

Left Planum Temporale Volume Reduction in Schizophrenia

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Background: The planum temporale, located on the posterior and superior surface of the temporal lobe, is a brain region thought to be a biological substrate of language and possibly implicated in the pathophysiology of schizophrenia. To investigate further the role of planum temporale abnormalities in schizophrenia, we measured gray matter volume underlying the planum temporale from high spatial resolution magnetic resonance imaging techniques.

Methods: Sixteen male patients with chronic schizophrenia and 16 control subjects were matched for age, sex, handedness, and parental socioeconomic status. Magnetic resonance imaging images were obtained from a 1.5-T magnet.

Results: Gray matter volume was significantly reduced in the left planum temporale (28.2%) in schizophrenic

patients compared with normal controls. Schizophrenic patients showed a reversal of the left greater than right planum temporale asymmetry found in normal controls. Heschl's gyrus (primary auditory cortex) showed no differences between the left and right sides in either group. Of note, the Suspiciousness/Persecution subscale score of the Positive and Negative Syndrome Scale was associated with reduced left planum temporale volume in schizophrenic patients.

Conclusions: Patients with schizophrenia have reduced left planum temporale gray matter and a reversal of planum temporale asymmetry, which may underlie an impairment in language processing and symptoms of suspiciousness or persecution characteristic of schizophrenia.

Arch Gen Psychiatry. 1999;56:142-148

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THE PLANUM temporale (PT) is located on the posterosuperior surface of the temporal lobe. This brain region is of particular interest because it evinces the most left-right asymmetry in the human brain (left > right in two thirds of all brains).¹⁻³ The left PT is within Wernicke's area, which is critical for language and speech production.⁴ Moreover, left PT is linked to handedness and, among musicians, to perfect pitch perception.⁵⁻⁷ Of note, PT asymmetry is apparent by the 29th to 31st weeks of gestation, and thus abnormalities in this brain region may suggest a disruption of neurodevelopmental processes involved in hemispheric lateralization.⁸ Finally, phylogenetically, PT asymmetry first appears in higher nonhuman primates (chimpanzees) and increases in the human brain, suggesting a possible link with the evolution of language.⁹

The PT is also of interest to schizophrenia research because patients with schizophrenia have brain abnormalities that are more pronounced on the left side and include abnormalities in the su-

perior temporal gyrus (STG) and medial temporal lobe.¹⁰⁻¹² Additionally, left anterior STG volume reduction has been reported to correlate with auditory hallucinations,¹⁰ while left posterior STG volume reduction has been reported to correlate with severity of thought disorder.¹¹ This STG volume reduction in schizophrenic patients has been confirmed by several investigators.¹³⁻¹⁵

Because posterior STG includes both PT and Heschl's gyrus (HG) (primary auditory cortex adjacent to PT), it would be important to determine whether the PT and/or HG are abnormal in schizophrenia. There has been 1 postmortem study of PT that reported reduced cortical volume under the PT in schizophrenia as compared with controls.¹⁶ More recently, there have been 2 magnetic resonance imaging (MRI) studies that reported no differences in PT volumes between patients with schizophrenia and controls.^{17,18} Other investigators measuring PT area, however, reported a reversal of the left greater than right PT asymmetry found in normal controls.^{19,20} Others have not reported abnormalities in PT asymmetry in schizophrenia.²¹⁻²⁴

SUBJECTS AND METHODS

SUBJECTS

Subjects were from a new sample and did not include any subjects from our earlier study.¹¹ The patient sample consisted of 16 right-handed male schizophrenic patients (aged 20-55 years) from the Brockton Veterans Affairs Medical Center, Brockton, Mass. All patients met DSM-IV criteria for schizophrenia based on both the Structured Clinical Interview³¹ and on information from psychiatric records. Exclusion criteria included a history of neurologic illness or major head trauma, electroconvulsive therapy, or alcohol and drug abuse within the past 5 years or alcohol or drug dependence ever. All patients were receiving neuroleptic medication, with a mean daily dose equivalent to 443 ± 263 mg of chlorpromazine. The patients' mean \pm SD age was 45.1 ± 6.5 years, their mean age at symptom onset was 21.8 ± 2.6 years (range, 18-26 years), and their mean duration of illness was 23.3 ± 6.5 years (range, 15-36 years).

