suggesting a neurodevelopmental pathology (Weinberger, 1987). On the other hand, recent follow-up magnetic resonance imaging (MRI) studies have demonstrated progressive changes in the initial years subsequent to the onset of schizophrenia in the left superior temporal gyrus (STG) (Kasai et al., 2003a,b) and the frontal lobe (Gur et al., 1998; Ho et al., 2003b) but not in the medial temporal lobe structures (Wood et al., 2001; Kasai et al., 2003a). Interestingly, Ho et al. (2003b) suggested progressive ventricular enlargement in the early course of schizophrenia to be associated with a poorer clinical outcome. These longitudinal observations support that a subset of brain abnormalities may be associated with neurodegenerative processes after the onset of psychosis at least in a subgroup of schizophrenia, but the factors that influence these processes remain unclear.

A longer duration of untreated psychosis (DUP), which is defined as the time from manifestation of the first psychotic symptoms to the initiation of neuroleptic treatment, has been reported to be associated with treatment resistance and poor clinical outcome (reviewed by Marshall et al., 2005; Perkins et al., 2005), possibly reflecting the adverse neurotoxic effect of psychosis prior to the treatment (Keshavan, 1999). However, the effect of DUP on brain morphologic abnormalities in schizophrenia is still poorly understood. In an earlier volumetric MRI study of untreated first episode schizophrenia patients, an inverse correlation between pre-treatment illness duration and the volume of the left STG was reported (Keshavan et al., 1998), but subsequent studies failed to find a significant correlation between the DUP and morphology in whole brain (Fannon et al., 2000; Hoff et al., 2000; Hietala et al., 2003; Ho et al., 2003a), the frontal (Hietala et al., 2003) and temporal (Fannon et al., 2000; Hoff et al., 2000; Hietala et al., 2003) lobes, or the hippocampus (Ho et al., 2005). Using voxel-based morphometric analyses of MRI, Lappin et al. (2006) demonstrated that gray matter reductions for the left temporal and occipital regions are more marked in psychotic patients with a long DUP. However, their sample characteristics as well as definition of DUP were different from those of other studies; they defined the first contact with mental health services as treatment onset and included a more diverse population with a less severe psychosis. Thus, further studies are warranted to clarify the association between DUP and brain morphology in schizophrenia especially for the specific regions of the brain such as the left posterior portions of the STG, where progressive morphologic changes after the onset of psychosis have been demonstrated (Kasai et al., 2003a,b). To our knowledge, however, no brain morphologic studies have examined volumetric changes in the specific subregions of the STG in relation to the length of DUP in schizophrenia.

In the present study, we used MRI to investigate the relation between the DUP and brain morphologic abnormalities in schizophrenia patients whose duration of illness was less than five years. Regions of interest (ROIs) for the volumetric measurements were placed in the superior temporal sub-regions and the medial temporal and frontal lobe structures because we have previously found significant volume changes in these regions (Suzuki et al., 2005b; Zhou et al., 2005; Takahashi et al., 2006). We predicted from previous cross-sectional (Keshavan et al., 1998; Hietala et al., 2003; Ho et al., 2005) and longitudinal (Wood et al., 2001; Kasai et al., 2003a,b) observations that the DUP of schizophrenia patients would be related to volume in the left STG but not in the medial temporal and frontal lobe regions.

2. Methods

2.1. Subjects

Right-handed schizophrenia patients who met the ICD-10 criteria for research (World Health Organization, 1993) were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital. Diagnoses were made following structured clinical interviews by psychiatrists with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). Clinical symptoms were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b). The patients who underwent an MRI scan were screened for study eligibility by an experienced psychiatrist (TT) on the basis of a structured clinical interview and exhaustive review of the clinical records. Whenever possible, a close family member of the patient was interviewed by psychiatrists to provide additional information. Inclusion criteria were: (1) a duration of illness of less than five years; (2) time point of the illness onset defined by the beginning of delusions, hallucinations, or marked formal thought disorder could be identified; and (3) not receiving neuroleptic medication prior to the onset of overt psychosis. The study population was not restricted to first-episode schizophrenia patients because we intended to include a sufficient sample of patients to cover a broad range of DUP values. The DUP was

defined as the duration in months from the illness onset to the initiation of antipsychotic treatment (Hoff et al., 2000). The time point of the onset of psychosis was identified using all available clinical data obtained from a detailed review of the clinical records and from interviews with the patients and their close relatives. The inter-rater intraclass correlation coefficient (ICC) for the assessment of DUP in our laboratory was 0.91.

Of the initial 62 patients for whom volumetric data were available, four patients were excluded because they had been on neuroleptic medication before the apparent onset of schizophrenia for their prodromal symptoms, and five were excluded because of limited information relating to their illness onset. Among the remaining 53 patients [26 males and 27 females, mean age=25.6± 4.8 years, mean illness duration=43.9±46.6 months (range=1.0–168.0), mean DUP=9.4±18.8 months (median=2.0, range=0.1–120)], 38 patients with a duration of illness of less than five years (20 males and 18 females) remained eligible; their mean illness duration and mean DUP were 18.8 months (S.D.=15.7, range=1.0–48.0) and 6.6 months (S.D.=10.7, median=2.0, range=0.1–47.0), respectively. Fourteen of the 38 patients were outpatients, and 24 patients underwent an MRI scan during admission. Ten of the 38 patients came to the university hospital directly, and the other 28 were referred; 21 patients from psychiatrists and seven by way of others (e.g. other services in the same university hospital). All patients have consistently received adequate clinical follow-up for more than six months after the onset of illness, and none of the 38 patients' diagnosis has changed during the follow-up period (mean follow-up period after MRI scanning=3.5 years, S.D.=2.1). Of the 38 patients, 27 were diagnosed with paranoid schizophrenia, 10 with undifferentiated schizophrenia, and 1 with catatonic schizophrenia. They were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness, or substance abuse. All but one of the female patients were on neuroleptic medication at the time of scanning; 15 were being treated with typical neuroleptics (8 males, 7 females) and 22 (12 males, 10 females) were receiving atypical ones. There was no significant difference in the gender ratio between the typical and atypical groups (chi-square test, chi-square=0.01, P=0.942). Demographic and clinical data of the subjects are shown in Table 1. Although the male patients were significantly taller (male patients, 170.2± 4.5 cm; female patients, 157.4±3.8 cm; ANOVA, F=81.09, df=1, 36, P<0.001) and heavier (male patients, 64.3±13.7 kg; female patients, 50.9±6.3 kg; ANOVA, F=14.54, df=1, 36, P<0.001) than the female patients, there were no significant differences between male and female patients in age, education, parental education, age at onset, DUP, duration of illness, duration of medication, and medication dosage. There were no significant differences between male and female patients in the total score or the subscale scores for SAPS and SANS.

This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

MRI scans were acquired with a 1.5-T Magnetom Vision (Siemens Medical System, Inc, Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were: repetition time=24 ms; echo time=5 ms; flip angle=40°; field of view=256 mm; and matrix size=256×256 pixels. The voxel size was 1.0×1.0×1.0 mm^3.

Image processing for volumetric analysis has been described in detail elsewhere (Takahashi et al., 2002). Briefly, on a Unix workstation (Silicon Graphics, Inc, Mountain View, CA, USA), the image data were processed using the software package Dr View 5.3 (Asahi Kasei Joho System Co, Ltd, Tokyo, Japan). Brain images were realigned in three dimensions to standardize for differences in head tilt during image acquisition

Table 1
Clinical and demographic characteristics of patients with schizophrenia

	Schizophrenia patients (N=38)
Male/female	20/18
Age (years)	24.1±4.3 (range, 18.3–32.7)
Height (cm)	164.1±7.7
Weight (kg)	57.9±12.7
Education (years)	13.5±1.8
Parental education (years)	12.5±2.2
Age at onset (years)	22.6±4.6
Duration of untreated psychosis (months)	6.6±10.7 (median=2.0)
Duration of illness (months)	18.8±15.7
Duration of medication (months)	11.8±15.7
Drug dose (mg/day, haloperidol equiv.)[a]	10.8±7.8
Total SAPS score	23.5±19.4
Total SANS score	49.9±25.0

The values represent means±S.D.s.
SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
[a] The different typical and atypical neuroleptic dosages were converted into haloperidol equivalents using guidelines established by Toru (2001).

and were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure–posterior commissure line. The whole cerebrum was manually separated from the brainstem and cerebellum. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semi-automatically segment the voxels into gray matter, white matter, and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Zhou et al., 2003).

