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Neural predictors and effects of cognitive behavioral therapy for depression: the role of emotional reactivity and regulation

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Abstract

Background. Cognitive behavioral therapy (CBT) is an effective treatment for many patients suffering from major depressive disorder (MDD), but predictors of treatment outcome are lacking, and little is known about its neural mechanisms. We recently identified longitudinal changes in neural correlates of conscious emotion regulation that scaled with clinical responses to CBT for MDD, using a negative autobiographical memory-based task.

Methods. We now examine the neural correlates of emotional reactivity and emotion regulation during viewing of emotionally salient images as predictors of treatment outcome with CBT for MDD, and the relationship between longitudinal change in functional magnetic resonance imaging (fMRI) responses and clinical outcomes. Thirty-two participants with current MDD underwent baseline MRI scanning followed by 14 sessions of CBT. The fMRI task measured emotional reactivity and emotion regulation on separate trials using standardized images from the International Affective Pictures System. Twenty-one participants completed post-treatment scanning. Last observation carried forward was used to estimate clinical outcome for non-completers.

Results. Pre-treatment emotional reactivity Blood Oxygen Level-Dependent (BOLD) signal within hippocampus including CA1 predicted worse treatment outcome. In contrast, better treatment outcome was associated with increased down-regulation of BOLD activity during emotion regulation from time 1 to time 2 in precuneus, occipital cortex, and middle frontal gyrus.

Conclusions. CBT may modulate the neural circuitry of emotion regulation. The neural correlates of emotional reactivity may be more strongly predictive of CBT outcome. The finding that treatment outcome was predicted by BOLD signal in CA1 may suggest overgeneralized memory as a negative prognostic factor in CBT outcome.

Background

Major depressive disorder (MDD) is a debilitating psychiatric illness, with significant health care costs and social implications (Gotlib and Hammen, 2009), affecting an estimated 300 million people worldwide. The treatment of MDD is hampered by our inability to effectively match existing treatments to patients most likely to benefit from them. While some clinical trials find comparable efficacy of cognitive behavioral therapy (CBT) and antidepressant medication in the treatment of MDD (Gloaguen *et al*., 1998; DeRubeis *et al*., 2008), a substantial proportion of patients treated with either modality fail to achieve remission (Hollon *et al*., 2002). The discovery of clinically useful moderators/predictors of treatment outcome is likely to improve clinical outcomes, as they may reduce the trial-and-error involved in treatment selection.

Depressed patients exhibit an attention bias toward, and increased memory for, negative stimuli (Leppanen, 2006). Using a negative affective priming task, Joorman *et al*. found that differences in the use of emotion regulation strategies play an important role in depression, and that deficits in cognitive control in depression are related to the use of maladaptive emotion regulation strategies (Gotlib and Joormann, 2010). Emotion regulation capacity is of particular relevance to MDD and its treatment given the significant role of psychosocial stress as a risk factor for the development of a major depressive episode (MDE) (Kendler *et al*., 1999). CBT for depression targets distorted patterns of negative thinking with an explicit goal of enhancing emotion regulation (Beck, 1995).

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Functional magnetic resonance imaging (fMRI) studies have revealed abnormalities in the neural bases of both emotional reactivity and emotion regulation in MDD. For example, patients with MDD exhibit greater amygdala reactivity during emotion tasks than healthy volunteers in some studies (Siegle *et al.*, 2002; Drevets, 2003). One study found inverse-connectivity between ventromedial prefrontal cortex (vmPFC) and amygdala during reappraisal of negative stimuli in MDD, in contrast to the positive association observed between those regions in healthy volunteers (Johnstone *et al.*, 2007). Other studies have found greater vmPFC activity and less amygdala downregulation during reappraisal among depressed adolescents and young adults (Stephanou *et al.*, 2017), and a lack of sustained nucleus accumbens activity during positive emotional reappraisal in MDD (Heller *et al.*, 2009). A recent review identified decreased engagement of dorsolateral (dl) and ventrolateral (vl) PFC and enhanced amygdala activity during cognitive reappraisal in mood disorders (Zilverstand *et al.*, 2017).

fMRI studies of CBT treatment for depression have largely examined neural responses related to emotional reactivity as opposed to emotion regulation. Several studies have found pre-treatment neural responses to emotional stimuli to be predictive of treatment outcome with CBT for MDD. Specifically, lower baseline activity in anterior cingulate (Siegle *et al.*, 2006; Fu *et al.*, 2008; Costafreda *et al.*, 2009) and greater baseline activity in PFC (Ritchey *et al.*, 2011) and amygdala (Siegle *et al.*, 2006) in response to negative stimuli have been associated with better CBT treatment outcome. In general, individuals with depression had better treatment outcomes with CBT when they had less impairment in the neural networks involved in emotional processing (Fu *et al.*, 2008; Costafreda *et al.*, 2009).

Given some evidence of emotion regulation deficits in depression and the focus of CBT for depression on enhancing emotion regulation capacity, we recently investigated the relationship between the neural correlates of emotion regulation and CBT outcome in MDD using a conscious emotion regulation task involving recall of negative autobiographical memories (Rubin-Falcone *et al.*, 2017). We found that better CBT treatment outcome was associated with greater longitudinal Blood Oxygen Level-Dependent (BOLD) signal decreases during emotion regulation in mPFC, lingual gyrus and subgenual anterior cingulate (sgACC). One limitation of that paradigm is that the emotional stimuli utilized could not be standardized across participants. To complement this approach, we acquired data using an emotion regulation task involving standardized visual emotional stimuli from the International Affective Pictures System (IAPS), variants of which have been used multiple times in prior work [for a recent meta-analysis, see Buhle *et al.* (2014)]. This task was designed to examine two critical and distinct affective processes: reactivity to negative as opposed to neutral images, and effortful emotion regulation of responses to negative images using psychological distancing, a reappraisal tactic whereby stimuli are appraised in a rational, objective manner. Imaging was repeated post-treatment to identify longitudinal changes in affective processing related to treatment effects. A small cohort of healthy volunteers was also scanned before and after a 12-week waiting period.

We hypothesized that greater pre-treatment BOLD contrasts during emotion regulation, especially in regions associated with reappraisal (Buhle *et al.*, 2014), would predict better treatment outcome. Additionally, we hypothesized that clinical improvement would be associated with increases in emotion-regulation BOLD contrasts when re-assessed at post-treatment. Regarding emotional reactivity (negative *v.* neutral contrast), prior work supports the hypotheses that lower anterior cingulate responses and higher amygdala responses to negative stimuli at baseline would predict better treatment outcome (Siegle *et al.*, 2006; Fu *et al.*, 2008; Costafreda *et al.*, 2009) . Given that increased reactivity in amygdala is associated with MDD (Siegle *et al.*, 2002; Drevets, 2003), we hypothesized that amygdala reactivity would decrease following CBT, and that the magnitude of longitudinal reductions in amygdala reactivity would correlate with clinical improvement. Secondary hypotheses included that we would observe greater emotional reactivity and emotion regulation activity BOLD signals within the amygdala in the MDD group compared to healthy volunteers. Also, given emotion regulation deficits observed in MDD behaviorally (Gotlib and Joormann, 2010), we expected less emotion regulation activity BOLD signal within canonical emotion regulation-related regions dl- and vlPFC (Frith *et al.*, 1991; Golkar *et al.*, 2012) in the MDD compared to healthy volunteers. In order to thoroughly examine all available data, and to ensure that we were not limited by the selection of regions of interest (ROIs), analyses were conducted at both the ROI- and whole-brain voxel levels.

Methods

Sample

Subjects gave written informed consent. Participants were aged 18–60, MDD participants had a Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnosis of MDD as assessed using the Structured Clinical Interview (SCID) for DSM-IV (First *et al.*, 1995) and a 17-item Hamilton Rating Scale for Depression score ⩾16 (Hamilton, 1960). All MDD participants were unmedicated at baseline. First episode as well recurrent depression was allowed. Other current or past major psychiatric disorders, including bipolar disorder and psychotic disorders, were excluded, although anxiety and personality disorders were allowed. Prior CBT was not allowed, but contraindication to CBT as a primary treatment for depression, including prior non-response to an adequate trial of CBT, active psychosis, or severe suicidal ideation including a plan, was allowed. Healthy volunteers had a lack of current or past DSM-IV Axis 1 diagnosis as assessed by the SCID. Detailed exclusion and inclusion criteria can be found in our previous study in this cohort (Rubin-Falcone *et al.*, 2017).

