Regional Prefrontal Abnormalities During Working Memory in Schizophrenia: A Topography-based Functional Activation Study

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Abstract

Although most functional and structural neuroimaging studies have reported that cognitive deficits in patients with schizophrenia are associated with prefrontal abnormalities, their findings vary considerably. The aim of this study is to find evidence of functional abnormalities in the prefrontal cortex of schizophrenia patients on the basis of exact topographical parcellation. Magnetic resonance (MR) images were obtained in 12 patients with schizophrenia and 12 age- and sex-matched normal volunteers, and parceled into 8 frontal subregions using topographic landmarks. [^{15}O]H_2O PET scans were obtained during the visual working memory task and the control task, and the activities of the parceled frontal subregions were counted on the registered PET images. In the comparison of the subregional functional activities, the normal healthy group showed a tendency t o activate the right rostral anterior cingulate during the working memory task. Comparatively, the patient group showed reduced activation of the right orbitofrontal cortex and the right caudal anterior cingulate. The results suggest that the functional c hanges observed in schizophrenia may result from the abnormal activation of the neural system for the purpose of performing working memory tasks. In particular, reduced ventromedial prefrontal activities seem to play an important role in such cognitive impairment in schizophrenia.

Key Words: Schizophrenia, Frontal subregions, MRI, PET, Working memory Psychiatr Investig 2004;1(1):37-43

Introduction

In the past two decades, functional activation studies have been increasingly used to explore the pathophysiology of schizophrenia. Among the studies performed so far, the most popular approach was to use cognitive tasks specific to the frontal lobe functions. For example, there are a number of studies showing reduced activity in the prefrontal regions during certain tasks, such as the Wisconsin card sorting test [1], Tower of London Test[2], and a verbal fluency task [3]. However, since such tasks basically require various executive functions including working memory, it is difficult to conclude which specific cognitive function relates to the prefrontal abnormalities in schizophrenia. Therefore, a cognitive task which specifically activates working memory only would be more useful in functional activation studies designed to explore the prefrontal abnormalities in schizophrenia. It has been proposed that working memory, which is the process of holding and manipulating information online in the brain, consists of three main components, namely the central executive, visual sketch pad, and phonological loop [4]. In recent functional imaging studies, working memory, especially the central executive component, has been consistently shown to be closely related to prefrontal activities[5-7]. Working memory is important not only for the memory system itself, but also for the thinking process [8]. Impairments in working memory are viewed as constituting an important factor in the various cognitive abnormalities associated with schizophrenia, and are also thought to play a fundamental role in various clinical symptoms including formal thought disorder[9]. Recently, there have been a number of studies which demonstrated that abnormalities in prefrontal activation occur during the use of working memory in patients with schizophrenia, although the results are somewhat conflicting. Reduced PET or functional MR activities were found in the

right dorsolateral prefrontal areas during visual working memory[10, 11] and auditory working memory operations [12]. However, another auditory working memory study, using a task requiring the recall of verbally given words and sounds, showed that patients with schizophrenia had decreased activities in the lateral prefrontal areas, but not in the dorsolateral prefrontal area[13]. In addition, there was also a study reporting an opposite result, in that patients with schizophrenia did not show decreases in activation in the prefrontal areas, but instead increases in the left dorsolateral prefrontal area[14].

