Planum Temporale and Heschl Gyrus Volume Reduction in Schizophrenia

A Magnetic Resonance Imaging Study of First-Episode Patients

Yoshio Hirayasu, MD, PhD; Robert W. McCarley, MD; Dean F. Salisbury, PhD; Shin Tanaka, MD; Jun Soo Kwon, MD, PhD; Melissa Frumin, MD; Danielle Snyderman, BS; Deborah Yurgelun-Todd, PhD; Ron Kikinis, MD; Ferenc A. Jolesz, MD; Martha E. Shenton, PhD

Background: Magnetic resonance imaging studies in schizophrenia have revealed abnormalities in temporal lobe structures, including the superior temporal gyrus. More specifically, abnormalities have been reported in the posterior superior temporal gyrus, which includes the Heschl gyrus and planum temporale, the latter being an important substrate for language. However, the specificity of the Heschl gyrus and planum temporale structural abnormalities to schizophrenia vs affective psychosis, and the possible confounding roles of chronic morbidity and neuroleptic treatment, remain unclear.

Methods: Magnetic resonance images were acquired using a 1.5-T magnet from 20 first-episode (at first hospitalization) patients with schizophrenia (mean age, 27.3 years), 24 first-episode patients with manic psychosis (mean age, 23.6 years), and 22 controls (mean age, 24.5 years). There was no significant difference in age for the 3 groups. All brain images were uniformly aligned and then reformat ted and resampled to yield isotropic voxels.

Results: Gray matter volume of the left planum temporale differed among the 3 groups. The patients with schizophrenia had significantly smaller left planum temporale volume than controls (20.0%) and patients with mania (20.0%). Heschl gyrus gray matter volume (left and right) was also reduced in patients with schizophrenia compared with controls (13.1%) and patients with bipolar mania (16.8%).

Conclusions: Compared with controls and patients with bipolar manic psychosis, patients with first-episode schizophrenia showed left planum temporale gray matter volume reduction and bilateral Heschl gyrus gray matter volume reduction. These findings are similar to those reported in patients with chronic schizophrenia and suggest that such abnormalities are present at first episode and are specific to schizophrenia.

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The MRI studies that evaluate both patient groups may represent no asymmetry between left and right HG and no difference in asymmetry between patients with schizophrenia and those with affective psychosis at the time of first hospitalization. More specifically, 6 patients with schizophrenia had hallucinations, paranoia, ideas of reference, and delusions; 1 had hallucinations, delusions, and ideas of reference; 2 had hallucinations, paranoia, and ideas of reference; 2 had hallucinations and delusions; 2 had delusions and paranoia; 2 had hallucinations and paranoia; 2 had only hallucinations; and 3 had only delusions. Two patients with mania had hallucinations, paranoia, ideas of reference, and delusions; 2 had hallucinations, paranoia, and ideas of reference; 2 had hallucinations, paranoia, and ideas of reference; 2 had hallucinations and paranoia; 2 had hallucinations and paranoia; 2 had only hallucinations; and 3 had only delusions. Diagnoses were confirmed at 1-year follow-up. The median duration of psychotropic medication use before MRI was short (Table 1). In addition, duration of medication use and dosage of medication were not significantly correlated with any MRI volumes. In terms of operationalizing onset of psychosis, we selected date of first psychiatric hospitalization. Although onset ofprodromal symptoms may be a better indicator of actual onset of disease, in practice this retrospective measure is difficult to verify. For comparative purposes, we provided age at time of first medication use, which we believe to be more objective (most dates were from hospital records) and nonequivocal than prodrome onset and thus possibly a better estimate of symptom onset. A group of 22 control subjects (SCID nonpatient edition and SCID-I	extsuperscript{II}; 20 men, 2 women), group matched for age, was recruited through newspaper advertisements. The present study reflects an increase in sample size (N=64) over our previous study (N=46) and presents new, more detailed measures of posterior STG anatomy, partially but not completely coextensive with our previous measures of posterior STG.

