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.

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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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Key words exploratory eye movement · magnetic resonance imaging · voxel-based morphometry · inferior frontal gyrus · schizophrenia spectrum disorder

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)

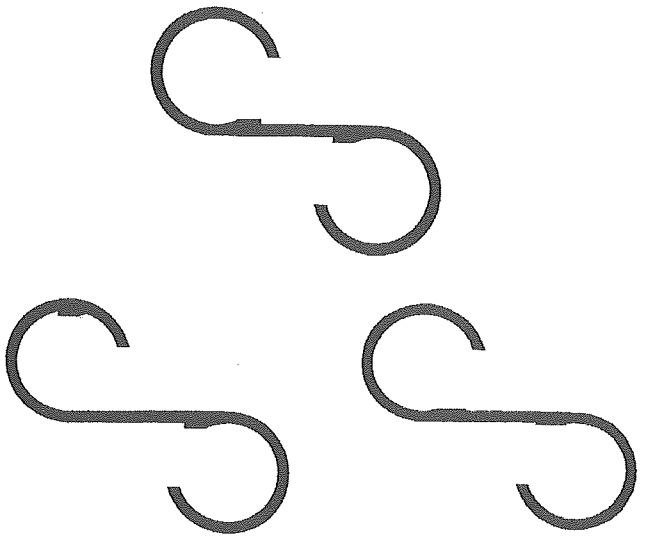

Fig. 1 The top figure is the original and the two bottom figures are slightly different from the original

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.

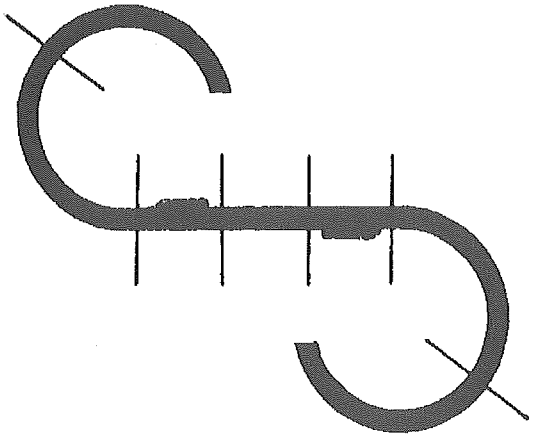

Fig. 2 The three figures were each divided into seven sections. The maximum possible score of responsive search score (RSS) was 7 for each figure

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

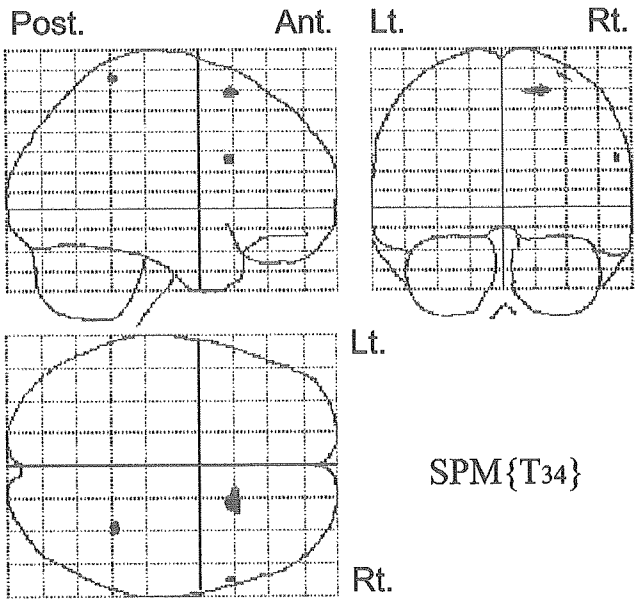

Fig. 3 Distribution of significant voxels with positive correlations between the RSS and the gray matter concentration. The SPM{t} is thresholded at $p < 0.05$ corrected for entire volume

