た。

まとめ

データマイニングの手法から，幻聴を伴う統合失調症と非統合失調症性精神病群の症候学的相違を比較した。その結果，統合失調症の幻聴は，「自生思考」⇒「表象性幻聴(Cluster I)」⇒「仮性幻覚」⇒「自我障害(Cluster II)」と，一方，非統合失調症性精神病群の幻聴は，「意識変容」⇒「知覚性幻聴(Cluster III)」⇒「妄想知覚」⇒「夢幻様状態(Cluster IV)」と進展すると解釈した。データマイニングによる探索的データ分析では妥当性の検証が不可欠である。そのため，今後，類型分類を手がかりとした非定型精神病の生物学的研究を進めていきたい。

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Volume reduction of the amygdala in patients with schizophrenia: a magnetic resonance imaging study

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Abstract

The amygdala is known to be involved in the pathology of schizophrenia. While only a limited number of studies in schizophrenia have measured the amygdala as a single structure. The aim of this study was to examine the hypothesis that patients with schizophrenia would show reduced volumes in the amygdala compared with normal controls. We investigated amygdala volume in 40 patients with schizophrenia (20 males, 20 females) and 40 age- and gender-matched normal controls using three-dimensional magnetic resonance imaging (MRI). Whole volumes of both the amygdala and the temporal lobe were measured on consecutive coronal 1-mm slices. The amygdala volume was significantly smaller in schizophrenia patients than in controls. Considering gender differences, male patients had significantly smaller volumes in the bilateral amygdala than male controls; female patients had a significantly reduced right amygdala compared with female controls. Furthermore, a significant left-smaller-than-right volumetric asymmetry of the amygdala was detected in male patients with schizophrenia. The results may be important for understanding the role of the amygdala in the pathophysiology of schizophrenia and the anatomical substrates of gender difference in the expressions of the illness.
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1. Introduction

The amygdala is a gray mass situated in the mediodorsal portion of the temporal lobe, rostral and

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dorsal to the tip of the inferior horn of the lateral ventricle. It is covered by a rudimentary cortex and caudally is continuous with the uncus of the parahippocampal gyrus (Malcolm, 1991). The anatomic connections suggest that the amygdala is one of the key components of the central circuit of emotion (Davidson, 2002). Previous studies have demonstrated that the amygdala is involved in emotion-related aspects of behavior, memory and learning (Weiskrantz, 1956; LeDoux, 1993; Ono et al., 1995; McCarley et al., 1999), especially those related to fear and aggression (Adolphs et al., 1998; Amaral, 2002). Furthermore, both lesion studies (Adolphs et al., 1994, 1998; Young et al., 1995) and functional imaging studies in humans (Breiter et al., 1996; Davidson, 2002; Gur et al., 2002) have demonstrated the amygdala's role in recognizing emotional facial expressions and production of negative emotion. Since schizophrenia is characterized by dysfunctions in thought, affect, social behavior and cognition (Seidman et al., 1999; Andreasen, 2000), the amygdala has become an interesting structure in studies of the pathophysiology of schizophrenia.

In recent years, a number of morphometric studies using post-mortem brain material (Bogerts et al., 1985, 1993a; Chance et al., 2002) and in vivo magnetic resonance (MRI) (Bogerts et al., 1990, 1993b; Breier et al., 1992; Shenton et al., 1992; Pearlson et al., 1997; Hirayasu et al., 1998; Bryant et al., 1999; Gur et al., 2000; Niemann et al., 2000; Levitt et al., 2001; Anderson et al., 2002) have been made on the structural variations (shape or size) of the amygdala in patients with schizophrenia. Most of these studies have combined the amygdala with the hippocampus as the amygdala-hippocampus complex, of which the anterior portion was thought to be primarily the amygdala and the posterior portion primarily the hippocampus (Bogerts et al., 1990, 1993b; Breier et al., 1992; Shenton et al., 1992; Hirayasu et al., 1998; Bryant et al., 1999; Niemann et al., 2000; Rajarethinam et al., 2001; Anderson et al., 2002). Only a limited number of studies have measured the amygdala as a single structure (Pearlson et al., 1997; Gur et al., 2000; Niemann et al., 2000; Levitt et al., 2001). The results have not been consistent. Most studies have reported volume reduction in patients with schizophrenia compared with healthy comparison subjects (Breier et al., 1992; Shenton et al., 1992; Pearlson et al., 1997; Hirayasu et al., 1998; Bryant et al., 1999), but a few studies reported negative results (Niemann et al., 2000; Chance et al., 2002). The different results may have derived from methodological differences including the sampling methods and analyses. Furthermore, the discrepancy among the MRI studies may be due to differences in image acquisition and structure definition or delineation; in particular, there has been marked variability in slice thickness, slice resolution, as well as whether consecutive slices and three-dimensional orientation have been employed. Although the hippocampus and the amygdala have quite different functions, both may be implicated in the pathophysiology of schizophrenia. As the amygdala is especially proposed to be involved in the emotional distortion of schizophrenia, it is necessary to separate the amygdala from the hippocampus and to measure the amygdala as a single structure.

