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Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing

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Cognitive behavioral therapy (CBT), an effective treatment for depression, targets self-referential processing of emotional stimuli. We examined the effects of CBT on brain functioning during self-referential processing in depressive patients using functional magnetic resonance imaging (fMRI). Depressive patients ($n = 23$) and healthy participants ($n = 15$) underwent fMRI scans during a self-referential task using emotional trait words. The depressive patients had fMRI scans before and after completing a total of 12 weekly sessions of group CBT for depression, whereas the healthy participants underwent fMRI scans 12 weeks apart with no intervention. Before undergoing CBT, the depressive patients showed hyperactivity in the medial prefrontal cortex (MPFC) during self-referential processing of negative words. Following CBT, MPFC and ventral anterior cingulate cortex (vACC) activity during self-referential processing among depressive patients was increased for positive stimuli, whereas it was decreased for negative stimuli. Improvements in depressive symptoms were negatively correlated with vACC activity during self-referential processing of negative stimuli. These results suggest that CBT-related improvements in depressive symptoms are associated with changes in MPFC and vACC activation during self-referential processing of emotional stimuli.

Keywords: depression; fMRI; cognitive behavioral therapy; self-referential processing; emotion

INTRODUCTION

Depression is an affective disorder characterized by emotional, cognitive and behavior dysfunction. Depressive mood, negative cognitive biases and behavioral withdrawal interact with each other, and this interaction helps maintain depressive symptoms (Beevers, 2005). Negative cognitive biases include negative thinking patterns and memory biases, and in general serve to sustain negative emotional processing. In turn, negative emotional processing repeatedly reinforces negative cognitive bias, thereby shaping maladaptive feedback loops (Teasdale, 1985). According to Beck's cognitive theory of depression, depressive patients frequently have negative thoughts about the self (Beck, 2008). This self-referential bias is a key dysfunctional cognition that maintains and intensifies depression. Self-referential bias is associated with rumination or maladaptive self-focus (Ingram, 1984; Pyszczynski and Greenberg, 1987; Nolen-Hoeksema *et al.*, 2008). Several studies provide evidence that rumination and maladaptive self-focus with regard to stressors or negative emotional events induce negative mood (Mor and Winquist, 2002; Moberly and Watkins, 2008).

The core brain regions involved in depression-related negative self-referential bias are the medial prefrontal cortex (MPFC), the ventral anterior cingulate cortex (vACC) and the amygdala. The MPFC shows aberrant engagement during self-reference processing (Northoff, 2007; Grimm *et al.*, 2009; Johnson *et al.*, 2009; Lemogne *et al.*, 2009, 2010, 2011, 2012). The vACC and amygdala are associated with evaluation of emotional stimuli and elicitation of emotional responses (Bush *et al.*, 2000; Siegle *et al.*, 2002; Habel *et al.*, 2005; Moran *et al.*, 2006). Therefore, we propose that the MPFC, vACC and amygdala might be involved in self-referential processing of negative emotional stimuli, and as such might constitute a dysfunctional cognitive–emotional neural circuit that underlies depression.

Cognitive behavioral therapy (CBT) seeks to disrupt the vicious cycle of depressed mood, dysfunctional cognition and behavioral inhibition that is observed in depressive disorders. CBT's targets include negative self-referential cognitions. A few studies have investigated the effects of CBT on brain functioning in depression. Resting state positron emission tomography (PET) studies have found that patients who receive CBT show increased activation in the dorsal ACC and decreased activation in the DLPFC and MPFC, compared with patients who receive pharmacotherapy (Goldapple *et al.*, 2004; Kennedy *et al.*, 2007). Using an experimental task to more directly engage affective processing, Fu *et al.* (2008) reported decreased amygdala activity in depressive patients following CBT, with dorsal ACC activity being associated with a clinical response. The results of these studies suggest that CBT might have an effect on the medial frontal region. We propose that the abnormal brain activation observed in depressive patients might not only reflect relatively simple processing of negative emotional stimuli, such as emotional faces or words but also more cognitively demanding processing such as self-referential processing of emotional stimuli (Grimm *et al.*, 2009; Lemogne *et al.*, 2009, 2010, 2012). However, no studies have examined how CBT might affect brain functioning associated with negative self-referential cognition. Thus, this relationship and the relationship between CBT and the neural connections between the frontal and limbic regions remain poorly understood.

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Our previous study revealed that depressive patients show high levels of activation in the MPFC and vACC during self-referential processing (Yoshimura *et al.*, 2010). Therefore, we hypothesize that depressive patients (before receiving CBT) would show greater MPFC and vACC activation relative to healthy participants. Goldapple *et al.* (2004) reported decreased activation in the MPFC at resting state following CBT but not after treatment with an antidepressant medication (paroxetine). Another study also suggested that antidepressants may have no effect on MPFC overactivation during self-referential processing in depression (Lemogne *et al.*, 2010). We hypothesize that abnormal MPFC, vACC and amygdala activation during a self-referential task involving negative stimuli might be attenuated following CBT. In addition, there is some evidence that depression-related neural activity is a sensitive predictor of CBT treatment outcomes (Siegle *et al.*, 2006; Fu *et al.*, 2008). Therefore, in this study we examined the potential association between treatment response to CBT and neural activity during self-referential processing of emotional stimuli.

