

Association Between Smaller Left Posterior Superior Temporal Gyrus Volume on Magnetic Resonance Imaging and Smaller Left Temporal P300 Amplitude in First-Episode Schizophrenia

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Background: In chronic schizophrenia, the P300 is broadly reduced and shows a localized left temporal deficit specifically associated with reduced gray matter volume of the left posterior superior temporal gyrus (STG). In first-episode patients, a similar left temporal P300 deficit is present in schizophrenia, but not in affective psychosis. The present study investigated whether the left temporal P300–left posterior STG volume association is selectively present in first-episode schizophrenia.

Method: P300 was recorded as first-episode subjects with schizophrenia (n=15) or affective psychosis (n=18) or control subjects (n=18) silently counted infrequent target tones amid standard tones. High-resolution spoiled gradient-recalled acquisition magnetic resonance images provided quantitative measures of temporal lobe gray matter regions of interest.

Results: Patients with first-episode schizophrenia displayed a reversed P300 temporal area asymmetry (smaller

on the left), while magnetic resonance imaging showed smaller gray matter volumes of left posterior STG relative to control subjects and patients with affective psychosis (15.4% and 11.0%, respectively), smaller gray matter volumes of left planum temporale (21.0% relative to both), and a smaller total Heschl's gyrus volume (14.6% and 21.1%, respectively). Left posterior STG and the left planum temporale, but not other regions of interest, were specifically and positively correlated ($r > 0.5$) with left temporal P300 voltage in patients with schizophrenia but not in patients with affective psychosis or in control subjects.

Conclusion: These results suggest that the left temporal P300 abnormality specifically associated with left posterior STG gray matter volume reduction is present at the first hospitalization for schizophrenia but is not present at the first hospitalization for affective psychosis.

Arch Gen Psychiatry. 2002;59:321-331

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THE MOST replicated electrophysiologic abnormality in schizophrenia is amplitude reduction of the auditory P300.¹⁻³ This event-related potential (ERP) is elicited when subjects detect rare target tones among differently pitched tones. Abnormalities in P300 may reflect deficits in cognitive updating, information processing, and selective attention.⁴⁻⁶ The P300 reduction in schizophrenia cannot be attributed to latency variability on individual trials or to absence of P300 on a subset of target trials,⁷⁻⁹ and persists even when clinical improvement is observed.^{8,10,11}

Patients with schizophrenia also show regional P300 amplitude reduction over the left temporal region.¹² The left-lateralized deficit in schizophrenia appears in patients not taking medication,¹³ with the use of a nose reference,¹⁴ with 64-channel recording,¹⁵ and at initial hospitalization,¹⁶ ap-

pears in never-medicated schizotypy,¹⁷ and has been independently replicated.^{2,18-31} Bruder et al² noted that most failures to replicate used a button-press response.^{8,32} In addition, difficult tasks, in which the overall amplitude of P300 is reduced, also diminish the abnormal P300 asymmetry in schizophrenia.^{9,30}

Patients with chronic or first-episode psychotic affective disorder show a normal lateral P300 topography, although an overall reduced P300 may be present.^{16,33} Thus, the left temporal P300 deficit appears especially intriguing because it is specific to schizophrenia.

P300 has multiple brain generators, including loci in temporal, frontal, and parietal lobes.³⁴⁻³⁸ We focus on the putative bilateral posterior temporal lobe generators. With the use of computed tomography, it was demonstrated that left sylvian fissure enlargement correlated with left temporal P300 abnormalities in schizo-

SUBJECTS AND METHODS

SUBJECTS

Clinical samples included only patients at first hospitalization, and consisted of 15 patients with schizophrenia (3 female and 12 male; 13 paranoid, 1 disorganized, and 1 undifferentiated) and 18 patients with affective disorder with psychotic features (3 female and 15 male; 17 with bipolar disorder [all in manic phase] and 1 with unipolar disorder [whose omission did not affect the statistical results reported herein]). The date of the first psychiatric hospitalization defined onset of psychosis, a commonly used definition of "first episode." We also measured the time of first medication, an objective estimate of symptom onset (most dates were from hospital records). (The validity of a retrospective measurement of onset of prodromal symptoms would have been difficult to verify [see discussions^{16,44,46}].) Nine of the 15 patients with schizophrenia were prescribed either antipsychotic, antidepressive, or mood-stabilizing medication before admission. For these 9 subjects, the mean duration of preadmission medication was 158.9 days; the median, 90 days; and the range, 3 to 730 days. Eight of the 18 patients with affective disorder were prescribed antipsychotic, antidepressive, or mood-stabilizing medication before this admission. For these 8 subjects, the mean duration was 217.3 days; the median, 150 days; and the range, 41 to 547 days. Patients were not necessarily medication compliant (by self-report). Eighteen normal control subjects (3 female and 15 male) were recruited from the general population through newspaper advertisements.

Patients' diagnoses were confirmed via the Structured Clinical Interview for *DSM-III-R*, Patient Version,⁴⁷ and control subjects were screened with the Structured Clinical Interview for *DSM-III-R*, Non-patient Edition,⁴⁸ by trained interviewers (D.F.S. and M.E.S.). Inclusion criteria were age between 18 and 55 years, IQ greater than 85, and normal hearing as assessed by audiometry. Any subject with a documented developmental disorder or learning disability, neurologic impairment, history of electroconvulsive therapy, seizures, head injury, or substance dependence within the past 5 years was excluded.

Groups did not differ in age and parental socioeconomic status. Patients with schizophrenia had significantly lower socioeconomic status than did control subjects, consistent with their illness. All were right-handed. Samples did not differ in basic cognitive performance, and patient groups were not different in medication dosages or clinical severity (**Table 1**). Consistent with previous studies,^{13,16,44,46} neither dose nor duration of medication was significantly correlated with P300 amplitudes or MR imaging volumes after Bonferroni correction in any group.

