Increased Temporal Lobe Glucose Use in Chronic Schizophrenic Patients

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Temporal lobe glucose metabolic rate was assessed in 21 off-medication patients with schizophrenia and 19 normal controls by positron emission tomography with ^{18}F-deoxyglucose. Patients with schizophrenia had significantly greater metabolic activity in the left than the right anterior temporal lobe, and the extent of this lateralization was in proportion to the severity of psychopathology.

Introduction

Since the late 19th century when Broca, Wernicke, Brodmann, and others first mapped certain cortical areas of the brain and attributed to them specific functions, the dominant temporal lobe has been considered to be central to communicative aspects of behavior and auditory integration (Wernicke 1874; Broca 1878; Brodmann 1909). Numerous reports relate temporal lobe lesions (i.e., tumor, stroke, and trauma) to behavioral and perceptual disturbances, such as visual or auditory hallucinations, disturbances in sense of self and reality, and intense episodic fear and despair—all symptoms associated with the schizophrenic disorders (Penfield 1954). Moreover, in one of the most extensive studies of head-injured individuals, at a 25-year follow-up, 14% had at least one episode of a schizophrenia-like illness subsequent to the head injury (Hillbom 1960). Psychosis-like disorders were more frequent in cases with left-sided lesions than in those with right-sided lesions, and 41% of all psychoses uncovered were associated with temporal lobe lesions.

Epidemiological surveys of patients with temporal lobe epilepsy have found a higher incidence of schizophrenia-like symptoms among those individuals than in the general population, and the diagnoses are occasionally confused on clinical treatment units (Rodin et al. 1956; Slater et al. 1963; Abenson 1970; Flor-Henry 1976; Perez and Trimble 1980). In addition, electroencephalographic (EEG) studies show an increased incidence of paroxysmal activity, spikes, and other abnormalities over the temporal lobes in medication-

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free schizophrenic patients who had no symptoms of a seizure disorder (Hill 1952; Ervin et al. 1955; Small et al. 1964; Tucker et al. 1965; Abenson 1970). Recently, reports of diminished size of the temporal lobe structures, especially parahippocampal gyrus, and cell disorientation in the hippocampus have been reported (Kovelman and Scheibel 1984; Bogerts et al. 1985; Brown et al. 1986; Jacob and Beckmann 1986; see also review by Roberts and Crow 1987). Within the temporal lobe, dopamine was found to be increased in the left, but not the right, amygdala (Reynolds 1983).

Cerebral blood flow studies have made systematic evaluation of the cortical surface possible. Ingvar and Franzen (1974), using the ^{133}Xe clearance method for measurement of cerebral blood flow, found a relative decrease in frontal/posterior flow in chronic schizophrenics, but their topographic maps do not reveal a temporal lobe difference between schizophrenics and normals. Decreased flow uniformly across regions was observed by Mubrin et al. (1982); studies by Mathew et al. (1981), Gur et al. (1983, 1985), and Ariel et al. (1982) do not present data specifically for the temporal flow probes.

Positron emission tomography (PET) studies (Phelps et al. 1979; Brownell et al. 1982) allow us to quantify rates of regional glucose metabolism at a relatively higher resolution in both the cortical surface and within the temporal lobe. We found higher relative glucose metabolic rates for the superior temporal region (L2, infraventricular slice) in resting schizophrenics. This sector had higher values on the left in schizophrenics and right in normals in preliminary analyses of seven patients receiving right forearm somatosensory stimulation (Buchsbaum et al. 1983). An asymmetry in the same direction for the mid-posterior sectors was seen in the patients of Sheppard et al. (1983) under resting conditions. Jernigan et al. (1985) showed higher relative temporal lobe metabolic rates in patients performing a vigilance task. In a preliminary analysis of the patients reported here, Post et al. (1987) found patients with schizophrenia to have increased metabolic rates in the temporal pole. Kishimoto et al. (1987) found no change in the temporal lobe of patients with schizophrenia. However, Wolkin et al. (1985) showed lower metabolic rates, both absolute and relative, in right and left temporal cortex, and Gur et al. (1987) showed lower absolute levels on the right and lower absolute and relative levels on the left (our computation from their Table 2, $t = 1.72$, $p < 0.10$). Cohen et al. (1987) also showed decreased absolute metabolic rates in the anterior temporal lobe in patients doing an auditory vigilance task. Other investigators have not provided specific data on the temporal lobe in their reports (Widen et al. 1983; Farkas et al. 1984). In our previous reports, we have examined large sectors of the cortical surface with emphasis on frontal/occipital differences (Buchsbaum et al. 1982a,b, 1984). In this report, we examine the temporal lobe in detail, using four different assessment techniques and the patient sample previously reported (Buchsbaum et al. 1984; Post et al. 1987).

