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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

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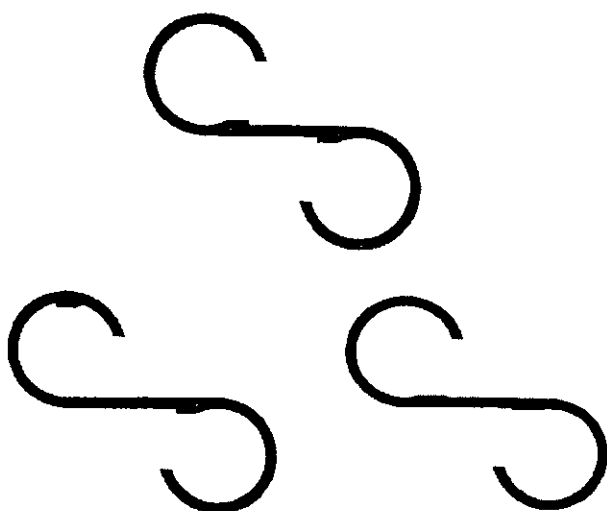
Fig. 1 The top figure is the original and the two bottom figures are slightly different from the original

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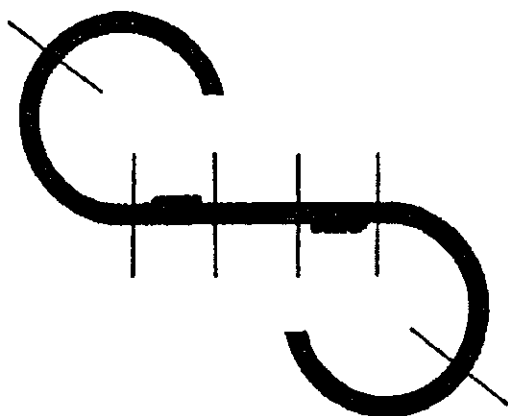
Fig. 2 The three figures were each divided into seven sections. The maximum possible score of responsive search score (RSS) was 7 for each figure

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 $= 256 \times 192$; voxel size $= 1.0 \times 1.0 \times 1.0$ 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.

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.

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

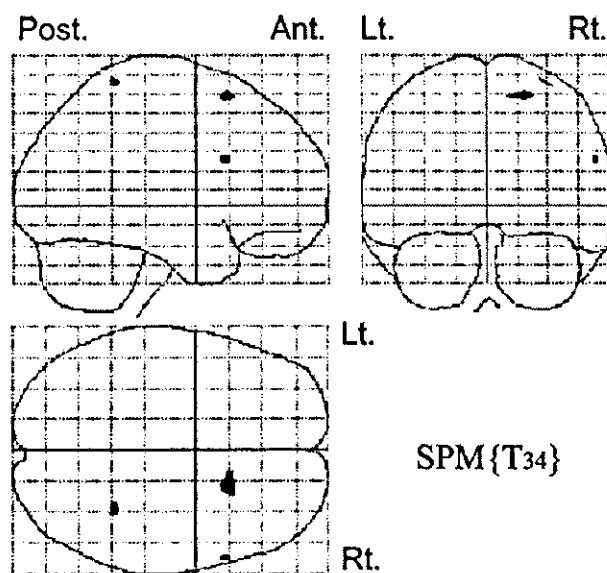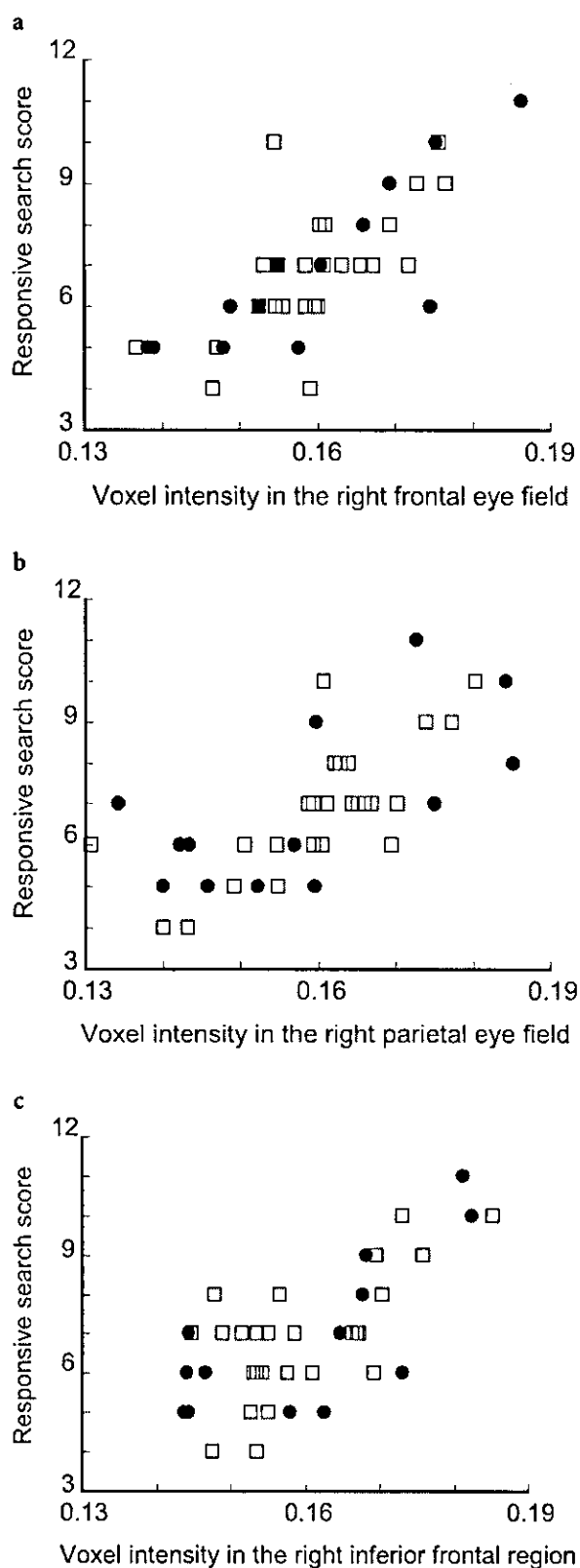|	Schizophrenia patients (n = 26)	Schizotypal patients (n = 13)
RSS	6.8 ± 1.6	7.2 ± 2.0
MNF	27.2 ± 3.8	28.7 ± 3.0
MDF (s)	0.41 ± 0.06	0.39 ± 0.05
MSL (deg)	5.7 ± 1.0	5.8 ± 0.6
ERF	4.8 ± 1.2	5.1 ± 0.8

