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The relationship between prefrontal brain volume and characteristics of memory strategy in schizophrenia spectrum disorders

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ABSTRACT

The present study investigated the relationship between memory strategy use and prefrontal gray/white matter volumes of healthy control subjects, patients with schizophrenia or schizotypal disorder. Gray/white matter volumes were measured for the superior, middle, inferior, ventral medial and orbital prefrontal regions, using high-resolution magnetic resonance (MR) images that were acquired from 35 patients with schizophrenia, 25 patients with schizotypal disorder and 19 healthy subjects. Participants were also administered the Japanese Verbal Learning Test (JVLT). In control subjects, larger left inferior frontal and straight gyrus's gray matter volumes were associated with higher semantic clustering rates on the JVLT, and smaller left inferior frontal gray matter volumes were associated with higher serial clustering ratio. In schizophrenic patients, smaller left orbitofrontal gray matter volumes were associated with lower semantic clustering rates on the JVLT. In schizotypal patients, smaller left inferior frontal white matter volume was associated with smaller serial clustering rates and larger semantic clustering rate. These findings suggest that semantic organization in schizophrenic patients might depend on mobilization of a memory strategy that is mediated by orbitofrontal cortex functioning. Failure to use a semantic organization strategy might be related to reduced volume in the inferior frontal gyrus. The findings for schizotypal patients suggest a compensation mechanism to remember the words using a serial processing strategy is at work when the inferior frontal gyrus cannot mediate semantic processing.

1. Introduction

Verbal memory deficits are commonly reported in patients with schizophrenia (Cirillo and Seidman, 2003; Matsui et al., 2007c; Saykin et al., 1991). Some researchers have proposed that schizophrenic patients are impaired in the use of certain memory strategies and make little use of spontaneous semantic organization, suggesting that they instead use another less efficient encoding strategy (Brebion et al., 2004; Chan et al., 2000; Gold et al., 1992; Matsui et al., 2006; Matsui et al., 2007a).

Several previous studies have examined the relationship between structural brain volumes and memory performance in schizophrenic patients. Seidman et al. (1994) found that impairment of verbal recall was associated with a smaller left dorsolateral prefrontal cortex area. Gur et al. (2000) found that higher orbitomedial prefrontal volumes were associated with better verbal memory in female schizophrenic patients, but not male. Sanfilipo et al. (2002) found a positive correlation between hippocampal volume and word memory in patients with schizophrenia. Baaré et al. (1999) reported that prefrontal volumes were associated with verbal recall performance in schizophrenic patients but not nonclinical control subjects. In contrast, several studies have reported no significant relationship between brain structural measures and memory performance in schizophrenia (Szeszko et al., 2000, Antonova et al., 2005). Using a voxel-based morphometry method, Antonova et al. (2005) reported that verbal memory was positively associated with inferior frontal gyrus volume in control subjects but not schizophrenic patients. Thus, studies to date on the relationship between structural brain volume and memory performance have produced inconsistent results. Moreover, the question of whether memory strategy deficits in schizophrenic patients are associated with structural abnormalities of the brain has not been resolved.

Abbreviations: ICV, intracranial cavity volume; IFG, inferior frontal gyrus; JVLT, the Japanese Verbal Learning Test; MFG, middle frontal gyrus; MMPI, the Minnesota Multiphasic Personality Inventory; OFC, orbitofrontal cortex; ROI, region of interest; SFG, superior frontal gyrus; SG, straight gyrus; VMFC, ventral medial prefrontal cortex.

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Several focal lesion (Alexander et al., 2003; Baldo et al., 2002; Gershberg and Shimamura, 1995) and functional neuroimaging studies (Fletcher et al., 1998; Savage et al., 2001) indicated that the frontal lobes have an important function in memory. In comparison with healthy control subjects, patients with prefrontal lesions are less likely to apply semantic organizational strategies during encoding and retrieval (Gershberg and Shimamura, 1995). In a positron emission tomography (PET) study by Fletcher et al. (1998), performance on a task to generate an organizational structure in a word list was associated with significant activation in the left prefrontal cortex in normal subjects, especially in the area adjacent to the left inferior frontal sulcus. In a functional magnetic resonance imaging (fMRI) study, the left inferior prefrontal cortex has been found to show increased activation during semantic encoding (Demb et al., 1995). Thus, an important aspect of the prefrontal contribution to memory function is the role that this region plays in the organization of material. Furthermore, a recent study using near-infrared spectroscopy showed activation of prefrontal cortex during a memory organization task in healthy people (Matsui et al., 2007b). Some activation studies have reported that schizophrenic patients tend to show diminished activation of the inferior prefrontal lobes as compared to control subjects, particularly during verbal memory tasks (Nohara et al., 2000; Ragland et al., 2001). Although brain function might not necessarily equate with brain structure, these findings regarding the memory function of the prefrontal area suggest that dysfunction of the inferior prefrontal cortex may be related to memory strategy deficits in patients with schizophrenia. Imaging studies of patients with schizophrenia have also reported frontal and temporal metabolic rate decreases that were paralleled by reduced frontal and temporal gray matter seen on anatomical MRI (Buchsbaum et al., 2007; Molina et al., 2005; Park et al., 2006). Taking these findings into consideration, we have developed the hypothesis that the prefrontal brain volume, especially the inferior prefrontal volume, would be associated with semantic memory processing in healthy control participants, but not in patients with schizophrenia.

Schizotypal (personality) disorder is characterized by oddities in appearance, perception and behavior that appear to represent a milder form of schizophrenia. Schizotypal disorder is genetically related to schizophrenia, and the two disorders share many biological features (see a review by Siever and Davis, 2004). Several recent brain structural imaging studies have identified specific structural abnormalities in schizotypal patients similar to those seen schizophrenia, although generally to a lesser degree and with the sparing of some brain regions (Siever and Davis, 2004). Moreover, neuropsychological studies have shown that unlike schizophrenia patients, who exhibit severe cognitive impairment across most cognitive functions, patients with schizotypal subjects exhibit moderate impairment across a few cognitive domains (Siever and Davis, 2004). We examined a wider range of cognitive measures in schizophrenia patients, schizotypal disorder patients, and healthy controls to clarify the similarities and differences in the neuropsychological function between these two disorders, and found impairment of verbal memory was common to both patients group (Matsui et al., 2007c). In addition, we found that problem of memory strategy was also common to both patients group (Matsui et al., 2006). Next, here we attempted to explore the pattern of correlations between brain structure and memory strategy in patients compared with control subjects.

A substantial number of brain imaging studies suggest that schizophrenia is associated with structural brain alterations, and gray matter reductions have repeatedly been reported in several regions (Shenton et al., 2001; Suzuki et al., 2005). The gray matter changes are thought to reflect an aberrant neuronal network in schizophrenia, suggesting that connecting tissue, i.e. white matter is also affected. White matter abnormalities have been interpreted as disturbed connectivity of neural networks. We have used an automated procedure for tissue segmentation of intracranial compartments related to cytoarchitecture and connectivity: gray matter—the somatodendritic tissue of neurons (cortical and deep), white matter—the axonal compartment of myelinated connecting fibers. A recent study that examined gray and white matter volumes in schizotypal and schizophrenia patients (Hazlett et al., 2008), indicated that schizophrenia patients showed an overall prefrontal volume loss in gray, but not in white matter, whereas schizotypal patients did not differ from normal people, and had greater-than-normal white matter volume in a part of the prefrontal lobe. Therefore, it seems that there are differences in the prefrontal lobe of schizotypal and schizophrenia patients. The present study investigated the relationship between memory strategy use and prefrontal gray/white matter volumes of subdivisions (Suzuki et al., 2005). We measured gray and white matter volumes of the superior, middle, inferior, ventral medial and orbital prefrontal regions in control subjects, patients with schizophrenia or schizotypal disorder using high-resolution MR images.

We explored the hypothesis that memory strategy–brain structure relationship is altered in patients with schizophrenia or schizotypal disorder and predicted that smaller prefrontal volumes would be associated with use of a less effective memory strategy, namely less use of semantic organization. We expected to find a positive relationship between effective use of semantic organization and left inferior prefrontal volume in healthy control subjects, but not patients. We also predicted the correlations between brain structure and memory strategy in schizophrenia would be different from those in schizotypal disorder. It was expected that patients with schizophrenia would have more alterations involving gray matter, whereas schizotypal patients would have more alterations involving white matter.

2. Methods

2.1. Participants

Thirty-five patients with schizophrenia (22 males, 13 females), 25 patients (17 males, 8 females) with schizotypal disorder and 19 healthy control subjects (10 males, 9 females) were included in this study. All participants were right-handed. Demographic and clinical data of the subjects are presented in Table 1.

Patients with schizophrenia were recruited from both inpatients and outpatient clinics and were diagnosed using the Comprehensive

Table 1
Demographic and clinical characteristics of participants

Variable	Schizophrenia (n=35)		Schizotypal disorder (n=25)		Control subjects (n=19)	
	Mean	SD	Mean	SD	Mean	SD
Male/female (n)	22/13		17/8		10/9	
Age (years)	23.8	5.2	24.9	4.5	27.1	6.7
Height (cm)	165.4	6.7	167.1	9.2	166.1	7.8
Weight (kg)	59.5	13.7	62.9	10.2	57.7	7.9
Education (years)	12.9	1.6	13.7	1.8	16.1[a]	2.8
Parental education (years)	12.5	2.1	12.3	1.8	12.2	2.4
Age at onset (years)	20.8	4.5	20.4	5.3		
Duration of illness (years)	3.1	3.4	4.2	3.6		
Duration of medication (years)	2.4	3.2	1.3	2.3		
Drug (mg/day, haloperidol equivalent)[b]	13.4[c]	9.6	2.5	2.7		
Total SAPS score	25.9	22.2	18.4	7.1		
Total SANS score	47.3	23.1	47.8	23.9		

SAPS, Scale for Assessment of Positive Symptoms; SANS, Scale for Assessment of Negative Symptoms.

