System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence, FLASH (fast low-angle shots), yielding 160–180 contiguous T1-weighted slices of 1.0 mm thickness in the sagittal plane. Imaging parameters were 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. The images were transferred to a Unix workstation (Silicon Graphics, Inc., Mountain View, CA, USA) and processed with the software package Dr. View 5.0 (Asahi Kasei Joho System Co., Ltd., Tokyo, Japan). The methods used for image processing have been described in detail elsewhere (Takahashi et al., 2002). Briefly, the scans were realigned in three dimensions to standardize for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure and posterior commissure (AC–PC) line. The signal-intensity histogram distributions from the T1-weighted images across the whole brain for each subject were used to segment the voxels semiautomatically into gray matter, white matter, and cerebrospinal fluid (CSF), according to the Alpert algorithm (Alpert et al., 1996). Before volumetric analysis, masks were semiautomatically 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. Magnetic field inhomogeneity in our scanner was monitored with weekly phantom scanning and daily basic control, and remained stable over the MR acquisition time. No visible effect on quality of segmentation was detected in any of the cases.

2.3. Volumetric measurements of regions of interest (ROIs)

For the first phase of the series, the whole frontal lobe was demarcated and then subdivided into three large functional parts: PCG (M1), cingulate gyrus (the limbic area), and prefrontal area (the cognitive area) (Fig. 1). All the volumetric measurements for all the regions of interest (ROIs) were performed in reformatted consecutive 1-mm-thick coronal slices (voxel size=1.0×1.0×1.0 mm). ROIs were defined mainly based on the intrinsic anatomical landmarks, which were largely the same as those applied by the Iowa group (Crespo-Facorro et al., 1999), with minor modifications. Below are the brief descriptions for the delineation methods on coronal slices.

2.3.1. Whole frontal lobe

On the lateral surface of the hemisphere, the posterior boundary was the central sulcus; on the medial wall, the callosal sulcus (CS) constituted the inferior boundary. Delineation began with the most rostral coronal slice that contained brain tissue and included all the tissues until the body of the corpus callosum (CC) appeared. After that, straight lines, which successively linked the marked points when they existed (i.e., the deepest point of the dorsal CS, the superior end of the circular sulcus of the insula, the inferior end of the circular sulcus of the insula, and the deepest point of the ventral CS), were used to remove the brain tissue inside this circle (i.e., basal ganglia, insular gyrus, white matter around them, and CC). More caudally, after the central sulcus appeared, a straight line that linked the deepest point of the central sulcus to that of the CS was used to demarcate the frontal lobe from the rest, until the central sulcus reached the most dorsomedial point; the coronal slice at this point corresponded to the most caudal slice that contained the frontal lobe tissue.

2.3.2. Precentral gyrus

The anterior and posterior boundaries were the precentral sulcus and the central sulcus, respectively. On the medial surface of the hemisphere, when the precentral sulcus did not extend to the cingulate sulcus, the paracentral sulcus was used as the anterior boundary (Crespo-Facorro et al., 1999); the inferior boundary was the cingulate sulcus. The delineation procedure on the coronal slices was as follows: (1) the inner boundary (which separated the PCG from the inner rest of the brain) was the inferior precentral sulcus when it existed; otherwise, a straight line that linked the deepest point of the superior precentral sulcus with that of the central sulcus was used; (2) the inferior boundary for the first several rostral slices was the Sylvian fissure and, after that, it became the inferior precentral sulcus (when it did not extend to the Sylvian fis-

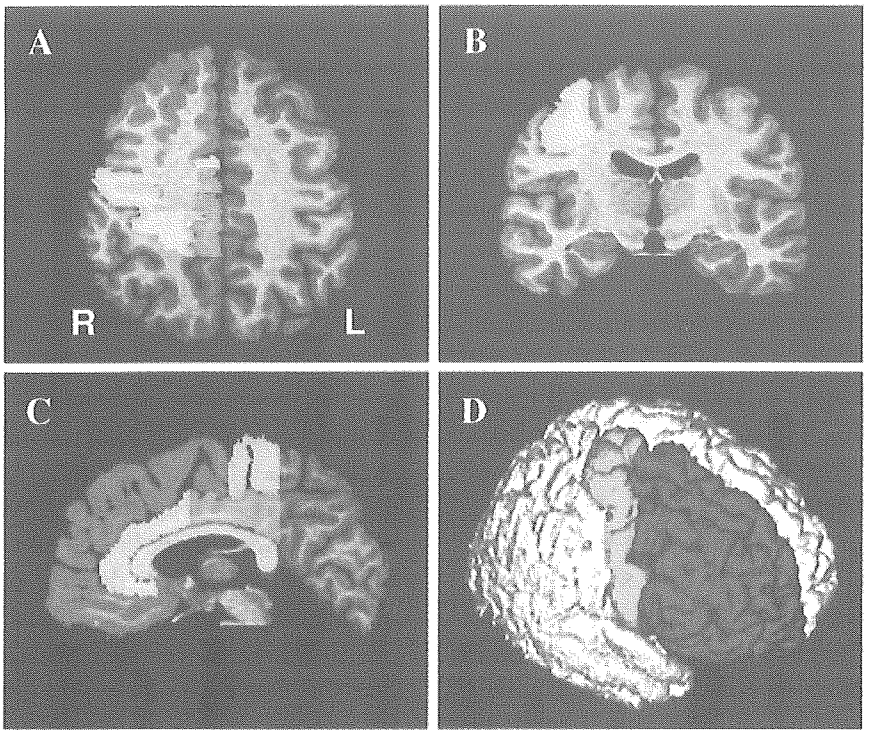

Fig. 1. Views of the frontal lobe regions of interest. (A–C). One set of the synchronous–orthogonal views in three dimensions (A, transaxial; B, coronal; C, sagittal); transaxial and sagittal views were automatically reconstructed when the delineation was performed on consecutive coronal slices. (D) The three-dimensional reconstructed image of the regions of interest. Regions are displayed in distinctive colors: the precentral gyrus in red, prefrontal region in blue, anterior cingulate in pink, and posterior cingulate in green. L, left hemisphere; R, right hemisphere.

sure, the anteriormost subcental sulcus was used; Kates et al., 2002); more caudally, when the central sulcus appeared, it was used as the inferior boundary; and (3) the superior boundary was the precentral sulcus; when two segments of the precentral sulcus appeared on a single coronal slice, the upper one was taken (Crespo-Facorro et al., 1999).

2.3.3. Cingulate gyrus

Delineation of the cingulate gyrus was performed within the range of the frontal lobe. The boundaries were the CS and the cingulate sulcus; a straight line that linked the deepest points of these two sulci was used for demarcation. In cases when the cingulate sulcus was segmented, we followed the rules of the Iowa group (Crespo-Facorro et al., 1999). Differing from them, however, the paracingulate gyrus, when extant, was not included; the principle for judgment of the existence of the paracingulate gyrus was same as in our previous study (Takahashi et al., 2002). In the present study, the cingulate gyrus was further subdivided into the anterior part (AnCiG; Brodmann's area [BA] 24) and the posterior part (PoCiG; BA23 and BA31) at the coronal level of the center of the anterior commissure, according to Talairach and Tournoux (1988), because of the lack of a gross anatomical boundary between them.

2.3.4. Prefrontal area

At present, we temporarily defined the portion of the frontal lobe other than the PCG and cingulate gyrus as the prefrontal area (Fig. 1). On the lateral surface, this area comprises the tissue rostral to the precentral sulcus; on the medial surface, the tissue dorsal to the cingulate sulcus and rostral to the medial extension of the precentral sulcus (or the paracentral sulcus, see Section 2.3.2); on the ventral surface, it covers the whole ventral structure of the frontal lobe (i.e., the straight gyrus and orbitofrontal gyri). In the present study, we did not separate the supplementary motor area (medial BA6) and the premotor area (lateral BA6) from the prefrontal area because of the absence of intrinsic boundaries demarcating these areas; this,

as well as further subdividing the prefrontal area into multiple units, remains a topic for future works.

2.3.5. Regional white matter

Regional white matter was also defined, which corresponded to the white matter involved in each ROI as defined above, and white matter volume was calculated automatically by applying a subprogram of Dr. View, which performed a calculation of 'logic and' between the ROI of a specific subregion and the whole cerebral white matter. Thus, on each coronal slice, the white matter for each ROI corresponded to the portion that was surrounded by the gyral cortex and the straight line that linked the deepest points of the landmark sulci. Before this calculation, the ROI of the whole cerebral white matter was obtained by applying the segmentation procedure as described in Section 2.2.

All measurements were performed by one rater (S.Z.), without knowledge of subjects' identity. The intrarater reliability was established by rating five subjects randomly sampled from the whole subject group; the interrater reliability was also established by independent ratings of five subjects by two skilled raters who were familiar with brain anatomy (S.Z. and H.H.). Before the intraclass correlation coefficients (ICC) were calculated, raters practised on another set of brains. The ICCs were over 0.95 for the whole frontal lobe and whole frontal white matter, 0.94 for the PCG, 0.93 for the AnCiG, and 0.96 for the PoCiG.