Methods

Subjects

The patient sample comprised 21 patients (15 men and 6 women; mean age ± SD = 28.4 ± 7 years) who were either hospitalized on several research units of the National Institute of Mental Health (n = 12) or were being followed as outpatients in the Washington, D.C. area (DeLisi et al. 1985). Patients from all sources met DSM-III criteria for schizophrenia as assessed by structured interviews. In addition, a clinical interview of all patients was completed by the senior author and the diagnosis confirmed; clinical

description and initial analyses of patient/normal differences are reported elsewhere (Buchsbaum et al. 1984). All patients were free of medication for a minimum of 15 days (mean of 39.2 ± 28 days; median 34 days; only 6 less than 4 weeks). On the day of the scan, patients were interviewed by a psychiatrist (L.E.D.), who scored an NIMH-modified, 26-item version (Dr. L. Bigelow at St. Elizabeths Hospital, Washington, D.C.) of the Brief Psychiatric Rating Scale (BPRS) based on the patient's behavior during the interview and experimental procedure. This psychiatrist did not have access to scan information.

Nineteen normal volunteers (mean age 31 ± 11, 13 men and 6 women) participated. Subjects were screened with a physical examination, laboratory chemistry, and psychiatric interview. Those with a family history of mental illness, medical problems, head trauma, or drug or alcohol abuse were excluded. One schizophrenic patient and two controls were left-handed. All subjects had normal plasma glucose.

Scan Procedure

Each subject was administered 3–5 mCi [^{18}F]2-deoxy-*D*-glucose (FDG) in a sound attenuated, darkened room. Each subject remained in a sitting position with his eyes closed for 30 min after the injection. During this time, somatosensory stimulation was applied to the right forearm for the purpose of activating the frontal lobes (Buchsbaum et al. 1983) and providing a standard situation for each subject response. The stimulation consisted of 1/sec shocks, ranging in intensity from barely perceptible to unpleasant (2–23 mA), presented in random order, each lasting 1 msec at a 1/sec rate. Six to seven sets of 256 stimuli were administered during the 30-min period postinjection using a standard evoked potential paradigm described elsewhere (Buchsbaum et al. 1981). The patient was then scanned with an Ortec ECAT II and 7–8 slices were obtained at 12–14-mm intervals parallel to the canthomeatal (CM) line.

Data Analysis

FDG use was quantified according to the model of Sokoloff et al. (1977) using our adaptation of a program developed by Sokoloff. Kinetic constants (K1, K2, K3) and the lumped constant from Phelps et al. (1979) were entered into a computerized program for conversion of each pixel of each slice from raw counts to rate of glucose use in micromoles per 100 grams tissue per minute. We followed the guidelines of Huang et al. (1980) and confined our scanning as much as possible to the 50–120-min postinjection period during which the three-constant model is accurate and percent error in metabolic rate due to inaccurate rate constants is minimized. Mean interval between FDG injection and scanning in normals and schizophrenics was equal.

Scan Slice Selection and Region of Interest Measurement

For the present analysis, three sets of slices and methods were selected to compare alternative strategies of data analysis. The analyses were done separately at the National Institute of Mental Health and at the University of California, Irvine.

For the temporal lobe analysis, we selected a slice best delineating the temporal lobe from other cerebral areas in a standard atlas (Matsui and Hirano 1978). The temporal poles were always separate from frontal lobes and cerebellar regions in this slice (Figure 1). It was no. 12 in the atlas, from the top down, and its height was 14% of total head