Following recent advances in computerized analyses of MR images allowing higher resolution, three-dimensional orientation and automatic segmentation of tissue (gray and white matter, and cerebrospinal fluid), it is now possible to delineate some small brain structures, such as the amygdala, with considerable reliability. The purpose of this study was to examine the focal volumetric variations of the amygdala in patients with schizophrenia. With the aid of high-resolution images with voxel size as 1.0 mm^3 (1.0×1.0×1.0 mm) and three-dimensional orientation, the measurement was performed on consecutive 1-mm-thick coronal slices after the brain tissue was auto-segmented into gray and white matter.

2. Methods

2.1. Subjects

There were 80 subjects in this study, 40 patients with schizophrenia (20 males and 20 females) and 40 normal controls (20 males and 20 females). All of the subjects were right-handed. The demographic and clinical characteristics of the subjects are shown in Table 1.

The patients with schizophrenia met ICD-10 diagnostic criteria for research (World Health Organ-

Table 1
Demographic and clinical characteristics of patients with schizophrenia and control subjects

Variable	Schizophrenia patients		Normal controls	
	Male (n=20)	Female (n=20)	Male (n=20)	Female (n=20)
Age (years)	26.4±5.1	25.9±5.19	25.5±5.6	24.8±6.2
Height (cm)[a]	170.9±5.5	159.0±3.9	172.6±3.9	159.2±3.8
Education (years)[b]	14.2±2.1	13.1±2.1	17.2±2.6	14.5±1.2
Parental education (years)	12.0±1.6	11.6±2.2	12.5±2.5	12.0±1.9
Age at onset (years)	21.6±4.7	21.2±3.9	–	–
Duration of illness (years)	4.8±4.3	5.2±4.6	–	–
Duration of medication (years)	3.3±3.1	4.1±3.8	–	–
Drug (mg/day, haloperidol equivalent)	7.7±5.2	10.8±12.2	–	–
Total SAPS score	19.5±18.0	27.5±18.4	–	–
Total SANS score	45.1±21.8	43.3±20.6	–	–

Values represent means±S.D.s.

[a] There were significant differences in height across the four groups (ANOVA, F=58.40, df=3,76, P<0.001). Post-hoc Scheffé's test showed male patients and male controls were taller than female patients (P<0.001) and female controls (P<0.001), respectively.

[b] There were significant differences in education across the four groups (ANOVA, F=14.10, df=3,76, P<0.001). Post-hoc Scheffé's test showed male controls having a higher level of education than female controls (P<0.01), female patients (P<0.001) and male patients (P<0.001), respectively.

ization, 1993) on schizophrenia, and they were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital. All but two of the patients were receiving antipsychotic medication. All patients were physically healthy at the time of scanning, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or substance abuse. Psychopathology was assessed by two trained psychiatrists using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) on the same day as the MRI study.

The control subjects were volunteers recruited from the hospital staff, and from medical and pharmaceutical students. Subjects were excluded if they had a history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. They were also screened for history of psychiatric disorder in their first-degree relatives. In addition, the Minnesota Multiphasic Personality Inventory (MMPI) was administered to all the controls, and subjects were excluded if any T-score of the validity scales or of the clinical scales exceeded 70. Two-way analysis of variance (ANOVA) showed the controls had a higher mean level of education than the patients. Post-hoc Scheffé's test showed that the male controls had a higher level of education than the other three groups. There was no significant difference between the patients and the controls in height, although the males were significantly taller than the females. There were no significant differences among the four groups in age or parental education, or between male and female patients in age at onset, duration of illness, medication dosage, duration of medication, and total or subscale scores on the SAPS and SANS.

