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Abnormal association between reduced magnetic mismatch field to speech sounds and smaller left planum temporale volume in schizophrenia

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Schizophrenia is associated with language-related dysfunction. A previous study [Schizophr. Res. 59 (2003c) 159] has shown that this abnormality is present at the level of automatic discrimination of change in speech sounds, as revealed by magnetoencephalographic recording of auditory mismatch field in response to across-category change in vowels. Here, we investigated the neuroanatomical substrate for this physiological abnormality. Thirteen patients with schizophrenia and 19 matched control subjects were examined using magnetoencephalography (MEG) and high-resolution magnetic resonance imaging (MRI) to evaluate both mismatch field strengths in response to change between vowel /a/ and /o/, and gray matter volumes of Heschl's gyrus (HG) and planum temporale (PT). The magnetic global field power of mismatch response to change in phonemes showed a bilateral reduction in patients with schizophrenia. The gray matter volume of left planum temporale, but not right planum temporale or bilateral Heschl's gyrus, was significantly smaller in patients with schizophrenia compared with that in control subjects. Furthermore, the phonetic mismatch strength in the left hemisphere was significantly correlated with left planum temporale gray matter volume in patients with schizophrenia only. These results suggest that structural abnormalities of the planum temporale may underlie the functional abnormalities of fundamental language-related processing in schizophrenia.

Keywords: Speech sounds; Heschl's gyrus; Planum temporale; Schizophrenia; Mismatch negativity

Introduction

Schizophrenia has long been characterized as a disorder, which incorporates cognitive dysfunction (reviewed in Andreasen et al., 1999; Green et al., 2000). Among many aspects of cognitive functioning, language-related dysfunctions, such as impaired verbal memory (Saykin et al., 1991, 1994) and thought disorder (e.g., Goldberg et al., 1998; Iwanami et al., 2000), have been consistently observed in patients with schizophrenia. Although these are complex, integrated aspects of language functions, at their earliest stage, language processing requires perception of phonemes. This fundamental process can be indexed by mismatch negativity (MMN), an event-related potential (ERP) elicited by auditory stimuli that deviate from preceding repetitive stimuli (Näätänen et al., 1978). Recently, a reduced amplitude of MMN in response to across-category change of vowel sounds has been demonstrated in patients with schizophrenia (Kasai et al., 2002a). Moreover, the reduction in MMN amplitude in patients with schizophrenia compared to control subjects was more distinct under the condition of vowel across-category change rather than under that of within-category (duration) change perception of a vowel or the change of physical features (duration) of a pure tone. Furthermore, Kasai et al. (2003c) replicated the findings of abnormal across-category change perception of speech sounds using magnetoencephalography (MEG) in an independent sample of patients with schizophrenia.

Our next goal would be to reveal the neuroanatomical substrate for this functional abnormality of speech sound perception in patients with schizophrenia. One promising strategy is to assess functional and structural abnormalities in a group of patients and evaluate the correlation between the two indices. A successful example has been provided by McCarley et al. (1993) who reported an abnormal association between reduced amplitude of P300 ERP in the left temporal area and gray matter volume of left posterior superior temporal gyrus as assessed by magnetic resonance imaging (MRI) in a group of chronic schizophrenia, and later, in an independent sample of first-episode schizophrenia (McCarley et al., 2002). We may apply a similar approach to address the question of which region of the brain is associated with the abnormalities of phonetic mismatch.

