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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 unmedicated Major Depressive Disorder (MDD). Twenty-four controls and 12 depressed adults 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 two 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.

Keywords

emotion regulation; major depressive disorder; default mode network; memory; fMRI

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

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[1]See Supplementary Material for verbatim instructions.

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 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 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 (Erk 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 reported 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 (Erk 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., 2004; 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—Twenty-seven controls and 14 depressed individuals participated. 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 two weeks later. Consent was obtained, consistent with an IRB-approved protocol. Participants were paid (MRI: $25/hour; memory: $10/hour) 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* x *Set* x *Picture Type* ANOVAs revealed only effects of *Picture Type* for valence (negative: 2.62±0.60; neutral: 5.55±0.47; $p = 0.001$) and arousal (negative: 6.96±0.31; neutral: 4.14±0.80; $p = 0.006$). 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 past 2 weeks for benzodiazepines, 6 weeks for SSRIs, 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 (one month or less, $n = 2$; two years or less, $n = 2$; unclear, $n = 1$). Controls reported no current or past Axis I diagnosis. Participants were 18 - 64 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 = negative, 3 = neutral, 5 = positive). 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 intensity 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[1].

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.

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 mm^3 voxels; 144 slices; TR = 2.2 s; TE1/2/3/4 = 1.54/3.36/5.18/ 7.01 ms; flip angle = 7 degrees), and T2*-weighted images sensitive to blood oxygen level-dependent contrast, acquired during the reappraisal task (3.0 mm^3 voxels; 46 slices; TR = 3 s; TE = 30 ms; flip angle = 85 degrees; transverse acquisition).

2.1.8. Recognition memory test—The 144 "old" pictures from the MRI session plus 144 "new" distracters 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-GDD], Anhedonic Depression [MASQ-AD], General Distress: Anxiety [MASQ-GDA], and Anxious Arousal [MASQ-AA]), the RRS (RRS-Brooding, 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-Brooding, RRS-Reflection, or ERQ-R scores.

2.2.3. Recognition memory: emotion analysis—A *Group* x *Gender* x *Confidence* (high, low) 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., 2005; Dougal 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 *Gender* x *Cue* 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: 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); segmentation of brain tissue (Smith, 2002); coregistration; normalization to MNI152 templates; re-sampling to 2 mm^3 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/*photo* trials in regions implicated in emotional arousal (amygdala; Ochnser 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 regressions—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., 2010a; 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 rating 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 disorder, and specific phobia), and another met criteria for binge eating disorder.

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 (Figure 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 (Figure 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 Figure 2 and Table 2, the main effect of *Reappraisal Condition* revealed activation in the left DLPFC, 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* x *Reappraisal Condition* ANOVAs. For the right amygdala, activation was simply extracted from the 5 significant voxels.

The main effect of *Reappraisal Condition* was significant in each region ($F(2, 68)$ values > 5.77, ps < .01). As depicted in Figure 2 (bar graphs), in every ROI activation was stronger on negative/*real* vs. negative/*look* trials ($t(35)$ values > 2.31, ps < 0.03) and negative/*photo* trials ($t(35)$ values > 4.20, ps < 0.001). Activation did not differ between negative/*look* and negative/*photo* trials in any region ($t(35)$ values < 1.52, ps > 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* x *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* x *Reappraisal Condition* interaction, but none were found. Psychophysiological interaction analyses were conducted to determine if functional connectivity of the right amygdala, left DLPFC, 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 DLPFC, right amygdala, and right cerebellum (Figure 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/*real* – negative/*photo*] contrast against [negative/*photo* – negative/*real*] valence rating scores revealed a correlation in the left cerebellum (Figure 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 (Figure 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 may wish to take additional steps to maximize the paradigm's sensitivity to depression (see section *4.4*).

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 (Figure 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.

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

Across groups, reappraisal modulated activation in the left DLPFC, left parietal cortex, rACC/medial PFC, and right amygdala. Left DLPFC 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 DLPFC—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 Figure 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).