All subjects gave written informed consent and were paid for their participation. All subjects underwent ERP and MR testing. The median interval between ERP testing and MR imaging was 8 days. Four patients with first-episode schizophrenia, 2 patients with first-episode affective psychosis, and 9 control subjects were drawn from the previously reported P300 study from our group.¹⁶ Fifteen patients with schizophrenia, 14 patients with affective disorder, and 15 control subjects were also included in a previously reported MR imaging study by our group of anterior-posterior STG and medial temporal lobe⁴⁴ (which included 17 patients with schizophrenia, 16 patients with affective disorder, and 18 control subjects). All current subjects were also in our MR imaging study of Heschl's gyrus and planum temporale⁴⁶ (which analyzed 20 patients with schizophrenia, 27 patients with affective disorder, and 22 control subjects). No subjects were in common with our initial MR imaging and MR imaging-ERP chronic schizophrenia studies.^{40,43}

P300 RECORDING

Subjects silently counted infrequent (15%) binaurally presented target tones (97 dB sound pressure level, 1.5 kHz, 50-millisecond duration, 10-millisecond rise/fall) among standard tones (97 dB, 1 kHz) against a background of 70-dB white noise. Electroencephalographic activity was recorded from the scalp through 28 tin electrodes in preconfigured caps (ElectroCap International, Eaton, Ohio) with the use of an amplifier-stimulator (Neuroscience, Milpitas, Calif) and recording software (Neuroscan Labs; Sterling, Va). Electrode sites included all 10-20 sites excluding T1/2, and including Oz, FTC1/2, TCP1/2, PO1/2, and CP1/2. Linked earlobes were the reference; the forehead was ground. Two electrodes located medially to the right eye, one above and one below, monitored vertical eye movements and blinks. Electrodes placed at the outer canthi of the eyes monitored horizontal eye movements. All impedances were below 3 k Ω , and the ears were matched within 1 k Ω . The electroencephalograph amplifier bandpass was 0.15 (6 dB/octave roll-off) to 40 Hz (36 dB/octave rolloff). Single trial epochs were digitized at 3.5 milliseconds per sample over 900 milliseconds, including a 100-millisecond prestimulus baseline. Averaging and artifact rejection were done offline.

The ERP responses were convolved with a zero phase-shift digital low-pass filter at 8.5 Hz (24 dB/octave; Neuroscan Labs) to remove ambient electrical noise, muscle artifact, and alpha contamination. Within each 200-trial block, epochs from each electrode site were baseline corrected by subtraction of the average prestimulus voltage and mathematically corrected for eye movement artifact.⁵³ Subsequently, epochs exceeding ± 50 μ V at F7, F8, Fp1, or Fp2 were rejected. Averages were computed for the brain

phrenia.³⁹ Using quantitative volumetric magnetic resonance (MR) imaging, we evaluated hippocampus, parahippocampal gyrus, and superior temporal gyrus (STG) regions of interest (ROI), and found reductions in gray matter volume on the left on MR images in patients with chronic schizophrenia⁴⁰ (see reviews^{41,42}). Only the left posterior STG gray matter volume correlated with the left temporal P300 amplitude reduction.⁴³

The previous study,⁴³ however, tested chronically ill patients, did not test an affective psychosis contrast group, and did not evaluate STG functional substructures of planum temporale and Heschl's gyrus. The present study addressed these limitations. We tested a first psychotic episode population largely free of potential chronicity confounds and a contrast group of patients with first-episode affective psychosis. We used the same P300

responses to target tones. Peak P300 amplitude, which accounts for individual variations in P300 latency, and latency were measured as the most positive point from 250 to 650 milliseconds at each recording site.

MR IMAGING PROCEDURES

The MR images were obtained with a 1.5-T scanner (GE Medical Systems, Milwaukee, Wis) by means of 2 acquisition protocols.^{44,46} A 3-dimensional Fourier transform spoiled gradient-recalled acquisition protocol produced 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). Voxels were 0.9375 × 0.9375 × 1.5 mm. Data were reformatted in the coronal plane as 124 coronal slices of 1.5-mm thickness and used for delineating and measuring temporal lobe regions. The second acquisition resulted in an axial series of contiguous double-echo (proton density and T2-weighted) images used to assess whole brain volume (repetition time, 3000 milliseconds; echo times, 30 and 80 milliseconds; 24-cm field of view; interleaved acquisition with 3-mm slice thickness). Voxels were 0.9375 × 0.9375 × 3 mm. A semiautomated segmentation procedure⁴⁰ was used on the axial double-echo slices to measure total intracranial contents (ICC), and an anisotropic diffusion filter was used to reduce noise before processing.^{54,55}

All analyses were performed blinded to subject identity, age, and diagnosis, and after uniform alignment of images in 3-dimensional space. The ROI included the gray matter of the STG, amygdala-hippocampal complex, and parahippocampal gyrus, which were outlined manually on a workstation (**Figure 1A**). The STG gray matter is lateral, and the amygdala-hippocampal complex is medial to it, with parahippocampal gyrus most ventral. Gyral boundaries for STG were made by means of sagittal MR images computed from coronal images. The ROI began anteriorly at the slice unambiguously depicting the temporal stem and extended posteriorly to the last slice showing the fornix along the border of the lateral ventricles. Anterior and posterior portions were divided at the first slice including the mammillary bodies.⁴⁰ To separate gray and white matter of STG from the rest of temporal lobe, a line was drawn in the deepest points of the sulci of the STG (sylvian point and superior temporal sulcus) for each slice. The internal boundary for STG was always white matter, and the external boundary, cerebrospinal fluid. Interrater reliability for these ROI by 3 raters (including Y.H.) for 3 cases were as follows: STG, $r=0.99$ ($F_{2,11}=6.66$); parahippocampal gyrus, $r=0.99$ ($F_{2,11}=11.3$); amygdala-hippocampus, $r=0.95$ ($F_{2,11}=3.71$).

The ROI definitions for the planum temporale and Heschl's gyrus volumes are detailed elsewhere^{45,46} and are similar to those of Barta et al.⁵⁶ Intraclass correlation coefficients for 10 randomly selected cases evaluated by 3 raters (including Y.H.) were as follows: $r=0.88$ (left Heschl's gyrus), $r=0.88$ (right Heschl's gyrus), $r=0.98$ (left planum temporale), and $r=0.95$ (right planum temporale).

DATA ANALYSES

Statistics were computed with SPSS software (SPSS Inc, Chicago, Ill). One-way analysis of variance (ANOVA) with post hoc Tukey honestly significant difference tests assessed group differences in demographic, clinical, and basic neuropsychological performance. For ERP measures, a mixed-model repeated-measures ANOVA was used to test for effects along the sagittal midline and over temporal lobes, with group (schizophrenia, affective disorder, and control) as the between-subjects factor and anterior-posterior (AP) site (frontal [Fz], central [Cz], and parietal [Pz]) or side (left and right midtemporal sites [T3 and T4] for lateral analyses) as the within-subjects factor. Subsequent mixed-model repeated-measures ANOVA pairing each group were conducted in the case of significant group effects or group interactions. For the AP site factor, the Huynh-Feldt ϵ was used to adjust degrees of freedom for multiple comparisons.

The ICC volume was used to control for differences in head size by computing relative volume: relative ROI volume = (ROI volume/ICC volume) × 100. (Testing absolute volumes with ICC as a covariate did not change the results reported below.) Group differences in ICC were assessed with 1-way ANOVA. Groups were not significantly different in ICC volume ($P>.34$; mean ± SD, control, 1541.8 ± 149.2 mL; schizophrenia, 1511.0 ± 105.2 mL; affective psychosis, 1480.4 ± 111.4 mL). Mixed-model repeated-measures ANOVAs were performed for each ROI, with group (schizophrenia, affective disorder, and control) as the between-subjects factor and hemisphere (left and right) as within-subjects factors. Subsequent mixed-model repeated-measures ANOVA pairing each group were conducted in the case of significant group effects. In the case of significant group × hemisphere interactions, 1-way ANOVA was performed comparing groups on each side.