After complete description of the study to the subjects, written informed consent was obtained. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University.

2.2. MRI method

2.2.1. MRI acquisition

Magnetic resonance images were acquired on a Magnetom Vision (Siemens Medical system, Erlangen, Germany) operating at 1.5 T with a three-dimensional gradient-echo sequence, Fast Low-Angle Shots (FLASH), yielding 160–180 contiguous 1.0-mm T1-weighted slices in the sagittal plane. Imaging parameters were as follows: repetition time (TR)=24 ms, echo time (TE)=5 ms, flip angle=40°, field of view=256 mm and matrix size=256×256 pixels. The voxel size was 1.0×1.0×1.0 mm. Magnetic field inhomogeneity in our scanner was monitored with weekly phantom scanning and daily basic quality control, and remained stable over the MR acquisition time for this study.

2.2.2. Image processing

Our methods used for image processing have been described in detail elsewhere (Kurokawa et al., 2000; Takahashi et al., 2002), but were briefly as follows. The images were transferred to a Unix workstation (Silicon Graphics, Mountain View, CA, USA). The data were coded randomly and processed with the software package Dr. View 5.0 (Asahi Kasei Joho System, Tokyo, Japan). Brain images were realigned in three dimensions to standardize the differences in head tilt during image acquisition. Standardized scans were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure–posterior commissure (AC-PC) line. Before volumetric analysis, masks were semi-automatically created to demarcate the outer extent of the intracranial contents, with the scalp and neck tissue removed. Minimal manual editing of the masks was required. The whole cerebrum was separated from the brainstem and cerebellum by manual editing on each coronal slice. The brainstem was removed in the plane parallel to the AC-PC plane and passing through the sulcus pontinus superior. Then, according to the Alpert algorithm (Alpert et al., 1996), the signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were used to segment the voxels semi-automatically into gray matter, white matter and CSF. The histogram of gray levels was computed and used to select the minimal intensity point between the gray matter and CSF peaks (lower intensity threshold) and between the gray and white matter peaks (upper intensity threshold). First, CSF was separated from cerebral tissue by the lower intensity threshold; then, the resulting tissue compartment was segmented into gray and white matter compartments by the upper intensity threshold. This segmentation was used as the basis for operator outlining of the regions of interest, as described below.

2.2.3. Measurements of temporal lobe

The measurement for the temporal lobe was performed on consecutive coronal 1-mm-thick slices. The most anterior slice was the plane from which the temporal pole began to appear; the most posterior slice was the plane including the last appearance of the fibers of the crux of the fornix. The temporal stem was divided by a line connecting the most inferior point of the insular cisterns to the most lateral point of the hippocampal or amygdaloid fissure. The superior boundary was the Sylvian fissure; the boundaries in other directions were the edges of the temporal lobe (Shenton et al., 1992).

2.2.4. Measurements of amygdala volume

The delineation for the amygdala is illustrated in Fig. 1. The delineation was performed on consecutive 1-mm-thick coronal slices, from anterior to posterior, with the corresponding orthogonal sagittal and axial planes presented simultaneously for determining the boundaries accurately. The most anterior slice was that on which the amygdala just appeared as oval-shaped gray matter (Bogerts et al., 1990). At the posterior end of the amygdala, the rounded cortical nucleus of amygdala transitions to a thin strip of gray matter, which in turn connects to the subiculum of the hippocampus (Convit et al., 1999). This strip of gray matter forms an anatomical structure known as the hippocampal–amygdala transitional area. On the coronal orientation, this area appears at the level of the mamillary bodies and coincides with the posterior pole of the amygdala (Convit et al., 1999). The most posterior slice of the amygdala was the plane where the strip of gray matter, i.e. the hippocampal–amygdala transitional area, appeared. The tail of the caudate is separated from the amygdala gray matter by a thin strip of white matter, and the inferior boundary is the hippocampus and contact with the upper of alveus. The medial border of the amygdala is a thin strip of parahippocampal white matter called the angular bundle, which separates it from the entorhinal cortex. The inferior–lateral boundary of the amygdala is the temporal lobe white matter and the extension of the temporal horn.

