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ORIGINAL PAPER

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Insular volume reduction in schizophrenia

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Abstract Structural and functional abnormalities of the insular cortex have been reported in patients with schizophrenia. Most studies have shown that the insular volumes in schizophrenia patients are smaller than those of healthy people. As the insular cortex is functio-anatomically divided into anterior and posterior subdivisons, recent research is focused on uncovering a specific subdivisional abnormality of the insula in patients with schizophrenia. A recent ROI-based volumetric MRI study demonstrated specific left anterior insular volume reduction in chronic schizophrenia patients (Makris N, Goldstein J, Kennedy D, Hodge S, Caviness V, Faraone S, Tsuang M, Seidman L (2006) Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophr Res 83:155–171). On the other hand, our VBM-based volumetric study revealed a reduction in right posterior insular volume (Yamada M, Hirao K, Namiki C, Hanakawa T, Fukuyama H, Hayashi T, Murai T (2007) Social cognition and frontal lobe pathology in schizophrenia: a voxel-based morphometric study. NeuroImage 35:292–298). In order to address these controversial results, ROI-based subdivisional volumetry was performed using the MRI images from the same population we analyzed in our previous VBM-study. The sample group comprised 20 schizophrenia patients and 20 matched healthy controls. Patients with schizophrenia showed a global reduction in insular gray matter volumes relative to healthy comparison subjects. In a simple comparison of the volumes of each subdivision between the groups, a statistically significant volume reduction in patients with schizophrenia was demonstrated only in the right posterior insula. This study suggests that insular abnormalities in schizophrenia would include anterior as well as posterior parts. Each subdivisional abnormality may impact on different aspects of the pathophysiology and psychopathology of schizophrenia; these relationships should be the focus of future research.

Key words schizophrenia · insular · volumetry · self-awareness

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Introduction

It has been postulated that dysfunction of the limbic system would be linked to difficulties in distinguishing between internal and external perceptions and regulating behaviors, ultimately allowing the emergence of the psychotic symptoms of schizophrenia; however, the underlying pathology remains to be elucidated [2, 9, 27]. The insular cortex is part of the limbic region, playing a key role in integrating perceptual experiences and affects to produce balanced behavior [1, 16].

There is converging evidence of a functio-anatomical abnormality of the insula in patients with schizophrenia. Functional neuroimaging studies suggest that insular hypometabolism [6] or decreased cerebral blood flow [4] might be involved in the pathophysiology of schizophrenia. Volumetric magnetic resonance imaging (MRI) studies of the insular cortex have almost unanimously indicated that there are morphological abnormalities of the insular gray matter in patients with schizophrenia [7, 10, 14, 18–21, 24, 25, 27].

However, what remains unsolved is whether the insular abnormality in schizophrenia is specific to a certain subdivision (or lateralized), or if it is bilateral and global. Regarding the laterality issue, the literature is inconsistent: some studies report bilateral insular volume reductions [10, 14, 20, 25], whereas others report left-sided volume reductions [19, 21, 24]. Right-sided insular volume reduction has also been reported in female subjects [7].

In addition to the laterality issue, what is important is the intrahemispheric functio-anatomical subdivision of the insular cortex. The insular cortex is anatomically divided into two major subdivisions (anterior and posterior lobules) by the central sulcus of the insula [22, 23]. Morphological separation between these two parts reflects, to some extent, the characteristics of the cytoarchitectonic composition and their different neural connections. The anterior insula represents the agranular and adjacent dysgranular insula, and is connected to the piriform, orbitofrontal, temporopolar and parahippocampal regions. Together with the above-mentioned areas, the anterior insula plays a role in the control of emotions and autonomic regulation. By contrast, the posterior insular lobule consists of the granular and adjacent regions, and is more closely connected to the somatosensory, auditory, and motor areas [17]. The posterior insula mainly connects with the primary and secondary somatosensory cortices (SI, SII), the superior and inferior parietal lobules, the orbitofrontal, prefrontal and premotor cortices, the auditory cortex (AI, AII), the superior and inferior temporal cortices, the basal ganglia and the thalamus [1, 17].

