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Longitudinal effects of cognitive behavioral therapy for depression on the neural correlates of emotion regulation

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ABSTRACT

Cognitive behavioral therapy (CBT) is effective for a substantial minority of patients suffering from major depressive disorder (MDD), but its mechanism of action at the neural level is not known. As core techniques of CBT seek to enhance emotion regulation, we scanned 31 MDD participants prior to 14 sessions of CBT using functional magnetic resonance imaging (fMRI) and a task in which participants engaged in a voluntary emotion regulation strategy while recalling negative autobiographical memories. Eighteen healthy controls were also scanned. Twenty-three MDD participants completed post-treatment fMRI scanning, and 12 healthy volunteers completed repeat scanning without intervention. Better treatment outcome was associated with longitudinal enhancement of the emotion regulation-dependent BOLD contrast within subgenual anterior cingulate, medial prefrontal cortex, and lingual gyrus. Baseline emotion regulation-dependent BOLD contrast did not predict treatment outcome or differ between MDD and control groups. CBT response may be mediated by enhanced downregulation of neural activity during emotion regulation; brain regions identified overlap with those found using a similar task in a normative sample, and include regions related to self-referential and emotion processing. Future studies should seek to determine specificity of this downregulation to CBT, and evaluate it as a treatment target in MDD.

1. Introduction

Major depressive disorder (MDD) is predicted to become the leading cause of disability by 2030 (Mathers et al., 2008). While treatment with evidence-based cognitive-behavioral therapy (CBT) for depression produces remission in a minority of patients (DeRubeis et al., 2005; Elkin et al., 1989; Luty et al., 2007), with comparable efficacy to other first-line antidepressant treatments (DeRubeis et al., 1999; Dobson et al., 2008; Trivedi et al., 2006), these treatments leave many depressed patients with significant symptoms and impaired functioning despite vigorous treatment. Treatment selection for MDD involves trial-and-error, due to the lack of known clinically useful moderators of treatment outcome. Task-based functional magnetic resonance imaging (fMRI) has been used to investigate neural predictors of treatment outcome with CBT for MDD and to map longitudinal changes produced by CBT in depression (Chuang et al., 2016; Forbes et al., 2010; Franklin et al., 2016; Fu et al., 2008; Ritchey et al., 2011; Siegle et al., 2006; Thompson et al., 2015; Yoshimura et al., 2013), largely by examining the neural correlates of tasks that elicit negative affect.

Deficits in emotion regulation may contribute to depression risk (Hopfinger et al., 2016) and psychopathology. In fMRI studies of emotion regulation, differences in blood-oxygen-level dependent (BOLD) activity and connectivity have been identified in depression (Heller et al., 2009; Johnstone et al., 2007). A key goal of CBT for depression is to develop improved capacities for voluntary regulation of emotion, accomplished through techniques including cognitive restructuring, behavioral activation, and behavioral experiments (Beck, 1995). Indeed, recent evidence suggests that both in-person inpatient CBT for depression (Forkmann et al., 2014) as well a computer-based CBT intervention (Morris et al., 2015) lead to improvements in a form

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of emotion regulation, cognitive reappraisal, and that improvement in reappraisal correlates with reduction in depression severity (Forkmann et al., 2014). We therefore sought to examine the neural correlates of emotion regulation as a predictor of treatment outcome with CBT for depression, and to examine the relationship of longitudinal changes in such emotion regulation-related activity to treatment outcome.

Negative autobiographical memories are particularly salient stimuli for emotion regulation tasks in depression due to their personal relevance, in contrast to other standardized stimuli. Kross et al. developed a fMRI paradigm in which participants recall a series of emotionally negative autobiographical memories and are instructed to either respond naturally ("feel" condition), or regulate their emotional responses in two other conditions ("analyze" and "accept" conditions) (Kross et al., 2009). The analyze strategy was designed as a memory analog of cognitive reappraisal strategies used in previous fMRI studies (Ochsner et al., 2002, 2004; Ray et al., 2005; Wager et al., 2008). During both regulation strategies, healthy volunteers showed reduced activity in brain regions associated with self-referential and affective processing, including subgenual anterior cingulate cortex, medial prefrontal cortex, and lingual gyrus.

We used a modified version of this task to examine the neural correlates of voluntary emotion regulation in a group of individuals with current MDD, both before and after a course of CBT for depression. As the "analyze" condition maps closely onto the core CBT technique of cognitive restructuring, it was selected as the regulation strategy for this study (Beck, 1995). A comparison group of healthy volunteers performed this fMRI task at comparable time-points without a treatment intervention. Given the observed suppression of activity during emotion regulation previously observed in a normal sample, we hypothesized: 1) the magnitude of emotion regulation-dependent BOLD signal reduction (i.e. "feel" > "analyze" contrast) would increase longitudinally as a function of better treatment outcome with CBT; 2) the magnitude of emotion regulation-dependent BOLD reduction at baseline would be correlated with better treatment outcome; and 3) healthy volunteers would show greater emotion regulation-dependent BOLD reduction in relevant brain regions than MDD participants. We conducted whole-brain voxelwise analyses as well as analyses at the region-of-interest (ROI) level, examining regions associated with emotion regulation of negative autobiographical memories in previous work (subgenual cingulate, dorsomedial prefrontal cortex, and lingual gyrus) (Kross et al., 2009).

