

Regular Article

Anterior cingulate cortex volume reduction in patients with panic disorder

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Aim: Recent neuroimaging studies have suggested that the anterior cingulate cortex (ACC) has an important role in the pathology of panic disorder. Despite numerous functional neuroimaging studies that have elucidated the strong relationship between functional abnormalities of the ACC and panic disorder and its symptoms and response to emotional tasks associated with panic disorder, there has been no study showing volumetric changes of the ACC or its subregions.

Methods: To clarify the structural abnormalities of ACC and its subregions, the combination of region of interest (ROI) and optimized voxel-based morphometry (VBM) methods were performed on 26 patients with panic disorder, and 26 age and sex-matched healthy subjects. In the ROI study, ACC was divided into four subregions: dorsal, rostral, subcallosal and subgenual ACC.

Results: The results of the manually traced ROI volume comparison showed significant volume reduction in the right dorsal ACC. VBM also showed a volume reduction in the right dorsal as well as a part of the rostral ACC as a compound mass.

Conclusions: Both manual ROI tracing and optimized VBM suggest a subregion-specific pattern of ACC volume deficit in panic disorder. In addition to functional abnormalities, these results suggest that structural abnormalities of the ACC contribute to the pathophysiology of panic disorder.

Key words: anterior cingulate cortex, magnetic resonance imaging, panic disorder, region of interest, voxel-based morphometry.

RECENT STUDIES HAVE suggested that brain abnormalities contribute to the occurrence of panic disorder, and many functional neuroimaging studies have shown that the functional abnormalities of the anterior cingulate cortex (ACC)–amygdala connection play an important role.^{1–5} While some

structural neuroimaging studies have shown abnormalities in the amygdala,^{6,7} there has been no report about structural change of ACC in patients with panic disorder.

ACC is a well studied region, with known anatomical and functional heterogeneities in its subdivisions. Bush *et al.* have suggested that the ACC is divided into two major subdivisions according to separate processing of cognitive and emotional information.⁸ One subdivision is the dorsal cognitive division (Brodmann's area [BA] 24b'–c' and 32') and the other is the rostral–ventral affective division (rostral area: BA 24a–c and 32; ventral area: BA 25 and 32). The

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dorsal cognitive subdivision has strong reciprocal interconnections with the lateral prefrontal cortex and parietal cortex,⁹ and governs various functions such as the modulation of attention and anticipation during cognitively demanding tasks.^{9–12} On the other hand, the rostral–ventral affective subdivision is connected with the amygdala, anterior insula and orbitofrontal cortex,⁹ and has the role of regulating emotional responses.^{11,12} Moreover, recent structural and functional imaging studies have focused on the subgenual region (BA 25). Abnormalities of this region have been shown in affective disorder,^{13,14} which is a common comorbidity with panic disorder, as well as the brain response to fear¹⁵ and sadness.¹⁶

Many functional neuroimaging studies have indicated a strong relationship between functional abnormalities of the ACC and panic disorder symptoms and responses to emotional tasks related to panic disorder. For example, Pillay *et al.* reported that the significant activation of the ACC (bilateral rostral and subgenual regions) was found in control subjects but was not found in patients with panic disorder when they were exposed to the fearful facial affects.⁴ Another study showed that injections of cholecystokinin tetrapeptide (CCK-4) for occurring panic attacks in healthy subjects activated ACC (BA 24, 32: rostral region).¹⁷ Furthermore, Fischer *et al.* showed that regional cerebral blood flow (rCBF) was decreased in right ACC (area 32) when a patient unexpectedly experienced a panic attack.¹⁸ These findings suggest that the functional abnormalities in the ACC, especially the rostral–ventral affective subdivision, is certainly related with panic disorder and its symptoms.