Makris et al. [15] recently measured the volumes of the insular subregions (left/right × anterior/posterior) using the central sulcus of the insula as a landmark for subdivisions, and investigated the volumetric alteration of the insula in patients with schizophrenia based on a volumetric MRI study. The authors reported that there was a significant reduction in insular cortical volume throughout the anterior insular lobules, and particularly in the left anterior lobule, in chronic schizophrenia patients compared with normal controls.

However, there are technical problems in previous volumetric MRI studies. Since the insula is a relatively small structure, it is difficult to clearly delineate it in images of low spatial resolution, especially when subdivisional volumetry is intended. Most studies have utilized lower magnetic field MR images (from 1.0 to 1.5 T) and obtained slices thicker than 1 mm (~1.5–3 mm). Such low quality protocols might lead to insufficient measurement of insular volumes.

Previously, our voxel-based morphometry (VBM) study revealed that there is a volume reduction in the right posterior insular lobules of patients with schizophrenia [26], in contrast to the results of Makris et al. [15]. Thus, to address these controversial results, a region-of-interest (ROI)-based subdivisional volumetry study was performed using the MRI images from the same population we analyzed in our previous VBM-study [26]. The analyzed structural MRI images were obtained using a 3.0 T MRI scanner with slices of an acceptable thickness (1 mm) to investigate changes in the volumes of the subdivisions of the insular cortex.

Methods

Participants

The participants are identical to those of our previous study [26]. The schizophrenia group comprised 20 patients (10 men and 10 women), referred to the Department of Psychiatry, Kyoto University Hospital. Exclusion criteria included a history of seizure disorder, head trauma resulting in a loss of consciousness, neurological illness or substance abuse. Based on the Structural Clinical Interview for DSM-IV (SCID), all patients met DSM-IV criteria for schizophrenia and clinical symptoms were rated according to the Positive and Negative Syndrome Scale (PANSS; [13]). All patients were being treated with antipsychotic medications and were physically healthy at the time of scanning. Haloperidol equivalents, which were calculated according to Inagaki et al. [11], were administered at 11.9 ± 8.9 mg/day. Among the 20 patients, 18 were being treated with atypical antipsychotic medications (12 with 6.63 ± 3.45 mg/day of risperidone, 5 with 10.00 ± 6.12 mg/day of olanzapine, 3 with 391.7 ± 278.8 mg/day of quetiapine, and 2 with 18.00 ± 6.00 mg/day of perospirone): 11 were being treated with a single atypical antipsychotic medication, three were being treated with multiple atypical antipsychotics, and four were being treated with atypical antipsychotics in combination with typical (haloperidol or chlorpromazine) antipsychotics. Two patients were being treated with multiple typical antipsychotics. Some patients (n = 8) were also receiving adjunctive anticholinergic treatment. The comparison group comprised 20 healthy individuals (10 men and 10 women) who were matched with the schizophrenia group with regard to age and education level. These subjects were also evaluated on the basis of SCID. They had no current or past history of psychiatric or neurologic diseases. In addition, they had no first degree relatives who had current or past psychotic episodes.

Table 1 indicates the demographic characteristics of the two groups. The estimated verbal and performance IQs were obtained from vocabulary and block design subtasks, respectively, using the Wechsler Adult Intelligence Scale-Revised (WAIS-R) by transforming the scores corrected for age into T scores.

After a complete description of the study to the participants, they gave written informed consent to a protocol approved by the Committee on Medical Ethics of Kyoto University.

MRI acquisition and pre-processing

MR images were obtained at Kyoto University Hospital on a 3-T whole-body scanner equipped with an 8-channel phased array coil (Trio, Siemens, Erlangen, Germany). The scanning parameters of the three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were as follows: TE = 4.38 ms; TR = 2000 ms; TI = 990 ms; FOV = 240; slice plane = axial; slice thickness = 1 mm; resolution = 0.94 × 0.94 × 1.0; and slice number = 208. In order to increase the signal/noise ratio, we scanned all participants three times and obtained average images from the three scans using statistical parametric mapping 2 (SPM2) software (The Wellcome Department of Imaging Neuroscience, London, U.K.) running in Matlab 6.5 (The Math Works, Natic, MA, U.S.).