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

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

a

Responsive search score

12

9

6

3

0.13　　　　　　0.16　　　　　　0.19

Voxel intensity in the right frontal eye field

b

Responsive search score

12

9

6

3

0.13　　　　　　0.16　　　　　　0.19

Voxel intensity in the right parietal eye field

c

Responsive search score

12

9

6

3

0.13　　　　　　0.16　　　　　　0.19

Voxel intensity in the right inferior frontal region

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

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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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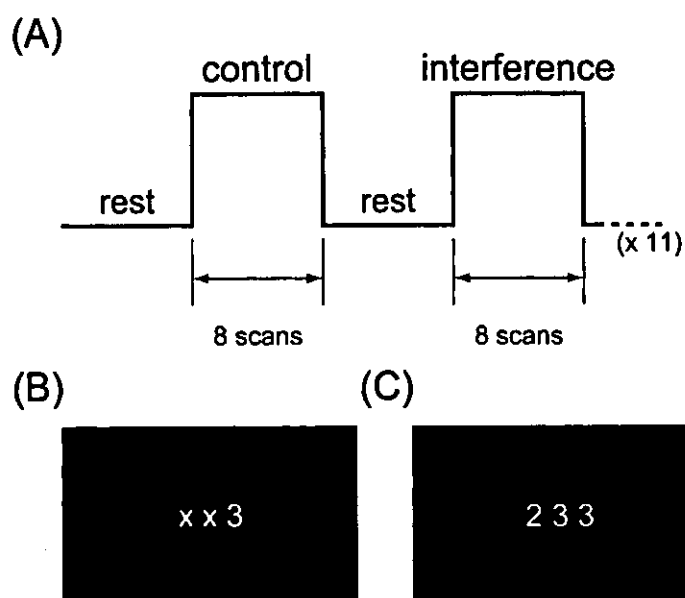
Pharmacological Modulations on the Human Cognitive Processes: An fMRI Study

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Pharmacological Modulations on the Human Cognitive Processes: An fMRI Study

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Fig. 1

Investigating modulatory effects of psychopharmacological agents in the human brain allows for not only functional characterization of particular neurotransmitter systems in the human cognition, but better understanding of pathophysiology and treatment of neuropsychiatric disorders[1]. Here we conducted a functional magnetic resonance imaging (fMRI) study to map effects of a dopamine D_2 antagonist (sultopride) on a decision-making process. In a single scanning session, ten male, right-handed, healthy subjects performed a Stroop-like cognitive interference task[2] (Fig. 1). In the absence of dopaminergic manipulations, comparison of blood oxygenation level dependent (BOLD) signals during the interference condition against those during the control condition revealed a widely distributed network implicated in the decision-making process with cognitive interference (Fig. 2A). Upon the administration of the D_2 antagonist, however, many of these regions exhibited decreased activities, and the effects were found to be most prominent in regions around the cerebellum, the thalamus, the anterior cingulate cortex, and the motor areas (Fig. 2B). Subsequent studies should address the role of individual components in the observed brain circuits, as well as what the decrements of activations mean in the neurophysiological context.

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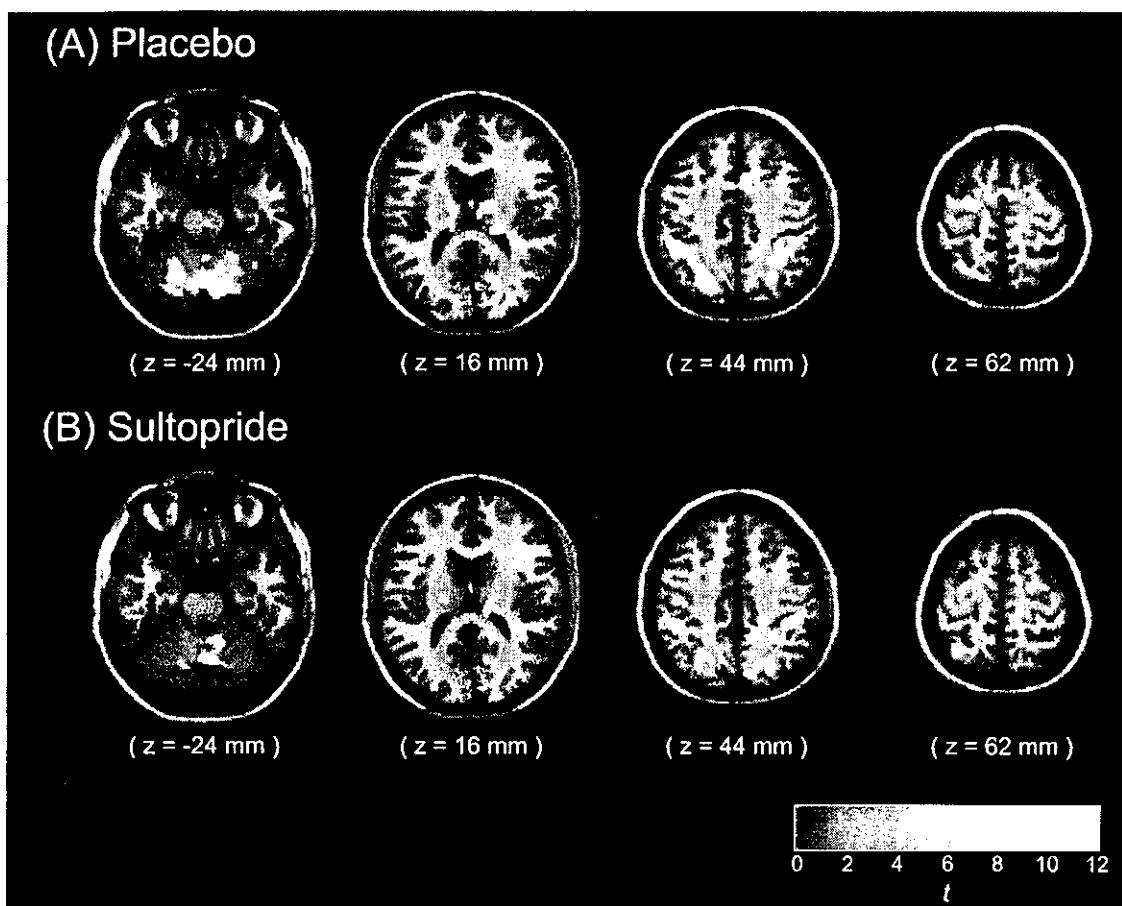
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Fig. 2