Previous structural neuroimaging studies have also shown a relationship between ACC and anxiety-related disorders. Yamasue *et al.* reported volume reduction of the left dorsal ACC in patients with post-traumatic stress disorder (PTSD).¹⁹ Several other PTSD studies have also shown volume reduction of various ACC subregions (Kitayama *et al.* right dorsal region;²⁰ Woodward *et al.*, left dorsal and rostral regions;²¹ Chen *et al.*, left rostral region²²). One structural study about pediatric obsessive–compulsive disorder has also revealed that the volume of the bilateral dorsal ACC was significantly smaller in the patients compared with control subjects.²³

Although there have been many reports that show functional abnormalities of the ACC in patients with panic disorder, and structural abnormalities of ACC in patients with anxiety-related disorders, to our

knowledge, there has been no report showing structural changes of the ACC and its subregions in patients with panic disorder. The purpose of the present study was to clarify the structural change of the ACC and its subregions in patients with panic disorder. The combination of region of interest (ROI) and optimized voxel-based morphometry (VBM) methods were employed in this study. It has been suggested that the manually traced ROI is superior in anatomical accuracy to the atlas-based ROI in VBM, however, it could be potentially influenced by the rater's biases and anatomical varieties such as sulcogyral patterns.²⁴ On the other hand, in VBM the volume is assessed beyond anatomical varieties through the spatial normalization process. At the same time, a disadvantage of VBM is that it can reduce information about individual differences in brain structure. So, it has been suggested that the manually traced ROIs and VBM provide different aspects of information and therefore should be used in tandem.²⁵ In the manually traced ROI method of this study, the ACC was divided into four subregions (dorsal, rostral, subcallosal and subgenual ACC) and the atlas-based ACC ROI in VBM was applied as a single region.

MATERIALS AND METHODS

Subjects

Twenty-six patients (10 males and 16 females) with panic disorder were recruited from the Department of Psychiatry at Yokohama City University Hospital. Their age and sex were matched by 26 healthy control subjects recruited from the local community and hospital staff. All subjects met the following criteria: age 19–57 years; IQ > 75²⁶ right-handed;²⁷ no history of seizures, head trauma with loss of consciousness, neurological disorders, or lifetime history of substance dependence.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)²⁸ was used to ascertain the diagnosis of panic disorder and to rule out other past or current Axis I disorders. Two trained psychiatrists (YH and TA) ran a diagnosis check on the patients using DSM-IV to obtain a consensus diagnosis. The Panic Disorder Severity Scale (PDSS)²⁹ and Global Assessment of Functioning (GAF)³⁰ were used for patients with panic disorder.

Patients with comorbid psychiatric disorders were excluded from the study, with the exception of major

depression and dysthymia, which are often associated with panic disorder. Therefore, the current study included four patients with a past history of major depression and one patient suffering from dysthymia at the time of the study. In addition, 11 patients had a past history of agoraphobia, and three were suffering from agoraphobia at the time of the study. The mean age of first medication was 34.1 years (SD = 10.8), and the mean illness duration was 3.8 years (SD = 3.3). Twenty-one patients were receiving antidepressants (17 patients, serotonin selective reuptake inhibitors; two patients, serotonin norepinephrine reuptake inhibitors; two patients, tricycles) and 19 patients were receiving benzodiazepines. No patient received mood stabilizers or antipsychotics which were thought to affect gray matter volume.^{31,32} The mean PDSS score of the patients was 8.7 (SD = 4.9), suggesting that most of the patients were successfully treated (the PDSS score ranges between 0 and 28. The higher the score the more severe the symptom).²⁹

For the control subjects, the SCID (Edition for Non-Patients) (SCID-NP)²⁸ and the Mini-International Neuropsychiatric Interview (MINI)^{33,34} were used to ascertain that the subjects had no Axis I disorders. In addition, none of their first-degree relatives had Axis I disorders.

The socio-economic status (SES) of all subjects and their parents was assessed using the Hollingshead Two-Factor Index.³⁵ As part of the clinical assessment, the State-Trait Anxiety Inventory (STAI)³⁶ and Self-Rating Depression Scale (SDS)³⁷ were also administered to all subjects. This study was approved by the Institutional Review Board and Ethics Committee of Yokohama City University, and was performed after obtaining written informed consent from all subjects.

