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ORIGINAL PAPER

Reduced gray matter volume of Brodmann's Area 45 is associated with severe psychotic symptoms in patients with schizophrenia

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Abstract Previous literature has suggested an important role of inferior frontal gyrus, which mainly consists of Brodmann's Area (BA) 44 and 45, in the pathophysiology of schizophrenia. While recent neuroimaging techniques have revealed differential functional correlates of BA 44 and 45 in healthy individuals, previous studies have not yet separately evaluated the gray matter volume reduction of BA 44 and 45 and their relationships to psychotic symptoms in patients with schizophrenia. In the present study, magnetic resonance images were obtained from 29 right-handed male patients with schizophrenia and from 29 age- and handedness-matched healthy male controls. The reliable manual tracing methodology was employed to measure the gray matter volume of BA 44 and BA 45. The severities of psychotic symptoms were evaluated using the five-factor model of positive and negative syndrome scale in the patient group. A significant gray matter volume reduction of both the BA 44 and BA 45 was found bilaterally in the patients with schizophrenia compared with the healthy controls. Among these inferior frontal sub-regions, reduced volume of right BA 45 revealed the largest effect size. In addition, the reduced volume of BA 45 in left hemisphere showed a significant association with the increased severity of delusional behavior, while the severity of disorganized and positive symptoms were correlated with the bilateral BA 45 volumes in the patient group. The findings support an important role of inferior frontal gyrus in the pathophysiology of schizophrenia. The present study further demonstrated that BA 45 might especially contribute to the production of psychotic symptoms in the patients with schizophrenia.

Keywords Schizophrenia · MRI · Broca's language area · Pars opercularis · Pars triangularis

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Introduction

Previous studies have suggested an important role of structural abnormality of inferior frontal gyrus including gray matter volume reduction and altered laterality in the pathophysiology of schizophrenia. Significantly reduced inferior frontal gyrus volume and its relationship to symptom severity have been reported in previous studies using manual-tracing volumetry in patients with schizophrenia [7, 31, 38]. In addition, most of previous studies employing computational morphology such as voxel-based morphometry (VBM) have also detected reduced gray matter volume and altered laterality in inferior frontal cortex from whole-brain analysis of the brain in patients with schizophrenia [3, 4, 6, 13, 19, 20, 27, 30, 36].

Inferior frontal gyrus, which mainly consists of Brodmann's Area (BA) 44 and 45, is anatomically [2] and functionally heterogeneous [8]. A limited number of previous studies have reliably measured the morphology of human inferior frontal sub-regions [12, 22, 23, 32]. These

pioneer studies utilized information about individual differences in sulcal and gyral pattern as the landmark delineating boundaries to realize reliability. For example, a recent study demonstrated several variants in the shape and location of the inferior frontal subregions across 108 normal adult individuals and between hemispheres [32]. However, although the borderlines of pars opercularis, mainly consisting of BA 44, and triangularis, mainly consisting of BA 45, run 3-dimensionally, no previous studies sufficiently utilized 3-dimensional information to identify the boundaries. Furthermore, although a recent study using computational morphometry showed that this variability is associated with the diagnosis of schizophrenia [35], no previous studies measured the volume of segmented inferior frontal sub-regions in patients with schizophrenia.

The functional correlates of BA 44 and 45 have been argued to be differing in the previous literature. For example, the different types of verbal fluency test differentially elicit the activation of these subregions (reviewed in [8]). While BA 44 is activated during phonologic verbal fluency tasks, BA 45 is activated during semantic ones. The deficits measured with semantic fluency test are well established and are argued to be a better trait marker for genetic liability than those with phonological fluency test in patients with schizophrenia [28, 40]. In addition, thought disorder, a characteristic symptom of schizophrenia, has been suggested to be associated with semantic processing abnormalities measured with semantic verbal fluency test [14]. A limited number of studies using functional neuroimaging further imply that the pars triangularis, mainly consisting of BA 45 [2], in particular plays an important role in the pathophysiology of schizophrenia [9, 35]. A recent VBM study also showed a structural abnormality, abnormal cerebral lateralization, in pars triangularis in patients with schizophrenia [20]. Taken together, these previous findings suggest that BA 45 might be particularly involved in the formation of schizophrenic symptoms associated with aberrant semantic processing. No previous study, however, segmented them to examine the morphology of Broca's region and its differential relationship to psychotic symptoms in patients with schizophrenia.