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

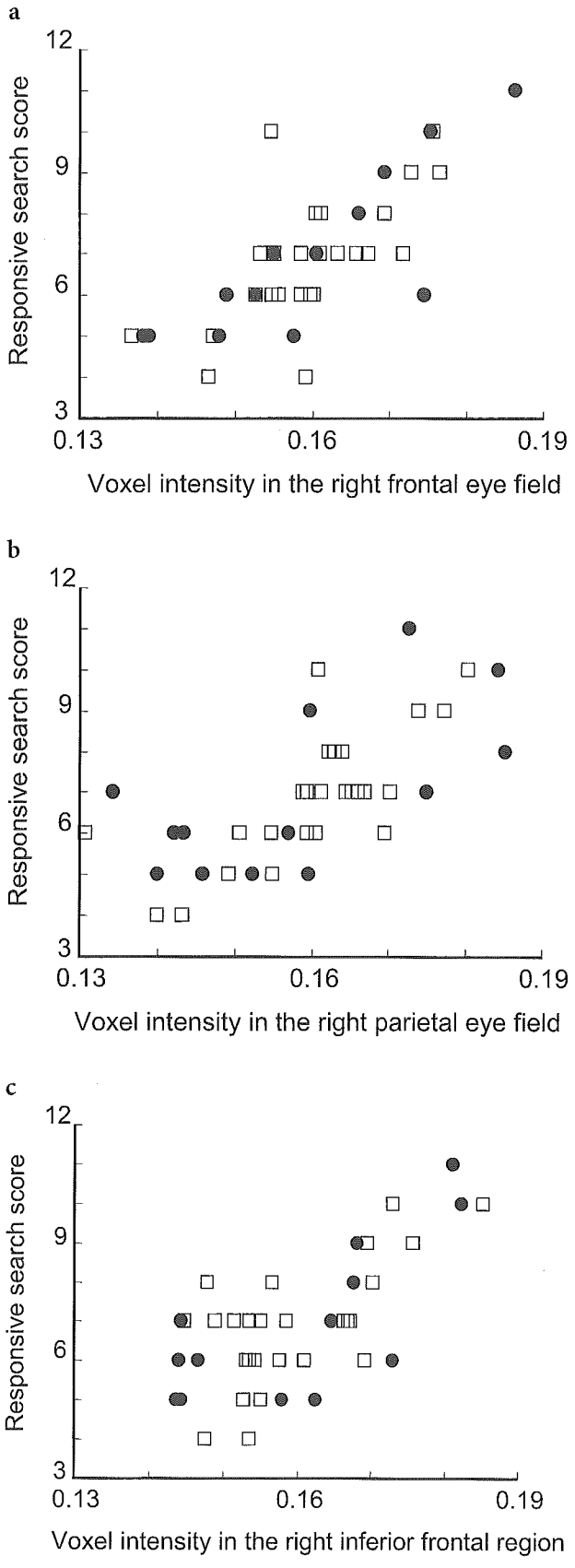

Fig. 4 Correlation between RSS and gray matter concentration in the right frontal eye field (**a**), right parietal eye field (**b**), and right inferior frontal region (**c**). □ schizophrenia; ● schizotypal disorder

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.

Committee on Medical Ethics of Toyama Medical and Pharmaceutical University.

There are considerable overlaps between the subjects in the present study and those in previous MRI studies from our group. Of the 25 patients with schizotypal disorder, 15 and 17 patients overlapped with those in the volumetric MRI studies of the anterior cingulate gyrus (Takahashi *et al.*, 2002*b*, 2004) and of the internal capsule (Suzuki *et al.*, 2004), respectively. Of the 53 patients with schizophrenia, 34 overlapped with those in the volumetric MRI studies (Takahashi *et al.*, 2002*a*; Zhou *et al.*, 2003; Niu *et al.*, 2004). In the VBM study by Kawasaki *et al.* (2004), 17 schizotypal patients and 20 schizophrenia patients were the same as those in the present study. In these previous studies, 37–54 of the control subjects also overlapped with those in the present study according to the stages of our research.

MRI acquisition and processing

MRI scans were acquired with a 1.5 T scanner (Vision; Siemens Medical System, 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 (echo time) = 5 ms; TR (repetition time) = 24 ms; flip angle = 40°; field of view = 256 mm; matrix size = 256 × 256.

Image processing for volumetric ROI analysis has been described in detail previously (Takahashi *et al.*, 2002*a*). Briefly, on a Unix workstation (Silicon Graphics, Mountain View, CA, USA), the image data were processed with the software package Dr View 5.0 (Asahi Kasei Joho System, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into entire contiguous coronal slices of 1 mm thickness perpendicular to the anterior commissure–posterior commissure line. The whole cerebrum was separated from the brainstem and cerebellum. The signal intensity histogram distributions across the whole cerebrum were used to segment the voxels semiautomatically into grey matter, white matter and cerebrospinal fluid (CSF). Using the thresholds between the tissue compartments, volumes of whole hemispheric grey matter and white matter were calculated. These whole hemispheric grey matter and white matter volumes summed to the whole cerebral hemisphere volume, which did not include CSF or ventricles. 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).

Volumetric analysis of ROIs

The ROIs for volumetric measurements were placed on the medial temporal structures and prefrontal cortex, as presented in Figs 1 and 2, respectively.

Medial temporal lobe

The amygdala, hippocampus and parahippocampal gyrus were manually outlined on consecutive coronal 1 mm slices with the corresponding sagittal and axial planes simultaneously presented for reference. Volumes of grey and white matter in each of these structures were measured together. The detailed procedures for delineation of these structures were described previously (Niu