2. Methods

2.1. Sample

Participants were recruited using online and print advertisements as well as through referrals from surrounding clinics and gave written informed consent prior to research participation. MDD inclusion criteria included: 1) Age18-60; 2) A DSM-IV diagnosis of MDD in a current major depressive episode (MDE) as assessed using the Structured Clinical Interview (SCID) for DSM-IV (First et al., 1995); 3) 17-item Hamilton Rating Scale for Depression (HRSD) score ≥ 16 (Hamilton, 1960); 4) Lack of significant benefit from any current psychiatric medications and ability to tolerate washout (if applicable); 5) Capacity to provide informed consent. MDD exclusion criteria included: 1) Unstable medical conditions; 2) alcohol or substance use disorder within the past 6 months; 3) Other current or past major psychiatric disorders including bipolar disorder; comorbid anxiety and personality disorders were allowed and are described in Table 1; 4) Pregnancy, currently lactating, planning to conceive during the course of study participation or abortion in the past two months; 5) Dementia; 6) A neurological disease or prior head trauma with evidence of cognitive impairment; 7) A first-degree family history of schizophrenia if the subject is less than 33 years old (to exclude possible prodromal phase of schizophrenia); 8) Contraindication to CBT as primary treatment for depression, including prior non-response to an adequate trial of CBT, active psychosis, or severe suicidal ideation including a plan. Healthy control inclusion criteria included: 1) Age 18–60; 2) Lack of current or past DSM-IV Axis-I diagnosis as assessed by the SCID; 3) Capacity to provide informed consent. Healthy control exclusion criteria included items 1,2,4,5 from the MDD exclusion criteria plus first-degree relative with history of major depression, schizophrenia, schizoaffective disorder, or suicide attempt, or two or more first-degree relatives with a history of substance dependence.

2.2. Clinical procedures and treatment

BDI (primary, (Beck et al., 1961)) and 17-item HRDS (secondary, (Hamilton, 1960)) scores were used as measures of pre- and post-treatment depression severity (BDI scores obtained at every session, HRDS scores every fourth session). Following 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 to twice-weekly for two weeks, then weekly thereafter. Study therapists were M.D.- or Ph.D.-level therapists with extensive training and experience conducting CBT, including training at the Beck Institute for Cognitive Behavioral Therapy. Therapists met weekly for peer supervision. Sessions were audiotaped, and adherence to CBT principles was assessed on at least one session per patient by the Beck Institute using the Cognitive Therapy Rating Scale (mean CTRS = 42.7 ± 5.9) (Young and Beck, 1980). A post-treatment MRI scan was performed at the conclusion of CBT. For healthy volunteers, the fMRI task was repeated at a comparable time-point without a treatment intervention.

Participant flow through the study is depicted in Fig. 1. For the participants that did not complete 14 sessions of CBT, last observation carried forward was applied, using the last BDI measurement obtained before dropout or medication augmentation. Two participants who did not complete CBT monotherapy due to clinical worsening, for whom medication was added to augment CBT, had timepoint 2 scans performed immediately prior to medication augmentation (following sessions 9 and 11 respectively); other CBT non-completers were only included in analyses related to time 1 MRI data. Of the 31 depressed participants included in the analysis, 14 were antidepressant-naive, 15 were unmedicated at enrollment but had a history of prior antidepressant use, and 2 were on an ineffective antidepressant medication at enrollment and completed a 3-week washout prior to scanning and treatment.

2.3. Image acquisition

MRI scans were acquired on two 3T SignaHDx scanners (General Electric Medical Systems, Milwaukee, WI), one at The New York State Psychiatric Institute and one at Weill Cornell Medical College, using the same 8-channel head coil. Scan site was included as a covariate in all analyses. T1-weighted MRI scans were acquired using the following parameters: TR = ~ 6 ms, TE = minimum 2400 ms, flip angle = 8, FOV = 25.6 × 25.6 cm, slice thickness = 1 mm, number of slices = 178, matrix size = 256 × 256 pixels. For functional scanning during the memories task, an Echo Planar Imaging (EPI) acquisition was obtained for each of four runs using the following parameters: TR = 2000 ms, TE = 26 ms, flip angle = 77, FOV = 22.4 × 22.4 cm, slice thickness = 3.5 mm, spacing = 3.5 mm, number of slices = 32, matrix size = 64 × 64 pixels, number of volumes = 115.