The rACC data in Figure 3 highlight the link between the DMN and reappraisal. Although DMN regions can show positive activations, the network was originally recognized because midline cortical regions showed consistent deactivation during task-based stimulus processing relative to passive control conditions (Raichle et al., 2001). In the current study, the rACC showed this response profile: all conditions yielded deactivations vs. fixation. Furthermore, predicting the order of reappraisal condition effects in this region is straightforward based on the DMN literature. DMN activation supports self-focused mentation, and when external stimuli are processed, this inward-directed mentation is reduced, leading to deactivation relative to baseline. Therefore, when reappraisal is used to increase the personal relevance of stimuli, rACC deactivation should be reduced because self-referential processing is ongoing. This is evident in Figure 3, as the negative/*real* condition yielded the weakest rACC deactivation.

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 results only support inferences about emotional flexibility and amplification of negative emotional experience.

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 and colleagues (2004) reported that when reappraisal was used to decrease negative emotion, bilateral PFC regions (along with many other regions) were more strongly activated during situation-focused vs. self-focused reappraisal. 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 acceptance strategy. Both the “analyze” and “accept” strategies reduced negative emotional experience,

but neither elicited stronger 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 (Figure 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.

4.3. Memory

As expected, memory accuracy was higher for confidently remembered negative vs. neutral pictures, and confidently remembered negative pictures elicited stronger right amygdala activation at encoding than negative misses. However, depression did not affect these results, and the amygdala result only emerged only when all participants were considered. This is consistent with a meta-analysis indicating that depression leaves memory for negative material intact (Burt et al., 1995). The memory advantage for negative vs. neutral material was not stronger in depressed participants vs. controls.

We found no effects of reappraisal on memory. This might reflect the 2-week delay following encoding, as positive effects of reappraisal on memory have been reported at delays of one hour or less (Dillon et al., 2007; Richards and Gross, 2000), but not one year (Erk et al., 2010b). Another critical factor concerns the reappraisal strategy and activation of the left ventrolateral PFC (VLPFC). Deep processing of verbal stimuli elicits left VLPFC activation (Fletcher et al., 2003; Otten et al., 2001) and supports explicit memory (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 two weeks 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.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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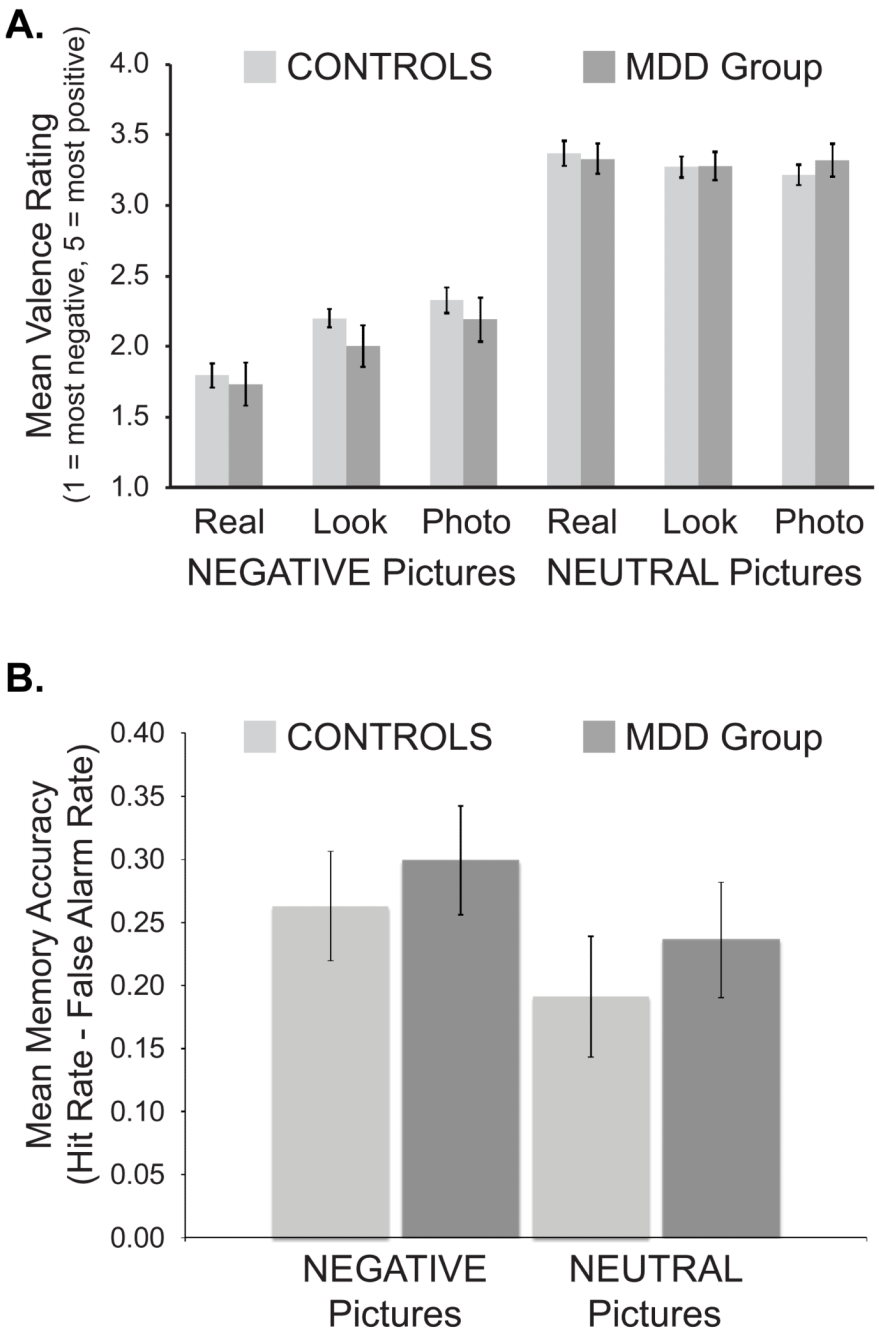