2.4. Statistical analysis

Statistical differences in the regional volumetric measures were analyzed for each ROI, using repeated measures multivariate analysis of variance (MANOVA) with intracranial volume (ICV) and age as covariates; group (patients, controls) and gender (male, female) as between-subject factors; and hemisphere (right, left) as a within-subject factor. Post hoc Tukey's honestly significant difference tests were used to follow up the significant main effects or interactions. Correlations between the volumetric measures and the severity of clinical symptoms in the SAPS and SANS were examined within a subgroup of patients (16 males and 22 females) with active psychotic symptoms who had at least one item of the SAPS rated as not less than 3 (moderate). To control for the differences in head size, relative values of regional volume ($100 \times$ regional volume/ICV) were used for all correlation analyses. Statistical significance was defined as $P<0.05$ (two-tailed).

3. Results

3.1. Volumes of regions of interest

Tables 2 and 3 present the regional gray matter and white matter volume measures, and the results of volume comparisons between groups, respectively.

3.1.1. Gray matter

MANCOVA revealed significant group effects in the cortices of the whole frontal lobe ($F=9.59$, $df=1,111$, $P=0.002$), prefrontal area ($F=4.70$, $df=1,111$, $P=0.032$), AnCiG ($F=6.79$, $df=1,111$, $P=0.010$), PoCiG ($F=15.46$, $df=1,111$, $P<0.001$), and PCG ($F=8.99$, $df=1,111$, $P=0.003$). Post hoc analysis showed that the significant cortical volume reduction for the AnCiG was unilateral (right side), while that for the other ROIs was bilateral.

Significant main effects of hemisphere were shown in the cortices of all ROIs. Post hoc analysis revealed that, except for the AnCiG and PoCiG (left smaller than right), ROIs in the left hemisphere were larger than in the right. A significant interaction of gender-by-hemisphere was also shown in the cortices of the whole frontal lobe and prefrontal area (post hoc: males larger than females bilaterally).

3.1.2. White matter

Except for the PoCiG ($F=5.77$, $df=1,111$, $P=0.018$; post hoc $P<0.01$ bilaterally), no significant main effect of diagnosis was shown in any other ROI. Significant main effects of gender and hemisphere were detected in the whole frontal lobe, prefrontal region, and PCG (post hoc tests, males larger than females bilaterally, and right larger than left). Main effects of gender in the AnCiG and of hemisphere in the PoCiG were also significant (post hoc tests, males larger than females bilaterally, and left larger than right).

Table 2
Gray matter volumes of the frontal lobe regions

Region of interest	Schizophrenia patients		Normal control subjects	
	Male ($n=31$)	Female ($n=28$)	Male ($n=30$)	Female ($n=28$)
Whole frontal lobe*,**,***,#				
Left	123.08 ± 14.05	110.83 ± 14.12	130.35 ± 12.68	118.92 ± 9.60
Right	118.95 ± 13.67	108.53 ± 13.18	125.41 ± 12.73	116.20 ± 8.63
Precentral gyrus*,**,#				
Left	18.55 ± 2.62	17.75 ± 2.63	20.06 ± 2.36	18.83 ± 1.73
Right	17.58 ± 2.21	16.64 ± 2.59	19.07 ± 2.80	17.89 ± 1.58
Cingulate gyrus (CinG)*,**,#				
Left	8.13 ± 1.76	7.47 ± 1.86	8.92 ± 2.29	8.77 ± 2.36
Right	9.49 ± 2.16	8.80 ± 1.73	10.65 ± 2.17	10.49 ± 1.45
Anterior CinG†,**,‡				
Left	3.98 ± 1.42	3.60 ± 1.49	4.20 ± 1.75	4.33 ± 1.89
Right	5.32 ± 1.74	4.55 ± 1.18	5.74 ± 1.81	5.71 ± 1.36
Posterior CinG *,§,#				
Left	4.15 ± 0.93	3.87 ± 0.85	4.72 ± 0.94	4.44 ± 0.83
Right	4.16 ± 1.28	4.25 ± 0.92	4.91 ± 0.74	4.77 ± 0.70
Prefrontal area†,**,***,#				
Left	96.40 ± 11.73	85.61 ± 11.02	101.37 ± 10.66	91.32 ± 8.52
Right	91.88 ± 11.23	83.09 ± 11.34	95.68 ± 10.81	87.82 ± 8.25

Values represent mean ± S.D. (cm^3); MANCOVA, multivariate analysis of covariance (see Methods).

* MANCOVA revealed a significant main effect of diagnosis ($F>8.99$, $df=1,111$, $P<0.005$).

** MANCOVA revealed a significant main effect of hemisphere ($F>39.01$, $df=1,113$, $P<0.001$).

*** MANCOVA revealed a significant gender-by-hemisphere interaction ($F>8.39$, $df=1,113$, $P<0.005$); post hoc Tukey's test showed significant difference between genders bilaterally ($P<0.001$).

\# Post hoc Tukey's test showed significant reduction in schizophrenia patients ($P<0.001$ bilaterally).

† MANCOVA revealed a significant main effect of diagnosis ($F>4.69$, $df=1,111$, $P<0.05$).

‡ Post hoc Tukey's test showed significant reduction in schizophrenia patients ($P=0.033$ on the right side).

§ MANCOVA revealed a significant main effect of hemisphere ($F=6.76$, $df=1,113$, $P=0.01$).

3.2. Relationships between volumetric measures and clinical variables

Cortical volumes of the whole frontal lobe (controls: left, $r=-0.31$, $df=57$, $P=0.017$; right, $r=-0.36$, $df=57$, $P=0.010$; patients: left, $r=-0.39$, $df=58$, $P=0.002$; right, $r=-0.45$, $df=58$, $P<0.001$) and prefrontal region (controls: left, $r=-0.28$, $df=57$, $P=0.035$; right, $r=-0.28$, $df=57$, $P=0.033$; patients: left, $r=-0.37$, $df=58$, $P<0.005$; right, $r=-0.45$, $df=58$, $P<0.001$) had significant negative correlations with age at scanning in both the patient group and the comparison group. In the patient group, cortical volumes of the whole frontal lobe (left, $r=-0.43$, $df=57$, $P=0.001$; right, $r=-0.47$, $df=57$, $P<0.001$) and prefrontal region (left, $r=-0.45$, $df=57$, $P<0.001$; right, $r=-0.49$, $df=57$, $P<0.001$) also had significant negative correlations with duration of illness. However, they did not remain significant when partial correlation controlling for age was applied. No significant correlations were found between any volumetric measures and clinical characteristics (i.e., age at onset, duration of antipsychotic medication, or dose of drugs).

Significant or near significant (trends) correlations between regional cortex volumes and symptom severities included the following: right PCG and the total score on the SAPS ($r=-0.32$, $df=36$, $P=0.049$), left PCG and SAPS subscore of bizarre behavior ($r=-0.32$, $df=36$, $P=0.052$); left PCG ($r=-0.28$, $df=36$, $P=0.085$) as well as the right PoCiG ($r=-0.28$, $df=36$, $P=0.089$) and SANS subscore of apathy; left AnCiG ($r=-0.31$, $df=36$, $P=0.060$) and the subscore of verbal hallucinations (by adding SAPS items 2 and 3).

The white matter volume of the right AnCiG was found to be correlated with the SANS subscore of attention deficits ($r=-0.337$, $df=36$,

Table 3
White matter volumes of the frontal lobe regions

Region of interest	Schizophrenia patients		Normal control subjects	
	Male (n=31)	Female (n=28)	Male (n=30)	Female (n=28)
Whole frontal lobe*,**,***				
Left	71.86 ± 13.35	67.00 ± 8.59	74.79 ± 12.17	67.71 ± 9.79
Right	78.53 ± 15.40	70.25 ± 10.03	79.80 ± 13.77	70.53 ± 11.54
Precentral gyrus*,**,***				
Left	12.00 ± 2.55	11.63 ± 1.66	12.99 ± 2.03	11.64 ± 1.59
Right	13.94 ± 3.48	12.81 ± 1.91	14.59 ± 2.64	12.54 ± 2.17
Cingulate gyrus (CinG)#,*				
Left	2.96 ± 0.80	2.66 ± 0.61	3.19 ± 0.75	2.88 ± 0.56
Right	2.68 ± 0.90	2.40 ± 0.54	3.11 ± 0.72	2.67 ± 0.53
Anterior CinG**				
Left	1.03 ± 0.39	0.85 ± 0.33	1.02 ± 0.34	0.97 ± 0.35
Right	1.04 ± 0.54	0.90 ± 0.31	1.19 ± 0.48	1.03 ± 0.29
Posterior CinG#,*				
Left	1.93 ± 0.54	1.81 ± 0.40	2.18 ± 0.52	1.91 ± 0.35
Right	1.64 ± 0.47	1.50 ± 0.42	1.91 ± 0.39	1.64 ± 0.48
Prefrontal area*,**,***				
Left	56.90 ± 10.59	52.71 ± 6.88	58.60 ± 10.28	53.19 ± 8.24
Right	61.91 ± 11.80	55.04 ± 8.22	62.11 ± 11.24	55.31 ± 9.47

Values represent mean ± S.D. (cm^3); MANCOVA, multivariate analysis of covariance (see Section 2).

