Original

An fMRI Study of an Abnormal Neurovascular Response in the Right Premotor Cortex during Inner Speech and the Relationship to Auditory Hallucinations in Patients with Schizophrenia

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Abstract : There is evidence for sensory and cognitive impairments at multiple levels in schizophrenia, which may be related to the clinical symptoms of the condition. Inner speech involves both auditory and language systems and dysfunction of inner speech and may be associated with auditory hallucinations in schizophrenia. We used functional magnetic resonance imaging to examine this association by measuring brain activation in 23 patients with schizophrenia and 23 healthy control individuals. The participants performed an auditory verbal working memory task that required inner speech in the form of subvocal rehearsal. The control participants showed prominent activation in the inferior frontal cortex (IFC), premotor cortex (PMC), superior temporal cortex (STC), and lateral parietal cortex (LPC) bilaterally, throughout the task. In contrast, patients with schizophrenia showed significant activation in STC bilaterally during encoding phase and in the IFC, PMC, STC, and LPC bilaterally during the recognition phase. A comparison between groups showed that controls had greater activation during rehearsal in the IFC, LPC, and PMC bilaterally than patients with schizophrenia. In the region-of-interest analysis, we observed a significant negative correlation between right PMC activation and Auditory Hallucination Rating Scale scores as well as the hallucination item in the Positive and Negative Syndrome Scale. These observations indicate that inner speech is impaired in schizophrenia and that the severity of auditory hallucinations is associated with abnormal activation in the right PMC during inner speech.

Key words : fMRI, verbal working memory, inner speech, auditory hallucinations, right premotor area

Introduction

Sensory and cognitive information processing is impaired at multiple levels in schizophrenia[1-5]. Previous studies of schizophrenia patients have emphasized auditory processing impairments[2, 3, 6], which were found at low levels with regard to pre-attending to sound, and at higher levels in

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relation to language processing[2, 3]. There is increasing evidence that impairment in auditory processing may be linked with the clinical symptoms of schizophrenia, and some studies have suggested a relationship between the abnormal auditory processing and auditory hallucinations[7, 8]. Delusions, thought disorder and auditory hallucinations are common symptoms of schizophrenia. Approximately 70% of patients with schizophrenia (SZs) have been estimated to experience auditory hallucinations at some point during their illness[9]. Auditory hallucinations generally have negative emotional content and as a result they often lead to a low quality of life and may cause abnormal behavior such as violence and functional disability[10]. The mechanisms of auditory hallucinations remain unknown, and approximately 25% of SZs are refractory to antipsychotic medications[11]. An improved understanding of the neural mechanisms responsible for auditory hallucinations could lead to the development of new management therapies for SZs.

There are several models of auditory hallucinations and an important cognitive model of abnormal auditory processing describes SZs that fail to adequately monitor their inner speech. These patients perceive the auditory hallucinations as voices from external sources, such as "alien" voices[6, 7, 12, 13]. The mechanism of inner speech has been investigated in healthy individuals in previous neuroimaging studies. Many of these studies observed activation in overt speech production areas including the inferior frontal cortex (IFC), insula, premotor cortex (PMC), and supplementary motor cortex during inner speech[14–16]. The superior temporal cortex (STC), anterior cingulate cortex, supramarginal gyrus (lateral parietal cortex, LPC), and middle temporal cortex are involved in inner speech[17, 18]. Thus, inner speech seems to be associated with activation in language-related brain areas, including areas that participate in overt speech production. Furthermore, many neuroimaging studies with SZs have found abnormal brain activation in these areas during inner speech[6, 13, 19] as well as activation in inner speech-related areas during auditory hallucinations. Therefore, auditory hallucinations may involve similar neural networks that overlap with those participating in inner speech[17, 20].

Nevertheless, there are inconsistencies among the findings of studies that examine brain activation in SZs during inner speech. In particular, these inconsistencies relate to the implications of specific areas of the brain during inner speech and auditory hallucinations. In the present study, we aimed to locate sites of abnormal brain function in SZs. For this purpose, we used functional magnetic resonance imaging (fMRI) and measured the blood oxygen level dependent (BOLD) signal during auditory verbal working memory, which necessarily involves inner speech in the form of subvocal rehearsal. The magnitude of brain activation during inner speech was examined for potential correlations with clinical scales of auditory hallucinations. We propose that SZs show the most severe functional impairment in language-related brain areas during inner speech, and these impaired areas could be linked to the severity of auditory hallucinations.