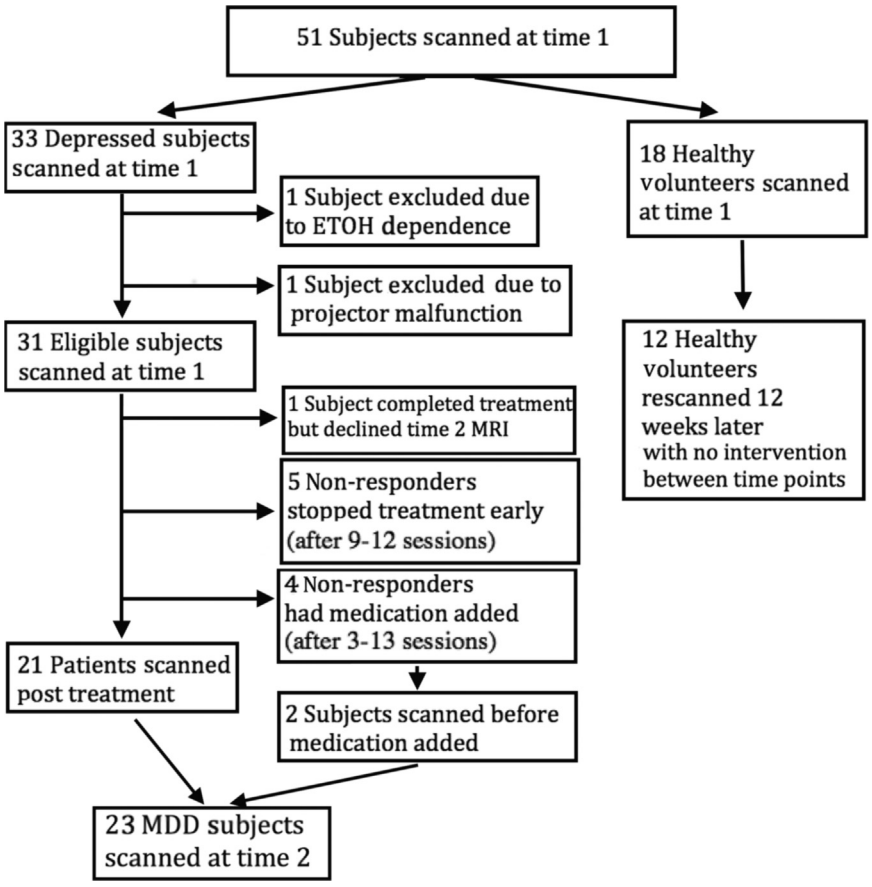

Fig. 1. Participant flow-chart.

2.4. fMRI task design and training

This task was similar to that in Kross et al. (2009). During a semi-structured interview prior to the time 1 scan, participants identified 12 upsetting memories from their lives during which they felt sad, hopeless, unlovable, incompetent, ashamed, humiliated, or neglected. Participants generated a cue phrase for each memory, which served as a prompt during the fMRI task. Six memories were used during each scan; if participants could not identify 12 memories at the baseline interview, a subsequent interview was conducted prior to the time 2 scan. Participants also identified 3 additional practice memories, of a different emotional type than used during scanning (anger, fear, or disgust), for use during task training.

On the day of the scan, participants were reminded of the negative autobiographical memories they generated during screening: each cue was randomly presented on screen and participants were instructed to press a button as soon as they could recall the memory to which it referred. Participants were then trained in the "feel" and "analyze" strategies by a research staff member using a script-driven training including examples with a hypothetical memory. For "feel" trials, participants were instructed to focus on the specific feelings they experienced while recalling event. For "analyze" trials, participants were instructed to identify their thoughts and feelings about the event, and to re-consider the situation from a more realistic, rational, and positive perspective. These techniques were then practiced with 3 practice memories. They then practiced the analyze and feel strategy on 3 practice memories they provided for this purpose. The staff member asked the participant what alternative cognitive responses they would use to reduce their emotional reaction to each memory, and if they had difficulty identifying adaptive, effective alternative responses, the research staff member provided coaching to them to provide additional training.

The task consisted of 3 blocks of memory presentations that alternated with an active baseline condition. Each block consisted of 2 "analyze" trials and 1 "feel" trial or vice-versa, with the sequence of trials counterbalanced across blocks. Trials consisted of a 2-second fixation followed by a 10-second presentation of the cue phrase to a memory, during which participants were instructed to recall the autobiographical memory that the cue indicated, followed by 3-s fixation, after which the cue phrase re-appeared with a strategy instruction ("feel" or "analyze") for 20 s. Participants then rated how emotionally negative they felt and how vivid was their recall of the memory on a 4-point scale, with question order counterbalanced within runs. Each question was shown until the participant responded, up to 3 s. Each memory appeared twice during the task, once during block 1 or 2, and once again during block 3 or 4, with alternating instructions with each presentation. Participants then completed an active baseline task: a 30-second spatial perception task during which they observed arrows pointing left or right and were asked to indicate the direction of the arrow. This task was designed to minimally engage the regulatory, memory, and emotional processes of interest (Stark and Squire, 2001).

2.5. Image processing

2.5.1. Pre-processing

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

2.5.2. fMRI statistical analysis

For each participant, we used a general linear model (GLM) to

Table 1
Demographic and clinical data.