2.2.5. Measurements of intracranial volume (ICV)

ICV was also measured to correct for differences in head size. Before measurement of ICV, 1-mm-thick coronal slices that had been corrected for head tilt were reformatted into consecutive 5-mm-thick sagittal slices with each voxel 1×1×5 mm. The intracranial cavity was manually traced in each sagittal slice, using anatomical landmarks according to Eritaia et al. (2000). ICV was calculated by summing the measured volumes of all slices. For insurance, ICV was measured

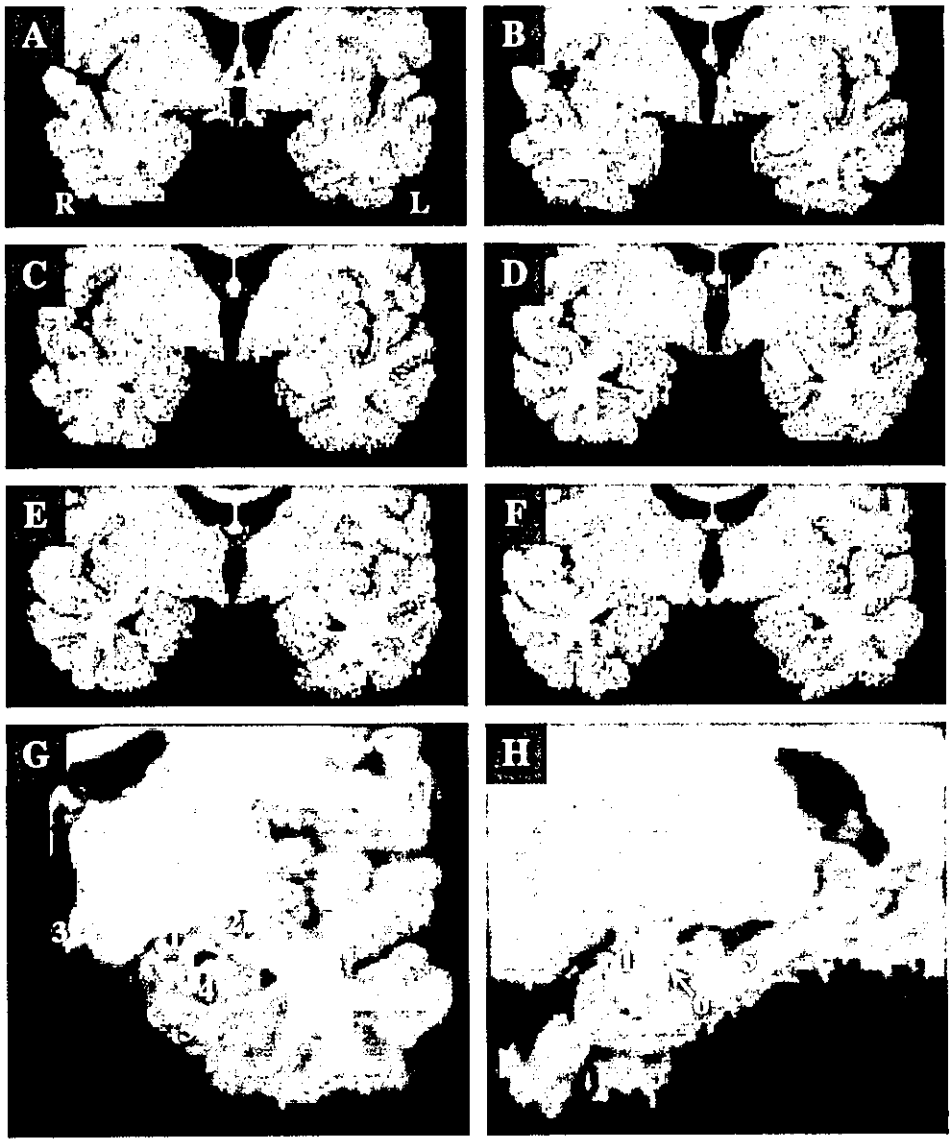

Fig. 1. Boundaries of the amygdala. Sample of coronal slices (panels A–F) shows the delineation of the left amygdala (in red), from anterior to posterior. Panel G (the last coronal slice that contains the amygdala) and H (a sagittal level corresponding to panel G) magnify the region around the amygdala and label the related anatomical structures used as landmarks: (1) amygdala, (2) tail of the caudate, (3) mamillary body, (4) hippocampus, (5) parahippocampal gyrus, (6) upper alveus. R: right, L: left.

using images from five randomly sampled subjects both on 1-mm-thick sagittal slices and 5-mm-thick sagittal slices, and the intraclass correlation coefficient (ICC) between these two strategies was 0.99.