As mentioned above, despite the existence of a considerable number of reports showing a tendency toward hypofrontality during working memory tasks, the findings of the frontal subregions are inconsistent. The reason for this may be due to differences in the subject groups, arising from the heterogeneity of the schizophrenic patients involved in these studies. The variety of paradigms used for the activation study may be another reason. There are two experimental paradigms that can be used for addressing working memory, the delayed matching task and the n-back task; the former generally emphasizes the information holding function of the prefrontal area during a certain period of time [15], whereas the latter includes information holding as well as the dynamic renewal of information through the prefrontal central executive [8, 16]. Moreover, differences in the measurement methodologies employed constitute another important factor which needs to be considered. In particular, this aspect is more critical in approaches using regions of interest (ROIs). It is inevitable that many brain regions defined as large ROIs in previous studies simultaneously include activated and suppressed subregions [17], and thus do not function homogenously. The findings of a particular study, therefore, depend on how the ROIs were defined. For these reasons, recent functional imaging studies have chosen the voxel-based approach, which is based on the linear proportional scaling system[18]. This has a significant benefit in that there is no need for artificial delineation of the ROIs, but has the disadvantage of causing the interindividual and interhemispheric variabilities to disappear. That is, the normalization of the results to a standard brain pattern, which is accomplished by performing linear and nonlinear transformation of the voxel-based analysis, forces the individuality of the functional organization to be effaced[19, 20].

Consequently, a new approach maintaining the individuality without artificial delineation is needed. This can be accomplished by topography-based delineation using sulcal landmarks on the MR images and measuring the activities on the coregistered PET images. Detailed topography-based parcellation methods have been reported in a series of studies [21-23], and subregional volumetric abnormalities were demonstrated using such methods[24].

This study was designed to investigate prefrontal functional abnormalities during the activation of working memory in patients with schizophrenia on the basis of topographically demarcated ROIs. We obtained MR images of patients with schizophrenia and normal healthy volunteers, subdivided the frontal lobe using the exact sulcal landmarks, and observed a difference in subregional PET activation during the working memory tasks between the two groups.

Materials and Methods

Subjects

The subjects were 12 patients with schizophrenia and 12 age- and sex-matched healthy volunteers. Each group contained 6 men and 6 women, all of whom were right-handed. The patients fulfilled the DSM-IV criteria for schizophrenia, as diagnosed by using the Structured Clinical Interview for DSM-IV (SCID-IV)[25]. The exclusion criteria for the study were any history of neurological or significant medical illnesses and any past history of substance abuse. The patient group had a mean age of 26.2 years (SD=4.0), a mean number of years of education of 14.7 (SD=1.6), a mean parental socioeconomic status [26] of 2.9 (SD=1.1), and a mean duration of illness of 2.8 years (SD=3.2) at the time the PET scan was performed. Symptom severity was assessed with the Positive and Negative Syndrome Scale [27]; the patients' mean scores were 14.1 (SD=6.6) for the positive symptoms, 17.6 (SD=6.8) for the negative symptoms, 31.3 (SD=6.0) for the general symptoms, and 62.9 (SD=10.7) overall. All of the patients were taking one or two atypical neuroleptics, such as risperidone, olanzapine and clozapine. The healthy volunteers were recruited through a newspaper and internet advertisement, and were excluded if any history of psychiatric or neurological disorder was present. They had a mean age of 25.6 (SD=4.8), a mean number of years of education of 15.3 (SD=1.6), and a mean parental socioeconomic status of 3.2 (SD=1.0), with these values not being significantly different from those of the patient group. All of the subjects were given a full outline of the study and written informed consent was obtained.

Brain MRI and the Frontal Lobe Parcellation

Three-dimensional T1-weighted spoiled gradient echo MR images were acquired on a 1.5 Tesla GE SIGNA Scanner (GE Medical Systems, Milwaukee, USA). The imaging parameters were as follows: 1.5mm sagittal slices, echo time=5.5ms, repetition time=14.4ms, number of excitations=1, rotation angle=20 degrees, field of view=210x210mm, and a matrix of 256x256 was used. The MR images were processed using an image-processing software package, ANALYZE (version 3.0, Mayo Foundation, USA). The images were resampled to 1.0 mm^3 iso-voxels, reoriented to the conventional position, and spatially realigned, so that the anterior-posterior axis of the brain was aligned parallel to the inter-commissural line, and the other two axes were aligned along the inter-hemispheric fissure. The data sets were then filtered using anisotropic diffusion methods to improve the signal to noise ratio. In order to extract those parts of the images corresponding to the brain, tissues exterior to the brain were removed from the images by the semi-automated region growing method. By employing the fuzzy C-means algorithm [28], the extracted brain images were segmented into three regions, namely the gray matter, white matter and cerebrospinal fluid. The intracranial volume was calculated by adding the subtotal volume of the three components. The frontal lobe was parcellated into 8 ROIs, namely the superior frontal gyrus, the middle frontal gyrus, the inferior frontal gyrus, the orbitofrontal cortex, the rostral anterior cingulate, the caudal anterior cingulate, the supplementary motor area and the precentral gyrus. The boundaries of each subregion were obtained from previous reports by a team in which one of the authors of the present study was included [21], and a detailed description of the parcellation method can be found in a previous report by one of the authors[24].