Table 1 Demographic, clinical, and neuropsychological characteristics of the subjects

	Schizophrenia (n = 20)		Healthy (n = 20)		Statistics	
	Mean	S.D.	Mean	S.D.	t (df = 38)	p
Age (years)	38.8	7.2	39.1	7.1	0.13	$p > 0.05$
Sex (male/female)	10/10		10/10		–	–
Handedness (right/left)	19/1		19/1		–	–
Education years	13.5	2.0	14.4	1.9	0.15	$p > 0.05$
Age at onset (years)	27.4	6.4	–	–	–	–
Duration of illness (years)	11.6	8.7	–	–	–	–
Drug (mg/day, haloperidol equivalent)	11.9	8.9	–	–	–	–
PANSS Total	64.5	19.8	–	–	–	–
PANSS Positive	16.4	6.7	–	–	–	–
PANSS Negative	15.7	6.5	–	–	–	–
PANSS General	32.4	10.1	–	–	–	–
VIQ	97.8	16.0	107.5	14.8	2.00	$p > 0.05$
PIQ	97.8	14.9	107.0	12.7	2.11	$p = 0.04$

ROI definition

The boundaries of the insular cortex were manually determined using MRIcro (Chris Rorden, University of Nottingham, Great Britain) on consecutive coronal slices. The most rostral coronal plane containing the insular cortex and the coronal plane containing the fusion of the superior and inferior circular insular sulci were chosen as anterior and posterior boundaries, respectively. On each coronal slice, the insular cortex was bounded superiorly by the superior circular insular sulcus, and inferiorly by the inferior circular insular sulcus or the orbitoinsular sulcus, following the procedure of Crespo-Facorro et al. [3]. In addition, following the procedure applied by Makris et al. [15], the central sulcus of the insula was considered as the landmark dividing the insular cortex into anterior and posterior parts; thus, this sulcus constitutes the inferior border of the anterior insular lobule and the superior border of the posterior insular lobule (Fig. 1). The volume of each lobule was calculated by multiplying the number of voxels assigned to that structure by the single-voxel volume $0.94 \times 0.94 \times 1.0$ mm^3. All measurements were carried out by the first author (TS) who was blind to subjects' identity, demographic data, diagnosis, and psychopathology.

To determine the reliability of the insular measurements, 10 subjects were randomly selected. Segmentation and parcellation was independently carried out by the first author and another researcher who was experienced at volumetric analysis. Both raters were blinded to participant details, including the study group and