A normal comparison group included 16 age-, handedness-, and sex-matched subjects who were recruited through a newspaper advertisement. These subjects were screened to exclude neurologic and psychiatric illness as well as alcohol abuse in themselves or in their first-degree relatives. Their mean age was 42.6 ± 8.0 years, which was not different from that of the patients. There were also no statistically significant differences between the 2 groups in parental socioeconomic status (normal controls, 2.3 ± 0.9 ; patients, 2.9 ± 1.2). However, socioeconomic status of the patients (4.4 ± 0.6) was significantly lower ($P < .001$) than that of controls (1.9 ± 1.0). Scores on the Wechsler Adult Intelligence Scale-Revised (WAIS-R)³² Information subscale were 11.7 ± 1.9 in controls and 10.3 ± 2.0 in patients ($P = .06$). All subjects were right-handed and gave written informed consent prior to study participation.

CLINICAL EVALUATIONS

The Positive and Negative Syndrome Scale (PANSS),³³ the Scale for the Assessment of Positive Symptoms (SAPS),³⁴ and the Scale for the Assessment of Negative Symptoms (SANS)³⁵ were administered to patients. All subjects were tested with the Information subscale of the WAIS-R. In addition, socioeconomic status and parental socioeconomic status were measured using the Hollingshead 2-factor index of socioeconomic status.³⁶

MRI IMAGE ACQUISITION AND PROCESSING

Magnetic resonance imaging scans were obtained for all subjects using a 1.5-T system located at Brigham and Women's Hospital, Boston. The scanning and image methods are described in detail elsewhere.^{11,37} Briefly, a spoiled gradient-recalled acquisition in steady-state imaging sequence was used to obtain contiguous images. Imaging parameters were as follows: time to repeat, 35 milliseconds; echo time, 5 milliseconds; 1 repetition; 45° nutation angle; 24-cm field of view; 1.0 excitations; and matrix, 256×256 (192 phase-encoding steps) \times 124. Voxel dimensions were $0.9375 \times 0.9375 \times 1.5$ mm.

Data were formatted in the coronal plane and analyzed as 124 coronal 1.5-mm-thick slices. This protocol was used for delineating and measuring the PT and HG because the coronal plane offers excellent visualization of PT, including direct assessment of the full depth of the sylvian fossa.³⁸ To assess the whole-brain volume, we obtained MRI images in an axial series of contiguous double-echo images (proton density and T₂ weight). The imaging parameters for this protocol were as follows: time to repeat, 3000 milliseconds; echo time, 30 and 80 milliseconds; 24-cm field of view; and an interleaved acquisition with 3-mm slice thickness. Voxel dimensions were $0.9375 \times 0.9375 \times 3$ mm.

The axial double-echo images were used as the input for the semiautomated segmentation procedure to measure total intracranial content (ICC). To reduce flow-related artifacts and to obtain low arterial signal intensity, gradient moment nulling and presaturation of a slab inferior to the head were performed in both axial and coronal acquisitions. An anisotropic diffusion filter was used to reduce noise prior to processing each set of scans.³⁹

DEFINITION OF HG AND PT

To measure the volume of PT, we first specified the anatomical landmarks for HG, since the posterior boundary of HG forms the anterior border of PT. It is well known that there is more than 1 transverse gyrus on the right side of the brain in most individuals.^{25,26} Multiple gyri on the right could, therefore, introduce a systemic bias toward finding relatively greater PT volume on the left. Thus if the transverse gyri were excluded on the right, the size of PT would be smaller on the right. Additionally, several anatomical variations complicate the identification and delineation of HG. Most have used the criteria of Steinmetz et al.,⁴⁰ which were originally derived from the Pfeiffer criteria,²⁵ to define and delineate HG and PT. Methodological considerations and anatomical variations of PT and HG measurement have also been extensively studied by Barta et al.³⁰ In the present study, we used criteria similar to those of Barta et al for delineating HG and PT. Accordingly, we defined the HG as commencing from a point at the posterior margin of the insula next to the end of an opercular branch of the postcentral gyrus, transversing the entire breadth of the superior aspect of the temporal lobe anterolateral, and terminating in the lateral border of STG.