The Mini-Mental State Examination was used to rule out dementia or delirium. In addition, the information subscale of the Wechsler Adult Intelligence Scale–Revised was used to estimate general information, and the digit-forward and -backward subscales of the Wechsler Adult Intelligence Scale–Revised were used to evaluate immediate and short-term memory, attention, and concentration. Socioeconomic status (SES) and parental SES were also assessed. Psychosis was further evaluated using the Brief Psychiatric Rating Scale (BPRS). Social functioning was evaluated using the Global Assessment Scale (Table 1). After a complete description of the study, written informed consent was obtained from all subjects. Subjects were paid for participating.

MRI ACQUISITION PROTOCOL AND MRI POSTPROCESSING

The MRIs were obtained on a 1.5-T scanner (General Electric Scanner; GE Medical Systems, Milwaukee, Wis). Details concerning pulse sequences are provided elsewhere. Briefly, there were 2 MRI protocols. The first was a coronal series of contiguous images (repetition time=35 milliseconds, echo time=5 milliseconds, 1 repetition, 45° nutation angle, 24-cm field of view, number of excitations=1.0, matrix=256×256 [192 phase encoding steps]×124). Voxel (volume of pixel) dimensions were 0.9375×0.9375×3 mm. Data were reformatted in the coronal plane and analyzed as 124 coronal 1.3-mm-thick slices. This protocol was used to measure PT and HG. The second was an axial series of contiguous double echo (proton density and T2-weighted) images (repetition time=3000 milliseconds, echo time=30 and 80 milliseconds, 24-cm field of view, an interleaved acquisition with 3-mm slice thickness). Voxel dimensions were 0.9375×0.9375×3 mm. This latter protocol was used to evaluate total intracranial volume. To reduce flow-related artifacts and to obtain low arterial signal intensity, presaturation of a slab inferior to the head was performed in both the axial and coronal...
There were no significant group differences in age. First-episode patients with schizophrenia showed significantly lower SES than comparison subjects, consistent with reduced functioning (Table 1). Parental SES was upper middle class or above for all groups, but parental SES of the schizophrenia group was lower than parental SES of the other 2 comparison groups. There were no significant differences between patients diagnosed as having schizophrenia and patients diagnosed as having mania on any of the clinical scale measures, age of first medication use, medication dose, or duration of illness. There were significant differences between the patient groups in 4 items of the BPRS. Patients with schizophrenia showed higher scores (mean±SD) in suspiciousness (schizophrenia, 4.26±1.88; mania, 2.96±2.14; \( t_{42}=2.07; \ P=.04 \)), hallucinatory behavior (schizophrenia, 3.05±1.81; mania, 2.00±1.01; \( t_{42}=2.06; \ P=.046 \)), and blunted affect (schizophrenia, 3.11±1.76; mania, 1.70±1.40; \( t_{42}=2.84; \ P=.007 \)) than patients with mania. In contrast, patients with mania showed higher scores for grandiosity (schizophrenia, 1.42±3.01; mania,
3.83±1.02; \( t_{22} = 3.32; P = .002 \). Total score on the BPRS, age of first medication use, and duration of medication use did not correlate with any ROI volumes. There was also no significant difference in ICC volume among the 3 groups.

**VOLUME OF THE PT AND HG**

The 3-factor ANCOVA revealed a significant group-by-side-by-region interaction (\( F_{2,61} = 4.41, P = .02 \)). Follow-up ANCOVA revealed a significant group-by-side interaction (\( F_{2,61} = 7.62, P = .001 \)) in PT. One-way ANCOVA showed that left PT differed among groups (\( F_{2,61} = 4.76, P = .01 \)), with the schizophrenia group significantly smaller than the control and mania groups (Tukey Honestly Significant Difference, \( P < .05 \)) (Table 2 and Figure 2). However, right PT was not different among groups.

