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Disorganization of semantic memory underlies alogia in schizophrenia: An analysis of verbal fluency performance in Japanese subjects

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Abstract

Patients with schizophrenia exhibit impaired semantic memory as well as deficits in a wide range of language-related functions, such as verbal fluency, comprehension and production of complex sentences. Since language and memory disturbances may underlie some of the psychotic symptoms of schizophrenia, the present study investigated the specific association between alogia (i.e. poverty of speech, poverty of content of speech, blocking, and increased latency of response) and semantic memory organization using the category fluency task (CFT) as a measure of verbal fluency. Thirty-eight patients with schizophrenia and an equal number of normal controls entered the study. Semantic structure was derived from multidimensional scaling analysis using sequential word outputs from the CFT. Patients with schizophrenia revealed disorganized semantic structure (e.g. irregular association of category members) compared with controls, consistent with previous reports. The patients were then divided into two groups, i.e. alogia- and non-alogia subjects, based on the Alogia scores from the Scale for the Assessment of Negative Symptoms (SANS). The symptom-based analysis showed that the semantic structure for the alogia group (Alogia score ≥ 2) was more disorganized than that for the non-alogia group (Alogia score ≤ 1) although the number of words produced did not differ between the two groups. The results of cluster analysis revealed the presence of bizarre coherence specifically in the alogia group. These results indicate that semantic memory disorganization may contribute to the symptom of alogia in schizophrenia. In addition, this is one of the few studies that examined verbal

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fluency in Japanese patients with schizophrenia and suggest that the language abnormalities in schizophrenia are universal.

Keywords: Category fluency; Semantic structure; Alogia; Schizophrenia; Multidimensional scaling analysis; Cluster analysis

1. Introduction

Patients with schizophrenia exhibit a wide range of the language-related disorders, including speech comprehension, semantic or grammar consistency, verbal fluency, and sentence complexity (for a review, see DeLisi, 2001). However, the mechanisms underlying these deficits, a core feature of schizophrenia, have not yet been fully clarified. DeLisi (2001) suggested that the language-related disturbances originate either from dysfunctions of the language ability specific to humans, or from more general cognitive deficits such as executive and/or memory dysfunction. The verbal fluency tasks (VFTs) are useful to assess such manifold disorders, as they evaluate both executive and semantic memory functions requiring language skills such as quick and spontaneous word production. Because of their versatility, the VFTs have been used to predict the functional outcomes and quality of life in patients with schizophrenia (Buchanan et al., 1994; Green, 1996; McGurk and Meltzer, 2000).

Typically, two types of the VFTs are used in the clinical assessment. One is the category fluency task (CFT), in which subjects are instructed to produce as many words of a certain category (e.g. dog, cat... etc. for the ANIMAL category) as possible within a designated time (e.g. 1 min). The other is the letter fluency task (LFT), in which an initial letter is given as a cue (e.g. F, A, S); subjects are requested to produce the words beginning with one of the letters (e.g. *f*lower, *f*urniture,... etc. for the "F" cue). The time limitation requires subjects to concentrate on the quick search, retrieval, and monitoring of verbal outputs with a minimal amount of intrusion and repetition. Thus, the CFT and LFT have been considered to be useful to assess an aspect of executive function. The CFT has also been used to evaluate semantic memory organization in patients with schizophrenia, as well-formed semantic associations based on certain criteria (e.g. size, domesticity, predation) are necessary to maximize production of words belonging to a certain category. Previous studies (Aloia et al., 1996; Moelter et al., 2001; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001) visualized semantic organization in the form of a "map" that is derived from the multidimensional scaling (MDS) analysis (Kruskal and Wish, 1978) by using sequential verbal outputs from the CFT.

Several investigations have indicated that verbal fluency performance is affected by cognitive or demographic status in patients with schizophrenia. For example, the severity of impairment in organization of semantic memory has been shown to be dependent, in part, on age at onset of the illness (Paulsen et al., 1996; Sumiyoshi et al., 2001). Others report that the number of words produced in the LFT (Bolla et al., 1990; Cauthen, 1978; Crawford et al., 1993) or CFT (Sumiyoshi et al., 2001) depends on verbal intelligence in patients with schizophrenia. Furthermore, we have recently found the degree of impairment in the performance on the LFT depends on the orthography systems (e.g. alphabetical versus non-alphabetical) used by patients (Sumiyoshi et al., 2004).

Attempts have been made to find the relationship between positive or negative psychotic symptoms of schizophrenia and verbal fluency performance. Thus, patients with severe thought disorders have been reported to show overall deficits in verbal fluency performance (Kuperberg et al., 1998) or selective impairment in the performance on the CFT (Aloia et al., 1996; Feinstein et al., 1998; Goldberg et al., 1998; Gourovitch et al., 1996). Several studies (Allen et al., 1993; Howanitz et al., 2000) have indicated that negative symptoms as a whole also inhibit rigorous word productions in patients with schizophrenia. On the other hand, specific domains of negative symptoms, such as withdrawal-retardation (Mahurin et al.,

1998) and alogia representing "difficulties in fluent and logical thinking", (i.e. poverty of speech, poverty of content of speech, blocking, and increased latency of response) have been reported to be associated with verbal fluency performance (Joyce et al., 1996; Stolar et al., 1994; Sumiyoshi et al., 2004). Specifically, Joyce et al. (1996) found a significant negative correlation between the Alogia score from the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) and the enhancement of verbal outputs by cueing. Stolar et al. (1994) also reported that the severity of alogia, but not affective flattening, was negatively correlated with the number of words produced. Overall, these findings suggest that the reduction of verbal outputs in the CFT is related with the alogia symptoms in patients with schizophrenia. However, the specific association between organization of semantic memory, as measured by the CFT, and alogia symptoms has never been examined.

The purpose of the present study was to investigate the relation between psychotic symptoms, specifically alogia, and the degradation of semantic memory organization in patients with schizophrenia. Based on the previous findings, as discussed above, we hypothesized that schizophrenia subjects with severe alogia symptoms would exhibit more disturbed semantic memory organization compared to those with less alogia. Firstly, multiple regression analysis was conducted to examine the correlation between psychotic symptoms, as assessed by the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) and SANS, and word production as measured by the VFTs. Next, multidimensional scaling (MDS) analysis, using data from the CFT, was performed evaluate the semantic structure in patients with schizophrenia as a whole. Finally, we compared semantic structures between patients with severe alogia and those with less alogia by applying MDS and cluster analyses.

2. Method

2.1. Subjects

Thirty-eight subjects (male/female=20/18) who met DSM-IV criteria (American Psychiatric Association, 1994) for schizophrenia, and an equal number of normal control volunteers entered the study. They were recruited from Toyama Medical and Pharmaceutical University Hospital and Fukushima Medical University Hospital. Diagnosis was made by experienced psychiatrists using medical history and all available information. Patients known to be abusing alcohol or other illicit drugs, or those with epilepsy, brain damage, or neurologic disorders, were excluded from the study. The dose of concurrently administered neuroleptics was converted into the equivalent amount of haloperidol in milligrams per day. The volunteers, who did not meet any criteria for DSM-IV disorders, were recruited as normal controls. Both patients and normal controls were provided with a detailed description of the study, and gave written informed consent. This study was approved by the Institutional Review Board at each site. The Vocabulary and Block Design subtests from the WAIS-R (Wechsler, 1981) were administered to most patients (N=36) and all normal controls to assess the level of intelligence. The two subtests were chosen because they are considered to be representative of verbal- and performance intelligence, respectively (Silverstein, 1982).

2.2. Procedure

The CFT and LFT, as well as the subtests from the WAIS-R, were administered by well-trained psychologists. SAPS and SANS were administered by experienced psychologists or stuff doctors. The intra-class correlations for these psychopathology measures were higher than 0.80 (Sumiyoshi et al., 2001a,b). The instruction of the VFTs followed the usual norm (Spreen and Strauss, 1998); subjects were asked to produce as many words as possible within 1 min. The verbatim responses were recorded by the examiners in the generated order. ANIMAL and FRUIT were used for the cues in the CFT, while "KA" and "TA" were used for the LFT according to our previous study (Sumiyoshi et al., 2004). These letters were chosen because the frequency of words beginning with "KA" was higher than that of "TA" in the Japanese lexicon (Amano and Kondo, 2000). This frequency contrast was analogous to that between "S" and "F" in the FAS form of the LFT in English.