All measurements for temporal lobe and amygdala were performed by one rater (L.N.). Intrarater reliability was established by rating five subjects randomly sampled from the whole subject group. The intrarater ICCs for volumes obtained by the same rater on two occasions were above 0.99 for all ROIs. Interrater reliability was also established by rating five subjects independently by two skilled raters who were rather familiar with brain anatomy (L.N. and H.H.). Before the ICC was set up, practice was done on another set of brains. The interrater ICCs were higher than 0.98 for all ROIs.

2.3. Statistical analysis

Statistical differences in the regional volume measures were analyzed with repeated measures multivariate analysis of variance (MANCOVA) for each region, with diagnosis (patients, comparison subjects) and gender (male, female) as between-

subject factors, hemisphere (right, left) as a within-subject factor, and ICV and age as covariates. ICV was used to control for differences in head size. Post-hoc Tukey's honestly significant difference tests were employed to follow up the significant main effects or interactions yielded by these analyses. Multiple linear regression (step backward method, entry and removal threshold were 0.01 and 0.05, respectively) was used to detect correlations between the amygdala volume and clinical data, the dependent variable was the amygdala volume, and independent variables included age, ICV, age onset, duration of illness, dose of neuroleptic medication, duration of neuroleptic medication, total score on the SAPS and total score on the SANS. Results were considered significant at $P<0.05$ (two-tailed) for all the statistics in this study.

3. Results

3.1. Volumes of the temporal lobe

The volumes of the temporal lobe in patients with schizophrenia and normal controls are shown in Table 2. MANCOVA for the temporal lobe showed only a significant main effect of hemisphere. The volume of the left temporal lobe was significantly smaller than that of the right temporal lobe in both the patients and the controls. There was no significant effect of diagnosis or gender and no significant interactions among factors.

3.2. Volumes of amygdala

The volumes of the amygdala in patients with schizophrenia and normal controls are shown in Table 2. MANCOVA for the amygdala showed significant main effects of diagnosis (the patient group had significantly smaller amygdala volume than the control group), hemisphere (left amygdala was significantly smaller than right amygdala) and gender (males had significantly larger amygdala than females); and significant diagnosis-by-gender interaction and significant diagnosis-by-gender-by-hemisphere interaction. Post-hoc analyses following two-way interactions (diagnosis-by-gender) revealed that male patients had significantly smaller amygdala than male controls, but there was no significant difference between female patients and female controls. Post-hoc analyses following three-way interactions (diagnosis-by-gender-by-hemisphere) revealed that male patients had significantly smaller volumes in bilateral amygdala than male controls. Although there was no significant difference in the left amygdala between female patients and female controls, the female patients had a significantly smaller right amygdala than the female controls. Within the normal control group, the amygdala was significantly larger bilat-

Table 2
Absolute volumes of the amygdala and temporal lobe in patients with schizophrenia and control subjects

Brain region		Schizophrenia patients		Normal controls		Effect sizes (Male/female)
		Male (n=20)	Female (n=20)	Male (n=20)	Female (n=20)	
Temporal lobe (cm^3)[a]	left	80.11±7.30	81.97±6.61	72.34±5.53	72.34±5.53	0.27/0.36
	right	84.00±7.90	84.99±6.70	76.98±4.34	76.98±4.34	0.14/0.59
Amygdala (cm^3)[b]	left	1.04±0.15[c,d]	1.23±0.13[e]	1.04±0.09	1.04±0.09	1.35/0.42
	right	1.13±0.15[c,f]	1.26±0.15[e]	1.09±0.08	1.09±0.08	0.87/0.99

Absolute values represent means±S.D.s.

[a] Significant main effect of hemisphere (F=78.94, df=1,76, $P<0.001$).

[b] Significant main effect: diagnosis (F=20.79, df=1,74, $P<0.001$), gender (F=5.23, df=1,74, $P<0.05$), hemisphere (F= 11.81, df=1,76, $P<0.001$); significant effect of interaction: diagnosis-by-gender (F=4.46, df=1,74, $P<0.05$), diagnosis-by-gender-by-hemisphere (F=4.82, df=1,76, $P<0.05$).

[c] Significant difference compared with the male control subjects ($P<0.001$).

[d] Significant difference compared with the right side in the male patients ($P<0.05$).