	Controls (N = 18)	MDD (N = 31)	*p*-value (Control vs. MDD, 2-tailed *t*-test)
Age	33 ± 10.3	34.2 ± 10.2	0.7
Initial Hamilton Depression Severity (17-Item)	1 ± 1.5	19.1 ± 4.4	< 0.001
Initial Beck Depression Inventory	0.4 ± 1.7	28 ± 7.7	< 0.001
Final Hamilton Depression Severity (17-Item)	0.4 ± 0.9	12.8 ± 6.5	< 0.001
Final Beck Depression Inventory	1.1 ± 2.6	15.5 ± 8.4	< 0.001
Brown-Goodwin Aggression Score	13.3 ± 3.1	15.5 ± 3	0.03
Years of Education	14.9 ± 1.9	16.5 ± 2.6	0.03
Age at Onset	n/a	16 ± 15.4	
Number of Previous Depressive Episodes	n/a	6.9 ± 25.8	
Length of Current Major Depressive Episode (weeks)	n/a	161.3 ± 223.5	
Categorical variables	**N (%)**		***p*-value (Control vs. MDD, Fisher's Exact)**
Female	11 (61)	19 (55)	1
Scanned at Cornell	5 (28)	11 (35)	0.75
Prior Exposure to Anti-Depressants	n/a	17 (62)	
Suicidal Ideation Present	n/a	8 (27)	
First Degree Relative With Major Depression	n/a	12 (44)	
Past Alchohol or Canabis Abuse	n/a	4 (14)	
Comorbid Anxiety Disorder	n/a	12 (39)	
Comorbid Personality Disorder	n/a	10 (32)	
Comorbid Dysthymia	n/a	1 (3)	
Race/Ethnicity			
Asian	2 (11)	3 (10)	
African American	5 (28)	3 (10)	
Caucasian	8 (44)	17 (55)	
Hispanic	2 (11)	3 (10)	
> 1 Race	0 (0)	4 (13)	

identify brain activity associated with the period during which the subject was processing memories using either the “feel” or “analyze” strategy. The GLM was convolved with a double gamma hemodynamic response function for 5 epochs consisting of: the “feel” and “analyze” cues, the initial memory recall cues, the valence question periods, and the vividness question periods. Rather than using periods of unmodeled fixation (which allow for unconstrained cognitive activity) as an implicit model baseline, we used periods of an active perceptual task (the arrows task) as an umodeled implicit baseline. This was done in order to minimize the occurrence of memory recall outside of the cue periods.

F-Tests were performed to identify clusters in which “feel” signal was greater than “analyze” and vice-versa. Each participant's four runs were combined using a Fixed Effects GLM approach in order to consider the average across all runs.

To identify brain regions where the differences in response between “analyze” and “feel” differed between depressed participants and controls, an *F*-Test was performed between the “feel” > ”analyze” images from time point 1 of the two groups. The average within each diagnostic group was also examined. In order to identify clusters where the “feel” > ”analyze” contrast was associated with current depression severity, baseline BDI score was regressed onto the “feel” > ”analyze” contrast at time 1. In order to identify clusters where the time 1 “feel” > ”analyze” contrast predicted treatment outcome, final BDI was regressed onto the “feel” > ”analyze” contrast at time 1, while covarying for baseline BDI. In order to identify clusters in which change in the “feel” > ”analyze” contrast scaled with clinical improvement, *F*-Tests were performed between Time 1 and Time 2 “feel” > ”analyze” parameter estimates and then final BDI score was regressed onto the result, while covarying for baseline BDI. Analyses were repeated using HDRS score as a secondary outcome measure (see Appendix B).

Higher level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 and stage 2 (Woolrich, 2008). Clusters were identified using a minimum *z*-score of 3.1 and a corrected cluster significance threshold of $p < 0.05$ (Worsley, 2001). The voxel-wise threshold of 3.1 was chosen in order to prevent false positives, as recent critiques of cluster-based thresholding have shown false positives to be common when less stringent thresholds are applied to null data (Eklund et al., 2016; Woo et al., 2014). Scan site was included as a nuisance regressor for each analysis.

2.6. ROI analysis

In order to examine the relationship between treatment outcome and emotion regulation-dependent BOLD suppression within the centers of emotion regulation identified in the paradigm-originating Kross et al. study (Kross et al., 2009), a region of interest (ROI) analysis was performed. ROIs considered were 3 spheres with centers corresponding to the emotion-regulation activation peaks by Kross et al. (lingual gyrus: -12,-43,-2; subgenual anterior cingulate (sgACC): 0,14,-5; and medial prefrontal cortex (mPFC): 6,59,7), with radii of 8 mm (all coordinates in talairach space). Mean parameter estimates for the emotion regulation task were extracted within each sphere for each subject at time 1, and from the time 1 vs time 2 *F*-test. Correlations between the values at time 1 and final BDI score were performed to look for a prediction effect, and time 1 vs. time 2 values were correlated with final BDI to look for longitudinal treatment effects. Scan site and baseline BDI were included as co-variates in these analyses.

3. Results

3.1. Clinical characteristics and treatment outcome

MDD participants were moderately depressed (mean BDI = 28.7 ± 7.7). After treatment, mean BDI scores were 15.5 ± 8.4 in the full MDD sample (40 ± 35% improvement), and 12.5 ± 6.9 in the 22 completers (51 ± 33% improvement). Remission rate (final BDI < = 10) was 32% in intent-to-treat (ITT) sample and 41% in completers; response rate (reduction in BDI > = 50%) was 45% in ITT sample and 59% in completers. Clinical and demographic data are described in Table 1.