Brain PET and Cognitive Activation

PET imaging data acquisition Scans were obtained using an ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN, USA). Before the first injection of the tracer, a 7-min transmission scan was performed for the purpose of attenuation

correction. Emission scans during the performance of the cognitive tasks started after an intravenous bolus injection of 30-50 mCi of [$^{15}O]H_2O$ in 5-7 ml saline and continued for 100 seconds, being recorded in the form of twenty 5-s frames. The injections were repeated at intervals of about 15 minutes. The acquired data were reconstructed in a 128x128x47 matrix with a pixel size of 2.1x 2.1 x3.4mm by means of a filtered back-projection algorithm employing a Shepp-Logan filter with a cut-off frequency of 0.3 cycles/pixel. Based on the time-activity curves, only the twelve frames, reflecting the 60 seconds after peak activity was reached, were summed and used to construct the static cerebral blood flow images.

Cognitive tasks In order to avoid evoking a confounding factor by poor performance, all of the subjects were trained at an explanatory session before the real PET scan was performed, during which they had to read a set of instructions describing the rules of the task, and practice the procedure described in the written instructions until they were able to perform the performance correctly. The subjects performed six tasks, of which only two were used for this study's analysis. The first task reflected simple focused attention, and was used as a control task. In this task, a circle, a rectangle and a triangle were shown randomly and the subjects were told to respond whenever the circle was presented. The second task was an experimental task with a 2-back working memory condition, in which the subjects were asked to respond whenever the circle was presented and the penultimate stimulus was also the circle. Figure 1. shows the actual stimuli and the target position. Each task consisted of 80 stimuli items and the stimuli were projected for 0.5 seconds each at 1.5-second intervals. Each task had 28 targets among 80 stimuli items, and the frequency as well as the distribution of the targets were matched. The mouse-clicking responses of the subjects were automatically stored and used for the calculation of the adequacy of the performance. The adequacy of the performance was measured by evaluating the correct answer rate, according to the equation {(total number of stimuli - error response)/total number of stimuli}x100%. The errors included missing targets and mistakenly responding to non-target stimuli. The task stimuli were automatically projected at a distance of 40 cm from subjects' eyes by means of a 15 inch LCD monitor, and the subjects were asked to click the mouse with their index finger in order to respond.

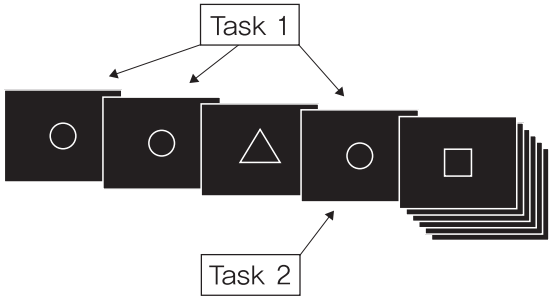

FIGURE 1 Examples showing the course of events and the targets in the control task (Task 1) and the experimental working memory task (Task 2). The stimuli consisted of simple, visually presented pictures, namely circles, equilateral quadrangles and equilateral triangles. The subjects were requested to respond whenever the circle was presented (Task 1), or only when the circle was presented again after having been presented two steps earlier (Task 2).The frequency and distribution of the targets were matched between the two tasks

Subregional Functional Measurement

Image preprocessing for the coregistration The PET images were transferred to a personal computer, and converted to the ANALYZE software file format. In order to increase the signal to noise ratio, the images were smoothed by means of a 16mm FWHM Gaussian kernel included in Statistical Parametric Mapping (SPM) 99 (Institute of Neurology, University College of London, UK) implemented in Matlab (Mathworks Inc., USA). The smoothed images were coregistered on T1-weighted MR images of the same subject using ANALYZE, and the information concerning the frontal lobe parcellation was loaded onto the MR images. Figure 2. shows the traced frontal subregions and the registered PET image loaded on the MR image.