[a] $p<0.01$ compared with schizophrenia or schizoptypal disorder (Tukey post hoc tests).

[b] The different typical and atypical antipsychotic dosages were converted into haloperidol equivalents using the guideline by Inagaki and Inada (2006).

[c] $p<0.01$ compared with schizotypal disorder (two-tailed t test).

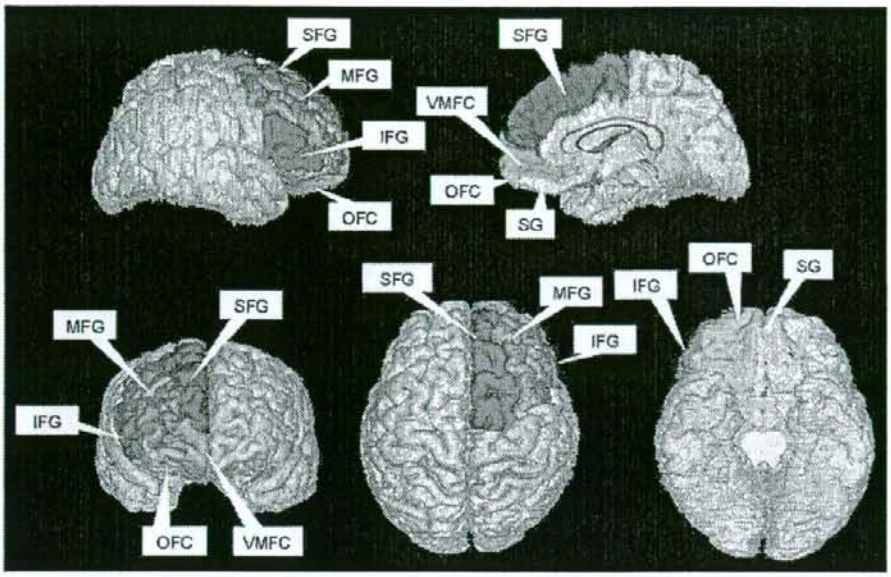

Fig. 1. Three-dimensional reconstructed images of prefrontal regions of interest, presenting right lateral, right medial, dorsal, ventral and anterior views of the brain. SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; VMFC, ventral medial prefrontal cortex; OFC, orbitofrontal cortex; SG, straight gyrus.

Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) and Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First et al., 1996). They fulfilled both ICD-10 (World Health Organization, 1993) and DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia. All schizophrenic patients were receiving antipsychotic medication; 14 patients were treated with typical antipsychotics and 21 patients were receiving atypical antipsychotics. The clinical status of the schizophrenia patients who participated in this study was relatively stable since they were partially remitted or remitted. All patients were physically healthy. None had a history of head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. Clinical symptoms were rated by well-trained psychiatrists or a psychologist within one week of the MRI scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) and Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). Inter-rater intraclass correlation coefficients were over 0.92 for all the subscale scores and the total scores of the SANS and the SAPS.

The patients with schizotypal disorder were recruited from among patients who visited the clinics of the Department of Neuropsychiatry, Toyama University Hospital. These patients all manifested schizotypal features with distress or associated problems in their lives. Structured clinical interviews were performed using the CASH and Structured Clinical Interview for DSM-IV axis II disorders (SCID-II) (First et al., 1997). They all met ICD-10 criteria for schizotypal disorder as well as DSM-IV criteria for schizotypal personality disorder. None of the subjects was judged to meet ICD-10 or DSM-IV criteria for schizophrenia currently or previously. At the time of MRI scanning, four of the schizotypal patients were antipsychotic-naïve and 21 were being treated with low doses of antipsychotics; five patients were treated with typical antipsychotics and 16 patients were receiving atypical antipsychotics. All schizotypal subjects have received consistent clinical follow-up, and none of them has developed schizophrenia to date.

The control participants consisted of healthy volunteers recruited by advertisements from the community, as well as hospital staff and students. They were interviewed by psychiatrists or psychologists using a questionnaire concerning their family and past histories, and presence of current illness based on the SCID non-patient form (First et al., 1996). Subjects were excluded if they had a history of psychiatric illness on an Axis I or II of DSM-IV, head trauma, neurological illness, serious medical or surgical illness, substance abuse disorder, or past substance dependence/abuse. Control subjects were also screened for history of psychiatric disorders on an Axis I or II in their first-degree relatives. All control subjects were given the Japanese version of the Minnesota Multiphasic Personality Inventory (New Japanese MMPI Committee, 1993, 1997) because our previous study (Matsui et al., 2002) identified the usefulness of the MMPI subscales in detecting subjects with the schizotypal personality disorder trait. Participants were excluded if they had abnormal profiles; a T-score exceeding 70 for the validity scales or the clinical basic scales.

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 University.

2.2. Memory measure

Participants were individually administered the Japanese Verbal Learning Test (JVLT) (Matsui et al., 2006) by experienced

Table 2
Results of the Japanese Verbal Learning Test

	Schizophrenia		Schizotypal disorder		Control subjects	
	Mean	SD	Mean	SD	Mean	SD
Total recalls	23.6***	9.0	27.9**	10.9	36.8	6.6
Number of semantic clustering	7.5***	5.9	9.8**	9.0	18.7	9.2
Number of serial clustering	3.6	2.8	5.1	4.0	3.9	2.8
Number of subjective clustering	0.9	1.3	1.0	1.7	0.8	1.0
Semantic clustering ratio	0.28**	0.16	0.29**	0.22	0.49	0.20
Serial clustering ratio	0.16	0.14	0.22*	0.15	0.11	0.07
Subjective clustering ratio	0.09	0.13	0.08	0.12	0.05	0.07

*** $p<0.001$ compared with control subjects using post hoc test of Kruskal–Wallis test.
** $p<0.01$ compared with control subjects using post hoc test of Kruskal–Wallis test.
* $p<0.05$ compared with control subjects using post hoc test of Kruskal–Wallis test.

Table 3
Volumes of left prefrontal cortex subcomponents in each group

Regions of interest		Schizophrenia patients		Schizotypal disorder patients		Control subjects	
		Mean	SD	Mean	SD	Mean	SD
Intracranial volume							
	Male	1548.6[a]	127.7	1587.4	106.9	1570.1[a]	105.2
	Female	1386.5	119.9	1449.8	174.1	1386.1	84.0
Whole prefrontal							
Gray matter	Male	97.7	10.4	98.0	14.4	97.3	8.3
	Female	85.4	13.2	93.6	11.9	86.9	8.0
White matter	Male	45.6	8.5	47.4	8.4	49.2	6.0
	Female	42.5	6.6	42.6	6.3	45.1	7.5
Superior frontal gyrus							
Gray matter	Male	29.4	4.2	28.8	5.4	31.5	4.8
	Female	25.8	3.8	27.7	3.5	27.7	3.2
White matter	Male	11.3	2.7	11.2	2.7	11.6	2.9
	Female	10.1	2.2	9.5	1.9	11.4	2.8
Middle frontal gyrus							
Gray matter	Male	28.2	4.4	29.5	7.2	27.7	4.2
	Female	24.9	5.7	26.7	4.2	23.7	4.4
White matter	Male	8.2	2.2	9.3	2.1	8.7	1.7
	Female	7.9	1.9	7.8	1.5	8.2	1.5
Inferior frontal gyrus							
Gray matter	Male	13.5[b]	1.7	13.5	2.8	13.7	1.6
	Female	11.4	1.7	14.2[c]	3.4	12.3	0.8
White matter	Male	5.6	1.1	5.7	1.4	6.1	1.7
	Female	5.1	1.1	5.7	1.2	5.5	0.8
Ventral medial prefrontal cortex							
Gray matter	Male	5.9	1.2	5.8	1.2	6.0	1.4
	Female	5.0	1.1	5.3	1.4	5.3	1.1
White matter	Male	0.7	0.4	0.7	0.3	0.9	0.3
	Female	0.6[e]	0.2	0.6[e]	0.2	0.9	0.3
Orbitofrontal cortex							
Gray matter	Male	16.0	1.9	15.8	1.8	14.4	0.6
	Female	14.2	2.4	15.0	1.2	14.0	1.5
White matter	Male	2.9	0.8	3.1	1.1	2.9	0.6
	Female	2.9	0.9	2.6	0.6	2.8	0.6
Straight gyrus							
Gray matter	Male	2.8[d]	0.4	3.0	0.5	3.3[b]	0.4
	Female	2.8	0.3	3.4[c,d]	0.5	2.8	0.4

Values represent mean ± SD of measured volume (cm^3).
a) $p<0.001$ compared with female; b) $p<0.05$ compared with female c) $p<0.05$ compared with schizophrenia; d) $p<0.05$ compared with controls; e) $p<0.01$ compared with controls.

psychologists. The test was presented within one week of the MRI scanning. The JVLT comprises a 16-word list based on Gold et al. (1992) and measures the degree to which examinees employ semantic organization when encoding the word list. Four exemplars from each four categories are included, such that related items never appear consecutively in the list. Thus, the unblocked list was a memory task for words that could be categorized implicitly that could be used to measure the degree of semantic organization in recall. The list words were selected from common Japanese words (Ogawa, 1972) so that the frequency of each word was approximately the same. Three trials involving each list were presented consecutively. The words were presented at a rate of one word per second and the subjects were required to recall the words after each 16-word set was presented.

