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Short communication

Cognitive behavioral therapy changes functional connectivity between medial prefrontal and anterior cingulate cortices

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ABSTRACT

Background: Depression is characterized by negative self-cognition. Our previous study (Yoshimura et al. 2014) revealed changes in brain activity after cognitive behavioral therapy (CBT) for depression, but changes in functional connectivity were not assessed.
Method: This study included 29 depressive patients and 15 healthy control participants. Functional Magnetic Resonance Imaging was used to investigate possible CBT-related functional connectivity changes associated with negative emotional self-referential processing. Depressed and healthy participants (overlapping with our previous study, Yoshimura et al. 2014) were included. We defined a seed region (medial prefrontal cortex) and coupled region (ACC) based on our previous study, and we examined changes in MPFC-ACC functional connectivity from pretreatment to posttreatment.
Results: CBT was associated with reduced functional connectivity between the MPFC and ACC. Symptom change with CBT was positively correlated with change in MPFC-ACC functional connectivity.
Limitations: Patients received pharmacotherapy including antidepressant. The present sample size was quite small and more study is needed. Statistical threshold in fMRI analysis was relatively liberal.
Conclusions: CBT for depression may disrupt MPFC-ACC connectivity, with associated improvements in depressive symptoms and dysfunctional cognition.

1. Introduction

Depressive disorder is an affective disorder that is a major burden on society and presents significant challenges to global mental health (Collins Thomas et al., 2013). One of the main goals of clinical psychology is thus to establish effective psychological treatments for depression. Although cognitive behavioral therapy (CBT) has been shown to be an effective psychological treatment for depression, many patients with depression fail to respond to CBT (DeRubeis et al., 2005). To reveal predictors of treatment, it is important to investigate the psychological and neural bases of depression.

Depression is psychologically characterized by excessive negative emotion and dysfunctional cognition about the self (Beck, 2008). The core brain regions involved in depression-related negative self-referential cognition are the medial prefrontal cortex (MPFC; Lemogne et al., 2012) and the anterior cingulate cortex (ACC; Yoshimura et al., 2010). Several studies have revealed that psychotherapy for depression, particularly cognitive behavioral therapy (CBT), affects these brain regions. Our previous study (Yoshimura et al., 2014) showed that depression-related MPFC and ACC hyperactivity during self-referential processing of negatively valenced words decreased after 12 sessions of CBT. These results suggest that CBT-related improvements in depressive symptoms are associated with changes in MPFC and ACC activation during self-referential processing of emotional stimuli. A recent review (Barsaglini et al., 2014) suggested that psychological treatment for depression (including CBT) works to correct abnormal activation patterns in fronto-limbic circuitry.

On the other hand, resting-state and task-related fMRI studies of brain connectivity have revealed excessive abnormal connectivity in the default mode network (DMN), which consists of central midline

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structures. In the context of self-referential processing, previous studies (Lemogne et al., 2009; Yoshimura et al., 2010) showed increased functional connectivity between the MPFC and ACC in depression. Zhu et al. (2012) found increased functional connectivity in the MPFC and ACC for depressive patients at resting state fMRI. In addition, a recent meta-analysis reported increased DMN connectivity in depression (Hamilton et al., 2015). These findings indicate that high density connectivity within the DMN results in abnormal cognitive and affective processing and is an important biological marker of depression.

A recent systematic review has suggested that there is a relationship between antidepressants and DMN connectivity (Gudayol-Ferré et al., 2015). However, many neuroimaging investigations of CBT treatment effects have only focused on activation changes. In a resting fMRI study, Du et al. (2016) reported that group CBT decreased low-frequency fluctuations at the middle frontal gyrus and connectivity between the middle frontal gyrus and insula. Few studies have examined changes in fronto-limbic functional connectivity associated with psychological treatment. But based on our previous studies and other findings of effects of hyperconnectivity within the DMN on depression, it is reasonable to examine fronto-limbic connectivity associated with CBT for depression.

Some research has focused on the biological markers of treatment response in depression. Pizzagalli (2011) reported relationships between the rostral ACC and antidepressants. Siegle et al. (2012, 2006) proposed that the subgenual ACC plays an overarching role in the context of the response to CBT. They reported correlations between pretreatment subgenual ACC activity in response to negative stimuli and residual depressive symptoms, and their results suggest that it is useful to classify treatment response by subgenual ACC activity. Liu et al. (2015) also showed relationships between subgenual ACC and antidepressants. Although the location of the relevant ACC subregion has been inconsistently identified, these studies suggest that the ACC region from rostral to pregenual is associated with treatment effects for depression.

The purpose of this study was to examine whether functional connectivity between the MPFC and ACC in depression is altered by CBT. Based on our previous reports (Yoshimura et al., 2010, 2014), we hypothesized that depression-related MPFC-ACC functional connectivity may decrease after CBT. We also hypothesized that CBT-related changes in MPFC-ACC connectivity may be associated with changes in depression-related symptoms. To examine this possibility, we performed a correlational analysis that included MPFC-ACC connectivity changes with CBT and changes of depressive symptoms measured using self-reports.

2. Method

2.1. Participants

Depressive patients (n=29) were recruited from outpatients of the Department of Psychiatry and Neurosciences at the Hiroshima University Hospital. Inclusion criteria were as follows: (a) the patient's diagnosis was established by a psychiatrist using the Structured Clinical Interview for DSM-IV-TR (SCID), and (b) the patient met the criteria for major depressive disorder according to the DSM-IV-TR. Exclusion criteria included 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, tricyclic antidepressant) for a minimum of 8 weeks without remission of symptoms. Fourteen patients received other drugs, such as antipsychotic, anti-anxiety, or hypnotic medication. Drug types and doses were maintained over the course of the group CBT treatment. Demographic and clinical characteristics of the participants are presented in Table 1. 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. The dataset of 15 control participants and 23/29 depressive participants were the same as that used in our previous study (Yoshimura et al., 2014).

Table 1
Demographic, clinical characteristics data of the sample.

	Depressive patients		Healthy control participants	
	time 1 (baseline)	time 2 (post-CBT)	time 1	time 2
Age	37.4 ± 7.1		36.7 ± 8.2	
Gender	10 female, 19 male		7 female, 8 male	
Depressive episodes (#)	1.8 ± 0.8		–	
Duration of depressive episode (weeks)	60.0 ± 114.5		–	
Duration of illness (months)	18.3 ± 14.6		–	
Dosage of antidepressant (mg; equivalent dose of imipramine)	153.13 ± 114		–	
Beck Depression Inventory	21.4 ± 8.8	12.3 ± 8.2	6.4 ± 5.1	4.9 ± 4.5
Hamilton Rating Scale for Depression	11.5 ± 5.7	6.3 ± 4.4	–	
Behavioral response (Judgment ratio in self/ negative condition)	42.2 ± 23.0	34.7 ± 24.5	12.67 ± 8.6	12.67 ± 10.8

Judgment ratio was calculated by percentage of "yes" response as compared with all response in self/negative condition.

The Ethics Committee of Hiroshima University approved the study protocol. After the study protocol was explained, informed consent was obtained from all participants.

2.2. Evaluation and treatment protocol

The patients participated in 12 weekly, 90 min CBT sessions conducted by a clinical psychologist with groups of five or six participants.

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 assess psychological aspects of depression. A more detailed treatment protocol is described in our previous report (Matsunaga et al., 2010).

3. Experimental design

Participants underwent fMRI scans while they completed the self-referential tasks. They 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. (Because we were only interested in activity during self-referential processing, the other-referential condition was excluded from the present analysis.) In the *semantic-processing condition*, participants judged whether or not it