Pearson correlations were performed to assess the relationship between the absolute volume of ROIs and P300 amplitude.⁴³ Conservative 2-tailed probabilities were used. Our prediction, based on previous work,⁴³ was that reduced left temporal P300 amplitudes would be specifically correlated with posterior STG and planum temporale volume in patients with schizophrenia, but not in those with affective disorder or control subjects. Results were considered significant at $P<.05$.

protocol¹⁶ and ROI definitions^{40,44} as in the previous study,⁴³ but added planum temporale (a major substrate of language processing,^{45,46} largely, but not completely, coextensive with posterior STG) and Heschl's gyrus (primary auditory cortex).

To be specifically associated with the left temporal P300 deficit, the ROI's volume should be positively correlated with left temporal P300 amplitude, but not with P300

from other sites. Any ROI associated with global P300 amplitude reduction cannot explain a topographically local reduction. Absolute MR imaging volumes are correlated with P300 amplitude as the absolute volume of neurons, especially their dendrites, gives rise to the absolute P300 voltages.⁴³ On the basis of previous work from our group,⁴³ we predict a left temporal P300–left posterior STG/planum association in first-episode schizophrenia.

Table 1. Subject Demographics*

	Mean (SD)		
	Schizophrenia (n = 15)	Affective Psychosis (n = 18)	Control Subjects (n = 18)
Sex, No. F	3	3	3
Age, y	27.6 (7.6)	23.5 (3.9)	24.9 (4.9)
SES†	3.3 (1.4)†	2.7 (1.3)	1.8 (0.6)†
Parental SES [‡]	2.1 (1.0)	1.6 (0.8)	1.4 (0.9)
MMSE	28.5 (2.9)	29.2 (1.3)	28.8 (1.3)
WAIS-R Information	20.1 (6.8)	21.1 (5.3)	22.9 (3.4)
WAIS-R Digits Forward	8.0 (1.7)	8.1 (1.9)	8.9 (2.3)
WAIS-R Digits Backward	6.9 (2.7)	6.3 (2.2)	7.7 (2.7)
Oldfield Handedness Index [§]	0.75 (0.15)	0.71 (0.22)	0.80 (0.16)
Medications§	262.7 (242.5)	196.5 (162.7)	...
BPRS [¶]	37.3 (9.4)	35.6 (11.1)	...
GAS [¶]	38.5 (12.1)	37.2 (10.7)	...

*SES indicates socioeconomic status; MMSE, Mini-Mental State Examination; WAIS-R, Wechsler Adult Intelligence Scale-Revised; BPRS, Brief Psychiatric Rating Scale; and GAS, Global Assessment Scale.

†Only SES was significantly different among groups ($F_{2,48} = 6.54$, $P = .003$). Post hoc Tukey honestly significant difference test demonstrated that the first-episode schizophrenia and control groups were significantly different ($P < .05$).

‡For parental SES, 5 represents the lowest SES and 1, the highest.

§Medications in chlorpromazine equivalents. Patients were exposed to the following medications at hospitalization. Schizophrenia group: haloperidol, 2 patients; perphenazine, 3; perphenazine and divalproex sodium, 2; perphenazine and trazodone hydrochloride, 1; perphenazine, clozapine, and divalproex, 1; olanzapine, 1; fluphenazine hydrochloride, 1; risperidone, 1; risperidone and divalproex, 1; fluoxetine hydrochloride, 1; and lithium carbonate, clozapine, and trifluoperazine hydrochloride, 1. Affective psychosis group: perphenazine, 3 patients; lithium carbonate and perphenazine, 2; lithium carbonate and haloperidol, 1; lithium carbonate and loxapine, 1; lithium carbonate and risperidone, 1; perphenazine and propranolol, 1; perphenazine and divalproex, 1; perphenazine and risperidone, 1; bupropion hydrochloride and risperidone, 1; fluoxetine and thioridazine hydrochloride, 1; divalproex, 1; olanzapine, thiothixene, divalproex, and trazodone, 1; and unmedicated, 1.

RESULTS

P300 TOPOGRAPHY

Although the patients showed smaller P300 amplitudes than control subjects anteriorly along the sagittal midline (**Figure 2**), there were no significant differences among groups (group: $P > .7$). All groups showed the expected posteriorly maximum P300 (AP site: $F_{2,96} = 91.37$, $P < .001$, $\epsilon = 0.88$). Groups did not differ in P300 peak latency along the sagittal midline ($P > .3$), and all groups showed the expected increase in P300 latency posteriorly (AP site: $F_{2,96} = 18.94$, $P < .001$, $\epsilon = 1.0$).

Over the midtemporal sites (T3 and T4), the groups showed significantly different lateral topographies (group \times side: $F_{2,48} = 9.46$, $P < .001$). The schizophrenia group was significantly asymmetrical compared with the affective psychosis group (group \times side: $F_{1,31} = 11.0$, $P = .002$) and with the control group (group \times side: $F_{1,31} = 17.01$, $P < .001$). In contrast, both the affective psychosis group and the control group showed a significant but different asymmetry from the schizophrenic group, with P300 amplitude larger over the left temporal site than the right (side: $F_{1,34} = 10.93$, $P = .002$). Com-

parison of groups at each midtemporal site showed significant group differences at the left midtemporal site (T3, $F_{2,48} = 3.29$, $P = .046$), but not at the right midtemporal site (T4). Post hoc analyses of T3 showed that the patients with schizophrenia displayed smaller amplitudes than did controls (4.99 vs 6.75 μV , $P < .05$).

GRAY MATTER VOLUMES

Groups were compared for all ROI, including anterior and posterior subdivisions (**Table 2**). Analysis of anterior STG showed that groups did not differ in volumes, and that the 3 groups showed an anterior STG larger on the right (hemisphere: $F_{2,48} = 45.98$, $P < .001$). Groups did not differ significantly in posterior STG volumes (group: $F_{2,48} = 2.97$, $P = .06$). Groups differed significantly in hemispheric lateralization for posterior STG volumes (group \times hemisphere: $F_{2,48} = 3.67$, $P = .03$). Separate 1-way ANOVA for left and right posterior STG between the 3 groups showed a significant difference only in left posterior STG volumes ($F_{2,48} = 6.77$, $P < .003$). Post hoc comparisons demonstrated a significant left posterior STG volume difference between schizophrenic patients and control subjects ($P < .05$; relative volumes of 0.406% and 0.480%, respectively) and between schizophrenic patients and patients with affective psychosis ($P < .05$; 0.406% and 0.456% relative volumes, respectively).