Materials and Methods

Participants

We recruited SZs from Karasuyama Hospital, Showa University School of Medicine, Tokyo,

Table 1. Demographic data and clinical scale scores

	HCs	SZs
Number	23 (male = 17, female = 6)	23 (male = 13, female = 10)
Age (years)	36.4 ± 8.7	35.1 ± 7.2
IQ [a]	109.3 ± 9.1	97.0 ± 10.9
Length of illness (years)	–	10.3 ± 7.3
Chlorpromazine equivalents (mg / d)	–	829.3 ± 509.1
PANSS (P) score	–	17.1 ± 6.0
PANSS (H) score	–	3.7 ± 1.9
PANSS (N) score	–	18.7 ± 5.9
PANSS (G) score	–	36.3 ± 12.9
AHS score	–	18.7 ± 12.5

Mean ± standard division. HCs : Healthy controls, SZs : Schizophrenia patients, PANSS : Positive and Negative Syndrome Scale, (P) : (Positive scale), (N) : (Negative scale), (H) : (Hallucination item scale), (G) : (Global psychopathology scale), AHS : Auditory Hallucination Rating Scale.
[a] Assessed by the Japanese version of the National Adult Reading Test (JART).

Japan from September 2010 to May 2013. Initially, we recruited 35 SZs for the MRI examination, and subsequently twelve patients were removed for various reasons. The patients who were removed included six for large head movement, one for lack of patience, and one because of an earthquake that occurred during scanning. Another four patients had an accuracy rate below 60% and therefore did not perform the task satisfactorily. The data from 23 SZs (median age, 35.1 years [range, 23-49] ; 13 males and 10 females) were analyzed in this study. The SZ patients who participated in the study included 16 inpatients and seven outpatients, with five first-episode patients. Diagnoses were made by two psychiatrists and were based on the Structured Clinical Interview for DSM-IV. Patients were excluded if they had other major psychiatric or neurological disease, a severe somatic disorder, alcohol intake within 24 h before examination, current or past alcohol abuse or substance abuse. Psychiatric symptoms were assessed according to the Positive and Negative Syndrome Scale (PANSS), and the severity of auditory hallucinations was rated by the Auditory Hallucination Rating Scale (AHS) and by hallucination item (P3) of the PANSS. The patients who participated in this study experienced mainly auditory hallucinations even though the P3 item evaluates visual, olfactory, cenesthetic and auditory hallucinations. Therefore, we used P3 to quantify the severity of auditory hallucinations. In addition to SZs, we recruited 23 age-matched healthy controls (HCs) (median age, 36.4 years [range, 27-50] ; 17 males and six females) to participate in this study. Screening of these HCs with a medical questionnaire ensured that none of them had any current or prior history of psychiatric illness. Additional exclusion criteria for HCs included those employed for SZs. All participants were right handed, and their intellectual functioning was assessed using the Japanese Adult Reading Test. Detailed demographical and clinical data are presented in Table 1. This study was approved by the Ethics Committee of the Faculty of Medicine, Showa University. All
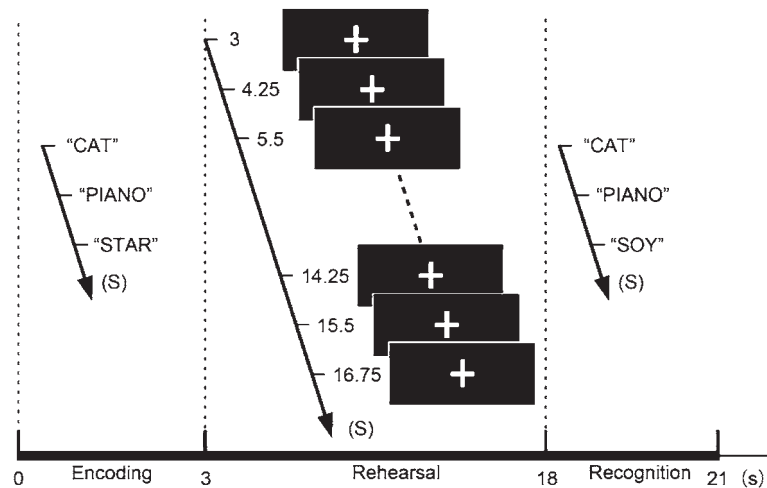
Fig. 1. Auditory verbal working memory paradigm
An example sequence of the stimuli presented in a single trial is shown. During the encoding phase, a list of three words was sequentially presented binaurally through earphones. During the rehearsal phase, a red crosshair flashed every second and participants were asked to rehearse a word in their mind every time it flashed. During the retrieval phase, a list of three words was presented again through earphones. The participants were asked to press a button to indicate if the list of words in the retrieval phase was the same as the one presented in the encoding phase.

