Phase-Specific Brain Change of Spatial Working Memory Processing in Genetic and Ultra-High Risk Groups of Schizophrenia

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Spatial working memory (WM) processing has 3 distinct phases: encoding, maintenance, and retrieval and its dysfunction is a core feature in schizophrenia. We examined phase-specific brain activations associated with spatial WM in first-degree relatives of schizophrenia (genetic high risk, GHR), ultra-high risk (UHR) subjects, patients with schizophrenia, and healthy controls. We used an event-related functional magnetic resonance imaging in 17 GHR subjects, 21 UHR subjects, 15 clinically stable patients with schizophrenia and 16 healthy controls, while subjects were performing a spatial delayed-response task. During the encoding phase, the GHR group showed increased activation in the fronto-parietal regions, whereas the UHR and schizophrenia groups showed significantly less activation in these regions than did the healthy control group. Especially, frontal activation was strongest in GHR subjects, followed by healthy controls, and occurred to a lesser degree in the UHR group, with the least activation occurring in the schizophrenia group. During the maintenance phase, the thalamus showed a differential activation, similar to frontal activation pattern during the encoding phase. During the retrieval phase, no prominent differential activations were found. Increased activations were observed in the superior temporal gyrus during the encoding and maintenance phases in the GHR, UHR, and schizophrenia groups relative to healthy controls. Our findings suggest that functional deficits associated with spatial WM processing emerge in the UHR before the onset of schizophrenia and compensatory neural processes exist in the GHR with genetic liability to schizophrenia.

Key words: spatial working memory/functional MRI/ schizophrenia/first-degree relative/ultra-high risk

Introduction

Working memory (WM) is commonly defined as a process of holding online and manipulating information in the brain for short periods of time. Its dysfunction is one of the candidate biological markers in the pathophysiology of schizophrenia. In particular, spatial WM impairment has been proposed as a core feature in schizophrenia. Patients with schizophrenia perform worse than healthy control subjects on spatial WM tasks. In addition, spatial WM deficits have been found in subjects who are either genetically or clinically at high risk for schizophrenia. Pirkola et al found that patients with schizophrenia and their unaffected co-twins performed significantly worse than control subjects on the spatial WM task, supporting the hypothesis that impairment in spatial WM might effectively reflect an expression of genetic liability to schizophrenia. Smith et al reported that adolescents at clinical high risk for schizophrenia showed deficits in spatial WM compared with controls.

Numerous functional imaging studies have examined WM in patients with schizophrenia. Kim et al found prefrontal-parietal functional disconnection during WM processing in schizophrenia using [15O]H2O positron emission tomography. Another study examined WM-related brain activations in ultra-high risk (UHR) subjects as well as in patients with schizophrenia. Before the onset of psychosis, UHR subjects showed decreased activation in the frontal and parietal cortices during the N-back task compared with healthy controls. Furthermore, the extent of reduced activation in high-risk subjects was less severe than in those with psychosis. On the other hand, several functional imaging studies...
that have assessed WM in unaffected relatives of patients with schizophrenia have demonstrated increased task-elicited activation in the prefrontal cortex, suggesting compensatory activation in the region in order to maintain their normal behaviors.\textsuperscript{9-11} However, as yet, evidences on spatial WM-related brain change in subjects at risk of schizophrenia are limited.

Spatial WM is not a unitary process but has 3 distinct phases: encoding, maintenance, and retrieval. Each phase may be associated with a distinct pattern of brain activity.\textsuperscript{12-14} In particular, it has been suggested that deficits in encoding stimuli play an important role in WM dysfunction in schizophrenia.\textsuperscript{15} Schlosser et al\textsuperscript{16} showed that patients with schizophrenia have reduced activation in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) during the encoding phase. However, many previous WM-related studies have used the N-back task and block designs, which had limitations when exploring these subcomponents of the WM processing. In addition, there have been no functional imaging studies to evaluate brain activities in both unaffected relatives of patients with schizophrenia and UHR subjects in comparison with patients with schizophrenia and normal controls.