Total (left+right) Heschl's gyrus volume was significantly different among groups (group: $F_{2,48} = 8.77$, $P = .001$). The schizophrenia group showed reduced total Heschl's gyrus volumes compared with the first-episode affective psychosis group (group: $F_{1,31} = 18.35$, $P < .001$) and the control group (group: $F_{1,31} = 7.00$, $P = .01$). All 3 groups showed greater Heschl's gyrus volume on the left (hemisphere: $F_{2,48} = 10.61$, $P = .002$). Although a separate 1-way ANOVA indicated that left Heschl's volume was selectively reduced in schizophrenia (Table 2), the group \times side interaction was not significant ($P > .4$).

Total (left+right) planum temporale volumes were not significantly different between groups (group: $P > .29$), but groups showed significantly different volume asymmetries (group \times hemisphere: $F_{2,48} = 6.93$, $P = .002$). Post hoc tests showed that the schizophrenia group had a significantly smaller left planum temporale volume (0.124%) than both the affective psychosis (0.157%) and control (0.157%) groups.

For the anterior amygdala-hippocampus (predominantly amygdala), there were no significant relative volume differences between groups ($P > .23$). Groups showed larger total anterior amygdala-hippocampus relative volumes on the right (hemisphere: $F_{1,48} = 56.24$, $P < .001$). For posterior amygdala-hippocampus (predominantly hippocampus) volumes, groups were not significantly different (group: $F_{2,48} = 2.60$, $P = .085$). No hippocampal volume asymmetry was present in any group.

For the parahippocampal gyrus, data were missing because of technical problems from 4 patients with affective psychosis and 3 control subjects. Groups were not significantly different in relative parahippocampal gyrus volume ($P > .22$), nor were there any effects of hemisphere ($P > .49$) or any interaction between group and hemisphere ($P > .44$).

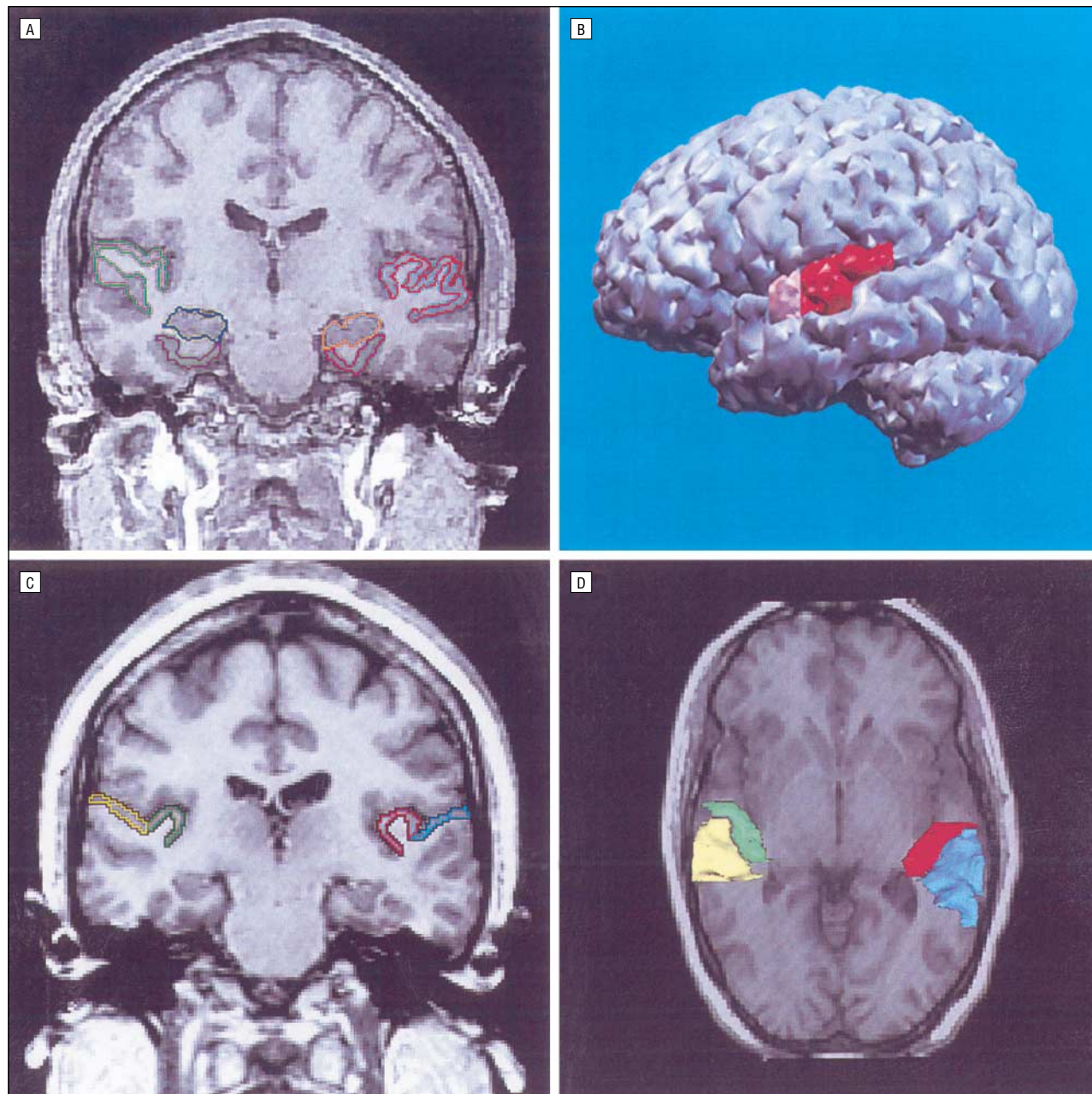


Figure 1. Specific regions of interest examined in this study. A, Coronal slice (1.5 mm) of the temporal lobe of a normal comparison subject. The regions of interest illustrated are the gray matter of the superior temporal gyrus (subject left, red; subject right, green); more medially, the amygdala-hippocampal complex is shown (left, orange; right, blue) with the parahippocampal gyrus underneath (left, pink; right, purple). B, Left lateral view of 3-dimensional reconstructions of the cortical surface with anterior superior temporal gyrus (light pink) and posterior superior temporal gyrus (red). C, Coronal slice (1.5 mm) through the temporal lobe of a normal control subject. The regions of interest here are the gray matter of Heschl's gyrus (HG) (red on subject left and green on subject right) and the gray matter of planum temporale (PT) (labeled yellow on subject right and blue on subject left). D, Three-dimensional reconstruction of HG and PT superimposed on an axial magnetic resonance slice. Anterior is top; HG is red on subject left and green on subject right; and PT is blue on subject left and yellow on subject right.

CORRELATION OF P300 AND GRAY MATTER VOLUMES

P300 amplitude was associated with the volume of several ROI (**Table 3**). The anterior STG, although not reduced in volume in any of the groups, showed significant correlations with P300 amplitude in the patient samples, but not in control subjects. These correlations did not, however, show specificity with left temporal P300 amplitudes. Instead, anterior STG-P300 correla-

tions were more diffuse and included frontal and contralateral sites.