participants gave written informed consent to participate in the study after its purpose was fully explained.

Task

The participants in the study were provided with an auditory verbal working memory task to create a situation in which inner speech was necessarily involved. We adopted a slightly modified version of the experimental paradigm used in a previous fMRI study by Hashimoto *et al*[21]. The task in each trial consisted of three different phases and a rest period : an encoding phase (3 s), a rehearsal phase (15 s), a rest period (16 s), and a recognition phase (3 s). One session lasted 10 min 4 s, including the initial and final rest periods. In each trial, three different words were presented at one word per second at the beginning of the encoding phase, during which time the participants were required to memorize them for subsequent recall. During the rehearsal phase, a red crosshair flashed every 1250 ms, and participants were asked to covertly rehearse one of the three words presented each time the crosshair flashed. Presentation of the flashing crosshair was essential because it enabled each participant to rehearse words at the same rate during the long rehearsal phase. In the recognition phase, we presented another three-word list. Participants were asked to press the right button if both lists had the same words in the same order and the left button if the lists were different. Participants were subjected to a total auditory presentation of 48 words (three words × 16 trials ; Fig. 1).

Participant responses in terms of their response time and accuracy data were collected via a fiber-optic response pad that was connected to a PC interface (Current Designs, Philadelphia, PA, USA). The stimuli presentation and response collection were controlled using the Neurobehavioral System's Presentation software (Neurobehavioral Systems, Albany, CA, USA).

Stimuli

Forty-eight Japanese nouns consisting of two to four syllables were presented as auditory words. Each stimulus was presented in a female voice using speech synthesizer software (Voice TEXT editor, HOYA Service Co., Tokyo, Japan). Each stimulus was presented binaurally through an MRI-compatible high fidelity headset (Resonance Technology Inc., San Diego, CA, USA) every 1 s (duration : 400−800 ms ; interstimulus interval : 200−600 ms) at a maximum intensity of 85 dB SPL. Visual stimuli were projected onto a screen placed at their feet. A reverse mirror was mounted on the head coil to allow the participants to view the screen.

Data acquisition

The BOLD signal was measured by T2-weighted echo-planar imaging (EPI : TE : 40 ms, TR : 2000 ms, flip angle 90°, voxel size : 3.43 × 3.43 mm ; FOV : 220 mm, thickness : 3 mm with a 1-mm slice gap, matrix size $= 64 \times 64$, 27 axial slices) on a 1.5-T scanner (General Electric, Milwaukee, WI, USA) using a phased-array whole-head coil. In the verbal working memory paradigm, 306 EPI volumes were acquired, and the first four volumes were discarded to allow for T1 equilibration. For anatomical localization of brain activation, high-resolution T1-weighted images of the whole brain were acquired using a standard spoiled grass gradient pulse 3-D MRI sequence from each participant (128 sagittal slices, in-plane resolution : 0.86 × 0.86 mm, 1.4-mm slice thickness).