In addition to classically known speech production or language-related function, recent neuroimaging studies have further suggested that this area is implicated in execution, action observation, action understanding, and imitation, that is, organization of action and/or thought as well as understanding of others' intention and emotions (reviewed in [25]). Therefore, neural substrates of structural abnormality of inferior frontal gyrus in schizophrenia might be associated with the organization of action or thought as well as understanding of others' intention and emotions. Considering the pivotal role of BA 45 in semantic processing, the functional correlates of structural disruption of BA 45 in patients with schizophrenia were predicted to be associated with disorganization of thought and/or action and delusion. Previous studies have proposed the five-factor model to be best solution for the structure of schizophrenic symptoms [34]. Therefore, the positive and disorganized symptoms in a recently proposed five-factor model [33] were employed to examine correlates of BA 45 structural abnormality. "Delusional behavior" was also utilized to assess clinical correlates of BA 45 since previous structural MRI studies have reported a correlation between regional neocortical volume and this index [29, 37].

The aims of the present study were: (1) to establish the reliable ways utilizing 3 dimensional anatomical information of measuring the segmented volume of inferior frontal sub-regions (BA 44 and 45), (2) to identify the gray matter volume reduction of these sub-regions in patients with schizophrenia compared with normal controls, and (3) to identify differential clinical correlates of BA 44 and 45 morphology, particularly the correlation between volume of BA 45 and severity of psychotic symptoms, such as positive symptoms, delusional behavior and disorganized symptoms in patients with schizophrenia.

Materials and methods

Subjects

Twenty-nine male in- and outpatients with schizophrenia were recruited from the Department of Neuropsychiatry, University of Tokyo Hospital, Japan. Diagnosis of schizophrenia was determined for each patient according to DSM-IV criteria through the Structured Clinical Interview for DSM-IV Axis I Disorder Clinical Version [10] by a trained psychiatrist (H.Y.). All patients received neuroleptics. Sixteen patients received typical antipsychotics alone, while five patients received atypical antipsychotics alone and eight patients received both typical and atypical ones. Psychiatric symptoms were evaluated by a trained psychiatrist (H.Y.) using the Positive and Negative Syndrome Scale (PANSS) [21] within 3 days before MRI scanning. The evaluator was fully trained according to the previous study to satisfy the reliability criteria [21]. Positive symptoms, Negative symptoms, Disorganized symptoms, Excitement, and Emotional distress in the five-factor model [33], and delusional behavior scores [29, 37] were calculated from the subscales of PANSS. The calculation algorithm is as follows. Positive symptoms: P1 (delusion) +P3 (hallucinatory behavior) +P5 (grandiosity) +P6 (suspiciousness) +G1 (somatic concern) +G9 (unusual thought content) +G12 (lack of judgment and insight) +G16 (active social avoidance) −N5 (difficulty in abstract

thinking); Negative symptoms: N1 (blunted affect) +N2 (emotional withdrawal) +N3 (poor rapport) +N4 (passive apathetic social withdrawal) +N6 (lack of spontaneity and flow of conversation) +G7 (motor retardation) +G8 (uncooperativeness) +G13 (disturbance of volition) +G16 (active social avoidance) -P2 (conceptual disorganization); Disorganized symptoms: P2 (conceptual disorganization) +N5 (difficulty in abstract thinking) +N7 (stereotyped thinking) +G5 (mannerisms and posturing) +G9 (unusual thought content) +G10 (disorientation) +G11 (poor attention) +G12 (lack of judgment and insight) +G13 (disturbance of volition) +G15 (preoccupation); Excitement: P4 (excitement) +P5 (grandiosity) +P7 (hostility) +N3 (poor rapport) +G4 (tension) +G8 (uncooperativeness) +G14 (poor impulse control) +G16 (active social avoidance); Emotional distress: P6 (suspiciousness) +G1 (somatic concern) +G2 (anxiety) +G3 (guilt feeling) +G4 (tension) +G6 (depression) +G15 (preoccupation) +G16 (active social avoidance); Delusional behavior: P1 (delusion) +P5 (grandiosity) +P6 (suspiciousness) +G9 (unusual thought content). Twenty-nine age- and gender-matched healthy subjects were also employed as controls. The healthy controls were interviewed by a trained psychiatrist (H.Y.) to be screened for the presence or absence of neuropsychiatric disorders through the Structured Clinical Interview for DSM-IV Axis I Disorder Non-patient Edition [1, 11]. The socioeconomic status (SES) and parental SES were assessed using the Hollingshead scale [15]. The patients with schizophrenia showed a significantly lower self and parental SES than the control subjects. All the participants were right-handed, determined using the Edinburgh Inventory [26]; with a laterality index of >0.8 as the cutoff for right-handedness. The demographic characteristics of the participants are shown in Table 1.