Magnetic resonance imaging

Magnetic resonance imaging images were acquired with a 1.5-T Magnetom Symphony (Siemens Medical System, Erlangen, Germany) at Yokohama City University Hospital. A series of 128 contiguous T1-weighted slices in the sagittal plane were acquired using a Turbo FLASH sequence with the following parameters: echo time (TE) = 3.93 msec, repetition time (TR) = 1960 msec, inversion time (TI) = 1100 msec, flip angle = 15°, field of view = 24 cm, matrix = 256 × 256 × 128, voxel dimensions = 0.9375 × 0.9375 × 1.5 mm.

For the measurement of the intracranial contents (ICC), 60 contiguous Turbo SE 3-mm axial slices were obtained throughout the extent of the brain. Imaging parameters were: TE = 93 msec, TR = 3400 msec, field of view = 24 cm, matrix = 256 × 256, voxel dimensions = 0.9375 × 0.9375 × 3.0 mm. No gross abnormalities were found in the scans when they were evaluated by a clinical neuroradiologist.

Region of interest

The ACC ROI was manually delineated without knowledge of subject profiles using a software package for medical image analysis (3D Slicer; software available at <http://www.slicer.org>). We used the same ROI definition of the ACC that McCormick *et al.* had described previously,³⁸ and divided the ACC into four subregions (dorsal, rostral, subcallosal, and subgenual ACC; Fig. 1). We also followed their criteria on how to treat a double-gyrus pattern in the cingulate cortex, and did not include the second (outer) cingulate gyrus within an ACC ROI when it was considered to be paracingulate gyrus. Although a brief summary of each ACC ROI definition is provided below, more detailed definition is described in the previous report by McCormick *et al.*³⁸

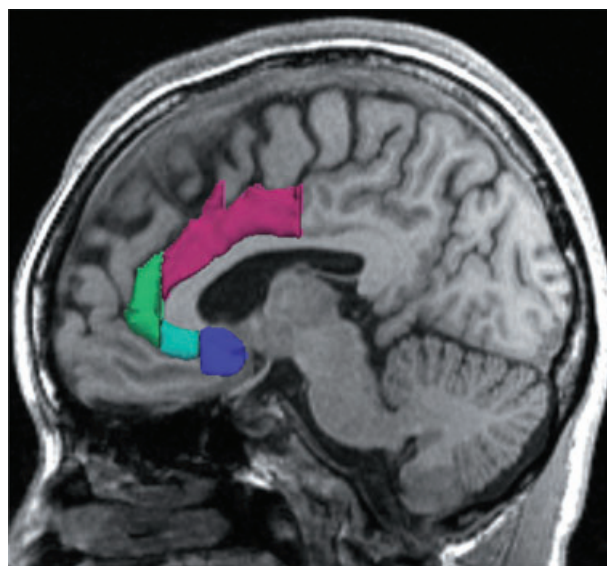


Figure 1. The definition of the region of interest. Anterior cingulate cortex (ACC) was divided into four subregions, dorsal ACC (red), rostral ACC (green), subcallosal ACC (light blue) and subgenual ACC (dark blue).

Dorsal anterior cingulate cortex

The posterior boundary was decided as follows. First, the point that the cingulate sulcus (CS) and ascending marginal sulcus joined was identified in the sagittal view. Second, from where they join, the horizontal transition of CS was confirmed following the CS anteriorly. Finally, the first vertically oriented gyrus was identified, and this point was the posterior boundary. The dorsal ACC was traced on coronal slices. The anterior boundary was delineated as one slice posterior to the coronal plane where the connection of the corpus callosum in each hemisphere was no longer connected. This ACC region corresponds to BA 24.^{12,39}

Rostral anterior cingulate cortex

The coronal plane that was one slice before the anterior margin of the dorsal ACC was the posterior boundary of the rostral ACC. The rostral ACC was traced on alternating coronal slices. This region corresponds to BA 24a, 24b and 24c.^{38,39}