Data analysis

All data processing and analyses were conducted using Statistical Parametric Mapping software (SPM8 ; Wellcome Department of Cognitive Neurology, London, UK) running on MATLAB version 2009b (The MathWorks, Natick, MA, USA). The remaining 302 volumes were corrected for slice timing differences (sync interpolation), and then spatially realigned using a rigid-body transform to account for head movement over time. These images were normalized to the standard Montreal Neurological Institute template, and then smoothed with an 8-mm full-width half-maximum Gaussian kernel. In a first-level general linear model analysis, task-related activation was modeled using four separate regressors for encoding, early rehearsal, late rehearsal, and recognition, each of which was set at 0, 6, 12, and 18 s from the onset of each trial, respectively. We used the late rehearsal regressor to assess rehearsal-related activation because the early rehearsal regressor was similar in timing to the sensory stimulation ; therefore, the brain activation was contaminated by the sensory stimuli[22]. The contrast image was included in the second-level analysis that examined random effects. The statistical threshold was set to a family-wise error corrected $P < 0.05$ at the voxel-level.
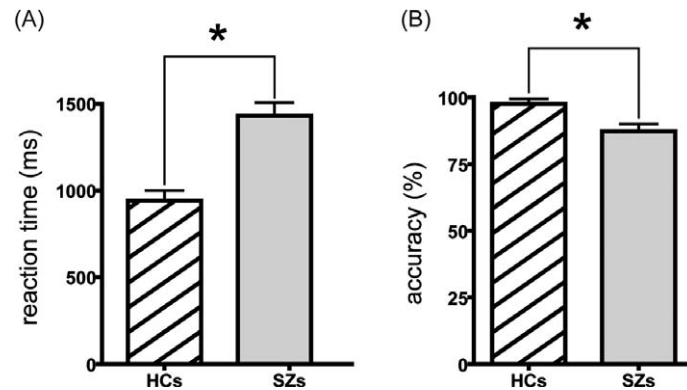
(A)

(B)

Fig. 2. Behavioral task results
(A) The reaction time of schizophrenia patients (SZs) was longer than healthy control participants (HCs). (B) SZs showed lower accuracy than HCs. *denotes a significant difference (P < 0.05).

In addition to the voxel-by-voxel whole brain analysis, we conducted a region-of-interest (ROI) analysis to determine which speech production-related regions correlated with the severity of auditory hallucinations. We selected IFC, LPC, and PMC as ROIs because these regions showed the most prominent abnormal activation in SZs (see Results). Previous studies have shown that these regions are involved in speech production. Furthermore, we focused on activation during the rehearsal phase, which is thought to reflect inner speech in the absence of auditory stimulation. Parameter estimates of activation for the contrast between the late rehearsal and rest were extracted using the Mars-bar toolbox for SPM. The ROIs were set as a sphere with a 6-mm radius centered on the focus of activation. Pearson product-moment correlation coefficients were calculated between the extracted parameter estimate and two auditory hallucination scales (AHS and P3 item in PANSS).

Results

Behavioral data

The mean reaction time of SZs (1426.0 ± 118.0 ms) was longer than that of HCs (935.9 ± 76.0 ms, t-test, $P = 0.001$). The mean accuracy rate was 97.6 ± 0.9% for HCs and 87.2 ± 2.8% for SZs (t-test, $P = 0.001$; Fig. 2). Because of a technical problem, the behavioral data of one schizophrenia patient was not collected.

fMRI data

HCs showed activation across large areas of the IFC, PMC, STC, and LPC bilaterally through all three phases. In contrast, SZs showed significant brain activation mainly in the STC bilaterally during encoding, but in the IFC, PMC, STC, and LPC bilaterally during recognition. Only a small cluster of activation in the temporoparietal region was found during rehearsal.