[e] Significant difference compared with the female control subjects ($P<0.001$).

[f] Significant difference compared with the female patients ($P<0.001$).

[g] Significant difference compared with the female control subjects ($P<0.001$).

erally in males than in females; neither in males nor in females was there any significant difference between hemispheres in the volume of the amygdala. Within the patient group, a significantly larger amygdala in males compared with females was only seen on the right side, and the hemisphere difference was only seen in the male patients, the male patients having a significantly smaller left amygdala compared with the right amygdala.

3.3. Relationship between amygdala volume and clinical data

There were no significant correlations between amygdala volume and scores on both the SANS and the SAPS. The left amygdala had a significant negative correlation with the duration of illness (standardized coefficients $\beta=-0.439$, $P<0.005$). No correlations were found for the right amygdala (standardized coefficients $\beta=-0.157$, $P=0.223$).

4. Discussion

The main findings of this study were that patients with schizophrenia as a whole had a significant volume reduction in the amygdala compared with normal controls, and such a reduction was shown bilaterally in male patients with schizophrenia (compared with male normal controls) but only in the right amygdala in the female patients (compared with female normal subjects). In addition, we detected a significant volumetric lateralization of the amygdala in male patients with schizophrenia alone, presented as a significantly smaller left amygdala compared with the right amygdala.

In this study, we found a significant volume reduction of the amygdala in patients with schizophrenia compared with normal controls. The result was consistent with several in vivo imaging studies (Breier et al., 1992; Pearlson et al., 1997; Hirayasu et al., 1998; Bryant et al., 1999; Gur et al., 1999; Anderson et al., 2002), although some methodological differences existed among these studies. Postmortem studies have also evidenced amygdala volume reduction in patients with schizophrenia (Bogerts et al., 1985, 1993a), but some negative reports also exist (Staal et al., 2000; Rajarethinam et al., 2001; Chance et al., 2002). Additionally, neurochemical studies have reported increased dopamine and its metabolite in the amygdala in lesioned rats (Kurachi et al., 2000) and patients with schizophrenia (Reynolds, 1983). Deficits in GABA uptake sites may also be correlated with increased dopamine in the amygdala, perhaps via a presynaptic effect on dopamine neuronal activity (Simpson et al., 1989; Reynolds et al., 1990). These studies indicated a relationship between increased dopamine and lesion brain tissue. Our results further support the hypothesis of amygdala volume reductions as a component of the brain morphometric abnormalities in patients with schizophrenia.

More interesting, in the present study, post-hoc analyses revealed that the amygdala volume reduction in schizophrenia was bilateral for males and unilateral (right hemisphere) for females. This suggests that morphometric abnormalities of the amygdala were more diffuse and severe in male patients with schizophrenia than in female patients. This is consistent with previous studies which demonstrated that brain morphometric abnormalities were more likely to be found in males with schizophrenia, e.g., enlargement of the lateral ventricles (Andreasen et al., 1990; Goldstein, 1996, 1997; Nopoulos et al., 1997) and reduction of medial temporal lobe volume, especially the hippocampus–amygdala complex (Bogerts et al., 1990; Gur et al., 2000). From the aspect of clinical course of the illness, male patients have more negative symptoms, earlier onset and worse long-term outcome, while female patients have better premorbid competence, experience more positive and affective symptoms, and have better treatment response (Angermeyer et al., 1990; Gur et al., 1996; Lewine et al., 1996; Goldstein, 1997). Moreover, neuropsychological studies have evidenced that patients with withdrawn syndromes show superior recognition memory for faces compared with recognition memory for words, particularly male patients with anhedonia (Gruzelier and Phelan, 1991; Gruzelier and Richardson, 1994; Gruzelier and Doig, 1996). The sex chromosomal or hormonal environment during brain growth and development is probably an important factor in producing normal sex dimorphisms and modulating brain abnormalities in schizophrenia (Geschwind and Galaburda, 1985; Crow, 1990; Nopoulos et al.,

2000). However, the gender differences in symptomatology and neuropsychology may also reflect differences in neuroanatomical measures.