To delineate HG on MRI scans, we first used axial images to manually outline HG. Axial images were used because they most clearly showed HG. The marks made on the axial outlines, once reformatted, helped to accurately pinpoint the location of HG on the coronal images. Next, the most posterior image with a mark was found in the coronal series. If a gyral pattern was present in the marked area, the region of interest (ROI) was drawn. Drawing then continued to the most anterior slice with a mark. If no gyrus was seen (just flat gray matter), the coronal images were examined anteriorly until a gyrus appeared. Only the cusp of the lateral edge was included as Heschl's sulcus reached the lateral border of STG. The cusp was defined as the edge of gray matter of HG up to the level of the white matter, ie, the roof of the white matter of STG was the inferior boundary of the cusp. At this point, drawings were made straight across the

Continued on next page

gray matter to draw the boundary of the white matter. Finally, ROIs were checked on sagittal images to confirm the accuracy of the HG boundaries.

The PT was measured after HG. On coronal images, the area lateral to the HG was considered the PT. The anterior boundary of PT was the posterior border of HG. The lateral border of PT was defined as the superolateral margin of the STG. The cutting cusp in the lateral border was the edge of the gray matter of PT up to the level of the white matter, which was the same process used for HG definitions. On the coronal images, gray matter volume was measured beneath the PT up to the end of the sylvian fissure. The ascending ramus of the sylvian fissure was then followed. Thus, our definition of the PT included the PT proper and parietal extension. **Figure 1** shows the ROIs of PT and HG in coronal, sagittal, and axial slices as well as a 3-dimensional reconstruction of the temporal lobes that clearly depicts both the PT and HG.

Interrater reliability was computed for the ROIs by 3 independent raters (J.S.K., Y.H., and I.A.F.) who were blind to group membership. Ten cases were randomly selected for interrater reliability. An intraclass correlation coefficient was used to compute interrater reliability based on the 3 raters: 0.92 (left HG), 0.90 (right HG), 0.93 (left PT), and 0.91 (right PT).

STATISTICAL ANALYSES

We used a mixed-model analysis of covariance (ANCOVA) with 3 factors: 1 between-subjects factor (group [patients and controls]) and 2 within-subjects factors (side [left and right] and region [HG and PT]). Follow-up analysis included a 2-factor (group and side) ANCOVA for each region (HG and PT) and post hoc Bonferroni tests for individual regions with left and right separately. Age and total ICC were used as covariates for the analysis. For the relative volume, ICC was used to control for differences in head size by computing relative percent volume for specific ROIs: ie, relative ROI volume=(ROI volume/ICC volume) \times 100. In addition, an asymmetry coefficient (AC) was calculated by using the formula $(R - L)/0.5 \times (R+L)$, where R and L were the PT or HG volumes on the left and right sides, respectively. Subjects were classified as leftward asymmetry ($AC < -0.05$), symmetry ($-0.05 < AC < 0.05$), or rightward asymmetry ($AC > 0.05$) according to Galaburda et al.⁴¹ The χ^2 test was used to compare the distribution of asymmetry. Exploratory analyses of the relationship between volume of the PT and psychopathology scales were evaluated using Spearman r correlation coefficients. Data are presented as mean \pm SD unless otherwise indicated. $P \leq .05$ was accepted as the level of significance.

Such inconsistencies in the literature are likely due to both differences in the definition of the border of PT/HG and to different methods of measurement. First, the definitional difficulties include the fact that there is more than 1 transverse gyrus on the right in most individuals and

on the left in about one third,^{25,26} and the fact that the size of PT depends on whether the secondary gyrus of Heschl is included. Moreover, some investigators consider the second gyrus to be HG,^{27,28} while others consider the most anterior transverse gyrus to be HG and the more posterior transverse gyrus to be part of PT.^{3,29} Thus, clear and uniform anatomical criteria for the boundaries are needed for comparison of studies (see Barta et al.³⁰ for a thoughtful review).