In this study, we performed event-related functional magnetic resonance imaging (fMRI) study to explore phase-specific activation patterns associated with spatial WM processing using a spatial delayed-response task\textsuperscript{17} in individuals at high risk for schizophrenia, i.e., first-degree relatives of schizophrenia patients (genetic high risk, GHR) with genetic liability but without any clinical manifestations, and UHR subjects experiencing prodromal symptoms before onset of florid psychotic symptoms. To the best of our knowledge, this is the first event-related fMRI study assessing phase-specific brain changes using a spatial WM task in the GHR, UHR, and schizophrenia groups.

### Methods

#### Subjects

The subjects enrolled in this study were part of a prospective longitudinal project investigating individuals at high risk for psychosis at the Seoul Youth Clinic. The GHR group was composed of 17 subjects who had a family history of schizophrenia and were clinically asymptomatic. Subjects in the GHR group had 2 first-degree relatives with schizophrenia ($n = 5$) or 1 first-degree and at least 1 second-degree relative with schizophrenia ($n = 12$). The UHR group consisted of 21 subjects. Five subjects were receiving psychotropic drugs at the time of assessment (low-dose atypical antipsychotics, $n = 5$; antidepressant, $n = 1$). All subjects in the UHR group had no family history of schizophrenia. The schizophrenia group consisted of 15 clinically stable patients diagnosed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV) (SCID-IV).\textsuperscript{18} All were receiving atypical antipsychotics. The healthy control group consisted of 16 age- and sex-matched subjects. All were healthy and this was confirmed with SCID-nonpatient version. They had no lifetime history of any psychiatric disorder or treatment and no first- to third-degree relatives with psychiatric disorders. These subjects were recruited via an Internet advertisement or through the social networks of hospital staff. Demographic and clinical characteristics of the subjects are summarized in table I.

Exclusion criteria included a known history of substance abuse or dependence, neurological disease, or brain injury; evidence of medical illness that could manifest psychiatric symptoms; and intellectual disability (intelligence quotient [IQ] < 70). All subjects provided written informed consent, and parental consent was obtained for subjects younger than 18 years of age. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea.

#### Clinical Interviews and Assessments

Procedures for clinical interview and assessment were as described in our previous report.\textsuperscript{19,20} At intake, all potential subjects participated in an intensive clinical interview with 2 experienced psychiatrists who used the SCID-IV to identify past and current psychiatric illnesses. UHR status was determined based on the Comprehensive Assessment of At-Risk Mental States (CAARMS).\textsuperscript{21} The CAARMS is a semistructured interview schedule to provide a comprehensive assessment of psychopathology indicating imminent development of psychotic disorder and to determine if an individual meets UHR status. It was also applied to GHR subjects to assess their clinical status. The Family Interview for Genetic Studies were used to investigate the family history of psychiatric disorders and degree of genetic loading for schizophrenia in subjects classified as GHR.\textsuperscript{22} As to the diagnosis of the proband, the relatives with schizophrenia were the subjects who had been followed up regularly in our hospital or the private clinic. And they were also diagnosed according to the DSM-IV. Psychotic symptoms were assessed using a Positive and Negative Syndrome Scale (PANSS)\textsuperscript{23} at the time of study recruitment in the schizophrenia and UHR groups. The Korean version of the Wechsler Adult Intelligence Scale was administered to all subjects to obtain an estimated IQ.

#### Spatial WM Task Design

We employed the modified spatial delayed-response task,\textsuperscript{17} which consisted of an encoding phase, during which subjects saw circles which they were asked to remember, followed by a maintenance phase, during which subjects attempted to maintain the information,
Spatial Working Memory in High Risk for Schizophrenia

Table 1. Demographic, Clinical, and Behavioral Data in Study Subjects

<table>
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<tr>
<th>Variables</th>
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<th>GHR (N = 17)</th>
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<th>Schizophrenia (N = 15)</th>
<th>F, t, χ²</th>
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<td>Age (years)</td>
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<td>20.71 5.50</td>
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Note: GHR, genetic high risk; UHR, ultra-high risk; SES, socioeconomic status; PANSS, Positive and Negative Syndrome Scale; CAARMS, Comprehensive Assessment of At-Risk Mental States.