Figure 1.

Behavioral results. (A) *Valence ratings*. There was a *Cue* x *Picture Type* interaction, $F(2, 62) = 19.66$, $p < 0.001$, that did not vary by *Group* (*Group* x *Cue* x *Picture Type*, $F(2, 62) = 1.18$, $p = 0.32$). A *Cue* effect was seen on negative trials, $F(2, 62) = 22.79$, $p < 0.001$, but not neutral trials ($F(2, 62) = 2.60$, $p = 0.08$). Valence ratings were lowest on negative/*real* trials, intermediate on negative/*look* trials, and highest on negative/*photo* trials ($t(34)$ values > 2.69, ps < 0.02). (B) Memory accuracy for pictures remembered with high confidence. Accuracy was characterized by a *Confidence* x *Picture Type* interaction, $F(1, 24) = 8.71$, $p = 0.007$, but this did not interact with *Group* (*Group* x *Confidence x Picture Type*, $F < 1$). Accuracy was higher for negative (0.28±0.16) vs. neutral (0.21±0.18) pictures recognized

with high confidence, $t(27) = 3.57$, $p = 0.001$, but not low confidence, $t(27) < 1$, $p = 0.60$ (data not shown). Error bars denote standard error of the mean.

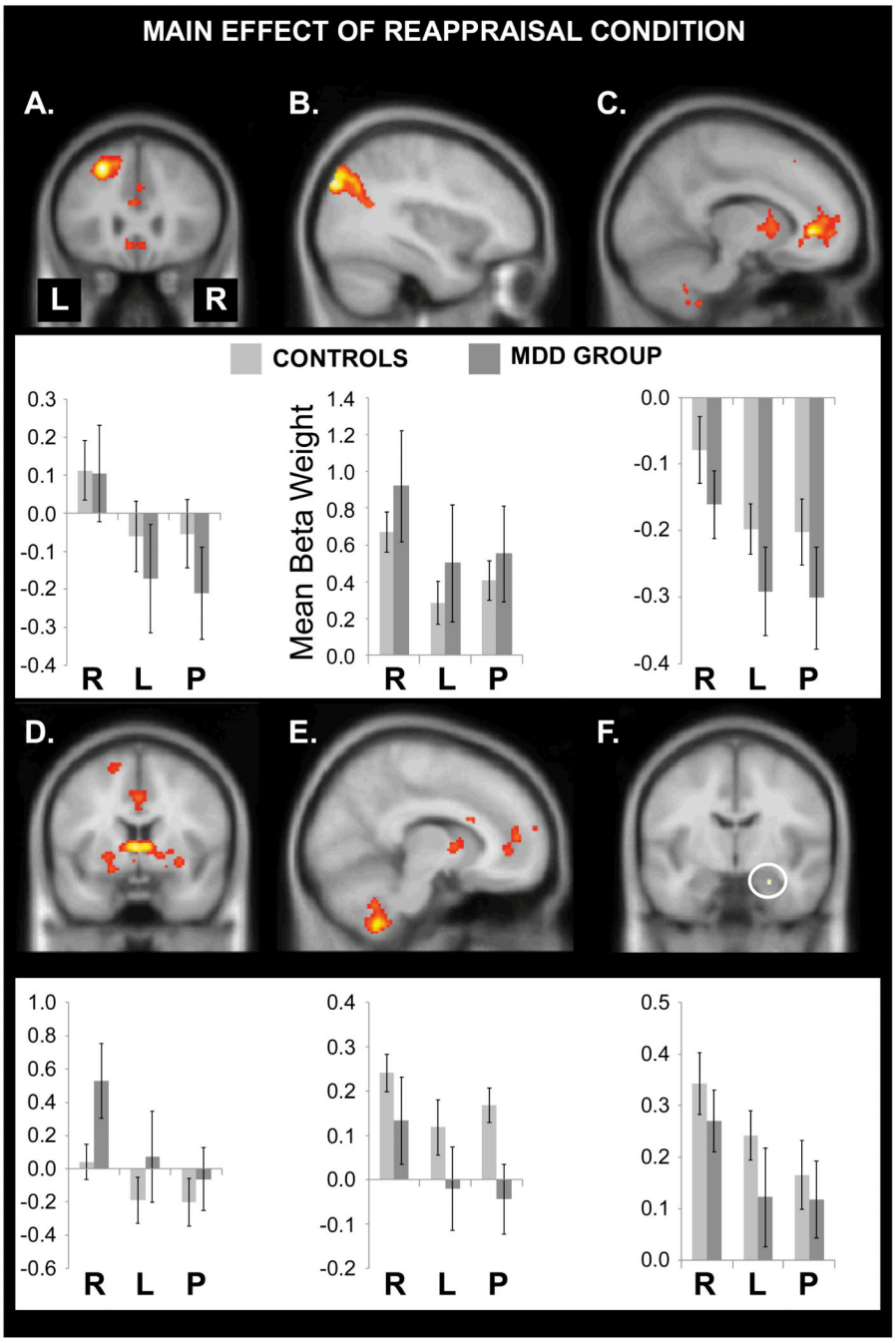

Figure 2.

Main effects of *Reappraisal Condition*. Reappraisal modulated brain activation elicited by negative pictures in (A) left DLPFC, (B) left parietal cortex, (C) rostral anterior cingulate extending into medial PFC, (D) anteroventral caudate, (E) the cerebellum, and (F) the right amygdala. The *y*-axes indicate the size of the mean beta weights for controls (light gray bars) and depressed participants (dark gray bars); the *x*-axes indicate the reappraisal condition (R = *real*, L = *look*, P = *photo*). Error bars show the standard error of the mean. No significant group differences were observed.