Left posterior STG volume in the first-episode schizophrenia group was significantly correlated with P300 amplitude at the midtemporal site, T3 (**Figure 3**). The maps (Figure 3B) show that the volume of the left posterior STG in the first-episode schizophrenia group was correlated with P300 across the left temporal scalp area, precisely the areas where P300 showed regionally specific reduction in those patients. (This correlation was not

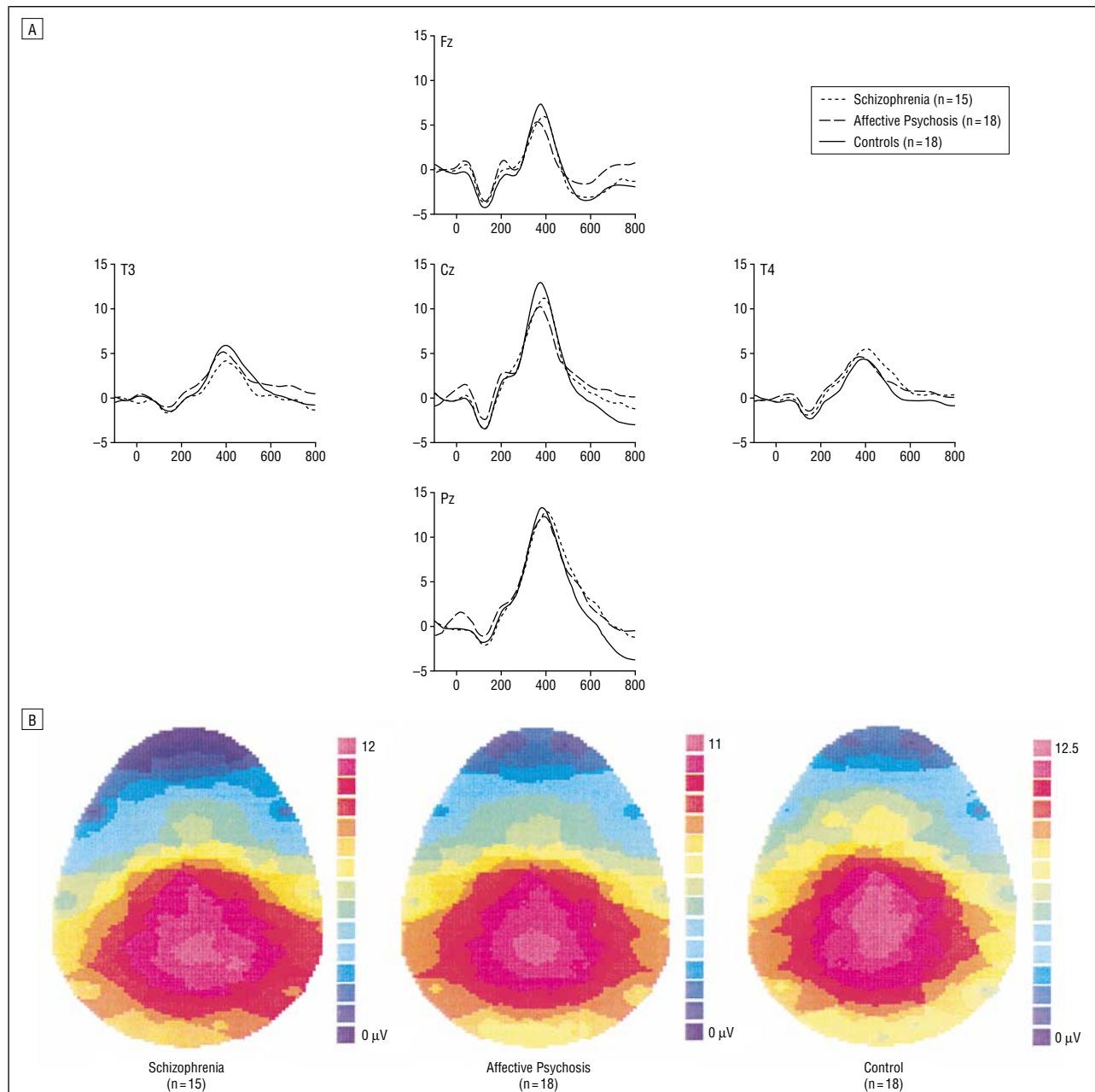


Figure 2. P300 to target tones. A, Event-related potential waveforms along the sagittal and coronal midlines. Note the relatively large P300 in all groups at the frontal central and posterior sites. By contrast, the schizophrenia group shows a reduction at T3, resulting in a significantly asymmetric P300. B, Topography of P300 across the surface of the scalp. Note the regionally selective reduction of P300 voltage in patients with schizophrenia from sites overlying the left temporal lobe.

driven by those schizophrenic patients with the smallest volumes. A median split on the schizophrenia group based on the absolute volume of the STG [6.34 mL] showed no significant differences in P300 amplitude at temporal sites [$P > .44$], and both subsamples were reduced over the left temporal lobe [side: $F_{1,13} = 8.09$, $P = .01$]. The magnitude of the left posterior STG volume–P300 amplitude correlations progressively diminished with greater distance away from the left temporal scalp region. In contrast, there were no significant correlations between left posterior STG volumes and P300 in the other 2 groups. Right posterior STG volumes showed

no correlation with P300 amplitude anywhere on the scalp for any group.

A correlation between left Heschl's gyrus volume in the first-episode schizophrenia group and P300 amplitude at T3 was present ($r = .53$, $P = .047$; **Figure 4**). However, there was little specificity of the correlations for the left temporal site, since moderate r values were present over much of the scalp and there was a significant correlation at FTC2, a site overlying right frontal and temporal lobes ($r = .54$, $P = .04$). As predicted, left Heschl's gyrus volume did not significantly correlate with P300 amplitude in the other 2 groups.