Since the unblocked list has a latent semantic structure, participants can facilitate performance by clustering the words into categories during recall. Clustering during recall indicates the extent that participants recognize and process the semantic content of the words. Greater clustering will lead to greater word recall than by chance alone. Indices of clustering according to the serial order of word presentation (Serial Clustering) and semantic content (Semantic Clustering) were calculated as the number of clustering / the number of total recall ratio. In addition, an index of Subjective Clustering, designed to quantify the degree to which an individual utilizes an idiosyncratic clustering strategy in recalling the target list, was calculated using the number of clustering / the number of total recall ratio. This Subjective Clustering does not conform to the standard strategies of Semantic or Serial Clustering, and can occur by grouping words together in a seemingly arbitrary manner that is presumably meaningful to the individuals (Stricker et al., 2002). Concretely, Subjective Clustering score is computed by awarding one point each time two consecutively recalled words on one trial are recalled together in the same forward or backward direction on the next trial. Real Subjective Clustering is the total Subjective Clustering score minus Semantic Clustering and Serial Clustering.

2.3. MRI acquisition and processing

MRI scans were acquired with a 1.5 T scanner (Vision, Siemens Medical System, Inc., Erlangen, Germany). A three-dimensional T1-weighted gradient-echo sequence FLASH (Fast Low-Angle Shots) with 1×1×1 mm voxels was used. Imaging parameters were: TE=5 ms; TR=24 ms; flip angle=40°; field of view=256 mm; matrix size=256×256. The image data were processed on a Unix workstation (Silicon Graphics, Inc., Mountain View, CA, USA) with the software package Dr. View 5.0 (Asahi Kasei Joho System Co., Ltd., Tokyo, Japan). Image processing for volumetric ROI analysis was previously described in detail (Takahashi et al., 2002).

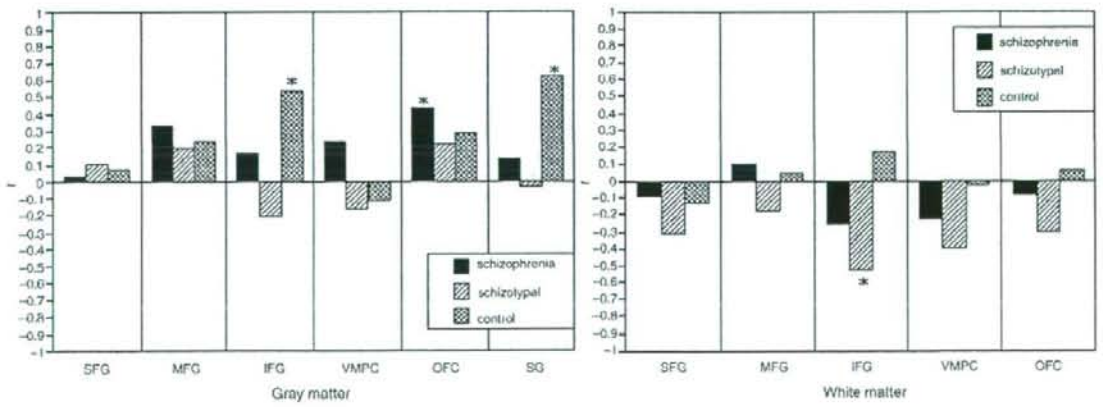

Fig. 2. Correlations between semantic clustering and brain volume. Left side shows gray matter volume, while right side shows white matter volume. SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; VMFC, ventral medial prefrontal cortex; OFC, orbitofrontal cortex; SG, straight gyrus *$p<0.025$.

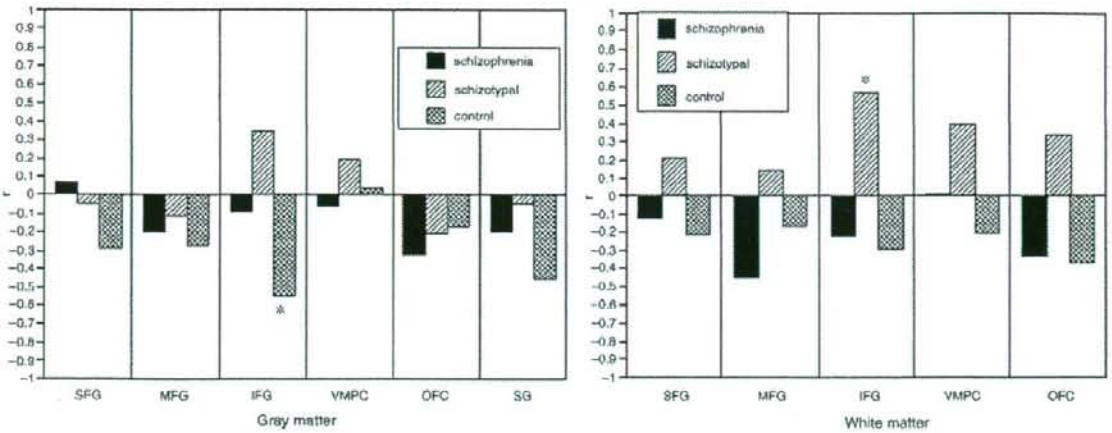

Fig. 3. Correlations between serial clustering and brain volume. Left side shows gray matter volume, while right side shows white matter volume. SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; VMFC, ventral medial prefrontal cortex; OFC, orbitofrontal cortex; SG, straight gyrus *$p<0.025$.

2.4. Volumetric analysis of ROIs

The ROIs for volumetric measurements were placed on the prefrontal cortex as presented in Fig. 1. Parcellation of the frontal lobe into subcomponents was performed according to the anatomical landmarks intrinsic to the brain (sulci/gyri). The prefrontal region was marked out and subdivided into superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, ventral medial prefrontal cortex, orbitofrontal cortex and straight gyrus, according to criteria and landmarks described in previous report by Suzuki et al. (2005). All the volumetric measurements were performed on reformatted consecutive 1-mm coronal slices by manual outlining. Gray and white matter volumes of the regional cortices were calculated by applying the segmentation procedure described previously. The straight gyrus has little white matter, so only gray matter volume was shown for this subdivision. Two trained raters who were blind to the subjects' identities measured the volumes of the prefrontal regions. Inter- and intra-rater intraclass correlation coefficients in five randomly selected brains were over 0.92 for each prefrontal ROI. Intracranial volume (ICV) was measured by manual tracing of the intracranial cavity on reformatted 5-mm-thick sagittal slices as described previously (Zhou et al., 2003).

2.5. Statistical analysis

Each memory index was analyzed using Kruskal–Wallis test with diagnostic group as between-subject factors. Post hoc tests by Siegel and Castellan (1988) were employed to follow-up the significant main effects or interactions yielded by Kruskal–Wallis tests. Statistical differences in the regional volume measures were analyzed with repeated measures multivariate analysis of covariance (MANCOVA) with ICV and age as covariates for each region, with diagnosis group and gender as between-subject factors. For the comparison of ICV, only age was treated as a covariate. Post hoc Turkey's tests were employed to follow-up the significant main effects or interactions yielded by MANCOVAs.

Because of the skewed distribution in memory organization measures, correlations between the MRI volume measures and the memory organization measures were investigated by using nonparametric statistics. Spearman's correlation coefficients were used to

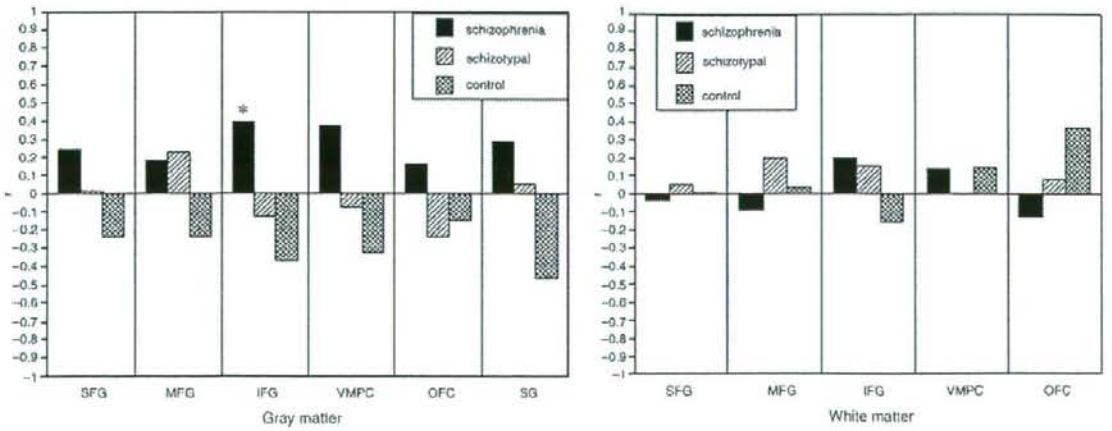

Fig. 4. Correlations between subjective clustering and brain volume. Left side shows gray matter volume, while right side shows white matter volume. SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; VMFC, ventral medial prefrontal cortex; OFC, orbitofrontal cortex; SG, straight gyrus *$p<0.025$.

examine the relationships between the memory organization index (semantic, serial, and subjective clustering ratios) and each prefrontal MRI volume. To minimize false-positive errors, we considered the predictors to be significant at $p<.025$ following Antonova et al. (2005). Since the correlations between structural volumes and cognitive functions observes in ROI studies are modest (rarely exceeding 0.350–0.400) (Antonova et al., 2004), a more conservative p value would have substantially increased the risk of type II error (Antonova et al., 2005).

Finally, Spearman's correlation coefficients because of the skewed distribution in the clinical variables were calculated to examine relationships between the ROI volumes or memory indices and the clinical variables. Statistical significance was defined as $p<0.05$ (two-tailed). A Bonferroni correction was applied for these correlational analyses.