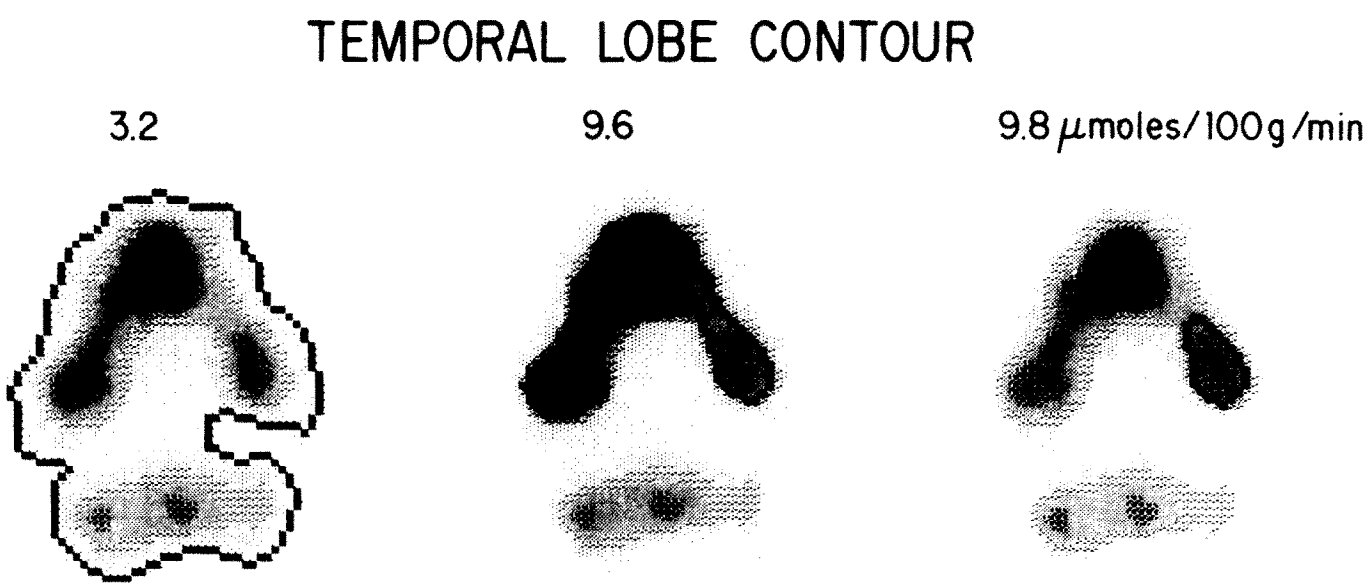

Figure 1. Example of technique for outlining temporal lobe. Contour threshold at 3.2 μmol glucose/100 g/min outlines whole slice with small invagination on right petrous bone. Raising threshold to 9.6 outlines frontal and temporal cortex. Progressing steps of 0.2 μmol are then used until only the temporal lobe is outlined; this occurs on the next step at 9.8. This outline is then selected, and mean glucose metabolic rate within is calculated.

height above the CM line. Seventeen patients (12 men and 5 women) and 18 normals had such a slice. A program with a boundary-finding algorithm (see Buchsbaum et al. 1984) was used to outline the temporal poles. The algorithm searched for the lowest glucose metabolic rate with which a boundary surrounding the temporal pole could be formed, lower values forming an outline that also included the frontal lobe (Figure 1). Within the outline, the mean and the maximum glucose values were calculated. Left/right ratios were also formed.

For a region of interest analysis, we selected the 21% slice in Matsui and Hirano (1978) as our prototype. This slice has midbrain at its center and is circular. Slices showing the temporal poles as separate regions were rejected as too low. The image from this atlas was photographed, digitized, filtered by replacement of each pixel by the average of the surrounding 7 × 7 pixel square array, a moving average, and stored for reference. This was done to allow the boundary-finding algorithm to draw a smooth contour similar to the one drawn on the PET images. With the same boundary-finding algorithm, the image was outlined and the vertical meridian fitted by linear regression using least-squares to the midpoints of line segments joining the right and left edges for each pixel row of the image. This line was bisected and a horizontal 90° meridian calculated. Then, under cursor control, a 3 × 3 pixel box (0.3 cm^3 voxel) was placed in the center of the superior, middle, and inferior temporal gyrus, and the superior and inferior hippocampal gyrus, as identified by Matsui and Hirano (Figure 2). The proportional locations of these boxes on the anteroposterior (AP) and lateral directions were then transferred automatically to the PET slices and mean glucose metabolic rates calculated for the left- and right-sided boxes (right side as mirror image of left around the vertical meridian) (Figure 3). PET studies (normals and schizophrenics) were reviewed without knowledge of diagnosis, and the slices most consistent with 21% plate in the atlas were selected. The mean slice height in subjects selected as matching the atlas was actually 24.6% (32 mm) above the CM line. Three schizophrenics and one normal had no slice judged as sufficiently matching the atlas plate—the slice images in these subjects passed from one clearly showing basal ganglia to one showing only the temporal poles (leaving 18 patients and 18 volunteers in the region of interest analysis). Next, the entire slice was outlined using a computer algorithm, as in Buchsbaum et al. (1984). Analysis was carried out on values of glucose metabolic rate in micromoles per 100 grams per minute and on glucose metabolic rate/mean glucose metabolic rate in whole slice.