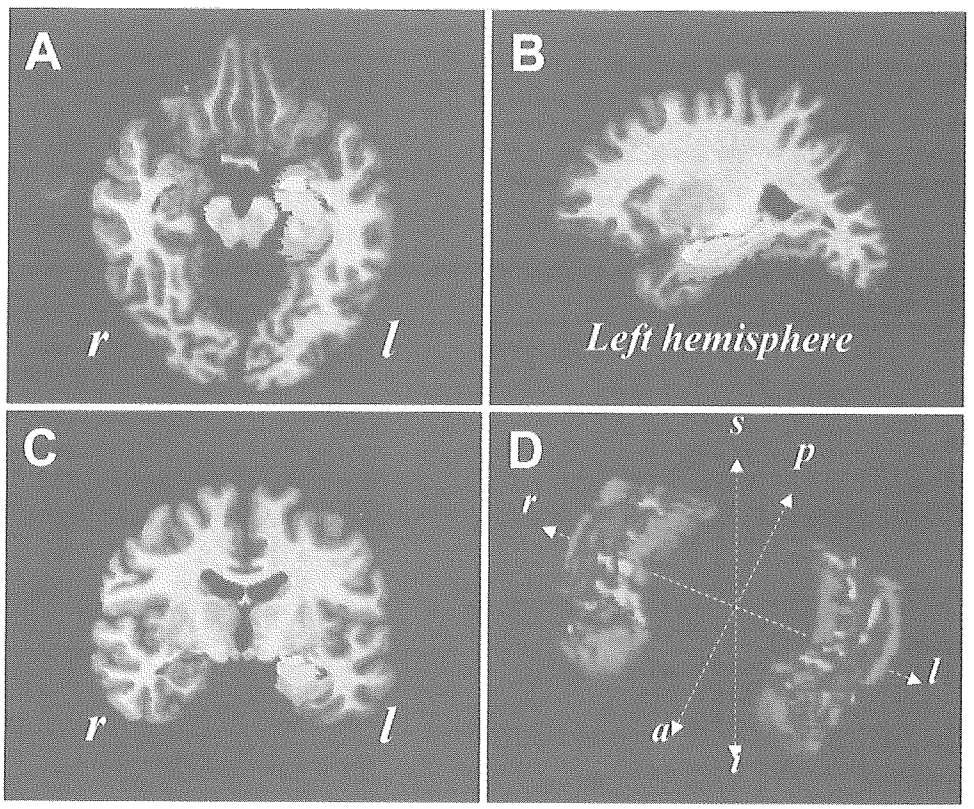

Fig. 1 Delineations of medial temporal regions of interest taken from mutually orthogonal transaxial (**A**), sagittal (**B**) and coronal (**C**) planes. A three-dimensional reconstructed image of the three regions is also shown (**D**). Each of the regions is differentially coloured: amygdala (green), hippocampus (red) and parahippocampal gyrus (blue). a, anterior; i, inferior; l, left; p, posterior; r, right; s, superior.