3. Results

3.1. Results of JVLT

Scores for each memory index on the JVLT are presented in Table 2. There were significant main effects of group in the Kruskal–Wallis tests for the number of total recalls ($H=22.36$, $p<0.0001$), the number of semantic clustering ($H=16.84$, $p<0.001$), ratio of semantic clustering ($H=22.36$, $p<0.005$) and rate of serial clustering ($H=6.19$, $p<0.05$). Post hoc tests showed that controls recalled more words and produced more semantic clustering than the schizophrenia patients (total recalls, $p<0.001$; semantic clustering, $p<0.001$) and schizotypal patients (total recalls, $p<0.01$; semantic clustering, $p<0.01$). In addition, post hoc tests showed controls had a higher semantic clustering rate than schizophrenia patents ($p<0.01$) and schizotypal patients ($p<0.01$), but there was no difference between schizophrenia patients and schizotypal patients, and controls had a lower serial clustering rate than schizotypal patients ($p<0.05$). There were no significant differences among diagnostic groups regarding the number of serial clustering and subjective clustering and rate of subjective clustering.

3.2. Results for MRI volume

Volumes of measured ROIs are presented in Table 3. There was no significant main effect of diagnosis in the volumes of intracranial cavity (ICV), whole prefrontal gray or white matter. There was a significant main effect of gender in ICV ($F_{(1,72)}=30.53$, $p<0.001$). Among the prefrontal cortex subcomponents, MANCOVA revealed significant main effects of diagnosis in gray matter volume of the straight gyrus ($F_{(2,71)}=4.52$, $p<0.05$) and white matter volume of the ventral medial prefrontal cortex ($F_{(2,71)}=4.80$, $p<0.05$). A significant interaction between diagnosis and gender was observed in gray matter volume of the inferior frontal gyrus ($F_{(2,71)}=3.18$, $p<0.05$) and the straight gyrus ($F_{(2,71)}=5.86$, $p<0.01$). Post hoc tests showed that schizophrenic patients had smaller gray matter volume of the straight gyrus than schizotypal patients ($p<0.01$). In male, schizophrenic patients had smaller straight gyrus than control subjects ($p<0.05$). In female, schizotypal patients had larger straight gyrus than schizophrenic patients ($p<0.05$) and control subjects ($p<0.05$). Controls had larger white matter volume of the ventral medial prefrontal cortex than schizophrenia ($p<0.01$) and schizotypal patients ($p<0.01$). In female, schizophrenic patients had less gray matter volume of the inferior frontal gyrus than schizotypal patients ($p<0.05$). In schizophrenia, male patients had larger gray matter volume of the inferior frontal gyrus than female patients ($p<0.05$).

3.3. Correlations between volume measures and memory organization indices

The results of Spearman's correlation coefficients between the memory organization index (semantic, serial, and subjective clustering ratios) and each prefrontal MRI volume are presented in Figs. 2–4. In control subjects, semantic clustering ratio was positively correlated with gray matter volumes of the inferior frontal gyrus ($r_{(17)}=0.53$, $p=0.019$) (Fig. 5) and straight gyrus ($r_{(17)}=0.62$, $p=0.004$), and serial clustering ratio was negatively correlated with gray matter volumes of the inferior frontal gyrus ($r_{(17)}=-0.55$, $p=0.014$). There were no other significant correlations in control subjects.

In patients with schizophrenia, semantic clustering ratio was positively correlated with gray matter volume of the orbitofrontal cortex ($r_{(33)}=0.44$, $p=0.009$), and subjective clustering ratio was positively correlated with gray matter volumes of the inferior frontal gyrus ($r_{(33)}=0.39$, $p=0.022$). In schizotypal patients, semantic clustering ratio was negatively correlated with white matter of the inferior

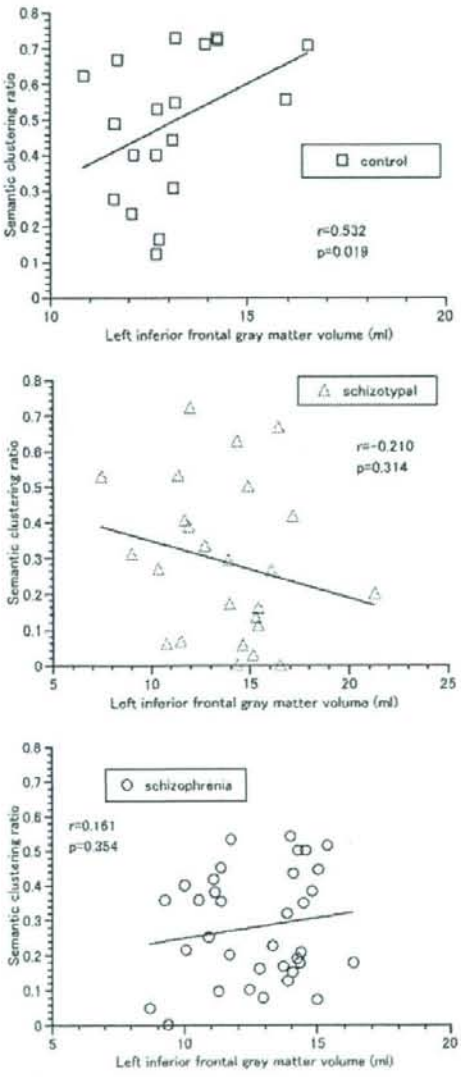

Fig. 5. Three scatter plots display the relationship between semantic clustering ratio and left inferior frontal gray matter volume in controls, schizotypal and schizophrenic patients.

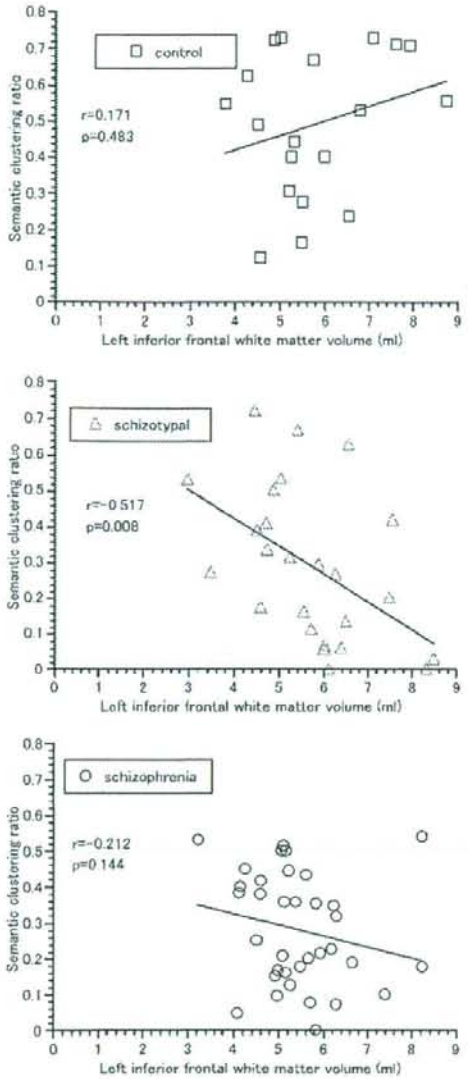

Fig. 6. Three scatter plots display the relationship between semantic clustering ratio and left inferior frontal white matter volume in controls, schizotypal and schizophrenic patients.

frontal gyrus ($r_{(23)}$=−0.52, p=0.008) (Fig. 6), while serial clustering ratio was positively correlated with white matter of the inferior frontal gyrus ($r_{(23)}$=0.57, p=0.003). There were no any other significant correlations in patients.

3.4. Correlations between volume measures or memory indices and clinical variables

Correlational analyses did not reveal any significant relationships between the volume measures of each ROI and daily dosage of antipsychotic medication or duration of medication in either of the patient groups. Similarly, memory index scores did not correlate with these medication variables. Finally, neither volume measures nor memory indices were significantly correlated with age at onset of illness or duration of illness in patients with schizophrenia or schizotypal disorder.

4. Discussion

To our knowledge, this study is the first to investigate the relationship between prefrontal volumes and memory strategy usage in patients with schizophrenia spectrum disorder. In this study, superior, middle, inferior, ventral medial and orbital prefrontal gray and white matter volume were measured in patients with schizophrenia, schizotypal disorder, or control subjects using detailed methods for subdividing the prefrontal lobes based on sulcul anatomy. In control subjects, larger left inferior frontal and straight gyrus's gray matter volumes were associated with higher semantic clustering rates on the JVLT, and smaller left inferior frontal gray matter volumes were associated with higher serial clustering ratio. On the other hand, in schizophrenic patients, smaller left orbitofrontal gray matter volumes were associated with smaller semantic clustering rates on the JVLT, and smaller left inferior frontal gray matter volumes were related to higher subjective clustering. In schizotypal patients, however, smaller left inferior frontal white matter volume was associated with smaller serial clustering rate and larger semantic clustering rate.

As predicted, in control subjects, left inferior frontal gray matter volume was positively associated with semantic clustering during memory for words. This suggests that the larger left inferior frontal cortex is related to the efficient memory strategy of healthy people. Antonova et al. (2005) have also reported that the inferior frontal volume was positively associated with verbal memory in control subjects. So far, there has been no direct study investigating the relationship between brain structures and memory strategy. However, an association between left inferior frontal activation and semantic clustering has been found in previous functional neuroimaging studies (Nohara et al., 2000; Ragland et al., 2001). Although brain structures may not always be correlated with brain functions, some previous MRI studies have reported that brain functions, such as the brain metabolic rate, is correlated with brain volume (Buchsbaum et al., 2007; Molina et al., 2005; Park et al., 2006). Taken together, the findings of this study and previous studies suggest that left inferior frontal cortex may participate in maintaining an efficient memory strategy for semantic clustering. Unexpectedly, gray matter volume of straight gyrus was also positively associated with semantic clustering in control subjects. However, there are a few studies that have examined the relationship between straight gyrus and memory function and have reported that the partial resection of the straight gyrus resulted in selective impairment of memory (Szatkowska et al., 2001, 2004). The straight gyrus has dense inhibitory connections with the superior temporal gyrus and the centers of the auditory cortex, and it is a part of the emotional-memory network involved in the recall of episodic and autobiographical memories, as well as in the short-term maintenance of information (Szatkowska et al., 2001). Similarly, current findings in control subjects are also indicative of the role of the straight gyrus in memory.