Second, most studies report the length or area of PT or HG. However, these linear measures are difficult to perform and may be somewhat inaccurate because the PT is not flat but rather curved and crenelated. Thus, in light of the potential difficulties of measurement and definition of PT area or length, we decided instead to measure the volume of gray matter under the PT and HG as a more reliable measure. We report a study of PT wherein we measured the volume of gray matter under the PT from high spatial resolution MRI scans (1.5-mm slices) in a new sample of schizophrenic patients and in a normal control group.

RESULTS

VOLUME OF THE PT AND HG

The 2-factor ANCOVA revealed a significant interaction of group \times side \times region ($F_{1,30}=8.64, P=.006$). Follow-up 2-factor ANCOVA showed that there was a significant main effect for group ($F_{1,28}=4.71, P=.04$) and side ($F_{1,30}=9.68, P=.004$) for PT. There was also a significant group \times side interaction ($F_{1,30}=15.64, P<.001$), indicating that schizophrenic patients had smaller left PT than controls ($P<.001$ with Bonferroni correction). However, right PT was not different between groups ($P>0.1$ with Bonferroni correction). For HG, there were no main effects for group ($F_{1,28}=1.14, P=.30$), side ($F_{1,30}=1.19, P=.28$), or group \times side interaction ($F_{1,30}=0.02, P=.88$). The volumes of PT and HG are presented in **Table 1**, where the patients have a 28.2% left PT volume reduction. **Figure 2** shows the scatterplot of PT for both schizophrenic patients and controls.

ASYMMETRY COEFFICIENT OF PT AND HG

An analysis of variance examining the effects of group and region on asymmetry in the patients vs controls showed a significant main effect for group ($F_{1,28}=11.59, P=.02$) and for group \times region interaction ($F_{1,30}=5.35, P=.03$). Post hoc Bonferroni tests showed that schizophrenic patients had a reversal of the left greater than right PT asymmetry normally found in controls (controls, -0.353 ; patients, $0.025, P=.03$). When the subjects were classified as leftward asymmetry, symmetry, and rightward asymmetry, the distribution of asymmetry coefficients was significantly different between schizophrenic patients and normal controls (χ^2_2 test= $14.56, P<.001$) (**Table 2**). Schizophrenic patients showed more rightward asymmetry as compared with normal controls. However, HG showed no significant difference for asymmetry coefficients between groups (controls, -0.71 ; patients, $-0.48; P=.84$).