2.3. Volumetric analyses of regions of interest (ROIs)

Fig. 1 shows the ROIs observed in this study. The gray matter volumes of the superior temporal subregions [Heschl's gyrus, planum temporale, and caudal superior temporal gyrus (STG)] and the frontal lobe structures (prefrontal cortex and anterior cingulate gyrus) were obtained by using the above-mentioned segmentation procedure. For the medial temporal lobe structures (amygdala and hippocampus), volumes of gray and white matter were measured together. We selected these ROIs because of significant volume reductions in schizophrenia as demonstrated in our previous publications (Suzuki et al., 2005b; Zhou et al., 2005; Takahashi et al., 2006). Each ROI was manually traced on 1-mm consecutive coronal slices with the corresponding sagittal and axial planes simultaneously presented for reference.

2.3.1. Superior temporal sub-regions

As described previously (Takahashi et al., 2006), we first traced the whole STG and segmented it into supratemporal and lateral portions by the lateral limb of the supratemporal plane. The whole STG was traced posteriorly to the end of the horizontal limb of the sylvian fissure. Heschl's gyrus was traced posterior to

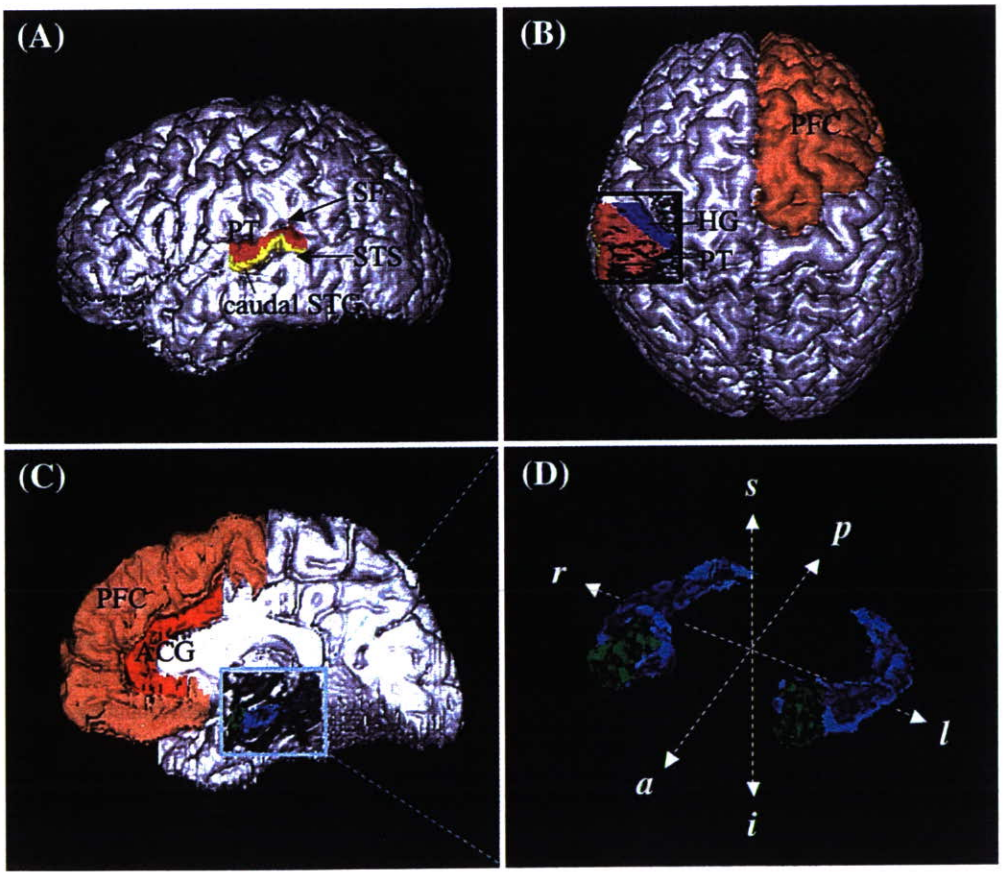

Fig. 1. Three-dimensional reconstructed images of regions of interest (ROIs) presenting lateral (A), dorsal (B), and medial (C) views of the brain. The parietal lobe in panel B and the temporal lobe in panel C are partially cut off to disclose the ROIs examined. Panel D shows a reconstructed image of the amygdala (green) and hippocampus (light blue). Detailed delineation methods for each ROI (Niu et al., 2004; Suzuki et al., 2005b; Zhou et al., 2005; Takahashi et al., 2006) and for the sub-regions of the prefrontal cortex (Suzuki et al., 2005b) have been described in our previous publications. Abbreviations: a = anterior; ACG = anterior cingulate gyrus; HG = Heschl's gyrus; i = inferior; l = left; p = posterior; PFC = prefrontal cortex; PT = planum temporale; r = right; s = superior; SF = sylvian fissure; STG = superior temporal gyrus; STS = superior temporal sulcus.

anterior, beginning with the first slice containing Heschl's sulcus and ending anteriorly with the slice containing the most anterior point of Heschl's sulcus or the sulcus intermedius if it existed. On each coronal slice, Heschl's gyrus was bounded medially by the sylvian fissure, inferior circular insular sulcus, or the first transverse sulcus and laterally by Heschl's sulcus. When two convolutions oriented separately from the retroinsular regions, the most anterior gyrus was regarded as Heschl's gyrus. When they oriented medially from the common stem, however, both were defined as Heschl's gyrus. After tracing Heschl's gyrus which takes a diagonal course on the superatemporal plane of the STG, the region lying posterolateral to the gyrus within the remaining gray matter of the supratemporal plane was regarded as the planum temporale. The lateral portion of the STG was further divided into the rostral and caudal STG by the plane including the anterior tip of Heschl's gyrus.

2.3.2. Medial temporal structures

The procedures for delineation of the amygdala and hippocampus were described in detail previously (Niu et al., 2004; Suzuki et al., 2005a,b). The amygdala was traced rostral to caudal, beginning with the first slice containing its oval-shaped gray matter and ending caudally with the most anterior slice containing the thin strip of gray matter of the hippocampal–amygdala transitional area. The inferior border of the amygdala in contact with the hippocampus head was determined by reference to the sagittal plane; the alveus was used to differentiate these structures. The amygdala was separated by thin strips of white matter from the entorhinal cortex medially, and from the claustrum and tail of the caudate nucleus superio-laterally. The inferio-lateral boundary was the temporal lobe white matter and the extension of the temporal horn.

The hippocampus was bounded superiorly by the alveus and inferiorly by the white matter of the parahippocampal gyrus. The lateral and medial boundaries were the inferior horn of the lateral ventricle and the mesial edge of the temporal lobe, respectively.

2.3.3. Frontal lobe regions

Delineation of the frontal lobe regions was partially based on the works of Rademacher et al. (1992) and Crespo-Facorro et al. (1999). Parcellation of the frontal lobe into sub-regions was performed according to the anatomical landmarks intrinsic to the brain (sulci/gyri) as described elsewhere (Zhou et al., 2005). First, the entire frontal lobe was separated from the rest of the brain by the central sulcus. The prefrontal area was demarcated by subtracting the precentral gyrus and the cingulate gyrus from the frontal lobe. The cingulate gyrus was subdivided into anterior and posterior parts at the level of the center of the anterior commissure. The paracingulate gyrus if present was included in the prefrontal area.

Four trained raters (HH, LN, SZ, and TT) measured the ROI volumes described above without any knowledge of the subjects' identity, gender, or diagnosis. Intra- and inter-rater intraclass correlation coefficients in a subset of five randomly selected brains were over 0.92 for all ROIs.