The present findings in patients supported the hypothesis of an altered memory strategy–brain structure relationship in patients with schizophrenia and schizotypal disorder, relative to control subjects. The present study also showed that the orbitofrontal cortex is associated with semantic clustering in schizophrenic patients. In schizophrenia patients, there was no relationship between inferior frontal gray matter volume and semantic clustering as shown in control subjects. Antonova et al. (2005) have also reported that there was no correlation between inferior frontal volume and verbal memory in patients with schizophrenia, though they did not use an index of memory strategy. The specificity of the present finding may indicate a feature of the relationship between brain structure and memory strategy in patients with schizophrenia. Namely, it is possible

that efficient memory strategy use in schizophrenia patients is related to orbitofrontal cortex rather than inferior frontal cortex, which was predictive in functional neuroimaging studies of nonclinical participants (Demb et al., 1995; Wagner et al., 2001). Consistent with this finding, Gur et al. (2000) found that higher orbitomedial region volume was associated with better verbal memory in female patients with schizophrenia. Ragland et al. (2004) reported that patients overactivated the orbitofrontal cortex during recognition and retrieval success. Heckers et al. (1998) and Weiss et al. (2003) also found frontopolar and orbitofrontal overactivation in schizophrenia. Taken together, these findings suggest that dysfunction in the orbitofrontal cortex might be involved in the memory impairments found in schizophrenic patients. Savage et al. (2001) reported a PET study that measured semantic organization on the California Verbal Learning Test. They identified three prefrontal regions (the inferior frontal gyrus, the dorsolateral prefrontal cortex, and the orbitofrontal cortex) which each appear to make distinct contributions to strategic verbal memory. Savage et al. (2001) found that semantic processing is supported by regions in the left inferior prefrontal cortex, whereas updating, manipulating, and monitoring operations are mediated by the dorsolateral prefrontal cortex. In addition to the above areas, activation in the orbitofrontal cortex increased during verbal encoding. These authors were therefore able to demonstrate the important role of the orbitofrontal cortex in initiating the early mobilization of effective behavioral strategies in novel situations. Based on Savage et al. (2001), our findings suggest that semantic organization in schizophrenic patients may depend on strategy mobilization that is mediated by the orbitofrontal cortex. This finding showed the association between gray matter volume of the orbitofrontal cortex and semantic clustering was specific to schizophrenia patients. In addition, subjective clustering was positively correlated with gray matter volume of the inferior frontal gyrus. This relationship was not seen in controls and schizotypal patients, in which semantic, and not subjective clustering was associated with the inferior frontal volume. This suggests that a more idiosyncratic clustering strategy might be related to higher inferior frontal volume in only patients with schizophrenia. Therefore, the association between inferior frontal gray matter volume and the use of an idiosyncratic strategy, instead of the semantic strategy, may be a characteristic of schizophrenic patients alone. It is suggested that in future studies the neural mechanism of this strategy should be examined by using functional neuroimaging.

On the other hand, associations between any gray matter volume and semantic clustering were lacking in schizotypal patients. Different brain-memory strategy relationships were found for the two patient groups. For schizophrenic patients, smaller orbitofrontal gray matter volumes were related to less use of semantic clustering. This relationship did not occur in schizotypal patients. Moreover, in schizotypal patients, there was no correlation between semantic clustering rate and inferior frontal gray matter volume as was the case in control subjects. However, there was a negative correlation between the semantic clustering rate and inferior frontal white matter volume, whereas there was a positive correlation between serial clustering rate and inferior frontal white matter volume. Semantic clustering rate in patients with schizotypal disorder and schizophrenia was low in comparison to control subjects. In addition, patients with schizotypal disorder had a higher rate of serial clustering than control subjects. This suggests that schizotypal patients failed to use semantic information to facilitate verbal encoding and retrieval, but that they used more superficial encoding strategies in comparison to control subjects. The neurobiological implications of this finding could be related to the finding that gray matter volume of left inferior frontal gyrus was not related to normal semantic memory processing in schizotypal patients. In addition, semantic processing seems to be negatively related to white matter volume of left inferior frontal gyrus and the possibility of some disturbance in the axonal interconnections of the structure should also be considered. The positive correlation between serial clustering rate and inferior frontal white matter volume suggests the operation of a compensation mechanism that is possible initiated when semantic processing cannot be conducted by the gray matter of the inferior frontal gyrus.

These findings must be interpreted with caution, for several reasons. Sample sizes were relatively small, which might restrict the generalization these findings to a larger group. Second limitation of this study is the number of performed tests for the investigation of brain structure-memory strategy relationships. We reduced the chance of false-positive errors by adopting a more conservative p value of 0.025 following Antonova et al. (2005). Because, such severe corrections as Bonferroni method would result in multiple type II errors (Antonova et al., 2005). Furthermore, brain areas other than the frontal lobes (e.g., medial temporal structures) also likely play an important role in memory performance. Future studies should combine functional and structural MRI methods for the study of memory dysfunction to disentangle these possibilities.

In summary, our findings suggest that larger left inferior frontal gray matter volume might be involved in the efficient memory strategy of healthy control subjects. Then, the present findings suggest that memory strategy use deficits in schizophrenic patients may be related to abnormalities in prefrontal lobe structures. More specifically, semantic organization in schizophrenic patients appears to depend on strategy mobilization that is mediated by the orbitofrontal cortex. The results for schizotypal patients suggest the operation of a compensation mechanism, because the inferior frontal gray matter volume was not related to semantic memory processing.

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Association between absence of the adhesio interthalamica and amygdala volume in schizophrenia

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Abstract

Abnormal neurodevelopment in midline structures such as the adhesio interthalamica (AI) has been reported in schizophrenia, but not consistently replicated. We investigated the prevalence and anterior–posterior length of the AI in 62 schizophrenia patients (32 males, 30 females) and 63 healthy controls (35 males, 28 females) using magnetic resonance imaging. We also explored the relation between the AI and volumetric measurements for the third ventricle, medial temporal structures (amygdala, hippocampus, and parahippocampal gyrus), superior temporal sub-regions, and frontal lobe regions (prefrontal area and anterior cingulate gyrus). The AI was absent in 24.2% (15/62) of the schizophrenia patients and in 9.5% (6/63) of the controls, showing a significant group difference. For the length of the AI, schizophrenia patients had a shorter AI than controls, and males had a shorter AI than females. The subjects without an AI had a significantly larger third ventricle and smaller parahippocampal gyrus than the subjects with an AI for both groups. We found a significant diagnosis-by-AI interaction for the amygdala. The schizophrenia patients without an AI had a smaller bilateral amygdala than those with an AI, whereas the AI was not associated with the volume of the amygdala in the control subjects. These findings suggest that the absence of AI in schizophrenia could be a marker of developmental abnormalities in the neural network including the thalamus and connected amygdaloid regions, which may play an important role in the pathogenesis of schizophrenia.

Keywords: Adhesio interthalamica; Massa intermedia; Amygdala; Thalamus; Schizophrenia; Magnetic resonance imaging

1. Introduction

The adhesio interthalamica (AI), or the massa intermedia, is a narrow bridge of glial cells that usually connects the medial surfaces of the thalami on each side of the third ventricle (Kretschmann and Weinrich, 1992). The AI is variable in size among individuals and missing or present just as a remnant in about 20–30% of human brains (Carpenter and Sutin, 1983; Percheron, 2004). Sexual dimorphism is also reported in the AI, which is smaller and more commonly absent in males than in females (Allen and Gorski, 1991). Although the functional significance of the AI in human brain is largely unknown

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(Percheron, 2004), its absence could be a marker of early developmental abnormalities in the midline brain structures because the AI develops during the early gestation period (Rosales et al., 1968; O'Rahilly and Muller, 1990).

In schizophrenia, midline cerebral malformations such as large cavum septi pellucidi (CSP) (Nopoulos et al., 1997b; Kwon et al., 1998; Kasai et al., 2004) or agenesis of the corpus callosum (reviewed by Innocenti et al., 2003) have been reported, possibly reflecting a neurodevelopmental pathology (Weinberger, 1987). With regard to the AI, several magnetic resonance imaging (MRI) studies reported an increased prevalence of its absence in schizophrenia patients compared with control subjects (Snyder et al., 1998; Nopoulos et al., 2001; Erbagci et al., 2002), though the results were not consistently replicated (Meisenzahl et al., 2000, 2002; de Souza Crippa et al., 2006). Meisenzahl et al. (2000, 2002) demonstrated that schizophrenia patients without an AI are characterized by more severe negative symptoms, but others (Nopoulos et al., 2001; Erbagci et al., 2002; de Souza Crippa et al., 2006) did not find a relationship between an absence of the AI and clinical symptomatology. These studies examined principally the prevalence of the AI, but the differences in the definition for the absence/presence of the AI or the imaging techniques (e.g., slice thickness) might have contributed to these inconsistencies. This problem could be partly resolved by also measuring the length or volume of the AI to assess the degree of the midline fusion of the thalami using high-resolution MRI.

The relationship of the AI with abnormalities in other brain structures reported in schizophrenia remains unclear. Previous MRI studies of the CSP in schizophrenia (Kwon et al., 1998; Kasai et al., 2004) suggested a possible relationship between neurodevelopmental abnormalities in midline structures and volume reduction of the medial temporal regions. However, de Souza Crippa et al. (2006) found no overlap between the AI's absence and an enlarged CSP in the same sample of schizophrenia patients, suggesting that these two midline brain abnormalities could not be categorized together. Although the data are not entirely consistent (Erbagci et al., 2002), the absence of the AI in schizophrenia is likely related to the third ventricle's enlargement (Snyder et al., 1998; Meisenzahl et al., 2002). For brain tissue, previous studies found no effect of the absence or presence of the AI on the total brain volume (Nopoulos et al., 2001; Meisenzahl et al., 2002). To our knowledge, however, no brain morphologic studies in schizophrenia have attempted a detailed examination of the association between the AI and volumetric measurements for specific brain regions such as the medial temporal lobe structures.