METHODS

Participants

Depressive patients ($n = 23$) were recruited from the outpatients of the Department of Psychiatry and Neurosciences of the Hiroshima University Hospital. Inclusion criteria were: (i) diagnosis established by a psychiatrist using the Structured Clinical Interview for DSM-IV and (ii) the patient met the criteria for major depressive disorder according to DSM-IV. Exclusion criteria consisted of current or previous diagnosis of a bipolar disorder, psychotic spectrum disorder, evidence of organic brain disorder, current high risk of suicide, substance abuse, mental retardation or serious somatic disease. All patients had been taking one or more antidepressant drugs (i.e. serotonin reuptake inhibitor, serotonin and noradrenalin reuptake inhibitor and tricyclic antidepressant) for a minimum of 8 weeks without remission of symptoms. Drug types and doses were maintained over the course of the group CBT treatment. The demographic and clinical characteristics of the participants are presented in Table 1. Nine patients in this study also participated in our previous study (Yoshimura *et al.*, 2010).

Healthy control participants ($n = 15$) were recruited from normal populations. These control participants endorsed no symptoms of depression and had no history of psychiatric disorder. All patients and control participants had normal vision, and reported no notable health or eye problems.

The Ethics Committee of Hiroshima University approved the study protocol. Informed consent was obtained from all participants.

Evaluation and treatment protocol

The depressive patients participated in 12 weekly, 90-min sessions of CBT conducted by a clinical psychologist with groups of five or six participants. The session topics were as follows: psychoeducation about depression; psychoeducation about group CBT; self-monitoring of automatic thoughts, behaviors and mood; understanding the relationship between cognition and mood; identifying negative self-talk; challenging negative self-talk; challenging and restructuring negative thinking about the self; looking for new ideas and invoking positive thinking; practicing the new ideas and positive thinking in daily life; evaluating one's own ideas and thinking during the last week, and setting up an action plan for the next week; reviewing the outcome of the program; and finally, relapse prevention.

Patients' progress was monitored regularly using the Beck Depression Inventory (BDI). The Hamilton Rating Scale for Depression (HRSD) was used to evaluate symptom improvement. The Dysfunctional Attitude Scale (DAS), Automatic Thoughts Questionnaire (ATQ) and Response Styles Questionnaire (RSQ) were used to measure psychological factors in depressive patients. A more detailed treatment protocol is described in our previous report (Matsunaga *et al.*, 2010).

The healthy control participants were administered the BDI at the start and end of the research ~12-week interval.

Experimental design

All participants underwent two functional magnetic resonance imaging (fMRI) scans, ~12 weeks apart, while they did the judgment tasks. For the depressive patients, the scans occurred before and after the completion of 12 weeks of CBT. The healthy control participants did not participate in any experimental intervention during the 12-week interval. Details of the experimental design have been described in our previous study (Yoshimura *et al.*, 2009, 2010).

In the judgment tasks administered during the fMRI scans, the participants were instructed to make one of four judgments about visually presented words. In the *self-reference condition*, participants judged whether or not each trait word described them. In the *other-reference condition*, participants judged whether or not each trait word described the Prime Minister of Japan (Jun-ichiro Koizumi). In the *semantic-processing condition*, participants judged whether or not it was difficult to define each trait word. In the *letter-processing condition*, participants assessed whether or not each trait word contained a specific target letter. The semantic-processing and letter-processing conditions were used to control for extraneous variables, such as the visual and motor processing of stimuli, as well as language processing.

The four judgment conditions each included both positive and negative word stimuli, resulting in a total of eight conditions overall. For all conditions, participants made a 'yes' or 'no' response by pressing a button with the right-hand index or middle finger, respectively. Button presses were recorded using an MRI-compatible keypad (Lumitouch; Lightwave Technologies, Richmond, BC, Canada). Participants performed each condition a total of four times, with each performance of a condition consisting of a block of five trials. At the onset of each condition block, a fixation cross was displayed for 1000 ms, followed by an instruction cue presented for 3000 ms (e.g. 'self-reference condition'). Participants then received five trials consisting of a fixation cross displayed for 1000 ms, followed by an adjective displayed for 3000 ms and the participant's response. A fixation point was then displayed for 4000 ms, followed by the instruction cue for the next block of five trials. Each condition was presented separately. The duration of each block was 28 s. To control for order effects, blocks within a run were presented in a pseudo-random order, with no two consecutive blocks featuring the same instructions. The total time for the self-reference task was 908 s. Both responses and reaction times were recorded using Presentation software.

fMRI data acquisition

fMRI was performed using a Symphony 1.5 T device (Siemens, Tokyo, Japan). A time-course series of 227 scans was acquired with T2*-weighted, gradient echo, echo-planar imaging (EPI) sequences. Each volume consisted of 38 slices, with a slice thickness of 4 mm with no gap, and covered the entire cerebral and cerebellar cortices. The interval between two successive acquisitions of the same image (TR) was 4000 ms, the echo time (TE) was 48 ms and the flip angle was 90°. The field of view (FOV) was 256 mm, and the matrix size was 64×64, giving voxel dimensions of $4 \times 4 \times 4$ mm. Scan acquisition was synchronized to the onset of each trial. After functional scanning, structural scans were acquired using a Tl-weighted gradient echo pulse sequence (TR = 12 ms; TE = 3.93 ms; flip angle 25°; FOV 256 mm; voxel dimensions of $1 \times 1 \times 1$ mm), which facilitated localization.