2.3. Data analysis

Multivariate analysis of variance (MANOVA) was conducted to compare the demographic and cognitive variables between normal controls and patients with schizophrenia. The number of words generated in the VFTs was analyzed by two-way analysis of variance (ANOVA) with the group (patients versus normal controls) as between-subject factor and task type (ANIMAL versus FRUIT versus KA versus TA) as within-subject factor. Multiple comparisons by Bonferroni/Dunn method were conducted when the main effect was significant.

For multiple regression analysis, the subscales of SAPS and SANS were classified into the following four domains; (1) Positive Symptom factor (delusions and hallucinations), (2) Disorganization factor (bizarre behavior and positive formal thought disorder), (3) Negative Symptom factor (affective flattening or blunting, avolition-apathy, anhedonia-associality, and attention), and (4) Alogia factor (alogia). The classification was based on previous studies of the relationship between verbal fluency performance and psychotic symptoms (Allen et al., 1993; Aloia et al., 1996; Feinstein et al., 1998; Goldberg et al., 1998; Howanitz et al., 2000; Joyce et al., 1996; Kuperberg et al., 1998; Mahurin et al., 1998; Rossell et al., 1999; Stolar et al., 1994). Because the max values differed between factors, raw scores were converted into the percentage score. Then, angular transformation was applied to the percentage scores for further analyses. Four independent multiple regression analyses for each task score (i.e. ANIMAL, FRUIT, "KA", and "TA") were conduced using the four psychosis domains (i.e. positive symptoms, disorganization, negative symptoms, alogia) as independent variables.

In the subgroup analysis, the patients were divided into two groups according to the Alogia score from the SANS (the sum of Poverty of Speech, Poverty of Content of Speech, Blocking, and Increased latency of Speech; MAX=20). The "alogia group" consisted of patients who showed an Alogia score of more than 1. The "non-alogia group" included patients with the Alogia score of 0 or 1. The mean Alogia score, as well as the demographic and cognitive variables, for these two subgroups are summarized in Table 1. The Alogia scores of the two groups were compared by *t*-test. In order to determine the difference in severity of language-related positive symptoms, scores of the Positive Formal Thought Disorder subscale from the SAPS (i.e. Tangentiality, Incoherence, Illogicality, Circumstantiality, Pressure of Speech, Distractible Speech, and Clanging; MAX=40) were also compared between alogia group and non-alogia group by *t*-test. MANOVA and two-way ANOVA were conducted for other variables.

Table 1
Demographic and cognitive variables for alogia- and non-alogia patients

	Alogia patients (N=21)	Non-alogia patients (N=17)
Male/female	8/13	9/8
Age (years)	27.17 (9.10)	34.18 (10.02)*,[a]
Education (years)	13.40 (2.60)	13.50 (2.16)
Neuroleptic dose (mg/day)[b]	9.71 (8.12)	8.58 (8.52)
Onset of illness (years)	20.48 (7.01)	22.33 (10.35)
Duration of illness (years)	6.09 (7.03)	12.00 (9.42)
SANS Alogia score	4.90 (3.01)**,[c]	0.18 (0.38)
Block Design (WAIS-R)	8.95 (2.97)	9.87 (3.58)
Vocabulary (WAIS-R)	8.33 (2.87)	9.27 (2.82)
CFT		
ANIMAL	14.57 (5.16)	16.59 (3.65)
FRUIT	10.11(3.03)	11.06 (3.68)
LFT		
"KA"	9.15 (4.22)	9.63 (3.62)
"TA"	8.05 (3.92)	9.38 (3.35)

WAIS-R, Wechsler Adult Intelligence Scale-Revised. CFT, Category Fluency Task; LFT, Letter Fluency Task; SANS, Scale for Assessment of Negative Symptoms. Values represent mean (standard deviation).

[a] Results from MANOVA.
[b] Haloperidol equivalent.
[c] Results from *t*-test.
* $p<0.05$.
** $p<0.01$.

MDS analysis was conducted to visualize semantic structures using data from the CFT. Hierarchical cluster analysis was performed to examine the coherence of the category items in the semantic structures for the alogia group and non-alogia group, respectively. In MDS and cluster analyses, specific algorithm was used to obtain the dissimilarity matrices from the sequential verbal outputs from the CFT. The details of the algorithm have been described in previous studies (Chan et al., 1993; Paulsen et al., 1996; Sumiyoshi et al., 2001). MDS and cluster analyses were carried out using SPSS version 10.0. Interval scales were applied for MDS analysis while the average linkage method was used for cluster analysis.

3. Results

3.1. Comparison between normal controls and schizophrenia patients

The results of MANOVA revealed a significant group difference between normal controls and patients with schizophrenia (Wilks' lambda=0.85, F=3.14, df=4,69, p<0.05). Normal controls outperformed the patients in the Block Design (normal controls=11.90 (S.D.=2.81), patients=9.32 (3.19); F=10.73, df=1,72, p<0.01) and Vocabulary (normal controls=11.50 (2.64), patients=9.33 (2.23); F=3.84, df=1,72=3.84, p<0.05). On the other hand, age (normal controls=29.50 (11.40), patients=30.30 (10.03); F=0.01, df=1,72, *n.s.*) and education (normal controls=14.18 (1.55), patients=13.45 (2.37); F=1.92, df=1,72, *n.s.*) did not differ between the two groups. As for the performance on the VFTs, normal controls (ANIMAL=18.95 (3.86), FRUIT=13.71 (3.26), KA=12.07 (3.54), TA=10.10 (2.01)) produced more words than the patients (ANIMAL=15.47 (4.66), FRUIT=10.56 (3.39), KA=9.36 (3.97), TA=8.62 (3.74)). ANOVA revealed significant main effects of group (F=10.44, df=1,61 p<0.01) and task type (F=98.74, df=3, 183, p<0.01) factors. Multiple comparisons of task type factor revealed significant differences between ANIMAL versus other tasks (p<0.01), FRUIT versus TA task (p<0.01), and KA versus TA (p<0.01) task.

The correlation coefficients between the VFT scores and the four symptom domains are presented in Table 2. Significant multiple regression models were derived only from the ANIMAL and TA scores. The Alogia factor remained as a significant independent variable in the model of the ANIMAL score (B=−3.67, t=−2.37, p<0.05), while the Negative factor was significant (B=−3.67, t=−2.35, p<0.05) in the model of the TA score.

Table 2
Correlation coefficients between verbal fluency scores and psychotic symptoms

	Animal	Fruit	KA	TA
POSITIVE	−0.11	−0.46	−2.44	−0.21
DISORG.	−0.09	0.09	0.1	0.02
NEGATIVE	−0.29*	−0.01	−0.28*	−0.37**,[a]
ALOGIA	−0.37**,[a]	−0.21	−0.05	−0.17

POSITIVE, positive symptom domains; DISORG., disorganization. NEGATIVE, negative symptom domains.
[a] Significant predictive variables in multiple regression models.
* p<0.05.
** p<0.01.

For the MDS analysis, 11 animals (CAT, DOG, COW, BEAR, ELEPHANT, GIRAFFE, LION, HORSE, MONKEY, TIGER, RABBIT) were selected based on the verbal outputs in the CFT; they were most frequently produced across the two groups. The semantic structures based on those items are presented in Fig. 1. Normal control subjects yielded a wild-domestic dimension (as the vertical axis: Fig. 1, left) while no clear dimension was detected in the patients (Fig. 1, right). Although the stress values were not so much different between the two groups, the RSQ value for the normal controls was greater than that for the patients (Fig. 1), suggesting a better-fit configuration for the normal control group.