In the present study, we used MRI to investigate the prevalence and length of the AI in schizophrenia patients and age- and gender-matched healthy controls for whom volumetric measurements of medial temporal lobe structures, frontal lobe structures and superior temporal sub-regions were available. We explored the relation of the AI to the volumes for these structures as well as the third ventricle. Based on previous MRI studies and hypothesized abnormal neurodevelopment in midline and medial temporal lobe structures in schizophrenia, we predicted that absence of the AI would be more common in schizophrenia patients than in controls, and that the absence or presence of the AI would be related to the volume of medial temporal lobe structures and the third ventricle in schizophrenia. We also examined the relationship between the AI and clinical symptoms in schizophrenia patients.

2. Methods

2.1. Subjects

Sixty-two schizophrenia patients [32 males and 30 females, mean age = 25.8 ± 4.9 (S.D.) years (range, 18–36)] were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama University Hospital. All patients fulfilled ICD-10 diagnostic criteria for research on schizophrenia (World Health Organization, 1993). All patients apart from one female were receiving neuroleptic medication; 31 patients were treated with typical neuroleptics and 30 patients were receiving atypical neuroleptics. Clinical symptoms were rated by well-trained psychiatrists at the time of scanning using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). There were no significant differences between the male and female patients in age, age at onset, duration of illness, dosage or duration of neuroleptic medication, or total or subscale scores for the SAPS and SANS.

The control subjects consisted of 63 healthy volunteers (35 males and 28 females) recruited from members of the community (n = 22), hospital staff (n = 13), and university students (n = 28). Their mean age was 24.4 ± 5.4 (S.D.) years (range, 18–38). They were given a questionnaire consisting of 15 items concerning their family, history, and present illness. They did not have any personal or family history of psychiatric illness in their first-degree relatives. The Minnesota Multiphasic Personality Inventory (MMPI) was administered to all the control candidates, and they were excluded if any

T-score for the validity scales or the clinical scales exceeded 70.

Demographic and clinical data of the subjects are presented in Table 1. This cohort largely overlaps with that in our previous MRI studies, which investigated the morphology of temporal and frontal lobe structures in schizophrenia (Niu et al., 2004; Suzuki et al., 2005; Zhou et al., 2005; Takahashi et al., 2006). All subjects were right-handed and physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or substance abuse. The subjects were screened for gross brain abnormalities by the neuroradiologists. However, subjects with a large CSP (3 schizophrenia patients and 3 healthy comparisons) were not excluded from the present study in order to investigate the possible relationship between large CSP and absent AI in the same group of subjects. They were matched for age, gender, height, and parental education. This study was approved by the Committee on Medical Ethics of the University of Toyama. After a complete description of the study, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

MRI scans were acquired with 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. The imaging parameters were as follows: 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 × 1.0 × 1.0 mm^3.

Detailed methods for image processing have been described elsewhere (Takahashi et al., 2002). Briefly, on a Unix workstation (Silicon Graphics, Inc, Mountain View, CA, USA), the image data were processed using the software package Dr View 5.3 (AJS Co, Ltd, Tokyo, Japan). Brain images were realigned in three dimensions to standardize differences in head tilt during image acquisition and were then reconstructed into contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure–posterior commissure line. The whole cerebrum was manually separated from the brainstem and cerebellum. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semi-automatically segment voxels into gray matter, white matter, and cerebrospinal fluid (CSF). The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Zhou et al., 2003).

2.3. Assessment of adhesio interthalamica (AI)

For the assessment of the length of the AI, the number of slices where an AI was clearly seen was counted on consecutive 1-mm coronal slices. Presence or absence of the AI was determined by viewing both coronal and axial 1-mm slices without gaps; when the AI could be identified as a gray matter bridge on three or more slices in

Table 1
Clinical and demographic characteristics of healthy control subjects and patients with schizophrenia

Variable	Healthy controls			Schizophrenia patients		
	All subjects (N=63)	Male (N=35)	Female (N=28)	All subjects (N=62)	Male (N=32)	Female (N=30)
Age (years)	24.4±5.4	24.1±5.1	24.8±5.9	25.8±4.9	25.6±4.8	26.0±5.1
Height (cm)	166.5±7.4	171.9[a]±4.3	159.7±4.1	164.8±7.7	170.7[a]±5.1	158.5±4.0
Education (years)	15.9[b]±2.5	16.6[c]±2.8	15.0±1.7	13.4±1.9	13.5±1.9	13.3±1.9
Parental education (years)	12.8±2.4	13.0±2.3	12.6±2.5	12.1±2.1	12.2±1.9	12.0±2.4
Age at onset (years)	–	–	–	22.0±4.4	22.1±4.5	22.0±4.2
Duration of illness (years)	–	–	–	3.9±4.1	3.5±3.9	4.4±4.3
Duration of medication (years)	–	–	–	2.8±3.3	2.4±2.9	3.3±3.7
Drug (mg/day, haloperidol equivalent)[d]	–	–	–	11.2±9.4	11.7±8.6	10.8±10.4
Total SAPS score	–	–	–	25.2±20.4	23.0±21.1	27.7±19.8
Total SANS score	–	–	–	46.8±23.4	50.0±22.4	43.4±24.4

Values represent means±S.D.s. 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 schizophrenia patients.

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

[d] The different typical and atypical neuroleptic dosages were converted into haloperidol equivalents using the guidelines of Toru (2001).

both coronal and axial views, it was considered present (Fig. 1). A recent MRI study by de Souza Crippa et al. (2006), who used similar imaging parameters to ours, defined the AI of at least two coronal 1-mm slices as present. However, there were only 2/125 (1.6%) subjects whose AI was absent if we adopted their criteria in our sample. We therefore used the above-mentioned method to assess the prevalence of the AI in this study.

The length and the presence or absence of the AI were assessed by one rater (TT), who was unaware of the subjects' identity, gender, and diagnosis. The AI was assessed in a subset of randomly selected 30 brains independently by two raters (TT and KN), and reassessed by the first rater after at least 4 weeks; both intra- and inter-rater intra-class correlation coefficients (ICC) for the length of the AI were over 0.97. For the presence or absence of the AI, intra- and inter-rater reliabilities were 100% (30/30 agreement) and 97% (29/30 agreement), respectively.

2.4. Volumetric analyses of regions of interest (ROIs)

The superior temporal sub-regions [Heschl's gyrus, planum temporale, and caudal superior temporal gyrus (STG)], the frontal lobe structures (prefrontal cortex and anterior cingulate gyrus), the medial temporal lobe structures (amygdala, hippocampus, and parahippocampal gyrus), and the third ventricle were manually traced on consecutive coronal 1-mm slices with the corresponding sagittal and axial planes simultaneously presented for reference. We selected these ROIs because of significant volume reductions in schizophrenia as demonstrated in our previous publications (Niu et al., 2004; Suzuki et al., 2005; Zhou et al., 2005; Takahashi et al., 2006) and the hypothesis that the abnormal neurodevelopment in midline structures would be related to the morphology in medial temporal lobe structures and the third ventricle.

Detailed delineation methods for the temporal (Niu et al., 2004; Suzuki et al., 2005; Takahashi et al., 2006) and frontal (Suzuki et al., 2005; Zhou et al., 2005) ROIs have been described elsewhere. The gray matter volumes of the superior temporal sub-regions and the frontal lobe structures were obtained by using the above-mentioned segmentation procedure. For the medial temporal lobe structures, volumes of gray and white matter were measured together.

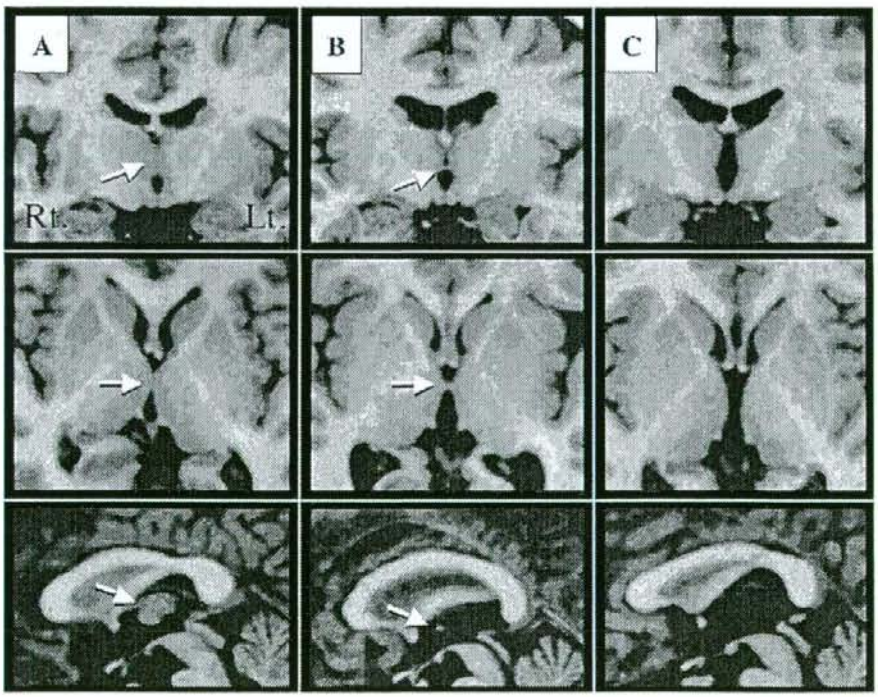

Fig. 1. Coronal (upper), axial (middle), and midsagittal (lower) views of the T1-weighted MR images (1-mm slice thickness) in subjects with (A) and without (B, C) the adhesio interthalamica (AI). Arrows indicate the position of the AI. Subject B has a narrow connection of two coronal slices (2 mm) between the thalami but was without an AI according to our definition (see text).