Subcallosal anterior cingulate cortex

The coronal plane that was one slice behind the posterior limit of the rostral ACC was the anterior boundary of the subcallosal ACC. One slice anterior to the coronal plane where the putamen was first seen within the basal ganglia was the posterior boundary. The superior boundary was the corpus callosum. This region corresponds to BA 24a.^{9,38,39}

Subgenual anterior cingulate cortex

One slice behind the posterior limit of the subcallosal ACC was the anterior boundary of the subgenual ACC. The superior boundary was the corpus callosum. The coronal plane where the paraterminal gyrus disappeared was the posterior boundary. The inferior boundary was not often continued with that of the subcallosal ACC, and it was located at the tip of the lower-most gyrus on the medial surface. This region corresponds to BA 25.^{9,38,39}

To determine interrater reliability, seven cases were randomly chosen from the whole study sample, and ROIs were independently traced by two different raters blinded to the diagnosis (TA and TR). Intraclass correlation coefficients obtained for the interrater reliability of volume measurements for four subregions

(right/left: dorsal 0.94/0.97, rostral 0.92/0.90, subcallosal 0.91/0.94, subgenual 0.92/0.90, ICC 0.99) and for intrarater reliability (right/left: dorsal 0.93/0.95, rostral 0.90/0.92, subcallosal 0.94/0.93, subgenual 0.91/0.90, ICC 0.99) were sufficiently high.

Independent-samples *t*-test was carried out using SPSS 11.0 (SPSS Inc, Chicago, IL, USA) to evaluate the group differences in each subregion of ACC. Relative volumes (absolute volume/ICC × 100) were used for the group comparison to control for head size difference. Alpha level was set at 0.0063 (= 0.05/8 subregions) to report a significant difference.

Optimized voxel-based morphometry

The theory and algorithm of VBM using the Statistical Parametric Mapping (SPM) 2 software (Wellcome Department of Cognitive Neurology, London, UK) have been well documented.⁴⁰ In the present study, VBM was performed using an optimized methodology.⁴¹ First, an optimized study-specific template set consisting of a T1 image and a priori gray, white, and cerebrospinal fluid probability maps, was created for the VBM analysis. This template set was constructed from brain scans taken from all subjects. All scans were first spatially normalized to the International Consortium for Brain Mapping template (Montreal Neurological Institute, Montreal, Canada), which approximates Talairach space. The normalized images of all participants were averaged and smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel and then used as a new template with a reduced scanner- and population-specific bias. In the second normalization step, we locally deformed each image of our entire group to the new study-specific template using a non-linear spatial transformation. The normalized images, using a modified-mixture model cluster analysis, were corrected for non-uniformities in signal intensity and then segmented into gray matter, white matter, cerebrospinal fluid and background, using study-specific customized prior probability maps. To remove unconnected non-brain voxels (e.g. rims between the brain surface and meninges), a series of morphological erosions and dilations were applied to the segmented images.⁴¹ To modulate the intensity, voxel values of the segmented images were multiplied by the measure of warped and unwarped structures derived from the non-linear step of the spatial normalization (Jacobian determinant). This step converts relative regional gray matter density to absolute

gray matter density, expressed as the amount of gray matter per unit volume of brain tissue prior to spatial normalization. Finally, the modulated images were smoothed using a 12-mm FWHM Gaussian kernel.

Group effect was assessed by using an analysis of covariance (ANCOVA) model. Intracranial volume, which was calculated in the VBM procedure, was treated as a confounding covariate to correct for global anatomical variations. To test our hypothesis with respect to regionally specific group effect, the estimates were compared by using two linear contrasts.⁴² The resulting set of voxel values for each contrast constituted a statistical parametric map of the *t* statistic [SPM(*t*)]. The SPM(*t*) values were transformed to the normal distribution [SPM(*Z*)] and with uncorrected threshold at uncorrected $P < 0.001$. Once the group difference was found in ACC, posthoc analysis was performed to investigate accurate regional changes using small-volume correction (SVC) with WFU Pickatlas software.⁴³ Significance levels were set at Family Wise Error (FWE)-corrected $P < 0.05$. Two patients and age- and sex-matched healthy subjects were excluded from the VBM analysis because of a technical error in the segmentation process.