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*P = .014, vs UHR (post-hoc); **P = .019, vs UHR (post-hoc); ***P < .05; ****P = .001, vs control (post-hoc); *****P = .008, vs control (post-hoc); ******P = .016, vs control (post-hoc).

and finally a retrieval phase, during which subjects were shown a probe and asked to indicate whether or not the probe was a subset of the encoded circles. To control for the sensorimotor component of the spatial WM task, a control task was conducted that required spatial location detection but not WM. This task was identical to the spatial WM task except that subjects did not have to memorize the position of red circles. Subjects were shown a red circle at the center of screen and pressed a button when a green probe circle appeared after 7.02 s. The subjects responded by pressing an MRI-compatible mouse button with the index and middle fingers of the right hand. Further details of the experimental task are presented in figure 1. Since the primary aim of the present study was to investigate phase-specific activation patterns associated with spatial WM processing, 3 kinds of memory-load sizes were collapsed together for data analysis.

**Image Acquisition**

Functional and structural images were acquired using a 1.5 Tesla whole-body scanner (AVANTO; Siemens, Erlangen, Germany). Functional images were acquired by a multi-slice echo-planar imaging sequence covering the whole cerebral (25 axial slices acquired in an interleaved manner, 5 mm slice thickness, repetition time = 2.34 s, echo time = 41 ms, flip angle = 90 degrees, field of view = 210 cm, 64 x 64

**Fig. 1.** Spatial working memory task used during functional magnetic resonance imaging assessment. For each trial, participants were shown an array of 1, 3, or 5 yellow circles positioned pseudo-randomly around a central fixation point and were asked to memorize the location of them for 2.34 s. After a maintenance period of 7.02 s, subjects were shown a single green probe circle and were asked to determine within period of 2.34 s, if the probe was in the same position as one of the target circles. During the entire task, subjects were asked to fixate on a central “+” and minimize their eye movement. During the scanning, subjects performed 72 total trials (18 trials per control task and memory load). ITI, intertrial interval.
matrix). High-resolution anatomical images were acquired in 176 contiguous axial slices for purposes of anatomical localization and coregistration.

Data Processing

Functional imaging analysis was performed with SPM2 software (www.fil.ion.ucl.ac.uk/spm). The first 3 volumes of each fMRI scan were discarded to allow for T1 equilibration. The remaining 810 volumes of each subject’s data set were realigned to correct for interscan movement and stereotactically normalized using sinc interpolation into the standard space defined by the Montreal Neurological Institute template. The scans were then smoothed with a Gaussian kernel of 8 mm full-width half-maximum to account for residual inter-subject differences. Low-frequency signal drifts were removed using a 300-s high-pass filter, and temporal autocorrelation in the fMRI time series was corrected using a first-order autoregressive model.

For the analyses, regressors were defined for the duration of the encoding and retrieval phases, respectively. For the maintenance phase, the boxcar regressor was convolved with a canonical hemodynamic impulse response function for the last 3.02 s of the maintenance phase. According to previous research, encoding activity extends to the subsequent phase and activity during the maintenance phase may be contaminated by activity in the encoding phase. Therefore, we followed the suggestion made by these previous studies that the onset of the maintenance phase should be separated by at least 4 s from the offset of encoding. Moreover, we used a variable-duration intertrial interval (2.34–9.36 s), which has previously been adopted to increase the separability of overlapping functions.

Differences in behavioral performance may complicate the interpretation of between-group differences in the neural activities. Lee et al. also suggested that error trials as well as correct trials influenced on the brain activity associated with spatial WM. Therefore, in order to exclude the effect of error trials and match behavioral performances among study groups, we analyzed neural activity for only correct trials.

Statistical Analysis

Comparisons of demographic variables among the 4 groups were conducted using ANOVA, independent sample t-test, and χ² test. A repeated-measure ANOVA was used in the analysis of task performance and region-of-interest (ROI) analysis.