Table 1 Demographic and clinical characteristics of the sample

	Depressive patients ($n = 23$)		Healthy control participants ($n = 15$)	
	Time 1 (baseline)	Time 2 (following CBT)	Time 1 (baseline)	Time 2 (following CBT)
Age	37.3 ± 7.2		36.7 ± 8.2	
Gender	7 female, 16 male		7 female, 8 male	
Depressive episodes (#)	1.7 ± 0.9		–	
Duration of depressive episode (weeks)	63.0 ± 125.1		–	
Duration of illness (months)	16.2 ± 12.6		–	
BDI	21.4 ± 8.5	13.1 ± 6.4	6.4 ± 5.1	4.9 ± 4.5
HRSD	11.0 ± 4.8	6.2 ± 4.6	–	–
DAS	155.0 ± 32.5	136.7 ± 36.1	–	–
ATQ (positive scale)	18.7 ± 9.2	21.0 ± 8.5	–	–
ATQ (negative scale)	90.5 ± 31.3	69.1 ± 27.5	–	–
RSQ (rumination scale)	46.5 ± 10.9	41.9 ± 10.3	–	–
RSQ (distraction scale)	18.7 ± 5.2	22.5 ± 22.5	–	–
Behavioral response ($n = 21$)				
Judgment ratio				
Self/positive	34.3 ± 24.8	44.8 ± 26.8	63.3 ± 20.8	57.0 ± 27.2
Self/negative	41.9 ± 21.8	34.8 ± 25.6	12.7 ± 8.6	12.7 ± 10.8
Reaction time (ms)				
Self/positive	1553.0 ± 195.7	1548.9 ± 199.1	1685.1 ± 231.2	1651.0 ± 291.7
Self/negative	1631.1 ± 267.7	1612.8 ± 257.8	1713.8 ± 256.7	1668.3 ± 329.7

fMRI data analysis

Image processing and statistical analyses were carried out using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, London, UK). The first two and last single volumes of the fMRI run were discarded because the MR signals were unsteady or empty. All EPI images were spatially normalized using the Montreal Neurological Institute (MNI) T1 template for group analysis. Imaging data were corrected for motion and smoothed with a 4-mm full-width, half-maximum Gaussian filter.

To perform image data analysis, a whole-brain voxel-by-voxel multiple linear regression model was employed at the individual participant level. The individual model comprised the covariate of no interest (realignment parameters). We examined the contrasts between the self-reference conditions and the sum of the two control conditions (semantic processing and letter processing) for both positive and negative valence words. As we were only interested in activity during self-referential processing, the other-referential condition was excluded from analysis. These contrasts were submitted to group analysis, using a random effect model. We conducted whole brain three-way repeated measures ANOVAs as implemented in SPM8 with group (patients *vs* healthy) as a between-subjects factor, and time (time 1 *vs* time 2) and emotional valence (positive *vs* negative) as within-subjects factors. To exclude gender effects, we added participant gender as a nuisance covariate. Activations were reported $P < 0.001$ (uncorrected) over the 30-voxel level. All coordinates are reported using the MNI coordinate space. Signal intensity from the three-way interaction active cluster was extracted using the volume of interest tool in SPM8, and multiple comparisons (Bonferroni correction) of three-way interaction effects were conducted using SPSS.

To examine the brain activation during the self-referential task that predicts subsequent CBT responses, we performed a correlational analysis between percentage improvement in HRSD score [= (1 − HRSD score at time 2/HRSD score at time 1) × 100] for each depressive patient after CBT, and activation of brain regions in depressive patients before CBT was received. In addition, to examine the changes of brain activation following CBT, which were associated with reduction of rumination [= −(rumination score at time 2/rumination score at time 1) − 1 × 100], we conducted a correlational analysis between reduction of rumination and activation of brain regions in depressive patients following CBT.

RESULTS

Effect of CBT

The CBT group treatment was generally effective in reducing depression, as indicated by changes in BDI scores, F (22, 1) = 23.74, $P < 0.001$, and HRSD scores, F (22, 1) = 23.60, $P < 0.001$. There were no significant correlations in initial HRSD scores before CBT and no percentage changes in HRSD scores as a function of CBT and BDI score changes for the depression. In addition, CBT contributed to changes in several psychological scales including the DAS, F (22, 1) = 7.80, $P < 0.05$, ATQ (negative scale), F (22, 1) = 12.02, $P < 0.005$, RSQ (rumination scale), F (22, 1) = 5.77, $P < 0.05$ and RSQ (distraction scale), F (22, 1) = 11.85, $P < 0.005$ (Table 1).

Behavioral data

We conducted a three-way ANOVA for the judgment ratio data in the self/positive and self/negative conditions with group (patients *vs* healthy) as a between-subjects factor, and time (time 1 *vs* time 2) and emotional valence (positive *vs* negative) as within-subjects factors. Due to a technical problem, the behavioral data of two depressive patients were incomplete; therefore, only 21 patients were included in the ANOVA. The three-way interaction was significant [F (1, 34) = 5.17, $P < 0.05$]. Multiple comparisons (a Bonferroni correction) showed significant judgment rate differences between time 1 and time 2 for the depressive patients in the self/positive condition ($P < 0.05$). In the self/negative condition, the difference between time 1 and time 2 for the depressive patients was marginally significant ($P = 0.073$).