3.2. fMRI

All analyses were performed looking at both tails of our contrast of interest (emotion regulation: “feel” > “analyze”, and its inverse:

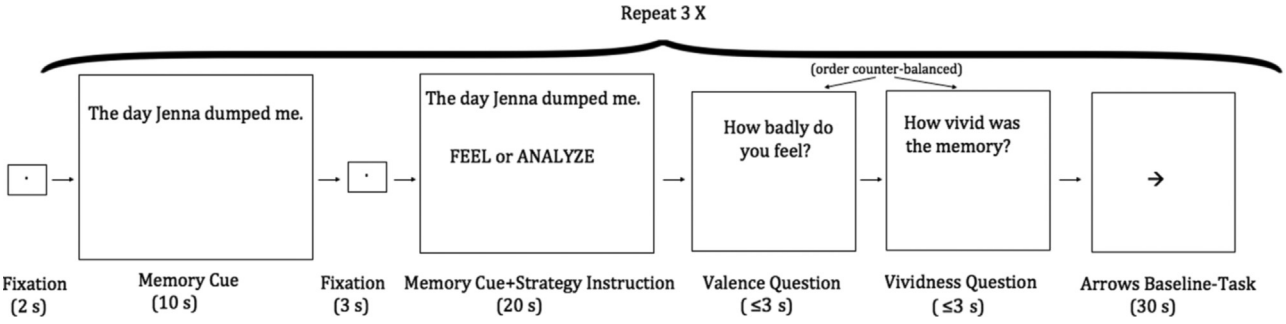

Fig. 2. Schematic of emotion regulation fMRI task design.

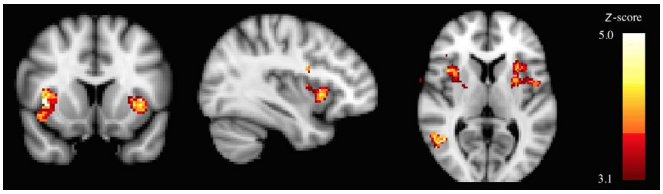

Fig. 3. Regions demonstrating significant reduction of emotion regulation-dependent BOLD signal ("Feel" > "Analyze" contrast) in the depressed group at time 1 (voxel-wise $z > 3.1$, cluster-wise FWE-corrected $p < 0.05$). Significant clusters identified in bilateral insula and right supramarginal gyrus.

"analyze" > "feel"). The inverse contrast did not result in whole-brain or ROI-level findings for any analysis; "emotion regulation-dependent BOLD reduction" below refers to the "feel" > "analyze" contrast (Fig. 2).

3.2.1. Main effect of emotion regulation (within-group)

At time 1, MDD participants had greater BOLD signal during the "feel" condition compared to the "analyze" condition in bilateral insula and right supramarginal gyrus (three clusters, see Fig. 3 and Table 2). No clusters were observed at the *a priori* threshold in the healthy volunteer group.

3.2.2. Effect of diagnosis (MDD vs. Controls)

Emotion regulation-dependent reduction of BOLD signal did not differ between MDD and control groups at the *a-priori* threshold.

3.2.3. Effect of depression severity within MDD

Emotion regulation-dependent reduction of BOLD signal at time 1 was not correlated with current depression severity (BDI-score) at time 1 at the *a priori* threshold.

3.2.4. Baseline emotion regulation signal and treatment outcome

Whole brain voxelwise analysis examining the relationship of pre-treatment emotion regulation-dependent reduction of BOLD signal to subsequent treatment outcome with CBT in the MDD group yielded no significant clusters at our *a priori* thresholds (voxel-level $z > 3.1$, corrected cluster level $p < 0.05$). There were no significant correlations between time 1 emotion regulation-dependent reduction of BOLD signal and treatment outcome at the ROI level ($p > 0.75$, all ROIs).

3.2.5. Longitudinal change in emotion regulation contrast as a function of treatment outcome

Change in emotion regulation-dependent reduction of BOLD signal from time 1 to time 2 for MDD participants was correlated with treatment outcome (defined as final BDI score while controlling for time 1 BDI), in a whole-brain analysis at *a priori* statistical threshold (voxel-wise $z > 3.1$, cluster-wise FWE-corrected $p < 0.05$) in medial frontal pole, left subgenual cingulate, lingual gyrus/cerebellum, left pre-central/supramarginal gyrus, and left putamen (4 clusters, Fig. 4 and Table 3). Greater emotion regulation-dependent reduction of BOLD signal in these clusters at time 2 than at time 1 was associated with better treatment outcome. Examination of this contrast using a secondary measure of treatment outcome, the HDRS, revealed activation in one of these regions, the lingual gyrus (details in supplement including figure B1 and table B1). At the ROI level, treatment outcome was correlated with change in emotion regulation-dependent reduction of BOLD signal in the same direction as voxelwise findings in mPFC ROI ($r = -0.4397$, $p = 0.0344$), and at a trend in the lingual gyrus ROI ($r = -0.374$, $p = 0.077$). Correlation was in the same direction but was not significant in sgACC ROI ($r = -0.317$, $p = 0.139$); this sgACC ROI was medial to the cluster identified in the whole-brain analysis above.

We did not observe a main effect of time on emotion regulation-dependent reduction of BOLD signal (time 1 vs. time 2) in either the healthy volunteers, who received no intervention, or in the MDD group; longitudinal effects in the MDD group were only observed when treatment outcome was considered.