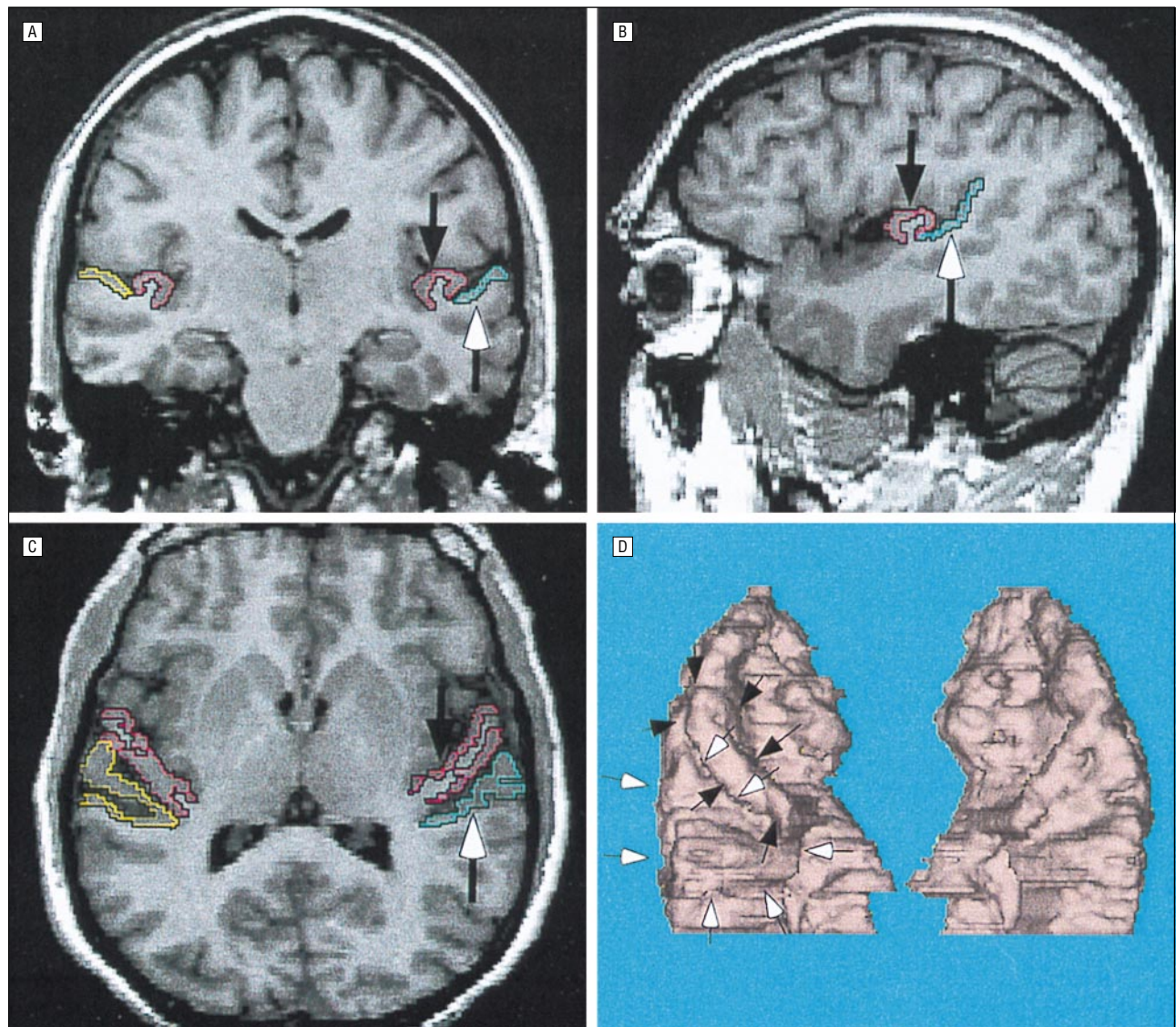


Figure 1. Delineation of the planum temporale and Heschl's gyrus regions of interest in (A) coronal, (B) sagittal, and (C) axial images. Heschl's gyrus is indicated by black arrows and the planum temporale by white arrows. D, Three-dimensional reconstruction of temporal lobes showing the outlines of the planum temporale (white arrows) and of Heschl's gyrus (black arrows).

CORRELATIONS BETWEEN PT VOLUME AND PSYCHOPATHOLOGY

In an exploratory analysis, there were no significant correlations between left PT volume reduction and scores on the PANSS Total, General, Negative, or Positive scales. There were also no correlations between left PT volume reduction and SAPS and SANS scores. However, among the subscales, the score on the Suspiciousness/Persecution subscale of the PANSS was correlated with left PT absolute volume (Spearman $r = -0.499$, $P < .05$) and showed a trend for correlation with left PT relative volume (Spearman $r = -0.455$, $P = .08$).

COMMENT

To our knowledge, this is the first MRI study to report reduced gray matter volume underlying PT in patients

with chronic schizophrenia compared with normal controls (28.2% left PT volume reduction). Schizophrenic patients also showed a reversal of the left greater than right PT asymmetry found in normal controls. These findings suggest that an abnormal left PT may be an important anomaly in schizophrenia that is associated with impairments in language processing and such symptoms as suspiciousness or persecution, which are characteristic of schizophrenia.

Although PT was not measured in our earlier study,¹¹ the present data are consistent with the earlier study's findings of left-lateralized volume reduction in posterior STG gray matter, since this region is coextensive with much of the PT. The postmortem study by Falkai et al¹⁶ used methods to measure PT volume that most closely resemble those in the current study. Their findings are also similar to ours in that they reported a 20% volume reduction in left PT in male patients with schizophrenia, whereas

on the right side, there was a trend toward an increase in volume. In addition, these investigators reported asymmetry coefficients for PT volume and anterior-posterior diameter that were significantly different between patients and controls. The smaller absolute gray matter volumes reported by Falkai et al for both controls and schizophrenic subjects, however, may stem at least in part from their use of older subjects and/or in part from the absence of normal in vivo vascular volume in the postmortem brain. We also note that, in the report by Falkai et al, the asymmetry coefficient for PT area was not different between groups. However, this may be due to the presence of an area measurement vs our volume measurement.