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MMN and its magnetic counterpart (magnetic mismatch field, MMF) in response to non-speech tonal sounds is generated in and around the primary auditory cortex in Heschl's gyrus (HG) [Brodmann's area (BA) 41/42] (Javitt et al., 1994; Kropotov et al., 1995). In contrast, two studies have indicated that mismatch activity in response to speech sounds is localized to planum temporale (PT) (Rinne et al., 1999; Tervaniemi et al., 2000). The PT is located on the superior temporal gyrus and the anterior portion of PT is part of the unimodal auditory association cortex (part of BA22) surrounding HG, whereas the posterior portion adjacent to the temporoparietal junction (other portions of BA22 and part of BA39–40) is partially coextensive with Wernicke's area, consisting of heteromodal association cortex (Mesulam, 2000; Pearlson, 1997). PT evinces the most prominent left–right asymmetry in the human brain (Geschwind and Levitsky, 1968), which is thought to reflect PT's critical role in language processing (Galaburda et al., 1978). Another line of studies has demonstrated structural abnormalities of PT in schizophrenia using MRI. For example, Kwon et al. (1999) reported left PT gray matter volume reduction in chronic schizophrenia and Hirayasu et al. (2000) reported smaller left PT gray matter volumes in patients with first-episode schizophrenia compared with first-episode patients with affective psychosis and control subjects. Taken together, it may be reasonable to hypothesize abnormal association between reduced phonetic mismatch and smaller gray matter volume of PT in patients with schizophrenia.

Accordingly, the present study assessed the relationships between MMF in response to change in vowel category and gray matter volume of PT as assessed by high-resolution MRI in a group of patients with schizophrenia. Moreover, the use of a whole-head MEG instead of a scalp ERP has two advantages in evaluating the association with PT volume. Magnetic fields are not influenced by intervening tissues of different conductivities in contrast to electrical fields, thus enabling an independent assessment of the left and right hemispheric functions. Moreover, MEG selectively detects tangential vectors of electrical currents, whereas EEG is more sensitive to currents radial to the scalp. Thus, the MEG recording predominantly detects mismatch response generated in the superior temporal plane, which has more tangentially oriented currents, although it is less sensitive to that from other generators such as the frontal component, which has predominantly radial currents (Giard et al., 1990; Kasai et al., 1999).

Methods

Subjects

Patient recruitment and diagnostic procedures are described in detail in Kasai et al. (2003c). All subjects in this study (13 schizophrenics and 19 controls) had been included in our previous MEG study (Kasai et al., 2003c; 16 schizophrenics and 19 controls). Three patients with schizophrenia were excluded since MRI was not available in two subjects and low image quality did not enable volumetric assessment in one subject. Thirteen right-handed (determined using the Edinburgh Inventory, Oldfield, 1971; a laterality index of ≥0.8 was the cut-off for right-handedness) in- and outpatients with schizophrenia were recruited from the Department of Neuropsychiatry, Hospital of Tokyo University, Japan. Seven were male, and six were female. Diagnosis of schizophrenia was determined for each patient according to DSM-IV (American Psychiatric Association, 1994) criteria through the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I) Clinical Version (First et al., 1997) by a trained psychiatrist (K.K.). The subtypes were disorganized (n = 5), catatonic (n = 2), paranoid (n = 2), and undifferentiated (n = 4). All patients received typical neuroleptics except for two neuroleptic-naïve patients. Psychiatric symptoms were evaluated by one psychiatrist (K.K.) using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) within 3 days before the MEG recording or MRI scanning. Nineteen right-handed age- and gender-matched healthy subjects were used as controls. Socioeconomic status (SES) and parental SES were assessed using the Hollingshead scale (Hollingshead, 1965). The patients with schizophrenia showed significantly lower socioeconomic status than the control subjects, whereas the parental SES did not differ significantly between groups (Table 1).

The exclusion criteria for both groups were neurological illness, hearing dysfunction, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, and substance abuse or addiction. An additional exclusion criterion for the control group was a history of psychiatric disease in themselves or a family history of axis I disorder in their first-degree relatives. The ethical committee of the University of Tokyo Hospital approved this study. All subjects gave written informed consent after a complete explanation of the study.

Table 1
Subject characteristics and symptom scores

Variable	Schizophrenic patients (n = 13)		Control subjects (n = 19)		t tests		
	Mean	SD	Mean	SD	df	t value	P
Age (range)	29.8 (20–39)	6.1	27.3 (20–52)	7.0	30	−1.0	0.31
Male/female	7/6		13/6				
Education, years	13.1	2.1	15.8	1.8	30	3.9	< 0.001
SES[a]	4.3	0.9	1.9	0.6	30	−9.0	< 0.001
Parental SES[a]	2.5	0.5	2.4	0.7	30	−0.8	0.45
Neuroleptic dose[b], mg/day	543	585	ÉÉ	É	É	ÉÉ	É
Onset of illness, years	21.4	7.6	ÉÉ	É	É	ÉÉ	É
Duration of illness, years (range)	8.4 (0–18)	6.5	ÉÉ	É	É	ÉÉ	É
PANSS positive subscale	14.2	5.7	ÉÉ	É	É	ÉÉ	É
Negative subscale	20.1	6.7	ÉÉ	É	É	ÉÉ	É
General psychopathology subscale	35.9	7.0	ÉÉ	É	É	ÉÉ	É