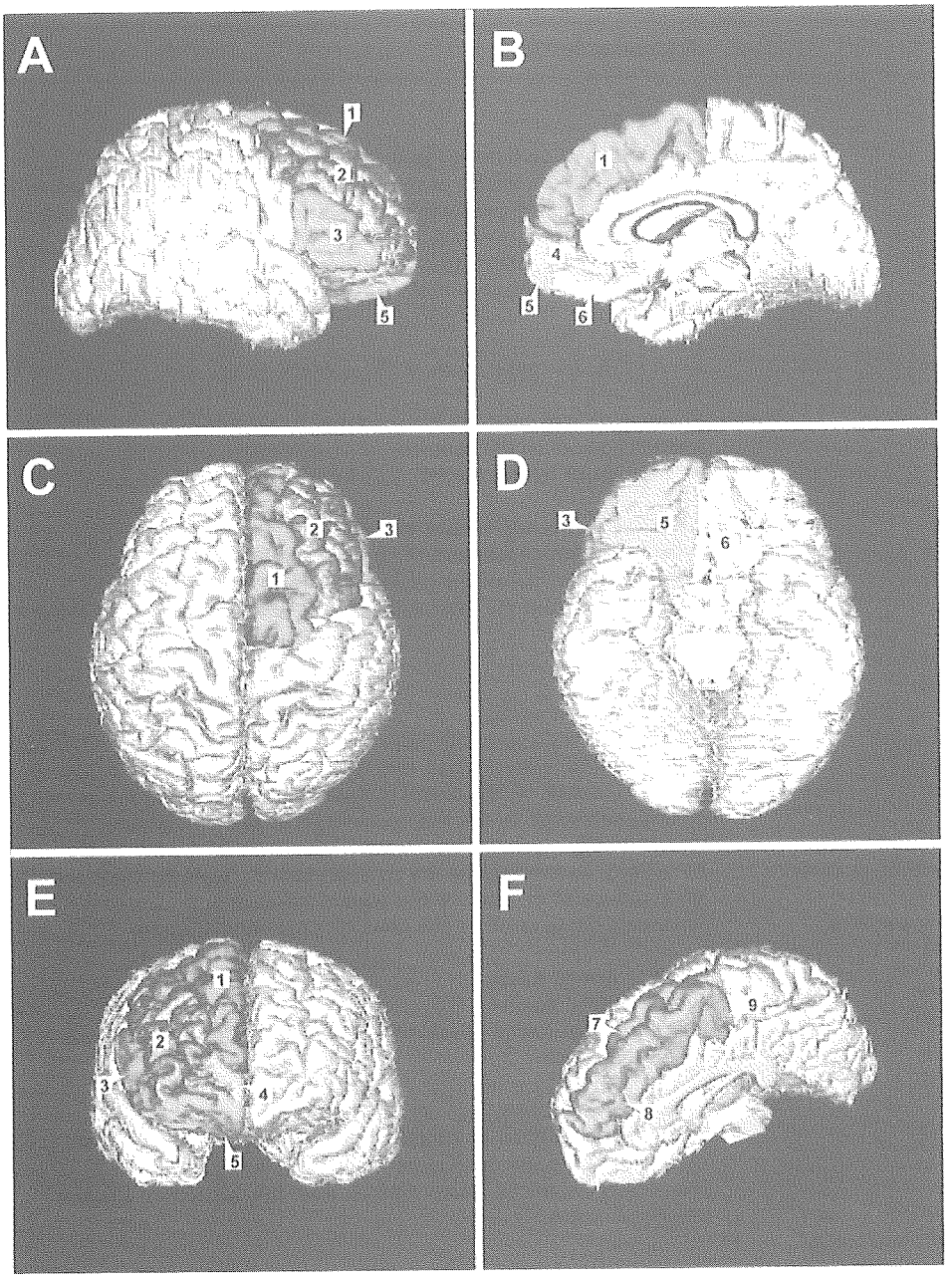

Fig. 2 Three-dimensional reconstructed images of prefrontal regions of interest presenting right lateral (**A**), right medial (**B**), dorsal (**C**), ventral (**D**) and anterior (**E**) views of the brain. Panel **F** demonstrates subdivisions of superior frontal gyrus. 1, superior frontal gyrus; 2, middle frontal gyrus; 3, inferior frontal gyrus; 4, ventral medial prefrontal cortex; 5, orbitofrontal cortex; 6, straight gyrus; 7, dorsolateral part of superior frontal gyrus; 8, dorsal medial prefrontal cortex; 9, supplementary motor cortex.

et al., 2004; Suzuki *et al.*, 2005*a*). The inferior border of the amygdala in contact with the hippocampal head was determined by reference to the sagittal plane since the boundary between the hippocampus and the amygdala is more readily identified on the sagittal plane (Convit *et al.*, 1999). Anatomical boundaries for these structures are presented in Table 2.

Prefrontal cortex

Delineation of the prefrontal cortex was partially based on the works of Rademacher *et al.* (1992) and Crespo-Facorro *et al.* (1999*a*). Parcellation of the frontal lobe into subcomponents was performed according to the anatomical landmarks that were, in principle, intrinsic to the brain (sulci/gyri). With the availability of synchronous–orthogonal views in three dimensions in conjunction with the context of gyri/sulci on successive slices, decisions about the landmarks could be made readily. First, the whole frontal lobe was separated from the rest of the brain by the central sulcus. The prefrontal area was demarcated by subtracting the precentral gyrus and the cingulate gyrus from the whole frontal lobe. By this definition of the prefrontal area, it inevitably includes the premotor cortex [Brodmann area (BA) 6 and part of BA 8]. The paracingulate gyrus (approximately corresponding to BA 32), when present, was included in the prefrontal area. After the extraction of the prefrontal

Table 2 Anatomical landmarks demarcating the regions of interest

Region	Anatomical landmark
Medial temporal region	
Amygdala	
Anterior border	Appearance of oval-shaped grey matter of the amygdala
Posterior border	Thin strip of grey matter of the hippocampal–amygdala transitional area
Superior border	Cerebrospinal fluid overlying the semilunar gyrus and its medial extension
Inferior border	Alveus
Lateral border	Temporal lobe white matter and extension of the temporal horn
Medial border	Thin strip of parahippocampal white matter (angular bundle)
Hippocampus	
Anterior border	Alveus
Posterior border	Level of the last appearance of fibres of the fornix
Superior border	Alveus
Inferior border	White matter of parahippocampal gyrus
Lateral border	Inferior horn of lateral ventricle
Medial border	Mesial edge of temporal lobe
Parahippocampal gyrus	
Anterior border	Level of the first appearance of the temporal stem
Posterior border	Level of the last appearance of fibres of the fornix
Superior border	Inferior grey border of the hippocampal formation
Lateral border	A line drawn from the most lateral border of the hippocampal flexure to the collateral sulcus
Prefrontal area	
Superior frontal gyrus (includes the paracingulate gyrus when it exists)	
Lateral inferior border	Superior frontal sulcus
Medial inferior border	Cingulate sulcus and, in the most anterior part, superior rostral sulcus
Anterior border	Frontomarginal sulcus, which extends from superior frontal sulcus
Posterior border	Precentral sulcus on the lateral surface and paracentral sulcus on the medial surface
Dorsolateral part	Medially separated by the superior margin of the hemisphere
Medial part	Dorsolaterally separated by the superior margin of the hemisphere
Dorsal medial prefrontal cortex	Posteriorly demarcated by the coronal plane through the most anterior tip of the inner surface of the genu of the corpus callosum
Supplementary motor area	Anteriorly demarcated by the same coronal plane as above
Middle frontal gyrus	
Superior border	Superior frontal sulcus
Inferior border	Inferior frontal sulcus
Anterior border	Frontomarginal sulcus, which extends from superior frontal sulcus
Posterior border	Precentral sulcus
Inferior frontal gyrus	
Superior border	Inferior frontal sulcus
Inferior border	Frontomarginal sulcus or lateral orbital sulcus in the anterior part and superior circular sulcus in the operculum
Anterior border	Frontomarginal sulcus, which extends from inferior frontal sulcus
Posterior border	Precentral sulcus
Ventral medial prefrontal cortex	
Superior border	Superior rostral sulcus in the anterior part and cingulate sulcus in the posterior part
Inferior border	Inferior rostral sulcus (the lowest visible sulcus in the medial surface of the hemisphere)
Anterior border	Frontomarginal sulcus, which extends from superior rostral sulcus
Posterior border	More posterior coronal plane through either of posterior extreme of cingulate sulcus or superior rostral sulcus
Orbitofrontal cortex	
Anterior/lateral border	Frontomarginal sulcus in the anterior part, lateral orbital sulcus in the intermediate part and inferior circular sulcus in the posterior part
Medial border	Superior rostral sulcus, which anteriorly merges into frontomarginal sulcus in the rostral part and olfactory sulcus on the ventral surface of the hemisphere
Posterior border	The most posterior coronal plane containing medial orbital gyrus
Straight gyrus	
Lateral border	Olfactory sulcus
Medial border	Inferior rostral sulcus (the lowest visible sulcus in the medial surface of the hemisphere)
Anterior border	Anterior extreme of olfactory sulcus
Posterior border	Olfactory trigone