The third ventricle was traced on the segmented CSF images based on the delineation method by Erbagci et al. (2002). The posterior border was defined as the slice on which the superior colliculi first fuse with the cerebrum and the anterior border where the lower portion of the ventricle opens into CSF of the outer brain surface. The ventricle was bounded laterally by the thalamus and superiorly by the crus of the fornix and the medial processes of the dorsomedial nucleus of the thalamus.

Intra- and inter-rater ICCs for volumetric analyses in a subset of five randomly selected brains were over 0.92 for all ROIs.

2.5. Statistical analysis

Chi-square tests, or Fisher's exact tests when expected cell sizes were below five, were used to assess the frequency of the AI. The length of the AI and the absolute volume of the third ventricle were analyzed using repeated measures multivariate analysis of covariance (MANCOVA) with ICV and age as covariates, and with diagnosis (schizophrenia patients, control subjects) and gender (male, female) as between-subject factors.

To explore the relation of the AI with the temporal and frontal regions as well as the third ventricle, the relative ROI volumes (100 × absolute volume/ICV) were analyzed using repeated measures MANCOVA with age as a covariate, and diagnostic group and the AI (presence versus absence) as between-subject factors. Male and female subjects were not separately treated for these analyses because the AI was absent for only three females (two patients and a control subject). For the temporal and frontal regions, hemisphere (left, right) was treated as a within-subject variable. Because of a significant diagnosis-by-AI interaction, the volumes of the amygdala and the anterior cingulate gyrus were then separately analyzed for each diagnostic group using repeated measures MANCOVA with only the AI as a between-subject factor. For the schizophrenia group, age, illness duration, duration of neuroleptic medication, and medication dosage were used as covariates. A post hoc Scheffé's test was employed to follow up the significant main effects yielded by these analyses. The correlation between the length of the AI and the relative ROI volumes in schizophrenia was examined using Pearson's partial correlation controlling for age, illness duration, duration of neuroleptic medication, and medication dosage. The same model but with only age as a control variable was adapted to the control subjects.

The relationship between the AI and the scores for the subscales of SAPS and SANS in schizophrenia was assessed using repeated measures MANCOVA with the AI as a between-subject factor. Pearson's partial correlation was also calculated between the length of the AI and these scores. For these analyses, age, illness duration, duration of neuroleptic medication, and medication dosage were used as control variables. Statistical significance was defined as $P < 0.05$ (two-tailed).

3. Results

Table 2 shows the measurements of the AI. The AI was absent in 15/62 schizophrenia patients (24.2%, 13 males and two females) and in 6/63 control subjects (9.5%, five males and one female), showing a significant group difference (chi-square = 4.81, $P = 0.028$). Its absence was significantly more common in males than in

Table 2
Prevalence and length of the adhesio interthalamica (AI) in healthy comparisons sujects and patients with schizophrenia

Subjects	AI absent [a]	AI length (mm) [b]	AI length (number of 1-mm coronal slices)											
			0	1	2	3	4	5	6	7	8	9	10	>11
	N (%)	Means±S.D.s	*N*											
Healthy controls (*N*=63)	6 (9.5)	9.2±3.2[c]	0	0	2	3	2	2	4	6	4	5	8	27
Male (*N*=35)	5 (14.3)	8.2±3.4	0	0	2	3	1	2	1	6	2	4	5	9
Female (*N*=28)	1 (3.6)	10.4±2.6[d]	0	0	0	0	1	0	3	0	2	1	3	18
Schizophrenia patients (*N*=62)	15 (24.2)[e]	6.7±3.4	2	0	6	6	6	3	7	6	8	2	5	11
Male (*N*=32)	13 (40.6)[f]	5.1±3.1	2	0	4	5	6	2	5	2	1	0	3	2
Female (*N*=30)	2 (6.7)	8.3±2.9[d]	0	0	2	1	0	1	2	4	7	2	2	9

[a] Chi-square test or Fisher's exact test was used.
[b] MANCOVA followed by Scheffé's test was used.
[c] $P<0.01$: compared with schizophrenia patients.
[d] $P<0.01$: compared with males.
[e] $P<0.05$: compared with controls.
[f] $P<0.01$: compared with female schizophrenia patients.

Table 3
Relative volume for regions of interest in subjects with or without an adhesio interthalamica (AI)

Brain region	Healthy controls		Schizophrenia patients		Analysis of covariance (df=1, 120)					
	Present AI	Absent AI	Present AI	Absent AI	Effect of AI		Effect of diagnosis		Diagnosis × AI	
	(N=57)	(N=6)	(N=47)	(N=15)	F	P	F	P	F	P
Third ventricle	0.102±0.036	0.141±0.022	0.110±0.038	0.179±0.068	20.35	<0.001	3.47	0.064	1.22	0.271
Heschl's gyrus GM					0.04	0.848	1.43	0.235	0.95	0.331
Left	0.138±0.033	0.141±0.044	0.121±0.034	0.125±0.035						
Right	0.110±0.034	0.088±0.015	0.096±0.027	0.096±0.034						
Planum temporale GM					0.02	0.877	8.41	0.004	0.25	0.619
Left	0.206±0.049	0.185±0.044	0.160±0.032	0.163±0.039						
Right	0.150±0.046	0.155±0.027	0.136±0.034	0.122±0.046						
Caudal STG GM					0.81	0.371	25.74	<0.001	0.80	0.373
Left	0.322±0.071	0.338±0.091	0.246±0.061	0.228±0.082						
Right	0.278±0.072	0.309±0.054	0.236±0.053	0.238±0.058						
Prefrontal cortex GM					1.48	0.227	3.94	0.050	0.24	0.624
Left	6.398±0.576	6.249±0.197	6.144±0.585	5.741±0.542						
Right	6.143±0.580	5.986±0.351	5.961±0.577	5.474±0.652						
Anterior cingulate gyrus GM					1.18	0.279	0.05	0.83	7.53	0.007
Left	0.292±0.114	0.230±0.095	0.250±0.094	0.285±0.114						
Right	0.386±0.107	0.293±0.116	0.331±0.096	0.319±0.109						
Amygdala					0.92	0.339	21.45	<0.001	4.02	0.047
Left	0.075±0.009	0.077±0.007	0.068±0.009	0.061±0.010						
Right	0.077±0.010	0.079±0.007	0.072±0.009	0.066±0.009						
Hippocampus					2.60	0.109	0.13	0.718	0.17	0.681
Left	0.201±0.022	0.194±0.017	0.197±0.025	0.186±0.018						
Right	0.216±0.020	0.199±0.019	0.211±0.026	0.200±0.017						
Parahippocampal gyrus					8.80	0.004	1.66	0.199	0.51	0.478
Left	0.478±0.051	0.451±0.031	0.489±0.047	0.459±0.046						
Right	0.490±0.048	0.438±0.034	0.491±0.039	0.467±0.045						

AI, adhesio interthalamica; GM, gray matter; STG, superior temporal gyrus.
Values represent means± S.D.s.
Relative volumes were calculated as follows: 100×absolute volume/intracranial volume. Absolute volumes for the STG (Takahashi et al., 2006), medial temporal structures (Niu et al., 2004; Suzuki et al., 2005), and frontal regions (Suzuki et al., 2005; Zhou et al., 2005) in a largely overlapping sample were published elsewhere.

females for schizophrenia patients ($P = 0.002$, Fisher's exact test) but not for controls ($P = 0.150$, Fisher's exact test). In this study, only one subject (male schizophrenia patient) presented both AI absence and large CSP. For the AI's length in the coronal direction, MANCOVA revealed significant main effects for group ($F = 22.45$, $df = 1, 119$, $P < 0.001$) and gender ($F = 8.03$, $df = 1, 119$, $P = 0.005$). Post hoc Scheffé's tests demonstrated that the schizophrenia patients had a shorter AI than controls ($P < 0.001$) and males had a shorter AI than females ($P < 0.001$). MANCOVA of the third ventricle revealed a significant main effect for group ($F = 6.46$, $df = 1, 119$, $P = 0.012$), where the third ventricle was significantly larger in the schizophrenia patients than in the controls (Scheffé's test, $P = 0.006$).

Table 3 shows a comparison of the relative ROI volumes between the subjects with and without an AI. A significant main effect of AI was revealed for the parahippocampal gyrus and the third ventricle, with the subjects missing an AI having a bilaterally smaller parahippocampal gyrus and larger third ventricle than the subjects with an AI (Scheffé's test, $P<0.001$ for both regions). A significant diagnosis-by-AI interaction was demonstrated for the amygdala and the anterior cingulate gyrus, showing that the AI affects these regions differently in each diagnostic group. Lower order MANCOVA of the amygdala for only schizophrenia patients revealed a significant main effect of AI ($F=4.39$, $df=1, 56$, $P=0.041$), where the patients without an AI had a smaller bilateral amygdala than those with an AI (Scheffé's test, $P=0.024$). However, there was no significant effect of AI for the volume of the amygdala in the control subjects ($F=0.36$, $df=1, 60$, $P=0.552$). In contrast, lower order MANCOVA of the anterior cingulate gyrus revealed a main effect of the AI only for the control subjects ($F=4.75$, $df=1, 60$, $P=0.033$); the healthy controls with an AI had a larger volume of the anterior cingulate gyrus than the controls without an AI (Scheffé's test, $P=0.022$).