Measurement of the subregional activities Because the total PET blood flow differed for each subject, preprocessing for the sake of calibration was done before calculating the blood flow of each separate subregion. After the mean image intensity of the total voxels was calculated, all voxels whose intensity was less than 12.5% of the calculated mean were eliminated, and the mean image intensity of the remaining voxels was recalculated. Since a standard blood flow rate of 50ml/min/dl was used for the recalculated mean image intensity, each voxel's blood flow rate was estimated by linear transformation. The adjusted mean ROI activity was calculated as the average of the estimated intensity values of all of the voxels for every parceled frontal subregion. Furthermore, the adjusted total ROI activity was calculated by multiplying the mean ROI activity by the ROI volume.

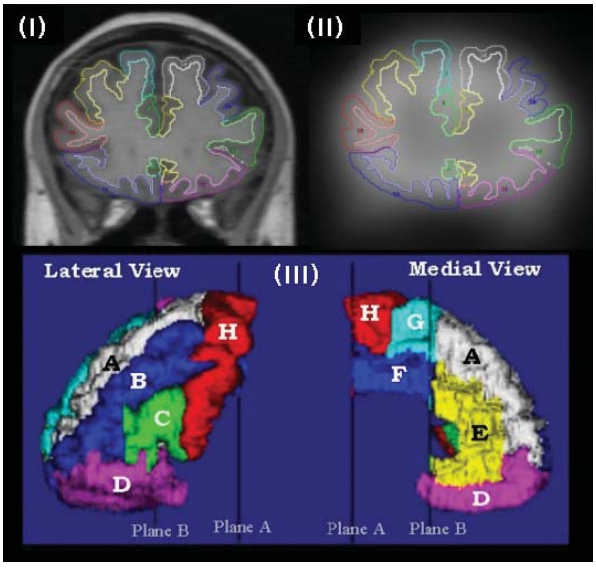

FIGURE 2 The frontal subregions traced on the magnetic resonance image (I) and applied to the registered image obtained with positron emission tomography (II). The 3D reconstructed frontal substructures displayed on the three different views (III); the regions consist of the superior frontal gyrus (A), the middle frontal gyrus (B), the inferior frontal gyrus (C), the orbitofrontal cortex (D), the rostral portion of the anterior cingulate (E), the caudal portion of the anterior cingulate (F), the supplementary motor area (G), and the precentral gyrus (H). Planes A and B indicate the artificial coronal planes, which are the posterior boundary of the medial portion of the frontal lobe in the case of plane A, and the anterior boundary of the supplementary motor area and caudal portion of the anterior cingulate, in the case of plane B

Statistical Analysis The group differences in the demographic factors and the correct response rate for the cognitive task were analyzed using the Wilcoxon rank sum test. In the case of the mean activities of the frontal subregions, the Wilcoxon rank sum test was also used for the comparison between the two groups in each task condition, whereas the Wilcoxon signed rank test was used for the comparison between the two task conditions in each group, and repeated measures ANOVA was used for the between-group differences in the changing rates between the task conditions. The same analysis method was applied to the total activities of all frontal subregions.

Results

Task performance

In the focused attention condition, the correct response rate was 99.9% (SD=0.37) in the healthy group and 99.6% (SD=0.62) in the patient group; there was no significant difference between the two groups (p=0.18). In the working memory condition, the correct response rate was 99.2% (SD=1.0) in the healthy group and 97.9% (SD=3.5) in the patient group; there was no significant difference between the two groups (p=0.32).