3.2. Comparison between alogia- and non-alogia patients

The results of comparisons of demographic and cognitive variables between the alogia- and non-alogia patients are presented in Table 1. The Alogia score for the alogia group was significantly higher than that for the non-alogia group (t=6.27, df=36, p<0.01). On the other hand, scores of the Positive Formal Thought Disorder subscale from the SAPS did not significantly differ between the two groups (alogia group=2.05 (5.51), non-alogia group=2.18 (3.11); t=0.09, df=36, *n.s.*). MANOVA showed no overall group difference (Wilks' lambda=0.79, F=2.11, df=4,31, *n.s.*) although age was significantly higher for the non-alogia group (F=4.72, df=1,34, p<0.05). The numbers of words produced in the CFT and LFT are also shown in Table 1. ANOVA revealed that task (F=53.03, df=3,93, p<0.01) but not group (F=0.35, df=1,31, *n.s.*) effect was significant, indicating verbal outputs did not differ significantly between the two groups for any measure of the VFTs.

The organization of semantic structure, as revealed by MDS analysis, is shown in Fig. 2. The most frequently produced 11 animals (CAT, DOG, BEAR, ELEPHANT, GIRAFFE, LION, HORSE, MONKEY, TIGER, RABBIT, SHEEP) across the two groups were chosen for the analysis. In the semantic configuration of the non-alogia group, carnivorous animals were located in the left and herbivorous ones

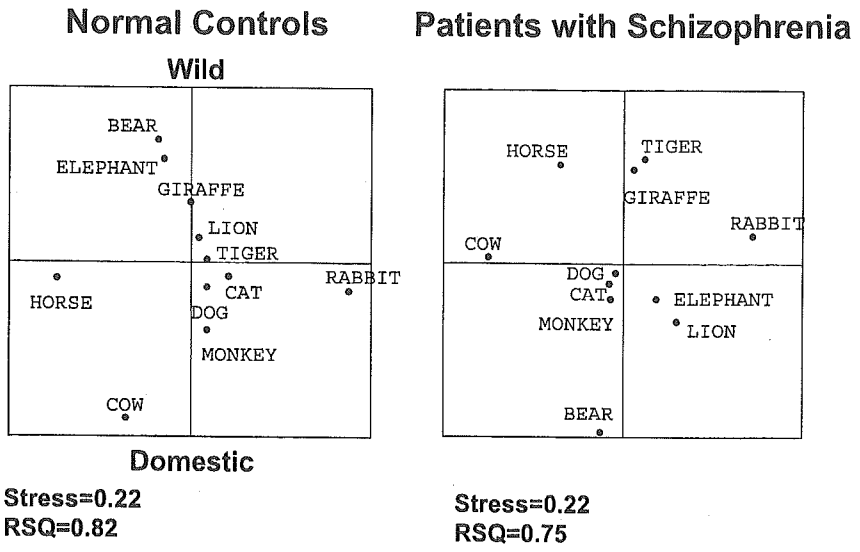

Fig. 1. Two-dimensional semantic structure as revealed by multidimensional scaling analysis in normal controls (N=38; left) and patients with schizophrenia (N=38; right).

in the right, thus creating a predation dimension (Fig. 2, left). On the other hand, no meaningful dimension was observed in the alogia group (Fig. 2, right).

The qualitative difference in the organization of semantic structure between the two groups of patients with schizophrenia became more apparent by cluster analysis. The circles in Fig. 2 represent highly cohesive clusters. In the non-alogia group, the clusters did not seem to represent specific meanings. On the other hand, the alogia group demonstrated oddly coherent clusters. For example, DOG and ELEPHANT made one cluster while CAT and MONKEY formed another one, and so on.

4. Discussion

The results of the present study confirmed the relationship between alogia symptoms and the performance on the VFTs in patients with schizophrenia. The Alogia factor remained as a significant independent variable in multiple regression analysis of the

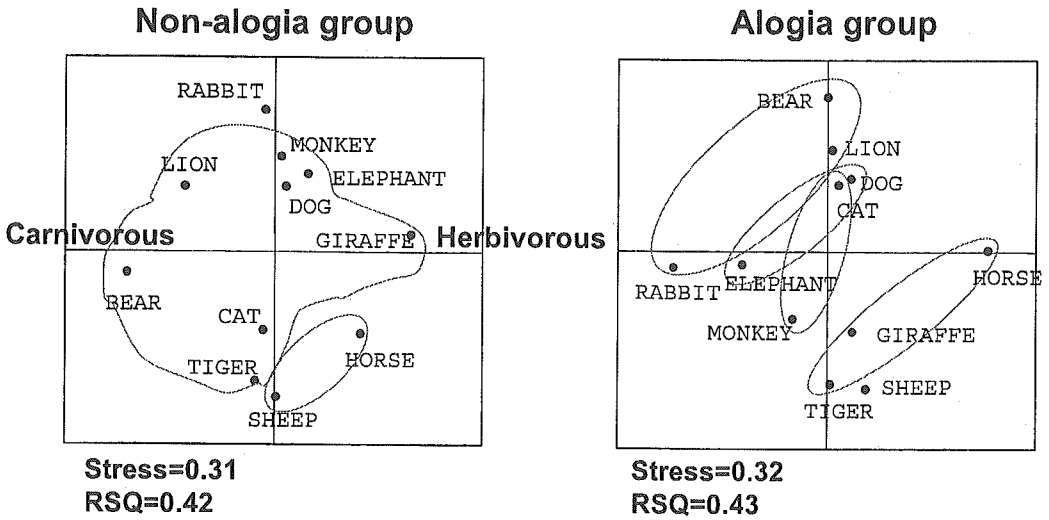

Fig. 2. Two-dimensional semantic structure for non-alogia (N=21; left) and alogia (N=17; right) patients with schizophrenia. The circles represent highly cohesive assemblies as revealed by cluster analysis.

ANIMAL score, indicating rigorous search of words in the CFT is negatively correlated with severity of alogia symptoms. The selective association of negative, but not positive, symptoms of schizophrenia with the degradation of semantic memory was further supported by the lack of difference in scores of the positive Formal Thought Disorder Subscale from SAPS between subjects with alogia symptoms and those without alogia. MDS analysis demonstrated that the semantic structure in patients with alogia symptoms had no meaningful dimension (i.e. semantically plausible criteria for the association of category members), in contrast to the non-alogia patients who exhibited a predation dimension. Furthermore, cluster analysis revealed the presence of oddly coherent clusters in the alogia group, in contrast to neutral clusters in the non-alogia patients. Overall, these results suggest that the disorganized semantic structure may underline alogia symptoms in patients with schizophrenia.

Stolar et al. (1994) reported a negative correlation between the number of words produced in the LFT and severity of alogia symptoms in subjects with schizophrenia, while the present study did not find a significant difference in the LFT score between alogia- and non-alogia patients. This discrepancy may be explained by the use of the different Alogia scores. Stolar et al. (1994) did not include "poverty of content of speech" in the Alogia score while we included this item, since it was assumed to be affected by the organization of semantic memory as measured by the CFT.

The comparison of data between schizophrenia patients as a whole and normal controls indicated impaired semantic structure in the patient group, in addition to decreased word production. Control subjects demonstrated a domestic–wild dimension in the semantic configuration, while it was dimensionless in patients with schizophrenia (Fig. 1). The deteriorated semantic structure in schizophrenia is consistent with the results of previous reports (Aloia et al., 1996; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001a).