For the peel analysis, we selected the data from the same 29% slice (35 mm) (Figure 4) used in our earlier analyses (Buchsbaum et al. 1982b). The slices were outlined using the same boundary-finding algorithm (set at 50% of maximum slice glucose, a value that produces a whole head oval). Following the fitting of meridians as described earlier, an 8-pixel thick radial scan was obtained, as shown in Figure 5. As with the other measures, left/right ratios and correlations with absolute and relative glucose use values were calculated. Data for the posterior temporal (L2 and L3 in Buchsbaum 1982b, 1984) was used. A volume of about 30–40 cm^3 was obtained.

Statistical Analysis

The data consist of glucose metabolic rates obtained on the left and right sides of the brain, from regions arranged in an anteroposterior sequence, in normals and schizophrenics. This arrangement lends itself to a three-way Analysis of Variance (ANOVA) (BMDP 2V; Dixon 1982), with hemisphere and anteroposterior (AP) position as repeated measures

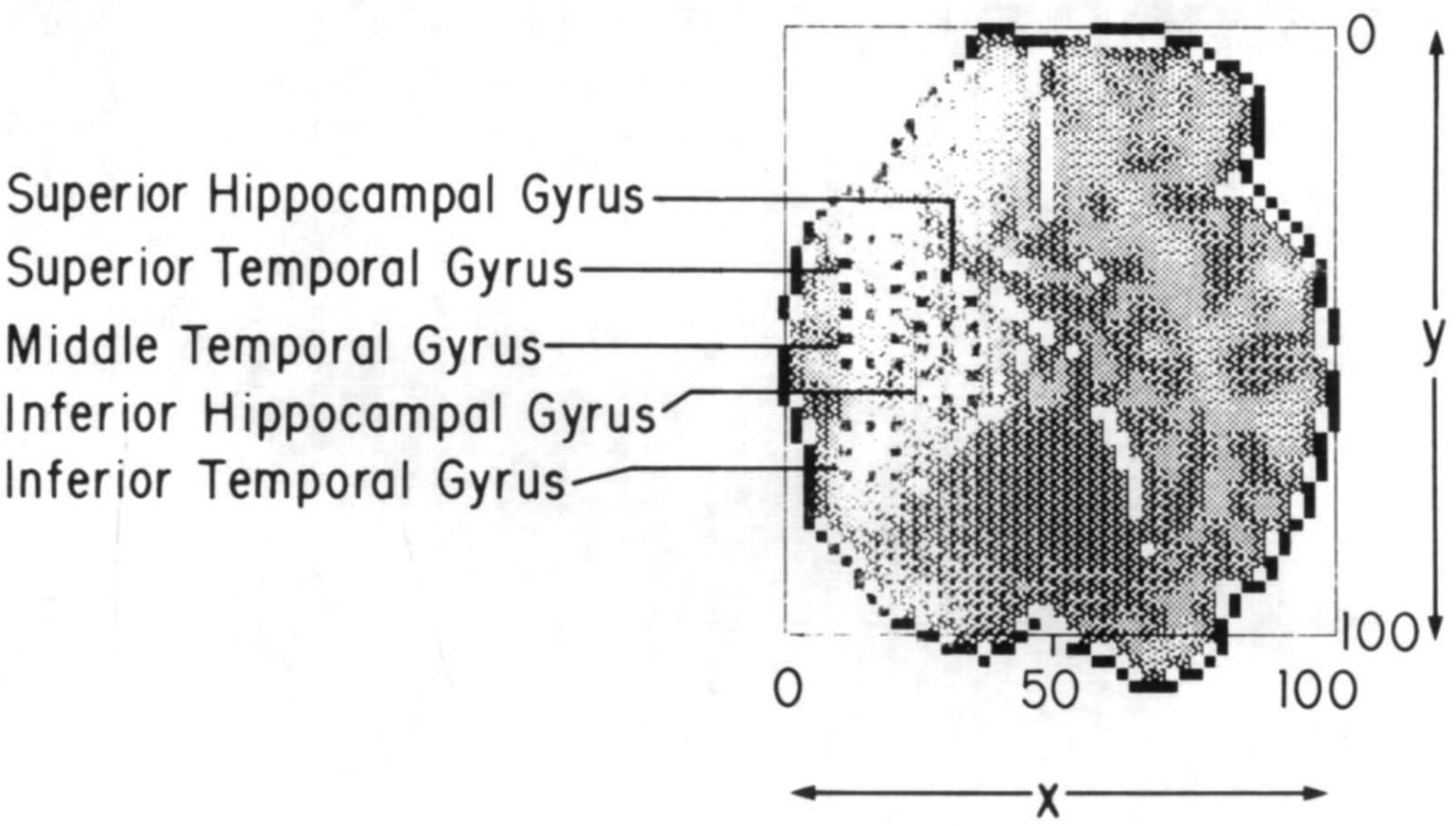

Figure 2. Digitized photograph of the human brain (Matsui-Hirano atlas) slice 11, 21% above the CM line illustrating box analysis. The brain image is outlined by the same computer algorithm used on actual PET images. Each box superimposed on the image has an X-coordinate (horizontal) and a Y-coordinate (vertical) expressed as a percent that fits the outline of the image, with the X-coordinate determined on the left and symmetrical about the midline of the brain. In the analysis, a box