2.4. Statistical analysis

The DUP values were log-transformed because of their highly skewed distribution (Fig. 2). Pearson's partial correlation controlling for age, age at illness onset, duration of neuroleptic medication, and medication dosage were calculated to examine relationships between the DUP and the relative volumes [(absolute volume/ICV)×100] for the Heschl's gyrus, planum temporale, caudal STG, hippocampus, amygdala, prefrontal area, and anterior cingulate gyrus. Age at illness onset was used as a covariate based on the evidence that it has a certain effect on brain morphology (e.g. Aso et al., 1995; Matsumoto et al., 2001). For the correlational analysis, the male and female patients were not separately treated because the effect involving gender was not significant for these relative ROI volumes [repeated measures multivariate analysis of covariance

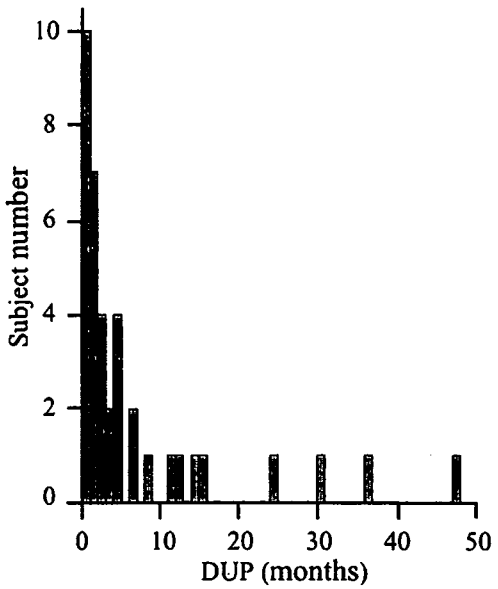

Fig. 2. The distribution of the duration of untreated psychosis (DUP) in patients with schizophrenia.

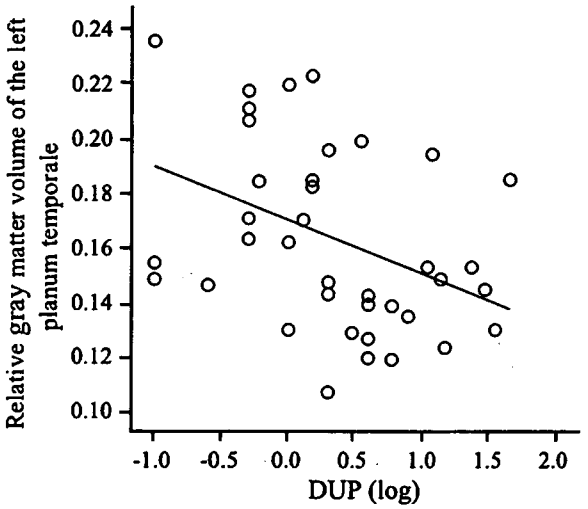

Fig. 3. Correlation between the duration of untreated psychosis (DUP) and relative gray matter volume of the left planum temporale (r= −0.589, P<0.001).

(MANCOVA) with age as a covariate; F=0.02 to 1.44; df=1, 35; P=0.238 to 0.879]. Multiple linear regression analysis was also performed with each volumetric measure as the dependent variable to investigate the independent contribution of the DUP, age, age at illness onset, and duration and dosage of neuroleptic medication. Correlations between the DUP and scores for subscales of the SAPS and SANS were analyzed by using Pearson's correlation coefficients.

Patients were then divided into two groups on the basis of the median DUP (2.0 months) as the cut-off point in order to further examine the effect of the DUP; short-DUP group (DUP ≤ 2.0 months, 10 males and 11 females, mean age=23.3±4.1 years) and long-DUP group (DUP>2.0 months, 10 males and 7 females, mean age=25.0±4.6 years). Although the long-DUP group tended to have a longer illness duration compared with the short-DUP group (long-DUP group, 24.3± 16.6 months; short-DUP group, 14.2±13.7 months; ANOVA, F=4.11, df=1, 36, P=0.050), there were no significant between-group differences in age, gender, age at illness onset, duration of neuroleptic medication, or medication dosage. The relative ROI volumes were analyzed using repeated measures MANCOVA with age as a covariate, group (short-DUP, long-DUP) as a between-subject factor, and hemisphere as a within-subject variable. The post hoc Scheffé's test was employed to

Table 2
Relation of duration of untreated psychosis (DUP) to volumes for each brain region in schizophrenia patients[a]

	Short-DUP group (DUP ≤ 2 months, N=21)		Long-DUP group (DUP>2 months, N=17)		Analysis of covariance[b] Effect of group		Pearson's partial correlation with log DUP	
Brain region (cm^3)	Mean	S.D.	Mean	S.D.	F (df=1,35)	P	r	P
Heschl's gyrus GM					1.52	0.225		
Left	1.79	0.54	1.64	0.52			−0.342	0.048
Right	1.43	0.51	1.28	0.33			−0.210	0.234
Planum temporale GM					**4.64**	**0.038**		
Left	2.60	0.57	2.16	0.43			**−0.589**	**<0.001**
Right	1.97	0.65	1.89	0.51			−0.160	0.367
Caudal STG GM					0.05	0.822		
Left	3.63	1.08	3.49	0.87			−0.311	0.074
Right	3.36	0.92	3.43	0.76			−0.120	0.501
Hippocampus					0.14	0.711		
Left	2.89	0.45	2.99	0.42			−0.013	0.940
Right	3.11	0.40	3.14	0.55			−0.051	0.773
Amygdala					1.60	0.215		
Left	0.97	0.16	1.03	0.19			0.123	0.488
Right	1.01	0.19	1.09	0.19			0.158	0.373
Prefrontal cortex GM					0.13	0.718		
Left	92.08	12.36	90.48	13.61			−0.097	0.586
Right	89.57	11.98	87.56	11.14			−0.247	0.159
Anterior cingulate gyrus GM					0.06	0.812		
Left	3.98	1.44	3.53	1.11			−0.241	0.169
Right	4.72	1.39	4.89	1.82			0.224	0.203

DUP, duration of untreated psychosis; GM, gray matter; STG, superior temporal gyrus.

[a] The absolute volumes for each region are shown in the table, but the statistical analyses for group comparison reported here are based on the relative volumes (100×absolute volume/intracranial volume).

[b] Group-by-side interaction was not observed for any region.

follow up the significant main effects or interactions yielded by these analyses. Statistical significance was defined as $P<0.05$ (two-tailed). The statistical software used was SPSS 12.0 (SPSS Inc., Chicago, Illinois).

3. Results

There was a significant inverse correlation between the DUP and the relative volume of gray matter in the left planum temporale (Pearson's partial correlation, $r=-0.589$, $P<0.001$) (Fig. 3). The other ROIs did not correlate with the DUP after a Bonferroni correction for multiple comparisons [seven ROIs in the left/right hemisphere; $P<0.004$ (0.05/14)] (Table 2). Based on our previous findings (Suzuki et al., 2005b), we further examined the correlation between the DUP and each sub-region of the prefrontal cortex (the superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, ventral medial prefrontal cortex, orbitofrontal cortex, and straight gyrus) but obtained no significant results (Pearson's partial correlation, $r=-0.316$ to 0.191, $P=0.069$ to 0.970). The correlation between the DUP and the volume of gray matter in the left planum temporale remained significant even after a Bonferroni correction that included the prefrontal sub-regions as ROIs [12 ROIs in the left/right hemisphere; $P<0.002$ (0.05/24)]. There was a weak correlation between the DUP and the score for bizarre behavior of SAPS (Pearson's correlation, $r=0.389$, $P=0.016$), but the correlation was not significant after the correction.

When the relative volume of gray matter in the left planum temporale was taken as a dependent variable in the linear multiple regression analysis, the DUP was the only included coefficient ($F=6.09$, $df=1, 36$, $P=0.019$, $R^2=0.145$) among the independent variables entered into the analysis (age, age at illness onset, DUP, duration of neuroleptic medication, and medication dosage). For the other regions, the DUP did not contribute to the volumetric measurements.

For the comparison between the short-DUP versus long-DUP groups, MANCOVA of the relative volume of gray matter in the planum temporale revealed a significant main effect for group ($F=4.64$, $df=1, 35$, $P=0.038$), with the long-DUP group having significantly smaller planum temporale gray matter than the short-DUP group (post hoc test, $P=0.024$). There were no differences in relative volume for the other regions between the two groups (Table 2).

When the patients were divided into two groups based on the type of neuroleptic medication (typical versus atypical), the two groups did not differ significantly in the volumetric measurements for any region (data not shown).