Comparison of the mean subregional activities

The mean activities of the frontal subregions are shown in Table 1. During both the control and working memory conditions, the mean activities of all subregions were lower in the patient group than in the healthy group. The areas where the patient group showed lower activities than the healthy group were the right caudal anterior cingulate gyrus, both sides of the superior frontal gyrus, the middle frontal gyrus, the inferior frontal gyrus, and the rostral anterior cingulate gyrus during the control condition, and both sides of the middle frontal gyrus, the inferior frontal gyrus, the rostral anterior cingulate, the caudal anterior cingulate, and the orbitofrontal cortex during the working memory condition. In the comparison of the subregional functional activities, the normal healthy group showed a tendency for the right rostral anterior cingulate to be activated during the working memory condition, whereas the patient group did not. Comparatively, the patient group showed reduced activation of the right orbitofrontal cortex and the right caudal anterior cingulate, whereas the healthy group showed no changes. As shown in Figure 3, the activities of the right orbitofrontal cortex during the working memory condition were

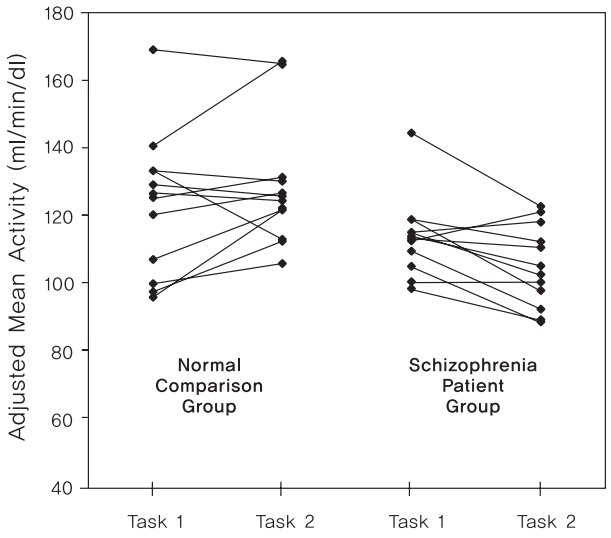

FIGURE 3 Changes of adjusted mean activities of the right orbitofrontal cortex. There is no statistical difference between the control task (Task 1) and the working memory task (Task 2) in the normal comparison group, whereas there is a tendency for the adjusted mean activity to be reduced in the working memory task when compared with the control task in the schizophrenia group (repeated measures ANOVA, p=0.006)

TABLE 1 Adjusted mean activities (ml/min/dl) of the frontal substructures between the control task (Task 1) and the working memory task (Task 2) in the normal comparison group and the schizophrenia group