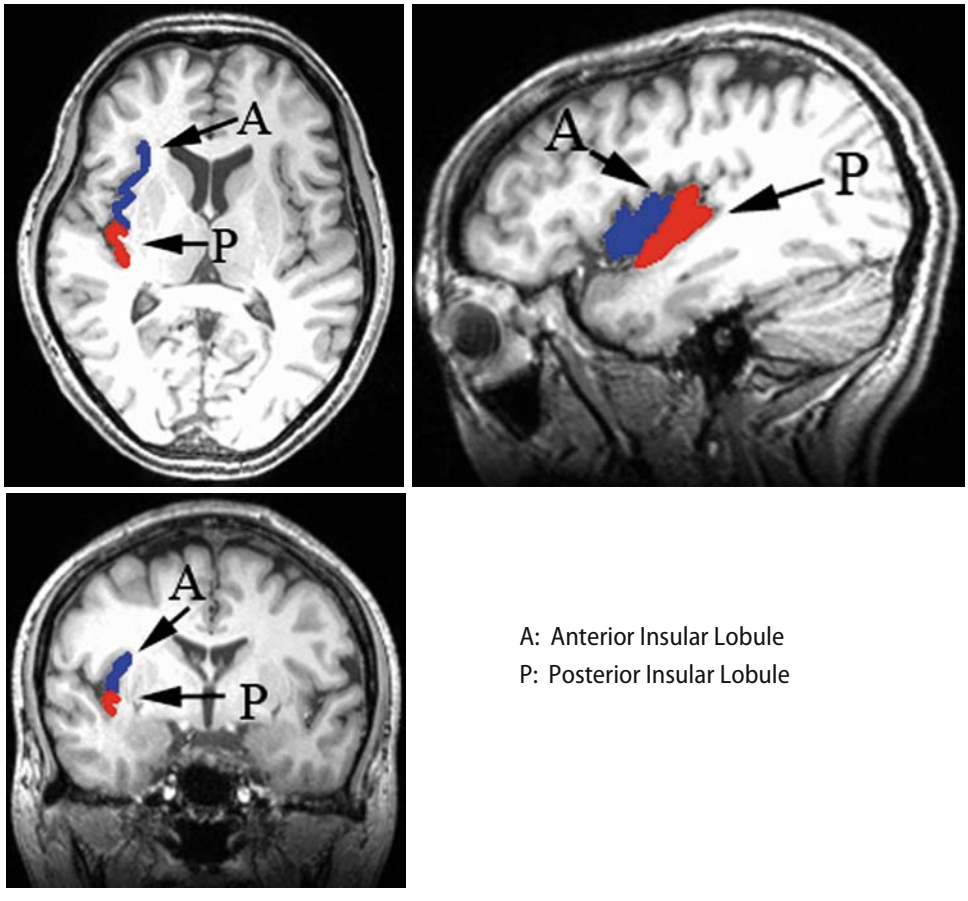

Figure 1 The anterior and posterior insular lobules

the results of neuropsychological tests, during the measurement. For the insula subregion, intrarater reliability ranged from 0.96 to 0.97; interrater reliability ranged from 0.90 to 0.92 using Cronbach's alpha coefficient.

Intracranial volume (ICV) measurement

Estimates of the global gray and white matter volumes and cerebrospinal fluid (CSF) volume were obtained after the automatic brain segmentation procedure had been carried out by SPM2 in our previous study [26]. Total ICV was the sum of the volumes of gray and white matters and CSF.

Statistical analysis

In group comparisons of the insular subdivisional gray matter volumes, the relative volume ([absolute ROI volume/ICV] × 100) was analyzed by repeated measures analysis of variance (ANOVA) with group (schizophrenia, control) as a between-subject factor, and hemisphere (left, right) and subregion (anterior, posterior) as within-subject variables. As mentioned in the introduction, each insular subdivision differs in its anatomical features, connectivity and functional roles. Thus, we were also interested in determining if the volumes of each insular subdivision differ significantly between the groups, especially for those of the left anterior and right posterior subdivisions, the volumes of which have been reported to be reduced in schizophrenia patients [15, 26]. Hence, separate group comparisons for each of the four subregional volumes were performed without correction for multiple comparisons of the four subregions.

Finally, in order to investigate the relationship between the gray matter volumes of the patients' insular subregions and their PANSS scores, parametric statistics were used if an initial exploration of the data set indicated a normal distribution; otherwise nonparametric statistics were applied.

For all of the resulting statistics, the significance threshold was set at $p < 0.05$. All of the above statistical analyses were performed using SPSS v.12.0.

Results

Demographic and clinical characteristics of patients and controls

Demographic and clinical data are summarized in Table 1. Two-tailed *t*-tests were applied to compare the differences in demographic and clinical variables between groups. The groups did not differ significantly in age, sex, handedness, education or estimated VIQ. The estimated PIQs of the schizophrenia subjects were significantly worse than those of healthy controls [controls = 107.0 (12.7); patients = 97.8 (14.9); $t = 2.11$; df = 38; $p = 0.04$].

Volume change

The ANOVA revealed a significant main effect of group (F = 4.280, df = 38, $p = 0.045$), subregion (F = 677.4, df = 38, $p < 0.001$) and a hemisphere-by-subregion interaction (F = 8.825, df = 38, $p = 0.005$), but no significant main effect of hemisphere (F = 0.019, df = 38, $p = 0.890$) and no significant group-by-hemisphere (F = 0.086, df = 38, $p = 0.771$), group-by-subregion (F = 0.041, df = 38, $p = 0.840$), or group-by-hemisphere-by-subregion (F = 1.027, df = 38, $p = 0.317$) interactions. This result suggests that patients with schizophrenia have a global (that is, non-specific to subregion or hemisphere) reduction in the volume of insular gray matter relative to healthy subjects. When subregional relative volumes were compared between groups separately, a significant difference was demonstrated only in the right posterior lobule (F = 4.960, df = 38, $p = 0.032$), but not in the other three subregions (Table 2 and Fig. 2).