is composed of a 3 × 3 pixel grid with each pixel equal to 2.5 mm, thus giving an approximate area of 56 mm^2 per box. The boxes' positions are identified on the photographic image and the percent X and Y-coordinates stored and automatically applied to all chosen PET glucose images. The locations for the areas were: superior temporal gyrus 16.3, 39.6; superior hippocampal gyrus 30.2, 45.8; middle temporal gyrus 16.3, 52.1; inferior hippocampal gyrus 30.2, 58.3; inferior temporal gyrus 16.3, 70.8.

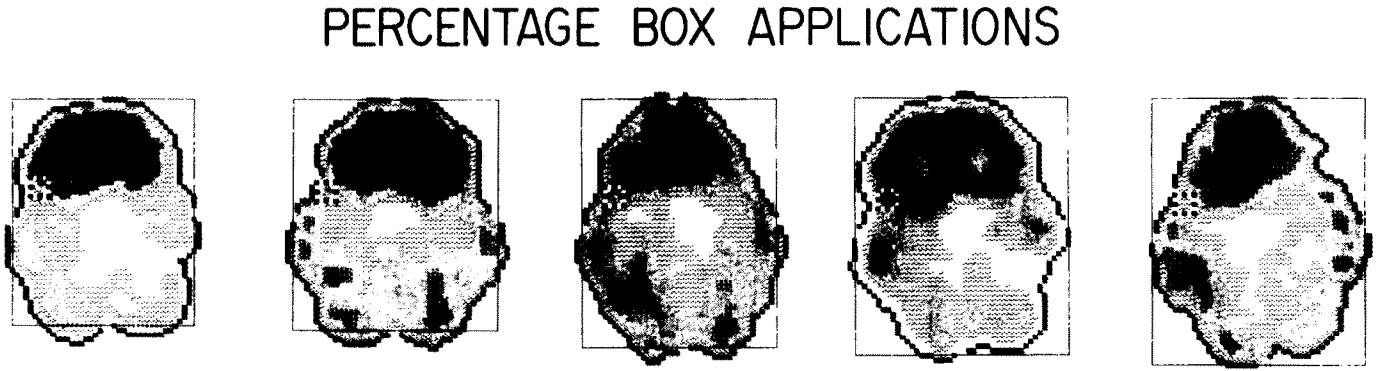

Figure 3. Application of superior temporal box to five typical individuals. Slice outline is generated by computer algorithm, slice maximum outside dimensions located, fine line outer box drawn, and 3 × 3 pixel box (heavy dotted box) located as percent X and percent Y of outside dimensions. The Y outside dimension is chosen at the midline so the tips of the occipital poles may extend over the posterior outside dimension line. This avoids biases to Y dimension caused by occipital pole variation in size or symmetry. Some variation in box placement can be seen, depending on whole slice shape. Note that the dividing line between frontal and temporal cortex cannot be unequivocally seen on a glucose metabolic rate image, and positioning the temporal box just posterior to the areas of high use in frontal cortex creates an unwarranted and possibly confounding bias—displacing the box to lower values. The percent placement avoids this bias and places the box at our best guess for the center of the temporal lobe.