[a] Socioeconomic status, assessed using the Hollingshead scale. Higher scores indicate lower status.
[b] Based on chlorpromazine equivalents.

MEG procedures

The MEG methodology was described in detail in Kasai et al. (2003c), which is briefly summarized below. The interval between MEG recording and MRI scanning was within 2 weeks, and the order was counterbalanced across subjects. Although the original experiment included three conditions eliciting three types of mismatch response (tone-duration, phoneme-duration, and across-phoneme), the present study focused on the third condition which was specifically found to be language-related (Kasai et al., 2001) and under which previous study found significant reduction in patients with schizophrenia (Kasai et al., 2003c).

Task procedures

The subjects were presented with sequences of auditory stimuli consisting of standard (Japanese vowel /a/, probability = 90%) and deviant (vowel /o/, probability = 10%) stimuli delivered randomly, except that each deviant stimulus was preceded by at least one standard stimulus. These vowel stimuli were spoken by a native-Japanese-speaking actor, digitized using the NeuroStim system (NeuroScan Inc., USA) and edited to have a duration of 150 ms, loudness of 70 dBSPL and rise/fall time of 10 ms. The frequency spectra for the vowels were as follows: /a/, formant (F) 0 = 140 Hz, F1 = 760, F2 = 1250, F3 = 2750, and F4 = 3600; /o/, F0 = 140 Hz, F1 = 480, F2 = 770, F3 = 2820, and F4 = 3600. The interstimulus interval (ISI) was 510 ± 20 ms. The stimuli were delivered binaurally through plastic tubes. The subjects were instructed to watch a silent film to ignore the stimuli.

Data collection

Magnetic fields were recorded in a magnetically shielded room (NKK Plant Engineering Co., Japan) with a 122-channel magnetometer (Neuromag Ltd., Finland; Knuutila et al., 1993). This whole-head magnetometer consists of 61 dual-sensor units each with two orthogonal planar gradiometers recording maximal signals directly above the source (Hämäläinen et al., 1993). The subjects sat on a chair with their head inside the helmet-shaped magnetometer. The position of the magnetometer with respect to the head was determined at the beginning of the task by recording the magnetic fields produced by currents fed into three indicator coils at predetermined locations on the scalp. The locations of these coils in relation to the preauricular points and nasion were determined with an Isotrak 3D-digitizer (Polhemus TM, USA) before the start of the experiment. Two electrodes were placed at the outer canthus and below the left eye to monitor eye movements.

MEG epochs were averaged online, separately for standard and deviant stimuli. The duration of the averaging period was 512 ms, including a 64-ms prestimulus baseline. The recording bandpass was 0.03–100 Hz, with a sampling rate of 500 Hz. The first 10 stimuli were automatically excluded from averaging. Epochs coinciding with electrooculogram movement or MEG exceeding 150 μV or 3000 fT/cm were also excluded from averaging. Each condition lasted until 100 deviant stimuli without contamination of artifacts were accepted. Averaged responses were digitally filtered with a bandpass of 1–30 Hz.

MRI acquisition

The MRI data were obtained on a 1.5-T scanner (General Electric Signa Horizon Lx version 8.2, GE Medical Systems, Milwaukee, WI, USA) as previously described (Kasai et al., 2003c). For manual measurement of brain structures, a three-dimensional fast-spoiled GRASS (gradient recalled acquisition with steady state) sequence was used because it affords excellent contrast between the gray matter and white matter for the evaluation of brain structures. The repetition time was 9.3 ms, the echo time 2.1 ms with one repetition, the nutation angle 45°, the field of view 24 cm, and the matrix 256 × 256 (192) × 124. Voxel dimensions were 0.9375 × 0.9375 × 1.5 mm. A trained neuroradiologist (Ha.Ya. or O.A.) evaluated the MRI scans and found no gross abnormalities in any subjects. The MEG-coordinate system was aligned with the MRI-based coordinates by identifying the left and right preauricular points, as well as the nasion, from the MRI slices.