Fig. 1 (A) Schematic diagram illustrating the cognitive interference task employed. A single scanning session consisted of blocks (containing eight scans) of control and interference trials interspaced by resting periods. During the trials, subjects are instructed to report by button press the identity of the number that differs from the other two. (B)-(C) Examples of the trials. During the control trials, the distractors were the letter 'x', whereas during the interference trials, the distractors were other numbers, thereby imposing higher cognitive demands.

Fig. 2 Activated regions during the interference trials in contrast to the control trials (A) with no dopaminergic manipulations and (B) under the administration of a D_2 antagonist (sultopride). The results are based on a group analysis with statistical parametric mapping (SPM) software[3] and with a statistical threshold of $P < 0.001$ (uncorrected).

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An fMRI study of differential neural response to affective pictures in schizophrenia

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Although emotional dysfunction is considered a fundamental symptom of schizophrenia, studies investigating the neural basis of emotional dysfunction in schizophrenia are few. Using functional magnetic resonance imaging (fMRI) and a task viewing affective pictures, we aimed to examine automatic emotional response and to elucidate the neural basis of impaired emotional processing in schizophrenia. Fifteen healthy volunteers and 15 schizophrenics were studied. During the scans, the subjects were instructed to indicate how each of the presented pictures made them feel. Whole brain activities in response to the affective pictures were measured by fMRI. Controls recruited the neural circuit including amygdaloid–hippocampal region, prefrontal cortex, thalamus, basal ganglia, cerebellum, midbrain, and visual cortex while viewing unpleasant pictures. Despite an equal behavioral result to controls, the patients showed less activation in the components of the circuit (right amygdala, bilateral hippocampal region, medial prefrontal cortex (MPFC), basal ganglia, thalamus, cerebellum, midbrain, and visual cortex). This study demonstrated functional abnormalities in the neural circuit of emotional processing in schizophrenia. In particular, decreased activation in the right amygdala and MPFC appears to be an important finding related to dysfunctional emotional behavior in schizophrenia.
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Keywords: Schizophrenia; Emotion; Functional magnetic resonance imaging; Amygdala; Prefrontal cortex; Affective pictures

Introduction

Emotional dysfunction such as "flattening affect" or "anhedonia" is considered to be one of the key symptoms of schizophrenia

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(Andreasen and Flaum, 1991). Recent functional imaging techniques have revealed dysfunction of the neural circuit (interrelationship among cortical region, thalamus, basal ganglia, and cerebellum) in schizophrenia (Andreasen et al., 1999; Schultz and Andreasen, 1999). Most studies focused on cognitive dysfunction (Andreasen et al., 1999), while studies investigating the neural basis of dysfunctional emotional processing in schizophrenia are limited (Gur et al., 2002; Paradiso et al., 2003; Phillips et al., 1999; Schneider et al., 1998; Taylor et al., 2002). Previous neuroimaging studies in normal subjects revealed the neuroanatomical correlates of emotional processing and the crucial role of the amygdala in processing negative emotions. In particular, left-sided activations in the amygdala while processing negative facial expressions have been consistently reported (Calder et al., 2001). Recent functional magnetic resonance imaging (fMRI) studies revealed that schizophrenic patients demonstrated decreased activation in the bilateral amygdala during an emotion induction task by facial expressions (Schneider et al., 1998) or decreased activation in the left amygdala during a discrimination task of emotional facial expressions (Gur et al., 2002). However, discriminating analogous facial expressions is an effortful cognitive process whether subjects categorize the facial expressions by gender or emotion. Cognitive demands for elaborate recognition or detailed rating may modulate the emotional response in the brain (Critchley et al., 2000; Hariri et al., 2000; Keightley et al., 2003; Lange et al., 2003; Taylor et al., 2003). In addition, it should be noted that emotional facial expressions do not necessarily elicit the subjective experience of emotions (Davidson and Irwin, 1999).