4. Discussion

To our knowledge, this is the first MRI study to report the relation between the duration of untreated psychosis (DUP) and volumetric measurements for several regions of the brain including the specific sub-regions of the superior temporal gyrus (STG) in schizophrenia. In this study, we demonstrated an inverse correlation between the DUP and the volume of gray matter in the left planum temporale. The relation between the DUP and the volume of the planum temporale was also supported by the comparison between the short- versus long-DUP group. Although the present study may be limited by the restriction of the analysis to a relatively small number of ROIs, our findings support the notion of a progressive–degenerative process in the gray matter of the left planum temporale during the initial untreated phase of schizophrenia. In contrast, we found no such correlation in the medial temporal or frontal lobe structures. Together with previous longitudinal findings as discussed later, our findings indicate that abnormalities in the medial temporal regions might be relatively static at least during the early course of the illness.

First, the issue of potential sampling problems in the present study should be addressed. Previous MRI studies that investigated the effect of DUP on brain morphology in schizophrenia have examined first-episode patients to control for confounding factors such as chronic psychosis and neuroleptic medication (Keshavan et al., 1994, 1998; Chakos et al., 1995; Gur et al., 1998). As discussed by Perkins et al. (2005), however, the effect of untreated psychosis might be underestimated when patients with a long DUP are excluded. We therefore included a population of patients with a somewhat broad range of illness duration by stipulating a maximum of five years as an inclusion criterion based on naturalistic (McGlashan, 1988; Mason et al., 1996) and neuroimaging (Gur et al., 1998; Madsen et al., 1999; Ho et al., 2003b; Kasai et al., 2003a,b) observations showing that the progression of the disease process in schizophrenia might occur predominantly during the first five years after illness onset. Nevertheless, the mean DUP in our sample (6.6 months, median=2.0) was rather shorter than that for previous studies in first-episode schizophrenia; the average mean DUP across studies lies between 1 to 2 years with the median DUP at about 6 months (reviewed by McGlashan, 1999). The DUP could be influenced by the regional characteristics of psychiatric services, and the mean DUP in our 53 subjects before stipulating (9.4 months, median=2.0) was relatively comparable with that of other university hospitals in Japan [Kobayashi, 2002,

mean DUP=8.7 month (median=1.0); Yamazawa et al., 2004, mean DUP=13.4 months (median=3.75)]. However, our sample characteristics might not be representative of those of the general population in Japan; we enrolled only relatively young schizophrenia patients as a sample of our original MRI studies, and a longer DUP is generally associated with higher rates of refusal to participate in these studies (McGlashan, 1999). Furthermore, the neuroleptic medication and the relatively small sample size might limit the ability to generalize our findings. In contrast to previous observations (reviewed by Marshall et al., 2005; Perkins et al., 2005), we found no significant correlation between the DUP and the severity of either positive or negative symptoms, perhaps because most patients had been treated for their symptoms by the time of the clinical assessment. The effect of medication on brain morphology will be discussed later as a limitation of the study.

The primary finding of the present study is the specific association between a decrease in the volume of gray matter in the left planum temporale and the length of the DUP in patients with schizophrenia. This finding is consistent with a previous MRI study by Keshavan et al. (1998) who reported a similar association between the volume of the left STG and the DUP in neuroleptic-naive patients with first-episode schizophrenia. Recent longitudinal MRI studies examining the progression of brain morphologic alterations in first-episode schizophrenia have demonstrated that the left posterior portions of the STG show progressive volumetric reductions in the initial 1.5 years following first hospitalization (Kasai et al., 2003a,b). With regard to the effect of neuroleptics, Keshavan et al. (1998) suggested from a one-year follow-up of their sample that the volume of the left STG tended to normalize following neuroleptic medication. Interestingly, a previous study of auditory event-related potentials (ERPs) in first-episode schizophrenia identified a neuroleptic-induced recovery of P300 amplitude in the left temporal area, which could be related to the volume of the planum temporale (McCarley et al., 2002), in short-DUP but not in long-DUP patients (Wang et al., 2005). These neuroimaging and neurophysiological observations of schizophrenia suggest a regional progressive pathological process in the left STG, especially the planum temporale, which might be particularly severe during the initial few years after the onset of psychosis but could be at least partly mitigated by the ameliorating effects of neuroleptics (Lieberman et al., 2005). Although the exact mechanisms for this possibly neurodegenerative process after the onset of schizophrenia remain unknown, Keshavan (1999) proposed that, if untreated, a persistent dopaminergic and consequent phasic glutamatergic excess could lead to adverse neurotoxic effects perhaps through increased oxidative stress (Coyle, 1996).

For the medial temporal lobe structures, we found no significant association between the DUP and the volume of the hippocampus or amygdala. These findings are in line with a previous volumetric MRI study that specifically focused on the morphology of the hippocampus; Ho et al. (2005) found no significant relationship between duration of untreated initial psychosis and the volume of the hippocampus in a large sample of first-episode psychosis patients. A recent voxel-based morphometric MRI study of first-episode psychosis found no reductions in gray matter associated with DUP in the medial temporal area either (Lappin et al., 2006). The medial temporal lobe has already decreased in volume by the onset of schizophrenia (Shenton et al., 2001; Vita et al., 2006) and a similar reduction has been identified also in subjects at genetic high-risk of developing schizophrenia (Lawrie et al., 2001; Keshavan et al., 2002; Seidman et al., 2002; Steel et al., 2002). Although recent MRI studies of clinical high-risk individuals suggested that medial temporal lobe volumes alter during the transition into psychosis (Pantelis et al., 2003; Velakoulis et al., 2006), previous follow-up studies in established cases of schizophrenia have generally shown no progressive changes in these regions during the early course after the onset of the illness (DeLisi et al., 1997; Lieberman et al., 2001; Wood et al., 2001; Kasai et al., 2003a). The association between right hippocampal volume and illness duration in chronic schizophrenia could reflect its neurodegeneration at later stages of the illness (Velakoulis et al., 1999, 2002). However, the present and these previous longitudinal findings are largely compatible with the neurodevelopmental model of schizophrenia (Weinberger, 1987) and suggest that the abnormalities in the medial temporal lobe structures, which might indicate genetic vulnerability to schizophrenia, are stable features of the early course of the illness.

Consistent with previous MRI studies (Hietala et al., 2003; Lappin et al., 2006), we found no association between the DUP and the volume of the frontal lobe structures in schizophrenia patients. In contrast, an earlier study using computed tomography (CT) reported that a longer DUP in first-episode schizophrenia patients was significantly correlated with frontal sulcal enlargement at first hospitalization (Madsen et al., 1999). In schizophrenia, involvement of the prefrontal cortex has been suggested to play a role in the manifestation of negative symptoms and cognitive impairments such as deficits in working memory and executive function

(Goldman-Rakic and Selemon, 1997). Although there seems general agreement that total prefrontal gray matter is reduced in schizophrenia patients compared with healthy controls (Shenton et al., 2001; Selemon et al., 2002), as discussed elsewhere (Suzuki et al., 2005b; Zhou et al., 2005), findings in studies that have parcellated the prefrontal cortex into sub-regions have yielded conflicting results. Also, the timing and course of the prefrontal abnormalities especially for the sub-regions of the cortex in schizophrenia remain largely unknown (Gur et al., 1998; Mathalon et al., 2001; Ho et al., 2003a,b; Sun et al., 2003). Although we found no significant correlation between the volume of the prefrontal cortex and the DUP even after subdividing the cortex into specific sub-regions, the progressive morphologic changes in these regions during the early course of schizophrenia as well as the possible effects of the DUP on the cortex's sub-regions seem worthy of further examination.

The findings of the present study should be interpreted with caution for several reasons. First, as mentioned above, the study is clearly limited by the use of neuroleptic-medicated patients. We therefore used the daily dosage and duration of neuroleptic medication as control variables for analyzing the correlation between the DUP and the ROI volumes to adjust for these potential confounding factors. Furthermore, daily dosage or duration of neuroleptic medication did not correlate with the volume of any ROI in this study. In addition, the inverse correlation between the DUP and the volume of the left planum temporale remained significant even when we used illness duration of less than three years as an inclusion criterion in order to reduce the confounds in the data due to the medication and chronicity of illness ($N=27$, $r=-0.665$, $P<0.001$). With regard to type of neuroleptic, recent MRI studies have reported different effects of typical and atypical neuroleptics on the morphology of the brain in first episode psychosis (Dazzan et al., 2005; Lieberman et al., 2005). In this study, however, type of neuroleptic medication (typical versus atypical) did not influence the volumetric measurements for any region. Second, our cross-sectional findings might not necessarily represent the progressive changes in the brain. As discussed by Lappin et al. (2006), it is possible that patients with severe brain morphologic abnormalities have an insidious onset of illness that could lead to a delay in treatment with a consequent longer DUP.