The exclusion criteria for both groups were current or past neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, and substance abuse or addiction. An additional exclusion criterion for the control group was a history of psychiatric disease in themselves or a family history of axis I disorder in their first-degree relatives. The ethical committee of the University of Tokyo Hospital approved this study (No. 397-1). After a complete explanation of the study to the subjects, written informed consent was obtained from every participant.

MRI acquisition

The methods of MRI acquisition were described in detail elsewhere [38]. Briefly, the MRI data were obtained using a 1.5-T scanner (General Electric Signa Horizon Lx version 8.2, GE Medical Systems, Milwaukee, WI, USA). Sagittal localizer images were obtained first, followed by double-echo spin-echo axial slices of whole brain. For volumetric analysis, three-dimensional Fourier–transform spoiled gradient recalled acquisition with steady state was used because it affords excellent contrast between the gray matter and white matter for the evaluation of brain structures. The repetition time was 35 ms, the echo time 7 ms with one repetition, the nutation angle 30 degrees, the field of view 24 cm and the matrix 256 × 256 (192) × 124. Voxel dimensions were 0.9375 × 0.9375 × 1.5 mm.

A trained neuroradiologist (Ha.Ya. or O.A.) evaluated the MRI scans and found no gross abnormalities in any of the subjects. Magnetic field inhomogeneity in our scanner was monitored with daily basic quality control, and has been stable over the MR acquisition time for this study.

Definition of region of interest (ROI)

The BA 44 and 45 gray matter regions of interest (ROIs) were outlined manually using a software package for medical image analysis (3D Slicer; software available at http://www.slicer.org). The manual tracing procedure

Table 1 Demographic characteristics of study participants

Variables	Patients with schizophrenia ($N = 29$)		Controls ($N = 29$)		t test	
	Mean	SD	Mean	SD	t value	p
Age (range)	30.9 (18–44)	6.4	28.9 (24–36)	3.9	−1.46	0.15
SES[a]	3.9	1.0	1.4	0.5	−11.83	<0.001
Parental SES[a]	2.6	0.6	1.9	0.6	−4.08	<0.001
Neuroleptic dose[b] (mg/day)	832	630	–	–		
Onset of illness (years)	22.8	5.4	–	–		
Duration of illness (years)	8.2	6.3	–	–		
Positive symptoms	16.8	6.1	–	–		
Negative symptoms	20.7	6.2	–	–		
General psychopathology	37.0	8.0	–	–		

[a] Socioeconomic status, assessed using the Hollingshead. Higher scores indicate lower status

[b] Based on chlorpromazine equivalents

throughout all the participants was completed by a trained rater (M.S.) without knowledge of diagnosis and participant's information. The anatomical landmarks to delineate BA 44 and 45 utilizing 3-dimensional information were developed based on previous studies examining inferior frontal gyrus [23, 32] and our previous studies utilizing 3-dimensional information in the other regions-of interest [18, 37].