We conducted a three-way ANOVA for the reaction times in same way as for the judgment ratios. Only a significant main effect of emotional valence was found [F (1, 34) = 4.71, $P < 0.05$]. Reaction times to negative stimuli were significantly slower than to positive stimuli ($P < 0.05$).

fMRI data

A three-way repeated measures ANOVA was conducted to examine possible differences across group, time and stimulus valence. There was

a significant three-way interaction effect (Figure 1) for the left vACC (MNI coordinates [*x*, *y*, *z*][0, 46, 6], cluster size = 156 voxels; $F = 34.09$, $df = 1,36$), left superior temporal cortex ([−54, −64, 26], cluster size = 70 voxels; $F = 23.67$, $df = 1,36$) and the left MPFC ([−6, 44, 44], cluster size = 33 voxels; $F = 20.84$, $df = 1,36$). *Post hoc* analysis revealed that healthy control participants showed significant activation increases relative to patients at time 1 (baseline) for the vACC, superior temporal cortex and MPFC in the self/positive condition (all $P < 0.01$). In the self/negative condition, patients showed significant activation increases relative to healthy participants at time 1 (baseline) for the vACC and MPFC (all $P < 0.05$). At time 2, patients showed increased activation in the self/positive condition compared with healthy participants for the vACC, superior temporal cortex and MPFC. In the self/negative condition, healthy participants showed significant activation increases relative to patients at time 2 for the vACC, superior temporal cortex and MPFC (all $P < 0.01$). In addition, for depressive patients, activation in these regions significantly increased from time 1 to time 2 for the self/positive condition (all $P < 0.05$). Correspondingly, activation in these regions was significantly decreased from time 1 to time 2 for the self/negative condition (all $P < 0.05$). On the other hand, for healthy control participants, activation in the MPFC and vACC was significantly decreased from time 1 to time 2 for the self/positive condition (all $P < 0.05$) and increased from time 1 to time 2 for the self/negative condition (all $P < 0.01$). For depressive patients at time 1, activation in the vACC, superior temporal cortex and MPFC in the self/negative condition significantly increased relative to that in the self/positive condition (all $P < 0.01$). At time 2, depressive patients in the self/negative condition showed significant activation increases relative to that in the self/positive condition for the vACC and superior temporal cortex (all $P < 0.05$). On the other hand, for healthy control participants at time 1, activation in the vACC and MPFC in the self/positive condition was significantly increased relative to that in the self/negative condition (all $P < 0.05$). At time 2, healthy control participants showed significantly increasing activation in the vACC, superior temporal cortex and MPFC in the self/negative condition relative to that in the self/positive condition (all $P < 0.01$).

There were no other significant interactions.

There was a significant negative correlation between percent changes in HRSD scores and vACC activation in the self/negative condition, before CBT was received ($r = -0.60$, $P < 0.01$; $r^2 = 0.36$, $P < 0.005$). This negative correlation indicates that patients with greater clinical improvement following CBT had lower activity in the vACC (Figure 2A).

In addition, there was a significant positive correlation between percent changes in the rumination score and vACC activation changes in the self/negative condition following CBT ($r = 0.49$, $P < 0.05$; $r^2 = 0.24$, $P < 0.05$). This positive correlation indicates that patients with greater