Reduced activation was most clearly observed in SZs in the group comparison during the
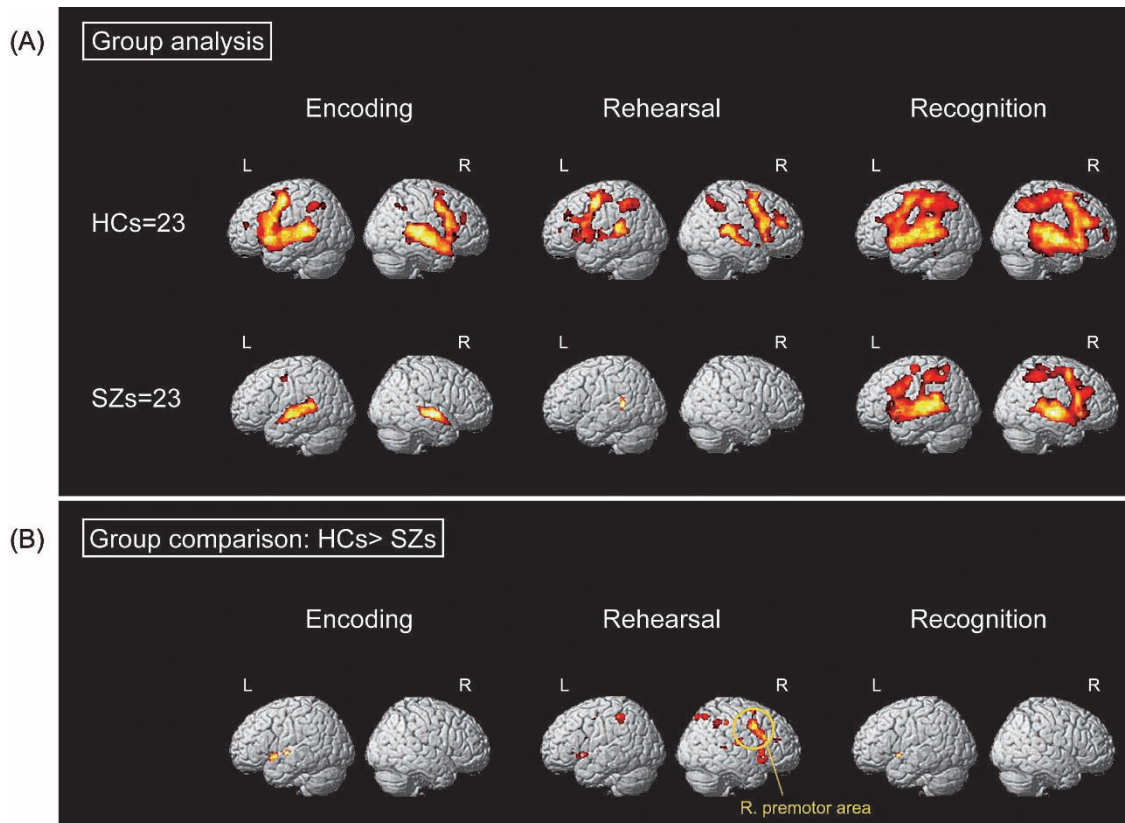
Fig. 3. Brain activation during the task
(A) Brain activation of healthy control participants (HCs) and schizophrenia patients (SZs) during the encoding, rehearsal, and recognition phases. (B) Comparison between HCs and SZs (HCs＞SZs) during the encoding, rehearsal, and recognition phases. During the rehearsal phase, group differences in right premotor activation were significant. The statistical threshold was $P<0.05$, corrected for multiple comparisons.

rehearsal phase especially in the IFC, LPC, and PMC bilaterally (Fig. 3). We did not observe any areas in which SZs showed greater activation than HCs. A list of areas showing significant activation during each task period is shown in Tables 2, 3, and 4.

To investigate areas in which abnormal activation may be associated with auditory hallucinations, we conducted an ROI analysis for the IFC, IPC, and PMC bilaterally using the magnitude of activation during rehearsal. A negative correlation was observed between the AHS score and activation in the right PMC (r＝−0.46, $P=0.028$), which also showed a marginally significant negative correlation with the PANSS (H) score (r＝−0.40, $P=0.058$, Fig. 4). No other ROI showed any significant correlation with the two auditory hallucination scales.

Discussion

In this study, we investigated brain activation during inner speech in SZs using an auditory verbal working memory task. As expected, abnormal activation was clearly observed in SZs during the rehearsal phase with reduced activation across large areas of the IFC, LPC, and PMC