The planes, where tracing of the BA 44 and 45 was mainly performed, were defined as described below. Although one orientation was mainly employed to trace the boundaries, it was essential to concurrently refer to the other orientations throughout tracing. First, on horizontal slices at most dorsal portions, the deepest sulcus positioning on the anterior end of the parietal lobe was identified as the central sulcus. Then, using the central sulcus as a landmark, precentral sulcus, which runs just anterior to central sulcus, was also identified on horizontal slices. Then, on sagittal slices at most lateral portions, inferior frontal gyrus appeared as a letter "M"-shaped structure locating just anterior to precentral sulcus in most cases. The posterior part of the "M"-shape was pars opercularis, mainly consisting of BA 44, which was located aside the precentral sulcus. The rest part of the "M"-shape was pars triangularis and a part of pars orbitalis, mainly consisting of BA 45. Pars opercularis was divided from pars triangularis and part of pars orbitalis by the vertical ascending ramus of the Sylvian fissure, which was also identified on sagittal slices with axial slice as reference plane. On sagittal slices with the coronal slice as reference, inferior frontal sulcus and Sylvian fissure were identified as the dorsal and ventral boundaries of pars opercularis, respectively. As for the medial boundary, pars opercularis was easily distinguished from insula by a circular sulcus of insula when seen in horizontal slices. In these ways, pars opercularis was bordered by precentral sulcus posteriorly, vertical ascending ramus of Sylvian fissure and its linearly prolonged line anteriorly, inferior frontal sulcus dorsally, and Sylvian fissure ventrally. The pars opercularis was considered as approximate BA 44 in this study. Since the rest part of the "M"-shape, pars triangularis and part of pars orbitalis, cytoarchitecturally mainly constitutes of BA 45 [2], these regions as a whole were considered to be approximate BA 45 in the present study. The BA 45 was bordered posteriorly by the vertical ascending transcending ramus of Sylvian fissure and by a straight line extended from same, inferior frontal sulcus dorsally and horizontal ramus of Sylvian fissure anteriorly (Fig. 1).

Anatomical variations of inferior frontal sub-regions

As a significant individual variability of gyral and sulcal pattern of inferior frontal sub-regions was identified, we categorized the variants of respective BA 44 and BA 45 into two simple subtypes in comparison with previous more elaborate categorization [2].

Brodmann Area 44 One gyral/sulcal pattern was most common with 108 of 116 cases. This pattern was labeled BA 44-Type I and consists of a single gyrus, which stands anterior to precentral sulcus, and posterior to vertical ascending ramus of the Sylvian fissure.

The other pattern (8 of 116 cases) was labeled BA 44-Type II. In this pattern the BA 44 were divided into two gyri on more internal slices. Even so, the vertical ascending ramus of the Sylvian fissure and the precentral sulcus were clearly identified, and we regarded the region bordered by these two sulci as BA 44.

Brodmann Area 45 The first and most common pattern, named BA 45-TypeI, was found in 82 of 116 cases. In this type, anterior ramus of Sylvian fissure is clearly distinguished, and the boundary of BA 45, vertical ascending transcending ramus of Sylvian fissure, inferior frontal sulcus, and anterior ramus of Sylvian fissure, is easily identified.

The second pattern (BA 45-TypeII) was found in 34 of 116 cases. In this pattern the Sylvian fissure did not produce an apparent anterior ramus, and the pars triangularis and orbitalis appeared conjoined. In this type, the ventral boundary of BA 45 is the Sylvian fissure itself or a straight line extended from the Sylvian fissure.

Group difference between Types I and II In both the BA 44 and 45, the volumes of type II were significantly larger than those of type I (left BA 44: $p < 0.001$; right BA 44: $p = 0.102$; left BA 45: $p < 0.001$; right BA 45: $p < 0.001$). The frequency of variant patterns of the patients was not statistically different from that of normal controls in either BA 44 or 45.

Reliability

The inter-rater reliabilities of the processes of ROI definition were estimated for two independent raters (Mo Su., and Sy Ya) who were blind to group membership. Ten cases were randomly selected for interrater reliability. Intraclass correlation coefficients of the gray matter of the BA 44 were 0.93 and 0.97 in the left and right hemispheres, respectively, and BA 45 was 0.93 and 0.97 in the left and right hemispheres, respectively.