Several studies found that the disturbances in verbal fluency performance are associated with impairment in executive function (i.e. improper searching or retrieval) in subjects with schizophrenia (Allen et al., 1993; Joyce et al., 1996; Maron et al., 2004). Joyce et al. (1996) observed increased word production by providing a cue (e.g. farm animal) in schizophrenia patients, suggesting that the impaired performance on the VFTs is the result of a disturbed retrieval process. On the other hand, other researchers argued that disorganization of semantic memory causes the deficits in the verbal fluency performance (Goldberg et al., 1998; Paulsen et al., 1996; Sumiyoshi et al., 2001a). This assumption is supported by several other studies (Aloia et al., 1996; Gourovitch et al., 1996; Phillips et al., in press) reporting that execution of the LFT was relatively intact compared with that of the CFT in patients with schizophrenia. Disproportionate degradation between the LFT and CFT in schizophrenia has been confirmed by a recent meta-analysis study (Bokat and Goldberg, 2003). Since well-formed semantic networks are required for efficient search and retrieval of words (Gruenewald and Gregory, 1980), the latter hypothesis that performance on the VFTs would depend largely on semantic organization appears more convincing. Phillips et al. (in press) also lend support to this concept, arguing that lexicon size is not remarkably reduced in patients with schizophrenia, as has been reported by Joyce et al. (1996) and Elvevag et al. (2001).

The present study showed the word production in the CFT (ANIMAL) was exclusively correlated with alogia symptoms. This finding is in agreement with Joyce et al. (1996) who suggested that the same domain of cognitive abnormality mediates both alogia and poor verbal fluency. We further speculate that the degradation of semantic memory precedes the emergence of psychotic symptoms in schizophrenia. Consistent with this hypothesis, cohort studies (Chen et al., 2000; Keefe et al., 1994) report the impaired performance on the CFT in family members of patients with schizophrenia. Furthermore, Chen et al. (2000) found selective deficits in the execution of the CFT, but not other cognitive tasks, in non-psychotic siblings of schizophrenia subjects. Based on these findings, Phillips et al. (in press) suggested that impaired performance on the CFT may predict the emergence of psychotic symptoms at a later stage in subjects who are vulnerable to developing schizophrenia.

Recent investigations have indicated that other language-related disturbances also represent trait markers of schizophrenia (for a review, see DeLisi,

2001). Several studies (e.g. DeLisi, 2001; Shedlack et al., 1997) found that sentence complexity is slightly reduced in family members of patients with schizophrenia. So far, some investigators from Japan have reported disturbances in information-processing (Sumiyoshi et al., 2000) and verbal memory (Matsui et al., 2004) in subjects who are susceptible to developing schizophrenia.

Neuroimaging studies have attempted to clarify the neural basis for degraded performance on the VFTs in patients with schizophrenia. An fMRI study (Curtis et al., 1998) reported that patients with schizophrenia showed poor activation of prefrontal cortex during the performance on the VFTs. In addition, other investigators have reported that poor prefrontal activations are associated with negative symptoms in subjects with schizophrenia (Liddle, 1996; Liddle et al., 1992). These findings indicate that attenuated neural activity in the prefrontal cortex is responsible for poor verbal fluency performance and negative symptoms in patients with schizophrenia. Moreover, the anterior part of the left prefrontal region is likely to be involved in semantic processing (Fiez, 1997). Functional disturbances of this part of the brain may possibly be associated with disorganized semantic memory in subjects with schizophrenia.

The effect of the language system or nationality should also be considered when assessing verbal fluency in patients with schizophrenia. Harvey et al. (2003) have reported the cross-national (e.g. U.S., U.K., and Canada) uniformity regarding the pattern of inefficient execution of the VFTs in patients with schizophrenia, i.e. less impaired performance on the LFT compared with the CFT. On the other hand, we have recently found a language-specific disturbance in the execution of the VFTs; the performance on the CFT and LFT are equally impaired in Japanese patients, unlike the cases with alphabetical-language speakers with schizophrenia (Sumiyoshi et al., 2004). Interestingly, recent neuroimaging studies (Callan et al., 2003; Paulesu et al., 2000; Sumiyoshi et al., 2003) have demonstrated the language-dependent differences in the patterns of the brain activities in normal control subjects undertaking cognitive tasks. It is speculated that similar effects of the language system, or orthography, on cognitive performance may be present in the brain activities of patients with schizophrenia.

The usefulness of analyzing semantic structures using the VFTs should be mentioned here. Since these tasks only require free recall of words, they are applicable to in patients with a wide range of clinical symptoms (van Beilen et al., in press). Elvevag et al. (2001) reported the limitation of MDS analysis of sequential verbal outputs from the CFT. They claimed that the verbal outputs are not uniform across patients with schizophrenia as a whole, resulting in a poor fit between the dissimilarity matrix and the spatial configuration. However, this type of variability could be reduced by classifying the patients into subgroups based on the source of idiosyncrasy, such as presence or absence of psychotic symptoms. In fact, the symptom-based subgroup analysis in our study revealed a group-specific degradation in the semantic structure (Fig. 2), suggesting the intra-group uniformity regarding verbal outputs.

In summary, using data from the CFT, we have demonstrated that alogia symptoms are highly correlated with disorganization of semantic memory in patients with schizophrenia. The results of the symptom-based subgroup analysis further indicate that the semantic memory deficits underlie the manifestation of negative symptoms such as alogia.

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Volumetric MRI study of the short and long insular cortices in schizophrenia spectrum disorders

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Abstract

We have previously reported volume reductions of the insular cortex in schizophrenia, but it is still not clear whether insular cortex volume loss preferentially involves the anterior (short insular cortex) or posterior (long insular cortex) portion. On the other hand, no volumetric studies of the brain have examined changes in insular cortex volume in subjects with schizotypal features. In this study, we separately investigated the volumes of the short and long insular cortex portions using magnetic resonance imaging in 37 schizotypal disorder patients (24 males, 13 females), 62 schizophrenia patients (32 males, 30 females), and 69 healthy controls (35 males, 34 females). While the volumes of the short and long insular cortex were significantly reduced in schizophrenia patients compared with schizotypal disorder patients and control subjects, there was no difference between schizotypal disorder patients and control subjects. These results suggest that the volume reduction of the insular cortex may be specific to overt schizophrenia without topographically specific localization.

Keywords: Magnetic resonance imaging; Insula; Schizophrenia; Schizotypal disorder

1. Introduction

Post-mortem (Jakob and Beckmann, 1986, 1989) and functional neuroimaging (Curtis et al., 1998; Shergill et al., 2000; Crespo-Facorro et al., 2001a,b; Surguladze et al., 2001; Desco et al., 2003) studies have suggested that insular cortex abnormalities are involved in the pathophysiology of schizophrenia. With regard to the morphology of the insular cortex in schizophrenia, recent volumetric magnetic resonance imaging (MRI) studies have reported that schizophrenia patients have a significantly smaller insular cortex volume than do control subjects

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(Crespo-Facorro et al., 2000; Kasai et al., 2003; Kim et al., 2003; Takahashi et al., 2004a). Several voxel-based analyses of MRI have also revealed a gray matter reduction of the insular cortex in patients with schizophrenia (Wright et al., 1999; Hulshoff Pol et al., 2001; Paillère-Martinot et al., 2001; Kubicki et al., 2002; Shapleske et al., 2002; Kawasaki et al., 2004).

There are distinct differences in the connectivities and functions of the anterior (short insular cortex) versus posterior (long insular cortex) portions of the insular cortex; these two subregions are diagonally divided by the central insular sulcus (Augustine, 1996; Duvernoy, 1999; Türe et al., 1999). However, most previous volumetric MRI studies (Crespo-Facorro et al., 2000; Kim et al., 2003; Takahashi et al., 2004a) have not taken into account these differences. Kasai et al. (2003) separately examined the short and long insular cortex and reported that insular volume loss associated with schizophrenia is not localized to a particular subregion, although their study might also have been limited in part by having bounded the two subregions not by their own anatomical boundaries but other anatomical landmarks, i.e. mamillary bodies. Thus, it remains unresolved whether the insular cortex volume reduction in schizophrenia preferentially involves the anterior (short insular cortex) or posterior (long insular cortex) portion.