Table 2 Insular volumes in subjects with schizophrenia and healthy controls

	Schizophrenia ($n = 20$)		Healthy ($n = 20$)		Statistics	
	Mean	S.D.	Mean	S.D.	t (df = 38)	p
Intracranial volume (ml)	1564.1	212.8	1617.3	172.3	0.87	0.39
Insular cortex volume						
Right anterior						
Absolute (ml)	3.5	0.59	3.5	0.35		
Relative (%)	0.23	0.029	0.22	0.027	−1.00	0.33
Right posterior						
Absolute (ml)	1.9	0.40	1.8	0.30		
Relative (%)	0.13	0.021	0.11	0.015	−2.20	0.032
Left anterior						
Absolute (ml)	3.7	0.59	3.6	0.47		
Relative (%)	0.24	0.029	0.22	0.026	−1.50	0.13
Left posterior						
Absolute (ml)	1.8	0.33	1.7	0.19		
Relative (%)	0.11	0.017	0.11	0.015	−1.20	0.24

Correlations between volumes and clinical measures

Age, age when first medicated, duration of medication treatment, or current dose of antipsychotic medication, were not correlated with any of the investigated relative volumes. No significant correlation was demonstrated between any of the investigated relative volumes and any of the three PANSS subscores (positive, negative and general scores).

Discussion

Three main findings emerge from this study: (1) schizophrenia patients show a global reduction in insular volumes; (2) among insular subregions, the right posterior insula was the only subregion in which patients showed a significant volume reduction; (3) in the patient group, none of the subregional insular volumes were associated with psychopathological measures.

Insular volume reduction in schizophrenia

Although, most previous studies have shown volume reduction in the insular gray matter in patients with schizophrenia, little is known regarding the subdivi-

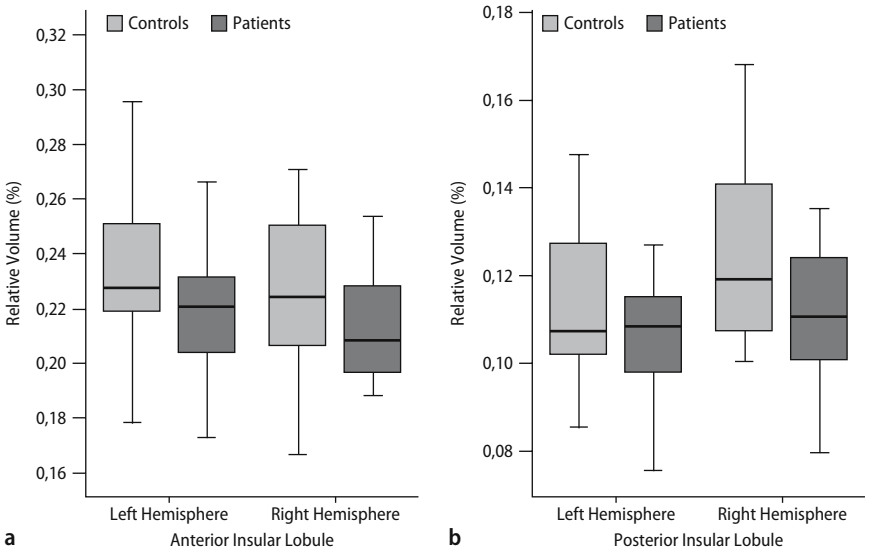

Figure 2 Box-plots of the relative volumes (%) of the insular lobules in the anterior (**a**) and posterior (**b**) zones of patients with chronic schizophrenia ($n = 20$) and healthy control subjects ($n = 20$). Means are indicated by horizontal lines. Each box encompasses 50% of the distribution of volumes

sional specificity of this volume reduction, as summarized in the Introduction. Our results, using high spatial resolution images, suggest that the insular abnormality is not subregion specific, but global, affecting the structure bilaterally as well as in both anterior and posterior subregions. Thus, the inconsistencies of the previous literature might be due to differences in patient characteristics as well as substantial measurement error variations associated with lower resolution images.