Furthermore, the current study demonstrated a left-smaller-than-right amygdala volume in male patients. This result is consistent with previous findings that brain structure abnormalities are more left-lateralized among males (Bogerts et al., 1990; Hass et al., 1991; Bryant et al., 1999; Shenton et al., 2001). Some MRI studies found that volume reduction of the amygdala was most prominent on the left in schizophrenia (Shenton et al., 1992, 2001; Hirayasu et al., 1998; Hulshoff Pol et al., 2001). Furthermore, Shenton et al. (2002) reported that left/right amygdala–hippocampal shape asymmetry was larger in patients with schizophrenia than in controls. Gruzelier et al. (1987, 1988) proposed two opposite patterns of lateral asymmetry were related to different syndromes: left-sided impairments were associated with a withdrawn (negative) syndrome and right-sided impairments were associated with an active (positive) syndrome. Functional neuroimaging studies have also been used to study schizophrenia. Male patients showed premorbid asymmetry in which recognition memory for faces was superior to recognition memory for words, which was predictive of the presenting negative symptoms (Gruzelier and Richardson, 1994; Gruzelier, 1999; Gruzelier et al., 1999). Other studies also found greater left than right amygdala activation during negative emotional facial expressions such as fear in humans (Breiter et al., 1996; Killgore and Yurgelun-Todd, 2001). The left amygdala appeared to be particularly important for the processing of external stimuli related to withdrawal behaviors, and this specialized function of the left amygdala was most prominent and clearly observed in males (Breiter et al., 1996). In addition, neurochemical post-mortem studies of schizophrenia demonstrated that a specific increase of dopamine and its metabolism is found in the left amygdala (Reynolds, 1983; Kurachi, 2003). These findings, together with our own, suggest a relatively special role of the left amygdala in schizophrenia compared with the right amygdala, especially in male patients. In our study, post-hoc analyses demonstrated a significant hemisphere effect (left < right) only in the male patients and consistent with the hypothesis regarding a left-hemisphere-predominant pathophysiology of schizophrenia (Gur, 1979; Petty, 1999). Male patients showing greater left lateralization is perhaps related to the fact that the male brain grows up later than the female brain and the left hemisphere later than the right (Geschwind and Galaburda, 1985). On the other hand, the present study has shown that volume reduction also occurs in female patients with the right amygdala being selected and the left amygdala spared. This seems to be consistent with neuropsychological observations to some extent, in that female patients with schizophrenia performed relatively worse on right hemisphere tasks, and it suggests that female schizophrenia may have right hemispheric dysfunction (Lewine, 1996).

It also may be of pathophysiological significance that the duration of illness was negatively correlated with left amygdala volume. Though no previous studies on the amygdala in schizophrenia have found the same correlation, similar correlations of other brain structures with illness duration have frequently been reported. For example, duration of illness in schizophrenia was positively correlated with abnormal asymmetry of frontal lobe and reduction of right frontal lobe volume (Turetsky et al., 1995), right hippocampal volume reduction (Velakoulis et al., 1999), right Sylvian fissure size (Aso et al., 2001), and relative temporal and prefrontal sucal cerebrospinal fluid (Molina et al., 2002). Recently, a voxel-based volumetric study (Velakoulis et al., 2002) found that right medial temporal, medial cerebellar and bilateral anterior cingulate gray matter volume, and white matter volume in the right posterior limb of the internal capsule, were all negatively correlated with illness duration. Our finding in the present study is consistent with these previous findings, especially when considering that the distribution of illness duration in this study exhibited a relative large range (0.5–180 months) and scattered evenly in this range, which can to some extent compensate for the disadvantage of a cross-sectional design in detecting longitudinal changes. This finding suggested the existence of progressive tissue loss in amygdala, especially the left side, as a component of a brain degenerative process, in chronic schizophrenia patients. In fact, using Pearson's partial correlation analysis controlling for age and ICV, we also detected a positive relationship of age at onset of illness, as well as the negative relationship of

duration of illness, with left amygdala volume. Considering that these two variables may confound each other because that patients with early onset would have longer duration of illness, we did a Pearson's correlation analysis between these two variables; it is not surprising that there was a trend toward a significant correlation between them (P=0.08). The results of later multiple linear regression held only for the contribution of the duration of illness, but excluded the effects of age at onset. So, from the statistical point of view, it also seems that the amygdala volume reduction should mainly reflect an ongoing degenerative process following the first episode of the disorder; changes in the premorbid period remain to be clarified.