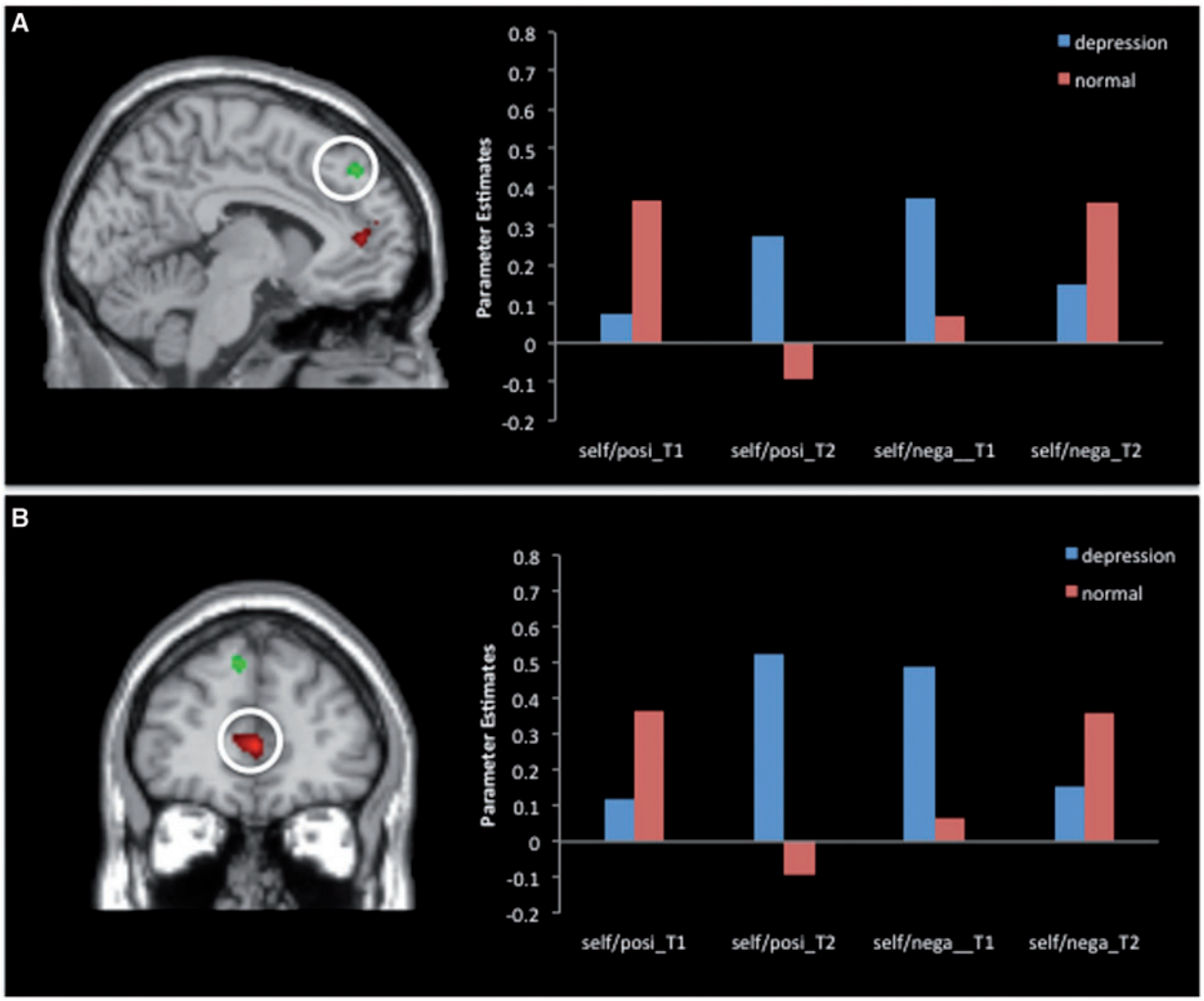

Fig. 1 (**A**) Picture and graph displays activation in the MPFC (green region) and parameter estimates for each condition in the three-way interaction. (**B**) Picture and graph displays activation in the vACC (red region) and parameter estimates for each condition in the three-way interaction. Both clusters of activities were overlaid on T1-weighted anatomical brain images.

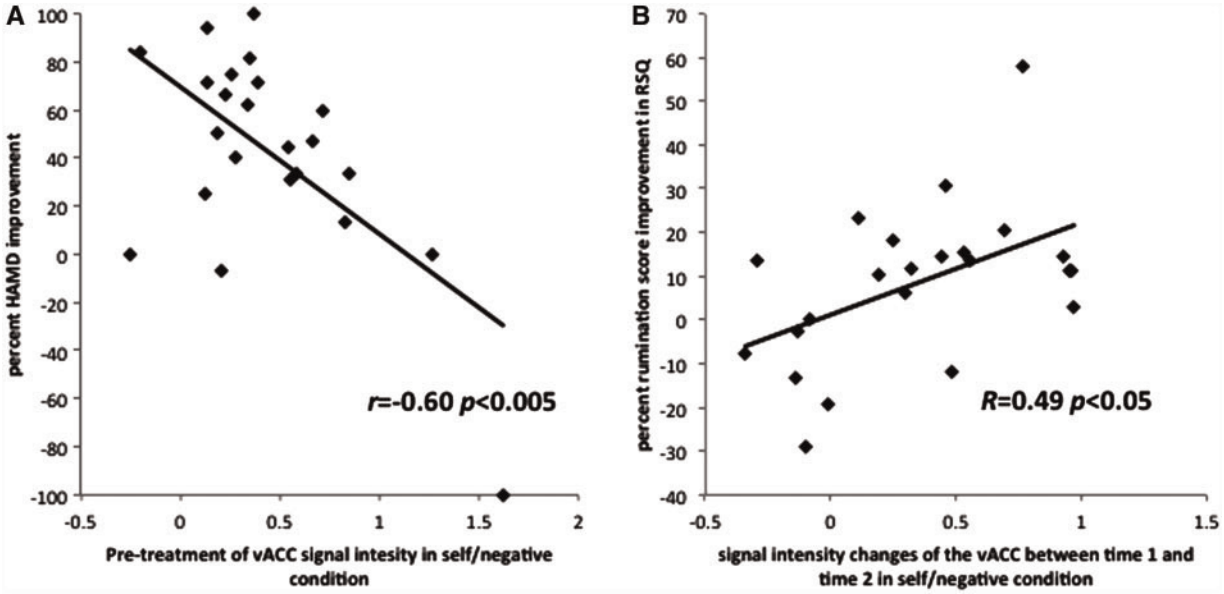

Fig. 2 Left scatter plot and associated correlation coefficient illustrate the relationship between vACC parameter estimates and percent symptom improvement in the self/negative condition (**A**). Right scatter plot and associated correlation coefficient illustrate the relationship between changes of vACC parameter estimates and percent changes of rumination score on the Rumination Styles Questionnaire in the self/negative condition following CBT (**B**).

improvement in rumination following CBT had more activation changes in the vACC (Figure 2B).

DISCUSSION

Self-referential processing of negative stimuli, as one form of negative rumination, is thought to be an important cognitive feature of depression (Nolen-Hoeksema *et al.*, 2008). Excessive negative self-rumination results in further deterioration of depressive mood (Nolen-Hoeksema *et al.*, 1993; Watkins and Moulds, 2005). CBT seeks to improve depressed mood by intervention at the level of cognitions and behaviors. In this study of depressive patients, we examined how CBT affects brain functioning that underlies self-referential processing of negative stimuli. Compared with control participants, depressive patients showed increased activation in the MPFC during the self/negative condition. Following group CBT, depressive patients showed decreased activation in the MPFC and vACC during self-referential processing of negative words, and increased activation in these regions during the processing of positive words. Correlational analysis revealed an association between treatment response and pre-treatment vACC activity during self/negative conditions. These findings represent the first report of CBT-related changes in vACC activity in depressive patients during self-referential processing of negative stimuli.