In summary, our cross-sectional findings of the relation between the DUP and brain morphologic abnormalities in schizophrenia suggest a progressive pathological process in the gray matter of the left planum temporale during the initial untreated phase of the illness. Further longitudinal studies with a larger sample without sustained neuroleptic treatment will be required to confirm our preliminary findings.

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Voxel-based analysis of P300 electrophysiological topography associated with positive and negative symptoms of schizophrenia

Yasuhiro Kawasaki*, Tomiki Sumiyoshi, Yuko Higuchi, Toru Ito, Masashi Takeuchi, Masayoshi Kurachi

Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, 2630 Sugitani, Toyama 930-0194, Japan

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Abstract

Abnormal P300 waveforms of the event-related potentials during the auditory oddball task are one of the most consistent findings in patients with schizophrenia. In the present study, we sought to test the hypothesis that the abnormal P300 waveform results from composite representation of neural activity in anatomically distinct brain regions responsible for the manifestation of positive and negative symptoms. We used the low-resolution brain electromagnetic tomography (LORETA) to obtain current density images of the P300 component from 26 patients with schizophrenia. The statistical parametric mapping (SPM) was applied to the LORETA images in order to identify brain regions that are related with the severity of psychotic symptoms as evaluated by the Brief Psychiatric Rating Scale (BPRS). The BPRS Total score was negatively correlated with the P300 current density in the left superior temporal gyrus ($r=-0.615$, corrected $p=0.009$) and that in the right medial frontal region ($r=-0.571$, corrected $p=0.019$) by means of SPM single-subject covariates model. These brain regions were included in the region-specific P300 sources as represented by the current density maxima (corrected $p<0.05$) using SPM one-sample t-test. A subsequent region-of-interest analysis of Pearson correlations revealed specific relationships between the Positive subscale score and the mean current density in the left superior temporal gyrus ($r=-0.528, p=0.005$) and between the Negative subscale score and the mean current densities in the medial frontal region ($r=-0.551$, $p=0.003$) and left superior temporal gyrus ($r=-0.499$, $p=0.009$). These results indicate that functional disturbances of neural networks involving the medial prefrontal and superior temporal regions may be responsible for the generation of positive and the negative psychotic symptoms of schizophrenia.

Keywords: Auditory P300 component; Low-resolution brain electromagnetic tomography; Positive and negative symptoms; Schizophrenia

1. Introduction

Endogenous event-related potentials (ERPs) have been extensively studied to clarify the pathophysiology of schizophrenia. In particular, the reduced amplitude of the P300 component during the auditory oddball task is one of the most consistent findings in patients with schizophrenia (Braff, 1993; Jeon and Polich, 2003; Roth and Cannon, 1972). However, the exact relationship between the clinical symptomatology of schizophrenia and the neurophysiological disturbances underlying the P300 abnormality has yet to be determined. Some researchers

* Corresponding author. Tel.: +81 76 434 7322; fax: +81 76 434 5030.
E-mail address: kawasaki@med.u-toyama.ac.jp (Y. Kawasaki).

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have found no significant correlations between P300 and psychotic symptoms (Blackwood et al., 1987; St. Clair et al., 1989), while others have reported an association of reduced P300 amplitudes with negative symptoms (Eikmeier et al., 1992; Liu et al., 2004; Pfefferbaum et al., 1989; Strik et al., 1993), positive symptoms (Egan et al., 1994; Higashima et al., 2002; Kawasaki et al., 1997; McCarley et al., 1989), or both (Frodl-Bauch et al., 1999; Mathalon et al., 2000; Turetsky et al., 1998). These inconsistent findings in the literature may reflect the heterogeneity of schizophrenia patients studied. Alternatively, it is reasonable to assume that anatomically distinct neural substrates responsible for positive or negative symptoms independently contribute to the generation of the P300 component, because this ERP measure is thought to be a composite representation of neural activity in anatomically distinct generators (Anderer et al., 2003; Mulert et al., 2004; Wang et al., 2003; Winterer et al., 2001).

Several techniques to estimate the current density of ERPs have been developed to identify the accurate electrophysiological sources in vivo. Data obtained from these methods are supposed to provide a three-dimensional configuration of intra-cerebral electrical activities by solving the ambiguity of the inverse problem (Pascual-Marqui, 1999). In the current study, the low-resolution brain electromagnetic tomography (LORETA) was used to compute the voxel-wise distribution of brain electrophysiological activity of the P300 component. The advantage of LORETA current density analysis is that it does not require the assumption of a specific number of sources, unlike the case with dipole source localization. The LORETA only assumes that neighboring neurons are simultaneously and synchronously activated, and approximates the current density distribution throughout the brain (Pascual-Marqui et al., 1994).

Intra-cranial recording methods have identified neural activations in the lateral and medial prefrontal areas, the superior temporal plane, the medial and lateral temporal lobes, and the medial and lateral parietal lobes of healthy subjects during an oddball task (Baudena et al., 1995; Halgren et al., 1995a,b). By using LORETA, it has been estimated that P300 sources are localized in the dorsoventrolateral prefrontal cortex, the medial frontal and parietal cortex, the insula, the middle-superior temporal gyrus, and the temporo-parietal junction (Anderer et al., 2003; Wang et al., 2003; Winterer et al., 2001). Prior studies with functional-MRI and electroencephalograms (EEGs) found that these brain regions are major generators of the P300 activity (Menon et al., 1997; Mulert et al., 2004), which has been confirmed by subsequent functional-MRI (Horn et al., 2003; Kiehl and Liddle, 2001; Linden et al., 1999) and regional blood flow (Ebmeier et al., 1995; Higashima et al., 2000) studies.

In the present study, we sought to identify brain regions in which the P300 current density is correlated with severity of psychotic symptoms of schizophrenia. For this purpose, we applied the statistical parametric mapping (SPM) (Friston et al., 1995) to LORETA current density images of the P300 component (Pae et al., 2003; Park et al., 2002). The hypothesis tested was that abnormal P300 generation in schizophrenia patients would result from a composite representation of neural activity in anatomically distinct brain regions responsible for the heterogeneity of symptom manifestations.

2. Methods

2.1. Subjects

This study was approved by the Committee on Medical Ethics of University of Toyama. Subjects consisted of 14 male and 12 female patients meeting DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994). All available clinical information and data obtained from detailed review of the clinical records and structured interviews using the Comprehensive Assessment of Symptoms and History (CASH). They were recruited from the Outpatient Clinic of the Department of Neuropsychiatry, University of Toyama Hospital. After the purpose and procedures of the study were fully explained, written informed consent was obtained. All were Japanese (i.e., Mongoloid) aged between 17 and 50 at the time of assessment, and were right-handed, as evaluated by the Handedness Inventory (Kameyama et al., 1981). Their mean (SD) age was 30.0 (9.7) years (range 17–50 years), with mean duration of illness of 7.1 (7.1) years (range 0.1–22 years). Seven patients were antipsychotic free and 19 were treated with antipsychotics with a mean daily dose of 2.8 (3.6) mg (risperidone equivalent). All patients were physically healthy at the time of the study, and none had a history of head trauma, serious medical or surgical illness, or substance abuse.

2.2. Clinical symptom assessment

The Brief Psychiatric Rating Scale (BPRS)-18 item version (Overall and Gorham, 1962) was administered on the same day or within a few days from the ERP testing by an experienced psychiatrist (Y.H.) who was not informed of medication status. In addition to the BPRS Total score, we also assessed scores of the Positive subscale (hallucinatory behavior, hostility, unusual thought

content) and Negative subscale (blunted affect, emotional withdrawal, motor retardation). The mean (SD) Total, Positive, and Negative subscale scores were 19.8 (12.2), 5.7 (4.3), and 5.6 (3.7), respectively.