As part of the study, the volume of the temporal lobe was also assessed. Regarding the volume of the whole temporal lobe, the present study revealed a significant main effect of hemisphere (left-small-than-right) in both patients and normal controls. No significant main effect of diagnosis or gender was found. In a review of 51 MRI studies evaluating the volume of the whole temporal lobe in schizophrenia, 31 (61%) studies reported smaller temporal lobe volumes than in controls, while 20 (39%) reported negative findings (Shenton, 2001). The disparities may be due to methodological differences.

In conclusion, we found volume reduction of the amygdala in patients with schizophrenia. This result provides further evidence for neuroanatomical deficits in schizophrenia, particularly in the left amygdala of male patients and the right amygdala of female patients. Our findings may be important for understanding the role of the amygdala in the pathophysiology of schizophrenia and the anatomical substrates of the gender differences in the expression of the illness.

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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.
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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.

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.

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.
* $p<0.05$.
** $p<0.01$.

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

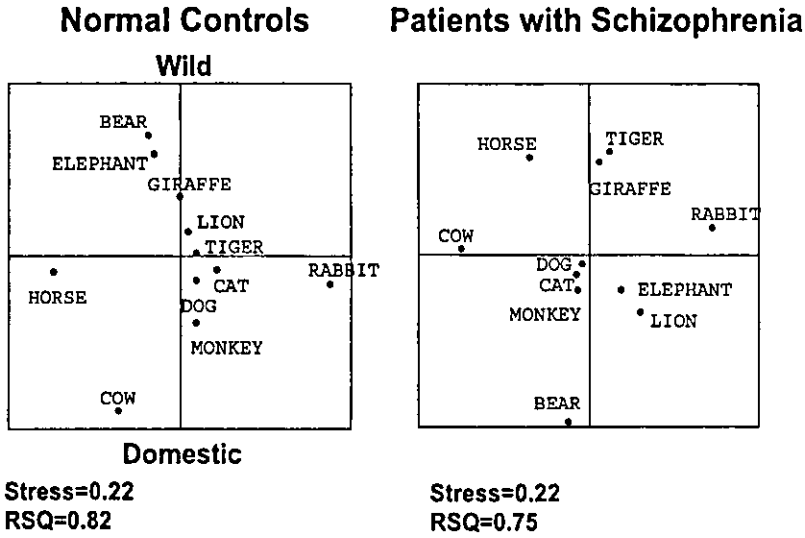

Fig. 1. Two-dimensional semantic structure as revealed by multidimensional scaling analysis in normal controls (N=38; left) and patients with schizophrenia (N=38; right).

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

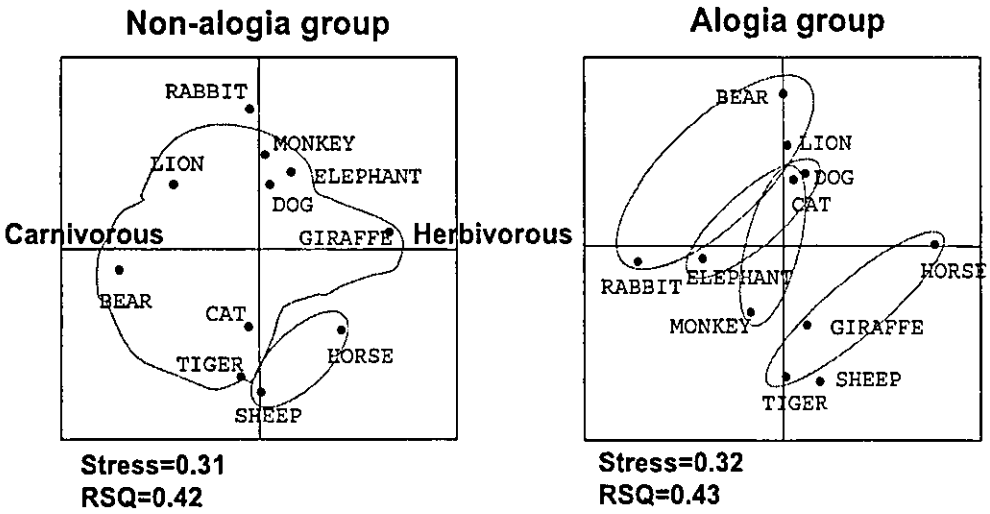

Fig. 2. Two-dimensional semantic structure for non-alogia (N=21; left) and alogia (N=17; right) patients with schizophrenia. The circles represent highly cohesive assemblies as revealed by cluster analysis.

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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