* MANCOVA revealed a significant main effect of hemisphere (F>13.08, df=1,113, P<0.001).

** MANCOVA revealed a significant main effect of gender (F>5.67, df=1,111, P<0.02).

*** MANCOVA revealed a significant gender-by-hemisphere interaction (F>7.32, df=1,113, P<0.01); post hoc Tukey's test showed significant difference between genders bilaterally (P<0.001).

\# MANCOVA revealed a significant main effect of diagnosis (F>5.77, df=1,111, P<0.02).

P=0.038). No other significant correlations were detected between regional white matter volumes and symptom severities. None of the correlations of symptom severity with ROI volume remained significant after Bonferroni correction for multiple comparisons.

4. Discussion

With high-resolution three-dimensional MR images, based on major gyri/sulci landmarks, we defined and measured the whole frontal lobe, prefrontal regions, PCG, and cingulate gyrus. Our study confirmed that patients with schizophrenia do have cortical volume reductions in the bilateral whole frontal lobes, prefrontal regions, and cingulate gyri (right AnCiG and bilateral PoCiG) compared with findings in normal controls. The most notable findings may be the significant volume reduction in the PCG cortex and its relationships with clinical manifestations of schizophrenia.

4.1. Gray and white matter of the whole (pre)frontal lobe

Consistent with our expectation, patients with schizophrenia in the present study showed significant cortical volume reductions in the whole frontal lobes as well as the prefrontal regions. The definitions for the ROIs were based on the main gyri/sulci landmarks; from this aspect, the results of the whole prefrontal region are comparable to two previous studies (Buchanan et al., 1998; Baaré et al., 1999), where patients had nonsignificant gray matter volume reductions in this region by 5–7%, similar to the present results. Use of small samples could be the main reason why similar magnitudes of volume reduction failed to reach statistical significance in both previous studies. Evidence from a study using first-episode schizophrenia patients also supports this finding (Hirayasu et al., 2001).

Although evidence from multiple lines has so far suggested white matter deficits in the frontal lobes of schizophrenia (reviewed by Davis et al., 2003), this

study did not detect any differences in the total frontal or prefrontal white matter volume. These results are consistent with a recently published study, which applied anatomical landmarks and a relatively large sample (Yamasue et al., 2004), as well as with several other important studies that applied carefully designed tracing methods (Baaré et al., 1999; Gur et al., 2000; Hirayasu et al., 2001). To our knowledge, among the few previous studies that have measured the frontal lobe fully based on anatomical landmarks, only one has reported volume reduction in the total prefrontal white matter of schizophrenia (Buchanan et al., 1998). Although the definition and delineation of total frontal white matter in the present study could be among the most comprehensive (Fig. 2), we would like to avoid a conclusion at present. For the next step of the series, we are separating the gyral white matter from the deeper white matter. The former could mainly represent the short association fibers and the latter the projections and long association fibers. Our previous voxel-based and volumetric MRI studies (Suzuki et al., 2002; Zhou et al., 2003) in the anterior internal capsule have provided strong evidence that schizophrenia patients have bilaterally reduced reciprocal corticothalamic connections, so we expect that such white matter deficits would be reflected in the prefrontal deeper white matter.

4.2. Anterior cingulate gyrus

Our group has been concentrating on the volume measurement of the AnCiG for years (Takahashi et al., 2002, 2003), while the present study is not a simple replica of our previous work and there are some improvements in methods, making it more complete. First, the ROI was extended to the whole AnCiG including the portion around the genu of the CC, which corresponded to a completed BA24. Second, instead of using relative values (to the whole cerebral volume) for MANCOVA with age as a covariate, the present study used absolute volumetric values with both age and ICV as covariates, thus avoiding the confounding of a coexisting smaller whole cerebrum. Third, the present study has a larger sample (patients: 59 vs. 40; controls: 58 vs. 40; 38 patients and 40 normal controls overlapped, respectively) and is thus more effective for examining group differences. However, the main results of these two studies are in congruence with each other: (1) the patient group had smaller gray matter volume (previous study

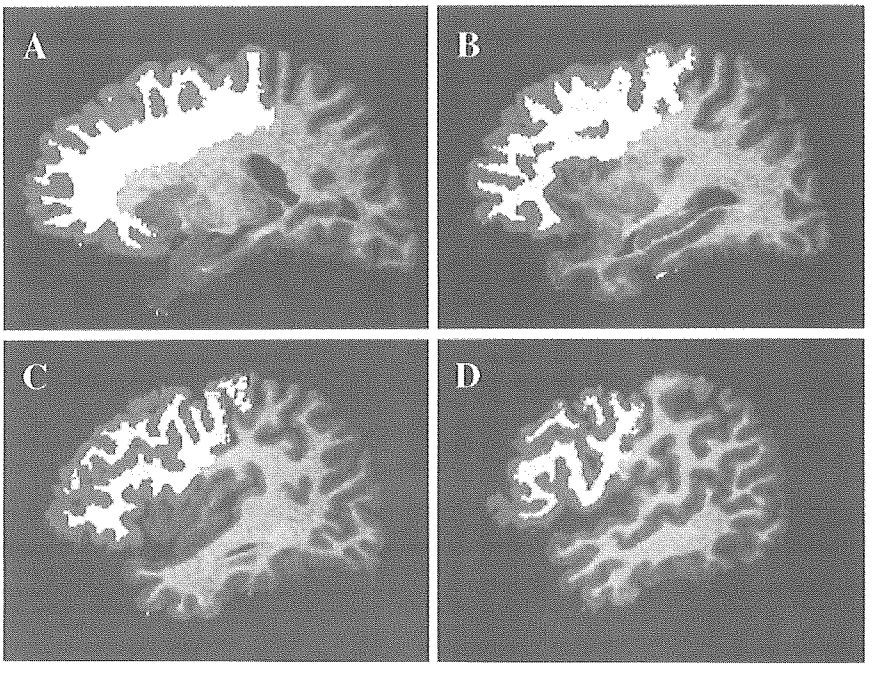

Fig. 2. Views of the frontal lobe tissues at different sagittal levels. (A–D). Views of the tissues (gray matter in blue and white matter in yellow) of the right frontal lobe at different sagittal levels. Sagittal views were automatically reconstructed synchronously when the delineation was performed on consecutive coronal slices. Distinct tissues were calculated automatically by applying the segmentation procedure described in Methods.

showed a trend, $P=0.061$); (2) significant gray matter reduction was detected only in the right AnCiG (which was limited to the female patients in the previous study); and (3) main effect of hemisphere in the whole sample expressed as right-larger-than-left (this asymmetry was observed to be diminished in female patients in the previous study).

4.3. Posterior cingulate gyrus

In contrast to the AnCiG, the PoCiG has not been extensively studied. The results of this study were consistent with the observation of reduced gray matter density in the PoCiG made by two voxel-based morphometric studies (Sowell et al., 2000; Hulshoff Pol et al., 2001), which was further demonstrated to predate the onset of frank schizophrenic symptoms and appear in association with their first expression (Pantelis et al., 2003). The present definition of the PoCiG within the frontal lobe corresponded largely to BA23 and BA31 (Talairach and Tournoux, 1988), which has diffusing reciprocal neural connections with multiple cortical and subcortical structures, including the AnCiG, prefrontal area, precuneus, superior temporal gyrus, parahippocampal cortex, and the anterior and lateral thalamic nuclei (reviewed by Maddock, 1999; Kobayashi, 2001). Such neural connections suggest that the PoCiG might subserve a variety of cognitive functions, especially those related to long-term memory as well as working memory (Andreasen et al., 1995). Observations from human lesion studies and PET studies support this concept (Maddock, 1999; Kobayashi, 2001). Patients with schizophrenia showed an increased resting perfusion or rate in the PoCiG compared with normal controls (Andreasen et al., 1997; Haznedar et al., 1997), and this was negatively correlated with Schneiderian first-rank symptoms (Franck et al., 2002); on the other hand, they also showed reduced activation in the same region during memory-related tasks (Kiehl and Liddle, 2001; Hofer et al., 2003). One possible explanation for this paradox is that overcompensation during the resting state resulted in a failure to respond to excessive demands. In other words, the functioning potential of the PoCiG in schizophrenia is diminished. The significant PoCiG tissue reduction in both gray matter and white matter, as demonstrated by this study, might be a substrate of such functional deficits.

More recently, Maddock (1999) and Maddock et al. (2003) proposed that the PoCiG's role in episodic memory functions may be specifically involved in the interactions between emotion and memory (i.e., in the modulation of memory by emotionally arousing stimuli). At present, there is a lack of direct evidence that deficits in the PoCiG are related to emotional abnormalities of schizophrenia; indirect evidence, however, shows that ketamine-induced emotional blunting in healthy men results in very different responses in the PoCiG (BA23), expressed as a success in activation to neutral stimuli but a failure in activation to fearful stimuli (Abel et al., 2003). Further understanding of the PoCiG in the pathophysiology of schizophrenia could be expected in the emotion–memory interface.