Table 2. Relative Volumes of Regions of Interest*

Region of Interest	Hemisphere	Mean (SD)			ANOVA	1-Way F	1-Way P	Post Hoc
		Schizophrenia (n = 15)	Affective Psychosis (n = 18)	Control (n = 18)				
ASTG	Left	0.096 (0.027)	0.098 (0.047)	0.100 (0.22)	H	0.04	.96	
	Right	0.127 (0.031)	0.123 (0.039)	0.128 (0.032)		0.14	.87	
PSTG	Left	0.406 (0.055)	0.456 (0.070)	0.480 (0.047)	G×H	6.77	.003	SZ<AFF, CON
	Right	0.436 (0.065)	0.444 (0.073)	0.460 (0.069)		0.51	.60	
Heschl's gyrus	Left	0.092 (0.019)	0.123 (0.022)	0.112 (0.027)	G, H	7.71	.001	SZ<AFF, CON
	Right	0.084 (0.020)	0.100 (0.020)	0.094 (0.034)		1.59	.21	
Planum temporale	Left	0.124 (0.024)	0.157 (0.040)	0.157 (0.036)	H, G×H	4.67	.014	SZ<AFF, CON
	Right	0.129 (0.027)	0.124 (0.032)	0.117 (0.023)		0.84	.44	
Amygdala	Left	0.130 (0.029)	0.116 (0.028)	0.127 (0.023)	H	1.26	.29	
	Right	0.148 (0.032)	0.134 (0.022)	0.144 (0.022)		1.41	.25	
Hippocampus	Left	0.239 (0.029)	0.250 (0.039)	0.265 (0.023)		2.65	.08	
	Right	0.242 (0.027)	0.253 (0.039)	0.264 (0.023)		2.14	.13	
PHG	Left	0.145 (0.029)	0.131 (0.024)	0.139 (0.025)		1.05	.36	
	Right	0.145 (0.026)	0.130 (0.024)	0.147 (0.027)		1.82	.17	

*For analysis of variance (ANOVA), G indicates group; H₂, hemisphere; and G×H, group × hemisphere interaction. Presence of factor symbol indicates significant effect in the main ANOVA with $P < .05$, $df = 2,48$ for G, G×H; 1,48 for H. One-way indicates comparison for each structure among the 3 groups separately for each side. Post hoc indicates the results of Tukey honestly significant difference testing in the case of significance in the 1-way. ASTG indicates anterior superior temporal gyrus; PSTG, posterior superior temporal gyrus; amygdala, anterior portion of hippocampus-amygdala complex; hippocampus, anterior portion of hippocampus-amygdala complex; PHG, parahippocampal gyrus; SZ, schizophrenia; AFF, affective psychosis; and CON, control. Degrees of freedom for all 1-way ANOVAs were 2,48, except for PHG, which were 2,41.

Although the left planum temporale volume and left midtemporal P300 association was only marginally significant according to our conservative 2-tailed probability ($r = .51, P = .053$), the left planum temporale volume showed a regionally specific association with the P300 deficit in the schizophrenia group (Figure 5). The correlation topography in the schizophrenia group between P300 amplitude and left planum temporale approximated that of the left posterior STG (Figure 3), including a maximum in the left temporal region and a progressively diminishing correlation pattern at sites progressively more distant from the left temporal maximum. The degree of the left temporal P300 correlations with the left planum temporale volume was smaller than with the left posterior STG volume, although not statistically significantly different. Note further that the right planum (not reduced in MR imaging volume) did not show significant correlations with P300 amplitude in first-episode schizophrenia. In the first-episode affective psychosis group, neither left nor right planum volume was significantly correlated with P300 amplitude. In control subjects, both left and right planum volumes showed some left and central electrode correlations with P300, but without the degree of left temporal P300 specificity of correlation in schizophrenia where there was a pathological reduction of volume.

There were no associations between the volume of medial temporal lobe structures and P300 amplitude anywhere on the scalp in either first-episode patient group. In control subjects, there were some significant but isolated correlations between P300 amplitude at posterior sites and medial temporal lobe structures.

COMMENT

Patients with first-episode (first-hospitalization) schizophrenia showed left-lateralized P300 amplitude reduc-

tion and left-lateralized reductions of posterior STG and planum temporale gray matter. In addition, these patients with first-episode schizophrenia demonstrated a topographically specific association between the left temporal scalp region P300 voltage reduction and reduced MR imaging gray matter volume of the posterior portion of the left superior temporal gyrus and, to a lesser degree, the left planum temporale. In contrast, neither patients with first-episode affective psychosis nor control subjects showed the left temporal scalp region P300 amplitude reduction, lateralized temporal lobe ROI volume reductions, or any regionally specific correlation between P300 left midtemporal amplitude and any ROI.

These data and previous data from our group⁴³ link functional abnormalities of P300 with anatomic abnormalities in schizophrenia and highlight the importance of left posterior STG gray matter in the production of the left temporal P300 deficit in schizophrenia. It is likely that the left-lateralized reductions in the P300 are due to reductions of gray matter in the underlying posterior temporal lobe generator. The left-lateralized P300 amplitude reduction in patients with first-episode schizophrenia replicated a previous report from our group.¹⁶ (The asymmetry persisted with removal of the 4 common patients with schizophrenia.) Interrelated regionally restricted P300 voltage abnormality and reduction in left posterior STG and planum temporale volume appear selective for schizophrenia and present at first hospitalization, even in the presence of relatively large and normal midline P300 amplitudes.

Recent reviews^{41,42,57} showed that 80% of MR imaging studies found left STG volume reduction in schizophrenia, the highest percentage of any cortical ROI. Left STG gray matter showed even more specificity, with volume reduction present in 100% of all studies. Since gray matter is the source of P300, any study not differentiat-

Table 3. Significant Correlations Between MR Imaging ROI and P300 (Pearson *r*)*

ROI	Schizophrenia (n = 15)		Affective Psychosis (n = 18)		Control (n = 18)	
	Site	<i>r</i> , <i>P</i>	Site	<i>r</i> , <i>P</i>	Site	<i>r</i> , <i>P</i>
LPSTG	T3	0.52, .047				
	T5	0.52, .048				
	TCP1	0.50, .055				
LHESCHL	T3	0.53, .044				
	FTC2	0.54, .039				
LPLANUM	T3	0.51, .053			T5	0.61, .007
					P3	0.48, .042
					P01	0.54, .022
LHIPP					T5	0.64, .004
					P01	0.48, .043
RHIPP					TCP2	0.47, .046
					P3	0.51, .03
LASTG	F3	0.52, .047	FTC1	0.48, .045		
	F4	0.60, .018	T4	0.48, .044		
	FTC2	0.69, .005	T6	0.51, .032		
	C3	0.55, .035				
	T4	0.72, .003				
	TCP1	0.58, .024				
RASTG	Fz	0.77, .001	FTC1	0.66, .003		
	F3	0.80, .001	T3	0.53, .023		
	F4	0.78, .001	C3	0.58, .011		
	FTC1	0.80, .001	T4	0.49, .04		
	FTC2	0.77, .001	TCP1	0.62, .006		
	T3	0.70, .004	TCP2	0.47, .049		
	C3	0.76, .001	T5	0.61, .008		
	Cz	-0.70, .003	P3	0.54, .022		
	C4	0.64, .01	T6	0.73, .001		
	T4	0.62, .014				
	TCP1	0.71, .003				
	CP1	0.70, .004				
	CP2	0.61, .015				
	P3	0.53, .042				
Pz	0.53, .044					

**P* values are 2-tailed. Only significant 2-tailed correlations are included (*P* < .05), with the exception of the left planum temporale, where a correlation with left temporal P300 was predicted. Correlations are between absolute gray matter volume and peak P300 amplitude at each specific site. Regions of interest (ROI) with specific associations with left temporal P300 values are presented first. Slight differences in *P* values for a given *r* value are due to rounding differences. LPSTG indicates left posterior superior temporal gyrus; LHESCHL, left Heschl's gyrus; LPLANUM, left planum temporale; LHIPP, left hippocampus; RHIPP, right hippocampus; LASTG, left anterior superior temporal gyrus; and RASTG, right anterior superior temporal gyrus.

ing STG gray and white matter might not show this STG-P300 correlation.^{58,59} Ford⁶⁰ found positive correlations between central P300 amplitude and overall cortical gray matter volume; the modeling by Menon et al⁶¹ of P300 dipole sources in healthy subjects as including sources in temporoparietal cortex appears compatible with our results.