Each phase-specific WM condition was contrasted with a control task to determine the network involved in WM and to remove the activation for perception of visual stimuli and motor response. The resultant contrast images were then entered into second-level (random-effects) analyses. One-sample t-tests were computed on the contrast images for each individual subject to determine regions of significant activation over all subjects. A height threshold of P < .0001, uncorrected for multiple comparisons and a cluster size greater than 15, was used across the whole brain. These statistical thresholds were chosen to prevent false positives due to multiple comparisons and to not lose statistically significant activities.

Second, we performed a 2-sample t-test for the between-group analysis, examining the differences among the GHR, UHR, schizophrenia, and healthy control groups. Significant areas in the between-group analysis were reported using the criteria of P < .001, uncorrected for multiple comparisons and a cluster size greater than 15.

Third, a linear trend analysis was applied to examine the data for any linear trend in brain activation across the 4 groups. Based on the results of between-group analysis and previous reports, this analysis would indicate that the order of activation would be GHR > control > UHR > schizophrenia. Significant areas in the linear trend analysis were also reported using the criteria of P < .001 (uncorrected) and a cluster size greater than 15. To confirm the differential pattern of activation across groups found in the linear trend analysis, we used a ROI approach. We selected regions based on the maximal number of activated voxels in the prefrontal cortex and the thalamus.

Correlational analyses using Pearson’s method were conducted to investigate the relationship among behavioral performance, clinical variables, and ROI values in the high risk and schizophrenia groups. We also examined the effect of medication on brain activity in patients with schizophrenia.

The statistical analyses for demographic, clinical, and behavioral data, as well as the ROI method and correlation analyses were 2-tailed, and significance was set at P < .05.

Results

Demographic and Clinical Data

As shown in table 1, no significant differences in age, sex ratio, handedness, parental socioeconomic status, or education level were found among the 4 groups. The UHR group showed a higher IQ compared with the GHR and schizophrenia groups (P = .014 and P = .019, respectively). No significant differences in PANSS scores were observed between UHR and schizophrenia patients. This may be due to the inclusion of schizophrenia patients who were in a clinically stable state after the recovery from their first psychotic episode. However, schizophrenia patients showed higher scores in the positive and negative subscales than did the UHR subjects, whereas UHR subjects showed higher scores in the general subscale than did schizophrenia patients. In addition, no clinical symptoms were observed in the GHR subjects.
**Behavioral Data**

Data on accuracy (correct response, %) and response time (RT, milli seconds) are shown in table 1. In the control task, no significant differences in the correct response rate were found among the 4 groups, whereas during the spatial WM task, a significant group difference was observed in the correct response rate \( (F_{3, 65} = 5.330, \ P = .002) \). Patients with schizophrenia showed impaired performance compared with healthy controls (post hoc t-test, \( P = .001 \)). We found a significant difference in RT during the spatial WM task among the 4 groups \( (F_{3, 65} = 4.593, \ P = .006) \) but not in the control task. GHR subjects and patients with schizophrenia showed delayed RT compared with healthy controls (post hoc t-test, \( P = .008 \) and \( P = .016 \), respectively).

**Imaging Data**

**Phase-Specific Activation Regions During Spatial WM Within Each Group.** During the encoding phase, healthy control subjects showed activation in a widespread network of cortical and subcortical regions across all memory-load sizes. Significant activations were identified in the bilateral occipital cortex (BA18, 19), bilateral superior frontal regions (BA6), right precentral gyrus (BA4), bilateral DLPFC (BA9), right ventrolateral prefrontal cortex (VLPFC, BA44), bilateral caudate, and right thalamus in healthy control subjects. In the GHR group, more widespread activation patterns were observed compared with the healthy control group. However, the UHR group recruited fewer brain regions during the encoding phase relative to the healthy control group, and the schizophrenia group recruited fewer brain regions still (figure 2).