2.3. ERP recording

The ERPs were recorded using an auditory oddball paradigm, based on our previous report (Sumiyoshi et al., 2006). EEGs were recorded with a 32-channel DC-amplifier (EEG-2100 version 2.22J, Nihon Kohden Corp., Tokyo, Japan). Recordings were performed using an electrocap (Electrocap Inc., Eaton, OH) in a sound-attenuated room. Auditory stimuli were delivered binaurally through headphones with variable inter-stimulus intervals ranging from 1.5 to 2.5 s. Target tones of 2000 Hz were randomly presented in a series of standard tones of 1000 Hz, with the presentation probability of 0.2 for the target tones. All tones were 100 ms in duration with a rise–fall time of 10 ms. Subjects were requested to press a button promptly and accurately in response to the infrequent target tones. EEG was recorded with 19 electrodes located at FP1, FP2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6, Fz, Cz, and Pz, according to the international 10–20 system. All electrodes were referred to the average amplitude of the ear electrodes (bandwidth=0.16–120 Hz, 60 Hz notch filter). Eye movement artifacts (blinks and eye movements) were rejected off-line. Electrode impedance was less than 10 kΩ. The recording epoch was 700 ms, including a 100-ms pre-stimulus baseline. Data were collected with a sampling rate of 500 Hz. A total of more than twenty EEG responses (mean=36.9) to target tones were averaged off-line. Averaging of ERP waves and related procedures was performed using EPLYZER II software (Kissei Comtec, Co. Ltd. Nagano, Japan).

2.4. LORETA analysis

LORETA images were obtained by estimating the current source density distribution for epochs of brain electric activity on a dense grid of 2394 voxels at 7-mm spatial resolution applied to the digitized Talairach atlas (Talairach and Tournoux, 1988), based on the established method (Pascual-Marqui, 1999; Pascual-Marqui et al., 1994). LORETA images represent the electrical activity at each voxel as amplitude of the computed current source density (mA/mm^2). We calculated LORETA images for each subject in the time frame 250–500 ms post-stimulus based on a previous report (Sumiyoshi et al., 2006). Obtained LORETA images were transformed 7 mm^3 ANALYZE format images (Mayo Clinic, Rochester, USA; http://www.mayo.edu/bir/) using a LORETA to SPM conversion utility (LOR2SPM, Institute of the Human Brain, St. Petersburg, Russia, http://www.ihb.spb.ru/~pet_lab/).

2.5. Voxel-wised analysis using SPM99

Statistical analysis was performed using SPM99 software (Wellcome Department of Cognitive Neurology, London; http//www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB 6.5 (Mathwork, Inc., Sherborn, MA, USA). For a statistical evaluation of region-specific generators, we conducted one-sample t-test with the hypothesis that the voxel-wise current density of a generator would be significantly increased in comparison with the global mean current density. In order to evaluate a relationship between the P300 current density and the BPRS Total score, a single-subject covariates design was applied. In these statistics we introduced two nuisance variables of subject's age and sex as covariates, and did not include global normalization in order to evaluate absolute values of the current density. Because of multiple comparison problems, SPM uses Gaussian random field theory (Friston et al., 1996; Worsley et al., 1996) to protect against family-wise false-positivities over the search volume. The random field correction to the p-values of the SPM plays the same role as the Bonferroni correction for single voxel data. Therefore, statistical significance was set at $p<0.05$ corrected for multiple comparisons of voxel-level statistics. As a general rule of the SPM software, the SPM{t} program conducts one-tailed statistical test.

2.6. Region-of-interest-based follow-up analysis

Following overall significant findings of SPM voxel-based relationship to the BPRS Total score, follow-up analysis of Pearson correlations focused on 4 relationships between regional current density and symptom subscale score, i.e. between the left superior temporal gyrus or medial frontal region vs. positive or negative symptoms. Accordingly, we conducted subsequent region-of-interest-based analysis using mean current density of cluster that consisted of statistically significant voxels of the SPM correlation analysis. We also evaluated relationships with demographic characteristics of the subject. Statistical significance was set at $p<0.0125$ considering the Bonferroni adjusted p-value of 0.05 out of 4 pair-wise measures.

3. Results

3.1. Voxel-wised analysis using SPM99

As illustrated in Fig. 1 results of the SPM one-sample *t*-test showed that P300 sources are localized in the bilateral medial frontal and medial parietal cortex, bilateral superior temporal gyrus, right temporo-parietal junction, and left lateral prefrontal cortex. MNI coordinates, and voxel-level *p*-values were given in Table 1. With regard to the relationship between the P300 current density and the BPRS Total score, voxel-based whole brain analysis without any hypothesis identified peak voxels of significant negative correlation located at the left superior temporal gyrus (MNI coordinates −59/−32/22; BA 42, $r=-0.615$, corrected $p=0.009$) and right medial frontal region (4/45/8; BA 32, $r=-0.571$, corrected $p=0.019$). There was no voxel indicating positive correlation. As shown in Fig. 2, statistically significant voxels formed clusters within these brain regions. These clusters consisted of 3 and 14 voxels for the left superior temporal gyrus and the medial frontal region, respectively, and were applied to the following region-of-interest analysis.

3.2. Region-of-interest-based follow-up analysis

Subsequent analysis focused on four relationships, i.e. between either of the two brain regions and positive or negative symptoms (Table 2). Mean current density values of the cluster in the superior temporal gyrus had significant relationships with the Positive subscale score (Fig. 3a), and the Negative subscale score. Mean current density values of the cluster in the medial frontal region had a significant relationship with the Negative subscale score (Fig. 3b). On the other hand, the correlation coefficient with the Positive subscale score did not reach the significance levels. As shown in Table 2, the mean current density of these clusters did not correlate with subject's sex, age, educational achievement, illness duration, or neuroleptic dose.

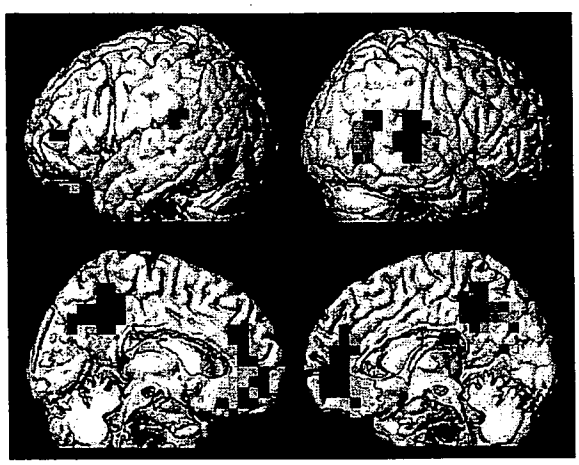

Fig. 1. One-sample *t*-test of statistical parametric map representing clusters of current density maxima as P300 sources, superimposed on the surface rendering of a single brain. All voxels were thresholded at $p<0.05$ corrected.

Table 1
Brain regions showing a significant current density value

Brain region		Voxel-level		MNI coordinates		
		T	Corrected *p*	*x*	*y*	*z*
Superior temporal gyrus	Lt.	9.90	<0.05	−59	−32	22
	Rt.	5.78	<0.05	50	−18	15
Medial frontal area	Rt.	7.98	<0.05	4	31	−20
	Lt.	7.51	<0.05	−10	45	−6
	Rt.	7.31	<0.05	4	45	8
Lateral prefrontal area	Lt.	7.74	<0.05	−38	45	8
Medial parietal area	Rt.	7.70	<0.05	4	−67	15
	Lt.	7.69	<0.05	−3	−74	29
	Rt.	7.05	<0.05	4	−53	29
Temporo-parietal junction	Rt.	6.97	<0.05	46	−67	15
	Rt.	6.05	<0.05	60	−25	−6

Lt., left hemisphere;Rt., right hemisphere.

4. Discussion

The results of the present study indicate region-specific P300 sources, as represented by the current density maxima, are localized in the medial frontal cortex, parietal cortex, and superior temporal gyrus bilaterally, as well as in the right temporo-parietal junction and the left lateral prefrontal cortex, in patients with schizophrenia. Because these regions have been shown to produce P300 sources also in healthy subjects, as elicited by LORETA (Anderer et al., 2003; Mulert et al., 2004; Wang et al., 2003; Winterer et al., 2001) and intra-cranial recordings (Baudena et al., 1995; Halgren et al., 1995a,b), it is conceivable that topographic distribution of the neural generators of the P300 component is not fundamentally different between schizophrenia patients and healthy subjects.