Several activation studies used affective pictures to elicit emotion in healthy volunteers (Lane et al., 1997a,b). The task of simply viewing emotionally salient pictures could minimize cognitive demands and would be suitable for examining automatic emotional response. Only a few positron emission tomography (PET) studies have investigated the emotional processing of affective pictures with a task of rating subjective emotional experience (Taylor et al., 2002) or with a task of emotional

perception (Paradiso et al., 2003) in schizophrenia, and these studies have not established consistent results for a better understanding of dysfunctional emotional processing in schizophrenia. To our knowledge, no fMRI study has examined the neural response across the whole brain to affective pictures in schizophrenia. In the present study, we used fMRI and a task with minimal cognitive demands to identify the neural circuit of automatic emotional processing. We expected the subjects to react to affective pictures without an effortful cognitive process and categorize them roughly according to their subjective emotional experiences. Comparing the neural responses of schizophrenic patients with those of healthy controls, we aimed to elucidate the neural basis of impaired emotional processing in schizophrenia.

Methods

Subjects

Fifteen schizophrenic patients (10 men and 5 women, mean age 29.0 years, SD = 6.9) meeting the DSM-IV criteria for schizophrenia were studied. Diagnoses were made by HT, YO, and the psychiatrists in charge based on a review of their charts and a conventionally semi-structured interview. Exclusion criteria were current or past substance abuse and a history of alcohol-related problems, mood disorder, or organic brain disease. Thirteen patients were recruited from the outpatient unit of Asai Hospital, and two were recruited from the inpatient unit. Eleven of the 15 patients received atypical neuroleptics (mean risperidone equivalent daily dosage = 1.60 mg, SD = 1.31), and the other four received no neuroleptics. The mean illness duration was 4.9 (SD = 4.9) years. Clinical symptoms were assessed by the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). The mean score of BPRS was 17.9 (SD = 5.7). The ratings were reviewed by HT and YO after the patient interview, and disagreements were resolved by consensus; consensus ratings were used in this study. Fifteen normal controls (nine men and six women, mean age 29.1 years, SD = 7.8) were recruited from the surrounding community. The candidates were carefully screened and standardized interviews were conducted by trained psychiatrists (HT and YO). They did not meet criteria for any psychiatric disorder. None of the controls were taking alcohol and medication at the time, nor did they have a history of psychiatric disorder, significant physical illness, head injury, neurological disorder, or alcohol or drug dependence. Patients had a tendency of a lower educational status (patients 13.7 ± 1.5 years, controls 14.9 ± 2.4 years; $P = 0.11$, t test). All of the patients and controls were right-handed, and they all underwent an MRI to rule out cerebral anatomic abnormalities. After the procedures had been fully explained to the subjects, written informed consent was obtained, as approved by the Ethics Committee.

Stimulus and self-rating

Stimulus materials were taken from the International Affective Picture System (IAPS) (Lang et al., 1997). Pictures were divided into three emotional classes (neutral, unpleasant, and pleasant) according to the subjective ratings provided by IAPS. We employed 40 pictures from each class. The mean valence and arousal ratings of 40 pictures were 5.87 (SD = 0.77) and 3.75 (SD = 1.11) for

neutral, 3.07 (SD = 0.69) and 5.75 (SD = 0.83) for unpleasant, and 7.42 (SD = 0.36) and 4.65 (SD = 0.95) for pleasant pictures. Slides of the three emotional classes were matched for content (faces, human figures, animals, objects, and scenery). The pictures were projected via a computer and a telephoto lens onto a screen with a mirror mounted on a head-coil. The experimental design consisted of eight blocks for each of the three conditions (neutral, unpleasant, and pleasant) interleaved with 20-s rest periods. During the rest condition, subjects viewed a crosshair projected at the center of the screen. In each 20-s block, five different pictures of the same emotional class were presented for 3.5 s each, with an interstimulus interval of 0.5 s. During the scans, the subjects were instructed to indicate how each picture made them feel by categorizing their subjective emotions into three emotional classes (neutral, unpleasant, and pleasant) using buttons. Signals from the buttons were transmitted to a computer outside the shielded room via infrared rays to confirm whether expected emotions were evoked in response to individual affective pictures. The rate of the appearance of expected categorizations from the 40 pictures of the same emotional class was calculated for each emotional condition. We compared the percentages of expected categorizations between the patient and control groups.

fMRI acquisition

The images were acquired with a 1.5-T Signa system (General Electric, Milwaukee, WI). Functional images of 240 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level-dependent (BOLD) contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; TE, 50 ms; TR, 4 s; matrix, 64 × 64; field of view, 24 × 24).

Analysis of functional imaging data

Data analysis was performed with statistical parametric mapping software package (SPM99) (Wellcome Department of Cognitive Neurology, London, UK) that runs with MATLAB (Mathworks, Natick, MA). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalized to the standard space defined by the Montreal Neurological Institute (MNI) template. After normalization, all scans had a resolution of 2 × 2 × 2 mm³. Functional images were spatially smoothed with a 3D isotropic Gaussian kernel (full width at half maximum of 8 mm). Low frequency noise was removed by applying a high-pass filter (cut-off period = 240 s) to the fMRI time series at each voxel. A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. These images were scaled to give a grand mean signal of 100 across all voxels in all images to remove global effects. Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convoluted with a hemodynamic response function. Statistical parametric maps for each contrast of the t statistic were calculated on a voxel-by-voxel basis. The t values were then transformed to unit normal distribution, resulting in z scores.