4.4. Precentral gyrus

The PCG cortex comprises the whole M1 (BA4) and a very small part of it is located by the most caudal edge of the premotor cortex (BA6) (Talairach and Tournoux, 1988), so it is rational to say that the PCG cortical volume reduction was mainly derived from M1. This finding is consistent with the observation of neuronal density reduction in M1 of postmortem schizophrenic brains (Benes et al., 1986). Reduced M1 volume could have partially resulted in impaired motor functioning as well as abnormal physiological and primitive reflexes in schizophrenia (Ismail et al., 1998); in fact, the presence of abnormal reflexes could have more directly suggested the existence of abnormalities in the upper motor neurons, which is quite in accord with the present finding. However, it would be difficult to fully understand the implications of the robust reduction of M1 volume observed in schizophrenia if M1 were merely an executive organ of voluntary movements. First, generally, patients with schizophrenia have grossly normal motor function; the soft signs of motor impairment are regarded as indicators of nonspecific brain damage (Andreasen et al., 1998). Second, no patient with overt movement disorders such as tardive dyskinesia was included in this study. Increased metabolic rate in M1 in patients with tardive dyskinesia has been reported and interpreted as the results of patients' maneuvers in trying to incorporate or suppress the involuntary movements,

or direct activation of the pallidothalamocortical tract (Pahl et al., 1995). In addition, in the present study, no significant correlation was found between the PCG measures and the dose/duration of neuroleptic medication, which seems to go against the possibility that the altered PCG cortex is due to antipsychotic medication. Thus, the mechanisms of M1 involvement in schizophrenia could have surpassed its traditionally acknowledged functional role as merely the "upper motor neuron."

M1 has recently been shown to be a crucial node in the processing of cognitive information related to motor function (e.g., spatial transformations, serial order coding, stimulus–response incompatibility, motor skill learning and memory, and motor imagery) (reviewed by Georgopoulos, 2000). More interestingly, corresponding to the monkey's mirror neuron in the premotor area F5 (Gallese et al., 1996; Rizzolatti et al., 1996), a similar mirror–neuron system (MNS) established in humans involves not only Broca's area (the human homologue of monkey F5), but also the M1, superior temporal sulcus (STS), and the inferior parietal lobule (Grafton et al., 1996; Hari et al., 1998; Nishitani and Hari, 2000). MNS (including M1) is activated by both action execution and action observation, and thus it appears to represent a system that matches observed events to similar internally generated actions, a necessary bridge from 'doing' to 'communicating,' as the link between actor and observer becomes a link between the sender and the receiver of each action-related message (Rizzolatti and Arbib, 1998), including linguistic (Rizzolatti and Arbib, 1998; Nishitani and Hari, 2002) and emotional information (Carr et al., 2003). MNS could be the core of the neural network of subjective perspective-taking (Ruby and Decety, 2001). Considering the anatomical and/or functional abnormalities in the Broca's area, STS, and parietal lobules demonstrated by previous studies (Pearlson et al., 1996; Buchanan et al., 2004) and in M1 in this study, which correspond to the key nodes of human MNS, we could speculate that an abnormal MNS exists in schizophrenia. This speculation also seems to be supported by the negative correlations between PCG cortical volume and the severity of symptoms, although these correlations should be interpreted with caution because of their weakness. Correlations were suggested for both positive and negative symptoms, possibly suggesting that the consequences of reduced M1 volume could be both distortion and decrease/loss of normal functions, which is in accord with M1 involvement in the MNS and recent physiological observations in multiple functional aspects of the human MNS (Rizzolatti and Arbib, 1998; Nishitani and Hari, 2002; Carr et al., 2003; Ruby and Decety, 2001; Gallese and Goldman, 1998). In fact, one earlier functional MRI study also reported a positive correlation of the PCG activity level with the severity of formal thought disorder in schizophrenia, but the potential significance has been overlooked (Kircher et al., 2001).

In summary, this study has confirmed that patients with schizophrenia do have cortical volume reductions in the whole frontal lobe and its subregions, while the status of white matter remains to be clarified in the future. Notably, findings in the PCG strongly suggested that M1 might play a role in the mechanisms of schizophrenia, which could be best understood in the cognitive–motor interface (as was the cerebellum in the framework of the cortical-subcortical cerebellar circuitry; Andreasen et al., 1998) as well as in the context of human MNS. More direct evidence may be expected from future functional studies especially designed for the MNS of schizophrenia.

Acknowledgments

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ORIGINAL PAPER

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Relationship between exploratory eye movements and brain morphology in schizophrenia spectrum patients

Voxel-based morphometry of three-dimensional magnetic resonance imaging

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Abstract The exploratory eye movements of schizophrenia patients and their relatives have been shown to differ from those of patients without schizophrenia and healthy controls. However the mechanism of exploratory eye movement disturbances in schizophrenia patients remains elusive. We investigated the relationship between the exploratory eye movements and brain morphology in 39 schizophrenia spectrum patients. Voxel-based morphometric analysis on three-dimensional magnetic resonance imaging was conducted by means of statistical parametric mapping 99. The decrease in the responsive search score, which is the total number of sections on which the eyes fixed in response to questioning in a comparison task, was significantly correlated with the decreased gray matter in the right frontal eye field (rFEF) including the right supplementary eye field (rSEF), right parietal eye field (rPEF), and right inferior frontal region. These results suggest that disturbance in exploratory eye movement in schizophrenia spectrum patients may be related to neural network dysfunction in FEF, SEF and PEF, which are the eye movement related areas, and in the inferior frontal region that may be related to information organization.

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Introduction

Disturbances in several aspects of eye movements have been reported in schizophrenia patients and their relatives (Diefendorf and Dogde 1908; Holzman et al. 1973; Shagass et al. 1976). Moriya et al. (1972) studied exploratory eye movements in schizophrenia patients while they were viewing a stationary horizontal S-shaped figure, and found that schizophrenia patients had significantly fewer eye fixations, longer mean duration of fixation and shorter mean scanning length than the controls. These characteristics were well confirmed by subsequent studies (Kojima et al. 1992, 2000; Tonoya et al. 2002), and were also seen in exploratory eye movements using figures from the Benton's visual retention test (Tsunoda et al. 1992) and the WAIS picture completion test (Kurachi et al. 1994). Using the horizontal S-shaped figures Kojima et al. (1990, 2001) and Matsushima et al. (1998) demonstrated that the responsive search score (RSS), which is the total number of sections on which the eyes fixed in response to questioning, "Are there any other differences?" in a comparison task, was significantly lower in schizophrenia patients than in normal controls or other psychiatric patients. In a WHO multi-center study, Kojima et al. (2001) reported that the RSS of patients with schizophrenia was significantly lower than those of depressed patients or healthy controls irrespective of geographical location. Parents of schizophrenia patients and their siblings also manifested lower RSS than those of healthy subjects (Xia et al. 1996; Takahashi et al. 1999). Thus RSS is thought to be a vulnerability marker for schizophrenia (Kojima et al. 2001).

Studies of brain morphology using neuroimaging techniques have provided substantial evidence that schizophrenia is associated with abnormalities in the

brain structure, and have brought about significant breakthroughs in our understanding of the neurobiology of schizophrenia (see reviews, Lawrie and Abukmeil 1998; Wright et al. 2000; Shenton et al. 2001). These abnormalities are also observed, but to a lesser degree, in subjects at familial risk for schizophrenia (Lawrie et al. 1999, 2001; Seidman et al. 2002; Van Erp et al. 2002), and patients with schizotypal personality disorder (see reviews, Dickey et al. 2002; Siever et al. 2002) or schizotypal disorder (Takahashi et al. 2002; Yoneyama et al. 2003; Kawasaki et al. 2004).

Disturbances in exploratory eye movements and brain structural changes have been reported not only in schizophrenia patients but also in their relatives. In view of the stability of performance in exploratory eye movements in these subjects, it could be postulated that their performance may be related with brain morphology, and that the observed findings share some underlying pathophysiology. The aim of this study was to elucidate a pattern of brain structural changes contributing to the exploratory eye movement disturbances in schizophrenia and related disorders. Two MRI studies using a region-of-interest approach revealed that RSS was negatively correlated with the width of the third ventricle and positively correlated with the volume of the temporal lobe and basal ganglia-thalamus in the right hemisphere (Takahashi et al. 1996; Matsuhima et al. 1996; Kojima et al. 2000). In addition, the known areas related to eye movements, such as frontal eye field and parietal eye field, are possibly involved in the disturbances of exploratory eye movements in the patients, but other areas of the brain might also be related to these disturbances. Therefore we used voxel-based morphometry (VBM) which enabled us to conduct comprehensive assessment throughout the brain. Previous studies suggested that the genetic pattern of schizophrenia and related disorders (i. e., schizophrenia spectrum disorders) observed in probands and relatives could be explained by a single underlying continuum of liability that differs only in severity (Tsuang et al. 1983; Kendler et al. 1984, 1995; Baron and Risch 1987). As schizotypal disorder of ICD-10 is believed to be part of the genetic "spectrum" of schizophrenia (World Health Organization 1993), we consider that the inclusion of subjects with schizotypal disorder as well as schizophrenia may be useful in attempts to clarify the underlying neurobiology of vulnerability to schizophrenia.

