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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)

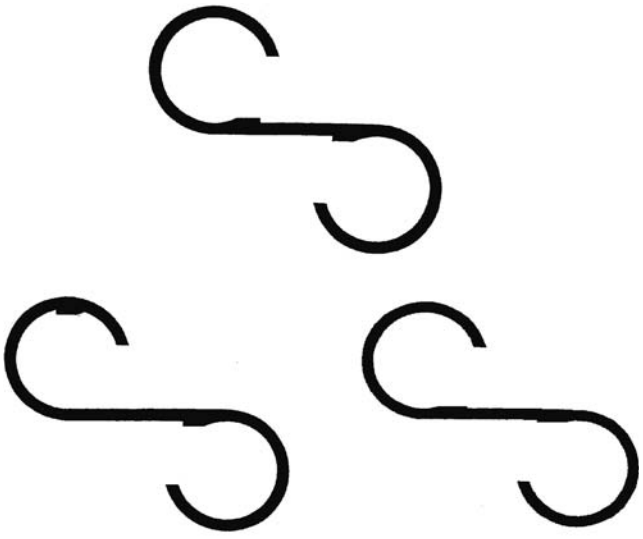

Fig. 1 The top figure is the original and the two bottom figures are slightly different from the original

■ **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.

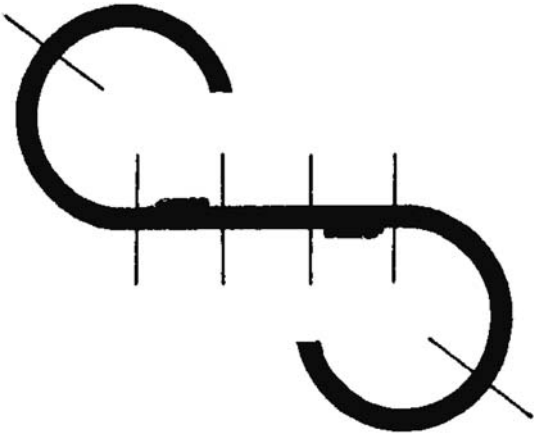

Fig. 2 The three figures were each divided into seven sections. The maximum possible score of responsive search score (RSS) was 7 for each figure

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

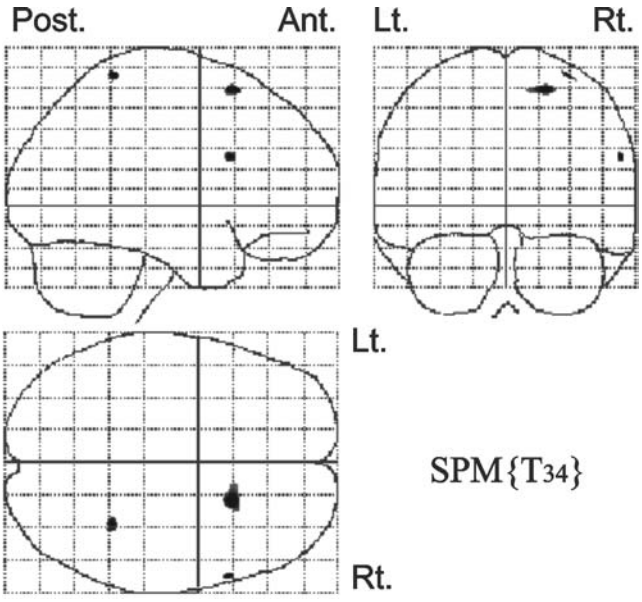

Fig. 3 Distribution of significant voxels with positive correlations between the RSS and the gray matter concentration. The SPM{t} is thresholded at $p < 0.05$ corrected for entire volume

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

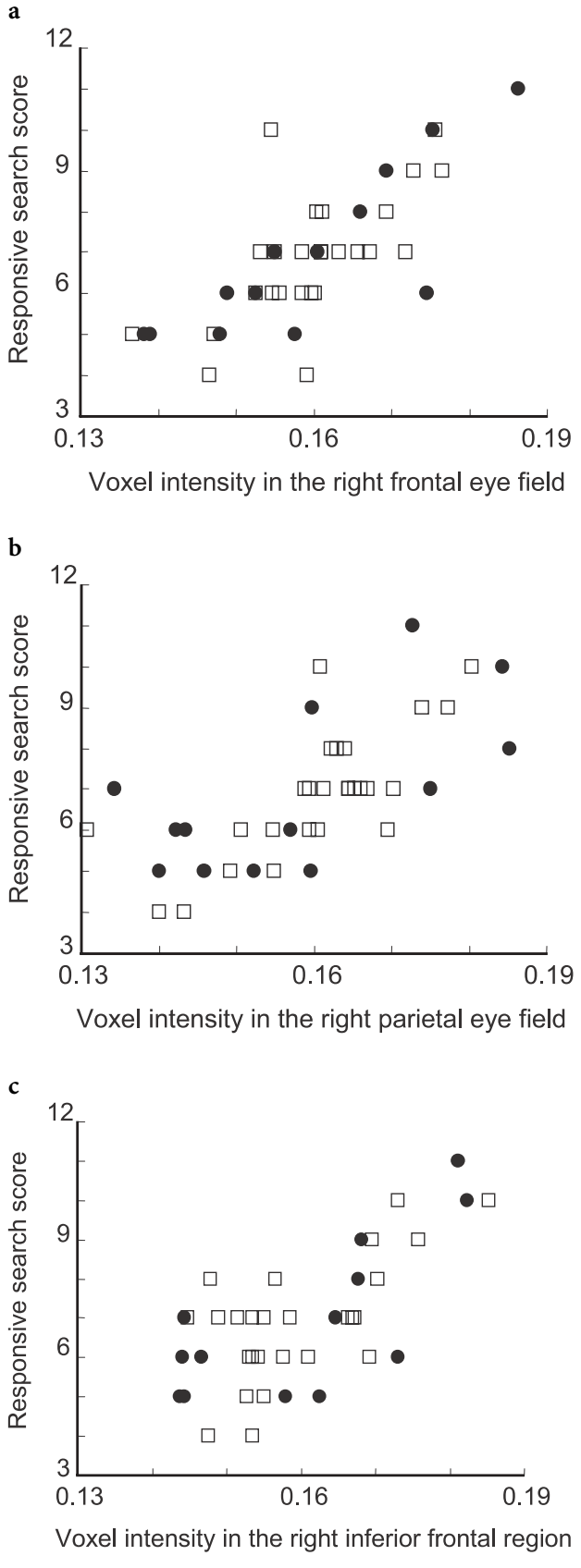

Fig. 4 Correlation between RSS and gray matter concentration in the right frontal eye field (**a**), right parietal eye field (**b**), and right inferior frontal region (**c**). □ schizophrenia; ● schizotypal disorder

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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