We assessed the neutral vs. rest, the unpleasant vs. rest, and the pleasant vs. rest contrasts. To assess the specific condition effect, we used the contrasts by subtracting the neutral condition from the pleasant condition and the unpleasant condition. A random effects

model, which estimates the error variance for each condition across the subjects, was implemented for group analysis. This procedure provides a better generalization to the population from which data are obtained. The contrast images were obtained from single-subject analysis and were entered into the group analysis. A one-

sample t test was applied to determine group activation for each effect. Significant clusters of activation were determined using the conjoint expected probability distribution of the height and extent of z scores with the height and extent threshold. In addition, we tested for relative differences in the pattern of neural activation by
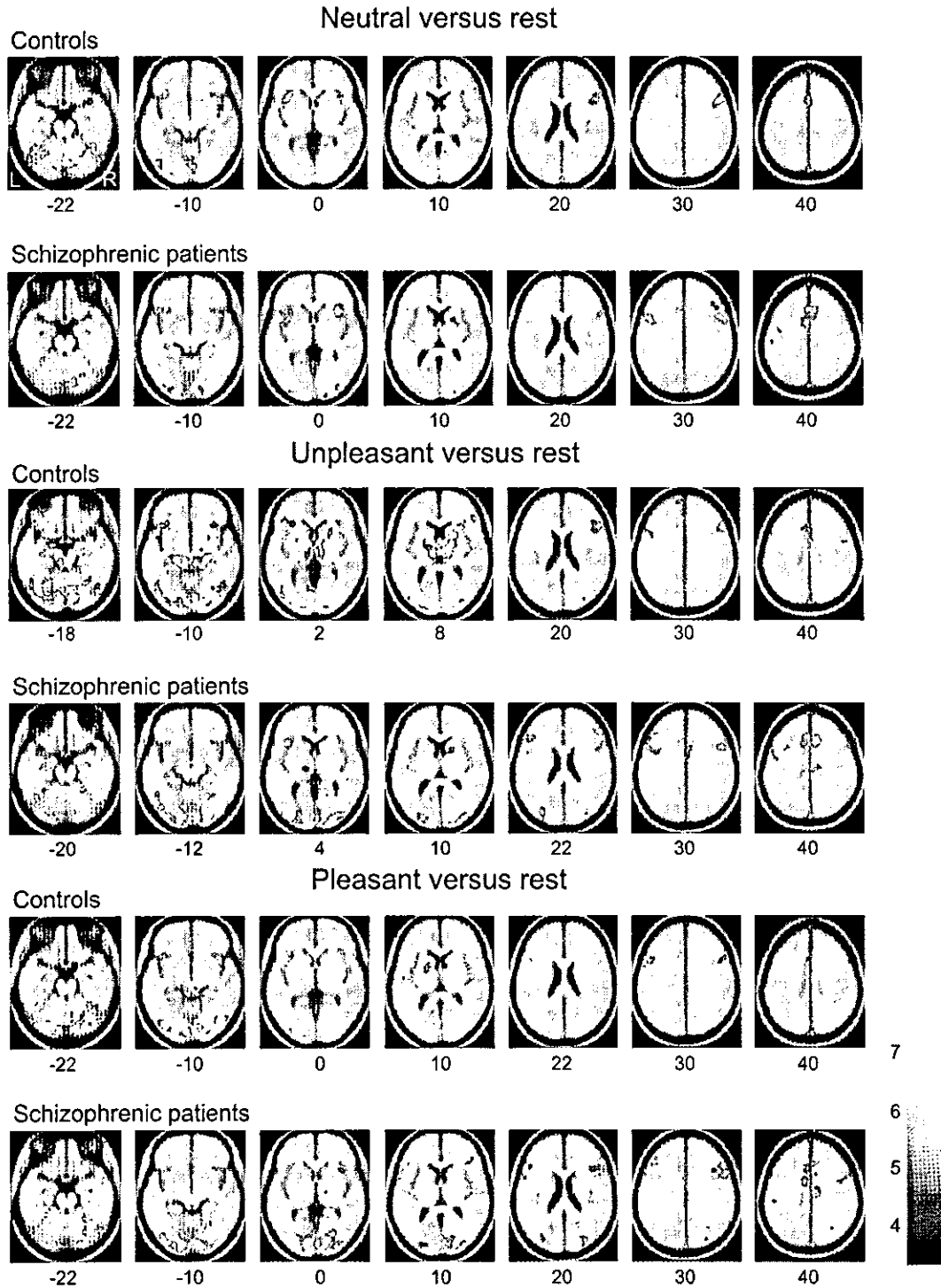

Fig. 1. Images showing brain regions of significant activation during the neutral and unpleasant conditions relative to the rest condition in 15 controls and 15 schizophrenic patients. The bar shows the range of the z score. Within the image, L indicates left and R indicates right. Significant differences were accepted at a height threshold ($z > 4.75$; $P < 0.000001$, uncorrected) and extent threshold (30 voxels). Numbers in the bottom row indicate the z coordinates of the Montreal Neurological Institute brain.

Table 1

Brain regions of significant activation during unpleasant condition relative to neutral in 15 controls and 15 schizophrenic patients

	Brain region	Brodmann's area	Coordinates[a]			z score[b]
			x	y	z	
Controls	Left lingual gyrus	17, 18, 19	−16	−88	−9	5.61
	Right lingual gyrus	17, 18, 19	8	−82	−1	5.33
	Left fusiform gyrus	19, 37	−32	−76	−8	5.8
	Right fusiform gyrus	18, 37	22	−88	−11	4.95
	Posterior cingulate	31	−2	−53	23	4.39
	Left hippocampal region	34, 35	−18	−26	−12	5.31
	Right hippocampal region	27, 28	24	−24	−9	5.55
	Left amygdala		−24	−3	−18	4.29
	Right amygdala		28	−1	−18	5.02
	Left thalamus		−10	0	7	4.71
	Right thalamus		18	−8	10	4.18
	Left caudate nucleus		−14	10	11	4.7
	Medial prefrontal cortex	9	−4	50	25	4.73
	Right orbitofrontal cortex	47	32	27	−6	4.65
	Cerebellum		32	−77	−18	6.18
	Midbrain		−6	−33	−8	5.35
Schizophrenia	Left lingual gyrus	17, 18, 19	−18	91	3	4.68
	Right lingual gyrus	17	14	−90	6	4.07
	Left fusiform gyrus	19	−20	−80	−11	4.3
	Right fusiform gyrus	19	24	−80	−11	4.33[c]
	Left amygdala		−22	−6	−18	4.56[c]

[a] Talairach and Tournoux coordinates in the local point of maximal activation included in the cluster.