Correlation

Once a significant volume reduction was found in the ROI or VBM method, a correlation analysis was per-

formed for each method separately. For the ROI method, the correlation analysis was carried out by two-tailed Pearson's correlation coefficients using SPSS 11.0. For VBM, global gray matter was treated as a confounding covariate effect, and the clinical variables were treated as the covariates of interest. To test hypotheses about regional specific covariate effects, the estimates were compared by using two linear contrasts (positive or negative correlation). Significance levels were set at corrected $P < 0.05$. Small-volume correction was also applied by using the maxima obtained using the group analysis at the center of a small volume.¹⁹ The relationship between the regional volume and the score of clinical and demographic variables was investigated. To evaluate medication effects on the brain, a total dose of antidepressants⁴⁴ or benzodiazepines⁴⁵ was also added in the correlation analysis.

RESULT

Clinical features

Demographic information for each group was summarized in Table 1. The *t*-tests revealed that there was no significant difference in demographic variables of age, sex, self and parental SES and IQ between patients with panic disorder and control subjects. The

Table 1. Demographic and clinical characteristics of the study groups

Characteristic or test	Patients with panic disorder (<i>n</i> = 26)		Control subjects (<i>n</i> = 26)		<i>t</i> -test	
	Mean	SD	Mean	SD	<i>t</i> (d.f. = 50)	<i>P</i>
Sex (M/F)	10/16		10/16			
Age (years)	37.7	10.1	38.2	9.7	0.18	0.86
Self SES	2.0	1.0	2.4	0.9	-1.64	0.11
Parental SES	2.1	0.77	2.4	0.77	-1.33	0.19
Total IQ	109.8	12.4	104.4	12.9	1.39	0.17
STAI-T	47.0	10.7	35.0	7.2	-4.71	<0.01*
STAI-S	44.6	6.9	31.7	6.9	-5.26	<0.01*
SDS	42.2	8.1	30.4	6.7	-5.63	<0.01*
PDSS	8.7	4.9				
GAF	67.7	10.5				
Age of first medication (years)	34.1	10.8				
Duration of illness (years)	3.8	3.3				

t-test was applied. * $P < 0.01$.

GAF, global assessment of functioning; in which lower score indicates higher status; PDSS, panic disorder severity scale; SDS, self-rating depression scale; SES, socio-economic status; STAI-S, state subscale of State-Trait Anxiety Inventory; STAI-T, trait subscale of State-Trait Anxiety Inventory.

Table 2. Absolute and relative volumes of anterior cingulate cortex (ACC) in patients with panic disorder and control subjects in the region of interest study

Region and volume type	Patients with panic disorder (<i>n</i> = 26)		Control subjects (<i>n</i> = 26)		<i>t</i> -test	
	Mean	SD	Mean	SD	<i>t</i> (d.f. = 50)	<i>P</i>
Intracranial content (mL)	1478	160	1517	164	0.874	0.194
Dorsal ACC						
Left						
Absolute volume (mL)	3.013	0.594	3.158	0.670		
Relative volume (%)	0.204	0.045	0.209	0.038	0.408	0.480
Right						
Absolute volume (mL)	3.067	0.534	3.568	0.747		
Relative volume (%)	0.206	0.029	0.237	0.046	2.878	0.0059*
Rostral ACC						
Left						
Absolute volume (mL)	2.903	2.146	2.300	0.659		
Relative volume (%)	0.198	0.143	0.153	0.045	−0.954	0.173
Right						
Absolute volume (mL)	2.100	0.738	2.22	0.75		
Relative volume (%)	0.139	0.039	0.148	0.049	0.732	0.234
Subcallosal ACC						
Left						
Absolute volume (mL)	0.423	0.129	0.438	0.155		
Relative volume (10 ^{−1} %)	0.283	0.074	0.291	0.101	0.346	0.364
Right						
Absolute volume (mL)	0.385	0.113	0.395	0.108		
Relative volume (10 ^{−1} %)	0.260	0.074	0.264	0.074	0.154	0.441
Subgenual ACC						
Left						
Absolute volume (mL)	0.503	0.105	0.514	0.110		
Relative volume (10 ^{−1} %)	0.342	0.082	0.342	0.079	0.019	0.492
Right						
Absolute volume (mL)	0.513	0.102	0.584	0.118		
Relative volume (10 ^{−1} %)	0.346	0.070	0.387	0.071	2.075	0.021