During the maintenance phase, the control group showed significant activations in the bilateral occipital cortex (BA17, 18), parietal cortex including the right inferior parietal lobule (IPL, BA40) and left precuneus (BA7), and the frontal cortex including the right superior frontal (BA6), right DLPFC (BA9), and bilateral VLPFC (BA44, 47). Additionally, the right ACC, right insula, and left thalamus were also significantly activated. The GHR, UHR, and schizophrenia groups showed almost

![Brain regions displaying increased activations during each phase of spatial working memory task in healthy control, genetic high risk (GHR), ultra-high risk (UHR), and schizophrenia. Color bars represent the T-value. Statistical threshold was \( P < .0001 \), uncorrected, \( k > 15 \) voxels.](image-url)
similar activation patterns to those of the control group. However, activations in the GHR group were more widespread, whereas those in the UHR and schizophrenia groups occurred to a lesser degree (figure 2).

During the retrieval phase, significant activations were identified among the control group in the bilateral parietal and right frontal areas. GHR subjects showed bilateral activation patterns in the parietal and ventrolateral prefrontal cortex (VLPFC). Activation in the right ACC was also observed in GHR subjects. UHR subjects showed activations in the bilateral IPL, and patients with schizophrenia showed activation in the right VLPFC and right ACC (figure 2).

Phase-Specific Activation Regions During Spatial WM in Between-Group Analysis. Encoding Phase. Compared with the healthy controls, GHR subjects showed increased activation in the right IPL, DLPFC, and superior temporal gyrus (STG) during the encoding phase. No regions displaying decreased activation in GHR subjects compared with healthy controls were observed. UHR subjects showed significantly decreased activation in the right IPL, DLPFC, and left inferior temporal gyrus compared with healthy controls, whereas a significant increase of activation in the right STG was observed in UHR subjects relative to the healthy controls. The schizophrenia patients also showed decreased brain activation in the right IPL and DLPFC compared with healthy controls but increased activations were observed in the STG of the schizophrenia group (figure 3, see online supplementary table 1).

Maintenance Phase. As shown in figure 3 and online supplementary table 2, the GHR group showed increased activation in the STG and in the left side of middle temporal gyrus (MTG), thalamus, and insula during the maintenance phase. No regions displayed decreased activation in the GHR group compared with the healthy control group. UHR subjects showed significantly decreased activation in the right parietal areas compared with healthy controls, whereas significant increases in the STG, MTG, insula, and ACC in UHR subjects relative to healthy controls were observed. The schizophrenia patients showed increased brain activation in the temporal regions compared with healthy controls, whereas decreased activation of the left thalamus in the schizophrenia group was prominent.

Retrieval Phase. Compared with healthy controls, GHR subjects showed increased activation in the right medial frontal gyrus and left precuneus during the retrieval phase. No region showed decreased activation in GHR subjects compared with healthy controls. UHR subjects showed significantly decreased activation in the right VLPFC compared with healthy controls, whereas significant increases in widespread brain regions including left DLPFC were observed in the UHR subjects relative to healthy controls. The schizophrenia group showed increased brain activation in the right side of the medial frontal gyrus, parahippocampal gyrus, and

Fig. 3. Brain regions showing different activation patterns during each phase of spatial working memory in between-group comparisons. (A) Genetic high risk group vs controls, (B) ultra-high risk group vs controls, and (C) schizophrenia vs controls. Red colors represent increased brain activation compared with healthy control group, while blue colors show decreased activation compared with healthy control group ($P < .001$, uncorrected, $k > 15$ voxels).
fusiform gyrus compared with healthy controls, whereas no decreased activation was found in the schizophrenia group (figure 3, see online supplementary table 3).

**Brain Regions Showing Differential Activation Patterns Across the 4 Groups.** To examine the data for a linear trend in activation across groups, based on previous researches\(^8\)\(^–\)\(^11\) and the results of between-group analysis, we used a linear trend analysis in subjects. During the encoding phase, significant differential activations were observed across the 4 groups in the DLPFC, VLPFC, ACC, thalamus, and caudate head, as shown in figure 4 and online supplementary table 4. To confirm these differential activations, we performed ROI analysis in the right DLPFC, right VLPFC, and left thalamus. We found significant between-group differences in the percent signal change in each region (\(F_{3, 65} = 18.403, P < .001\) in DLPFC; \(F_{3, 65} = 16.128, P < .001\) in VLPFC; \(F_{3, 65} = 38.860, P < .001\) in thalamus). Percent signal changes in these regions were greatest in the GHR group, intermediate in the healthy control group, still lower in the UHR group, and lowest in the schizophrenia group. Post hoc analysis confirmed that activations in the GHR, UHR, and schizophrenia groups were significantly different from those in the healthy control group (\(P < .05\)). During the maintenance phase, differential activation was observed across the 4 groups only in the thalamus. The ROI analysis showed a significant between-group difference in the percent signal change in the thalamus (\(F_{3, 65} = 26.403, P < .001\)), and the differential activation pattern was similar to that in the encoding phase. Post hoc analysis also revealed that activations in the GHR,
UHR, and schizophrenia groups were significantly different from those found in the healthy control group ($P < .05$). On the other hand, no significant differential activation was observed during the retrieval phase.