Previous studies have reported that the MPFC might play an important role in self-referential processing (Kelley *et al.*, 2002; Fossati *et al.*, 2003, 2004; Moran *et al.*, 2006; Schmitz *et al.*, 2006). In addition, our previous work revealed that the MPFC is associated with self-referential or other-referential processing of emotional stimuli (Yoshimura *et al.*, 2009). The vACC was also engaged, particularly during self-referential processing of negative emotional stimuli. In addition, our previous work (Yoshimura *et al.*, 2010) with depressive patients revealed that MPFC and vACC activations during self-referential processing of negative emotional stimuli are correlated with symptoms of depression. This relationship between the MPFC and the vACC might underlie a 'vicious cycle' of self-referential and negative emotional processing (Northoff, 2007).

This study identified decreased activation in the MPFC and vACC following CBT, which suggests one mechanism whereby CBT might attenuate depressive cognitive–emotional processing. In addition, CBT was associated with increased MPFC and vACC activity during self-referential processing of positive stimuli. Ritchey *et al.* (2011) reported increased ventral MPFC activity during the processing of positive stimuli following CBT. However, this CBT effect on brain activation was not emotion-specific, given that activation increases were identified for positive as well as neutral and negative stimuli.

These results suggest that the increases in more balanced, positive thinking and pleasant activity that follow successful CBT promote a more positive self-concept, such that the MPFC and vACC become more responsive to positive stimuli during self-referential processing. Previous functional brain imaging studies of CBT have reported that CBT alters resting state activation of the MPFC, ACC and dorsolateral prefrontal cortex (DLPFC) (Goldapple *et al.*, 2004; Seminowicz *et al.*, 2004). These data imply that CBT works to effect top-down modulation from the cortical to the limbic region (Goldapple *et al.*, 2004). Our findings appear to support top-down modulation, given the direct MPFC and vACC activation changes that we observed.

CBT for depression includes at least two essential components. One is identifying and correcting inaccurate thoughts associated with negative emotion (cognitive restructuring). Another is helping patients to engage in more pleasurable activities, such as exercise or listening to music (behavioral activation). Recent brain imaging studies of emotion regulation as a component of CBT report that the lateral prefrontal cortex and MPFC are associated with emotion regulation and that these regions inhibit the amygdala (Ochsner *et al.*, 2002; Ochsner and Gross, 2005; Etkin *et al.*, 2006; Wager *et al.*, 2008). CBT is thought to correct dysfunctional cognitive processes that maintain depression, such as rumination, overgeneralization and self-focused attention. These dysfunctional cognitive processes might be associated with amygdala or ventral/rostral ACC activation. Some research reports that improvements in depressive symptoms are associated with attenuated activation in these regions. However, this study did not find decreased amygdala activity during self-referential processing of negative stimuli. These results perhaps indicate that decreased negative emotional processing occurs concurrently with decreased self-referential processing.

On the other hand, Dichter *et al.* (2009) suggested that behavioral interventions for depression (behavioral activation therapy) might enhance brain reward system functioning, which includes regions such as the striatum involved in reward selection. We can assume that cognitive and behavioral interventions improve depressive symptoms to a similar degree, but perhaps via different mechanisms. The present intervention included both types of intervention and we could not relate these separate components to specific patterns of brain activation. Future research could distinguish between CBT components, and examine the effect of each component on brain functioning associated with changes in cognition and behavior.

CBT treatment response in this study was associated with vACC activation in the self/negative condition. The negative correlation between treatment response and vACC activation in the self/negative condition suggests that depressive patients with relatively low sensitivity to negative emotion benefitted most from CBT or other treatment. In the study of Siegle *et al.* (2006), depressive patients received CBT and participated in an fMRI scan during a self-referential task. They reported that treatment improvement was correlated with vACC activity before receiving CBT, as was also found in this study. They suggested that CBT is useful for depressive patients who cannot engage in sufficient emotional regulation.

Although our present results are consistent with the results of Siegle *et al.* (2006), we have a different interpretation. Because CBT decreased vACC activation during the self/negative condition, the vACC activation observed here was likely associated with self-referential processing in the form of rumination, rather than emotional regulation. In addition, recent research has reported an association between rumination and vACC function in the context of both self-referential processing and depression (Ray *et al.*, 2005; Cooney *et al.*, 2010; Berman *et al.*, 2011; Heatherton, 2011). These researchers suggest that vACC activity might reflect attention toward one's internal emotional state in depression.

However, not only self-referential tasks activate the vACC but also other cognitive tasks using emotional stimuli often activate the vACC in depression (Keedwell *et al.*, 2005; Fu *et al.*, 2008; Matthews *et al.*, 2008) One possible explanation about vACC functioning in depression may be that vACC activation reflects emotional processing which is emphasized by ruminative processing which focuses on negative aspects of self. Indeed, rumination is thought to be associated with less responsiveness to both antidepressant drugs and CBT (Ciesla and Roberts, 2002; Schmaling *et al.*, 2002), because depressive patients who have severe rumination might have difficulty learning CBT components, such as monitoring mood, emotion regulation and engaging positive activity. Patients who engage in limited rumination may typically respond quite well to standard CBT that is focused on challenging the content of negative cognitions. We consider that this interpretation is supported by the correlation between the reduction of rumination and activation changes in the vACC during the self/negative condition following CBT. However, vACC functioning in depression is a complicated issue, which needs further consideration.