Table 2.　Significant activation during the encoding phase

	Region	Cluster size	x	y	z	T
HCs	L. posterior STC	23054	−56	−38	12	14.3
	L. SFC / SMA		−6	4	60	14.2
	R. IFC / DLPFC		48	4	36	10.3
	L. IFC / premotor area		−40	−6	48	11.6
	L. IFC / FO		−50	8	28	10.2
	R. anterior STC		52	8	−14	10.4
	R. posterior STC		66	−24	8	12.0
	L. anterior STC		−56	−8	0	10.2
	R. posterior MTC		58	−12	−8	13.1
	L. insula		−48	10	4	12.2
	R. IPC		36	−56	42	6.5
	R. cerebellum / anterior lobe	780	12	−76	−16	6.8
	L. occipital cortex / lingual lobe	575	−10	−74	−4	7.4
	L. anterior STC / temporal pole	462	−44	22	−26	6.1
	R. anterior MTC	119	38	34	24	6.6
	R. insula	95	36	16	4	8.9
	L. anterior MTC	52	−30	44	16	6.3
	R. midbrain	14	4	−24	−12	5.8
	L. IPC	6	−44	−48	42	7.6
SZs	L. posterior STC	2109	−54	−30	2	10.5
	R. posterior MTC	1163	56	−10	−4	11.9
	L. IFC / premotor area	46	−54	−4	50	7.1
	L. SFC / SMA	32	−6	2	60	6.3
HCs＞SZs	R. pallidum	424	16	4	−4	5.7
	R. cingulate gyrus	114	10	22	34	6.0
	L. putamen	110	−14	12	−2	5.2
	L. posterior STC	97	−48	10	−6	6.1
	L. occipital cortex / lingual lobe	92	−18	−60	0	5.5
	L. anterior STC	58	−52	−8	0	5.7
	R. occipital cortex / lingual lobe	26	16	−76	−16	5.4
	L. SFC / SMA	11	−6	6	58	5.2

Statistical threshold was $P < 0.05$, corrected for multiple comparisons at the voxel level. HCs : Healthy controls, SZs : Schizophrenia patients, L : left, R : right, SFC : superior frontal cortex, IFC : inferior frontal cortex, SMA : supplementary motor area, FO : frontal operculum, DLPFC : dorsolateral prefrontal cortex, STC : superior temporal cortex, MTC : middle temporal cortex, IPC : inferior parietal cortex.

bilaterally during this phase. Abnormal activation in these language-related areas during inner speech are consistent with previous studies[6, 17]. We did not find increased activation in any brain areas of patients with schizophrenia. In the ROI analysis, activation in the right PMC consistently showed significant negative correlations with scores for the two auditory hallucination scales of AHS and PANSS（H）. The PMC processes sensory-related cognitive information and participates in planning, selecting, and executing movements[23]. Previous neuroimaging studies

Table 3. Significant activation during the rehearsal phase

	Region	Cluster size	x	y	z	T
HCs	L. MFC / SMA	12096	−8	−2	56	13.8
	R. anterior MFC		42	40	22	8.1
	R. posterior MFC		48	−2	46	10.3
	R. MFC / premotor area		32	0	54	9.2
	L. MFC / premotor area		−46	−4	48	12.3
	L. IFC		−56	8	20	8.0
	R. insula		32	26	0	10.6
	L. insula		−32	22	4	11.3
	L. putamen		−20	8	2	8.7
	R. posterior STC	1446	66	−44	10	11.0
	R. MTC		62	−14	−6	9.2
	L. IPC	897	−44	−42	44	9.3
	L. posterior STC		−56	−34	12	10.3
	R. posterior SPC / precuneus	554	34	−54	42	10.4
	R. caudate nucleus	129	18	4	12	8.0
	L. cerebellum / anterior lobe	82	−4	−50	−24	7.4
	L. anterior MFC	27	−28	46	8	7.5
	R. anterior STC	11	54	8	−12	8.1
SZs	L. posterior STC	143	−50	−44	12	7.2
HCs > SZs	R. MFC / premotor area	1070	46	4	40	6.7
	R. anterior MFC		38	2	38	5.5
	R. IFC		56	18	−6	6.2
	L. front-temporal space	634	22	−2	2	6.8
	R. cerebellum / inferior posterior lobe	555	−18	0	4	6.6
	L. insula	285	−4	−52	−20	5.9
	R. cerebellum / superior posterior lobe		8	−72	−18	5.8
	R. posterior SPC / precuneus	274	36	−50	40	6.9
	R. posterior SPC / precuneus	258	12	−72	52	6.2
	R. IPC	231	−36	−42	48	6.0
	L. IPC	113	64	−18	16	6.2
	R. postcentral gyrus	87	−18	−10	50	5.8
	R. putamen	83	−56	16	−4	5.7
	L. putamen	68	34	−64	54	5.9
	L. cerebellum / anterior lobe	52	−34	24	8	5.8

Statistical threshold was $P < 0.05$, corrected for multiple comparisons at the voxel level. HCs : Healthy controls, SZs : Schizophrenia patients, L : left, R : right, MFC : middle frontal cortex, IFC : inferior frontal cortex, SMA : supplementary motor area, FO : frontal operculum, STC : superior temporal cortex, MTC : middle temporal cortex, SPC : superior parietal cortex, IPC : inferior parietal cortex.