The intrarater reliabilities of the processes of ROI definition was also tested for one rater (Mo Su) at two separate times (approximately 12 months apart). Ten cases were randomly selected for intrarater reliability. Intraclass correlation coefficients were 0.99 and 0.99 for the gray matter

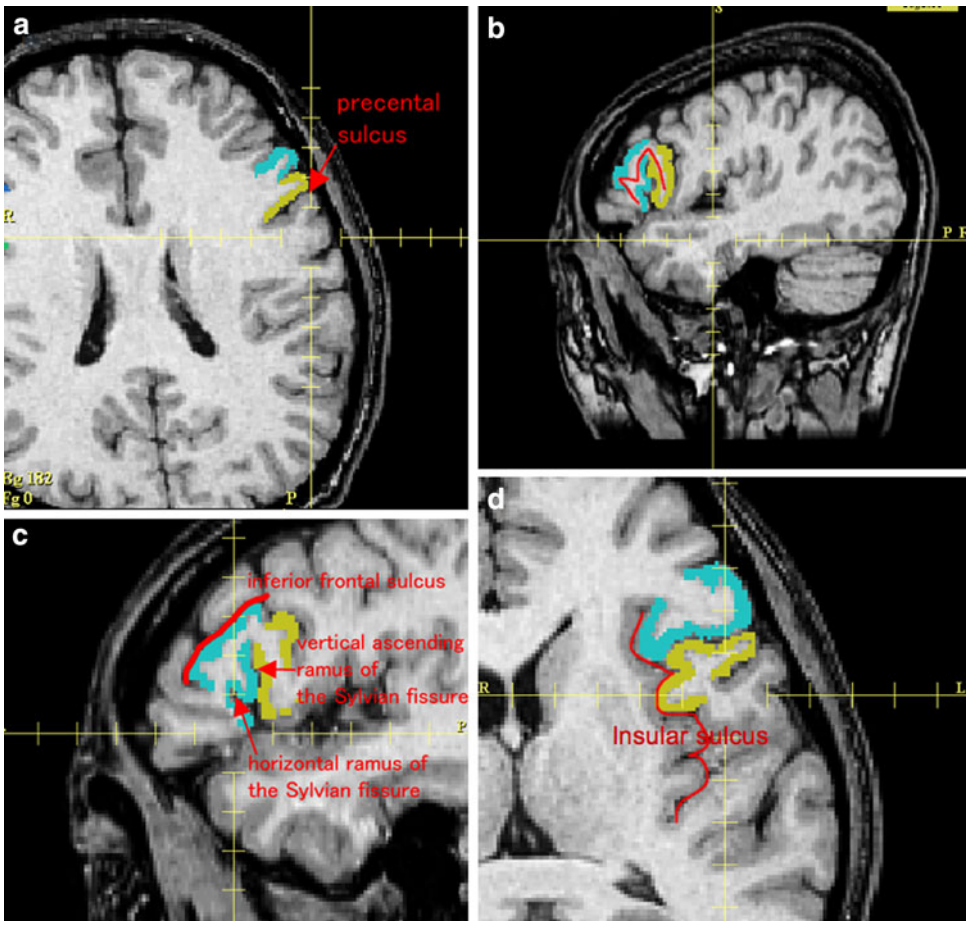

Fig. 1 The anatomical definition of pars opercularis (approximate BA 44) and triangularis (approximate BA 45). In MR images of a control subject with typical sulcal variation, pars opercularis and triangularis are marked in yellow and blue respectively. **a** An axial slice in which the pre-central sulcus is clearly identified. **b** A sagittal slice in which inferior frontal gyrus looks like a letter "M"-shaped structure locating just anterior to precentral sulcus. The posterior part of "M"-shape is pars opercularis (approximate BA 44), which is located aside with the precentral sulcus. The central and anterior part of "M"-shape is pars triangularis and part of pars orbitalis (approximate BA 45). **c** The anatomical boundaries of sub-regions were shown in a sagittal slice. Pars opercularis is divided from pars triangularis and part of pars orbitalis by vertical ascending ramus of the Sylvian fissure. The dorsal and ventral boundaries of pars opercularis are inferior frontal sulcus and Sylvian fissure respectively. **d** A horizontal slice shows the medial boundary of pars opercularis which is easily distinguished from insula by circular insular sulcus

of BA 44 in the left and right hemispheres, respectively, and 0.99 and 0.99 for the gray matter of BA 45 in the left and right hemispheres, respectively.