t-test was applied. **P* < 0.0063.

STAI-T, STAI-S and SDS scores were higher in the patients than the control subjects.

Region of interest

Volumetric measurements showed a 13.8% significant volume reduction in the right dorsal ACC (*t* = 2.88, *P* = 0.0059) in the patients with panic disorder compared with the control subjects (Table 2, Fig. 2). No other region revealed group differences between the patients and the controls.

Optimized voxel-based morphometry

The result of the optimized VBM with SVC showed significant volume reduction in the right dorsal

ACC and a part of the right rostral ACC (peak coordinate [*x*, *y*, *z* (mm)] = (6, 28, 36), *k* = 574, *Z* score = 3.92) (Fig. 3). There was no region that showed increased volume in the patients with panic disorder compared with the control subjects.

Correlation analysis

No correlation was found between the subregions showing significant structural alterations and demographic and clinical variables both in the ROI and VBM methods. The current study also did not find a correlation between the right rostral/dorsal ACC and total dose of antidepressants (*P* = 0.28/0.93 in the ROI, no significant findings in the VBM) or benzodi-

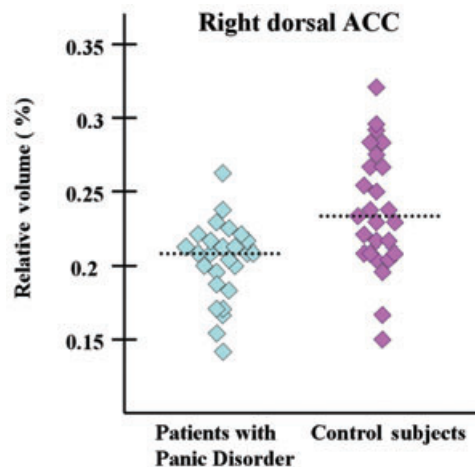


Figure 2. The result of the region of interest. The volume of the right dorsal anterior cingulate cortex (ACC) was reduced significantly in patients with panic disorder compared with control subjects.

azepines ($P = 0.69/0.13$ in the ROI, no significant findings in the VBM) in the patients with panic disorder.

DISCUSSION

The present volumetric study compared ACC volume in patients with panic disorder and control subjects using two methods: ROI volume comparison and optimized VBM. The result of the ROI volume comparison showed significant volume reduction in the right dorsal ACC in panic disorder patients compared to healthy controls. The finding from optimized VBM showed significant volume reduction in the right dorsal ACC partially extending to rostral ACC in patients compared to control subjects (Table 2, Figs 2, 3). Of particular note, manual ROI tracing and automated optimized VBM showed volume deficit in the largely overlapped ACC region despite their totally different methodologies. To our knowledge, this is the first report of a subregion-specific ACC volume deficit in patients with panic disorder.

The current study did not find any correlation between the right rostral/dorsal ACC and antidepressants or benzodiazepines. This might suggest that the psychotropic medication did not affect the group difference in ACC volume.

Previous reports have suggested that functional abnormalities in ACC–amygdala interaction play an

important role in panic disorder,^{1–5} and that neural activation in ACC, amygdala, or both are altered when subjects are exposed to an emotional task, especially a fear-related task. The rostral–ventral affective division of the ACC has strong neuronal connectivity with the amygdala,⁹ and has a role of regulating emotional responses.^{11,12} Functional neuroimaging studies have shown a relationship between abnormalities of these regions and panic disorder and its symptoms.