Clinical procedures and treatment

The Beck Depression Inventory (BDI) (Beck *et al.*, 1961) and Hamilton Rating Scale for Depression 17-item score (HRDS-17) (Hamilton, 1960) were used as measures of pre- and post-treatment depression severity. Suicidal ideation was measured at baseline with the Scale for Suicidal Ideation (Beck *et al.*, 1979). After baseline MRI scanning, 14 sessions of CBT for depression were administered over 12 weeks according to a treatment manual (Beck, 1979). Core techniques employed included cognitive-restructuring through the use of dysfunctional thought records; behavioral activation following initial activity monitoring approaches; behavioral experiments as a means to examine negative automatic predictions; and some work to identify and modify more deeply held patterns of negative thinking about oneself, one's life, and one's future ('intermediate beliefs' and 'core beliefs'). Forty-five-minute sessions occurred as close as possible

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to twice-weekly for 2 weeks, then weekly thereafter. Study therapists were M.D.- or Ph.D.-level therapists with extensive training in CBT. Additional details regarding clinical procedures can be found in our previous study in this cohort (Rubin-Falcone *et al.*, 2017).

Details of participant enrollment and flow are described in Fig. 1. For MDD participants who discontinued CBT monotherapy prior to the conclusion of treatment ($n = 9$), last observation carried forward (LOCF) was applied, using the last BDI and HDRS-17 measurements before participants either discontinued treatment prior to session 14 ($n = 5$) or before receiving pharmacotherapy as an augmentation to CBT during the course of standardized CBT due to clinical worsening ($n = 4$). Two participants who had medication added completed time 2 MRI scans prior to beginning pharmacotherapy, with the last BDI and HDRS-17 measured prior to adding medication used as the measure of post-treatment depression severity. All other subjects who discontinued CBT monotherapy did not complete time 2 scans. One subject was on an ineffective antidepressant medication at the time of enrollment and underwent a 3-week washout prior to baseline scanning and treatment.

Image acquisition

MRI scans were acquired on two 3T SignaHDx scanners (General Electric Medical Systems, Milwaukee, WI) at The New York State Psychiatric Institute and at Cornell University using the same 8-channel head coil. As described below, scan site was included as a covariate in all analyses. T1-weighted structural scans were acquired for functional image co-registration. For functional scanning during the emotional pictures task, an Echo planar imaging (EPI) acquisition was obtained for each of three runs. Pulse sequence parameters for both acquisition types are included in Appendix 1.

fMRI paradigm

Seventy-two negative images and 36 neutral images were selected on the basis of normative ratings from the IAPS (Lang *et al.*, 1993). Fifteen additional negative images of similar valence and arousal were used during training.

During a training session, participants were instructed that they would see a series of photographs, each preceded by an instruction cue word presented in the center of the screen: either LOOK or DISTANCE. For LOOK trials, participants were asked to look at and respond naturally to the upcoming image. For DISTANCE trials, participants were instructed to consider the image as a detached, objective, impartial observer, or to imagine that the pictured events occurred far away or a long time ago, as used in prior studies (Denny *et al.*, 2015*b*; Silvers *et al.*, 2016). In the presence of an experimenter, participants were asked to self-generate appropriate distancing strategies in response to two sample distancing trials. Participants then completed a fixed-timing set of practice trials with three trials of each of the three task conditions: LOOK paired with a neutral image ('Look Neutral'), LOOK paired with a negative image ('Look Negative'), and DISTANCE paired with a negative image ('Distance Negative'). Consistent with prior work (Ochsner *et al.*, 2004*a*; Denny and Ochsner, 2014; Denny *et al.*, 2015*b*), we did not include a 'distance neutral' condition, as this condition is difficult for participants to implement when an instruction to regulate is paired with neutral images that evoke minimal baseline emotional responses.

Once in the scanner, participants completed a computerized image-based reappraisal task similar to ones described previously (Ochsner *et al.*, 2002, 2004; Denny *et al.*, 2015*a*, 2015*b*; Silvers *et al.*, 2016). For each trial, the instruction cue was presented for 2 s, followed by presentation of an image for 8 s, a jittered intra-trial fixation interval of between 2 and 4 s (average = 3 s), a negative affect rating period of 4 s [on a scale of 1 (weak) to 4 (strong)], and finally a jittered inter-trial fixation interval of between 2 and 4 s (average = 3 s). During image presentation, participants were instructed to keep their eyes on the image for the entire time that it was on the screen.

At each of two sessions (i.e. pre- and post-CBT), participants completed 54 total trials divided evenly into three functional runs, with six trials per condition per run. Stimuli were matched for normative valence and arousal ratings across sessions. Further, across participants, stimuli were counterbalanced across sessions, and negative images were counterbalanced in their assignment to Look Negative and Distance Negative trials. Within a session, run order and order of trials within a run were randomized. Images presented at the time 2 scan were entirely non-overlapping with those at time 1.

Image processing

Pre-processing

The fMRI task data were processed using FEAT (FMRI Expert Analysis Tool) Version 5.98, a part of FSL (FMRIB's Software Library, https://www.fmrib.ox.ac.uk/fsl) (Woolrich *et al.*, 2009). Standard pre-processing motion outlier removal and non-linear co-registration was performed; a detailed summary of pre-processing methods can be found in Appendix 1.

fMRI statistical analysis

We used a general linear model (GLM) to identify brain activity associated with the three trial types: Look Negative, Distance Negative, and Look Neutral. Modeled regressors of no interest included the cue phase prior to each image presentation ('LOOK' and 'DISTANCE' modeled separately) as well as the valence rating epochs. The GLM was convolved with the canonical double gamma hemodynamic response function for all stimulus conditions.

The three runs were combined using a Fixed Effects GLM approach to consider the average across all runs. Three contrasts of interest were examined: areas where BOLD signal during Look Negative trials was greater compared with BOLD signal during Look Neutral trials (henceforth referred to as the emotional reactivity contrast); areas where BOLD signal during Distance Negative trials was higher compared to BOLD signal during Look Negative trials (henceforth referred to as emotion regulation-related activity); and the inverse of this contrast (henceforth referred to as emotion regulation-related deactivation). *F*-tests were performed to identify clusters in which BOLD signal during the two relevant trial types differed for each contrast.

The main effect of each contrast at time 1 was examined in each group. To identify brain regions where activation during each contrast differed between depressed participants and healthy volunteers, *t* tests were performed between the contrast images from time 1 scans of the two groups. Prediction of clinical improvement from time 1 (pre-treatment) fMRI scan data was examined by regressing final BDI score onto regulation and reactivity activity at time 1 while covarying for baseline BDI. Final HDRS-17 scores (while controlling for initial HDRS-17) also were analyzed in parallel fashion as an alternate outcome.