Methods

Subjects

The 39 subjects consisted of patients with schizophrenia (16 males and 10 females, 24.3 ± 6.7 years) or schizotypal disorder (6 males and 7 females, 24.3 ± 5.6 years) diagnosed according to ICD-10 diagnostic criteria for research (World Health Organization, 1993). After the purpose and procedures of the present study were fully explained, written informed consent was obtained individually from each of the subjects. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. All subjects were in- or outpatients of Toyama Medical and Pharmaceutical University Hospital. All available clinical information and data were obtained from a detailed review of the clinical records and structured clinical interviews by the Present State Examination (PSE) (Wings et al. 1974) and Structured Clinical Interview for DSM-IV axis II disorders (SCID-II) (First et al. 1996). The demographic and clinical characteristics of patients with schizophrenia and schizotypal disorder are summarized in Table 1. The two groups were matched in terms of age, height, education and duration of medication. However, there were significant differences in parental education (schizophrenia, 13.1 ± 2.4 years; schizotypal disorder, 11.7 ± 2.4 years; unpaired t-test, $p < 0.05$) and neuroleptic medication (schizophrenia, 9.2 ± 9.2 mg/day, haloperidol equiv.; schizotypal disorder, 4.4 ± 5.8 mg/day, haloperidol equiv.; unpaired t-test, $p < 0.05$). In schizophrenia patients, the mean duration of illness was 2.2 ± 2.5 years and age at onset was 20.9 ± 4.6 years. Patients with alcohol or drug dependency, visual disturbance, or neurological dysfunction were excluded from the study. All the subjects had at least 0.5–0.5 eye sight by naked or corrected vision.

Procedure

Eye mark recording

Each subject sat on a chair 1.2 m in front of a translucent screen and was given 3 stationary horizontal S-shaped figures (an original target figure and two figures that slightly differed from the target) (Fig. 1). The test figures were rear-projected onto the screen by means of a Kodak projector. The width of the figure was 33° horizontally and 27.5° vertically. While the patients were viewing the figures, the eye movements were recorded with a Nac V-type eye-mark recorder, a device that detects corneal reflections of infrared light. The subjects were given instructions of the following schema: (1) Each subject was shown a target figure for 15 s (retention task). (2) The subject was then asked to draw the target figure from memory immediately after viewing (reproduction task). (3) The subject was then shown a slightly different figure from the target figure for 15 s, which had one bump in a different position (Fig. 1). (4) Fifteen seconds later while the figure was still being viewed, the subject was asked if it differed from the target figure and, if so, how it differed. (5) When the subject had replied and while still viewing the figure, he/she was then asked, "Are there any other differences?" (This question was repeated until the subject stated there were no differences.) Steps 3–5 (comparison task) were repeated for a figure similar to the target and a figure without bumps. The recordings of eye movements were stored in a video tape recording system and were analyzed by a computer later. A fixation point was defined as a gaze held for more than 200 ms. The recorded tapes were analyzed by a computerized analyzing system.

Table 1 Clinical and demographic characteristics of patients with schizophrenia and patients with schizotypal disorder

	Schizophrenia patients (n = 26)	Schizotypal patients (n = 13)
Male/female	16/10	6/7
Age (years)	24.3±6.7	24.3±5.6
Height (cm)	165.8±9.3	166.3±7.0
Education (years)	12.8±2.0	13.7±2.4
Parental education (years)	13.1±2.4	11.7±2.4*
Age at onset	20.9±4.6	
Duration of illness (years)	2.2±2.5	
Duration of medication (years)	1.0±1.7	1.2±1.6
Drug (mg/day, haloperi. equiv)	9.2±9.2	4.4±5.8*

Values represent mean ± SD
* $p < 0.05$ (unpaired t-test)

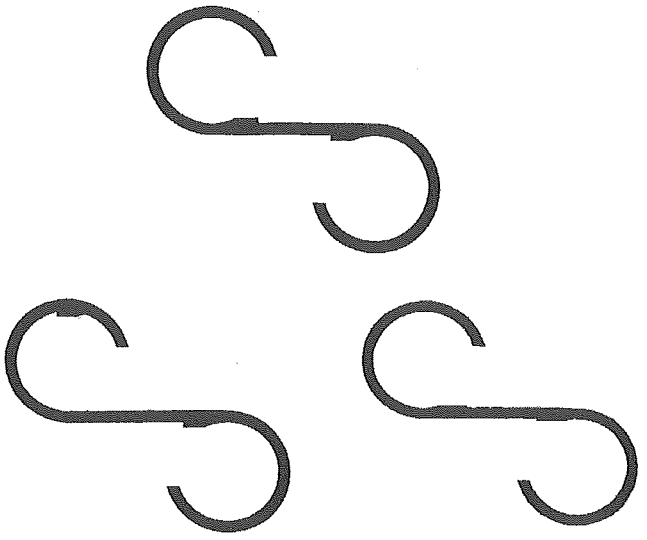

Fig. 1 The top figure is the original and the two bottom figures are slightly different from the original

Elementary components of eye movements. The following parameters were extracted: mean number of fixation points (MNF), mean duration (s) of a single fixation (MDF) and mean eye scanning length (degree) (MSL). The MNF, MDF and MSL during the subject's first 15-s viewing of the target figure were analyzed.

Responsive search score (RSS). The subject was then shown a slightly different figure from the target figure for 15 s, which had one bump in a different position (Fig. 1). Fifteen seconds later while the figure was still being viewed, the subject was asked if it differed from the target figure and, if so, how it differed. The two slightly different figures were each divided into seven sections (Fig. 2). The number of sections upon which the subject's eyes fixed one or more times was counted for 5 s immediately after the final question, "Are there any other differences?" was asked in step 5. The maximum possible score of RSS was 7 for each figure.

Evaluation of reproduced figures in two reproduction tasks. The subject drew the target figure from memory and their reproduction was evaluated according to the location of each bump and the composition of the figure as a whole. The maximum possible score of evaluation of the reproduced figure (ERF) was 7.

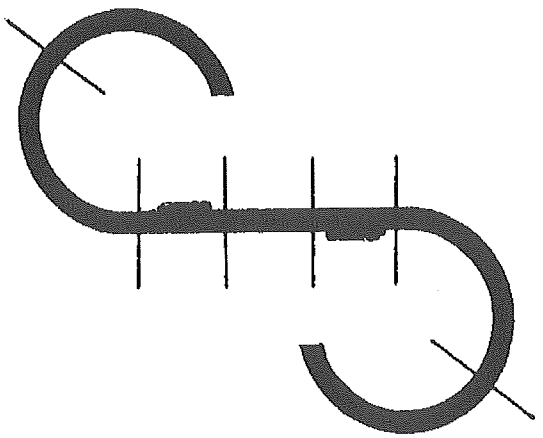

Fig. 2 The three figures were each divided into seven sections. The maximum possible score of responsive search score (RSS) was 7 for each figure

MRI

MRI data acquisition and image analysis. The subjects underwent brain MRI scanning with a Siemens 1.5 T Magnetom Vision system (Siemens Inc., Erlangen, Germany). A 3-D gradient-echo MRI sequence (fast low-angle shot, FLASH) yielding 160–180 contiguous slices 1.0 mm thick in the sagittal plane was used for volume analysis. Imaging parameters were: TE = 5 ms; TR = 24 ms; flip angle = 40°; field of view = 256 mm; matrix size = 256 x 192; voxel size = 1.0 x 1.0 x 1.0 mm. Image processing was performed on a Sun SPARC 20 workstation (Sun Microsystems Inc., Palo Alto, CA, USA) using ANALYZE version 7.5.5 (BRU, Mayo Foundation, Rochester, MN, USA). Images were first re-sliced in the axial plane with ANALYZE. Image analysis was performed by SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) running under MATLAB 5.3 (Mathworks Inc., Sherborn, MA, USA) according to the methodological description of Ashburner and Friston (2000). The first step was spatial normalization which involves transforming all the subjects' MRI images to the same stereotaxic space of Talairach and Tournoux (1998). The spatially normalized images were written out with $1.0 \times 1.0 \times 1.0$ mm voxels. Next, the normalized images were partitioned into gray matter, white matter, cerebrospinal fluid and other compartments by the modified mixture model cluster analysis technique (Ashburner and Friston, 1997) with correction for non-uniformity of the image intensity. The segmented images were then automatically processed to remove any remaining non-brain matter. The spatially normalized segments of gray matter were smoothed with a 12-mm full-width at half maximum (FWHM) isotropic Gaussian kernel. Each voxel in the smoothed image contains the average concentration of gray matter from around the voxel (i. e., gray matter concentration). This smoothing procedure has the advantage of rendering the data more normally distributed and of increasing the validity of parametric voxel-by-voxel statistical analysis.