[b] Significant differences were accepted at a height threshold ($z > 3.89$; $P < 0.00005$, uncorrected) and extent threshold (30 voxels).

[c] Right visual cortex and left amygdala in schizophrenia survived the height threshold but not the extent threshold.

subtracting the unpleasant minus neutral (U − N) contrasts of the patients from the U − N contrasts of the controls and vice versa. Between-group comparison was performed with a two-sample t test. Using the effect sizes, representing the percent signal change, of the U − N contrasts at the regional maxima uncovered in the between-group comparisons, we analyzed whether the BOLD signal change was correlated with the dosage of neuroleptics and the BPRS score. Coordinates of activation were converted from MNI coordinates to Talairach and Tournoux (1988) coordinates using the mni2tal algorithm (M. Brett, Cambridge, MA). Contrast images were overlaid onto a group mean anatomy image provided by SPM for viewing.

Results

Self-rating

The mean percentages of expected categorizations of the controls for the neutral, unpleasant, and pleasant pictures were 85.3% (SD = 8.3), 88.8% (SD = 11.3), and 59.0% (SD = 22.8), respectively, and those of the schizophrenic patients were 81.3% (SD = 8.3), 92.0% (SD = 9.5), and 55.0% (SD = 34.8), respectively. Two-way repeated-measures analysis of variance of the percentages of expected categorizations showed a significant main effect of condition ($F = 27.6$, $df = 2$, 84, $P < 0.001$), but not a significant main effect of group ($F = 0.26$, $df = 1$, 84, $P = 0.61$) or interaction ($F = 0.44$, $df = 2$, 84, $P = 0.64$). A post hoc test revealed that the percentage of expected category for the pleasant pictures was lower than those for the neutral and unpleasant pictures. That is, the subjects did not categorize the pleasant pictures as we had expected. Most of the remaining pictures not regarded as pleasant were categorized as neutral.
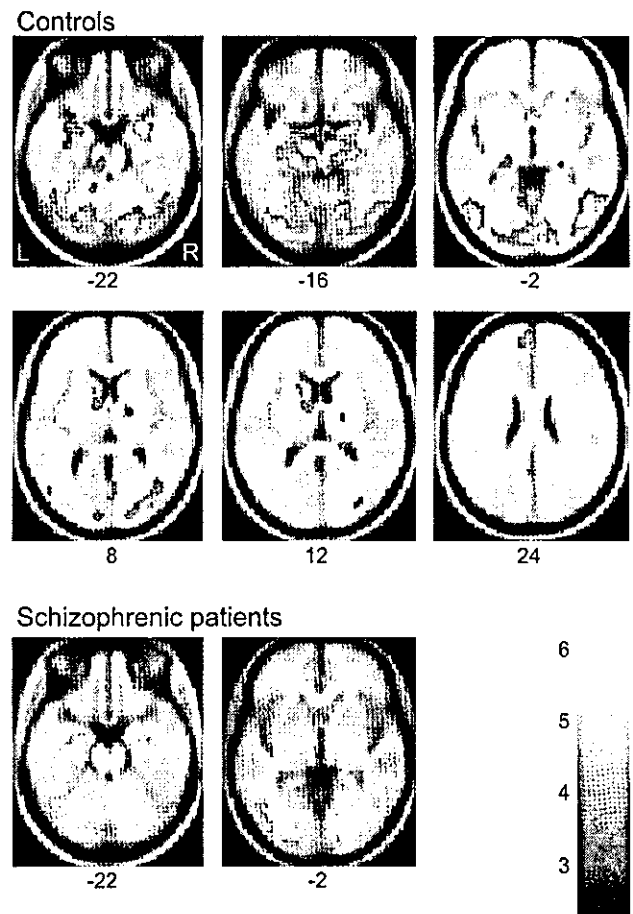

Fig. 2. Images showing brain regions of significant activation during unpleasant condition relative to neutral in 15 controls and 15 schizophrenic patients. The bar shows the range of the z score. Within the image, L indicates left and R indicates right. Significant differences were accepted at a height threshold ($z > 3.89$; $P < 0.00005$, uncorrected) and extent threshold (30 voxels). (Right visual cortex and left amygdala in the schizophrenic patients survived the height threshold but not the extent threshold.) Numbers in the bottom row indicate the z coordinates of the Montreal Neurological Institute brain.

fMRI data

Within-group comparisons

Both groups showed similar activation patterns in the neutral vs. rest contrast and in the pleasant vs. rest contrast (Fig. 1, top and bottom). Moreover, activation patterns in the neutral vs. rest contrast and the pleasant vs. rest contrast were also similar. In fact, significant activation in response to pleasant pictures relative to neutral pictures was seen only in the visual cortex (lingual gyrus) across groups (height threshold: $z > 4.75$ and extent threshold > 30 voxels). However, the two groups showed different activation patterns during the unpleasant condition compared to the rest condition (Fig. 1, middle). The controls demonstrated significant activation in response to unpleasant pictures relative to neutral pictures in the bilateral primary and secondary visual cortex, bilateral amygdala, bilateral hippocampal regions, medial prefrontal cortex (MPFC), right orbitofrontal cortex (OFC), bilateral thalamus, left caudate nucleus, cerebellum, and midbrain. Patients demonstrated significant activation in response to unpleasant pictures relative to neutral pictures in the bilateral primary and secondary visual cortex and left amygdala (Table 1 and Fig. 2).