area, it was subdivided into six subregions: the superior frontal gyrus, which was further subdivided into three parts (dorsolateral part, dorsal medial prefrontal cortex and supplementary motor cortex); middle frontal gyrus; inferior frontal gyrus; ventral medial prefrontal cortex; orbitofrontal cortex; and straight gyrus. Anatomical boundaries for each region are described in Table 2. All the volumetric measurements were performed on reformatted consecutive 1 mm coronal slices by manual outlining. Grey matter volumes of the regional cortices were calculated by applying the segmentation procedure described previously.

Three trained raters (S.Z., H.H. and L.N.), who were blinded to the subjects' identities, measured the volumes of the prefrontal regions, the amygdala, and the hippocampus and parahippocampal gyrus, respectively. Inter- and intra-rater intraclass correlation coefficients in five randomly selected brains were over 0.92 for the prefrontal ROIs and over 0.93 for the medial temporal ROIs.

Statistical analysis

Statistical differences in the regional volume measures were analysed by repeated measures multivariate analysis of covariance (MANCOVA) with ICV and age as covariates for each region, with diagnosis group (schizophrenia patients, schizotypal disorder patients, control subjects) and gender (male, female) as between-subject factors and hemisphere (right, left) as a within-subject factor. For the comparison of ICV, only age was treated as a covariate. *Post hoc* Tukey's tests were employed to follow up the significant main effects or interactions yielded by MANCOVAs. Pearson's partial correlation coefficients, controlling for ICV and age, were calculated to examine relationships between the ROI volumes and the clinical variables. Statistical significance was defined as $P < 0.05$ (two-tailed). To prevent a possible type I error due to multiple tests, a Bonferroni correction was applied for correlation analyses.

Results

Volumes of measured ROIs and results of MANCOVAs for the main effect of diagnosis are presented in Tables 3, 4 and 5. We report below the results concerning main effects of diagnosis or interactions involving diagnosis only when

Table 3 Volumes of intracranial cavity, cerebral hemisphere and cerebral grey and white matter in patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects

Regions of interest	Schizotypal disorder patients	Schizophrenia patients	Healthy comparison subjects	Diagnosis effect		
				F	df	*P*
Intracranial volume	1526 ± 150	1496 ± 155	1509 ± 128	0.71	2,130	0.492
Whole cerebral hemisphere				1.84	2,129	0.162
Left[§]	559.0 ± 56.6	538.6 ± 59.5	553.8 ± 48.8			
Right	566.1 ± 57.2	545.8 ± 60.4	561.3 ± 49.2			
Whole cerebral grey matter				4.89	2,129	0.008
Left[#]	362.1 ± 40.5	339.8 ± 39.3[†,‡]	356.4 ± 36.2			
Right	353.6 ± 40.3	329.9 ± 37.5[†,‡]	347.6 ± 35.6			
Whole cerebral white matter				1.69	2,129	0.187
Left[§]	197.0 ± 26.3	198.8 ± 33.1	197.3 ± 31.5			
Right	212.5 ± 29.3	215.9 ± 39.4	213.7 ± 36.0			

Values represent mean ± SD of measured volume (cm^3). *Post hoc* comparisons following multivariate analysis of variance with age and intracranial volume as covariates (MANCOVA) revealed: [†]$P < 0.01$, smaller than in controls; [‡]$P < 0.01$, smaller than in schizotypal disorder patients; [§]$P < 0.01$, smaller than on right hemisphere; [#]$P < 0.01$, larger than on right hemisphere.

Table 4 Volumes of medial temporal lobe structures in patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects

Regions of interest	Schizotypal disorder patients	Schizophrenia patients	Healthy comparison subjects	Diagnosis effect		
				F	df	*P*
Amygdala				19.08	2,129	<0.001
Left[§]	0.96 ± 0.13[†]	0.99 ± 0.15[†]	1.13 ± 0.14			
Right	0.97 ± 0.15[†]	1.05 ± 0.17[†]	1.15 ± 0.14			
Hippocampus				3.24	2,129	0.042
Left[§]	2.83 ± 0.37[‡]	2.89 ± 0.42[†]	3.04 ± 0.40			
Right	3.03 ± 0.39[‡]	3.09 ± 0.56[†]	3.24 ± 0.35			
Parahippocampal gyrus				0.34	2,129	0.706
Left	7.22 ± 0.73	7.01 ± 1.13	7.15 ± 0.90			
Right	7.22 ± 0.57	7.09 ± 1.08	7.31 ± 0.76			

Values represent mean ± SD of measured volume (cm^3). *Post hoc* comparisons following multivariate analysis of variance with age and intracranial volume as covariates (MANCOVA) revealed: [†]$P < 0.01$, [‡]$P < 0.05$, smaller than in controls; [§]$P < 0.01$, smaller than on right hemisphere.