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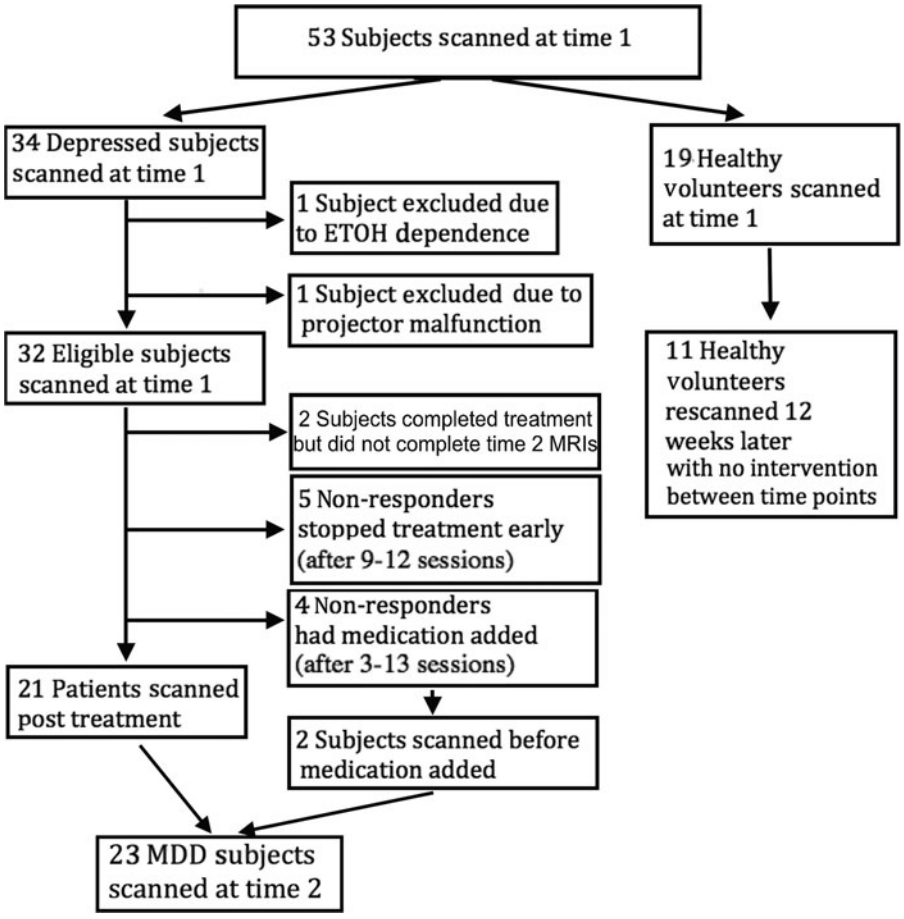

Fig. 1 Participant enrollment chart.

Change in brain activity after treatment was examined by performing *t* tests between time 1 and time 2 regulation and reactivity images. The results were compared between MDD participants and healthy volunteers, and the relationship between brain activity changes and treatment outcome was examined by regressing the change in contrasts onto treatment outcome (both BDI and HDRS-17, while controlling for initial severity). All depression scales were mean-centered prior to analysis.

Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 and stage 2, with automatic outlier detection (Woolrich, 2008). Clusters were identified with a voxel-wise minimum *z*-score of 3.1 [chosen to prevent false positives as described in recent critiques of cluster correction (Woo *et al.*, 2014; Eklund *et al.*, 2016)] and a family-wise-error corrected cluster significance threshold of $p < 0.05$ (Worsley, 2001). Cluster-peak location was identified in Montreal Neurological Institute (MNI) coordinates. Scan site was included as a regressor in all analyses.

ROI analysis

In order to avoid false-negatives, given the stringent whole-brain thresholds applied, we examined regulation-related BOLD deactivation and activity and reactivity-related BOLD activity within *a priori* regions of interest as outlined in the introduction. For emotional reactivity, ROIs considered were amygdala (where we expected to see longitudinal decreases) and subgenual anterior cingulate (where we expected time 1 signal to predict treatment outcome), identified using the WFU-pick atlas (Maldjian *et al.*, 2003). For emotion regulation, ROIs found to be related to emotion-regulation in a recent meta-analysis were considered (Buhle *et al.*, 2014), including right angular gyrus, right mid-frontal cortex, left temporal cortex, left occipital cortex, left inferior frontal gyrus, subgenual anterior cingulate, and right frontal cortex (regions defined by clustering meta-analysis results at $z > 2.3$), where we expected to see regulation-related activity. For these ROI analyses, mean parameter estimates for each contrast were extracted within each contrast-relevant ROI for each subject at time 1, and from the time 1 *v.* time 2 *t* test. One-sample *t* tests were performed on the time 1 mean parameter estimates (PEs) to look for a main effect of task at time 1, with the null hypothesis that the mean PE across subjects for each contrast would be 0. MDD and healthy volunteer group ROI values were compared using 2-sample *t* tests. Correlations between the values at time 1 and treatment outcome (BDI and HDRS-17) were performed to look for a prediction effect, and time 1 *v.* time 2 contrasts were also correlated with treatment outcome to look for change in fMRI signal that scaled with clinical outcome. Scan site was included as a covariate in all analyses, and initial depression severity was included as a covariate in all treatment outcome analyses. ROI results were considered significant at $p < 0.05$.

Results

Clinical characteristics and treatment outcome

Clinical and demographic data are described in Table 1. MDD participants were moderately depressed (mean BDI = 28.1 ± 7.6, mean HDRS-17 = 19.1 ± 4.4). After treatment, mean BDI scores

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Table 1. Clinical and demographic data

	Controls ($N = 19$)	MDD ($N = 32$)	p-Value (control *v.* MDD, two-tailed t test
Age	32.9 ± 10	34.8 ± 10.6	0.53
Initial Hamilton Depression Severity (17-item)	1 ± 1.5	19.1 ± 4.4	<0.001
Final Hamilton Depression Severity (17-item)	0.4 ± 0.9	12.9 ± 6.5	<0.001
Initial Beck Depression Inventory	0.4 ± 1.6	28.1 ± 7.6	<0.001
Final Beck Depression Inventory	1 ± 2.5	15.5 ± 8.4	<0.001
Brown-Goodwin Aggression Score	13.2 ± 3.1	15.4 ± 2.9	0.03
Years of education	15 ± 1.8	16.5 ± 2.6	0.04
Age at onset	n/a	16.3 ± 16.9	
Number of previous depressive episodes	n/a	2.9 ± 5.4	
Length of current major depressive episode (weeks)	n/a	202.2 ± 232.5	
Categorical variables	*N* (%)		p-Value (control *v.* MDD, Fisher's exact)
Female	12 (63)	20 (63)	1
Scanned at Cornell	5 (26)	12 (38)	0.12
Prior exposure to anti-depressants	n/a	15 (47)	
Suicidal ideation present	n/a	7 (22)	
Suicide attempter	n/a	0 (0)	
First degree relative to major depression	n/a	11 (34)	
Past alcohol abuse	n/a	2 (6)	
Past Cannabis abuse	n/a	2 (6)	
Comorbid post-traumatic stress disorder	n/a	3 (9)	
Comorbid social phobia	n/a	6 (19)	
Comorbid generalized anxiety disorder	n/a	1 (3)	
Comorbid panic disorder	n/a	1 (3)	
Comorbid simple phobia	n/a	1 (3)	
Comorbid obsessive-compulsive personality disorder	n/a	6 (19)	
Comorbid borderline personality disorder	n/a	3 (9)	
Comorbid avoidant personality disorder	n/a	2 (6)	
Comorbid paranoid personality disorder	n/a	1 (3)	
Comorbid dysthymia	n/a	1 (3)	
Race/ethnicity			
Asian	2 (11)	3 (9)	
African American	5 (26)	4 (13)	
Caucasian	9 (47)	16 (50)	
Hispanic	2 (11)	3 (9)	
>1 Race	0 (0)	4 (13)	

were 15.5 ± 8.4 in the entire MDD sample (40 ± 36% improvement), and 13 ± 7 among the 23 completers (51 ± 34% improvement). Final HDRS-17 scores were 12.9 ± 6.5 in the full sample and 11.2 ± 6.3 in the completers. Remission rate (final BDI $\leqslant$ 10) was 34% in intent-to-treat (ITT) sample and 44% in completers; response rate (reduction in BDI $\geqslant$ 50%) was 44% in ITT sample and 61% in completers. Using HDRS-17, remission rate (final HDRS-17 $\leqslant$ 7) was 22% in ITT sample and 33% in completers; response rate (reduction in HDRS-17 $\geqslant$ 50%) was 28% in ITT sample and 43% in completers.

Twelve MDD participants had comorbid anxiety disorders, and nine had comorbid personality disorders (disorders specified in Table 1).

MDD group emotional reactivity contrasts

MDD group emotional reactivity at time 1

At the pre-treatment scan, participants showed widespread brain activation during the emotional reactivity contrast, spanning three large clusters, including caudate, frontal pole, middle frontal

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gyrus, thalamus, cingulate, precuneus, posterior hippocampus, amygdala, brainstem, and putamen (a single cluster with a peak z of 7.65 at −48,6,28 with 29 276 voxels), and lateral occipital cortex/inferior temporal gyrus (right: peak Z 7.72 at 33,−54,−28 with 13 134 voxels; left: peak z 9.06 at −42,−52,−20 with 4305 voxels) as shown in Fig. 2*a* and reported in Table 2. Corrected p-values for each cluster were less than 0.001. The clusters in this result contained multiple distinct regions, so this analysis was repeated with a voxel-level z-threshold of 3.7, and was found to contain six distinct clusters (see Appendix 6).