Subjects with schizotypal features such as schizotypal disorder in ICD-10 (World Health Organization, 1992) or schizotypal personality disorder (SPD) in DSM-IV (American Psychiatric Association, 1994) share genetic, biological, and psychological features with schizophrenia and are thought to be part of the schizophrenia spectrum (Siever et al., 1993; Siever and Davis, 2004). Several recent brain structural imaging studies have identified specific structural abnormalities in schizotypal subjects similar to those seen in schizophrenia, although generally to a lesser degree and with the sparing of some brain regions (reviewed by Dickey et al., 2002a; Siever et al., 2002; Siever and Davis, 2004). The abnormalities include increased lateral ventricular size (Siever et al., 1995; Buchsbaum et al., 1997; Silverman et al., 1998), greater cerebrospinal fluid volume (Dickey et al., 2000), volume reduction in temporal lobe structures (Dickey et al., 1999, 2002b; Seidman et al., 1999; Downhill et al., 2001), and volume reduction in the thalamus (Hazlett et al., 1999; Seidman et al., 1999; Byne et al., 2001), basal ganglia (Shihabuddin et al., 2001; Levitt et al., 2002), and internal capsule (Suzuki et al., 2004), along with shape and size differences in the corpus callosum (Downhill et al., 2000) and asymmetry anomalies in the parahippocampal gyrus (Dickey et al., 1999) and the anterior cingulate gyrus (Takahashi et al., 2002b). The shared brain abnormalities between schizotypal and schizophrenia patients might represent a common denominator in schizophrenia spectrum disorders, whereas the differences might account for the sparing of schizotypal patients from the development of overt psychotic symptoms. Therefore, assessing schizotypal patients on brain regions such as the insular cortex that have been identified previously as impaired in schizophrenia patients is one possible strategy for advancing our understanding of pathogenesis of schizophrenia spectrum disorders. In addition, it is of interest to know the morphologic characteristics of the insular cortex, a brain region interconnected with both temporal and frontal regions (Augustine, 1996; Türe et al., 1999), in schizotypal disorder patients since the differential involvement of the frontal regions has been suggested to underlie the differences in phenomenology between schizophrenia and schizotypal patients while the abnormalities in temporal regions have been considered to be common to both disorders (Kurachi, 2003a,b; Siever and Davis, 2004). To our knowledge, however, no volumetric MRI studies have examined the insular cortex volume in subjects with schizotypal features.

In the present study, we followed the course of the central insular sulcus and accurately distinguished between the short and long insular cortex using three-dimensional MRI. We separately measured the volumes of the short and long insular cortex in schizophrenia patients, schizotypal disorder patients, and normal control subjects. The aims of the present study were to determine if the short and long insular cortices exhibited different patterns in terms of structural abnormalities in schizophrenia and to test the hypothesis that schizotypal disorder patients would have structural abnormalities in the insular cortex that were partly similar to those seen in overt schizophrenia.

2. Methods

2.1. Subjects

Thirty-seven schizotypal disorder patients (24 males and 13 females; mean age=25.8 years, SD=5.4, range=18–37) who met the ICD-10 criteria for research (World Health Organization, 1993) were examined. They were recruited from patients who visited the clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital, with schizotypal features accompanied by distress or associated problems in their lives and who needed to receive consistent clinical follow-up. Candidates who had a previous history of overt psychotic episode or met the ICD-10 criteria for schizophrenia during the follow-up period were excluded. The mental condition of each subject was assessed by well-trained psychiatrists approximately every 2 weeks to check for the emergence of overt psychotic symptoms as part of an early intervention program for psychoses, and none of the 37 patients have developed overt schizophrenia to date (mean follow-up period after MRI scanning=2.0 years, SD=1.7). All available clinical information and data obtained from a detailed review of the clinical records and structured interviews using the Comprehensive Assessment of Symptoms and History (CASH) including the chapter on premorbid or intermorbid personality (Andreasen et al., 1992) were stored in a database. The subjects were diagnosed by consensus reached by at least two experienced psychiatrists based on these data. Twenty-nine patients were outpatients, and the other eight underwent closer clinical and medical examinations including MRI during short-term admission. At the time of MRI scanning, 32 of the 37 patients were treated with low-dose antipsychotics, of which 11 patients were treated with typical neuroleptics and 21 patients received atypical neuroleptics. The remaining five patients were neuroleptic-naïve. Clinical symptoms were rated within 1 month of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b). Their mean scores for the SANS and SAPS were 42.4 (SD=23.0, range=5–84) and 16.0 (SD=8.9, range=0–31), respectively. Thirty-three of the 37 patients with schizotypal disorder were also assessed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). Their mean total BPRS score was 38.4 (SD=9.7, range=19–61).

The schizophrenic comparison group was composed of 62 patients with schizophrenia [32 males and 30 females, mean age=25.8±4.9 (SD) years, range=18–36], and this group contained 58 schizophrenia patients (31 males, 27 females) who were examined in our previous study of the whole insular cortex volume (Takahashi et al., 2004a). All patients fulfilled the ICD-10 diagnostic criteria for research on schizophrenia (World Health Organization, 1993). All but one of the schizophrenia patients were receiving neuroleptic medication; 30 patients were treated with typical neuroleptics and 31 patients with atypical neuroleptics. At the time of the MRI study, their mean scores on the SANS and SAPS were 46.8 (SD=23.4) and 25.2 (SD=20.4), respectively.

The control subjects consisted of 69 healthy volunteers [35 males and 34 females, mean age=24.0±6.5 (SD) years, range=18–38] recruited from among members of the community, hospital staff, and medical and pharmaceutical students, and included 61 subjects who participated in a previous study (Takahashi et al., 2004a). They were given a questionnaire consisting of 15 items concerning their family and past histories, as well as present illness. They did not have any personal or family history of psychiatric illness in their first-degree relatives. The control subjects were not screened with a standard measure such as the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First et al., 1997) and this may be a possible limitation of the study. However, all control candidates were interviewed and administered the Minnesota Multiphasic Personality Inventory (MMPI) by experienced clinical psychologists to obtain a rather homogenous control group without eccentric profiles on the MMPI. Although the MMPI has not proved very sensitive for the detection of schizotypy (Walters, 1983), approximately 17% of the candidates for normal controls were excluded for having an abnormal profile with a T-score for the validity scales or the clinical scales exceeding 70.

All subjects were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness or substance abuse. A handedness inventory developed by

Kameyama et al. (1981) consisting of 14 questions about hand preference was used to assess handedness; the subjects were right-handed except for one female patient with schizotypal disorder of unknown handedness.

The demographic and clinical characteristics of the control subjects, patients with schizotypal disorder and patients with schizophrenia are summarized in Table 1. The three groups were matched on age, height or parental education. Although there were more male than female schizotypal patients, the difference in the gender ratios among the three diagnostic groups was not statistically significant (chi-square analysis, $\chi^2=2.20$, $P=0.333$). The control subjects had attained a higher mean level of education than had the patients with either disorder (control subjects, 15.7 ± 2.5 years; schizophrenia patients, 13.4 ± 1.9 years; schizotypal patients, 13.5 ± 1.9 years; ANOVA, $F=23.28$, $df=2,165$, $P<0.001$). The total SAPS score for the schizophrenia patients was significantly higher than that for the schizotypal patients (ANOVA, $F=6.60$, $df=1,96$, $P=0.012$), although there were no significant differences between patients with schizophrenia and schizotypal disorder for the total score for SANS. There were significant differences in medication dosage (ANOVA, $F=17.95$, $df=1,97$, $P<0.001$); the patients with schizotypal disorder took significantly smaller amounts of neuroleptics than did the patients with schizophrenia. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study was given to the subjects, their written informed consent was obtained.

2.2. Magnetic resonance imaging procedures

Magnetic resonance images were obtained utilizing a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. Imaging parameters were repetition time=24 ms, echo time=5 ms, flip angle=40°, field of view=256 mm, and matrix size=256×256 pixels. The voxel size was $1.0\times1.0\times1.0$ mm^3. Magnetic field inhomogeneities in our scanner were monitored with weekly phantom scanning and daily basic quality control, and had been stable over the MR acquisition time for this study.