Recently, there have been 2 MRI studies from the Johns Hopkins (Baltimore, Md) group and 1 from the Maudsley Hospital (United Kingdom) group that investigated PT volume in patients with schizophrenia. In the first study, investigators reported an absence of the normal asymmetry for PT surface area in 14 patients with schizophrenia and 14 controls.²⁰ This group of patients, along with 14 new patients and 18 new controls, were the subjects of a second, more extended study.¹⁷ In the latter study, investigators measured surface area as well as gray matter volume of PT. Patients with schizophrenia showed no differences in the gray matter volume of left or right PT compared with normal controls, although patients showed an absence of normal asymmetry of PT surface area, depicted by a larger right PT area and somewhat smaller left PT area compared with normal controls. Thus, there were no correlations between

surface area and volume measures in their study. In the Maudsley family study,¹⁸ investigators also found no PT volume asymmetry in schizophrenic patients or in their relatives compared with normal controls. The mean volume of PT was 2.58 to 3.12 mL in the Johns Hopkins study, while it was 4.7 to 6.2 mL in the Maudsley study. These PT volumes are larger than those reported in our study. Possible explanations for volume difference come from the methods used to define PT. In the current study, to define the posterior boundary of PT, we included gray matter of PT up to and including the most posterior ascending ramus of sylvian fissure where the PT was still delineable. This posterior criterion for PT was the same as in the postmortem study by Falkai et al. In the studies by Barta et al¹⁷ and Frangou et al,¹⁸ the posterior boundary of PT was instead defined as the point of upward angulation of the posterior ascending ramus of sylvian fissure (horizontal ramus). If the ascending ramus was not steeply angled, this could have been a source of variation, as the authors themselves discussed. Another possible explanation for the volume difference might be the different samples used; ie, the subjects in our study were all male, whereas the previous 2 studies included both men and women. Of note, women have been reported to show a less consistent pattern of PT asymmetry compared with men.⁴² Thus, sex may be an important factor in assessing the PT and may actually account for some of the inconsistent findings reported in the literature.

Although it is well known that the PT is larger in the left hemisphere than in the right, little has been reported on HG in this regard. Musiek and Reeves⁴³ reported an asymmetrical length of HG (left>right) in

Table 1. Volumes of Gray Matter Under Planum Temporale (PT) and Heschl's Gyrus (HG) for Controls and Schizophrenic Patients*

	Absolute Volume, mL	Relative Volume, %
PT		
Left		
Patients	1.91 ± 0.50†	0.12 ± 0.03†
Controls	2.66 ± 0.44	0.17 ± 0.03
Right		
Patients	2.00 ± 0.58	0.13 ± 0.04
Controls	1.92 ± 0.60	0.12 ± 0.04
HG		
Left		
Patients	1.79 ± 0.50	0.12 ± 0.03
Controls	1.70 ± 0.52	0.11 ± 0.03
Right		
Patients	1.72 ± 0.52	0.11 ± 0.03
Controls	1.60 ± 0.49	0.10 ± 0.03

*Values are presented as mean ± SD.
†P<.001 compared with controls.

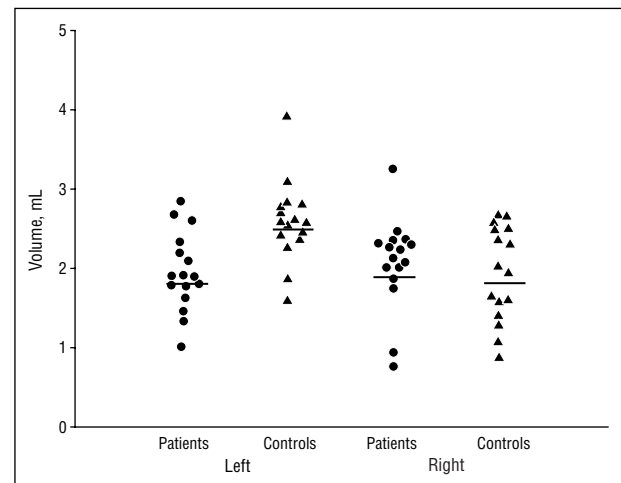


Figure 2. Left and right volumes of the planum temporale for controls and patients with schizophrenia. Horizontal lines indicate means.