The major finding of this study was that the severity of psychotic symptoms was negatively correlated with the P300 current density in the right medial prefrontal area and that in the left superior temporal gyrus in patients with schizophrenia. As shown in Fig. 2b, statistically significant voxels were distributed not only in the right medial prefrontal area but also in the left medial prefrontal area. Thus, although SPM analysis reported a significant peak coordinate corresponding to the right paracingulate gyrus

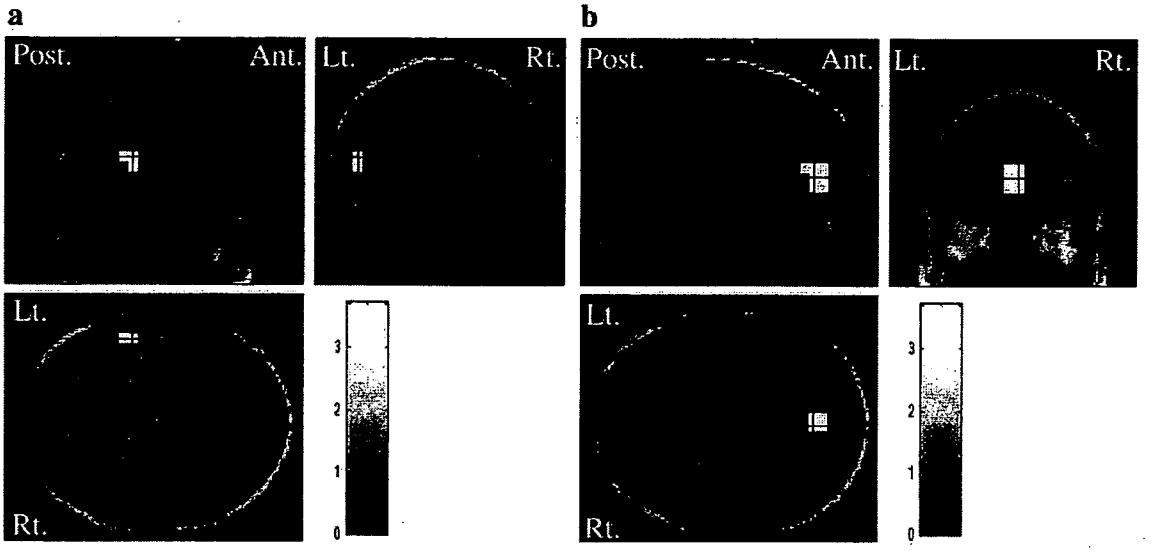

Fig. 2. Three orthogonal projections of significant voxels showing relationships between the BPRS Total score and the P300 current density in the left superior temporal gyrus (peak MNI coordinates; −59/−32/22, BA 42) (a), and right medial frontal region (peak MNI coordinates; 4/45/8, BA 32) (b) by means of single-subject covariates design of statistical parametric map. All voxels were thresholded at $p<0.05$ corrected. BPRS, Brief Psychiatric Rating Scale.

of area 32, the actual foci were assumed to be located at the medial prefrontal region bilaterally. The medial prefrontal area and left superior temporal gyrus were found to demonstrate the current density maxima. Thus, it is conceivable that pathological neural activities of anatomically distinct generators contribute to the generation of the abnormal P300 component.

Previous LORETA studies found that the current densities for P300 in the left prefrontal and temporal lobes (Wang et al., 2003; Winterer et al., 2001), and those in the anterior cingulate region (Neuhaus et al., 2007) were decreased in schizophrenia patients compared to healthy subjects. Our recent study (Sumiyoshi et al., 2006) with LORETA images of P300 indicated recovery of the left dominant pattern of neural activity in the superior temporal lobes in patients treated with olanzapine who showed improvement in psychopathology and verbal memory. These observations provide converging evidence that the medial prefrontal areas and the left superior temporal gyrus are responsible for the P300 abnormalities in patients with schizophrenia.

In order to further clarify the relationship between the specific neural networks responsible for the abnormalities of P300 and psychotic symptoms of schizophrenia, we conducted a correlation analysis according to the positive and negative symptoms dimension. Results revealed relationships between the negative symptoms subscale score and the current density in the medial frontal region, and between the positive symptoms subscale score and the current density in the left superior temporal gyrus. These results were consistent with the proposal that negative symptoms are associated with neural deficits in the frontal lobe, while those in the temporal lobe are responsible for positive symptoms (Andreasen and Olsen, 1982; Crow, 1980; Liddle, 1987). Moreover, the correlation analysis pointed to an additional relationship between the negative symptoms subscale score and the P300 current density in the left

Table 2
Relationships between the P300 regional current density and clinical and demographic characteristics

Brain region	Statistical valuables	BPRS subscore		Demographic and clinical characteristics				
		Positive	Negative	Sex	Age	Education	Duration	Medication
Superior temporal gyrus	*r*	−0.528	−0.499	0.144	0.129	0.070	−0.059	−0.044
	p	0.005	0.009	0.482	0.529	0.731	0.773	0.83
Medial frontal region	*r*	−0.434	−0.551	0.039	0.228	0.248	−0.021	0.216
	p	0.026	0.003	0.848	0.260	0.220	0.916	0.288

r, Pearson correlation coefficient; BPRS, Breaf Psychiatric Rating Scale.

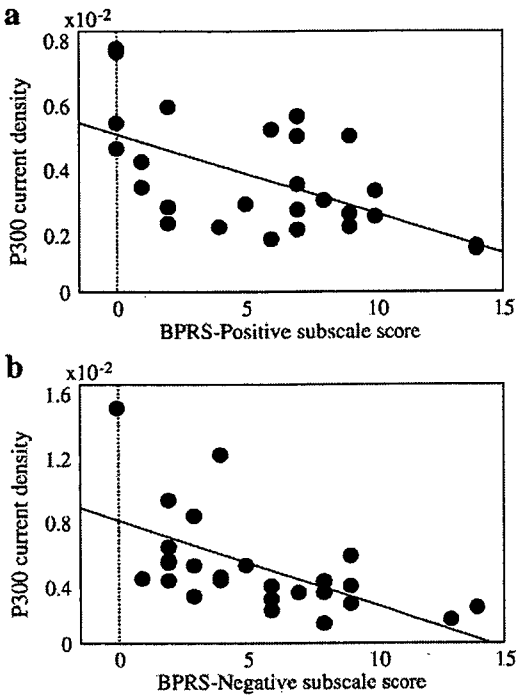

Fig. 3. Plots and regression lines of correlations between the BPRS Positive subscale score and the mean P300 current density of the cluster in the left superior temporal gyrus (a) and between the BPRS Negative subscale score and the mean P300 current density of the cluster in the medial frontal region (b). BPRS: Brief Psychiatric Rating Scale.

superior temporal gyrus. Taken together, the present results emphasize the concept that the abnormal functional connectivity of the fronto-temporal neural network plays a crucial role in the pathophysiology of schizophrenia (Friston and Frith, 1995; Kurachi, 2003; Lawrie et al., 2002; Meyer-Lindenberg et al., 2005).

Several limitations of the present study must be taken into account. Although positive and negative symptoms are independent dimensions, the insidious intra-subject relationship between the two symptomatological domains is often overlooked (Pogue-Geile and Zubin, 1988). Some of the subjects presented in our study were medicated while others were not. Variability of these characteristics might have confounded the clinical data, and raises the question of trait vs. state nature of the P300 component (Blackwood, 2000; Higashima et al., 2002). Stratification according to positive or negative symptoms may have been rather limited using the BPRS as a psychopathology scale. These factors might limit the relevance of the correlation analyses (Higashima et al., 1998; Kawasaki et al., 1994). A sufficient number of subjects and more detailed symptom evaluations are essential for further study to draw more definite conclusions.

In summary, application of SPM to LORETA images revealed that the severity of psychotic symptoms is negatively correlated with the P300 current density in the medial prefrontal areas and the left superior temporal gyrus in schizophrenia patients. The results of this study further indicate that specific neural networks involving the prefrontal and superior temporal regions may be responsible for the generation of positive and negative symptoms of schizophrenia.

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Contributors

Author Yasuhiro Kawasaki undertook the statistical analysis and wrote the first draft of the manuscript. Author Tomiki Sumiyoshi designed the study and wrote the protocol. Authors Yuko Higuchi, Toru Ito, and Masashi Takeuchi managed data collection and analyses. Author Masayoshi Kurach helped the literature searches. All authors contributed to and have approved the final manuscript.

Conflicts of interest

None.