Concerning the rostral ACC region, Bystritsky *et al.* demonstrated increased activity in the right rostral ACC during panic anticipation exposure.¹ Boshuisen *et al.* also showed activation in the bilateral rostral ACC during anticipatory anxiety as a result of pentagastrin injections in patients with panic disorder.⁴⁶ A CCK-4 trial study for occurring panic attacks showed that rostral ACC was activated when CCK-4 was injected in healthy subjects.¹⁷ Further more, Sakai *et al.* showed that the glucose utilization in left rostral ACC was decreased after cognitive-behavioral therapy was successful in patients with panic disorder.⁴⁷ Give that these findings show a functional relationship between rostral ACC and panic disorder, it seems reasonable that the current study showed the structural abnormalities in this region.

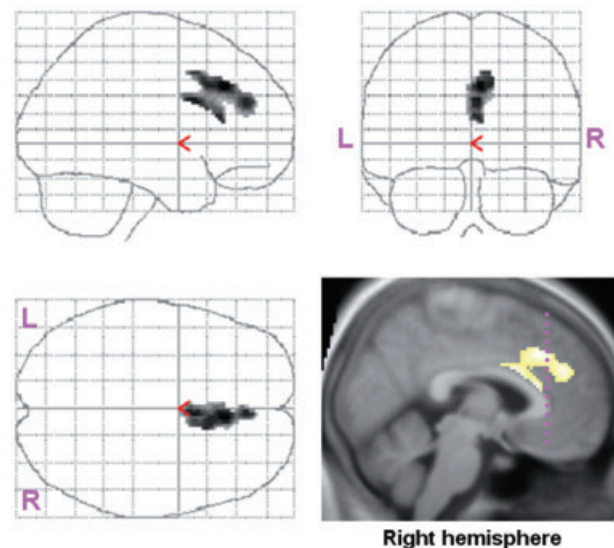


Figure 3. The result of the optimized voxel-based morphometry with small volume correction. The volume of the right dorsal and part of rostral anterior cingulate cortex were reduced significantly in patients with panic disorder compared with control subjects.

The present study also showed a volume reduction of the right dorsal ACC in patients with panic disorder compared with control subjects. Dorsal ACC is suggested to be a cognitive subdivision, governing various functions such as modulation of attention and anticipation of cognitively demanding tasks.^{9–11} Some structural neuroimaging studies of anxiety-related disorders such as PTSD have shown volume reduction in dorsal ACC.^{19–21} According to the recent reviews about ACC, the anterior part of the dorsal ACC was related to neural activations of not only the cognitive tasks but also the emotional tasks.⁸ Vogt also reported that the anterior part of dorsal ACC received input from the amygdala, and fear was mainly associated with activity in this region.¹⁶

Here we address methodological considerations. Our study included subjects who had a history of depressive disorders (four subjects, past history of major depression; one subject, current history of dysthymia). Since previous studies have reported brain structural changes in patients with depressive disorders, the effect of comorbid depression on the current results cannot totally be ruled out. When the examination was performed without these five subjects and age-, sex-matched five healthy subjects, the results of ROI showed the volume reduction in the right dorsal ACC at a less significant level ($t = 2.23$, $P = 0.031$), and VBM showed volume reduction in dorsal and rostral ACC but as smaller regions. We note here that structural differences between panic disorder patients with and without comorbid depression should be investigated in future studies with larger sample.

In conclusion, the present study demonstrated the first evidence of a subregion-specific volume deficit in the right dorsal ACC partially extending to rostral ACC in the patients with panic disorder. This subregion-specific pattern of ACC volume deficit in panic disorder was confirmed by both manual ROI tracing and optimized VBM methods. These findings may provide further evidence that not only functional but also structural abnormalities of ACC contribute to the pathophysiology of panic disorder.

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