Between-group comparisons

The group comparison of the U − N contrasts showed that schizophrenic patients demonstrated less activation in the right amygdala, bilateral hippocampal regions, MPFC, left visual cortex, left putamen, left caudate nucleus, left posterior thalamus, cerebellum, and midbrain (Table 2 and Fig. 3). No significantly greater activation was identified in schizophrenic patients in the between-group comparison of the U − N contrasts. We did not use between-group analysis for the pleasant minus neutral (P − N) contrast due to its meager activation across groups, possibly resulting from insufficient elicitation of pleasantness.

Correlations with BOLD signal change

There were no correlations between dosage of neuroleptics and signal change in the brain regions where patients showed decreased activation. In addition, no correlations were found between the BPRS score and signal change in these regions (Pearson's correlation analysis, $P > 0.05$).
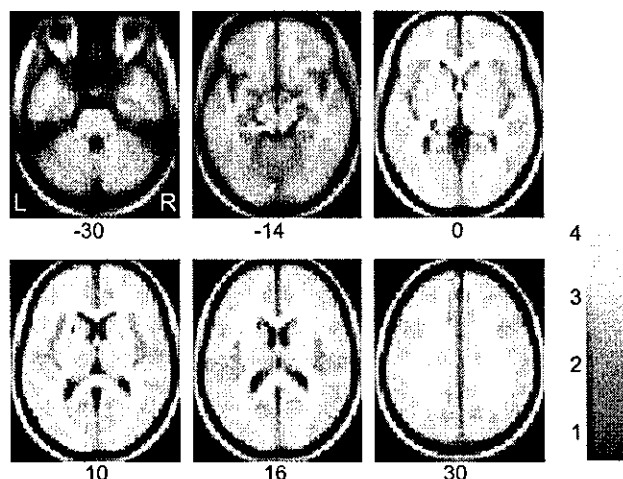

Fig. 3. Images showing brain area of relatively less activation (unpleasant minus neutral) in 15 schizophrenic patients compared with 15 normal controls. The bar shows the range of the z score. Within the image, L indicates left and R indicates right. Activation differences were considered significant at height threshold ($z > 2.57$; $P < 0.005$, uncorrected) and extent threshold (30 voxels). Numbers in the bottom row indicate the z coordinates of the Montreal Neurological Institute brain.

Discussion

In control subjects, we identified the neural circuit of the automatic emotional response to unpleasant pictures in the amygdaloid–hippocampal region, thalamus, OFC, MPFC, basal ganglia, cerebellum, midbrain, and visual cortex. We used evocative pictures with minimal cognitive demands so as to examine the automatic emotional response that requires no elaborate rating or categorization of stimuli for the subjects. Facial expressions do not necessarily elicit strong emotions, and cognitive demands such as discriminating analogous facial expressions might affect brain activations (Critchley et al., 2000; Hariri et al., 2000; Keightley et al., 2003; Lange et al., 2003; Taylor et al., 2003). Passive emotional tasks with minimal cognitive demands might activate the amygdala and other subcortical regions more often than emotional tasks with greater cognitive demands (Phan et al., 2002). Thus, we successfully observed robust activation in widespread cortical and subcortical regions as reported in previous studies (Lane et al., 1997a,b).

The cortical–basal ganglia–thalamic circuit has been implicated in cognitive or emotional processing (Alexander et al., 1986). The circuit involving the components of the cortical–basal ganglia–thalamic circuit along with the amygdala appears to be involved in the control of emotional behavior (Groenewegen and Uylings, 2000; Price et al., 1996), and dysfunction of this circuit is considered to cause mood disorder (Drevets, 2001).

Despite similar categorizations of pictures for the controls, patients demonstrated less activation in the amygdaloid–hippocampal region, MPFC, thalamus, basal ganglia, cerebellum, midbrain, and visual cortex. This finding represented evidence of functional abnormalities in the neural circuit involving the cortical–basal ganglia–thalamic circuit and the amygdala in schizophrenia. Our patients showed decreased cerebellar activation as well. Considering the fact that neuroimaging studies of schizophrenia using a variety of cognitive tasks have demonstrated a disruption in the cortical–cerebellar–thalamic–cortical circuit

Table 2

Brain regions with relatively less activation (unpleasant minus neutral) in 15 schizophrenic patients compared with 15 normal controls

Brain region	Brodmann's area	Coordinates[a]			z score[b]
		x	y	z	
Left lingual gyrus	18	−8	−88	−11	3.18
Left hippocampal region	30, 35	−14	−32	−12	3.83
Right hippocampal region	28	26	−24	−9	3.14
Right amygdala		24	−3	−13	3.39
Left thalamus		−22	−25	1	3.08
Left putamen		−20	12	9	2.88
Left caudate nucleus		−16	14	14	2.87
Medial prefrontal cortex	9	−2	54	25	3.21
Cerebellum		−14	−46	−23	3.06
Midbrain		−6	−26	−10	3.15

[a] Talairach and Tournoux coordinates in the local point maximal activation included in the cluster.

[b] Activation differences were considered significant at height threshold ($z > 2.57$; $P < 0.005$, uncorrected) and extent threshold (30 voxels).

(CCTCC) leading to cognitive deficits (Andreasen et al., 1999), the functional abnormalities in the CCTCC along with the limbic area might lead to the emotional dysfunction in schizophrenia. Our results could also be interpreted in this manner, supporting the notion that schizophrenic patients have disruption in the distributed neural circuit, although cortical regions vary depending on the task (Andreasen et al., 1999).