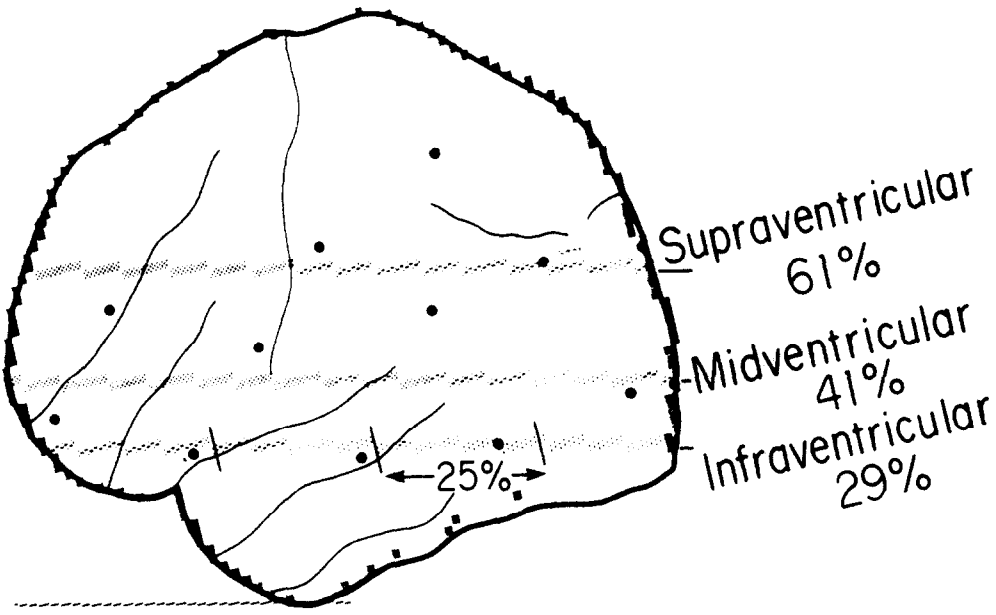

Figure 4. Hemisphere cortical peels are displayed on approximate equal area lateral brain outline (Buchsbaum et al. 1982c) with corresponding percentage of distance from canthomeatal (CM) line to top of head. Projection was developed from whole head coronal sections. PET slices are placed by conversion of vertical height above CM line to relative position on brain surface height. Each peel is divided into 4 sectors, numbered 1–4 from anterior to posterior for the ANOVA. Note correspondence between second and third 25% unit and temporal lobe for infraventricular slice.

factors and diagnostic group as an independent group factor. To avoid spurious inflation of degrees of freedom, the conservative or Huyhn-Feldt adjusted degrees of freedom are used. Where only one value for each hemisphere was obtained, or where a structure by hemisphere interaction was significant, *t*-tests were used to identify the effect.

In order to minimize type I errors from multiple tests on measurements in multiple brain areas, we used three strategies: repeated measures ANOVA with examination of group by structure interactions (one *F*-ratio rather than many *t*-tests), replication of results with the three regional assessment methods, and a prior selection of specific behavioral items for correlational analysis. These BPRS items were selected as salient to auditory hallucinations and related thought disorganization. Replication with higher resolution scans in a larger sample will provide more certain identification of the most important brain areas and behavioral symptoms.

Results

Temporal Lobe Outline Analysis

Schizophrenic patients had significantly increased mean and maximum metabolic rates of glucose use in both temporal lobes when compared with controls (Table 1). This was also true for the left temporal lobe using lobe/slice maximum ratios, and schizophrenics had significantly higher glucose use in the left than the right temporal lobe (paired *t*, $p < 0.03$). This asymmetry was not confirmed in normals. Pearson correlation coefficients