Table 5 Volumes of whole prefrontal grey and white matter and prefrontal cortex subcomponents in patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects

Regions of interest	Schizotypal disorder patients	Schizophrenia patients	Healthy comparison subjects	Diagnosis effect		
				F	*df*	*p*
Prefrontal grey matter				3.51	2,129	0.032
Left‡‡	97.18 ± 13.65	91.05 ± 12.32†,§	96.38 ± 9.88			
Right	94.99 ± 13.33††	88.16 ± 11.82†,§	92.38 ± 9.54			
Prefrontal white matter				1.34	2,129	0.264
Left§§	46.72 ± 7.07	44.54 ± 8.69	47.13 ± 7.66			
Right	49.73 ± 7.26	49.14 ± 10.05	50.28 ± 9.05			
Superior frontal gyrus				3.49	2,129	0.033
Left‡‡	28.91 ± 5.31	27.49 ± 4.21†	29.64 ± 4.05			
Right	27.65 ± 5.29	25.63 ± 4.37†,#	27.76 ± 3.95			
Dorsolateral part				0.53	2,129	0.589
Left‡‡	12.42 ± 3.19	12.34 ± 2.33	13.02 ± 2.81			
Right	12.27 ± 3.46	11.76 ± 2.83	12.34 ± 2.33			
Dorsal medial prefrontal cortex				4.84	2,129	0.009
Left‡‡	10.19 ± 2.35	9.16 ± 1.99†,#	10.16 ± 1.81			
Right	9.39 ± 1.92	8.72 ± 1.77†	9.73 ± 1.79			
Supplementary motor cortex				3.48	2,129	0.033
Left‡‡	6.30 ± 1.09	6.00 ± 1.00‡	6.47 ± 1.19			
Right	5.99 ± 1.56	5.14 ± 1.07‡,#	5.69 ± 1.23			
Middle frontal gyrus				2.90	2,129	0.058
Left‡‡	29.34 ± 5.67††	25.87 ± 4.95†,§	27.31 ± 4.62			
Right	28.44 ± 5.66††	25.50 ± 4.41§	26.53 ± 4.78			
Inferior frontal gyrus				4.92	2,129	0.008
Left‡‡	13.02 ± 2.65	12.58 ± 2.14†	13.87 ± 2.10			
Right	13.18 ± 2.22	12.05 ± 2.19†,§	12.89 ± 1.83			
Ventral medial prefrontal cortex				0.92	2,129	0.397
Left	5.61 ± 1.22	5.51 ± 1.21	5.84 ± 1.12			
Right	5.56 ± 1.03	5.48 ± 1.17	5.69 ± 1.23			
Orbitofrontal cortex				0.47	2,129	0.622
Left	15.69 ± 1.91	15.11 ± 2.03	15.44 ± 1.57			
Right	15.58 ± 1.87	15.07 ± 2.07	15.47 ± 1.45			
Straight gyrus				15.45	2,129	<0.001
Left	3.06 ± 0.49	2.89 ± 0.45†	3.31 ± 0.49			
Right	3.02 ± 0.51‡	2.92 ± 0.43†	3.31 ± 0.50			

Values represent mean ± SD of measured volume (cm^3). *Post hoc* comparisons following multivariate analysis of variance with age and intracranial volume as covariates (MANCOVA) revealed: †$P < 0.01$; ‡$P < 0.05$, smaller than in controls; §$P < 0.01$, #$P < 0.05$, smaller than in schizotypal disorder patients; ††$P < 0.05$, larger than in controls; ‡‡$P < 0.01$, larger than on right hemisphere; §§$P < 0.01$, smaller than on right hemisphere.

they were significant or had a nearly significant trend, and subsequent *post hoc* analyses.

Volumes of global brain structures

There were no significant differences in the volumes of intracranial cavity, whole cerebral hemisphere or whole cerebral white matter among diagnostic groups (Table 3). MANCOVAs revealed a significant main effect of diagnosis for the whole cerebral grey matter (Table 3). The volumes of whole cerebral grey matter were significantly smaller in the schizophrenia patients compared with the controls (*post hoc* tests, $P < 0.001$ for both hemispheres) and the schizotypal patients ($P < 0.001$ for both hemispheres).

Volumes of medial temporal lobe

A significant main effect of diagnosis in MANCOVA was revealed in the amygdala and the hippocampus (Table 4). *Post hoc* analyses demonstrated that, compared with the controls, the volume of the amygdala was significantly smaller in the patients with schizotypal disorder ($P < 0.001$ for both hemispheres) and schizophrenia ($P < 0.001$ for both hemispheres). The volume of the hippocampus was also significantly smaller in the patients with schizotypal disorder ($P = 0.039$ for the left and $P = 0.020$ for the right) and schizophrenia ($P = 0.009$ for the left and $P = 0.005$ for the right) than in the controls. There was no significant difference in the amygdala or hippocampus volume between schizotypal disorder and schizophrenia. The parahippocampal gyrus measures did not differ among diagnostic groups (Table 4).

Volumes of prefrontal cortex

A significant main effect of diagnosis in MANCOVA was observed in the total prefrontal grey matter but not in the total prefrontal white matter (Table 5). *Post hoc* analyses

demonstrated that the prefrontal grey matter volume was significantly smaller in the schizophrenia patients compared with the controls ($P < 0.001$ for both hemispheres) and the schizotypal patients ($P < 0.001$ for both hemispheres). In contrast, the schizotypal disorder patients had larger prefrontal grey matter than the controls in the right hemisphere ($P = 0.040$).