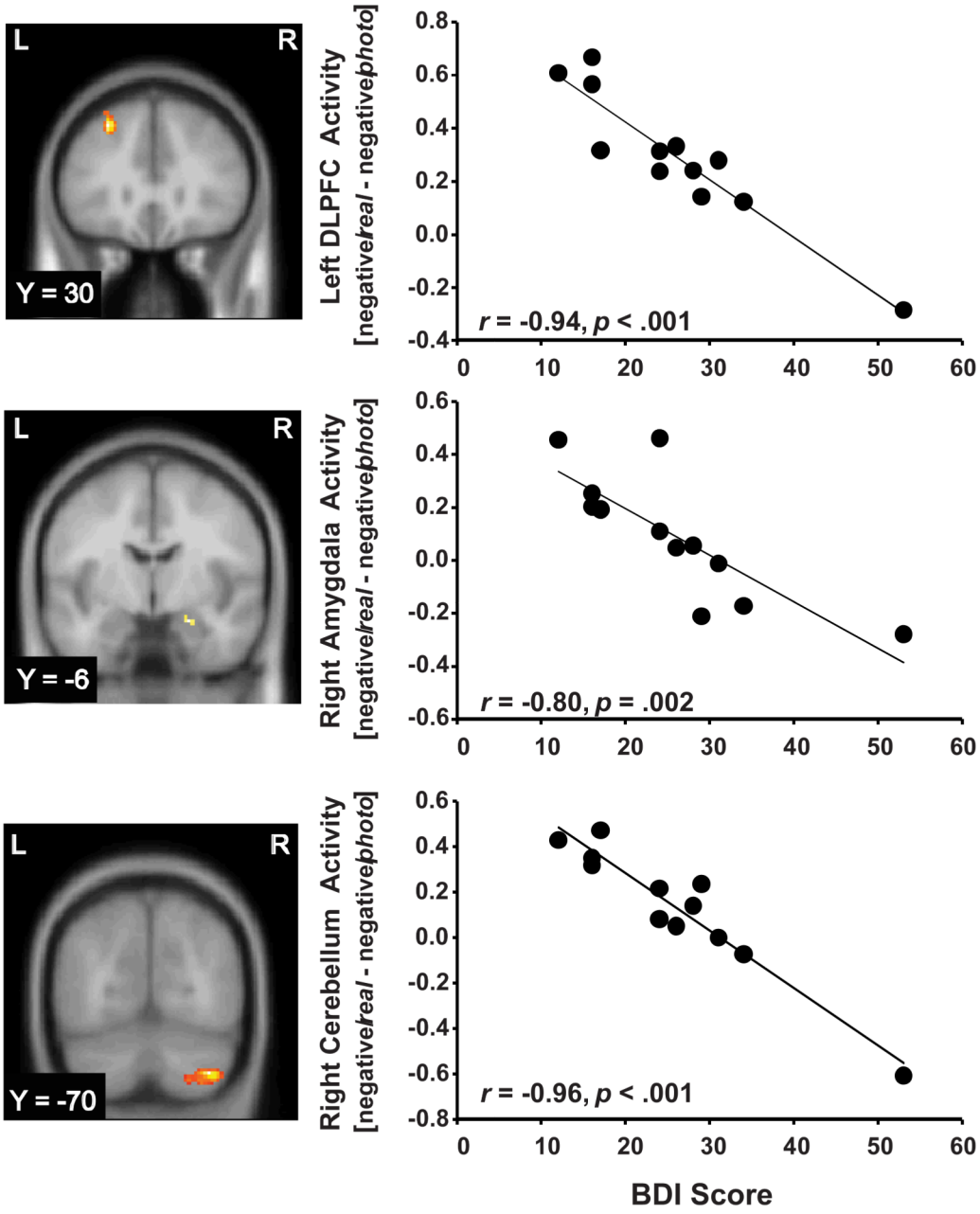

Figure 3.

Negative correlations in the MDD group between BDI scores and activity in the left DLPFC (peak voxel: −28, 30, 46; $Z = 4.50$; 306 voxels; cluster $p = 0.001$; $r(10) = -0.94$, $p < 0.001$), right amygdala (peak voxel: 22, −6, −18; $Z = 3.15$; 7 voxels; cluster $p = 0.051$; $r(10) = -0.80$, $p = 0.002$), and right cerebellum (peak voxel: 36, −70, −44; $Z = 4.86$; 226 voxels; cluster $p = 0.011$; $r(10) = -0.96$ $p < 0.001$) in the [negative/*real* – negative/*photo*] contrast. Excluding the subject with the highest BDI score did not substantially weaken the correlations (DLPFC: $r(9) = -0.87$, $p = 0.001$; amygdala: $r(9) = -0.78$, $p = 0.005$; cerebellum: $r(9) = -0.88$, $p = 0.001$).