Table 2. Asymmetry Coefficients of Planum Temporale in Schizophrenic Patients and Controls

Asymmetric Coefficient (AC)*	No. (%)		
	Leftward (AC <-0.05)	Symmetric (-0.05 < AC < 0.05)	Rightward (AC > 0.05)†
Controls	13 (81.3)	3 (18.8)	...
Patients	5 (31.3)	1 (6.3)	10 (62.5)

*Mean ± SD. $\chi^2_2 = 14.56$, P<.001.
†Ellipses indicate not applicable.

normal subjects in their postmortem study. But others reported no asymmetry between right and left HG and no difference in asymmetry between patients with schizophrenia and controls on MRI images.^{17,20,23} Only 1 group⁴⁴ using MRI reported that left HG volume was greater than right in normal controls as well as in patients with paranoid schizophrenia. This group also reported that, while male schizophrenic patients had smaller HG than the male comparison group, female patients had slightly larger HG than the female comparison group. Volume abnormalities of HG should therefore be further clarified in terms of sex and subtypes of schizophrenia.

Pearlson et al⁴⁵ suggested that the heteromodal association cortex might be a primary site of anatomical abnormalities in schizophrenia. The heteromodal association cortex is a highly organized and interconnected neocortical system that includes the PT, the dorsolateral prefrontal cortex, and the inferior parietal lobule. In the light of this hypothesis, our finding that HG did not differ between groups is consonant with other reports because HG is unimodal sensory cortex, rather than heteromodal association cortex.

With respect to clinical correlations, we reported a correlation between reduced volume of left PT and scores on the Suspiciousness/Persecution subscale of the PANSS. Asymmetry of the PT has been reported to be associated with thought disorder.^{19,20} And, although we did not find a correlation between PT abnormalities and total scores of SAPS or PANSS, we did note that suspiciousness or persecution, which might be linked with disordered thought in schizophrenia, was correlated with reduced volume of left PT in the present study. However, this exploratory finding needs replication.

In summary, despite some contradictory findings in the literature,^{13,46} our data are consistent with the view that schizophrenia is a disorder with marked abnormalities in the left hemisphere, particularly the left temporal lobe, in right-handed subjects. Volume reductions in the left hemisphere such as hippocampus and STG have been reported by several investigators.¹⁰⁻¹² It has also been suggested that the origin of schizophrenia might involve abnormal neural development of brain lateralization.⁴⁷ The right hemisphere, especially the temporal area, seems to develop earlier than the left for a short period of time, which may result in its being less likely to be impaired.⁴⁸ The period of vulnerability is more prolonged on the left, which could account for more opportunities for injuries. It is, however, unknown whether disturbances in the left hemisphere are related to genetics or exogenous insult. Nevertheless, if there is an insult to the fetal brain in the process of neurodevelopment, the left hemisphere would be more prone to disruption, which could possibly be related to the pathogenesis of schizophrenia.

The major limitation of this study is that the subject group included only patients with chronic schizophrenia, and it remains for future studies to reveal whether PT asymmetry is specific to schizophrenia. Also yet to be examined is the possibility of an association between reversed PT asymmetry and both neuropsychological semantic abnormalities related to temporal lobe^{49,50} and lateralized event-related potential abnormalities that may

involve the PT as an anatomical substrate, including P-300⁵¹ and mismatch negativity.⁵²

Accepted for publication September 22, 1998.

This study was supported, in part, by grants K02 MH-01110-04 and R29 MH-50747-04 (Dr Shenton) and R01 MH40799 (Dr McCarley) from the National Institute of Mental Health, Rockville, Md, and by a Medical Research Service Schizophrenia Center grant through the Department of Veterans Affairs, Washington, DC (Dr McCarley).

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