Among the prefrontal cortex subcomponents, MANCOVA revealed a significant main effect of diagnosis in the superior frontal gyrus, inferior frontal gyrus and straight gyrus, and an insignificant trend for main effect of diagnosis in the middle frontal gyrus (Table 5). When the superior frontal gyrus was further subdivided, a significant main effect of diagnosis was found only in the medial parts, such as the dorsal medial prefrontal cortex and supplementary motor cortex (Table 5). A significant interaction between diagnosis and gender was observed only in the inferior frontal gyrus [$F(2,129) = 3.97$, $P = 0.021$].

Post hoc analyses demonstrated that the superior frontal gyrus grey matter volume was significantly reduced in the schizophrenia patients compared with the controls ($P < 0.001$ for both hemispheres) and the schizotypal patients ($P = 0.014$ for the right) (Fig. 3A). In the superior frontal gyrus subdivisions, the schizophrenia patients had a significantly

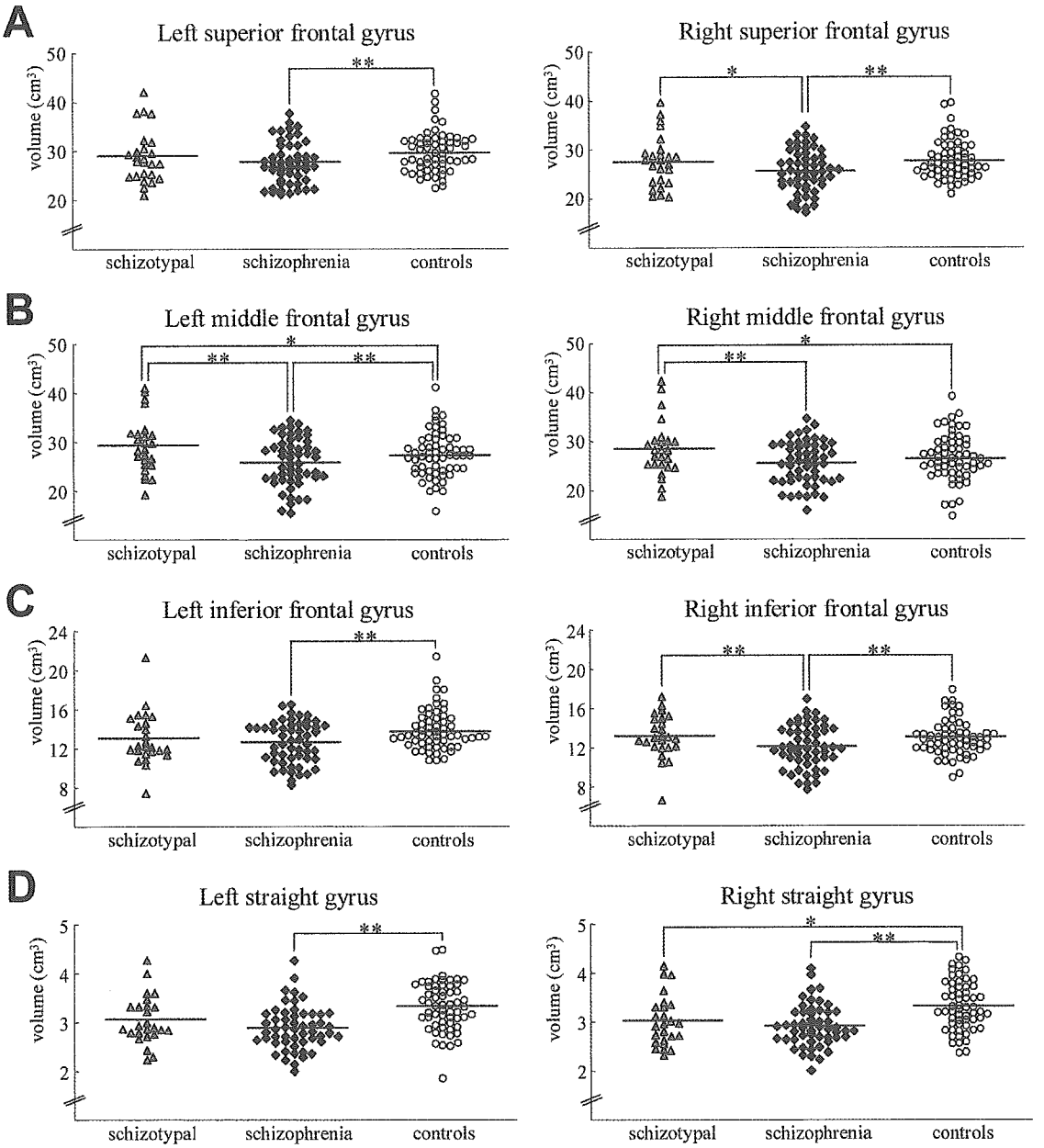

Fig. 3 Scatter plots of absolute volumes of grey matter for each prefrontal subcomponent in patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects: superior frontal gyrus (**A**), middle frontal gyrus (**B**), inferior frontal gyrus (**C**) and straight gyrus (**D**). Horizontal bars indicate means of each group. *$P < 0.05$; **$P < 0.01$: *post hoc* comparisons followed multivariate analysis of variance with age and intracranial volume as covariates.

smaller dorsal medial prefrontal cortex volume than the controls ($P < 0.001$ for both hemispheres) and the schizotypal patients ($P = 0.016$ for the left). The supplementary motor cortex volume in the schizophrenia patients was also significantly smaller than in the controls ($P = 0.022$ for the left and $P = 0.026$ for the right) and the schizotypal patients ($P = 0.013$ for the right).

