Working Memory Dysfunction with fMRI task and Gray Matter Difference in Schizophrenia Patients using Voxel Based Morphometry

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Purpose: The prefrontal cortex (PFC) and parietal cortex are important in performing working memory (WM) tasks. In this study we performed fMRI studies to compare the activation regions between the schizophrenic patients and controls using the 2-back WM task paradigm. In addition, the gray matter (GM) loss between these two groups was compared using the voxel based morphometry (VBM) analysis. The brain regions showing differences in fMRI and VBM studies were compared to investigate the consequence of structural atrophy on functional activation.

Methods: This study included 14 schizophrenic patients (M/F: 8/6) and 10 normal controls (M/F: 8/2). The diagnosis was made on the basis of interview with the Structured Clinical Interview for Axis I Disorders (SCID-I/NP) and the Diagnostic and Statistical Manual for Metal Disorders 4th edition (DSM-IV). The demographic data for each group are shown in Table 1. The MRI study was conducted on a clinical 1.5T MR scanner (Magnetom Vision Plus, Siemens, Erlangen, Germany). The fMRI employed a gradient-echo echo planar imaging (EPI) sequence (TR/TE=3000/60 msec, flip angle = 90, 240 x 240 mm field-of-view, 64 x 64 in-plane matrix) to detect blood oxygenation level dependent (BOLD) signal changes associated with neural activities. 24 axial slices with 6mm thickness were acquired from the whole brain. We used a 2-back WM test with Korean Alphabet (KA) as target cues. Subjects performed a sequential verbal WM test whereby a target response occurs when the current KA matches the second previous KA presented in the sequence. Each stimulus (1 second in duration) was given to the subject every 2.5 seconds. Groups of 12 stimuli were administered in 30-second blocks four times, interleaved by five resting conditions (30 seconds each). After the functional session, high-resolution 3D anatomical images were acquired for VBM analysis, using a 3D-FLASH sequence (TE/TR=4/9.7 msec, FA=12, slice thickness = 1.25 mm, 256 x 192 in-plane matrix). The images were first normalized to the Montreal Neurological Institute (MNI) coordinate using a 12-parameter affine transformation, and smoothed with an 8 mm isotropic Gaussian kernel, then averaged to obtain the template. The VBM analysis was performed using the AnCova model with sex, age, onset age, onset duration and MMSE in the design matrix. The z-map was thresholded at P<0.001 uncorrected. The voxels with the highest z-values represented the region where GM volume was significantly different between these two groups.

Table1. Demographic data of Schizophrenia patients and control

	Schizophrenia (N=10)	Normal (N=10)
Age (y)	28±7.3	22±6.6
Education (y)	13±2.5	14±2.2
I.Q	106±7.6	111±8.4
MMSE	29±1.3	30±0.7
Age at onset (y)	24±6.3	-
Duration (m)	13±30.8	-
VBM-GM (mm^3)	654	750
VBM-WM (mm^3)	429	513
VBM-CSF (mm^3)	453	454

Results: The clinical task accuracy of the patient group was 86± 9 % and that of the control group was 94±5 %. The accuracy was significantly higher in the control (Z=-2.108, p=0.035), indicating that working memory was impaired in schizophrenic patients. The fMRI activations in these two groups were compared to examine the differences, shown in Figure 1a. The regions showing increased activity in controls included the right superior frontal gyrus (BA8), middle frontal gyrus (left BA6 and right BA8), left precuneus (BA7), left fusiform (BA37), anterior bilateral insula, and left putamen. On the other hand, the patient group showed increased activities in the right inferior frontal gyrus in the lateral PFC (BA10/46) and right parietal lobule (BA40). A more liberal threshold condition of p< 0.001 was applied to examine any threshold-dependence of laterality in activities in PFC, but the activity was still observed solely on the right PFC. The VBM result show reductions in GM in Schizophrenia versus controls in the anterior cingulate (BA 24.31), medial frontal (BA 10), superior temporal, middle temporal and fusiform gyrus (BA20). The comparative fMRI and VBM results are summarized in Table 2.