3.3. Behavioral data

During baseline scanning, participants in both groups rated memories during the "feel" instruction as more emotionally negative than those during the "analyze" instruction (MDD: $t = -7.986$, $p < 0.001$; controls: $t = -4.95$, $p < 0.001$); MDD participants also rated emotions recalled during the "feel" prompt as more negative at time 1 compared to time 2 ($t = 2.30$, $p = 0.03$) (see Fig. 5). Detailed behavioral data are presented in Table 4.

We calculated a behavioral measure of emotion regulation success (BERS) for each participant, measured as the difference between mean emotional valence ratings during all "feel" condition trials vs. all "analyze" condition trials within scan. BERS did not differ significantly between MDD participants and controls at time 1, nor did it change significantly from time 1 to time 2 in either group. In the MDD group, neither baseline BERS nor change in BERS were associated with

Table 2
Clusters demonstrating significant emotion regulation-dependent BOLD reduction ("feel" > "analyze") within MDD group. All coordinates in MNI space, mm.

Region	Cluster size (voxels)	Corrected *p*-value	Maximum *z*-stat	Coordinates of maximum	Center of gravity
Right supramarginal gyrus	736	0.00518	4.88	(62, − 36, 26)	(58.4, − 40.1, 19.5)
Left insula	578	0.0132	4.24	(− 36, 12, 4)	(− 36, 7.2, 5.32)
Right insula	494	0.0224	4.65	(60, 0, 0)	(39.1, 7.61, 1.27)

Fig. 4. Regions where greater emotion regulation-dependent BOLD reduction 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 $z > 3.1$, cluster-wise FWE-corrected $p < 0.05$). Clusters included lingual gyrus, left precentral gyrus/putamen, left medial frontal pole, left subgenual cingulate and left supramarginal gyrus.

treatment outcome (all analyses $p \geq 0.47$). Data are summarized in Tables 4 and 5.

4. Discussion

4.1. Primary findings

The primary finding of this study is that emotion regulation-dependent reduction in BOLD signal is enhanced longitudinally as a function of clinical improvement with CBT for depression. This occurs in brain regions relevant to the cognitive control of emotion. While replication and extension in a placebo-controlled study would be necessary to confirm the specificity of these findings to CBT, these data support the possibility that enhancement of the neural correlates of emotion regulation may mediate the effects of CBT on depression severity. This finding appears to be associated with clinical improvement specifically, and not necessarily with general treatment effects, as we observed no mean change in the emotion regulation contrast from pre- to post-treatment at the group level in the MDD group irrespective of treatment outcome.

The longitudinal changes in emotion regulation-dependent BOLD contrast that correlate with treatment outcome may represent a change in self-referential processing of negative autobiographical memories, or in processing of the negative meaning of memories. A recent meta-analysis found self referential processing to be associated with brain activation in cortical midline structures, including medial orbitofrontal cortex and anterior cingulate (Nejad et al., 2013). We found that greater emotion regulation-dependent reduction of BOLD signal in these regions longitudinally to be associated with better treatment outcome. This appeared to be driven by reductions in BOLD signal during the analyze condition, rather than by increases during the feel condition (see Appendix C). Rostral mPFC is also involved in elaborating the negative meaning of stimuli to increase negative responses (Ochsner et al., 2009), and with attention to and awareness of emotion (Satpute et al., 2013). Moreover, its connectivity with amygdala and insula increase in the context of labeling a moderately aversive state as "bad" as opposed to "neutral" (Satpute et al., 2016). An alternative interpretation of this finding is that effective CBT allows individuals to better modulate these mPFC-dependent emotional elaboration/labeling processes.

Our findings are partially consistent with previous work examining longitudinal changes in BOLD fMRI responses following CBT using other task designs (Fu et al., 2008). A 2015 review looking at resting state fMRI data pre- and post- CBT reported that changes were most commonly observed in some of the same brain regions observed in our study, including anterior cingulate cortex (ACC) and ventromedial prefrontal cortex/orbitofrontal cortex (VMPFC/OFC) (Franklin et al., 2016). One study using a reward task showed that a reduction in clinical symptoms following CBT was accompanied by decreases in activation within bilateral sgACC (Straub et al., 2015). An fMRI study examining BOLD responses to visual stimuli of faces with parametrically-modulated levels of sadness identified longitudinal reductions in lingual gyrus activity to negative valence following CBT, in the same direction as our primary finding (Fu et al., 2008). This suggests a convergence of changes in BOLD-fMRI signal following CBT across a range of tasks.