Table 1
Clinical and demographic characteristics of normal control subjects, patients with schizotypal disorder, and patients with schizophrenia

Variable	Control subjects		Schizotypal patients		Schizophrenia patients	
	Male ($N=35$)	Female ($N=34$)	Male ($N=24$)	Female ($N=13$)	Male ($N=32$)	Female ($N=30$)
Age (years)	24.1 ± 5.1	23.8 ± 5.8	25.7 ± 5.8	25.9 ± 4.6	25.6 ± 4.8	26.0 ± 5.1
Height (cm)	171.9[a] ± 4.3	159.2 ± 4.5	170.8[a] ± 5.9	156.2 ± 4.6	170.7[a] ± 5.1	158.5 ± 4.0
Education (years)	16.6[b] ± 2.8	14.8 ± 1.6	13.4 ± 1.9	13.5 ± 2.0	13.5 ± 1.9	13.3 ± 1.9
Parental education (years)	13.0 ± 2.3	12.5 ± 2.3	12.1 ± 1.5	12.1 ± 2.3	12.2 ± 1.9	11.9 ± 2.4
Age at onset (years)	–	–	–	–	22.1 ± 4.5	21.9 ± 4.2
Duration of illness (years)	–	–	–	–	3.5 ± 3.9	4.4 ± 4.3
Duration of medication (years)	–	–	2.1 ± 3.8	0.9 ± 1.5	2.4 ± 2.9	3.3 ± 3.7
Drug (mg/day, haloperidol equiv.)[c]	–	–	5.1 ± 5.5	2.5 ± 1.6	11.7[d] ± 8.6	10.8[d] ± 10.4
Total SAPS score	–	–	15.8 ± 8.7	16.3 ± 10.1	23.0[e] ± 21.1	27.7[e] ± 19.8
Total SANS score	–	–	40.4 ± 23.4	46.5 ± 23.4	50.0 ± 22.4	43.4 ± 24.4

This values represent means ± SDs. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

ANOVA followed by Scheffé's test was used.

[a] $P<0.01$: compared with females.

[b] $P<0.01$: compared with female schizophrenia patients, male schizotypal patients, and female schizotypal patients; $P<0.05$: compared with female controls and male schizophrenia patients.

[c] The different typical and atypical neuroleptic dosages were converted into haloperidol equivalents according to Toru (2001).

[d] $P<0.01$: compared with schizotypal patients.

[e] $P<0.05$: compared with schizotypal patients.

The images were transferred to a Unix workstation (Silicon Graphics, Inc, Mountain View, CA., USA), and the data were randomly coded and analyzed using the software package Dr View 5.3 (Asahi Kasei Joho System Co, Ltd, Tokyo, Japan) without knowledge of the subjects' gender and diagnosis. Details of the data analyses have been previously described (Takahashi et al., 2002a). Briefly, the scans were realigned in three dimensions to standardize for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure–posterior commissure (AC-PC) line on the workstation. The signal-intensity histogram distributions from the T1-weighted images across the whole brain for each subject were used to segment the voxels semi-automatically into gray matter, white matter, and cerebrospinal fluid (CSF) according to the Alpert algorithm (Alpert et al., 1996). Although the images were not corrected for the magnetic field inhomogeneities, no visible effect on the quality of the segmentation was detected for any case. Before the volumetric analysis of the insular cortex, masks were semi-automatically created to demarcate the outer extent of the intracranial contents with the skull, scalp, and neck tissues removed, and therefore minimal manual editing of the masks was required.

2.3. Intracranial volume (ICV) measurements

Intracranial volume (ICV) was measured to correct for differences in head size. Before creation of the mask images, the 1-mm-thick coronal slices which had been corrected for head tilt were reformatted into consecutive 5-mm-thick sagittal slices with each voxel as $1 \times 1 \times 5$ mm^3. The intracranial cavity was manually traced for each slice using anatomical landmarks according to a study by Eritaia et al. (2000), and the ICV was calculated by summing the measured volumes of all slices.

2.4. Insular cortex measurements

First, based on the segmented gray matter images, the whole (short and long) insular cortex was traced on 1-mm consecutive coronal slices as described elsewhere (Takahashi et al., 2004a). Specifically, 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.

Next, we followed the course of the central insular sulcus in three dimensions from the limen insulae and distinguished between the short and long insular cortex on coronal 1-mm slices (Fig. 1). The insular cortex rostral to the slice showing the limen insulae was regarded as the short insular cortex. On more caudal coronal slices, the short and long insular cortices were divided in a superior–inferior direction by the central insular sulcus, which was readily identified on the coronal slices in most cases. As previously noted by Naidich et al. (2004), the central insular sulcus provided a prominent landmark on conventional sagittal images, even when it was not clearly seen on coronal slices.

All volumetric data reported in this study were measured by one rater (TT) who was unaware of the subjects' identity, gender, and diagnosis. To determine the reliability of the measurements, five subjects were randomly selected for a total of approximately 275 slices (approximately 55 slices per brain). The short and long insular cortices in a subset of these five subjects were measured independently by two raters (TT and RT), and intraclass correlation coefficients (ICCs) were calculated. The inter-rater ICCs of the short and long insular cortex measurements were greater than 0.93. Each volume was then remeasured after at least 4 weeks by the first rater; the intra-rater ICCs of the short and long insular cortex measurements were greater than 0.98.

2.5. Statistical analysis

The absolute insular cortex volume was analyzed using repeated measures multivariate analysis of variance (MANCOVA) with age, ICV, and dosage of neuroleptic medication as covariates, diagnosis and gender as between-subject factors, and hemisphere (left, right) and subregion (short, long) as within-subject variables. Since a significant main effect for the subregion was observed (F=2469.84; df=1,162;

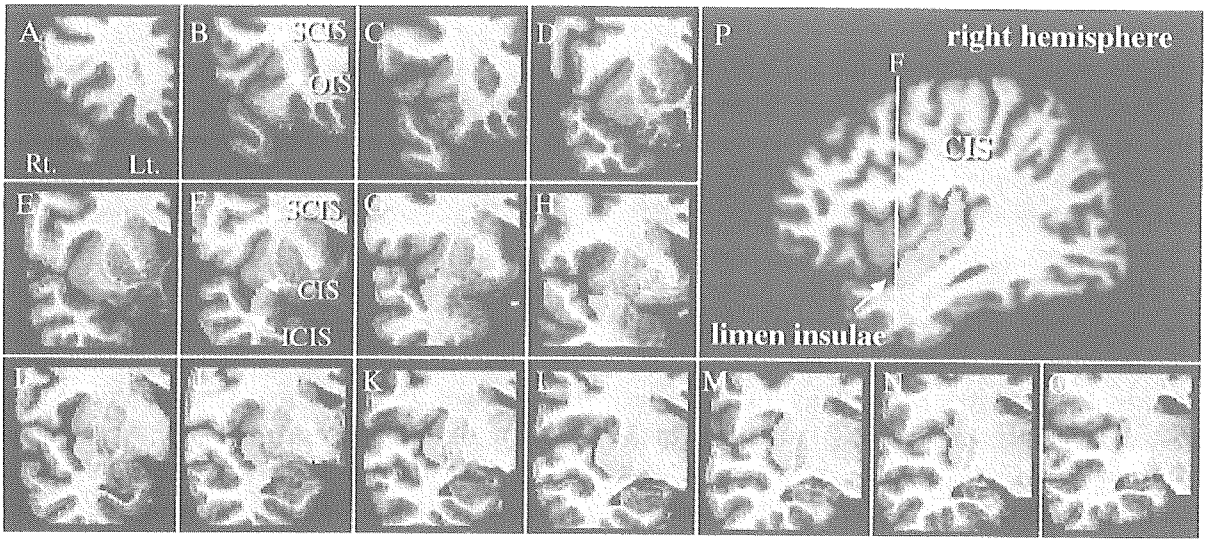

Fig. 1. Regions of interest manually traced in this study. The sample coronal slices (panels A-O) show delineations of the right short insular cortex (blue) and right long insular cortex (red), and panel P shows a sagittal view of the insular cortex in the right hemisphere. The coronal line F corresponds to panel F, a coronal slice showing the limen insulae. Abbreviations: CIS=central insular sulcus; ICIS=inferior circular insular sulcus; OIS=orbitoinsular sulcus; SCIS=superior circular insular sulcus.