Frontal substructures		Normal (n=12)		p*	Schizophrenia (n=12)		p*
		Task1	Task2		Task1	Task2	
R.	superior fronta gyrus	134.5 (19.4)	129.5 (13.7)	0.204	117.2 (12.7)	121.0 (13.9)	0.169
L.	superior frontal gyrus	133.5 (18.6)	128.9 (14.5)	0.211	115.8 (13.2)	118.9 (13.7)	0.204
R.	middle frontal gyrus	131.0 (17.0)	129.5 (11.9)	0.777	114.7 (10.2)	115.3 (12.9)	0.850
L.	middle fronta gyrus	129.3 (18.7)	127.3 (12.7)	0.733	112.4 (12.1)	113.5 (12.0)	0.926
R.	inferior frontal gyrus	141.0 (17.8)	140.5 (13.5)	1.000	122.6 (9.1)	122.0 (9.8)	0.895
L.	inferior frontal gyrus	138.3 (18.4)	137.0 (15.9)	0.970	118.9 (9.6)	118.2 (10.9)	0.622
R.	orbitofrontal cortex	123.4 (21.0)	128.9 (18.6)	0.151	114.0 (11.7)	105.3 (12.0)	0.012
L.	orbitofrontal cortex	122.5 (21.2)	128.2 (16.9)	0.301	111.9 (11.6)	103.9 (10.9)	0.055
R.	AC, rostral	158.0 (17.9)	161.5 (18.8)	0.036	142.0 (12.1)	141.3 (8.8)	0.733
L.	AC, rostral	156.6 (20.8)	156.9 (17.7)	0.556	138.9 (9.9)	136.9 (9.9)	0.339
R.	AC, caudal	151.8 (14.8)	153.4 (16.1)	0.569	137.8 (12.2)	133.0 (10.3)	0.043
L.	AC, caudal	148.2 (15.9)	150.1 (14.7)	0.380	136.6 (13.3)	129.8 (8.7)	0.129
R.	SMA	154.6 (17.4)	152.5 (14.2)	0.311	143.2 (19.4)	146.4 (17.7)	0.157
L.	SMA	150.7 (16.9)	149.0 (14.7)	0.301	145.0 (17.8)	146.5 (15.0)	0.482
R.	precentral gyrus	133.7 (16.6)	131.1 (14.0)	0.266	123.9 (12.8)	126.1 (13.8)	0.380
L.	precentral gyrus	130.4 (18.4)	128.3 (16.0)	0.380	122.0 (10.9)	124.4 (12.5)	0.240

R.: right, L.: left, AC: anterior cingulate, and SMA: supplementary motor area *p values were obtained from wilcoxon signed rank test in each group

TABLE 2 Adjusted total activities (ml/min) of the frontal substructures between the control task (Task 1) and the working memory task (Task 2) in the normal comparison group and the schizophrenia group

Frontal substructures		Normal (n=12)		p*	Schizophrenia (n=12)		p*
		Task1	Task2		Task1	Task2	
R.	superior frontal gyrus	18.8 (3.3)	18.1 (2.8)	0.151	15.0 (3.4)	15.5 (3.3)	0.151
L.	superior frontal gyrus	19.3 (3.4)	18.6 (3.4)	0.266	15.2 (3.6)	15.6 (3.6)	0.233
R.	middle frontal gyrus	29.4 (2.9)	29.1 (2.2)	0.791	22.6 (4.2)	22.7 (4.2)	0.970
L.	middle frontal gyrus	27.8 (3.8)	27.5 (4.1)	0.850	20.9 (5.0)	21.0 (4.6)	0.850
R.	inferior frontal gyrus	11.3 (3.7)	11.3 (3.8)	0.910	8.9 (2.5)	8.9 (2.5)	0.910
L.	inferior frontal gyrus	10.4 (2.9)	10.3 (2.5)	0.910	9.8 (2.2)	9.7 (2.2)	0.519
R.	orbitofrontal cortex	21.4 (3.7)	22.4 (4.3)	0.151	20.0 (2.0)	18.5 (2.0)	0.012
L.	orbitofrontal cortex	20.6 (4.7)	21.5 (4.2)	0.339	18.6 (2.5)	17.3 (2.4)	0.043
R.	AC, rostral	14.0 (2.1)	14.3 (2.6)	0.027	13.3 (3.5)	13.3 (3.3)	0.470
L.	AC, rostral	15.6 (2.9)	15.6 (2.8)	0.733	14.0 (3.6)	13.7 (3.5)	0.151
R.	AC, caudal	11.0 (1.0)	11.2 (1.4)	0.424	9.1 (1.5)	8.8 (1.5)	0.043
L.	AC, caudal	10.6 (1.9)	10.7 (1.9)	0.380	8.0 (1.3)	7.7 (1.4)	0.151
R.	SMA	4.1 (1.6)	4.1 (1.6)	0.380	2.4 (0.9)	2.4 (0.9)	0.147
L.	SMA	4.4 (1.3)	4.3 (1.3)	0.424	3.1 (1.7)	3.1 (1.6)	0.569
R.	precentral gyrus	19.5 (2.6)	19.1 (2.1)	0.301	16.9 (3.0)	17.2 (3.1)	0.301
L.	precentral gyrus	18.3 (2.9)	18.0 (3.1)	0.622	15.8 (3.1)	16.2 (3.2)	0.233

R.: right, L.: left, AC: anterior cingulate, SMA: supplementary motor area *p values were obtained from wilcoxon signed rank test in each group

increased in the healthy group, but decreased in the patient group. The significance of this feature was confirmed by repeated measures ANOVA (p=0.006).