Statistical analysis

For group comparison, we employed a repeated measures ANCOVA with 1 between-subject factor (group: schizophrenia, controls) and 2 within-subject factors (hemisphere: left/right; region: BA 44/45). The absolute volumes of ROIs were used as the dependent variable with intracranial volume (ICV) as a covariate to account for global anatomical variations. Once a significant group-by-region, group-by-hemisphere or group-by-region-by-hemisphere interaction was found, follow-up analyses using the student's t-tests for each region or hemisphere were performed. Statistical significance was set at $p < 0.05$. Of note, the statistical conclusions reported below remained the same when ANOVA with relative volume [(absolute ROI volume)/(ICV) $\times$ 100] as the dependent variable was employed. In addition, the effect size between patients and controls was computed for each ROI using relative volumes, because the results might be biased by group difference in absolute intracranial volumes. A repeated measures ANCOVA for group comparison of the absolute volumes of ROIs was also employed with ICV and parental SES as covariates, which showed a significant difference between diagnostic groups. Furthermore, in order to consider the possible confounding effect of antipsychotic medication type in the patients, we employed a repeated measures ANCOVA with 1 between-subject factor (group: typical antipsychotics alone ($n = 16$)/atypical alone or both typical and atypical

antipsychotics ($n = 13$)) and 2 within-subject factors (hemisphere: left/right; region: BA 44/45).

The associations between the regional volumes of ROIs and the severity of the five-factor symptoms of PANSS [33], and delusional behavior scores [29, 37] were further tested with Spearman's rank correlation in the patient group. Since the correlation between volumes of BA 45 and severity of positive and disorganized symptoms and delusional behavior were predicted in advance, statistical significance was set at $p < 0.05$ for these correlations. In contrast, since no theoretical hypothesis about the correlations between the other 3 symptom factors and regional volumes exists, statistical significance level was set at $p < 0.004$ after Bonferroni correction for 12 correlations (4 ROIs × 3 symptom factors). In addition, the correlations between volumes of ROIs and potential confounds, including age, self SES, parental SES, onset of illness, duration of illness, or dose of neuroleptics, were also tested using Spearman's rank correlation in each group separately. Since correlations between these potential confounds and volumes of ROIs were not hypothesized in advance, statistical significance was set at $p < 0.0014$ (Bonferroni correction for 36 correlations [24 for schizophrenia group {4 ROIs × 6 clinical measures}; 12 for control group {4 ROIs × 3 clinical measures}]).

Results

Volume of ROIs

The repeated measures ANCOVA showed a significant main effect of group ($F[1,55] = 4.59$, $p = 0.037$), while no significant group × hemisphere ($F[1,55] = 1.96$, $p = (0.167)$, group × region ($F[1,55] = 0.54$, $p = (0.465)$ or group × hemisphere × region ($F[1,55] = 1.03$, $p = (0.315)$ interaction was found. Post-hoc t tests indicated that the patients with schizophrenia had smaller volumes of both BA 44 and BA 45 bilaterally than healthy controls (Fig. 2). An evaluation of the effect size indicated that the effect size for the right BA 45 was the largest among all the four inferior frontal sub-regions we examined. The results are shown in Table 2. The statistical conclusions remained unchanged when we adopted ICV and parental SES as covariates. There was no statistically significant effect of types of neuroleptics in patients with schizophrenia.

Correlational analysis

The severe positive symptoms were significantly associated with both smaller left and right BA 45 volumes (Left: $\rho = -0.416$, $p = 0.025$; Right: $\rho = -0.378$, $p = 0.043$) in the patient group. The severe disorganized symptoms were also significantly associated with the reduced BA 45 volume bilaterally (Left: $\rho = -0.485$, $p = 0.008$; Right: $\rho = -0.493$, $p = 0.007$). Furthermore, the severe delusional behavior correlated significantly with the smaller BA 45 volume in the left hemisphere ($\rho = -0.492$, $p = 0.007$). In contrast, the severity of negative symptoms did not show any significant correlation with the volume of inferior frontal sub-regions. Of note, although the BA 45 volume showed significant correlations with the psychotic symptoms described earlier, the BA 44 volume showed no significant correlation with the symptom severity. The Fisher's Z-transformation showed a significant difference between the correlation of severity of delusional behavior with BA 45 and BA 44 ($z = 1.97$, $p = 0.048$), indicating that the correlation was specific to BA 45. The results are shown in Table 3. The severe excitement and emotional distress were associated with the smaller right BA 45 volumes (excitement: $\rho = -0.364$, $p = 0.053$; emotional distress: $\rho = -0.417$, $p = 0.025$) in the patient group, although these results did not remain statistically significant after Bonferroni correction for eight correlations.