Kross and colleagues' original work using this autobiographical memory emotion regulation task in healthy volunteers found

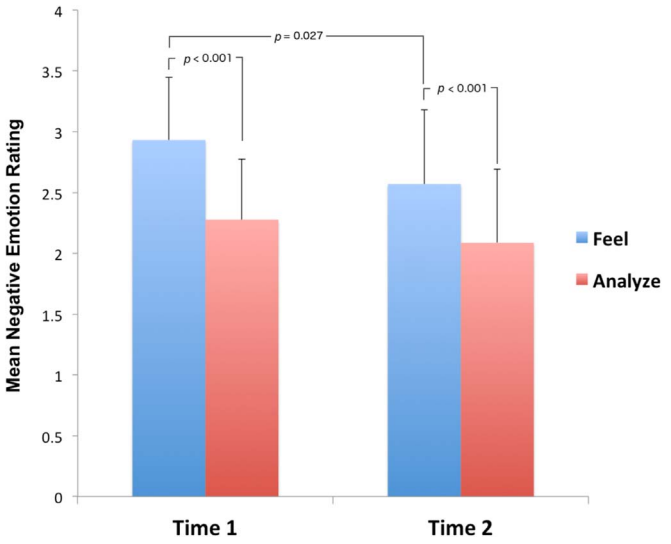

Fig. 5. Within-scanner valence ratings during "feel" and "analyze" conditions at time 1 and time 2 for depressed participants; "feel" at time 2 was rated significantly less upsetting than at time 1 ($p = 0.027$), and "analyze" was rated as less upsetting than "feel" at both time 1 and time 2 ($p < 0.001$ for both).

Table 4
Average in-scanner valence ratings per instruction (rated on a 4 point scale) and valence differences between groups and time points (*t, p*): Table 5: MDD group in-scanner valence ratings correlations with treatment outcome (*r, p*).

	Analyze	Feel	Feel-analyze
Average valence (4 point scale)			
Controls Time1	1.91 ± 0.54	2.52 ± 0.64	0.62 ± 0.54
Controls Time2	1.87 ± 0.49	2.54 ± 0.64	0.67 ± 0.60
MDD Time1	2.28 ± 0.51	2.93 ± 0.51	0.65 ± 0.48
MDD Time2	2.09 ± 0.60	2.57 ± 0.61	0.48 ± 0.45
Valence contrasts (*t,p*)			
Controls vs MDD Time1	− 2.48, 0.02*	− 2.50, 0.02*	− 0.26, 0.79
Controls vs MDD Time2	− 1.07, 0.29	− 0.13, 0.9	1.06, 0.3
Controls Time1 vs Time2	0.00, 1	− 0.15, 0.88	− 0.15, 0.88
MDD Time1 vs Time2	1.70, 0.1	2.30, 0.03*	0.72, 0.47

* $p < 0.05$

Table 3
Clusters where greater emotion regulation-dependent BOLD reduction at time 2 compared to time 1 are associated with better treatment outcome (lower final BDI score while covarying for baseline BDI score; voxel-wise $z > 3.1$, cluster-wise FWE-corrected $p < 0.05$). All coordinates in MNI space, mm.

Regions	Cluster Size (voxels)	Corrected *p*-value	Maximum *z*-stat	Coordinates of Maximum	Center of Gravity
Lingual gyrus/cerebellum	1482	0.00027	4.5	(20, − 60, − 24)	(7.97, − 67.9, − 15.2)
Left precentral gyrus/ putamen	1405	0.000372	4.59	(− 56, − 2, 10)	(− 39.2 − 18, 13.3)
Left medial frontal pole/subgenual cingulate	1008	0.00217	4.8	(2, 54, − 12)	(− 10.3, 42, − 14.1)
Left supramarginal gyrus	524	0.0265	4.73	(− 60, − 24, 10)	(− 59.8, − 27.1, 10.4)

Table 5
MDD group in-scanner valence ratings correlations with treatment outcome (*r, p*).

	Time1 valence correlations with:		Time 2 valence correlations with:		Time1-Time 2 Valence with:
Contrast	Time1 BDI	Change in BDI (Time 1- Time 2)	Time 2 BDI	Change in BDI (Time 1 - Time 2)	Change in BDI (Time 1 - Time 2)
Analyze	− 0.016, 0.93	0.098, 0.60	− 0.60, 0.003*	− 0.47, 0.023*	0.40, 0.06
Feel	0.13, 0.50	0.053, 0.78	− 0.65, 0.001*	− 0.43, 0.039*	0.33, 0.13
Feel-Analyze	0.072, 0.70	− 0.047, 0.80	− 0.076, 0.73	0.046, 0.83	− 0.033, 0.88

* $p < 0.05$

differences in activation between the “feel” and “analyze” conditions in lingual gyrus, subgenual anterior cingulate, and anterior medial prefrontal cortex (Kross et al., 2009). We found that changes in treatment outcome were associated with changes in emotion regulation activation in overlapping parts of lingual gyrus and mPFC and adjacent (more lateral) left subgenual cingulate in whole-brain voxelwise analysis, and in mPFC, with a trend in lingual gyrus, in ROI analyses. This implies that therapeutic effects of CBT for depression might be mediated by an enhancement of the neural correlates of emotion regulation observed in healthy individuals. Differences in MRI acquisition and analysis, as well as uncertainty associated with reported activations, may have also contributed to localization differences.

We found that changes in treatment outcome as assessed by HDRS-17 scores were also associated with changes in emotion regulation activation in lingual gyrus (see Appendix B), although not in other regions. The lingual gyrus is therefore strongly implicated in this analysis, as it was correlated with both treatment outcome measures despite their differences (patient vs therapist assessed, differential weights of mood vs. physical symptoms).