Dipole analysis

For each subject, equivalent current dipoles (ECDs) for MMF were calculated primarily according to the method of Alho et al. (1998). Briefly, the MMF was determined from the difference curves obtained by subtracting the response to standard stimuli from that to deviant stimuli. Then, ECDs were determined using a least-squares fit at 2-ms intervals from 100 to 250 ms. The calculation was performed separately for each hemisphere, utilizing a spherical head model constructed based on the individual MRI and a subset of 44 channels over the temporal brain areas. ECDs with a maximal goodness of fit (GOF) of ≥60% were included in the analysis. In this procedure, we reduced the number of the channels to 28–43 when the dipole was not calculated or a certain channel had a considerable amount of artifact. The mean GOF in the control and schizophrenia group was [85.5%, 81.3%] for the left hemisphere and [84.1%, 81.2%] for the right hemisphere, which were not significantly different between groups for either hemisphere ($p > 0.24$).

Magnetic counterpart of global field power

ECDs of MMF were not successfully determined for five schizophrenic patients and zero control subjects in the left hemisphere, and for three schizophrenic patients and one control subject in the right hemisphere. The frequency of failure in calculating ECDs was significantly higher in the group of patients with schizophrenia, compared to the control group, in the left hemisphere (chi-square = 8.67, $df = 1$, $P = 0.003$) but not in the right hemisphere (chi-square = 2.24, $df = 1$, $P = 0.14$). In the control group, visual inspection of the signals for one case indicated that MMF was strongly lateralized to the left hemisphere, possibly resulting in failure to calculate ECD in the right hemisphere. In the patients with schizophrenia, there were no gross artifacts or noises superimposed on averaged response curves that would account for the failure in calculating ECDs. The ECD is theoretically stronger when the neuronal activities are synchronized and regionalized. Thus, an alternative explanation for the failure to calculate ECDs may be that some patients with schizophrenia had deficits in the synchronization and regionalization of the neuronal population involved in MMF generation (Kasai et al., 2002b).

To utilize data from all the subjects in the statistical analyses, the magnitude of MMF responses was reassessed by applying global field power (GFP; Lehmann and Skrandies, 1980) to the analysis of MEG data (magnetic counterpart of global field power, or mGFP; Kasai et al., 2001, 2002b, 2003c; Kreitschmann-Andermahr et al., 1999). Firstly, the mGFP using the same 44 channels as in the dipole analysis was calculated for each subject, separately for each hemisphere. In this procedure, we reduced the number of

the channels to 28–43 when a certain channel had a considerable amount of artifacts. The peak latency of MMF for an individual subject was determined by the individual mGFP curve as a function of time. Second, the grand mean mGFP curves were plotted. Then, the MMF power for each subject was determined as mGFP averaged across a 100-ms time window around the peak latency of the grand mean mGFP. The mGFP has been shown to be a good substitute for the ECD strength in our previous studies (Kasai et al., 2001, 2002b, 2003c).

MRI processing

The HG and PT gray matter regions of interest (ROIs) and intracranial contents (ICCs) were outlined manually using a software package for medical image analysis (3D Slicer; software available at http://www.slicer.org) without knowledge of diagnosis or measurements of MEG (Fig. 1). The landmarks to delineate HG and PT gray matter were similar to those described in Kasai et al. (2003b). Briefly, HG was first identified in the axial plane, a demarcation that helped pinpoint the location of HG on coronal images. In most cases, HG represented a single transverse convolution. In cases where more than one transverse convolution was present, we followed the literature definition; when multiple convolutions originated medially from a common stem, all were defined as HG (the sulcus(i) between these convolutions represents the sulcus intermedius of Beck); when they originated separately from the retroinsular regions, only the most anterior gyrus was labeled as HG and more posterior gyri were identified as PT. The posterior border of HG (Heschl's sulcus) defined the anterior border of PT. Posteriorly, PT gray matter was traced on coronal images to the end of the Sylvian fissure, and the gray matter of the ascending ramus of the Sylvian fissure was also included. Thus, our definition of the PT included PT proper and its parietal extension. Once drawn, both HG and PT ROIs could be viewed in any plane and as a three-dimensional object for any further editing.