Statistical analysis. Statistical evaluations to estimate the relationships between exploratory eye movement and voxelwise gray matter concentration were performed by an analysis of covariance (AnCova) model for global normalization with overall grand mean scaling (Friston et al. 1990). This statistical option normalized the segmented brain images to the same total amount of gray matter, while preserving regional differences in gray matter concentration. Gender and age were also treated as confounding covariates.

Each of the elementary components of eye movements, RSS, and ERF was treated as a covariate of interest. To test the hypothesis about regionally specific covariate effects, the estimates were conducted using two linear regression contrasts (increasing or decreasing gray matter associated with increasing covariate). The resulting set of voxel values for each contrast constitutes a statistical parametric map of the t statistic (i. e., SPM{t}). Since statistics based on cluster spatial extent are not valid for VBM using SPM99, voxelwise parametric statistical tests were performed using the general linear model. To correct multiple comparisons, significance levels for one-tailed SPM{t} statistics were set at $p < 0.05$ corrected for the entire search volume of gray matter.

Since the SPM99 uses standard brains from the Montreal Neurological Institute (MNI) and the template does not perfectly match the Talairach space, we estimated the Talairach-brain coordinates with a nonlinear transform of MNI brain to Talairach.

Comparison of gray matter between patients with schizophrenia and schizotypal disorder was also examined by an AnCova model of SPM99. Age and gender were treated as confounding covariates and a corrected p-value was chosen as $p < 0.05$.

Correlations between eye movement parameters or gray matter concentration and medication dosage or duration of medication were analyzed using Spearman's rank correlation coefficients. Statistical significance was defined as $p < 0.05$.

Results

RSS and elementary components of eye movements in the patients

Table 2 shows a comparison between schizophrenic and schizotypal patients in eye movement parameters. There were no significant differences between both patient groups in RSS, MNF, MDF, MSL or ERF. These parameters of eye movements had no significant correlation with neuroleptic dosage or duration of medication in patients with schizophrenia and those with schizotypal disorder.

Relationship between eye movements and gray matter concentrations

The results of the SPM{t} analysis were displayed in three orthogonal planes by using a glass brain, which allowed visual inspection of the statistical results. Among the parameters of eye movements only a score of RSS as a covariate revealed statistical significant foci with corrected $p < 0.05$ (Fig. 3). As shown in Table 3, the decreased score of RSS was significantly correlated with the decreased gray matter in the right frontal eye field (areas 6 and 8 of Brodmann) partly including the supplementary eye field, the right parietal eye field (area 40 of Brodmann), and the right inferior frontal region (area 44 of Brodmann). There was no significant difference in gray matter concentration between the patients with schizophrenia and those with schizotypal disorder.

Table 2 Comparison between schizophrenia patients and schizotypal patients of eye movement parameters

	Schizophrenia patients (n = 26)	Schizotypal patients (n = 13)
RSS	6.8±1.6	7.2±2.0
MNF	27.2±3.8	28.7±3.0
MDF (s)	0.41±0.06	0.39±0.05
MSL (deg)	5.7±1.0	5.8±0.6
ERF	4.8±1.2	5.1±0.8

RSS responsive search score; *MNF* mean number of fixation points; *MDF* mean duration of a single fixation; *MSL*, mean scanning length; *ERF* evaluation of reproduced figure
All parameters had no significant differences (unpaired t-test, n. s.)

Table 3 Peak coordinates of significant regions and their corrected p values

Regions	t value	corrected p value	Peak coordinate		
			x	y	z
Right frontal eye field	6.32	0.009	18	13	54
Right parietal eye field	5.91	0.024	35	−48	53
Right inferior frontal region	5.87	0.027	53	12	23

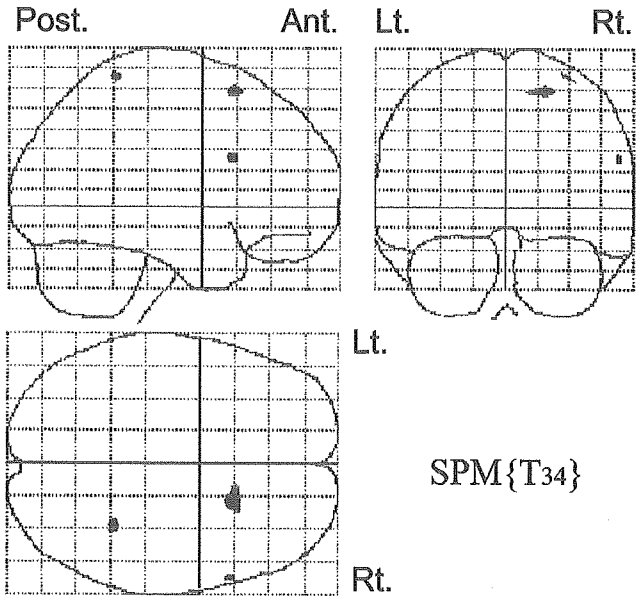

Fig. 3 Distribution of significant voxels with positive correlations between the RSS and the gray matter concentration. The SPM{t} is thresholded at $p < 0.05$ corrected for entire volume

Scatter plots of voxel wise gray matter concentration against RSS at the peak coordinates of the right frontal eye field, right parietal eye field and right inferior frontal region are shown in Fig. 4. The correlational pattern of two diagnostic groups was mutually indistinguishable, and thus the observed relationship could not be biased by diagnosis-related differences in gray matter volume and/or task performance. The gray matter concentration of these areas did not correlate with medication dosage or duration of neuroleptic medication.

Discussion

The major finding of this study was that the decreased RSS was significantly correlated with the decreased gray matter in the right frontal eye field including the supplementary eye field, the right parietal eye field, and the right inferior frontal region in schizophrenia spectrum patients. In the present study, RSSs of schizophrenia and schizotypal disorder patients were 6.8 ± 1.6 (S. D.) and 7.2 ± 2.0 respectively. These values were well in accordance with those of a WHO multi-center study (Kojima et al. 2001), namely RSSs in patients with schizophrenia distributed from 2 to 13, with numerous scores assigned between 6 and 8, while healthy controls showed scores between 8 and 13, with a peak at 10. The RSS showed no significant difference between the patients with schizophrenia and schizotypal disorder, meaning that there was no significant effect of psychosis. This is consistent with the reports that parents of schizophrenia patients and their siblings had lower RSS than those of healthy subjects, and there was no significant difference in RSS between the patients and their siblings (Xia et al. 1996; Takahashi et al. 1999; Kojima et al. 2000). These findings

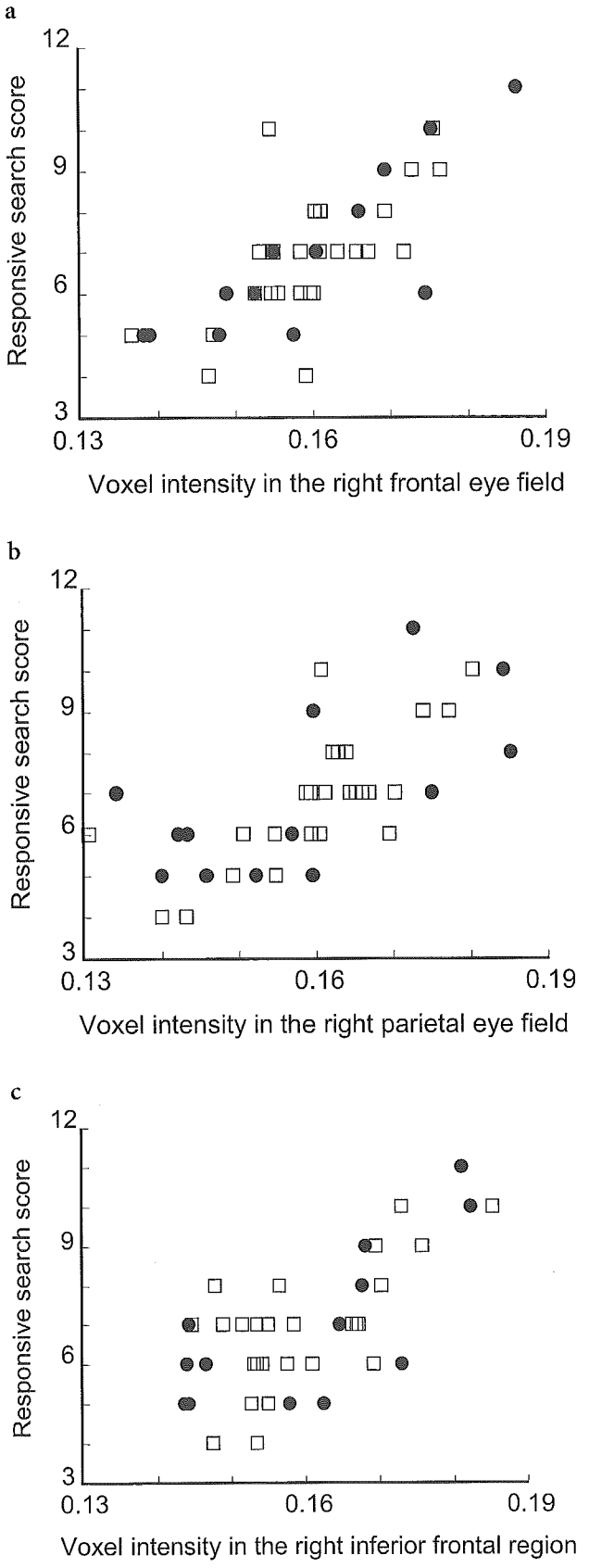

Fig. 4 Correlation between RSS and gray matter concentration in the right frontal eye field (**a**), right parietal eye field (**b**), and right inferior frontal region (**c**). □ schizophrenia; ● schizotypal disorder

support the view that RSS is a useful candidate to elucidate putative vulnerability to schizophrenia that is common to schizophrenia spectrum disorder.