Within *a priori* ROIs, emotional reactivity-related BOLD signal was significant within amygdala ($T = 3.61$, df = 31, $p = 0.001$), but not within ACC.

Emotional reactivity prediction of treatment outcome

There were no significant clusters in which the emotional reactivity contrast for the pre-treatment scan predicted treatment outcome using the BDI, our primary clinical outcome measure. However, using the HDRS-17, there was an association between higher pre-treatment emotional reactivity-related BOLD signal in right hippocampus and poorer treatment outcome (peak $z = 4.19$ at 34,−4,−30 with 294 voxels, corrected $p = 0.042$ which does not survive correction for multiple contrasts) (Fig. 2*b*). Although this result was unilateral at our primary threshold, it was bilateral at a looser exploratory threshold ($z > 2.3$, $k > 50$ voxels; left hippocampus: peak $z = 3.26$ at −22,−18,−26 with 127 voxels). We also re-examined BDI analyses at this lower statistical threshold, and observed a relationship between the emotional reactivity contrast and BDI in a more inferolateral portion of right hippocampus (peak $z = 3.47$ at 18,−38,−20 with 91 voxels). See Appendix 4 for additional details about these looser threshold results.

Considering *a priori* ROIs, pre-treatment emotional reactivity-related BOLD signal in amygdala and ACC did not predict treatment outcome based on either HDRS-17 or BDI scores (HDRS-17: amygdala: $r = 0.16$, $p = 0.39$; ACC: $r = 0.04$, $p = 0.80$. BDI: amygdala: $r = 0.25$, $p = 0.16$; ACC: $r = 0.08$, $p = 0.65$).

MDD group emotional reactivity longitudinal changes

In whole-brain analyses, emotional reactivity-related BOLD signal did not change at the group level from pre- to post-treatment, nor was the change in emotional reactivity-related BOLD signal from pre- to post-treatment associated with treatment outcome as assessed by BDI or HDRS-17.

At the ROI level, correlations between changes in emotional reactivity contrast in amygdala and ACC were not significant using the BDI or the HDRS-17. There were no significant changes at the ROI level from pre- to post-treatment scans, independent of treatment outcome.

3.3 MDD group emotion regulation

MDD group emotion regulation BOLD activity at time 1

At our specified statistical threshold, no significant clusters were identified showing emotion regulation-related activations at time 1 within our MDD sample. At a lower exploratory threshold ($z > 2.3$, $k > 50$), emotion regulation-related activations were observed in vlPFC, along with middle temporal and supramarginal gyrus (see section 'Emotion regulation activity at time 1' in Appendix 4).

ROI-based analysis in *a priori* regions defined from a recent reappraisal meta-analysis (Buhle *et al.*, 2014) demonstrated significant emotion regulation-related activation at time 1 in left temporal gyrus ($T = 2.1$, $p = 0.044$).

Emotion regulation-related BOLD activation at pre-treatment was not associated with treatment outcome as assessed by HDRS-17 or BDI in either whole-brain or ROI analyses.

3.3.2 MDD group emotion regulation BOLD deactivation at time 1

MDD participants showed emotion regulation-related deactivation in periaqueductal gray (PAG), thalamus, and left post central gyrus/posterior cingulate. Results are shown in Fig. 3*a* and reported in Table 2.

MDD group emotion regulation longitudinal changes

An increase in emotion regulation-related deactivation from pre-treatment to post-treatment was associated with better clinical outcome (as assessed by BDI) in right dlPFC [middle: max z 4.63 at 32,28,36 with 618 voxels, corrected $p < 0.001$, (<0.004 Bonferroni-corrected for four primary contrasts); superior: max z 5.08 at 34,8,54 with 557 voxels, corrected $p = 0.0018$, (0.007 Bonferroni-corrected)], precuneus [max z 4.18 at 12,−72,44 with 272 voxels, corrected $p = 0.038$, (0.152 Bonferroni-corrected)], and lateral occipital cortex [max z 4.22 at 36,−58,34 with 393 voxels, corrected $p = 0.001$, (0.004 Bonferroni-corrected)], shown in Fig. 3*b* and reported in Table 2. There were no significant clusters for this contrast when using HDRS-17 in place of BDI.

There were no pre- *v.* post-treatment changes in emotion regulation BOLD signal at the group level, independent of treatment outcome.

There were no treatment-related changes in BOLD signal or correlations between treatment outcome and signal change, for any a priori ROI.

MDD group behavioral results

A behavioral measure of emotion regulation success did not predict treatment outcome ($r = 0.14$, $p = 0.48$), nor were longitudinal changes in this measure associated with treatment outcome ($r = -0.29$, $p = 0.19$). A behavioral measure of emotional reactivity at time 1 was correlated with treatment outcome approaching significance ($r = 0.37$, $p = 0.05$). Detailed behavioral data can be found in Appendix 2.

MDD v. healthy volunteer group contrast

For both contrasts (emotional reactivity and emotion regulation), no significant main effect of group (MDD *v.* healthy volunteers) was observed at baseline, at either the voxel or ROI levels. Similarly, no group-by-time interactions were observed (see Appendix 3).

More detailed results of analyses in healthy volunteers, including healthy volunteer group means, longitudinal changes, and behavioral outcomes, can be found in Appendix 3.

Completer only analyses

When prediction and group analyses were repeated using only the 23 completer subjects, there were no significant clusters for any contrast.

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Table 2. Significant cluster information. Results were thresholded voxel-wise at $z > 3.1$ and cluster corrected $p < 0.05$

Contrast	Cluster-wise *p*-value (FWE-corrected)	Size (2 mm voxels)	Peak *Z* score	Peak coordinates (MNI space, mm)	Regions
Reactivity at time 1	<0.001	29 276	7.65	−48,6,28	Brainstem, thalamus, caudate, frontal pole, middle frontal gyrus, cingulate, precuneus, posterior hippocampus, amygdala, putamen
	<0.001	13 134	7.72	44,−54,−18	Right lateral occipital, fusiform, inferior temporal
	<0.001	4305	9.06	−42,−52,−20	Left lateral occipital, fusiform, inferior temporal
Reactivity at time 1 prediction of Hamilton outcome	0.0422	294	4.19	34,−4,−30	Right anterior hippocampus
Regulation deactivation at time 1	0.0092	491	4.51	6,−30,−12	Brain stem, periaqueductal gray, cerebellum
	0.021	388	4.11	−28,−28,32	Left posterior cingulate, postcentral gyrus, adjacent white matter
	0.0259	370	4.1	−4,−6,0	Thalamus
Regulation longitudinal correlation with BDI outcome	<0.001	618	4.63	32,28,36	Right middle frontal gyrus
	0.0018	557	5.08	34,8,54	Right superior middle frontal gyrus
	0.001	393	4.22	36,−58,34	Right lateral occipital cortex
	0.038	272	4.18	12,−72,44	Right precuneus

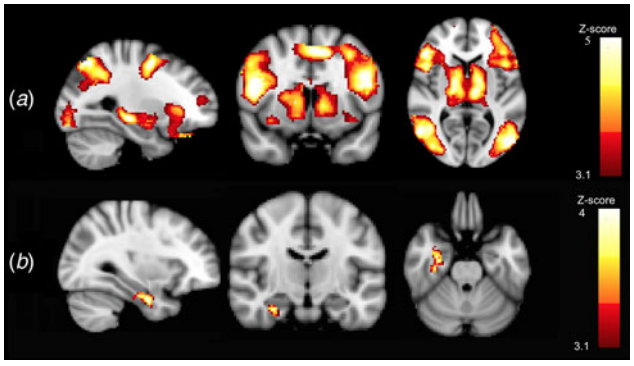

Fig. 2 (*a*) Mean emotional reactivity (LOOK NEG > LOOK NEU) BOLD signal at time 1. Occipital, parietal, dorsal prefrontal, and cingulate cortices, as well as caudate, thalamus, and hippocampus are included regions. (*b*) Regions where higher emotional reactivity (LOOK NEG > LOOK NEU) BOLD signal at baseline was associated with worse treatment outcome as assessed by HDRS-17. Anterior superior hippocampus is included. All results were thresholded voxel-wise at $z > 3.1$ and cluster corrected $p < 0.05$.