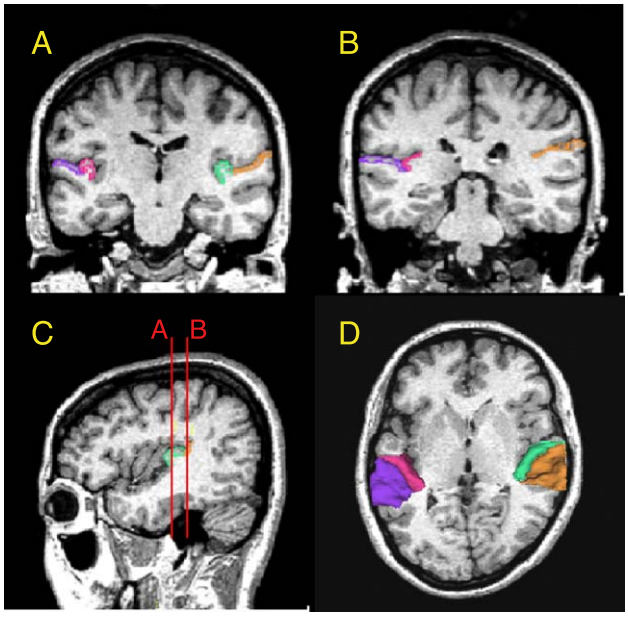

Fig. 1. (Panels A and B) Delineation of Heschl's gyrus and planum temporale in a coronal slice in rostral and caudal part of regions of interest, respectively, based on MRI data of a control subject. The gray matter of Heschl's gyrus is labeled green on subject left and wine-red on subject right. The gray matter of planum temporale is orange on subject left and violet on subject right. (C) Sagittal view of the Heschl's gyrus and planum temporale in the left hemisphere. The coronal lines A and B correspond to the planes of panels A and B, respectively. (D) Three-dimensional reconstruction of Heschl's gyrus and planum temporale gray matter superimposed on the axial plane. Each region is labeled using the same color as that in panels A, B and C.

For the ICC, brain matter was manually traced along the outside border of the brain on sagittal slices. Total cerebral gray and white mater (including brainstem, temporal lobes, the optic chiasma, the pituitary and cerebellum), cerebrospinal fluid, dura matter, and sinuses were included. All odd slices were considered. The base of the cerebellum demarcated the inferior border.

For interrater reliability, two raters (H.Y. and N.K. for HG/PT, H.Y. and M.U. for ICC), blind to group membership, independently drew ROIs. Ten cases were selected at random, and the raters drew ROIs on every slice. The intraclass correlation coefficient was 0.99/0.98 for left/right HG gray matter, 0.99/0.97 for left/right PT gray matter, and >0.99 for ICC, respectively. Intrarater reliability, computed by using all of the slices from one randomly selected brain and measured by one rater (H.Y.) at two separate times (approximately 6 months apart), was >0.99 for all structures.

Statistical analyses

Group comparison

Repeated-measures ANOVAs were performed for between-group comparison of MMF power/peak latency, adopting group (schizophrenia, control) as the between-subject factor and hemisphere (left, right) as the within-subject factor. For ROI analysis, we used a repeated-measures ANOVA, using relative volumes with one between-subject factor (group: schizophrenia, controls) and two within-subject factors (hemisphere: left and right; region: HG and PT). Once a significant group-by-region or group-by-region-by-hemisphere interaction was found, follow-up analyses using repeated-measures ANOVA separately for each region (HG or PT) were performed. Then, in the case of group-by-hemisphere interaction, post hoc t tests separately for each hemisphere were conducted. Although ICC was not different between groups [control subjects, mean, 1490 mL (SD = 110); schizophrenic patients, mean, 1510 mL (SD = 95); $t(30) = 0.57$, $P = 0.58$], the relative volumes [100 × absolute ROI volume] / ICC] were used as the dependent variable as is the standard method for MRI studies in schizophrenia (e.g., Bryant et al., 1999; Kasai et al., 2003a,b; Shenton et al., 1992). Of note, the statistical conclusions reported below remained the same when ANCOVA with absolute volume as the dependent variable and ICC as the covariate was used.