Kojima et al. (1992) reported relationships between exploratory eye movement and neuropsychological tests in schizophrenia patients. In their study, RSS correlated with performance IQ and nonverbal subtests of the WAIS which may involve right posterior hemispheric function, and the Maze test which is thought to reflect the right frontal function. Matsushima et al. (1992) reported that both patients with right frontal lobe lesions and schizophrenia patients had lower scores than normal controls for the number of eye fixations and total eye scanning length, but the RSS was low only in the schizophrenia group. Previous MRI studies reported that RSS was negatively correlated with the width of the third ventricle estimated by two axial slices (Takahashi et al. 1996) and positively correlated with the volume of the right temporal lobe and basal ganglia-thalamus measured by two coronal slices (Matsuhima et al. 1996; Kojima et al. 2000). These findings suggest that decreased RSS may not be due to localized brain damage but to more widespread changes. The observed pattern of right-sided fronto-parietal brain regions in the present study may reflect the underlying neural mechanism responsible for the exploratory eye movement disturbances in schizophrenia.

Previous studies indicated that the neural network associated with eye movement functions consists mainly of three cortical centers: the frontal eye field in the premotor area, the supplementary eye field in the rostral part of the supplementary motor area, and the parietal eye field in the posterior parietal cortex (Goldberg and Segraves 1989; Andersen and Gnadt 1989; Pierrot-Deseilligny et al. 1997). The frontal eye field is essential for systematic intentional exploration of space. The supplementary eye field is concerned with the timing of eye movement. The parietal eye field is involved in visuo-spatial integration and reflexive spatial exploration (Pierrot-Deseilligny et al. 1995; Heide et al. 1998; Gaymard et al. 1998). Moreover, Corbetta et al. (1998) suggested that various voluntary eye movements and the visuo-spatial directed attention processes are mediated by the same neural circuit, and therefore are tightly integrated at the neural level. Because the cortical areas observed in the present study are quite identical with the previously postulated fronto-parietal neural circuit for normal eye movement function, it seems highly probable that a deficit of the fronto-parietal neural network is responsible for the eye movement abnormalities in schizophrenia.

Decreased frontal volume has been reported by several post-mortem (Benes et al. 1991; Selemon et al. 1995) and MRI (Zipursky et al. 1992; Schlaepfer et al. 1994) studies of schizophrenia. In particular, Buchanan et al. (1998) reported that patients with schizophrenia exhibited a relatively selective gray matter volume reduction in the bilateral inferior frontal cortex. Voxel-based morphometry in our laboratory also revealed the decreased

gray matter in the inferior frontal regions in patients with schizophrenia and schizotypal disorder, some of which overlapped with the subjects in the present study (Suzuki et al. 2002; Kawasaki et al. 2004). Kojima et al. (2001) postulated that RSS reflects the interpersonal response and the degree of mental attitude. An intriguing relationship has emerged from the present study, showing a significant relationship between decreased RSS and the gray matter decrease in the right inferior frontal region. As several lines of evidence suggest that the inferior frontal gyrus or its adjacent region in the left hemisphere participates in verbal memory organization (Fletscher et al. 1998; Nohara et al. 2000; Hagino et al. 2002), it is conceivable that the homologous region in the right hemisphere participates in nonverbal organization of information. RSS may imply an organizational visual (nonverbal) search process, and this may be the reason why RSS is related with the gray matter volume in the right inferior frontal region.

In the present study, there was no significant difference in RSSs between patients with schizophrenia and schizotypal disorder, consistent with the view that RSS is a vulnerability marker for schizophrenia. RSS may further reflect the degree of vulnerability to schizophrenia, as suggested by the explicit study by Matsushima et al. (1999) which revealed that the RSS of the discordant twin group was higher than those of the concordant twin group, but lower than the normal twin group. Thus, there is a possibility that RSSs in patients with schizophrenia and schizotypal disorder may show a significant difference, when a larger number of subjects is studied.

Several limitations of the present study need to be addressed. First, although it has been shown that VBM is capable of detecting both circumscribed and diffuse areas of gray matter loss, gray matter reductions in areas of high variability in gray matter volume may not be detected (Wright et al. 1999), In addition, a region-of-interest volumetric method is needed for precise volume measurement of a certain brain region. Thus, the present findings should be confirmed by region-of-interest volumetric methods. Second, the relationships between the RSS and brain morphology should be studied in a sufficient number of healthy controls. It is necessary to clarify whether the same pattern would hold in controls. Third, although the observed patterns of exploratory eye movements in schizophrenia and schizotypal subjects showed no significant differences, schizophrenia and schizotypal subjects should be studied separately. Further studies with functional as well as structural neuroimaging studies will elucidate the neural mechanism of exploratory eye movement impairment in schizophrenia.

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Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis

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Common abnormalities within the schizophrenia spectrum may be essential for the pathogenesis of schizophrenia, but additional pathological changes may be required for the development of full-blown schizophrenia. Clarifying the neurobiological similarities and differences between established schizophrenia and a milder form of schizophrenia spectrum disorder would potentially discriminate the pathophysiological mechanisms underlying the core features of the schizophrenia spectrum from those associated with overt psychosis. High-resolution MRIs were acquired from 25 patients with schizotypal disorder, 53 patients with schizophrenia and 59 healthy volunteers matched for age, gender, handedness and parental education. Volumetric measurements of the medial temporal structures and the prefrontal cortex subcomponents were performed using consecutive 1-mm thick coronal slices. Parcellation of the prefrontal cortex into subcomponents was performed according to the intrinsic anatomical landmarks of the frontal sulci/gyri. Compared with the controls, the bilateral volumes of the amygdala and the hippocampus were reduced comparably in the schizotypal and schizophrenia patients. The parahippocampal gyrus volume did not differ significantly between diagnostic groups. Total prefrontal grey matter volumes were smaller bilaterally in the schizophrenia patients than in the controls and the schizotypal patients, whereas the schizotypal patients had larger prefrontal grey matter than the controls in the right hemisphere. In the schizophrenia patients, grey matter volumes of the bilateral superior frontal gyrus, left middle frontal gyrus, bilateral inferior frontal gyrus and bilateral straight gyrus were smaller than those in the controls. The schizophrenia patients also had reduced grey matter volumes in the right superior frontal gyrus, bilateral middle frontal gyrus and right inferior frontal gyrus relative to the schizotypal patients. Compared with the controls, the schizotypal patients had larger volumes of the bilateral middle frontal gyrus and smaller volumes of the right straight gyrus. There were no significant between-group differences in volumes of the ventral medial prefrontal cortex or the orbitofrontal cortex. These findings suggest that volume reductions in the amygdala and hippocampus are the common morphological substrates for the schizophrenia spectrum, which presumably represent the vulnerability. Additional widespread involvement of the prefrontal cortex in schizophrenia may lead to the loss of inhibitory control in other brain regions and suggests (although it is not specifically be related to) its critical role in the manifestation of overt psychosis.

Keywords: schizotypal disorder; schizophrenia; MRI; medial temporal lobe; prefrontal cortex

Abbreviations: BA = Brodmann area; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ICD-10 = International Classification of Diseases, 10th edition; ICV = intracranial volume; MANCOVA = multivariate analysis of covariance; ROI = region of interest; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; VBM = voxel-based morphometry

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Introduction

Pathological deviations genetically and phenomenologically related to schizophrenia are grouped under the schizophrenia spectrum. This concept reflects the assumption that schizophrenia has a multifactorial aetiology in which multiple susceptibility genes interact with environmental insults to yield a range of phenotypes (Siever and Davis, 2004). Common neurobiological abnormalities in the schizophrenia spectrum may be essential for the pathogenesis of schizophrenia. However, some additional pathological changes may also be required for the development of full-blown schizophrenia. Schizotypal (personality) disorder is thought to be a prototypic disorder within the schizophrenia spectrum (Siever *et al.*, 2002). It is genetically related to schizophrenia (Siever *et al.*, 1990; Kendler *et al.*, 1993) and characterized by odd behaviour and attenuated forms of the features seen in schizophrenia without manifestation of overt and sustained psychosis (World Health Organization, 1993; American Psychiatric Association, 1994). Clarifying the neurobiological similarities and differences between established schizophrenia and schizotypal (personality) disorder would potentially discriminate the pathophysiological mechanisms underlying the core features of the schizophrenia spectrum from those associated with overt psychosis. Thus, this strategy may provide a clue to the mechanisms underlying the development of schizophrenic psychosis.