$P<0.001$), the absolute volumes for the short and long insular cortex were then separately analyzed using the same model but with only hemisphere as a within-subject variable. As the schizotypal disorder patients took significantly smaller amounts of neuroleptics than the schizophrenia patients, the dosage of neuroleptic medication was used as the covariate for these analyses. For the comparison of the ICV, height was treated as covariate; groups did not significantly differ in ICV volume (Table 2). Post hoc Spjotvoll and Stoline tests, modified Tukey's tests for unequal sample size, were carried out to follow up the significant main effects or interactions yielded by these analyses (Fig. 2).

To analyze volume changes in relation to clinical symptoms, Spearman's rank correlation was calculated between the relative volumes for the long and short insular cortex and scores for the subscales of SAPS and SANS. The relative insular cortex volume, used to control for differences in head size, was obtained by dividing the absolute volume of the insular cortex by ICV and multiplying the result by 100. To examine the

Table 2
Intracranial volume (ICV) and absolute insular cortex volume in control subjects, patients with schizotypal disorder, and patients with schizophrenia

Brain region	Control subjects				Schizotypal patients				Schizophrenia patients				Analysis of covariance		
	Male (N=35)		Female (N=34)		Male (N=24)		Female (N=13)		Male (N=32)		Female (N=30)		Diagnosis effect[a]		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	P
ICV (cm^3)	1579	99	1384	108	1584	108	1420	154	1567	136	1391	101	1.13	2, 161	0.325[b]
Short insular cortex (mm^3)													3.19	2, 159	0.044[c]
Left	5588	601	4808	686	5347	652	4981	542	5095	661	4689	695			
Right	5349	637	4695	588	5261	699	5112	807	4855	556	4458	639			
Long insular cortex (mm^3)													5.26	2, 159	0.006[c]
Left	2795	493	2649	449	2911	628	2899	481	2763	500	2357	550			
Right	2678	429	2627	336	2906	377	2650	405	2676	448	2372	474			

[a] For the other main effects and interactions, and the results of post hoc tests, see the text.
[b] Height was used as covariate.
[c] Age, ICV, and dosage of neuroleptic medication were used as covariates.

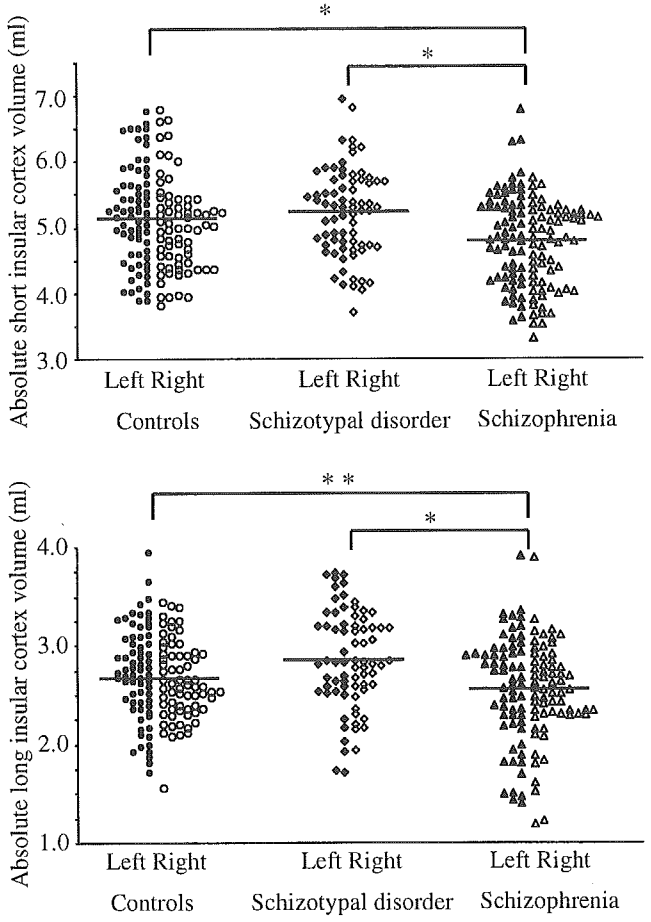

Fig. 2. Absolute volumes of the short and long insular cortex in control subjects (35 males, 34 females), schizotypal disorder patients (24 males, 13 females), and schizophrenia patients (32 males, 30 females). Horizontal lines indicate means. Post hoc Spjotvoll and Stoline tests: $*P<0.01$, $**P<0.05$.

effects of neuroleptic medication, correlations between the relative volumes for the long and short insular cortices and daily medication dosage and duration of neuroleptic medication were analyzed using Spearman's rank correlation coefficients. For the patients with schizophrenia, the correlation between the relative insular cortex volume and illness duration or age of onset was also analyzed. For these analyses, statistical significance was defined as $P<0.05$.

3. Results

3.1. Insular cortex measurements

Table 2 summarizes the short and long insular cortex measurements in schizophrenia patients, schizotypal disorder patients, and control subjects. Repeated measures MANCOVA revealed significant main effects for diagnosis ($F=6.06$; $df=2,159$; $P=0.003$), hemisphere ($F=23.55$; $df=1,162$; $P<0.001$), and subregion ($F=2469.84$; $df=1,162$; $P<0.001$). However, there was no significant diagnosis × subregion interaction ($F=1.80$; $df=2,162$; $P=0.169$). This indicates that the between-group difference in insular cortex volume was not specific for one subregion.

Lower order MANCOVA of the short insular cortex revealed significant main effects for diagnosis ($F=3.19$; $df=2,159$; $P=0.044$) and hemisphere ($F=8.91$; $df=1,162$; $P=0.003$), where patients with schizophrenia had a significantly smaller short insular cortex than schizotypal patients (post hoc test, $P=0.001$) and control subjects (post hoc test, $P=0.001$) bilaterally, and the short insular cortex volume was larger for the left than the right hemisphere for all diagnostic groups (post hoc test, $P=0.002$). There was no significant difference in short insular cortex volume between schizotypal disorder patients and control subjects (post hoc test, $P=0.827$), and no main effect for gender ($F=2.35$; $df=1,159$; $P=0.127$) or interaction among the factors was observed.

Lower order MANCOVA of the long insular cortex revealed significant main effects for diagnosis ($F=5.26$; $df=2,159$; $P=0.006$). Post hoc analyses showed the long insular cortex to be significantly reduced in the schizophrenia patients compared with the schizotypal disorder patients ($P<0.001$) and with the controls ($P=0.044$). No significant difference in the long insular cortex volume emerged between the schizotypal disorder patients and control subjects ($P=0.074$). There was no significant main effect for gender ($F=1.73$; $df=1,159$; $P=0.190$) or hemisphere ($F=3.79$; $df=1,162$; $P=0.053$), and no interaction among the factors was found.

3.2. Clinical correlations

For both patient groups, there were no significant correlations between the volumes for the short and long insular cortex and the scores for the subscales of the SAPS or SANS. For schizotypal disorder patients, the short and long insular cortex volumes were not correlated with the medication dosage or duration of

neuroleptic medication. For schizophrenia patients, insular cortex volume was negatively correlated with illness duration (right short insular cortex, Spearman's rho=0.39, $P=0.002$; left long insular cortex, Spearman's rho=0.47, $P<0.001$) and duration of neuroleptic medication (right short insular cortex, Spearman's rho=0.38, $P=0.002$) even after Bonferroni correction for multiple comparisons was made [i.e. $P<0.003$ (0.05/16)]. However, insular cortex volume was not correlated with age at onset of illness or dosage of neuroleptic medication.

4. Discussion

To our knowledge, this is the first volumetric MRI study to separately investigate sulcally defined short and long insular cortex volumes in schizophrenia spectrum disorders. The primary positive finding of this study was a significant volume reduction in the short and long insular cortices without a pattern of topographically specific localization for schizophrenia patients compared with schizotypal disorder patients and control subjects. In contrast, we found no volume differences in the short or long insular cortices between schizotypal disorder patients and normal controls.