Correlational analysis

The association between the absolute volume of ROIs in the left/right hemisphere and the phonetic MMF in the ipsilateral hemisphere was tested using Pearson's correlation separately for each group. Although multiple tests were performed, we did not use the Bonferroni correction because the correlation was calculated under the hypothesis that left/right PT volume is correlated with phonetic MMF in the same hemisphere in the group of patients with schizophrenia.

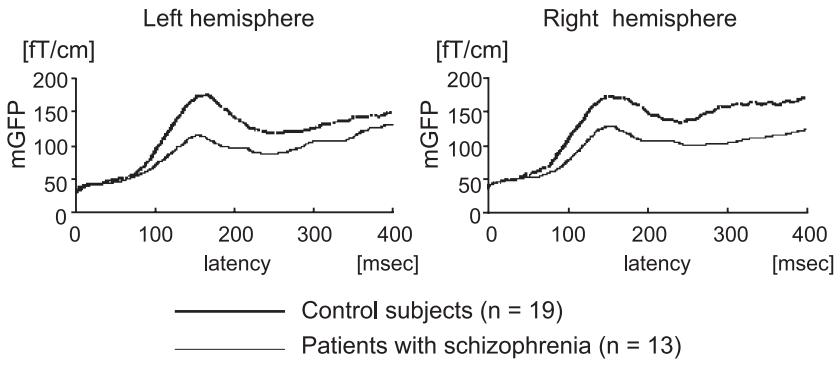

Fig. 2. Grand mean magnetic global field power (GFP) waveforms under the across-phoneme change condition for each hemisphere. Thick lines are for control subjects (N = 19) and thin lines for patients with schizophrenia (N = 13).

Additionally, Spearman's rho was calculated for exploring correlations between the clinical measures (age, SES, parental SES, years of education, onset of illness, duration of illness, and neuroleptic dose) and MMF/volume measures in each group separately.

Results

MMF

Groups were significantly different in MMF power [$F(1,30)$ = 12.3, P = 0.001], whereas the group-by-hemisphere interaction was not significant [$F(1,30)$ = 0.423, P = 0.52]. These results suggest a bilateral reduction of phonetic MMF in patients with schizophrenia compared with control subjects. For the latency, there was no significant main effect of diagnosis [$F(1,30)$ = 0.061, P = 0.081] or group-by-hemisphere interaction [$F(1,30)$ = 0.248, P = 0.62], indicating no significant difference in MMF peak latency between groups (Fig. 2, Table 2).

Volumes of ROIs

The repeated-measures ANOVA revealed a significant interaction of group × side × region [$F(1,30)$ = 15.2, P < 0.001]. The follow-up ANOVA showed that there was a significant main effect of group [$F(1,30)$ = 4.98, P = 0.033] and hemisphere [$F(1, 30)$ = 15.2, P = 0.001] for PT. There was also a significant group × side interaction [$F(1,30)$ = 9.07, P = 0.005], indicating that patients with schizophrenia had smaller left PT than controls [post hoc test, $t(1,30)$ = 3.99, P < 0.001]. However, right PT was not significantly different between groups [$t(1,30)$ = 0.17, P = 0.87]. For HG, there were no main effects for group [$F(1,30)$ = 0.568, P = 0.46] or side [$F(1,30)$ = 0.57, P = 0.46], or interaction between group and hemisphere [$F(1,30)$ = 2.27, P = 0.14].