There were no significant correlations between ROIs and potential confounds; age, self SES, parental SES, onset of illness, duration of illness, or dose of neuroleptics (corrected p's > 0.5).

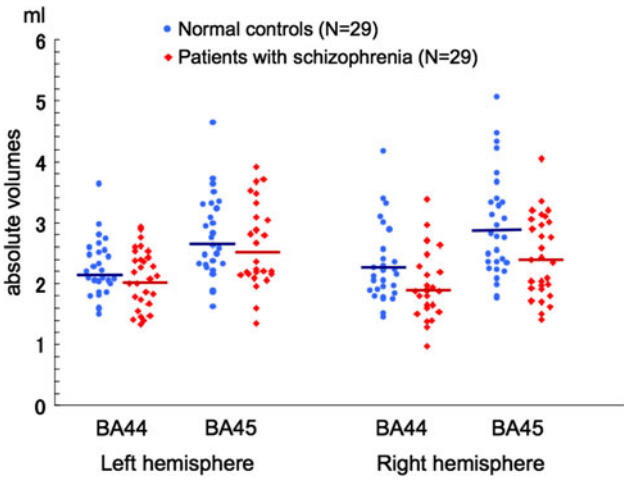

Fig. 2 The plots of gray matter volume of Regions-of-interest. *Scatter plots* show absolute volumes of Brodmann's area 44 (BA 44) and 45 (BA 45) for patients with schizophrenia ($n = 29$) and controls ($n = 29$). *Horizontal lines* indicate means of each group

Discussion

The present findings employing a highly reliable manual tracing methodology demonstrated that the male patients with schizophrenia had significantly reduced volumes of both the BA 44 and BA 45 bilaterally compared with the

Table 2 Volumetric measures and statistical results

Variables	Patients with schizophrenia ($n = 29$)		Controls ($n = 29$)		Effect sizes*	Repeated measures analysis of variance			
						Group	Group × Hemisphere	Group × Region	Group × Region × Hemisphere
	Mean	SD	Mean	SD		F (p)	F (p)	F (p)	F (p)
Intracranial volume	1,620	139	1,649	122	0.24				
Left hemisphere									
Area 44	1.92	0.49	2.06	0.48	0.24	4.59 (0.037)	1.96 (0.17)	0.54 (0.47)	1.03 (0.32)
Area 45	2.43	0.67	2.54	0.68	0.10				
Right hemisphere									
Area 44	1.84	0.60	2.10	0.63	0.37				
Area 45	2.27	0.67	2.76	0.86	0.51				

Effect sizes are calculated as: (MEANnc-MEANsc)/SDnc, MEANnc (sc): Group mean of relative volumes of normal controls (patients with schizophrenia)

Table 3 Association between volumetric measures and symptoms

	Left hemisphere		Right hemishere	
	Area 44	Area 45	Area 44	Area 45
Positive symptoms	−0.08	−0.42*	0.02	−0.38*
Negative symptoms	0.02	−0.04	0.08	−0.30
Disorganization symptoms	−0.15	−0.49**	−0.17	−0.49**
Delusional behavior	0.01	−0.49**	−0.13	−0.13

Spearman's rho is presented. * $p < 0.05$, ** $p < 0.01$

healthy male controls. In particular, the present parcellation study found for the first time that the BA 45 volume in right hemisphere showed the largest effect size among the four inferior frontal sub-regions. In addition, the reduced volume of BA 45 specifically showed significant associations with the increased severity of disorganized, positive symptoms and delusional behavior in the patient group, with the specificity being confirmed by Fisher's r to z transformation.