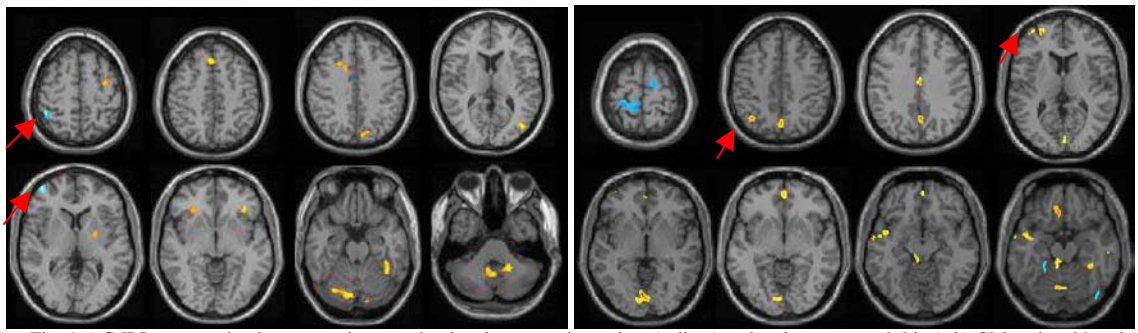

Fig. 1 a) fMRI group activation comparison results showing control > patient (yellow) and patient > control (blue). b) GM regional loss in patients compared to controls using VBM. Significance is set at uncorrected P< 0.001. The main regions were cingulate (BA24, 31), lingual gyrus (BA18), fusiform gyrus (BA20), middle temporal, superior temporal, parietal (BA7) middle frontal and superior frontal (BA10).

Discussion: The working memory of schizophrenic patients was significantly impaired compared to controls. Such impairment was related to the differences in functional activation in fMRI studies, and was associated with structural difference in the VBM analysis. GM volume loss in schizophrenic patients was found in the anterior cingulate, medial frontal gyrus, inferior frontal gyrus, superior temporal and medial temporal gyrus. It was assumed that schizophrenic patients have ineffective neural connectivity for working memory, thus we expect to find different activity patterns compared to controls. The fMRI reveals that the parietal lobe (BA40) and PFC (BA10/46) show elevated activation in the patient group (areas highlighted in red in Table 2), and interestingly these regions show corresponding GM loss in VBM analysis. The parietal area, as an important locus in working memory that provides a temporary "sketch pad" for mnemonic processes, has been implicated in abnormal working memory processing in schizophrenia [*Walter et al. Schizophrenia Research 2003; 61:175–184*]. The prefrontal areas (BA10/46) are involved in the manipulation, integration, and control of executive functions in the working memory process. Based on the important role of the prefrontal and parietal areas in WM, the results suggest that schizophrenic patients have to enhance the activity in these regions in order to compensate for the GM volumetric loss. In contrast, the patient group shows decreased activation in the fusiform gyrus, precuneus, middle temporal, middle frontal, and superior frontal regions compared to controls (areas highlighted in blue in Table 2), and these regions also show corresponding GM loss in VBM, suggesting that the decreased activity may be related to structural changes. However, since they are not involved in working memory process, no elevated activity is needed to perform working memory tasks. Therefore, combining functional study with structural study, as demonstrated in this work, can provide a powerful tool to investigate the association between neural activation and structural atrophy.

Table 2. Comparison between fMRI and VBM(+:increase, -:decrease) in the patient to control

Region	BA	*fMRI result*	*VBM result*
Cingulate	24/31		4.47(-)
Fusiform gyrus	37/20	3.26(-)	2.35(-)
Precuneus		3.57(-)	4.52(-)
Insula		3.24(-)	
Middle temporal		3.57(-)	4.90(-)
Superior temporal			4.68(-)
Parietal	7/40	3.37(+)	4.57(-)
Middle frontal	6/8	3.03(-)	3.80(-)
Superior frontal	8/10	3.41(-)	3.52(-)
Inferior frontal	10/46	3.31(+)	2.60(-)
Lingual gyrus	18		3.39(-)
Putamen		2.97(-)	