Correlational analyses

The left hemisphere MMF in response to change in speech sounds showed a significant positive correlation with gray matter

Table 2
Volumetric and magnetic mismatch field measurements

	Control Subjects (n = 19)				Schizophrenic Patients (n = 13)				Repeated-measures analysis of variance[a]					
	LH		RH		LH		RH		Group		Hemisphere		Group × hemisphere	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	P	F	P	F	P
Magnetic mismatch field measurements														
Magnetic global field power	153	47	154	45	103	37	113	29	12.3	0.001[§]	0.643	0.43	0.423	0.52
Peak latency	160	19	162	29	165	28	161	26	0.061	0.81	0.044	0.84	0.248	0.62
Volumetric measurements														
Planum temporale, absolute volume, mL	2.29	0.57	2.38	0.64	1.57	0.56	2.39	0.62						
Planum temporale, relative volume[b], %	0.15	0.037	0.16	0.047	0.10[§]	0.032	0.158	0.04	4.98	0.033[§]	15.2	0.001[§]	9.07	0.005[c,§]
Heschl's gyrus, absolute volume, mL	1.37	0.37	1.52	0.35	1.57	0.42	1.52	0.37						
Heschl's gyrus, relative volume, %	0.092	0.024	0.10	0.02	0.10	0.026	0.10	0.023	0.568	0.46	0.57	0.46	2.27	0.14

LH/RH, left/right hemisphere.
[a] The degrees of freedom were (1,30) for all statistics.
[b] Calculated by the following formula: absolute volume/intracranial content (ICC) ∗ 100. ICC was not different between groups [control subjects, mean, 1490 ml (SD=110); schizophrenic patients, mean, 1510 ml (SD=95); $t(30)$=0.57, P = 0.58].
[c] Post hoc analysis indicated that there was a significant group difference for the left [$t(1,30)$ = 3.99, P < 0.001] but not for the right hemisphere [$t(1,30)$ = 0.17, P = 0.87].
[§] Reached significance.

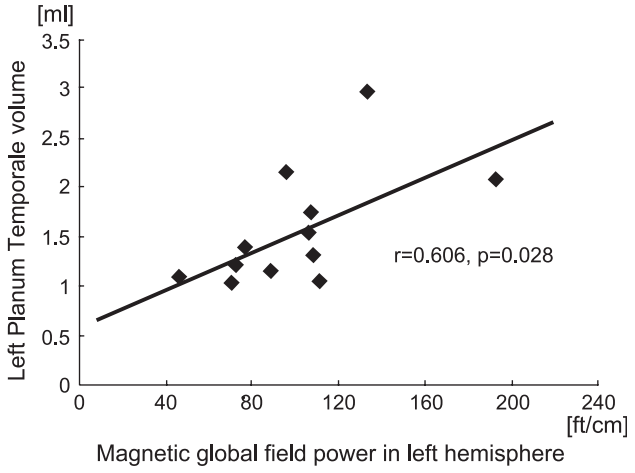

Fig. 3. Scatterplot depicting a correlation between the phonetic mismatch strength in the left hemisphere and the gray matter volume of left planum temporale in patients with schizophrenia ($r = 0.606$, $N = 13$, $P = 0.028$).

volume of the left PT in the group of patients with schizophrenia ($r = 0.606$, $P = 0.028$) but not in the control group ($r = -0.038$, $P = 0.88$) (Fig. 3). The left hemisphere MMF was not significantly correlated with left HG volume in either group, nor was the right hemisphere MMF correlated with right HG or PT volume in either group (range of r: −0.095 to +0.296, range of P: 0.33–0.96). There were no significant correlations between the MMF/ROI measures and age, SES, parental SES, years of education, onset of illness, duration of illness, or neuroleptic dose.

Discussion

In this group of patients with schizophrenia, left PT gray matter volume reduction was associated with bilateral reduction of MMF power in response to change in phoneme category. The findings of significant reduction in left PT but not right, and normal HG volume is in accordance with those of a previous study using a chronic schizophrenia sample by Kwon et al. (1999), although two studies examining first-episode schizophrenia sample (Hirayasu et al., 2000; Kasai et al., 2003a,b,c) have found reduced HG volumes. Moreover, the present study demonstrates that these two indices were significantly and specifically correlated in the group of patients with schizophrenia. Consistent with our hypothesis, these results suggest that structural abnormalities in the PT may underlie the basis for functional abnormalities of fundamental speech sound perception in patients with schizophrenia. Although there have been more than a dozen publications of MMN or MMF in patients with schizophrenia since the initial report of Shelley et al. (1991), none have sought to relate the MMN/MMF abnormality with volumetric reduction in the brain regions generating it. Thus, this study is the first to link MMN/MMF attenuation to volumetric reduction in the superior temporal neocortex in schizophrenia.