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SYNAPSE 61:391–400 (2007)

Effect of Prefrontal Cortex Inactivation on Behavioral and Neurochemical Abnormalities in Rats With Excitotoxic Lesions of the Entorhinal Cortex

TAKASHI UEHARA,* TOMIKI SUMIYOSHI, TADASU MATSUOKA, HIROKO ITOH, AND MASAYOSHI KURACHI
Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Science, Toyama, Japan

KEY WORDS limbic; dopamine; medial prefrontal cortex; entorhinal cortex; lesions; animal model; schizophrenia

ABSTRACT Morphological studies report reductions in the volume of medial temporal lobe structures and the prefrontal cortex in subjects with schizophrenia. The present study was performed to clarify the role of prefrontal–temporo–limbic system in the manifestation of psychosis, using entorhinal cortical lesion rats as a vulnerability animal model. Quinolinic acid (lesion group) or phosphate buffer (sham group) was infused into the left entorhinal cortex (EC) of male Wistar rats. On the 28th postoperative day, methamphetamine (MAP; 1 mg/kg, i.p.)-induced dopamine (DA) release in the nucleus accumbens (NAC) and the basolateral amygdala (BLA), as well as locomotor activity and prepulse inhibition (PPI), was measured following microinfusion of lidocaine or the cerebrospinal fluid (CSF) into the medial prefrontal cortex (mPFC). Lesions of the EC resulted in enhancement of MAP-induced DA release in the NAC and BLA. Further analysis revealed that the enhancement by EC lesions of MAP-induce DA release in the NAC was particularly evident in the lidocaine-infused rats. EC lesions also enhanced MAP-induced locomotor activity, especially in the lidocaine-treated animals. By contrast, infusion of lidocaine into mPFC attenuated MAP-induced DA release in the BLA, irrespective of the lesion status. Both EC lesions and lidocaine infusion disrupted PPI. These results indicate that inactivation of the mPFC, as well as structural abnormalities in the EC, leads to dysregulation of DAergic neurotransmissions in the limbic regions. The implications of these findings in relation to the neural basis for psychosis vulnerability are discussed. **Synapse 61:391–400, 2007.**

INTRODUCTION

Schizophrenia is a chronic mental illness that typically starts in the late adolescence or early adulthood, and in most cases, persists throughout life. Although the pathophysiology of schizophrenia remains unclear, some convincing hypotheses have been postulated. The most prevailing one concerns dysregulation of dopaminergic (DAergic) neurotransmission in the limbic brain regions (Carlsson, 1988). Thus, Grace (1991, 2000) hypothesized that the imbalance between the tonic (basal) and the phasic (evoked) DA release in subcortical regions causes psychotic symptoms of schizophrenia, while Seeman et al. (2006) argued that an increase in the high-affinity states of D2 receptors elicits psychosis.

Morphological studies have demonstrated reductions in the volume of the temporal lobe structures, including hippocampus, amygdala, and parahippocampal gyrus (Bogerts et al., 1985, 1990; Falkai et al., 1988; Harrison, 1999; Lawrie and Abukmeil, 1998; Suzuki et al., 2005b). Especially, these structural abnormalities are predominant in the left hemi-

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*Correspondence to: Takashi Uehara, MD, PhD, Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Science, 2630 Sugitani, Toyama 930-0194, Japan.
E-mail: uehara@med.u-toyama.ac.jp

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sphere (Degreef et al., 1992; Kawasaki et al., 1993). Roberts (1991) proposed that the structural changes in the brain of schizophrenia patients originate in the parahippocampal gyrus, or entorhinal cortex (EC), followed by an asymmetrical development. The volume reduction in the parahippocampal gyrus has been reported to be correlated with severity of positive psychotic symptoms (Bogerts, 1997).

On the basis of these findings, we have reported that excitotoxic lesions of the left EC elicit increased tissue concentrations of DA (Kurachi et al., 2000; Uehara et al., 2000) and augmentation of methamphetamine (MAP, 2 mg/kg)- or stress-induced DA release in the basolateral amygdala (BLA) (Uehara et al., 2000, 2003, 2004). Furthermore, the EC lesioned rats exhibited significantly greater MAP (1 mg/kg, i.p.)-induced locomotor activity than did sham-operated animals, while these lesioned rats did not show a significant change in MAP (1 mg/kg, i.p.)-induced DA release in the nucleus accumbens (NAC) (Sumiyoshi et al., 2004). A subsequent study (Sumiyoshi et al., 2005) found a marked (twofold) increase in the proportion of the high-affinity state of D2 receptors in the striatum of EC lesioned rats without a significant change in the D1 receptor component. These findings suggest that the supersensitivity of DA receptors in the subcortical regions contributes to the behavioral abnormalities observed in the EC lesion rats (Seeman et al., 2006; Sumiyoshi et al., 2004, 2005). Thus, rats with EC lesions are thought to represent an animal model of psychosis vulnerability (Seeman et al., 2006; Sumiyoshi et al., 2004, 2005).

The prefrontal cortex has been a main focus in the search for the neural substrates responsible for the pathophysiology of schizophrenia. Thus, neuroimaging and neuropathological studies have implicated hypofunction of the prefrontal cortex (Andreasen et al., 1997; Liddle et al., 1992). Anatomically, reductions in the volume of the prefrontal gray matter have been reported in patients with schizophrenia (Selemon et al., 2002; Shenton et al., 2001; Zhou et al., 2005).

Siever and Davis (2004) predicted that the volume reductions of the temporal lobes are a common pathophysiology across schizophrenia-spectrum disorders, including schizotypal disorder, whereas the frontal lobe volumes are reduced specifically in patients with overt psychosis but not those with schizotypal disorder. Consistent with this hypothesis, morphometric studies using magnetic resonance imaging in our laboratory demonstrated reductions in the gray matter volume of the left medial temporal region both in patients with schizophrenia and those with schizotypal disorder, whereas schizophrenia patients showed a greater change in the frontal lobe (Kawasaki et al., 2004; Suzuki et al., 2005b). Based on these findings, Kurachi (Kurachi, 2003a,b) argued that latent dysfunction of the temporal regions becomes overt by additional pathological changes in the frontal lobes, leading to the manifestation of positive psychotic symptoms.

Taken together, it is hypothesized that prefrontal dysfunction would elicit excessive DAergic neurotransmission in the limbic system in subjects with structural abnormalities in the temporal lobes, such as the volume reduction in the left EC. Although there has been a limited number of reports on the role of the medial prefrontal cortex (mPFC) and hippocampus in the regulation of DAergic activity (Goto and O'Donnell, 2004; Lipska et al., 1998), these studies did not observe increased DA response to stressors in the limbic structure. In fact, mPFC lesions have been found to elicit an effect opposite to that by neonatal lesions of the ventral hippocampus with regard to DAergic activity (Goto and O'Donnell, 2004; Lipska et al., 1998).

In this study, we sought to determine whether reversible inactivation of the mPFC would produce exaggerated DA transmissions, as indicated by behavioral (prepulse inhibition (PPI), locomotor activity) and neurochemical (DA release) measures, in rats with or without EC lesions, manipulations we previously reported (Kurachi et al., 2000; Sumiyoshi et al., 2004, 2005; Uehara et al., 2003, 2004). We expected that transient, reversible inactivation of mPFC would produce enhanced DA responsivity in the BLA and NAC of EC-lesioned, but not control rats.

MATERIALS AND METHODS

Animals

Male Wistar rats (postnatal day 7 weeks; Japan SLC, Japan) weighing 220–240 g were housed in a standard cage (four to five per cage) at 24 ± 2°C under a 12-h light (0700–1900 hrs)-12-h dark cycle. Experimental procedures complied with the National Institutes of Health guide for the care and use of laboratory animals. All experiments were reviewed and approved by the Committee of Animal Research, University of Toyama.

Surgery

Anesthesia was induced by pentobarbital sodium (40 mg/kg, i.p., Nembutal®, Abbott Laboratories, IL). The rats were mounted on a stereotaxic apparatus. An incision was made on the skin overlying the skull, and 0.5 μl of quinolinic acid (Sigma-Aldrich, St. Louis, MO, pH 7.4, 150 mM) or the equal volume of phosphate-buffered saline (pH 7.4, 0.1 M) was infused into the left EC with a Model PDH 2000 infusion pump (Harvard Apparatus, MA) at the rate of 0.2 μl/min through a 30-gauge stainless steel cannulae. The coordinates used were: anterior (A) 7.6 mm, lateral (L) 5.0 mm, and ventral (V) 7.3 mm with respect to the bregma (Paxinos and Watson, 1998). The injection cannulae were left in place for an additional 5 min