The anterior and posterior portions of the insular cortex have been reported to have cytoarchitectural, connectional, and functional differences (Augustine, 1996; Duvernoy, 1999; Türe et al., 1999). The anterior portion, which is divided into three short insular gyri, has extensive connections with the frontal lobe. In contrast, the posterior portion of the insular cortex is formed by one or two long insular gyri and is seen to connect with both the parietal and temporal lobes. Functional neuroimaging studies have suggested that the short insular cortex is more involved in emotional and language-related functions, whereas the long insular cortex includes somatosensory and auditory processing areas [as reviewed by Augustine (1996), Nagai et al. (2001), Bamiou et al. (2003), and Naidich et al. (2004)]. Our findings are consistent with a recent MRI study by Kasai et al. (2003), who reported that both anterior and posterior insulae were significantly reduced in schizophrenia patients compared with control subjects and that group differences were not localized to a particular subregion. For the present study, we used the central insular sulcus as an anatomical boundary between the short and long insular cortex, whereas Kasai et al. (2003) used an alternative extrinsic landmark (mamillary body). Disruption of the paralimbic neural network including the insula has been proposed to contribute to the pathophysiology of schizophrenia by previous structural MRI studies (Goldstein et al., 1999; Shapleske et al., 2002). More specifically, functional neuroimaging studies have reported that various cognitive dysfunctions in schizophrenia such as emotional deficit (Crespo-Facorro et al., 2001a), recognition memory impairment (Crespo-Facorro et al., 2001b) or abnormal audiovisual speech perception (Surguladze et al., 2001) are mediated at least in part by the insular cortex. The insular cortex is engaged in a variety of cognitive functions, but its topographical localization has not been fully established. From the present and previous studies, it appears that the involvement of the insular cortex in schizophrenia is widespread and diffusely distributed rather than being specifically located in the anterior or posterior portion.

The sample characteristics of the clinic-based schizotypal disorder patients in our laboratory have been described in previous publications (Takahashi et al., 2002b, 2004b; Yoneyama et al., 2003; Kawasaki et al., 2004; Suzuki et al., 2004). The present study may not have been completely framed for direct comparisons with several previous studies in subjects with SPD since there are subtle but distinct differences between the diagnostic categories of schizotypal disorder (ICD-10) and SPD (DSM-IV). SPD is a stable personality, but schizotypal disorder in contrast requires a period of at least 2 years and the criteria include occasional transient quasi-psychotic episodes. Although all of the schizotypal subjects in this study also fulfilled DSM-IV criteria for SPD on Axis II, an additional diagnosis of brief psychotic disorder on Axis I was considered in eight subjects who experienced occasional transient quasi-psychotic episodes. In addition, schizotypal disorder "occasionally evolves into overt schizophrenia." Thus, schizotypal disorder in ICD-10 includes prodromal schizophrenia in addition to SPD as defined in DSM-IV. However, prior to the onset of psychosis, the clinical manifestations of two groups of patients who later develop schizophrenia or not are indistinguishable. The follow-up periods for the schizotypal patients in this

study were relatively short and some of them may have been at risk for developing psychosis later; they could be diagnosed as being in the prodromal phase of schizophrenia but not as SPD according to the concept of DSM-IV. We therefore adopted the ICD-10 criteria for schizotypal disorder in the present study. With regard to the symptom severity, the total BPRS score of our schizotypal subjects (mean=38.4, SD=9.7) was comparable to those (mean=37.5, SD=6.2) of previous MRI studies on mostly neuroleptic-free clinic-based subjects with SPD (Hazlett et al., 1999; Byne et al., 2001). However, our cohort may have included subjects with more serious symptoms than the SPD subjects in previous studies since most of the schizotypal disorder patients in the present study were taking neuroleptic medications.

Our results suggest that the volumes for the short and long insular cortices were reduced in overt schizophrenia but were preserved in schizotypal disorder. This may explain the decreased magnitude in cognitive/social deficits and symptomatology for schizotypal disorder relative to schizophrenia. Interestingly, it has been suggested that the abnormalities associated with the insular cortex are relevant to hallucinations (Crespo-Facorro et al., 2000; Shergill et al., 2000; Shapleske et al., 2002), which are a cardinal feature of schizophrenia but not prominently seen in schizotypal subjects. In a recent review of neurobiological abnormalities found in SPD, Siever and Davis (2004) hypothesized that while temporal volume reductions appear to be common to both SPD and schizophrenia, there may be preservation of frontal lobe volume in SPD compared with schizophrenia. Despite the above-mentioned differences in the sample characteristics between laboratories, Kurachi (2003a,b) suggested a similar hypothesis based on studies concerning cognitive characteristics and brain morphologic changes in schizotypal disorder and schizophrenia patients, i.e., the temporal lobe changes may underlie a vulnerability to schizophrenia and latent dysfunction in these lesions may become clinically apparent due to additional frontal lobe changes in schizophrenia. Based on these hypotheses, it may be reasonable to suppose that the long insular cortex, connecting with the temporal regions, is reduced in schizotypal patients as well as schizophrenia patients, while the short insular cortex, which has close connections with frontal cortex, is preserved in schizotypal patients. Such parallel reductions in associated regions in SPD were found in the volume of the thalamus; Byne et al. (2001) reported that size of the pulvinar, which projects to temporal lobe structures, was reduced in SPD as well as schizophrenia patients, while the size of the dorsomedial nucleus of the thalamus, associated with the prefrontal regions, was decreased only in the schizophrenia patients. Contrary to predictions, however, the present findings suggest that the insular cortex in schizotypal disorder patients shows no topographically specific volume changes. Although not supported directly by the present findings, the validity of these hypotheses seems worthy of further testing. Additional comprehensive assessment of multiple brain regions in the same group would be essential for the understanding of the brain morphologic characteristics of the schizotypal patients.

Some limitations of the present study should be mentioned. First, our results were not in agreement with those of a previous voxel-based MRI study carried out by our group (Kawasaki et al., 2004), in which reduced gray matter of the left insular cortex was found in schizotypal disorder patients. Although the validity of VBM has been tested in comparison with conventional region-of-interest (ROI) measurements (Wright et al., 1999; Suzuki et al., 2002), as discussed by Kasai et al. (2003), the results of the voxel-based methods could remain at odds with manual ROI methods, which are the current gold standard. Although we cannot clearly explain the reason for the differences in the results between the VBM and manual ROI analyses, the morphologic changes of the adjacent structures such as the superior temporal gyrus or the inferior frontal gyrus might have influenced the results for the insular cortex. A second limitation is that most of the patients were receiving neuroleptic medication. A relationship between brain morphologic features and neuroleptic medication has been reported in schizophrenia (Keshavan et al., 1994, 1998; Chakos et al., 1995; Gur et al., 1998), and insular cortex volume in schizophrenia was negatively correlated with duration of neuroleptic medication in the present study. This correlation was not found for the schizotypal patients, and the dosage of neuroleptic medication taken at the time of the scan in this study was not related to insular cortex volume. However, the

effects of cumulative years of medication treatment on the schizophrenia patients cannot be ruled out. A third limitation is that the control subjects in the present study were not selected to be educationally equivalent to the patients with both disorders. However, we optimally matched the parental education among the three groups according to the notion that matching on the basis of the educational level of the parents may reduce confounding factors in selection of control groups when brain measures are studied (Andreasen et al., 1990). In addition to these limitations, the relatively small sample size of female schizotypal disorder patients also limited our ability to generalize the findings of the present study. The morphologic characteristics of this disorder should be extensively examined with a larger female sample in future studies to confirm and extend the present findings.

In conclusion, the volume reduction of the insular cortex may be specific to overt schizophrenia, although there is no evidence for a topographically specific pattern of volume loss between the short and long insular cortices. The findings of the present study suggest that insular involvement may be implicated in the manifestation of overt psychosis.

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