have indicated that activation occurs in this area during inner speech [16], which suggests that the PMC may play a major role in producing inner speech. Several previous studies have described abnormal activation in the right hemisphere during inner speech or other language-related tasks

Table 4.   Significant activation during the recognition phase

	Region	Cluster size	x	y	z	T
HCs	R. anterior STC	48745	60	−8	−4	20.2
	R. anterior MFC		48	30	22	14.7
	L. anterior MFC		−38	42	26	7.1
	L. MFC / SMA		−6	−4	62	19.9
	L. MFC / premotor area		−40	0	42	15.2
	L. IFC / anterior insula		−34	18	−4	11.3
	L. posterior IFC		−34	−62	44	11.3
	L. SMA / cingulate gyrus		−6	12	44	16.0
	R. posterior STC		58	−28	4	16.8
	L. anterior STC		−52	−4	−2	15.6
	L. posterior STC		−52	−45	16	14.7
	L. STC / Hechel's gyrus		−62	−16	6	15.2
	L. MTC		−58	−36	4	15.9
	R. insula		34	22	−4	16.5
	L. insula		−44	4	0	18.2
	R. IPC		38	−62	44	11.9
	R. postcentral gyrus		40	−26	52	10.1
	L. putamen		−24	0	2	13.2
	R. midbrain		12	−12	−4	14.5
	L. cerebellum anterior lobe	3310	−18	−56	−26	9.0
	R. occipital cortex / cuneus		12	−80	8	8.0
	R. occipital cortex / lingual gyrus		−18	−50	−8	7.1
	L. occipital cortex / lingual gyrus		−22	−62	0	8.9
	R. cerebellum anterior lobe		20	−60	−26	8.8
	R. parietal cortex / precuneus	172	10	−70	44	7.6
	R. SFC	101	30	58	0	6.9
	L. parietal lobe / precuneus	41	−10	−76	42	6.8
	L. ITC	19	−56	−42	−22	6.7
SZs	L. MTC	8819	−56	−32	4	17.3
	L. anterior MFC		−40	22	28	9.1
	L. MFC / premotor area		−46	0	38	8.5
	L. anterior STC		−50	6	−2	13.3
	L. insula		−36	20	6	10.6
	L. IPC		−52	−30	50	8.2
	R. MTC	7118	58	−16	−4	15.7
	R. IFC		52	10	10	10.6
	R. insula		40	18	0	12.2
	L. SMA / cingulate gyrus	1966	0	18	52	11.4
	R. MFC / SMA		4	−2	64	10.9
	L. midbrain	1565	−10	−18	−6	12.1
	L. postcentral gyrus	1076	54	−20	54	8.2
	R. MFC / premotor area		44	0	46	10.2
	R. IPC		40	−52	46	8.1
	L. MFC / premotor area	332	−30	−10	62	7.6
	L. cingulate gyrus	13	−6	−24	28	6.7
HCs > SZs	L. insula	30	−44	4	−2	5.6