The amygdala and PFC are considered to be key nodes of the neural circuit of emotional processing, the former a main signal generator and the latter a modulator (Davidson, 2002; Drevets, 2000). Previous fMRI studies using facial expressions showed decreased activation in the bilateral amygdala (Schneider et al., 1998) or left amygdala (Gur et al., 2002) in schizophrenia. However, our patients showed significantly less activation in the right amygdala. These inconsistent findings might be due to differences in the emotional tasks. The left amygdala activation has been consistently reported in the processing of emotional facial expressions (Calder et al., 2001), and the right amygdala has been suggested to have a higher affinity with picture processing (Keightley et al., 2003; Markowitsch, 1998). It has also been suggested that cognitive or attention-demanding aspects of the emotional task could attenuate amygdala activation (Critchley et al., 2000; Hariri et al., 2000; Keightley et al., 2003; Taylor et al., 2003). Using affective pictures and minimizing cognitive demands, we demonstrated robust activation in the right amygdala as well as in the left amygdala in controls. This result concerning right amygdala activation could be attributed to group differences. Another interpretation of patients showing less activation in the right amygdala might be possible. Several lines of evidence have suggested the functional laterality of the amygdala, that is, the right amygdala may engage in a rapid automatic processing of ambiguous information, while the left amygdala may participate in conscious evaluation of significant stimuli (Critchley et al., 2000; Markowitsch, 1998; Morris et al., 1998, 1999; Phelps et al., 2001; Wright et al., 2001). Taking this into account, schizophrenic patients might have relatively intact function of conscious processing of significant information, leading to a categorization of pictures similar to that of controls, but impairment of the rapid, automatic processing of salient stimuli. In other words, patients could assign significance to stimuli through conscious processing, but they might have diminished automatic emotional response to external stimuli.

A PET study using IAPS reported that schizophrenic patients showed decreased activation in the right amygdala in response to non-aversive pictures (Taylor et al., 2002). In that study, non-aversive pictures elicited robust activation in the bilateral amygdala and aversive pictures failed to elicit greater activation in the amygdala relative to non-aversive pictures. In other words, their non-aversive pictures were not "neutral" and they might have contained emotionally salient features. In this regard, our result is consistent with this previous finding. By contrast, another recent PET study using IAPS reported decreased activation in the left amygdala in schizophrenia (Paradiso et al., 2003). Unfortunately, the study did not set up a neutral condition. Without such a condition, it remains unclear whether the decreased activation in response to unpleasant pictures stems from impairment in emotional processing of unpleasant pictures or in a more basic cognitive function such as visual perception or object recognition. We ruled out the latter possibility by comparing the activation in response to neutral stimuli across groups. Obviously, more research is needed on the abnormal amygdala function in schizophrenia.

Within the PFC, another key node of the neural circuit of emotional processing, we found decreased activation in the MPFC in patients. The MPFC was commonly activated in studies about emotional response in healthy subjects, and its activation was not specific to particular emotion or induction methods with or without cognitive components (Phan et al., 2002). The MPFC is assumed to play general roles in emotional processing such as attention to emotion, identification or regulation of emotion (Reiman et al., 1997; Teasdale et al., 1999), and guiding motivational behavior by modulating or appraising autonomic emotional responses (Drevets, 2001; Epstein et al., 1999; Phillips et al., 2003). The decreased activation in the MPFC in our patients appears to be an important finding with respect to abnormal motivational behavior in schizophrenia. In contrast, the PET study using IAPS showed hyperactivation in the MPFC in schizophrenia, contrary to the author's expectation (Taylor et al., 2002). These contradictory results therefore emphasize the need for further studies of the activation of the MPFC in schizophrenia.

The present study has several limitations. First, most of the patients were taking neuroleptic medications, possibly affecting neural activation. They were, however, taking atypical neuroleptics, and at relatively low doses. To our knowledge, there has been no previous study on the effect of neuroleptics on the BOLD response of emotional processing. Compared to typical neuroleptics, atypical neuroleptics have shown less influence on BOLD contrast in the motor area or thalamus during a finger-tapping task (Braus et al., 1999; Muller and Klein, 2000). Future studies with neuroleptic-naive patients, where the effect of neuroleptics can be controlled, will clarify this possible limitation. Second, we could not demonstrate any correlation between signal changes and BPRS scores in patients, possibly due to a lack of dispersion in the psychopathology of the patients, most of them being non-deficit outpatients with mild psychiatric symptoms. Third, the unpleasant pictures contained emotional features ranging from fear to disgust, and we could not differentiate the processing of particular emotions. In the processing of fear, the amygdala plays a central role. In contrast, the basal ganglia rather than the amygdala is considered to be essential in the processing of disgust (Calder et al., 2001; Phan et al., 2002). Thus, activation in the components of the neural circuit, the amygdala and basal ganglia, might reflect both emotional processing. Finally, we have difficulties in measuring emotional behaviors. This point has implications for the interpretation of the discrepancy between normal behavioral result and the abnormal neural activations observed in schizophrenic patients, as was also reported in previous studies (Gur et al., 2002; Paradiso et al., 2003; Schneider et al., 1998; Taylor et al., 2002). Our task could be regarded as an emotion-induction task. However, the finding needs to be interpreted cautiously because, strictly speaking, our task was testing the access to autonoetic perception of elicited emotions. It might be possible that the ability of schizophrenic patients to access their emotions (categorization of feeling) was different from that of normal controls. Our behavioral results might not necessarily reflect gut-level elicited emotion that drives emotional behavior. Autonomic data such as skin conductance responses would help to measure gut-level emotional response.

In conclusion, we investigated the automatic emotional response in healthy controls and schizophrenic patients. By using a task with minimal cognitive demands, we identified robust activation across the neural circuit of emotional processing including the amygdaloid–hippocampal region, prefrontal cortex, thalamus, and basal ganglia in response to unpleasant stimuli in the controls.

Schizophrenic patients demonstrated less activation in the components of the circuit. In particular, decreased activation in the right amygdala and MPFC, the key structures in the circuit, could be related, respectively, to diminished automatic emotional response to external stimuli and impairment in regulating emotional responses to guide emotional behavior in schizophrenia.

Acknowledgments

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