Convergent evidence suggests that the pathological process in schizophrenia predominantly affects the fronto-temporolimbic-paralimbic regions (Shenton *et al.*, 2001; Suzuki *et al.*, 2002). The hippocampal formation and the prefrontal cortex are two of the major structures that have received the most attention in the search for the neural substrate of schizophrenia. Slight but significant volume reductions in the hippocampus, amygdala and frontal lobe have been reported in a number of volumetric MRI studies of schizophrenia (see reviews: Lawrie and Abukmeil, 1998; Harrison, 1999; Shenton *et al.*, 2001). Dysfunction of these regions has been implicated in the cardinal characteristics of schizophrenia. Involvement of the hippocampal formation has been suggested to play a role in manifesting psychotic symptoms and verbal memory deficits in schizophrenia patients (Friston *et al.*, 1992; Liddle *et al.*, 1992; Goldberg *et al.*, 1994), while prefrontal abnormalities have been related to negative symptoms and cognitive impairments, such as deficits in working memory, executive and problem solving functions (Goldman-Rakic and Selemon, 1997).

There is increasing evidence of alterations in the brain structures of schizotypal subjects (see reviews: Dickey *et al.*, 2002*a*; Siever and Davis, 2004). Our previous study using voxel-based morphometry (VBM) demonstrated that grey matter reduction in the medial temporal region was common to patients with schizophrenia and schizotypal disorder, but schizophrenia patients showed more widespread involvement of the frontal lobe than schizotypal subjects (Kawasaki *et al.*, 2004). These findings need to be confirmed by detailed volumetric region of interest (ROI) analyses. However, only a single volumetric study, by Dickey and colleagues (Dickey *et al.*, 1999), has examined the medial temporal lobe structures in schizotypal subjects and found no abnormality in the amygdala or hippocampus volume. Previous MRI studies have provided evidence of preserved volume of the brain structures densely interconnected with the prefrontal cortex in schizotypal subjects relative to schizophrenia (Byne *et al.*, 2001; Takahashi *et al.*, 2002*b*, 2004; Suzuki *et al.*, 2004). These findings suggest that the prefrontal cortex may be structurally spared in schizotypal subjects. As to the prefrontal cortex *per se*, however, only preliminary data referring to preserved frontal lobe volume in schizotypal patients have been reported (Siever and Davis, 2004). Siever and Davis (2004) have made an extensive review of neurobiological findings in subjects with schizotypal personality disorder and proposed a model regarding the pathophysiology of the schizophrenia spectrum disorders. Their model also predicted that temporal volume reductions would be common across the schizophrenia spectrum disorders, whereas frontal volumes would be more preserved in schizotypal subjects than in schizophrenia patients. More data on the volume changes of both the medial temporal lobe and the prefrontal cortex in schizotypal subjects are needed for comparison with those in schizophrenia patients. Detailed volumetric analyses of both structures in the same subjects would allow more compelling conclusions to be drawn. In addition, the great multiplicity of structural and functional organization within the prefrontal cortex necessitates examination of the structural alterations in each subcomponent of the prefrontal cortex. This has been conducted in several studies of schizophrenia patients (Wible *et al.*, 1997; Buchanan *et al.*, 1998, 2004; Goldstein *et al.*, 1999; Crespo-Facorro *et al.*, 2000; Convit *et al.*, 2001; Yamasue *et al.*, 2004) but has never been reported for schizotypal subjects.

The present study aimed to elucidate the implications of structural abnormalities of the medial temporal structures and the prefrontal cortex in the manifestation of psychosis in schizophrenia. We employed high-resolution MRI and performed volumetric assessments of the amygdala, hippocampus, parahippocampal gyrus and prefrontal cortex in patients with schizotypal disorder, comparable patients with established schizophrenia and healthy control subjects. The prefrontal cortex was subdivided into subcomponents according to the intrinsic anatomical landmarks. We hypothesized, from our previous VBM findings (Kurachi, 2003*a*, *b*; Kawasaki *et al.*, 2004) and the model by Siever and Davis (2004) that patients with schizotypal disorder would have volume deficits in the medial temporal lobe but limited abnormalities in the prefrontal cortex, whereas patients with schizophrenia would show volume reductions in the medial temporal lobe as well as in widespread regions of the prefrontal cortex.

Methods

Subjects

Twenty-five patients (15 males, 10 females) with schizotypal disorder, 53 patients with schizophrenia (32 males, 21 females) and 59 control subjects (35 males, 24 females) were included in this study. All subjects were right-handed. Demographic and clinical data of the subjects are presented in Table 1.

The patients with schizotypal disorder were recruited from among the subjects who visited the clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital manifesting schizotypal features with distress or associated problems in their lives. Structured clinical interviews were performed using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen *et al.*, 1992) and Structured Clinical Interview for DSM-IV axis II disorders (SCID-II) (First *et al.*, 1997). They all met the criteria for schizotypal disorder in the International Classification of Diseases, 10th edition (ICD-10) (World Health Organization, 1993) as well as the criteria for schizotypal personality disorder in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994). Based on the data from the CASH and SCID-II, subjects were diagnosed by a consensus of at least two experienced psychiatrists, and when necessary the propriety of including cases in the study was discussed among clinical staff members involved. None of the subjects was judged to meet the criteria for schizophrenia of ICD-10 or of DSM-IV currently or previously. At the time of MRI scanning, six patients were neuroleptic-naive and 19 patients were being treated with low doses of antipsychotics; six patients were being treated with typical neuroleptics and 13 patients were receiving atypical neuroleptics. All subjects have received consistent clinical follow-up and none of them has developed overt schizophrenia to date (mean follow-up period after MRI scanning = 2.5 years, SD = 1.9). Four of the 25 patients with schizotypal disorder were relatives of individuals with schizophrenia. Since schizotypal subjects rarely present themselves for clinical care, our clinic-based sample was considered to be somewhat more severely ill than may be expected of schizotypal individuals among the general population.

The patients with schizophrenia were diagnosed based on the CASH and Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) (First *et al.*, 1996). They fulfilled both ICD-10 and DSM-IV criteria for schizophrenia. All schizophrenia patients apart from one female patient were receiving neuroleptic medication; 25 patients were being treated with typical neuroleptics and 27 patients were receiving atypical neuroleptics. The clinical status of the schizophrenia patients was variable; some of them were in an active psychotic episode and others were in partial remission or in a residual phase. All patients with schizotypal disorder and schizophrenia were physically healthy and 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 psychologist within 1 month of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) and the 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 control subjects consisted of healthy volunteers recruited from among the community and hospital staff or were medical and pharmaceutical students. They were interviewed by psychiatrists using the questionnaire concerning their family and past histories, and present illness. 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 a history of psychiatric disorders in their first-degree relatives. All control subjects were given the Minnesota Multiphasic Personality Inventory, and subjects were excluded if they had abnormal profiles with any T-score exceeding 70. The three groups were matched for age, sex, handedness, height and parental education (Table 1).

After complete description of the study to the subjects, written informed consent was obtained. This study was approved by the

Table 1 Demographic and clinical characteristics of patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects

	Schizotypal disorder patients (n = 25)	Schizophrenia patients (n = 53)	Healthy comparison subjects (n = 59)
Male/female	15/10	32/21	35/24
Handedness	25 right	53 right	59 right
Age (years)	25.5 ± 5.7	25.3 ± 5.0	24.3 ± 5.3
Height (cm)	164.6 ± 8.7	166.1 ± 7.3	167.0 ± 7.3
Weight (kg)	60.3 ± 9.7	61.7 ± 12.7	58.1 ± 9.4
Education (years)	13.5 ± 1.8†	13.2 ± 1.9†	16.0 ± 2.5
Parental education (years)	12.1 ± 1.9	12.2 ± 2.1	12.8 ± 2.4
Age at onset (years)	–	21.7 ± 4.5	–
Duration of illness (years)	–	3.7 ± 3.8	–
Total SAPS score	16.0 ± 8.5	24.1 ± 20.5	–
Total SANS score	46.8 ± 24.5	45.7 ± 22.5	–
Drug dose (mg/day, haloperidol equivalent)*	3.9 ± 4.7	11.6 ± 9.4‡	–
Duration of medication (years)	0.3 ± 0.4	2.7 ± 3.1‡	–

Values represent mean ± SD. *Neuroleptic dosages of different classes of antipsychotic drugs were converted into haloperidol equivalents using the guideline by Toru (2001). *Post hoc* comparisons following analysis of variance (ANOVA) revealed: †$P < 0.01$, smaller than in controls; ‡$P < 0.01$, larger than in schizotypal disorder patients. SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms.