivity and psychopathology, thus remains an important goal for future work.