4.2. Main effects of emotion regulation

At baseline, MDD participants exhibited decreased activity in the “analyze” as compared to the “feel” condition in bilateral anterior insula. This finding is consistent with work identifying decreased insula activity during reappraisal in healthy volunteers (Goldin et al., 2008; Holland and Kensinger, 2013). In contrast, a meta-analysis examining fMRI studies of emotional reappraisal found increased activity during reappraisal in left anterior insula (Buhle et al., 2014). However, the majority of the task designs from the studies included in that meta-analysis used reappraisal to images rather than memories, and were performed in healthy volunteers. Regulation of anterior insula activity during reappraisal is not unexpected given its role in emotion processing (Gasquoine, 2014), of adjacent regions in cognitive control (Wager and Barrett, 2017), and of pre-stimulus activity in insula predicting subsequent emotion regulation success (Denny et al., 2014). Pre-treatment resting glucose metabolism in anterior insula was identified as a predictor of differential outcome to CBT vs. escitalopram in a recent randomized clinical trial (McGrath et al., 2013), although we did not observe prediction effects related to insula activity in the current study.

4.3. Other findings

We did not observe differences in emotion regulation-dependent BOLD contrast between the depressed and control groups, nor did we observe a main effect of emotion regulation within the control group. This may be partly explained by limitations in statistical power due to sample size of the control group (n = 18), and to the less aversive memories elicited by the control group. While some studies have identified emotion regulation deficits in depression at the behavioral level (Gotlib and Joormann, 2010; Kircanski et al., 2012), a recent fMRI study has suggested intact emotion regulation-related activity in depressed individuals (Dillon and Pizzagalli, 2013). Similarly, pre-treatment emotion regulation-related activity did not predict treatment outcome with CBT in the MDD group. Although previous studies have been able to predict CBT outcome with fMRI (Costafreda et al., 2009; Siegle et al., 2006; Thompson et al., 2015), they generally used tasks related to emotional reactivity, and not regulation. These findings suggest that while emotion regulation-related activity may be intact in MDD, enhancement of this activity via CBT may contribute to clinical improvement.

4.4. Study limitations

The primary limitations of the study were the lack of randomization to different treatment conditions, including a placebo condition, and the modest sample size, particularly in the healthy volunteer group. In addition, our sample included patients with comorbid anxiety disorders (N = 12) and personality disorders (N = 10, five of whom also had anxiety disorders), so we cannot be sure of our finding's specificity to MDD. Replication in a larger sample and with randomization to different treatment conditions will be crucial in future studies to evaluate the specificity of our findings to CBT.

Although the relationship between treatment outcome and change in emotion regulation-related BOLD suppression may represent a change in self-referential processing of autobiographical memories, this could not be examined more closely in our study because ratings of self-referential thinking were not acquired. Future work could acquire longitudinal measures of self-referential processing (using a scale such as the Ruminative Response Scale (Treynor et al., 2003)) to relate to fMRI data and clinical outcome.

The stimuli for the task used here have high levels of face validity, as they are highly relevant to the participant and potentially to their depression. However, they are not standardized across participants, and use of novel stimuli may also have a role in testing cognitive reappraisal.

It is well known that MDD patients tend to over-generalize negative memories (Williams et al., 2007). It is possible that the recall of memories could have differed between MDD and controls groups for this reason. Of note, depressed participants and healthy volunteers were similarly able to associate each memory with a specific date. The primary findings of this study are related to treatment effects within the depressed group alone; however, an overgeneralization effect in the depressed sample could be a possible confound in the analyses comparing diagnostic groups.

Given our strong prior interest in the three regions used for ROI analyses, we believe that a finding (in mPFC) that is not corrected for multiple comparisons across the ROIs (using a Bonferroni factor of 3) constitutes a significant finding. Replication of this finding in an independent sample is required.

4.5. Future directions

We found that longitudinal increases in emotion regulation BOLD contrast in several anatomically distant regions was associated with treatment outcome with CBT. Further work examining functional connectivity may identify functional networks whose synchronous activity may relate to treatment outcome in CBT.

Our study examined a form of emotion regulation seeking to decrease emotionally negative responses to aversive memories, but given

fMRI findings in depression related to upregulation of positive affect (Johnstone et al., 2007), it would also be interesting to examine this form of emotion regulation and its relationship to CBT outcome. Combination of task-based fMRI with other biomarkers (Fujino et al., 2015; Harkness et al., 2012; Lueken et al., 2015; Nemeroff et al., 2003; Stiles-Shields et al., 2015) may enhance power to predict treatment outcome and understand longitudinal effects of treatment.

Finally, if reduced engagement of medial prefrontal cortex, anterior cingulate, and lingual gyrus during conscious regulation of emotion is validated as a mediator of outcome with CBT for MDD, novel treatment approaches may be considered to enhance neuroplasticity in these regions during CBT, using pharmacological or brain stimulation interventions (Bajbouj and Padberg, 2014; Herrmann et al., 2017).

4.6. Conclusions

Clinical improvement following CBT for depression is associated with longitudinal changes in emotion regulation-dependent BOLD contrast, in regions including anterior cingulate, medial orbitofrontal cortex, and lingual gyrus. This suggests a possible neural mediator of CBT effects in MDD, related to conscious regulation of affective and self-relevance processing of aversive memories.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2017.11.002

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