For HG, there was a significant main effect for group (\( F_{2,61} = 4.67, P = .01 \)), with no group-by-side interaction (\( F_{2,61} = 0.21, P = .98 \)). Post hoc tests revealed that total (left and right) HG gray matter volume was significantly smaller in schizophrenic patients compared with patients with mania and healthy control subjects (Tukey Honestly Significant Difference, \( P < .05 \)) but that group differences for left and right HG did not reach significance by 1-way ANCOVA (\( F_{2,61} = 2.11, P = .13; F_{2,61} = 2.49, P = .09 \), respectively) (Table 2 and Figure 2). However, HG was significantly asymmetrical in all subjects (\( F_{1,61} = 4.19, P = .04 \)).

Note that, compared with controls and patients with mania, patients with schizophrenia show gray matter volume reductions of 20.0% in left PT (effect size = 0.91). In addition, compared with controls, patients with schizophrenia show gray matter volume reductions of 15.3% in left HG (effect size = 0.71) and 10.6% in right HG (effect size = 0.44). For HG (left + right), patients with schizophrenia, compared with controls and patients with mania, showed 13.1% (effect size = 0.87) and 16.8% (effect size = 1.16) volume reduction, respectively.

**CORRELATIONS BETWEEN ROI VOLUMES AND PSYCHOPATHOLOGY**

In an exploratory analysis, no factors or items of the BPRS significantly correlated (\( P < .05 \)) with absolute or relative volumes of PT or HG in first-episode schizophrenia or in first-episode mania. In addition, none of the cognitive tests were statistically significantly correlated with HG and PT volumes in this study.

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*SES indicates socioeconomic status; MMSE, Mini-Mental State Examination; WAIS-R, Wechsler Adult Intelligence Scale–Revised; GAS, Global Assessment Scale; CPZ equiv, chlorpromazine equivalent; BPRS, Brief Psychiatric Rating Scale; and ellipses, data not applicable. Handedness was assessed by a modified Oldfield Inventory (Oldfield, 1971), right-handed being above 0.

†Statistical significance was determined by a 1-factor analysis of variance.

‡Higher scores indicate lower SES.

§Post hoc Tukey Honestly Significant Difference test showed significant difference (\( P < .05 \)) compared with patients with mania and comparison subjects.
time of first hospitalization and are specific to schizophrenia.

Musiek and Reeves reported an asymmetrical length of HG (left greater than right) in healthy subjects. However, findings have been inconsistent in MRI studies of schizophrenia. For example, reported a left HG volume greater than the right in controls and patients diagnosed as having paranoid schizophrenia. The present results indicate an asymmetry of HG in all groups but also suggest bilateral HG reduction in the schizophrenia group. This raises the interesting question of primary auditory sensory deficits in schizophrenia, a question not yet completely investigated. For example, have documented that patients with schizophrenia have more difficulty than controls in differentiating high and low tones presented against a background of noise, and these patients often also show deficits in mismatch negativity, an electrophysiological index of echoic memory processes.

In the present study, clinical measures and ROIs were not significantly correlated. In patients with chronic disease, left anterior STG volume reduction has been reported to correlate with auditory hallucinations, and left posterior STG volume reduction has been reported to correlate with severity of thought disorder. Moreover, our laboratory found the suspiciousness/persecution subscale score of the Positive and Negative Syndrome Scale was associated with reduced left PT volume in patients diagnosed as having chronic schizophrenia. Correlations between clinical measures and reduced volumes in patients with chronic schizophrenia have been reported by several investigators. However, few MRI studies of first-episode schizophrenia have reported an association between structural abnormalities and symptoms. We suggest that at the time of first hospitalization symptom-MRI correlations might be less than in chronic schizophrenia because of either a lack of stability in psychiatric symptoms or an absence of more marked structural alterations.
The specificity of MRI abnormalities to schizophrenic vs affective psychosis is a long-standing conundrum, as is the more general question of whether these psychoses are manifestations of a single disorder. Our previous report indicated that volume reduction in left posterior STG gray matter was specific to schizophrenia, although volume reduction of the posterior amygdala-hippocampal complex was not different between patients diagnosed as having first-episode schizophrenia and patients diagnosed as having first-episode bipolar mania. A recent report by Velakoulis et al also showed left hippocampal volume reduction in first-episode schizophrenia and schizophreniform psychosis compared with healthy subjects, but, once again, no differences were reported between first-episode schizophrenia and first-episode affective psychosis. These findings suggest that abnormalities in left STG gray matter, including PT and HG, are specific to schizophrenic psychosis, in contrast to abnormalities in medial temporal structures. Furthermore, Schlaepfer et al reported that patients with bipolar disorder did not show heteromodal cerebral cortex volume reduction, whereas gray matter volume was