The gray matter volume of both BA 44 and BA 45 was significantly and bilaterally smaller in the patients with schizophrenia than in the controls. The current results are consistent with the previous findings of bilateral inferior frontal gyrus volume reduction without sub-regional segmentation in patients with schizophrenia [7, 31, 38]. In addition, the previous studies employing computational voxel-based analysis also showed regional gray matter volume reduction in the inferior frontal gyrus [3, 4, 6, 13, 19, 27, 30, 36]. Since the present sub-regional segmentation study revealed the highest effect size of gray matter volume reduction in the right BA 45, the present study not only replicated the previous findings of inferior frontal gyrus volume reduction but also extended them to identify the right BA 45 as the site of greatest volume reduction.

The current parcellation study uncovered a correlation between reduced BA 45 volume and positive, disorganized, and delusional behaviors in the patient group. While the severity of disorganized and positive symptoms showed a negative correlation with the volume of BA 45 bilaterally, the severity of delusional behavior showed a negative correlation with the volume of BA 45 in left hemisphere alone. The laterality of the present findings is consistent with previous studies reporting the association between language processing, such as semantic verbal fluency task, and left BA 45 in healthy subjects [28, 40]. In contrast to language processing, inferior frontal gyrus involvement in interpersonal aspect behaviors, such as imitation of other's behavior, is not lateralized to the left hemisphere [5]. F-MRI studies revealed that understanding another person's intention is associated with right inferior frontal gyrus, although the area mainly consists of right pars opercularis [16]. The present study showing correlation between reduced right BA 45 volume and severe psychotic symptoms is also consistent with these previous studies.

The specificity of correlation of BA 45 with psychotic symptom severity including delusional behavior, as confirmed by Fisher's r to z transformation, is consistent with the previous findings of a small number of functional imaging studies that have examined this issue. For example, Wisco et al. [35] recently found that an area within the pars triangularis of the left inferior frontal gyrus showed significantly different cortical folding patterns in the patient group compared with the control group. Dollfus et al. [9] found lower BOLD signal changes during a language task in patients as compared with their control subjects in a network comprising areas of the left middle temporal gyrus, the left angular gyrus, and the pars triangularis of the left inferior frontal gyrus. The present study is consistent with these functional imaging studies,

and in addition, provides support at the brain structural level for the notion that BA 45, mainly consisting of pars triangularis, plays an important role in the pathophysiology of schizophrenia.

Here we address the methodological considerations and future direction of our study. First, since the present study sample included patients with chronic schizophrenia and antipsychotic medications, the effect of chronic illness [18] and medication [24] on the present findings cannot be totally ruled out. The volumes of ROIs did not show any significant correlation with duration of illness and daily dose of neuroleptics. In addition, the main effect of antipsychotic medication type was not significant when we employed repeated measures ANOVA in the patients. However, the effect of cumulative dosage still remained unclear. Therefore, future studies should employ patients with first episode schizophrenia and minimum medication. Second, parental SES of the patients was significantly lower than those of controls. Though the parental SES did not show any significant correlation with the volumes of ROIs and the statistical conclusions remained unchanged when we covaried parental SES, the effect of parental SES on the present findings cannot be totally ruled out. Third, the possible sexual-dimorphism in the structural abnormality of inferior frontal gyrus in patients with schizophrenia is still unclear since the present study participants were all male. As significant gender differences in cortical thickness [17] and behavioral correlates [39] of inferior frontal gyrus have been reported, future study should address the issue. Finally, since cytoarchitectonic borders with significant inter-individual variability do not consistently coincide with sulcal contours as shown by Amunts et al. [2], it should be noted that the current definition utilizing sulcal pattern cannot exactly reflect cytoarchitectonic borders.

In conclusion, the present findings employing a reliable manual-tracing method demonstrated that the male patients with schizophrenia had significantly reduced volumes of both the BA 44 and BA 45 compared with the healthy male controls bilaterally. In particular, the BA 45 volume in right hemisphere revealed the largest effect size among the inferior frontal sub-regions. In addition, the reduced volume of BA 45 showed significant associations with the increased severity of disorganized, positive symptoms and delusional behavior in the patient group. Of note, the Fisher's Z-transformation confirmed a differential relationship of delusional behavior with reduced volume of BA 45, rather than BA 44. These results indicate a significant role of inferior frontal gyrus, especially BA 45, in the pathophysiology of schizophrenia.

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