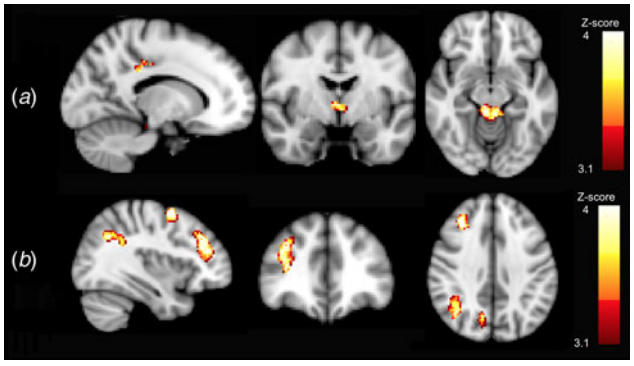

Fig. 3 (*a*) Mean emotion regulation deactivation (LOOK NEG > DIST NEG) BOLD signal at time 1. Regions included brainstem, anterior cingulate, and thalamus. (*b*) Regions where decreases in mean emotion regulation (LOOK NEG > DIST NEG) BOLD signal from time 1 to time 2 were associated with better treatment outcome as assessed with BDI. Regions included right middle frontal gyrus, lateral occipital cortex, and precuneus. All results were thresholded voxel-wise at $z > 3.1$ and cluster corrected $p < 0.05$.

Conclusions

In this study examining the neural correlates of emotional reactivity and emotion regulation in relationship to treatment outcome with CBT for depression, we observed two key findings, one related to prediction of treatment outcome, and one related to pre- *v.* post-treatment fMRI changes associated with clinical improvement. Specifically, greater BOLD-fMRI responses to emotionally aversive images in hippocampus predicted less clinical improvement with CBT for depression, while greater deactivation of BOLD signal during emotion regulation from pre- to post-treatment in precuneus and dlPFC correlated with better treatment outcome.

At pre-treatment, we found that greater emotional reactivity-related BOLD signal in right anterior inferior hippocampus, overlapping with CA1, predicted less clinical improvement with CBT. One possible interpretation of these data is that for individuals with greater hippocampal activation to aversive images, exposure to these images triggered recall of self-relevant aversive memories – memories that may have heightened their self-reports of negative affect. MDD is associated with the overgeneralization of negative memories, whereby patients recall entire categories of memories that re-enforce negative biases (Kircanski *et al.*, 2012). Such overgeneralization may be associated with a ruminative, rigid cognitive style that may limit the effectiveness of the cognitive interventions of CBT for depression. Overgeneral autobiographical memory is associated with worse longitudinal course of depression severity in a community sample, broadly consistent with this hypothesis (Van Daele *et al.*, 2014). Right CA1 is

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associated with encoding events that overlap with previous experiences (Schlichting *et al.*, 2014), so its activation is consistent with this interpretation. Although hippocampus activity during emotional reactivity has not been found to predict CBT treatment outcome in previous studies, lower activity in anterior cingulate (Siegle *et al.*, 2006; Fu *et al.*, 2008; Costafreda *et al.*, 2009) and greater activity in vmPFC (Ritchey *et al.*, 2011) and amygdala (Siegle *et al.*, 2006) during negative stimuli have been found to be associated with better treatment outcome. Our result adds to a growing body of literature which suggests that neural responses to emotional stimuli predict CBT outcome and identifies another relevant region of interest.

At time 1, we observed emotion-regulation-related deactivation in PAG and cingulate, regions associated with threat-related responding in general, and pain and vicarious pain-related responses more specifically (Linnman *et al.*, 2012; Simons *et al.*, 2014; Yesudas and Lee, 2015). We found that greater deactivation of BOLD signal during emotion regulation from pre- to post-treatment in precuneus and dlPFC correlated with better treatment outcome. Given the role of precuneus in self-referential processing (Herold *et al.*, 2016), this may reflect greater disengagement in self-referential processing as a function of successful CBT. Consistent with this explanation, this result was driven by activity during the regulation (Distance Negative) epoch in both regions as opposed to the Look Negative epoch (see Appendix 5). Deactivation of BOLD signal in dlPFC, which is associated more with the maintenance of goal-relevant information and the regulation of emotions (Frith *et al.*, 1991; Golkar *et al.*, 2012), changed in the same direction as the precuneus signal. A speculative interpretation of this somewhat paradoxical finding is that depressed patients who improve following CBT may be able to engage in effective distancing with greater efficiency and less effort, requiring less cognitive control, reflected by decreased signal during distancing. The distancing strategy used in this task is less cognitively taxing than some other reappraisal strategies (Dorfel *et al.*, 2014), has been shown to have lasting effects in amygdala but not PFC (Denny *et al.*, 2015*b*), and after learning it participants have reported decreased stress without deliberately applying the strategy (Denny and Ochsner, 2014), all of which is consistent with this interpretation.

We did not observe significant differences between the MDD and healthy volunteer groups in either the emotional reactivity or emotion regulation contrast. Due to the small sample size of our control group (19 at time 1, 11 with follow-up data), we were underpowered to detect all but large effects, making this result difficult to interpret. Other groups have reported differences in fMRI findings within MDD participants related to both emotional reactivity (Siegle *et al.*, 2002; Drevets, 2003) and emotion regulation (Stephanou *et al.*, 2017; Zilverstand *et al.*, 2017).

In our sample, neural correlates of emotional reactivity predicted treatment outcome, whereas neural correlates of emotion regulation did not. Conversely, longitudinal changes in emotion regulation-related activity, but not emotional reactivity-related activity, were associated with clinical improvement. This is consistent with our previous work using a different emotion regulation task involving aversive memories in this same cohort (Rubin-Falcone *et al.*, 2017), which found no predictive effects of emotion regulation but observed longitudinal effects of emotion-regulation-related processing in relevant brain regions (cingulate, mPFC, lingual gyrus) that scaled with clinical improvement. This result is also partially consistent with a recent study of a form of cognitive-behavioral therapy (prolonged exposure therapy) in post-traumatic stress disorder (PTSD), which also found that higher pre-treatment emotional reactivity-related BOLD signal in another subcortical region (amygdala) predicted worse treatment outcome (Fonzo *et al.*, 2017*a*), but that emotion regulation-related BOLD signal in left dlPFC was increased after treatment (Fonzo *et al.*, 2017*b*). While emotion regulation findings are divergent between that study and the current one, the convergent emotion reactivity findings suggest that limbic/subcortical responses to affective stimuli might be a negative prognostic factor for cognitive behavioral therapies across both anxiety and mood disorders. They also suggest that these treatments have an impact on the neurologic underpinnings of deliberate emotion regulation.

Previous fMRI findings related to pharmacotherapy for depression provide additional context to our current findings with CBT. Lower BOLD signal in dlPFC, cingulate, and subcortical regions while processing emotionally negative words is predictive of positive selective serotonin reuptake inhibitor (SSRI) outcome in MDD (Miller *et al.*, 2013), as is reduced BOLD signal in amygdala during exposure to threatening and happy images (Williams *et al.*, 2015). These findings are in the opposite direction of our results may point to a potential biomarker of differential outcome to these two types of treatments. On the other hand, BOLD activation in regions including dlPFC during emotion processing tasks have been reported to increase (Fales *et al.*, 2009; Delaveau *et al.*, 2011) and decrease (Rosenblau *et al.*, 2012) post SSRI treatment, suggesting our longitudinal finding is not specific to CBT.

Limitations

The sample size of this study is small, and findings require replication in a larger sample. Lacking a placebo or alternative treatment arm, it is not possible to determine the specificity of our findings for CBT. In addition, the small sample size of healthy volunteers enrolled in this study was not adequately powered for definitive contrasts between MDD participants and healthy volunteers.