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reduced in patients with schizophrenia. More specifically, asymmetry reversal was reported for posterior STG in patients diagnosed as having schizophrenia but not in patients diagnosed as having bipolar disorder.29 Zipursky et al.48 similarly found global volume reduction in gray matter in first-episode psychotic patients but not in first-episode affective psychotic patients. Harvey et al.60 also reported a decrease in cortical volume in patients with schizophrenia but not in patients with bipolar disorder. Since we have not investigated fronto-parietal cortex, 2 other areas possibly implicated in schizophrenic and affective pathology,12 conclusions drawn herein about specificity apply only to the regions we have studied.

There are several caveats to this study. First, the sex distribution of our sample did not allow us to investigate this variable. We anticipate doing so in the future. Second, a previous study by our group failed to show a significant volume difference in HG between patients with chronic schizophrenia and controls.49 One possible reason may be that different methods were used. In the previous study, post-MRI realignment was not performed, whereas in the present study we used a newly developed postrealignment procedure and a new method for resampling of voxels. When we evaluated the 2 methods, with and without realignment before ROI tracing (N = 10; 5 patients with schizophrenia and 5 controls), we found no significant volume difference between the 2 methods for PT or HG in either schizophrenic patients or control subjects. We also found no differences in intraclass correlation coefficients between the 2 methods. A more likely explanation for the difference in HG and PT in this study, but for only PT in our previous study, might be the differences in the samples. Third, operationalizing first episode as time of first hospitalization rather than as time of prodromal symptom onset may overestimate age at onset yet provides an unequivocal measure. First hospitalization is used synonymously with first episode as time of first hospitalization, which may help to clarify the clinical picture for patients with significant symptoms before hospitalization.

In conclusion, our findings of volume reduction in PT and HG in first-episode schizophrenia suggest the presence of structural abnormalities in regions associated with auditory processing and language. Finally, we suggest that studies of patients with recent-onset disease provide a major advantage in having fewer confounds from chronicity variables and, additionally, offer a baseline for longitudinal studies evaluating the presence or absence of progression of MRI changes over time.

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From the Clinical Neuroscience Division, Laboratory of Neuroscience, Department of Psychiatry, Brockton Veterans Affairs Medical Center, and Harvard Medical School, Brockton, Mass (Dr S Hirayasu, McCarey, Salisbury, Tanaka, Kwon, Frumin, and Shenton and Ms Snyderman); Cognitive Neuroscience Laboratory, McLean Hospital (Drs McCarey, Salisbury, and Shenton), and Brain Imaging Center, McLean Hospital (Dr Yurgelun-Todd), Belmont, Mass; and The Surgical Planning Laboratory, MRI Division, Brigham and Women’s Hospital, Department of Radiology, Harvard Medical School, Boston, Mass (Drs Kikinis and Jolesz). Dr Hirayasu is now with the Department of Neuropsychiatry, Kyorin University School of Medicine, Tokyo, Japan. Dr Kwon is now with the Department of Psychiatry, Seoul National University Medical College, Seoul, Korea.

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Reprints: Martha E. Shenton, PhD, or Robert W. McCarey, MD, Department of Psychiatry (116A), VAMC-Brockton, Harvard Medical School, 940 Belmont St, Brockton, MA 02301 (e-mail: martha_shenton@hms.harvard.edu; robert_mccarey@hms.harvard.edu).

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