**Correlation of Brain Activation With Behavioral Data, Clinical Variables, and Medication Status in Each Group.** A significant negative correlation was observed between CAARMS total score and percent signal change in the left thalamus of the UHR group during the maintenance phase ($r = -.469$, $P = .032$). To investigate the effect of medication on brain activity in patients with schizophrenia, we converted the dose of antipsychotics to the chlorpromazine equivalent dose. However, no significant correlations between medication status and percent signal change in ROIs were found in patients with schizophrenia.

**Discussion**

To our knowledge, this study is the first report on phase-specific brain changes associated with spatial WM in subjects at high risk for schizophrenia, either genetically or clinically, as well as in schizophrenia patients using event-related fMRI. We found that phase-specific functional abnormalities in the neural substrates for spatial WM were present before the onset of schizophrenia. In particular, these brain changes were prominent during the encoding and maintenance phases. GHR subjects with genetic liability but without any clinical manifestations showed increased activity in the spatial WM network, suggesting compensatory activity for decreased efficiency to achieve a similar level of performance as healthy controls. As clinical symptoms emerged and the illness progressed, brain activities in the frontal region during the encoding phase and in the thalamus during the maintenance phase gradually decreased, resulting in spatial WM impairments.

In terms of behavioral performance, schizophrenia patients showed impaired accuracy on the spatial WM task compared with healthy controls, whereas GHR and UHR subjects did not. The UHR group did show decreased accuracy compared with the GHR group but not to a statistically significant degree. In addition, there was no significant difference in accuracy between the GHR and healthy control group, although there have been reports about spatial WM deficits in relatives of schizophrenia patients. This might be due to the nature of task applied or analysis of data with collapsed memory loads. It is necessary to perform analysis of data according to the level of memory loads in the further study. With respect to RT, the GHR and schizophrenia groups showed significantly increased RT compared with the healthy control group, but the UHR group did not. This suggests that the GHR group worked harder to maintain normal accuracy. In addition, it is also possible that increased RT with normal accuracy in the GHR group may be associated with the slower end of the speed-accuracy tradeoff curve. This may be due to the strategic difference in order to maintain normal accuracy between the GHR and healthy control group. However, the schizophrenia group, whose illness progressed, revealed impaired performance on the spatial WM task.

We found that functional disturbances in spatial WM network were prominent during the encoding phase in both high risk and schizophrenia groups. In particular, activity in the fronto-parietal regions including the DLPFC and IPL was increased in the GHR group and decreased in the UHR and schizophrenia groups. Previous studies have suggested that multiple brain regions, such as the prefrontal cortex, parietal regions, cingulate, or basal ganglia are involved in encoding deficits of WM in schizophrenia. Meda et al observed that schizophrenia patients showed less engagement of the fronto-parietal network in encoding visuospatial stimuli, contributing to poor WM performance. No study to date has investigated encoding-related brain activity in subjects at UHR for schizophrenia. Moreover, it was of great interest in the current results that the DLPFC showed a differential activation pattern during the encoding phase, with activation greatest in the GHR group, intermediate in the healthy control group, further reduced in the UHR group, and lowest in the schizophrenia group. Taken together, increased activation in the fronto-parietal circuit of the GHR group might represent compensatory activity for underlying functional deficits, although these subjects had no clinical symptoms. As the illness progresses, decreased activation in these regions, as found in the UHR and schizophrenia groups, might indicate cognitive failure. In addition, deficits in encoding spatial information or the use of a different encoding strategy might explain deficits in maintenance or retrieval processes in schizophrenia.