The middle frontal gyrus volume was significantly smaller in the schizophrenia patients compared with the controls ($P = 0.002$ for the left) and the schizotypal patients ($P < 0.001$ for both hemisphere) (Fig. 3B). Further, the schizotypal patients had significantly larger middle frontal gyrus volume than the controls ($P = 0.026$ for both hemispheres) (Fig. 3B).

The inferior frontal gyrus volume was significantly reduced in the schizophrenia patients compared with the controls ($P < 0.001$ for both hemispheres) and the schizotypal patients ($P < 0.001$ for the right) (Fig. 3C). As a significant diagnosis × gender interaction was also found, we made *post hoc* comparisons separately in each gender. In the male subjects, significant volume reductions of the left inferior frontal gyrus were found in the patients with schizotypal disorder ($P = 0.001$) and schizophrenia ($P = 0.020$) compared with the controls. The female patients with schizophrenia had a significantly smaller volume than the patients with schizotypal disorder ($P < 0.001$ for both hemispheres) and the controls ($P < 0.001$ for the left and $P = 0.001$ for the right).

Compared with the controls, the straight gyrus volume was significantly smaller in the patients with schizotypal disorder ($P = 0.037$ for the right) and schizophrenia ($P < 0.001$ for both hemispheres) (Fig. 3D).

Correlations between volume measures and clinical variables

Partial correlation analyses controlling for ICV and age did not reveal any significant correlation between the volume measures of each ROI and daily dosage of neuroleptic medication or duration of medication in either the schizotypal disorder or the schizophrenia group. In addition, the volume measures were not significantly correlated with age at onset of illness or duration of illness in the schizophrenia patients.

To test the possibility that increases in the prefrontal cortex volumes in the schizotypal group reflect the compensatory mechanism secondary to the medial temporal lobe abnormalities, partial correlation coefficients were calculated between the volume of the right prefrontal grey matter or the bilateral middle frontal gyri and the volume of the amygdala or the hippocampus. The right hippocampal volume was significantly correlated with the right prefrontal grey matter volume ($r = -0.620$, $P = 0.002$) and the left middle frontal gyrus volume ($r = -0.607$, $P = 0.002$) even after Bonferroni correction ($P < 0.004$).

Discussion

There are two main points in this study: (i) volumes of the amygdala and the hippocampus were commonly reduced in patients with schizophrenia and schizotypal disorder; (ii) volumes of the subcomponents of the prefrontal cortex were widely reduced in schizophrenia patients, whereas those in schizotypal subjects were mostly preserved.

Temporolimbic pathology as vulnerability

Consistent with the previous VBM study (Kawasaki *et al.*, 2004), the present results suggest that the volume reduction of the amygdala and hippocampus is a common morphological basis for the schizophrenia spectrum. Studies of family members of patients with schizophrenia have also revealed evidence of medial temporal abnormalities similar to those found in schizophrenia patients (Lawrie *et al.*, 1999; Seidman *et al.*, 1999, 2002; Van Erp *et al.*, 2002). Schizotypal disorder has dual aspects that are contradictory in relation to the liability to schizophrenia. Schizotypal subjects are generally spared overt psychosis in spite of the presence of incipient psychotic symptoms. On the other hand, they have a higher incidence of developing schizophrenia than the general population (Fenton and McGlashan, 1989). Thus they are assumed to have vulnerability to schizophrenia but are simultaneously protected from developing full-blown psychosis. Our findings support the notion that reduced temporolimbic volume represents a vulnerability marker, which is necessary but not sufficient for developing schizophrenia (Seidman *et al.*, 2002; Kurachi, 2003*a*, *b*).

Prefrontal involvement in schizophrenia

There seems general agreement that total prefrontal grey matter is reduced in patients with schizophrenia compared with healthy subjects (Shenton *et al.*, 2001; Selemon *et al.*, 2002). However, findings in previous studies that have parcellated the prefrontal cortex into subcomponents have varied in spatial distribution of the gross anatomical changes within the prefrontal cortex in schizophrenia (Buchanan *et al.*, 1998, 2004; Baaré *et al.*, 1999; Goldstein *et al.*, 1999; Crespo-Facorro *et al.*, 2000; Gur *et al.*, 2000; Sanfilipo *et al.*, 2000; Convit *et al.*, 2001; Yamasue *et al.*, 2004). These inconsistencies may be due, in large part, to the use of different image measurement procedures. In particular, there has been substantial variability among studies in definitions of boundaries subdividing the prefrontal cortex into subcomponents.

The present study demarcated the prefrontal ROIs by fully taking account of the anatomical landmarks intrinsic to the frontal lobe, and revealed widespread alterations in volume of the prefrontal cortex in schizophrenia. This is consistent with the observation that schizophrenia patients have deficits in extensive neurobehavioural domains involving the prefrontal cortex, such as cognition including executive functions, motivation and emotion (Goldman-Rakic and Selemon, 1997).

The present study also suggested a considerable preference for anatomical involvement of the prefrontal cortex in schizophrenia. When the superior frontal gyrus was subdivided into dorsolateral and medial parts, significant volume reduction