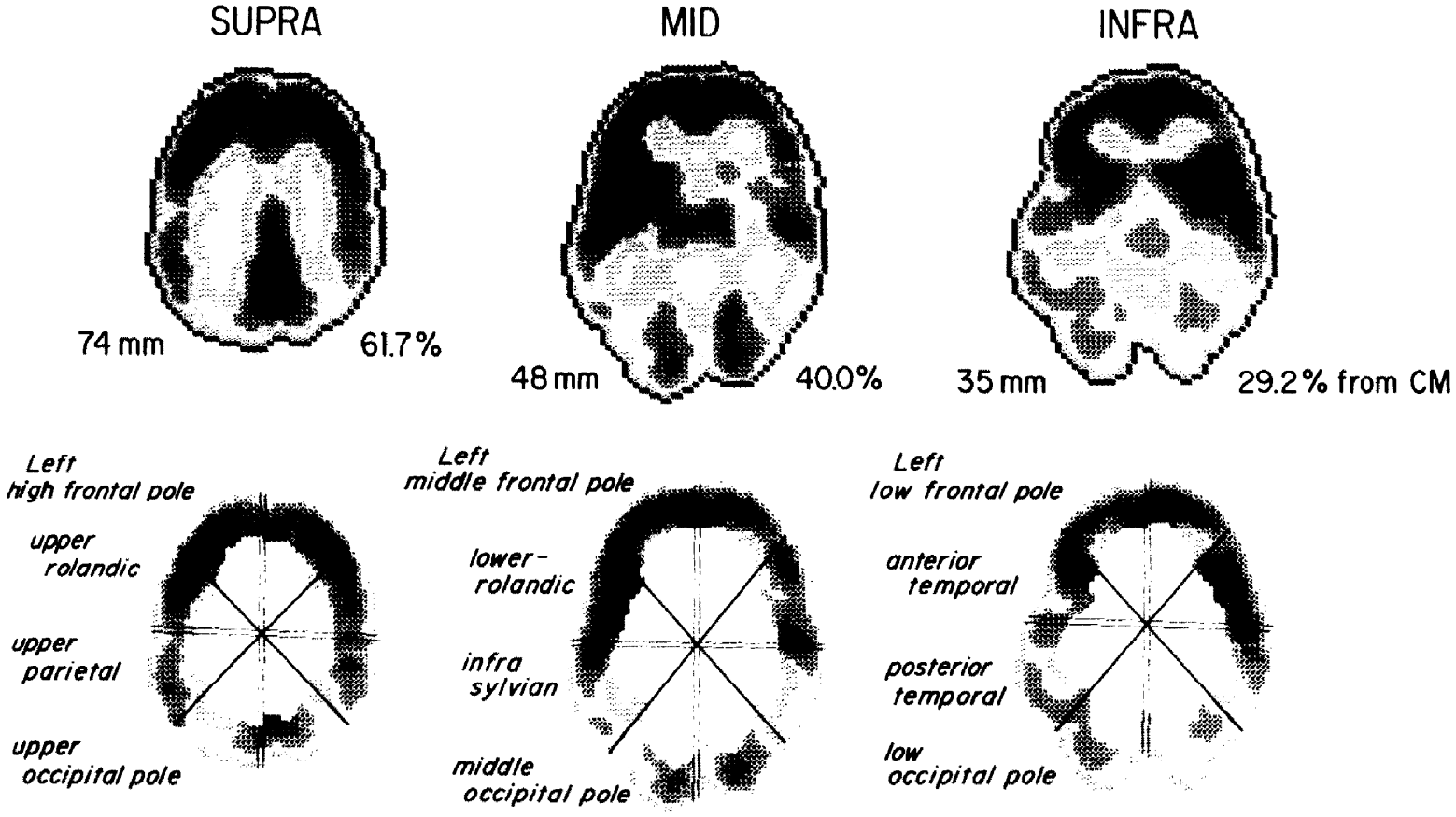

Figure 5. Peel technique shows infraventricular slice and identification of anterior (L2) and posterior temporal lobe sectors (L3) (right).

Table 1. Anterior Inferior Temporal Lobe Outline Analysis

	Left		Right		Left/right maximum
	Mean	Maximum	Mean	Maximum	
Schizophrenics (n = 17)	17.0 ± 3.4	19.8 ± 3.9	15.9 ± 3.8	18.8 ± 3.9	1.06 ± 0.12
Controls (n = 18)	12.9 ± 3.9	15.1 ± 4.2	13.0 ± 3.8	15.5 ± 4.1	0.98 ± 0.18
t	3.3	3.4	2.2	2.5	1.5
p	0.002	0.002	0.04	0.02	0.14

These sites were available on only 17 patients and 18 controls.

for all ratings on the BPRS were nonsignificant. Absolute glucose levels in micromoles glucose per 100 grams per minute or maximum levels on either left or right sides also showed no significant ($p < 0.05$) correlation with any BPRS ratings.

The three left-handed individuals (one schizophrenic and two normals) did not tend to have lower left/right ratios compared with right-handed individuals.

The maximum total slice activity for patients was 30.0 ± 6.4 μmol/100 g/min, which did not differ significantly from that for controls (24.11 ± 7.6).