Correlational analyses between the length of the AI and ROI volumes were adopted only for the amygdala based on the results of the above-mentioned MANCOVA analyses in order to prevent a possible type I error. The length of the AI was weakly correlated with the relative volume of the amygdala in schizophrenia patients (left, $r=0.29$, $P=0.028$; right, $r=0.29$, $P=0.027$) but not in control subjects (left, $r=0.09$, $P=0.485$; right, $r=0.11$, $P=0.400$).

For the clinical correlations, MANCOVA revealed a significant main effect of AI only for the score for avolition–apathy of the SANS ($F=4.33$, $df=1, 56$, $P=0.042$), with the patients missing an AI having higher scores than those with an AI. There were weak negative correlations between the length of the AI and the scores for alogia ($r=-0.28$, $P=0.035$) and avolition–apathy ($r=-0.27$, $P=0.045$) of the SANS, but these were not significant after Bonferroni corrections for multiple comparisons.

4. Discussion

In this study, we found that the adhesio interthalamica (AI) was more often absent and significantly shorter in the schizophrenia patients than in control subjects. The schizophrenia patients without an AI had significantly smaller bilateral amygdala volumes than the patients with an AI, but the AI was not related to the volume of the amygdala in the control subjects. Correlational analyses also supported that the relationship between the length of the AI and amygdala volume was specific to schizophrenia. These findings suggest that the absent or shorter AI of schizophrenia could be a marker of early developmental abnormalities in the midline brain structures as well as in the amygdala, which may play an important role in the pathogenesis of schizophrenia (Kurachi, 2003).

The prevalence of an absent AI in this study (24.2% in the schizophrenia patients and 9.5% in the controls) was comparable with that in previous MRI studies [18.4–34.6% in the patients and 10.5–22.3% in the controls (Snyder et al., 1998; Meisenzahl et al., 2000, 2002; Nopoulos et al., 2001; Erbagci et al., 2002; de Souza Crippa et al., 2006)]. Nevertheless, differences among these studies in imaging techniques, criteria used to define the AI as absent/present, and sample characteristics make it difficult to compare the data directly. For example, several studies defined the AI as present if it could be identified in at least two coronal slices (Snyder et al., 1998; Nopoulos et al., 2001; Erbagci et al., 2002; de Souza Crippa et al., 2006), but differences in slice thickness might lead to conflicting results. In fact, two MRI studies with relatively thick slices (3 mm), which could potentially miss a narrow connection between the thalami, reported a higher prevalence of the absent AI especially for schizophrenia patients (Snyder et al., 1998; Erbagci et al., 2002). Three studies used both coronal and axial views to define the AI (Meisenzahl et al., 2000, 2002; Nopoulos et al., 2001), while the others used only the coronal slices (Snyder et al., 1998; Erbagci et al., 2002; de Souza Crippa et al., 2006). A difference in gender ratios or ethnicity of the sample among the reports is also an important consideration, because interethnic differences in brain morphology were reported (Zilles et al., 2001), and there seem to be gender differences in the degree or

pattern of brain morphologic abnormalities in schizophrenia (Nopoulos et al., 1997a; Lawrie and Abukmeil, 1998; Pearlson and Marsh, 1999). Sexual dimorphism of the prevalence of the AI in healthy subjects has also been reported (Allen and Gorski, 1991). Out of six previous MRI studies of the AI in schizophrenia, however, four have included only male (Meisenzahl et al., 2000, 2002) or many more male than female (Snyder et al., 1998; de Souza Crippa et al., 2006) subjects. In order to eliminate these methodological problems, we assessed the absence/presence of the AI in both coronal and axial directions and also measured the anterior–posterior length of the AI using 1-mm thick continuous slices in a relatively large sample balanced by gender. As mentioned earlier, we found only 2/125 subjects to be without an AI (two male schizophrenia patients) if we defined the AI as present when it was identified in at least two coronal slices (2 mm). We therefore considered the narrow connection of 2 mm or less between the thalami to be just a remnant (Percheron, 2004), and defined the AI as present if it was found in at least three slices for both coronal and axial views. With regard to the gender effects, our results suggest a gender by diagnostic interaction, with only the male patients with schizophrenia having an increased frequency of absent AI as compared with healthy comparisons.

The principal focus of this study is the relationship between the AI and volumetric measurements for other brain regions. The subjects without an AI had a significantly larger third ventricle and smaller parahippocampal gyrus than those with an AI for both schizophrenia and healthy individuals. These findings support the notion that the AI develops in concert with prominent features of the ventricular system (O'Rahilly and Muller, 1990; Snyder et al., 1998) and further imply the interaction between the AI and the parahippocampal gyrus in normal neurodevelopment during early gestation. In schizophrenia, the patients without an AI had a smaller bilateral amygdala than those with an AI, while the AI was not related to the volume of the amygdala in the control subjects. The schizophrenia patients were also characterized by a lack of a normal relationship between the AI and anterior cingulate gyrus volume. Interestingly, the midline nuclei of the thalamus including the AI might have efferent connections with the amygdaloid nuclei and the anterior cingulate cortex (Graff-Radford, 1997). Animal studies have shown that the AI is involved in regulating the release of dopamine in the basal ganglia (Cheramy et al., 1984; Romo et al., 1984), and the dopaminergic system of the primate thalamus, which influences the activity of the amygdaloid regions, is implicated in higher brain functions (Sanchez-Gonzalez et al., 2005). It seems tempting to speculate that disturbed neural networks including these regions during early neurodevelopment and consequent dopaminergic abnormalities contribute to the pathogenesis of schizophrenia. However, this notion could only be tentatively asserted because the role of the AI in humans is largely unknown as discussed below. Of note, we found no association of the AI with the superior temporal gyrus and frontal lobe structures in schizophrenia, where neurodegenerative processes have been suggested from the progressive changes in volume after the onset of the illness (Gur et al., 1998; Ho et al., 2003; Kasai et al., 2003a, b). Our finding of a specific association between the AI and the amygdala in schizophrenia is consistent with the hypothesis that the abnormalities of medial temporal lobe structures in schizophrenia are related to an abnormal neurodevelopment of midline structures (Kwon et al., 1998; Kasai et al., 2004). Although we found little overlap between the absence of an AI and an enlarged CSP in our sample of schizophrenia patients, the patients with a large CSP also had smaller volumes of bilateral amygdala than those without (Takahashi et al., in submission). The amygdala is one of the major structures that have received the most attention in the search for the neural substrate of schizophrenia. A significant reduction in the volume of the amygdala has been demonstrated in a number of MRI studies on schizophrenia (Shenton et al., 2001). Malfunctioning of the amygdala and related regions has been implicated in the cardinal features of schizophrenia such as positive Schneiderian symptoms, cognitive characteristics, and deficits in social behavior (Kurachi, 2003). Our findings further support the structural aberration of the amygdala in schizophrenia to be at least partly neurodevelopmental in origin.

In this study, we found a weak correlation between negative symptoms and the AI in schizophrenia patients. Together with previous reports by Meisenzahl et al. (2000, 2002), the present finding may support the hypothesis by Andreasen et al. (1994) that the variety of symptoms in schizophrenia could be explained by abnormalities in midline neural circuits. However, it is rather difficult to interpret the clinical symptomatology of schizophrenia in view of the role of the AI. The AI is well developed in mammals as a neural pathway between the thalami and motor, premotor, and prefrontal areas, but highly regressive and of negligible functional significance in humans (Allen and Gorski, 1991; Percheron, 2004). Although similar associations with the negative symptoms of schizophrenia have been found for the corpus callosum, another midline structure involved in inter-hemispheric connectivity (Günther

et al., 1991; Tibbo et al., 1998), the functional relevance of the AI to the psychopathology of the illness remains obscure.

A few possible confounding factors in the present study should be taken into account. First, the small number of healthy subjects without an AI ($n=6$) limited our ability to generalize the finding of the present study. The results of this study should be confirmed by an additional study with a large number of subjects without an AI. Second, the absence of an AI in this study may not be fully explained by abnormal neurodevelopment, because the AI undergoes increasing atrophy especially after the third decade and even disappears in older individuals (Rosales et al., 1968). We included relatively young subjects in this study to reduce the confounding factors concerning age, but found a negative correlation between the length of the AI and age for both groups (healthy controls, $r=-0.33$, $P=0.007$; schizophrenia patients, $r=-0.37$, $P=0.003$). Although we optimally matched age between the groups and also used age as a control variable in all analyses, the effects of age might have affected the results. A third limitation is related to the sample characteristics. The subjects in this study were not matched for parental socioeconomic level, which may influence brain development. We optimally matched parental education between the groups, but various environmental factors related to lower social classes such as obstetric complications, prenatal infections, and nutritional deprivation might have biased the results of this study. For the schizophrenia patients, most patients in this study were on neuroleptic medication, which could influence the volumetric results (Keshavan et al., 1994, 1998; Chakos et al., 1995; Gur et al., 1998). However, in this study, the dosage or duration of neuroleptic medication was not correlated with any of the measurements of volume or the length of the AI. When the patients were divided into two groups based on the type of neuroleptic medication (typical versus atypical), the two groups did not differ significantly in the length or the prevalence of the AI (data not shown). In addition, the effects of medication alone could not easily explain the specific correlation between the AI and the volume of the amygdala found in schizophrenia. In addition to these limitations, we did not measure the volume of the thalamus, which could directly influence the development of the AI, because it was difficult to accurately define the thalamic boundaries on T1-weighted MR images. Future studies with voxel-based morphometry or an ROI approach should search for the association between the thalamus volume and AI.

In conclusion, we found an increased prevalence of an absent AI and a specific association between the AI and the volume of the amygdala in schizophrenia patients. The findings of this study suggest that the absent AI of schizophrenia could be a marker of early developmental abnormalities in the midline brain structures as well as in the amygdala, which is thought to be a key structure in a neural circuit that underlies the pathogenesis of the illness.

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