Statistical threshold was $P < 0.05$, corrected for multiple comparisons at the voxel level. HCs : Healthy controls, SZs : Schizophrenia patients, L : left, R : right, SFC : superior frontal cortex, MFC : middle frontal cortex, IFC : inferior frontal cortex, SMA : supplementary motor area, STC : superior temporal cortex, MTC : middle temporal cortex, ITC : inferior temporal cortex, IPC : inferior parietal cortex.
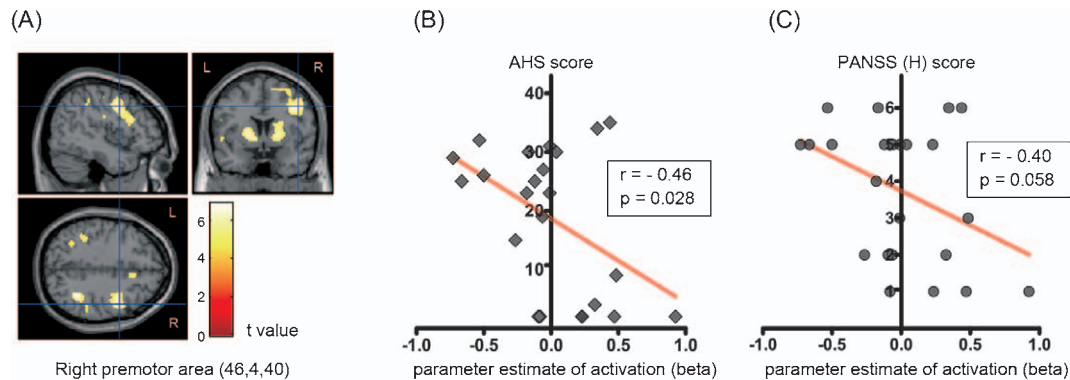
Fig. 4. Association between right premotor activation and the severity of auditory hallucinations (A) The location of the seed area in right premotor cortex (PMC). The center of the seed area is shown in the Montreal Neurological Institute space. (B) Parameter estimate of activation in the right PMC during the rehearsal phase was plotted against the score of Auditory Hallucination Rating Scale (AHS). (C) The parameter estimate of activation in the right PMC during the rehearsal phase was plotted against the score of the hallucination item (P3) of Positive and Negative Syndrome Scale (PANSS).

in schizophrenia [6, 24, 25]. Furthermore, an fMRI study found significant activation in the right hemisphere during auditory hallucinations [12]. Considering these previous findings, dysfunctional activity in the right hemisphere language function may be associated with the pathology and symptoms of schizophrenia.

This study had several limitations. Firstly, the accuracy of task performance for SZs was lower than that for HCs because the patients may not have fully performed the repetition during the rehearsal phase. All of the participants showed an accuracy rate higher than 60%, confirming that they were at least partially engaged in the task. Secondly, SZs may have experienced auditory hallucinations during the task, which could affect their brain activation but we did not determine this directly. It is likely that no auditory hallucinations were severe enough to disable the patients from performing the task because the accuracy of participants was higher than 60%. Thirdly, a previous study indicated that there is a difference in brain activation between males and females [26], which was not analyzed in this study. Therefore, future studies should strictly control the number of male and female participants in each group. Fourthly, the BOLD signal was measured on an 1.5 T MRI scanner in this study, but 3 T MRI scanners are becoming standard in the field of human neuroimaging. Therefore, the difference in the static magnetic field strength may have influenced the results because magnetic susceptibility varies across brain regions depending on their anatomical features. Several 3 T fMRI studies have suggested that other brain regions such as the IFC are related to auditory hallucinations [12, 25], whereas this study indicates that the right PMC is related to the severity of auditory hallucinations. This finding does not exclude the possibility that other regions may be involved in auditory hallucinations. The limited signal-to-noise ratio of the 1.5 T system could have failed to detect significant signal changes in other brain regions that are responsible for the generation of auditory hallucinations. Finally, our study used a conventional fMRI protocol in terms of both spatial (∼ 3 mm) and

temporal（2 sec）resolutions. In particular, we acknowledge that the temporal resolution of our protocol is not fine enough for tracking a complex time-course of neural activity at the millisecond timescale. Therefore, our findings should be compared with any future studies that use electroencephalogram（EEG）and / or magnetoencephalography（MEG）at higher temporal resolutions. In addition, the use of the MRI system with a higher static magnetic field (*e.g.* 3 Tesla) together with improved scanning sequences may reveal finer anatomical information of the brain circuits responsible for auditory hallucinations that were undetected by our MRI system.

The present study demonstrates that SZs have impairments with inner speech, and have abnormal right PMC function during inner speech, which is correlated with auditory hallucinations. Auditory hallucinations in SZs have complicated characteristics that may be affected by abnormal inner speech and by other factors such as memory, thoughts and impaired memory function, which could lead to auditory hallucinations [27, 28]. Other studies have suggested an association between auditory hallucinations and dysfunction in the primary auditory cortex regions involved in low-level auditory processing rather than in language processing [2, 29]. Additional studies are needed to elucidate the mechanism of auditory hallucinations. We suggest that evaluations of abnormal auditory processing should be conducted at multiple levels to clarify changes in brain functions between pre- and post-medication periods using a within-subject design. Such studies would be useful in advancing our understanding of the mechanisms of auditory hallucinations.

Conflict of interest

The authors have declared no conflict of interest.

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