Gray matter volume reductions of posterior STG and planum temporale lateralized to the left are congruent with previous demonstrations of reversed planum temporale asymmetry in schizophrenia, particularly as planum temporale may contain cortical circuits crucial for language comprehension.^{45,46} Of particular relevance in patients with schizophrenia was Bruder and colleagues' report⁶² of the lack of the normal right ear (left hemisphere) dominance for syllable perception in a dichotic listening task, a finding linked to a reduced N2 and P300 left temporal area amplitude. It is enticing to speculate

that the left planum temporale contains neural circuits fundamental to the thought disorder of schizophrenia and that the abnormalities observed in both the MR imaging volume and P300 function may relate to underlying circuit abnormalities in this cortical substrate of language and auditory processing.

Limitations of the present study include the fact that extratemporal ROI were not examined. It is possible that other ROI, especially frontal and parietal, might show correlations with P300. For example, parietal MR imaging right supramarginal gyrus volumes in patients with chronic schizophrenia⁶³ showed significant positive correlations (*r* > .51, *P* ≤ .05) with left and right centroparietal P300 voltages. However, there were no significant correlations with temporal electrodes, suggesting that this region exerted its main effect centrally and paracentrally. A further limitation is that the current samples do not contain enough women to examine sex effects.

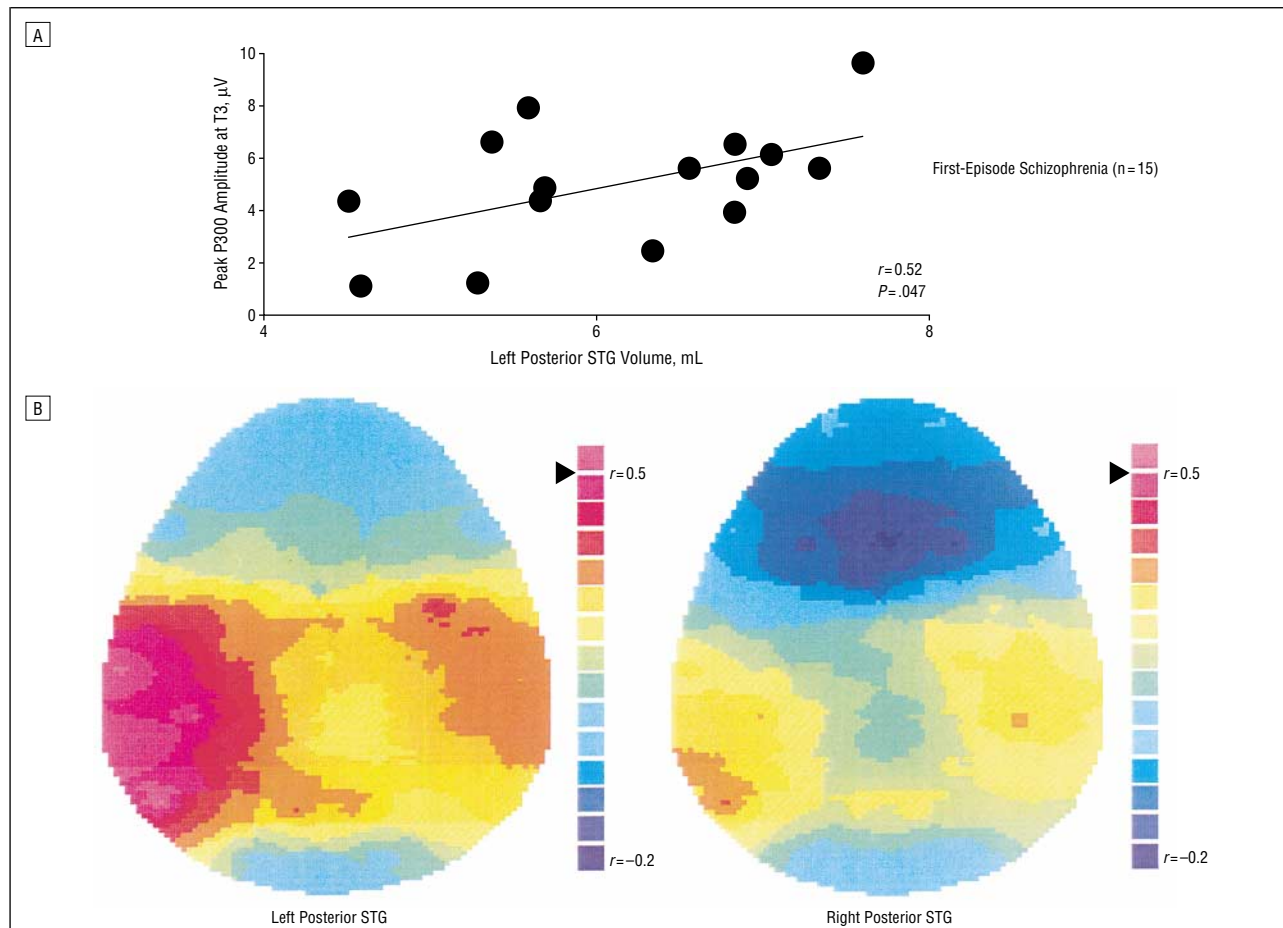


Figure 3. Pearson correlation between posterior superior temporal gyrus (STG) and P300. A, The amplitude of P300 recorded from the T3 site, overlying the middle of the temporal lobe, is significantly correlated with the size of the left posterior STG gray matter. B, Topography of the color-coded magnitude of Pearson correlation coefficients between left and right posterior STG and P300 across the whole surface of the scalp. Arrow on color code bar indicates the $P < .05$ level of statistical significance. Note that the gray matter volume of the left posterior STG shows a regionally selective association with P300 amplitude, showing a strong correlation with P300 recorded over the left temporal lobe, precisely the area where P300 is abnormally small in schizophrenia. By contrast, the gray matter volume of the right posterior STG is not significantly correlated with P300 amplitude anywhere across the surface of the scalp.