Comparison of the total subregional activities

The total activities of the frontal subregions are shown in Table 2. The total subregional activities during the control and working memory conditions were all lower in the patient group than in the healthy group. During the control condition, this tendency toward lower activity in the patient group was especially marked in the right supplementary motor area, both sides of the superior frontal gyrus, the precentral gyrus and the caudal anterior cingulate. In the case of the working memory condition, the right superior frontal gyrus, both sides of the middle frontal gyrus, the orbitofrontal cortex, the supplementary motor area and the caudal anterior cingulate showed lower total activities in the patient group, as compared with the healthy group. In addition, as in the case of the mean subregional activities during working memory, the normal healthy group showed significant activation only in the right rostral anterior cingulate, whereas the patient group showed significantly reduced activation in the right orbitofrontal cortex and the right caudal anterior cingulate.

Discussion

The key to the validity of this study's result lies in the exact topographical parcellation of the frontal cortex. The validity of the parcellation method used in this study was already proved in a previous study [21]. We used eight frontal subregions defined by topography-based parcellation as the areas of measurement of the functional activity. We assumed that using this method would substantially help us to overcome the limitations of the voxel-based analysis method that has been widely used in recent functional neuroimaging studies. The voxel-based analysis method spatially normalizes all brain images to a standard and, therefore, the individuality of functional organization is inevitably effaced. In the current study, however, we used the subjects' own MR image instead of the normalized brain and, in this way, we were able to investigate the functional changes during cognitive load for each frontal subregion, using boundaries based on anatomical landmarks. The core hypothesis which forms the basis of this new method is that the functional map of the neocortex is individually unique, and that this individuality is directly reflected in various topographical features, such as the shapes and sizes of the sulcus and gyrus. In other words, this kind of topographical individuality reflects the cytoarchitectonic differences[29].

In fact, when classifying the cerebral cortex at the cytoarchitectonic level, each functional region should have a close spatial relationship with the corresponding region defined at the microstructural level [30]. The definition of the cerebral cortex map based on the equi-territorial hypothesis between functional and microstructural division is not yet sufficiently developed for it to be put to general use. For the time being, the best method of reflecting cytoarchitectonic diversity is to consider the morphological aspects of the gyrus and sulcus. Therefore, we used the ROI based on topographical parcellation, as this provides a viable alternative for the measurement of functional activity. Our method addresses the issue of the brain structure-function relationship in schizophrenia, because the total subregional activity includes certain aspects of the subregional volume. There can be a temporal discrepancy between the structural and functional changes. There have been arguments as to when these structural and functional changes begin in patients with schizophrenia. The 'abnormal neurodevelopment' hypothesis [31], which states that problems occur during the prenatal and postnatal neurodevelopment period, has become generally accepted. On the other hand, some researchers have continued to support the 'neurodegenerative' hypothesis[32] which states that progressive changes continue after the onset of illness. Our data do not support either of these two hypotheses. Given that the results we obtained for both the mean and total subregional activities were very similar, it is

possible to conclude that the prefrontal functional changes in schizophrenia are not affected by the structural volume changes.