For longitudinal analyses, a group by time interaction would be ideal for addressing the possible confound of time between scans. However, we were underpowered in our control sample (11 subjects with longitudinal data), and did not observe such an effect (see Appendix 3). We therefore performed analyses examining the effect of time on BOLD contrasts within the MDD group, both as a function of treatment outcome and as a main effect. A signal was observed relative to treatment outcome but there was no main effect of time independent of this, suggesting that the observed results may be driven more by CBT effectiveness rather than by time or practice effects.

Twelve participants had comorbid anxiety disorders. It is therefore possible that improvements in anxiety symptoms partially drove the results, which is a potential confound. No scale of anxiety symptoms was acquired, so it is difficult to interpret specific differentiation between the brain bases of depression and anxiety as they relate to treatment outcome. Of note, meta-analyses examining effects of CBT on fMRI activations identify overlapping changes with treatment for both anxiety and depressive disorders (Messina *et al.*, 2013).

There were no significant results when prediction and group analyses were repeated using only the 23 completer subjects. This is likely due to reduced power within the smaller sample size of completers. Alternatively, it is possible that the clinical outcomes of individuals who dropped out early are driving the observed findings in the LOCF analyses.

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Although voxel-level analyses were rigorously thresholded, we did not apply additional correction across contrasts. Cluster-level *p*-values for all contrasts excluding the prediction finding would survive Bonferroni correction for our four primary hypotheses (two contrasts, two analyses: prediction and longitudinal), but this study still requires replication.

Although we were able to identify pre-treatment predictors of treatment outcome, longitudinal changes with treatment, and pre-treatment group effects of emotional reactivity and emotion regulation deactivation, we only observed baseline emotion regulation-related activation in a canonical emotion-regulation-related region (vlPFC) (Buhle *et al.*, 2014) when applying a lower statistical threshold to whole-brain voxel-wise analyses. This might be due to the fact that the distancing strategy used in this experiment is less cognitively taxing than strategies used in similar studies, such as re-interpretation (Dorfel *et al.*, 2014).

Future directions

This work requires replication. Future studies should include randomization to placebo and other active treatment arms to determine the specificity of the findings. One of our key findings, of emotion regulation-related BOLD signal in right superior middle frontal gyrus scaling with clinical improvement, converges with another study of emotion-regulation based treatment (Fonzo *et al.*, 2017*b*). The authors of that study observed that this region is involved in switching between stimulus-dependent and stimulus-independent attention (Burgess *et al.*, 2007), relevant to the refocusing of attention during emotion regulation. This region may therefore be a promising target for stimulation with transcranial magnetic stimulation (TMS) or similar therapies, perhaps in combination with CBT, to facilitate the adaptive neural effects on effective emotion regulation.

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Conflict of interest. Dr Miller's family previously owned stock in Johnson & Johnson, unrelated to the current manuscript. Dr Oquendo receives royalties for the commercial use of the Columbia Suicide Severity Rating Scale. Her family owns stock in Bristol Myers Squibb. Dr Mann receives royalties from the Research Foundation for Mental Hygiene for commercial use of the C-SSRS. Drs Ochsner, Zanderigo, Kishon, Doré, Mr Rubin-Falcone, Mr Weber, and Ms Delaparte have no conflicts of interest to declare.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Appendix 1 Pulse sequence parameters, image processing/analysis

T1-weighted structural scans were acquired the following parameters: TR = ~6 ms, TE = minimum 2400 ms, flip angle = 8, FOV = 25.6 cm × 25.6 cm, slice thickness = 1 mm, number of slices = 178, matrix size = 256 × 256 pixels. EPI acquisition was obtained for each of three runs using the following parameters: TR = 2000 ms, TE = 26 ms, flip angle = 77, FOV = 22.4 cm × 22.4 cm, slice thickness = 3.5 mm, spacing = 3.5 mm, number of slices = 32, matrix size = 64 × 64 pixels, number of volumes = 201.

Skull-stripping and field correction of T1-weighted structural images was done with Atropos (Avants *et al.*, 2011). fMRI task data were processed using FEAT (FMRI Expert Analysis Tool) Version 5.98, a part of FSL (FMRIB's Software Library, https://www.fmrib.ox.ac.uk/fsl) (Woolrich *et al.*, 2009). Motion correction was performed using FMRIB's Linear Image Registration Tool (MCFLIRT) (Jenkinson *et al.*, 2002). Outlier volumes with severe motion were identified using the root-mean-square intensity difference between each 3D volume and a reference volume [FSL's implementation of the DVARS metric (Power *et al.*, 2012)] and were subsequently regressed out by using separate indicator regressors for each outlier volume. Slice-timing correction was done with Fourier-space time-series phase-shifting, and non-brain voxels were removed from the EPI image with Brain Extraction Tool (BET) (Smith, 2002). A Gaussian kernel with a full-width half-maximum of 8.0 mm was used for spatial smoothing; grand-mean intensity normalization of the entire 4D dataset was done by a single multiplicative factor; temporal filtering was done using a high-pass cutoff of 100 s (Gaussian-weighted least-squares straight line fitting, $\sigma = 50.0$ s); and each run's first three volumes were discarded for intensity equilibration.

Structural image normalization to standard space was performed with FLIRT (Jenkinson *et al.*, 2002); 4D functional data were registered to the first volume of functional acquisition using a transformation with 7 degrees of freedom (df), then registered to the T1-weighted structural image with 6

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Table A1. MDD group behavioral results

Average valence (four point scale, ±s.e.)	Look neg	Dist neg	Look Neu	BERS (look neg-dist neg)	EER (look neg-look neu)
Time 1	2.39 ± 0.56	2.03 ± 0.54	1.18 ± 0.25	0.36 ± 0.39	1.21 ± 0.54
Time 2	2.24 ± 0.41	1.89 ± 0.42	1.18 ± 0.23	0.35 ± 0.44	1.08 ± 0.41
Contrasts (*t*,*p*)					
Time 1 *v.* time 2	0.49, 0.63	0.62, 0.54	−0.52, 0.6	−0.19, 0.85	0.74, 0.47
Correlations (*r*,*p*)					
Time 1 *v.* time 1 BDI	0.2, 0.3	0.22, 0.26	0.03, 0.86	−0.02, 0.94	0.19, 0.32
Time 1 *v.* percent decrease BDI	0.33, 0.08*	0.24, 0.2	−0.06, 0.76	0.14, 0.48	0.37, 0.05*
Time 2–time 1 *v.* percent decrease in BDI	−0.45, 0.03**	−0.21, 0.33	−0.29, 0.18	−0.29, 0.19	−0.39, 0.07*
Time 1 *v.* time 1 HDRS	0.12, 0.53	0.05, 0.8	0.09, 0.64	0.11, 0.59	0.08, 0.67
Time 1 *v.* percent decrease HDRS	0.28, 0.14	0.16, 0.42	−0.03, 0.88	0.19, 0.33	0.31, 0.1
Time 2–time 1 *v.* percent decrease in HDRS	−0.26, 0.23	−0.05, 0.82	0.12, 0.6	−0.22, 0.31	−0.32, 0.13

df; and finally normalized to standard space [Montreal Neurological Institute (MNI) space] with 12 df. Normalizations were then further refined with FNIRT nonlinear registration (Andersson *et al.*, 2007*a*, 2007*b*).

Appendix 2 MDD behavioral outcomes

All behavioral results are summarized in Table A1. During scanning, participants rated their responses to pictures during the Look Negative condition as more negative than those during the Distance Negative condition, both at time 1 ($t = 4.74$, $p < 0.001$) and at time 2 ($t = 3.1$, $p = 0.005$), validating the effects of the distancing strategy at the level of self-report of emotional experience. Mean valence ratings within each condition (Look Negative, Distance Negative or Look Neutral) did not change from time 1 to time 2 (IAPS photographs were matched but entirely non-overlapping between times 1 and 2).

We calculated a behavioral measure of *emotion regulation success* (BERS) for each participant, measured as the difference between mean emotional valence ratings during all Look Negative trials *v.* all Distance Negative trials within scan. BERS did not change with treatment, and neither baseline BERS nor change in BERS was associated with treatment outcome as assessed by percent change in BDI.