Limitations

This study has limitations. First, patient symptom severity was relatively mild. The present findings remain to be generalized to patients with more severe depression. Second, the depressive patients who participated in this study received pharmacotherapy throughout their participation in CBT, such that their treatment histories were not controlled. Thus, we could not rule out pharmacological treatment effects on the brain activity that we observed in this study. It might be possible that changes of brain activation and clinical symptoms were due to pharmacotherapy or spontaneous rather than produced solely by CBT. Third, test–retest reliability of the task used in this study was poor. The fMRI indicated that healthy participants showed increasing activity in the vACC and MPFC in the self/negative condition, and decreasing activity in these regions from time 1 to time 2. Some other research studies have reported variability of signal change by repeated fMRI measurement (Johnstone *et al.*, 2005; Fu *et al.*, 2008; Jensen *et al.*, 2012). We consider that if the signal changes that we found in both depressive and healthy participants were spontaneous, then the direction of signal change might be same. But the signal changes from time 1 to time 2 between depressive and healthy participants were in opposite directions. In addition, there were no significant correlations between brain activity and BDI or behavioral data in the healthy participants. It is difficult to speculate about the reason for these relative activation changes from time 1 to time 2, but activation changes from time 1 to time 2 in depressive patients were explained by receiving CBT or other antidepressant effects.

In summary, we found that CBT influences MPFC and vACC functioning related to self-referential processing of negative emotional stimuli. It is therefore possible that the effect of CBT on depressive symptoms is mediated by MPFC and vACC activity associated with self-referential processing. In addition, this study suggests the possibility that vACC functioning could be a useful index for treatment response to CBT for depression.

Conflict of Interest

None declared.

REFERENCES

Beck, A.T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *The American Journal of Psychiatry*, *165*(8), 969–77.

Beevers, C.G. (2005). Cognitive vulnerability to depression: a dual process model. *Clinical Psychology Review*, *25*(7), 975–1002.

Berman, M.G., Peltier, S., Nee, D.E., Kross, E., Deldin, P.J., Jonides, J. (2011). Depression, rumination and the default network. *Social Cognitive and Affective Neuroscience*, *6*(5), 548–55.

Bush, G., Luu, P., Posner, M.I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Science*, *4*(6), 215–22.

Ciesla, J.A., Roberts, J.E. (2002). Self-directed thought and response to treatment for depression: a preliminary investigation. *Journal of Cognitive Psychotherapy*, *16*(4), 435–53.

Cooney, R.E., Joormann, J., Eugène, F., Dennis, E.L., Gotlib, I.H. (2010). Neural correlates of rumination in depression. *Cognitive, Affective, & Behavioral Neuroscience*, *10*(4), 470–8.

Dichter, G.S., Felder, J.N., Petty, C., Bizzell, J., Ernst, M., Smoski, M.J. (2009). The effects of psychotherapy on neural responses to rewards in major depression. *Biological Psychiatry*, *66*(9), 886–97.

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*, *51*(6), 871–82.

Fossati, P., Hevenor, S.J., Graham, S.J., et al. (2003). In search of the emotional self: an fMRI study using positive and negative emotional words. *The American Journal of Psychiatry*, *160*(11), 1938–45.

Fossati, P., Hevenor, S.J., Lepage, M., et al. (2004). Distributed self in episodic memory: neural correlates of successful retrieval of self-encoded positive and negative personality traits. *Neuroimage*, *22*(4), 1596–604.

Fu, C.H., Williams, S.C., Cleare, A.J., et al. (2008). Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. *Biological Psychiatry*, *64*(6), 505–12.

Goldapple, K., Segal, Z., Garson, C., et al. (2004). Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. *Archives of General Psychiatry*, *61*(1), 34–41.

Grimm, S., Ernst, J., Boesiger, P., et al. (2009). Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical-cortical midline structures. *Human Brain Mapping*, *30*(8), 2617–27.

Habel, U., Klein, M., Kellermann, T., Shah, N.J., Schneider, F. (2005). Same or different? Neural correlates of happy and sad mood in healthy males. *Neuroimage*, *26*(1), 206–14.

Heatherton, T. (2011). Neuroscience of Self and Self-Regulation. *Annual Review of Psychology*, *62*, 363–90.

Ingram, R.E. (1984). Toward an information-processing analysis of depression. *Cognitive Therapy and Research*, *8*(5), 443–77.

Jensen, K.B., Kosek, E., Wicksell, R., et al. (2012). Treatment with Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients suffering from chronic pain. *Pain*, *153*(7), 1495–1503.

Johnson, M.K., Nolen-Hoeksema, S., Mitchell, K.J., Levin, Y. (2009). Medial cortex activity, self-reflection and depression. *Social Cognitive and Affective Neuroscience*, *4*(4), 313–27.

Johnstone, T., Somerville, L.H., Alexander, A.L., et al. (2005). Stability of amygdala BOLD response to fearful faces over multiple scan sessions. *NeuroImage*, *25*(4), 1112–23.

Keedwell, P.A., Andrew, C., Williams, S.C.R., Brammer, M.J., Phillips, M.L. (2005). A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. *Biological Psychiatry*, *58*(6), 495–503.

Kelley, W.M., Macrae, C.N., Wyland, C.L., Caglar, S., Inati, S., Heatherton, T.F. (2002). Finding the self? An event-related fMRI study. *Journal of Cognitive Neuroscience*, *14*(5), 785–94.

Kennedy, S.H., Konarski, J.Z., Segal, Z.V., et al. (2007). Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *American Journal of Psychiatry*, *164*(5), 778–88.

Lemogne, C., Delaveau, P., Freton, M., Guionnet, S., Fossati, P. (2012). Medial prefrontal cortex and the self in major depression. *Journal of Affective Disorders*, *136*(1–2), e1–11.