Specifically, in contrast to the recent study by Makris et al. [15], which is, other than our studies, the only study to investigate the insular subregional volumes in schizophrenia by dividing the insula into anterior and posterior sections, we did not demonstrate a specific volume reduction in the left anterior insula. This discordance might originate from differences in the characteristics of the patients investigated; for example, the illness durations in the patients in Makris' study (22.5 ± 10.9 years) were twice as long as those in ours (11.6 ± 8.7 years). However, the difference in methodological protocols would also be important. We traced an average of 50 coronal slices per subject when measuring the insular cortex; among these, 30 covered the posterior insular cortex. We believe that this method, using 1 mm-thick slices, can provide a more exact measure of the subregional volumes than that of Makris et al. [15], using 3 mm-thick coronal slices.

Although we did not demonstrate a statistically significant group difference in left anterior insular volumes, our assertion is not that the left anterior insula is not involved in the pathophysiology of schizophrenia, but that the left anterior insula is not specifically involved. Anterior and posterior subdivisions of the insula are involved in different neural circuitries, and bear a differential impact on our cognition and behavior. We suspect that the functions of both subdivisions would be compromised in schizophrenia. Pathology of the anterior insula, together with other limbic and paralimbic structures, mainly affects emotional processes modulating our behaviors. Pathology of the posterior subdivision would have a different impact.

Regarding the effect of medication on regional volumes, we found no significant correlation between antipsychotic doses and subdivisional insular volumes. Dazzan et al. [5] reported that typical but not atypical antipsychotics are likely to induce regional cortical volume reductions, including a volume reduction in the insula, among first episode schizophrenia patients. The lack of an association of medication with insular volumes in our current study might be due to the fact that most of the patients were being treated with atypical antipsychotics.

The volume change in the right posterior lobule

The main result of our analysis should be interpreted as a global reduction in the volume of the insula. However, in a separate group comparison for each subdivision, the only subregion in which a significant difference in volumes was found was the right posterior insula, although this difference was marginal without correction for multiple comparisons. Comparing the methodological advantages and disadvantages of VBM and manual ROI analysis, Kubicki et al. [14] recommended the initial use of VBM in an exploratory manner and subsequent confirmatory analyses by application of manual ROI tracing. Such an approach has been demonstrated to be successful in our analysis regarding the insular cortical volumes of schizophrenia: an initial whole-brain VBM analysis revealed a reduced volume region in the right posterior part of the insula [26], and this preliminary result was further confirmed by the present analysis using manual ROI tracing.

Although not fully elucidated, recent neuroimaging studies provide a clue to the possible functional sig-

nificance of this particular subregion of the human insula. Based on a lesion study analyzing an unselected sample of stroke patients with right brain damage, Karnath et al. [12] reported that right posterior insula lesions are specifically associated with "anosognosia" for hemiplegia/hemiparesis. On the other hand, in an activation study by Farrer et al. [8] using positron emission tomography (PET), healthy subjects were requested to indicate whether movements they saw on a computer screen corresponded to their executed movements, or were controlled by another person. The experiment showed decreased activity in the right posterior insula with a decreasing feeling of controlling the movement; that is, when subjects experienced a mismatch between what they did and what they saw. By contrast, this activity was increased when the afferent input matched their own actions. A possible interpretation of these findings is that the right posterior insula plays an important role in integrating signals related to self-awareness and establishing a boundary between self and others.

Although speculative, considering the functional significance of this region, some of the core characteristics of the psychopathology of schizophrenia could be explained by a dysfunctional right posterior insula: lack of insight could be explained straightforwardly as compromised self-awareness, while multimodal hallucinations could also be interpreted as a consequence of misintegration of sensory inputs into self-awareness.

Unfortunately, we did not find any correlation between psychopathological measures and the volume of any of the insular subregions, including the right posterior insula. The small sample size or non-uniformity of the subjects investigated (including both first episode subjects and more chronic subjects) might have affected our results of non-association between psychopathology and insular volumes. However, previous studies are also controversial regarding the association of psychopathology and insular volume reduction. If the above-mentioned role of the right posterior insula and its possible impact on psychopathology are true, such a putative association could be demonstrated using specifically-designed cognitive tasks or psychopathological measures to capture aspects of self-awareness in schizophrenia; this is the goal of our future studies.

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