We calculated a behavioral measure of *experienced emotional reactivity* (EER) as the difference between mean emotional valence ratings during Look Negative condition trials *v.* Look Neutral condition trials within scan. Correlation between EER and treatment outcome as assessed by BDI approached significance ($r = 0.37$, $p = 0.05$).

Appendix 3 Analyses of control subjects

All coordinates given are in MNI space with 2 mm voxels. All analyses were performed with $Z > 3.1$ p(FWE-corrected) < 0.05.

Control group emotional reactivity at time 1

Controls showed emotion reactivity BOLD activation in occipital cortex only (Fig. A1; left: max $Z = 5.28$ at 32,−82,−26 with 2387 voxels, cluster $p < 0.001$; right: max $Z = 6.1$ at 30,−90,−4 with 2122 voxels, cluster $p < 0.001$). There was no significant difference between MDD and control subjects at the voxel level in a direct *F*-test comparison. There were no significant ROI findings in amygdala or anterior cingulate.

Control group longitudinal changes in emotional reactivity

Controls showed a significant decrease in emotion reactivity BOLD signal between time 1 and time 2 in right occipital cortex (max $Z = 5.33$ at 20, −105,−10 with 616 voxels, Fig. A2). This is believed to be a practice effect, since the participants had not seen the IAPS images before time 1 scanning and were therefore more upset by them, but were prepared for them at time 2. There were no longitudinal differences between MDD and control subjects at the voxel or ROI level, or any changes at the ROI level for controls.

Control group emotion regulation

Control subjects had decreased BOLD signal during emotion regulation in left supramarginal gyrus (emotion regulation deactivation; Fig. A3; max Z is 4.52 at −66,−20,30 with 342 voxels, cluster $p = 0.033$).

There was no voxel-level emotion-regulation activity associated BOLD signal at our statistical cutoff. There were no significant findings at the ROI level within the control group at time 1.

There were no significant differences in emotion regulation BOLD signal between MDD and control groups at the voxel or ROI level.

Control subjects did not show any longitudinal changes in emotion regulation in any voxel-wise clusters or ROIs, nor did longitudinal changes differ between MDD and control groups.

Control group behavioral outcomes

Behavioral outcomes for controls and control *v.* MDD behavioral comparisons are summarized in Table A2. During scanning, like the MDD group, control participants rated negative-valence pictures during the 'look' instruction as more emotionally negative than those during the 'distance' instruction at time 1 ($t = 4.85$, $p < 0.001$), and at time 2 ($t = 6.38$, $p < 0.001$). Neither controls or MDD subjects had different 'look' or 'distance' ratings between time 1 and time 2, and MDD and control groups did not rate 'distance' or 'look' trails differently at either time point. Ratings of neutral images did not differ between groups at either time point or differ between time points for either group.

Our behavioral measure of emotion regulation success (BERS) was higher in the control group compared to the MDD group at both time 1 ($t = -1.72$, $p = 0.09$) and time 2 ($t = -2.3$, $p = 0.03$). BERS did not change significantly from time 1 to time 2 in either group.

Our behavioral measure of emotional reactivity (BER) did not differ between time 1 and time 2 for either group or differ between groups at either time point.

Appendix 4 Low-threshold results

This section contains results from exploratory voxel-level analyses thresholded at $Z > 2.3$, $k > 50$ with no cluster correction. These analyses were performed to further examine contrasts of particular interest in order to avoid false negatives or further interoperate the data.

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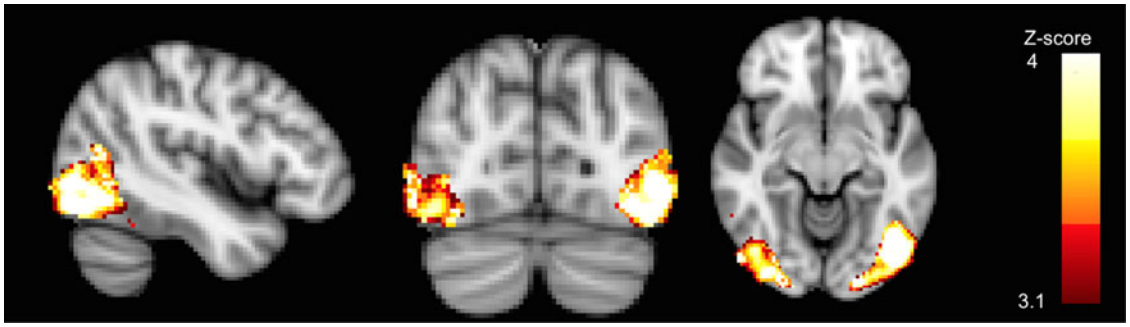

Fig. A1. Regions of significant emotional reactivity BOLD signal for control subjects.

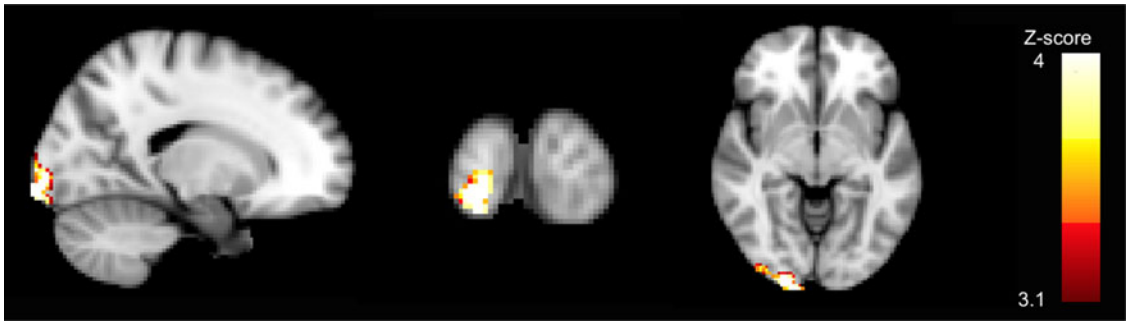

Fig. A2. Regions of significant emotional reactivity BOLD signal longitudinal decreases for control subjects.

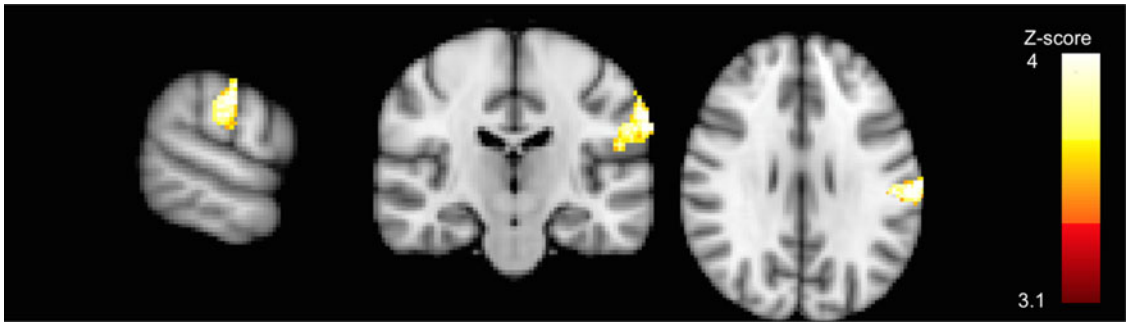

Fig. A3. Regions of significant emotion regulation deactivation BOLD signal for control subjects.