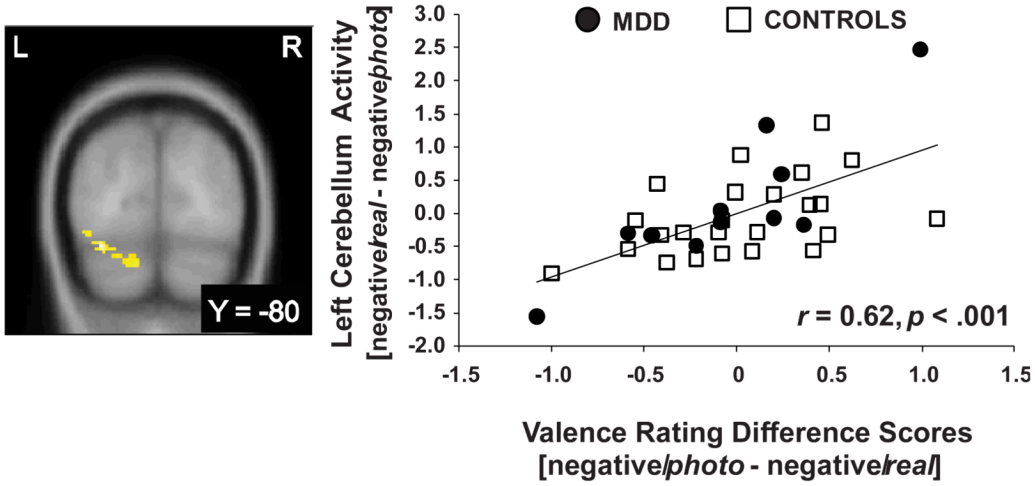

Figure 4.

Positive correlation between left cerebellum activity in the [negative/*real* – negative/*photo*] contrast and [negative/*photo* – negative/*real*] valence rating difference scores, across groups (peak voxel: −34, −80, −20; $Z = 3.98$, 363 voxels; cluster $p = 0.009$; $r(33) = 0.62$, $p < 0.001$). Increased brain activation is positively correlated with a stronger shift in subjective experience. Both brain activation and ratings scores are mean centered.

Table 1

Demographics and Self-Report Data

Variable	Controls	Depressed	t / χ^2	p
	MRI Session			
Number of MDEs	--	2.33 (1.56)	--	--
Age at first MDE	--	18.58 (7.65)	--	--
Gender	12 f, 12 m	7 f, 5 m	0.22	0.637
Age (years)	34.42 (14.93)	31.00 (8.20)	0.89	0.382
Education (years)	15.88 (1.51)	15.33 (2.06)	0.90	0.376
BDI-II (fMRI session)	1.63 (2.34)	25.83 (10.94)	−7.58	< 0.001
BDI-II (memory session) *	1.18 (2.65)	21.42 (10.10)	−6.81	< 0.001
MASQ-GDD	13.29 (2.05)	37.33 (10.24)	−8.06	< 0.001
MASQ-AD	47.38 (12.24)	83.08 (8.97)	−8.95	< 0.001
MASQ-GDA	13.17 (2.06)	25.00 (5.31)	−7.45	< 0.001
MASQ-AA	18.38 (1.58)	27.33 (10.88)	−2.84	0.016
RRS-Brooding	7.42 (2.08)	12.58 (3.53)	−5.54	< 0.001
RRS-Depression	17.67 (5.06)	32.25 (6.52)	−7.40	< 0.001
RRS-Reflection	9.46 (4.01)	11.33 (3.60)	−1.37	0.181
ERQ-Reappraisal	30.96 (4.36)	27.83 (8.74)	1.17	0.262
ERQ-Suppression	12.13 (4.03)	14.67 (4.58)	−1.71	0.097
VVIQ	29.25 (9.86)	33.50 (9.89)	−1.22	0.232
WTAR-standardized score †	117.00 (7.17)	102.30 (13.83)	2.54	0.028

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

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

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

Table 2

Effects of Reappraisal and Group on fMRI Activation Elicited by Negative Pictures

Region	*x*	*y*	*z*	Voxels	Z-score	FWE-corrected p-value
Main Effect of Reappraisal Condition						
Left middle frontal gyrus	−26	26	46	821	5.71	0.001
Left lateral occipital cortex (superior division)	−36	−84	36	1742	5.42	0.004
Rostral anterior cingulate	−12	38	0	2220	5.34	0.005
Caudate (anteroventral)	−2	4	4	856	5.33	0.005
Right cerebellum	10	−52	−54	545	4.78	0.067
Right amygdala*	24	−8	−22	5	3.36	0.023
Main Effect of Group						
No significant activations.						
Group x Reappraisal Condition Interaction						
No significant activations.						

Note. *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.