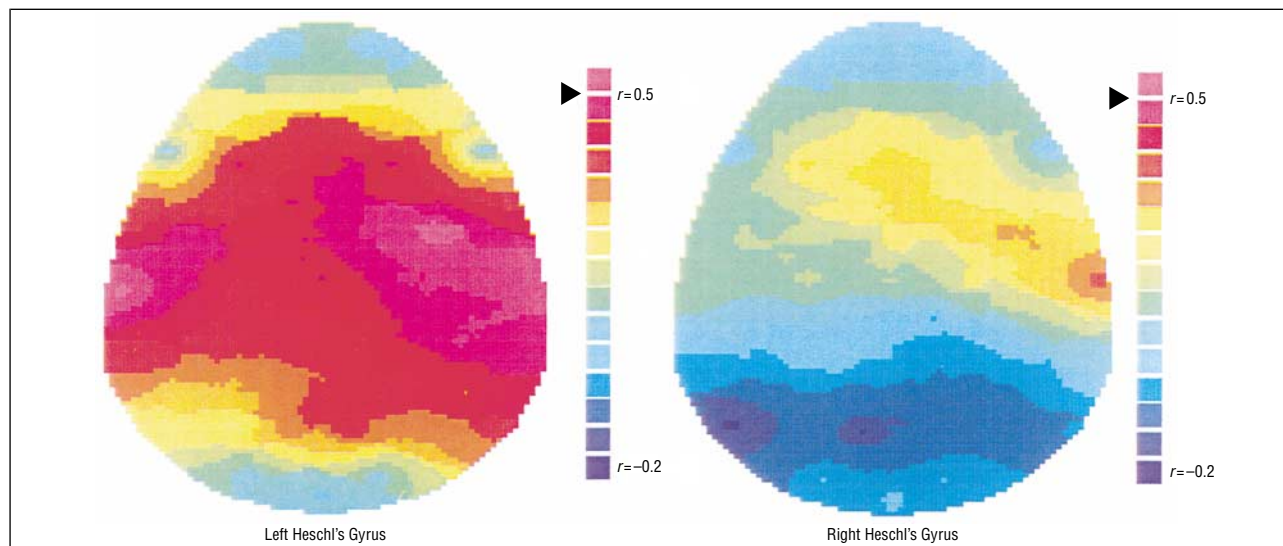


Figure 4. Topography of the correlation between left and right Heschl's gyri and P300. See "Correlation of P300 and Gray Matter Volumes" subsection of the "Results" section for description.

In addition, it might be argued that the left temporal P300 and cortical structural associations reflect only a subset of the associations found in these data. How-

ever, we again emphasize that a crucial factor for interpretation must be the left temporal P300 regional selectivity of the association, which was satisfied only by those

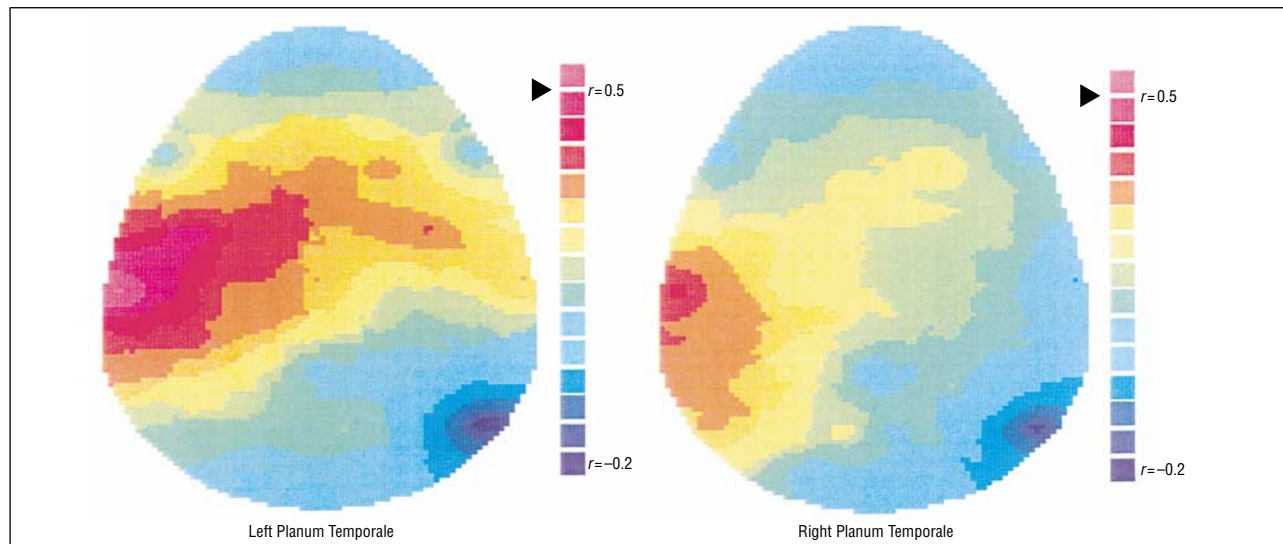


Figure 5. Topography of the correlation between left and right planum temporale and P300. See “Correlation of P300 and Gray Matter Volumes” subsection of the “Results” section for description.

associations. This study used the classic method of correlating an anatomic abnormality (“lesion”) in a disorder with functional information, such as that used by Knight et al³⁵ with ERP measures, a host of investigators with neuropsychological data,^{64,65} and the original analysis of functional data dating back to Dax (1836; as reported by Kolb and Wishaw⁶⁶), Broca,⁶⁷ and Wernicke⁶⁸ localizing language and speech functions to the left hemisphere on the basis of postmortem lesion data. We cannot rule out the possibility that the correlation might be from some (unknown) third abnormality, although this hypothetical possibility appears remote on the basis of our knowledge of structural changes and P300 sources. In summary, the present data suggest that schizophrenia involves abnormalities in the structure of the left posterior STG and a functional abnormality, the left temporal P300 scalp deficit, which is itself associated with the reduced volume of the left posterior STG. Furthermore, these interrelated structural and functional abnormalities are present at the first hospitalization in patients with schizophrenia and are specific to schizophrenia rather than related to psychotic features in general. Future work will include longitudinal assessments to determine whether pathological changes over time are observed in structural or functional measures and, if so, how these measures interrelate. An additional goal will be to relate these brain measures to the clinical symptoms of these patients with first-episode schizophrenia so as to link the basic physiologic and anatomic measures to clinical features.

Submitted for publication November 28, 2000; final revision received June 13, 2001; accepted June 26, 2001.

This work was supported in part by MERIT and Schizophrenia Center Awards from the Department of Veterans Affairs Medical Research Service, Washington, DC; grants 40799 (Dr McCarley), 01110 (Dr Shenton), and 50740 (Dr Shenton) from the National Institute of Mental Health, Rockville, Md; and the National Alliance for Research in Schizophrenia and Depression, Great Neck, NY (Dr Salisbury).

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