Table A2. Control group behavioral results

Average valence (four point scale ±STD)	Look neg	Dist neg	Loo Neu	BERS (look neg-dist neg)	BER (look neg-look neu)
Control time 1	2.44 ± 0.59	1.85 ± 0.49	1.12 ± 0.26	0.59 ± 0.53	1.32 ± 0.55
Control time 2	2.38 ± 0.68	1.67 ± 0.51	1.1 ± 0.19	0.7 ± 0.36	1.27 ± 0.68
Contrasts (*t*,*p*)					
Control time 1 *v.* time 2	0.26, 0.8	0.92, 0.37	−0.61, 0.55	−0.63, 0.54	0.4, 0.69
Time 1 control *v.* MDD	−0.31, 0.76	1.14, 0.26	0.77, 0.44	−1.72, 0.09*	−0.68, 0.5
Time 2 control *v.* MDD	−0.7, 0.49	1.34, 0.19	1.01, 0.32	−2.3, 0.03**	−1.17, 0.25
Time 2 time 1 control *v.* MDD	0.04, 0.97	0.72, 0.48	−0.02, 0.99	−0.53, 0.6	0.06, 0.96

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Table A3. Emotional reactivity treatment prediction low-threshold results

Contrast	Size (2 mm voxels)	Peak *Z* score	Peak coordinates (MNI space, mm)	Regions
Higher reactivity predicts better outcome-HDRS-17	60	3.47	−34,−96,−10	Left occipital cortex
	58	2.79	14,−90,4	Right occipital pole
Higher reactivity predicts worse outcome-HDRS-17	1738	3.85	46,24,−30	Right hippocampus, parahippocampal gyrus, temporal cortex
	427	3.86	−38,−78,34	Left lateral occipital cortex
	337	3.56	54,−18,6	Right insular cortex
	322	4.1	44,−80,30	Left occipital cortex
	206	3.68	22,−56,16	Right precuneus
	165	3.29	−46,−12,10	Left insular cortex
	127	3.26	−22,−18,−26	Left hippocampus
	125	3.23	48,44,14	Right frontal pole
	115	2.96	−24,−38,−12	Left hippocampus/parahippocampal gyrus
	96	3.18	62,0,32	Right precentral gyrus
	94	3.63	−26,66,16	Left frontal pole
	58	3.19	−50,14,−22	Left temporal pole
	54	3.11	66,−52,10	Right middle temporal gyrus
Higher reactivity predicts better outcome-BDI	433	4.11	52,−34,50	Right supramarginal gyrus
	255	3.91	0,28,10	Anterior cingulate
	208	3.46	16,−80,8	Right intracalarine cortex
	105	3.59	−10,−54,−20	Cerebellum
	100	3.41	−46,−52,56	Left angular gyrus
	92	3.22	8,−88,28	Right occipital pole
	87	3.2	6,−102,4	Right occipital pole
	64	3.2	−30,28,20	Left middle frontal gyrus
	60	2.82	24,−10,10	Right putamen
	52	3.07	10,−50,−12	Cerebellum
	51	3.56	36,−64,60)	Right lateral occipital cortex
Higher reactivity predicts worse outcome-BDI	755	3.77	−38,−84,34	Left occipital cortex
	282	3.33	54,−74,26	Right occipital cortex
	278	3.16	−32,−40,−14	Left temporal fusiform
	154	2.91	42,−22,−32	Right temporal fusiform
	91	3.47	18,−38,−20	Right hippocampus/parahippocampal gyrus
	86	3.21	−54,−14,−6	Left superior temporal gyrus
	73	3.18	62,−8,−22	Right middle temporal gyrus
	60	2.96	36,−34,−18	Right temporal fusiform cortex
	53	2.82	−26,−20,−20	Left hippocampus

Emotional reactivity at time 1 prediction of treatment outcome

Higher time 1 emotion reactivity BOLD signal correlated with worse HDRS-17 outcome in right hippocampus at our a priori strict threshold. At the loose threshold only, higher reactivity BOLD signal was associated with worse treatment outcome as assessed by both HDRS-17 and BDI in hippocampus and additional regions including occipital and temporal cortex, and as assessed by HDRS-17 only in frontal pole and precuneus. Higher reactivity BOLD signal was associated with better treatment as assessed by both measures in occipital cortex, and as assessed by BDI in several other regions. Results are summarized in Table A3.

Emotion regulation activity at time 1

Both groups showed emotion regulation deactivation at time 1 at the strict threshold.

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Table A4. Emotion regulation activity at time 1 low threshold results

Contrast	Size (2 mm voxels)	Peak *Z* score	Peak coordinates (MNI space, mm)	Regions
Controls regulation activity	112	3.17	−56,−56,38	Left angular/supramarginal gyrus
	101	3.07	−42,−70,42	Left superior lateral occipital cortex
	63	2.93	−28,22,42	left superior middle frontal gyrus
MDD regulation activity	517	3.62	−44,44,−12	Left frontal pole
	390	4.09	48,46,−4	Right frontal pole
	363	3.82	−56,−46,40	Left posterior supramarginal gyrus
	324	3.39	−66,−46,−2	Left middle temporal gyrus
	119	3.41	38,42,20	Right frontal pole
	87	3.18	52,−32,−10	Right middle temporal gyrus
	70	3.2	−50,26,−14	Left frontal orbital cortex

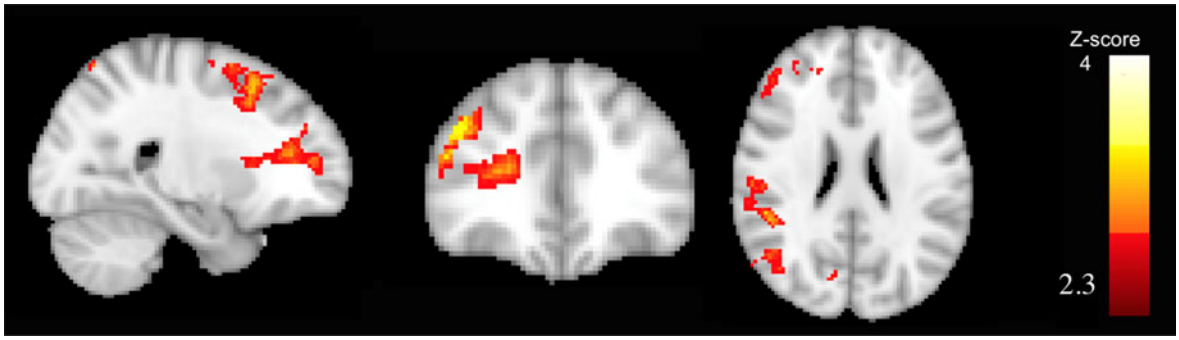

Fig. A4. Regions where lower BOLD signal during the Distance Negative condition at time 2 compared to time 1 was associated with better treatment outcome (lower final BDI score while covarying for baseline BDI score; voxel-wise $z > 2.3$, cluster size $k > 50$). Activation was present in regions similar to the emotion regulation condition, while the Look Negative condition alone had no significant results.

Table A5. Significant clusters in emotional reactivity contrast with voxel-wise $z > 3.7$, cluster-wise $p < 0.05$

Cluster-wise *p*-value (FWE-corrected)	Size (2 mm voxels)	Peak *Z* score	Peak coordinates (MNI space, mm)	Regions
<0.0001	7457	6.28	−4,14,46	Anterior cingulate/left middle and inferior frontal gyrus/left insula
<0.0001	7281	5.71	−8,−12,0	Bilateral thalamus, caudate, hippocampus, brainstem
<0.0001	4753	6.15	−40,−52,58	Bilateral supramarginal gyrus
<0.0001	3865	6.77	44,−58,−18	Right inferior lateral occipital cortex
<0.0001	3602	6.34	48,10,26	Right insula/inferior and middle frontal gyrus
<0.0001	3332	8.21	−44,−64,−16	Left inferior lateral occipital cortex

While neither group had significant regulation activity at the strict threshold, at the loose threshold both groups showed activity in frontal, occipital, and motor regions. Results are summarized in Table A4.

Appendix 5 Distance negative condition

In order to determine if one contrast was driving the observed longitudinal correlations with treatment outcome, treatment outcome as assessed with final BDI was regressed onto longitudinal changes in brain activation during each contrast (Distance Negative or Look Negative) alone (while co-varying for initial BDI and scan site).

At $z > 2.3$, $k > 50$, lower BOLD signal during the Distance Negative condition at time 2 compared to time 1 was associated with better treatment outcome in regions overlapping with the primary emotion regulation longitudinal result (see Fig. A4), while treatment outcome was not associated with changes in the Look Negative contrast at that threshold. This implies that decreased activity during the Distance Negative condition was driving the results, and not an increase in activity during the Look Negative condition.

Appendix 6 Emotional reactivity at increased threshold

In order to examine distinct regions associated with emotional reactivity, the emotion reactivity contrast was re-examined at a voxel-wise z threshold of 3.7 and a cluster-wise FWE-corrected p-threshold of 0.05.

We found six distinct clusters, described in Table A5.

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