Lemogne, C., Gorwood, P., Bergouignan, L., Pélissolo, A., Lehéricy, S., Fossati, P. (2011). Negative affectivity, self-referential processing and the cortical midline structures. *Social Cognitive and Affective Neuroscience*, *6*(4), 426–33.

Lemogne, C., le Bastard, G., Mayberg, H., et al. (2009). In search of the depressive self: extended medial prefrontal network during self-referential processing in major depression. *Social Cognitive and Affective Neuroscience*, *4*(3), 305–12.

Lemogne, C., Mayberg, H., Bergouignan, L., et al. (2010). Self-referential processing and the prefrontal cortex over the course of depression: a pilot study. *Journal of Affective Disorders*, *124*(1–2), 196–201.

Matsunaga, M., Okamoto, Y., Suzuki, S., et al. (2010). Psychosocial functioning in patients with Treatment-Resistant Depression after group cognitive behavioral therapy. *BMC Psychiatry*, *10*, 22.

Matthews, S.C., Strigo, I.A., Simmons, A.N., Yang, T.T., Paulus, M.P. (2008). Decreased functional coupling of the amygdala and supragenual cingulate is related to increased depression in unmedicated individuals with current major depressive disorder. *Journal of Affective Disorders*, *111*(1), 13–20.

Moberly, N.J., Watkins, E.R. (2008). Ruminative self-focus and negative affect: an experience sampling study. *Journal of Abnormal Psychology*, *117*(2), 314–23.

Mor, N., Winquist, J. (2002). Self-focused attention and negative affect: a meta-analysis. *Psychological Bulletin*, *128*(4), 638–62.

Moran, J.M., Macrae, C.N., Heatherton, T.F., Wyland, C.L., Kelley, W.M. (2006). Neuroanatomical evidence for distinct cognitive and affective components of self. *Journal of Cognitive Neuroscience*, *18*(9), 1586–94.

Nolen-Hoeksema, S., Morrow, J., Fredrickson, B.L. (1993). Response styles and the duration of episodes of depressed mood. *Journal of Abnormal Psychology*, *102*(1), 20–8.

Nolen-Hoeksema, S., Wisco, B.E., Lyubomirsky, S. (2008). Rethinking rumination. *Perspectives on Psychological Science*, *3*(5), 400–24.

Northoff, G. (2007). Psychopathology and pathophysiology of the self in depression—neuropsychiatric hypothesis. *Journal of Affective Disorders*, *104*(1–3), 1–14.

Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, *14*(8), 1215–29.

Ochsner, K.N., Gross, J.J. (2005). The cognitive control of emotion. *Trends in Cognitive Science*, *9*(5), 242–9.

Pyszczynski, T., Greenberg, J. (1987). Self-regulatory perseveration and the depressive self-focusing style: a self-awareness theory of reactive depression. *Psychological Bulletin*, *102*(1), 122–38.

Ray, R.D., Ochsner, K.N., Cooper, J.C., Robertson, E.R., Gabrieli, J.D., Gross, J.J. (2005). Individual differences in trait rumination and the neural systems supporting cognitive reappraisal. *Cognitive, Affective and Behavioral Neuroscience*, *5*(2), 156–68.

Ritchey, M., Dolcos, F., Eddington, K.M., Strauman, T.J., Cabeza, R. (2011). Neural correlates of emotional processing in depression: changes with cognitive behavioral therapy and predictors of treatment response. *Journal of Psychiatric Research*, *45*(5), 577–87.

Schmaling, K.B., Dimidjian, S., Katon, W., Sullivan, M. (2002). Response styles among patients with minor depression and dysthymia in primary care. *Journal of Abnormal Psychology*, *111*(2), 350–6.

Schmitz, T.W., Rowley, H.A., Kawahara, T.N., Johnson, S.C. (2006). Neural correlates of self-evaluative accuracy after traumatic brain injury. *Neuropsychologia*, *44*(5), 762–73.

Seminowicz, D.A., Mayberg, H.S., McIntosh, A.R., et al. (2004). Limbic-frontal circuitry in major depression: a path modeling metanalysis. *Neuroimage*, *22*(1), 409–18.

Siegle, G.J., Carter, C.S., Thase, M.E. (2006). Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. *Americal Journal of Psychiatry*, *163*(4), 735–8.

Siegle, G.J., Steinhauer, S.R., Thase, M.E., Stenger, V.A., Carter, C.S. (2002). Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biological Psychiatry*, *51*(9), 693–707.

Teasdale, J.D. (1985). Psychological treatments for depression: how do they work? *Behaviour Research and Therapy*, *23*(2), 157–65.

Wager, T.D., Davidson, M.L., Hughes, B.L., Lindquist, M.A., Ochsner, K.N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron*, *59*(6), 1037–50.

Watkins, E., Moulds, M. (2005). Distinct modes of ruminative self-focus: impact of abstract versus concrete rumination on problem solving in depression. *Emotion*, *5*(3), 319–28.

Yoshimura, S., Okamoto, Y., Onoda, K., et al. (2010). Rostral anterior cingulate cortex activity mediates the relationship between the depressive symptoms and the medial prefrontal cortex activity. *Journal of Affective Disorders*, *122*(1–2), 76–85.

Yoshimura, S., Ueda, K., Suzuki, S., Onoda, K., Okamoto, Y., Yamawaki, S. (2009). Self-referential processing of negative stimuli within the ventral anterior cingulate gyrus and right amygdala. *Brain and Cognition*, *69*(1), 218–25.