It is well known from previous reports that the dorsolateral prefrontal cortex (DLPFC) plays a critical role in working memory[8, 16]. In the current study, however, there was no significant change in the subregional activities within the DLPFC during the working memory condition in either the patient or the healthy group. Stevens et al [13]. did not find any difference in the DLPFC between the patient and control groups either. Instead, our study showed important differences in the anterior cingulate between the patient and the healthy group. Working memory loading caused increased activity in the right rostral anterior cingulate in the healthy group, but not in the patient group. Moreover, it caused no significant change in the right caudal anterior cingulate in the healthy group, but a decrease in the patient group. Some previous studies have indicated that impaired activation of the anterior cingulate cortex might be the basis for verbal fluency deficit [33] or declarative memory[34] in schizophrenia. In addition, as shown in Figure 3, the slightly increased activation in the orbitofrontal cortex during working memory in the healthy group was contrasted by a significant decrease in the patient group. Considering that the patient group demonstrated excellent performance without showing any significant difference from the healthy group, this result indicates that patients with schizophrenia have a different activation pattern from that of the control group for working memory. The nature of the functional impairment of working memory in schizophrenia remains obscure, but it can be said that the neural system is abnormally activated when performing the working memory condition. Previous studies have emphasized the role of the DLPFC in this abnormally activated neural system, but the current study suggests that the anterior cingulate and the orbitofrontal cortex also play an important role. It is not yet known whether these differences in functional activation reflect a quantitatively inefficient neural system or an abnormality in terms of quality. It should be mentioned that subtle focal changes might not be detected with the method used in this study. A negative result is possible if activation occurs in a limited area during working memory, instead of in a generalized area of any of the frontal subregions. For example, although focal activity in the supplementary motor area was reduced in the patients with schizophrenia in other studies, in which a different visual working memory task and voxel-based analysis was used [10, 11], such finding could not be observed in the relatively large ROI that was employed in the current study. Therefore, even if activation did not appear in some subregions in this study, the possibility of regional activation cannot be ruled out. In fact, subtle regional activity changes are well described in another report using voxel-based analysis[35].

The primary limitation of this study is the effect of medication. All of the subjects in the patient group were taking various atypical antipsychotics. The confounding effect of antipsychotics medication on memory-related activation of specific brain regions has been suggested in some, although few, previous reports. For example, typical and atypical antipsychotics have different effects on the patient's performance during a cognitive task [36]. Moreover, it has been reported that risperidone can cause a distortion in the cortical activation changes that occur during working memory tasks in various brain areas, such as the right prefrontal area, the supplementary motor area and the posterior parietal cortex [37]. As presented in the tables, in the comparison between the two groups in the same task condition, the patient group showed a tendency to have reduced activities in most of the frontal subregions compared to the healthy group. This result may be related to the hypofrontality of schizophrenia, but the possibility of there being a secondary effect caused by the antipsychotic medication cannot be ruled out. However, because the change in functional activation was first observed within the group, the antipsychotic effect was controllable in the between-group difference of the within-group change. Neuroimaging studies of working memory mapping in patients with schizophrenia have proved the existence of 'task-related hypofrontality'[10, 38]. This has the effect of producing artificially poor task performance in certain patients which can be confused with functional impairment[39]. In fact, poor performance can be due to a lack of effort or motivation, the use of an inappropriate strategy, or difficulty in performing the task[40]. When the task is too difficult, the subjects utilize cognitive and emotional processes that have no relation to working memory, such as error monitoring, compensatory behavior, withdrawal from the task, the expression of an embarrassed feeling, or proffering a guess. In the current study, however, in order to eliminate these confounding factors as much as possible, we used a relatively easy task and allowed the subjects to have sufficient practice before the actual task performance, and thus the performance of the patient group did not show much difference from the healthy group. In conclusion, to overcome the limitations of previous neuroimaging studies, in the current study, we used exact topographical parcellation to observe the functional abnormality of the prefrontal areas during working memory in schizophrenia. One of the remarkable findings was the reduced functional responses in the right anterior cingulate and in the right orbitofrontal cortex. These abnormalities may be related to the cognitive deficits and impairment of the neural circuits in schizophrenia.

Acknowledgment

This study was supported dy a grant of the Biomedical Brain Research Center Grant, Ministry of Health & Welfare, Republic of Korea. (0405-NS01-0704-0001).

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