Although this cross-sectional study using a chronic sample does not answer the timing of the presence of the abnormal function–structural relationships, this may be already present pre- or peri-onset. Another possible explanation may be that progression of phonetic mismatch and planum volume reduction may occur concurrently, resulting in a strong association specific to patients with schizophrenia. Supporting this interpretation, Salisbury et al. (2002) reported that MMN was within normal range in a sample of first-episode schizophrenia but significantly reduced in an independent sample of chronic schizophrenia. Moreover, Kasai et al. (2003a,b) reported progressive decrease of gray matter volume of left posterior superior temporal gyrus, more specifically, left PT and HG, in patients with first-episode schizophrenia. These findings may support a concurrent deterioration of structure and function of the superior temporal neocortex in patients with schizophrenia.Although phonetic mismatch abnormalities were found in both hemispheres, present examination showed significant volume reduction of PT and its association with mismatch measures only in the left hemisphere. A previous study (Kasai et al., 2003b) indicated that progressive decrease of PT volume was only observed in the left hemisphere during the 1.5-year period following first hospitalization. If we hypothesize concurrent ongoing structural and functional deterioration in the superior temporal neocortex and consider the relatively short duration of illness in our sample, it may explain why abnormal relationships were more evident in the left hemisphere in our sample. If the present study recruited very chronic patients, it would not be surprising to find such relationships in both hemispheres, as Mathalon et al. (2001) showed that progressive decrease of superior temporal gyrus gray matter volume was present bilaterally in chronic patients with schizophrenia.

Previous findings from basic neuroscience suggest that MMN represents a selective current flow through open, unblocked *N*-methyl-D-aspartate (NMDA) channels on NMDA-type glutamate receptors (Javitt et al., 1996). Javitt et al. (1996) used a combination of intracortical recording and pharmacological micromanipulations in awake monkeys to demonstrate that both competitive and noncompetitive NMDA antagonists block the generation of MMN without affecting prior obligatory activity in the primary auditory cortex. Furthermore, they suggested that the MMN generation depends on the functional interaction between excitatory and inhibitory processes within cortex mediated by NMDA and $GABA_A$ receptors, respectively. In addition, the underlying mechanism involved in the progressive superior temporal volume reduction seen in schizophrenia (Kasai et al., 2003a,b) may involve the failure of NMDA-dependent recurrent inhibition that inactivates GABA neurons, thereby disinhibiting cholinergic and glutamatergic pathways through which excitotoxic activity is expressed, with consequent damage to dendritic spines and cell bodies of cerebrocortical neurons (Konradi and Heckers, 2003; McCarley et al., 1996). These lines of evidence may suggest an ongoing NMDA-mediated pathological process surrounding the superior temporal neocortex in patients with schizophrenia. The findings of the present study may at least partly support this hypothesis, although this discussion remains speculative due to the cross-sectional design of this study. In future, a longitudinal study employing a combination of neurophysiological, anatomical, and chemical (e.g., D-serine, Hashimoto et al., 2003) indices will be necessary to test the hypothesis.

Limitations of this study include mixed gender distribution and the cross-sectional nature. The PT is a brain structure where the presence of sexual dimorphism is well known (Kulynych et al., 1994). Investigating first-episode patients, follow-up of the patient cohort, and evaluating specificity of the findings to schizophrenia as compared with other psychopathological groups will be necessary in future studies.

In conclusion, the combination of MEG and volumetric MRI successfully reveals abnormal relationship between the phonetic mismatch strength in the left hemisphere and left PT gray matter

volume in schizophrenic patients but not in control subjects. These results suggest that structural abnormalities of PT may underlie the basis for functional abnormalities of fundamental language-related processing in schizophrenia.

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