During the maintenance phase, the thalamus showed prominent functional changes associated with spatial WM processing. We found increased activation in the GHR group and decreased activation in the schizophrenia group compared with the healthy controls. Moreover, a differential pattern of activation was observed in the thalamus across the groups. The thalamus may be related to risk for schizophrenia, in part because of its intimate connection to the DLPFC, and its role in memory functions. Thalamic dysfunction was also reported in GHR subjects using proton magnetic resonance spectroscopy, suggesting that its dysfunction may be a vulnerability marker of schizophrenia. Its specific role in the maintenance of information has been elucidated by neurophysiological recordings during the maintenance period of delayed-response tasks. However, few studies have investigated thalamic involvement in the maintenance of WM in humans. In the present study, a negative correlation between CAARMS total score and percent signal change in the thalamus was found in the

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The Authors have declared that there are no conflicts of interest.

**Supplementary Material**

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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UHR group during the maintenance phase. Furthermore, decreased thalamic activity in patients with schizophrenia was not related to the effects of medication. Therefore, gradual decrease of activity from the UHR to schizophrenia suggests that the thalamic dysfunction may be already present in UHR subjects before the onset of florid psychotic symptoms and be progressive after the onset of schizophrenia. On the other hand, increased activity in the thalamus of the GHR group suggests that GHR subjects are compensating the thalamic deficits during the maintenance of spatial WM processing. This hypothesis that increased brain activation in subjects at GHR may be part of compensatory mechanism could be supported by other research conducted in those at genetic risk for Alzheimer disease. Yassa et al reported that asymptomatic offspring of Alzheimer disease patients showed increased brain activation in response to a spatial cognitive challenge, suggesting that compensatory increased activation is associated with genetic risk for Alzheimer disease.

Activations in the STG were significantly increased in the GHR, UHR, and schizophrenia subjects relative to healthy control during both the encoding and maintenance phases. Several functional imaging studies conducted in patients with schizophrenia have reported abnormalities in the STG associated with cognitive tasks. Healthy subjects showed deactivation in the STG during a WM task, whereas patients with schizophrenia had increased activation in this region. Subjects at risk of psychosis also failed to deactivate the STG during WM tasks, although the response was intermediate between patients with schizophrenia and healthy controls. In the present study, increased activation in the STG of the GHR and UHR groups could reflect impaired attention or strategy of spatial WM processing in subjects at high risk for schizophrenia.

During the retrieval phase, no differential patterns of activation were observed across the groups. However, the UHR subjects revealed greater activations in the widespread brain regions including fronto-temporo-parietal areas than did healthy controls. Especially, recruitment of left fronto-parietal regions in the UHR group raises the possibility that its elevated activation represents a compensatory mechanism for deficits in the brain activity during the encoding and maintenance phases in order to maintain normal spatial WM performance.

This study has some limitations. First, it is a cross-sectional investigation, and further longitudinal studies are needed using subjects with or without conversion to psychosis. Second, medication may have affected brain activation changes. However, only 5 UHR subjects were using antipsychotics and their doses were relatively low. In addition, no significant correlations between dose of antipsychotics and brain activation were found in the schizophrenia patients.

In summary, our findings prove that phase-specific functional changes related to spatial WM are present in regions consisting of spatial WM network, such as the fronto-parietal, thalamic, and STG areas in subjects at high risk for schizophrenia, either genetically or clinically, before the onset of schizophrenia. Especially, enhanced brain activity in the GHR group and decreased activity in the UHR group were observed in the fronto-parietal regions during the encoding phase and in the thalamus during the maintenance phase, although their behavioral accuracies of spatial WM tasks were normal. These results suggest that functional deficits associated with spatial WM processing emerge in the UHR before the onset of schizophrenia and compensatory neural processes exist in the GHR with genetic liability to schizophrenia.

Supplementary Material

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References

10. Seidman LJ, Thermens HW, Poldrack RA, et al. Altered brain activation in dorsolateral prefrontal cortex in adolescents...