Region of Interest Analysis

Results from the region of interest (ROI) analysis were generally similar (Table 2). First, schizophrenics and controls were compared with a three-way ANOVA with independent groups (normals, schizophrenics), hemisphere (left, right), and structures (superior, middle, inferior temporal gyrus, superior, inferior, hippocampal gyrus) as the three factors. Patients had higher glucose metabolic rate values (22.8 ± 6.0) than normals (18.5 ± 4.9) ($F = 6.90$; df = 1,35, $p < 0.02$). The left side (21.1) was higher than the right (20.0) across all structures and both diagnostic groups ($F = 9.43$, df = 1,35, $p < 0.005$). The asymmetry was least marked for the superior temporal box (left 22.4, right 22.1 μmol/100 g/min) and increased inferiorly (left minus right differences, superior temporal 0.3, superior hippocampus, 0.8, midtemporal 0.9, inferior hippocampus, 1.3, and inferior temporal 2.1). This was confirmed statistically with a hemisphere by structure interaction ($F = 2.75$, df = 3.20 and 112 by Huynh-

Table 2. Region of Interest Analysis

	Normal				Schizophrenic			
	Left		Right		Left		Right	
Area	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Ant. sup. temporal	20.3	5.5	20.1	4.9	24.5	5.3	24.3	5.7
Ant. sup. hippocampus	18.1	4.5	17.7	4.3	22.9	6.0	21.9	6.0
Midtemporal	19.6	4.8	18.7	4.5	24.4	6.9	23.3	6.4
Post. inf. hippocampus	17.7	5.1	16.5	4.5	21.7	5.6	20.1	5.2
Post. inf. temporal	18.7	5.9	17.9	5.5	23.7	6.3	20.4	5.6
Mean	18.9	5.2	18.1	4.8	23.5	5.7	22.0	5.6

See text for three-way ANOVA.

Feldt adjustment, $p < 0.04$). Linear trend analysis with AP direction confirmed it more strongly ($F = 6.8$, df = 1,35, $p < 0.02$). No interaction with group reached 0.05 significance either with corrected degrees of freedom or multivariate T-square (BMDP4V; Dixon 1982). This analysis contained all right-handed patients and one left-handed control; the control had left minus right differences of 0.2 for the superior temporal box and 2.6 for the inferior temporal box, closely matching the mean values obtained for the whole group.

To examine whether or not the temporal asymmetry was different from previously reported hypofrontality, we entered the glucose metabolic rates for the supraventricular slice frontal lobe peel sectors (L1 and R1) (Buchsbaum et al. 1984) and the inferior temporal lobe values into a three-way ANOVA (diagnostic group by lobe by hemisphere). Patients with schizophrenia had relatively higher left hemisphere glucose metabolic rates than normal controls (hemisphere by group interaction, $F = 4.59$, $p = 0.04$), and this was more marked in the temporal lobe than in the frontal lobe (lobe by hemisphere by group interaction, $p = 0.05$, $F = 4.00$).

Increased glucose metabolic rate in the temporal lobe was weakly associated with hypofrontality. We examined the correlations among our index of hypofrontality, the ratio of metabolic rate in the frontal cortex/occipital cortex (supraventricular slice level; see Buchsbaum et al. 1984), and glucose metabolic rate in the 10 regions of interest in the temporal lobe. Correlations were calculated for the left and right hemisphere hypofrontality ratios separately, yielding 20 correlation coefficients, all 20 negative and one statistically significant (left hemisphere hypofrontality versus left inferior temporal lobe, $r = 0.49$, $p < 0.05$). Correlations between relative metabolic rate in frontal cortex (anterior sectors/whole slice metabolic rate) and the temporal lobe regions of interest were all nonsignificant. Correlations between metabolic rate in micromoles per 100 grams per minute in frontal lobe regions and temporal lobe regions were all uniformly positive and in the 0.70 range, reflecting the strong individual differences in whole brain metabolic rate.

The ratio of left superior temporal/right superior temporal glucose use was 1.03 ± 0.16 (SD) in patients with schizophrenia. This region was chosen for further analysis to maximize the contribution of auditory areas. Its ratio correlated significantly ($r = 0.47$, $p < 0.05$) with the day of procedure BPRS hallucinatory statement/behavior combined score (Table 3).

Other significant BPRS correlations with the superior temporal gyrus left/right ratio were found. These included BPRS total ($r = 0.52$) among the preselected scales shown in Table 3 and other exploratory scales not in the table, mannerisms and posturing ($r = 0.54$), hostility ($r = 0.53$), motor retardation ($r = 0.48$), and uncooperativeness ($r = 0.59$). Near zero correlations were seen for excitement, distractibility, social incompetence, loss of functioning, and sexual preoccupation. Where correlations were significant, they were positive (Table 3) correlations, indicating an association between relative left hemisphere hypermetabolism and psychopathology. Even more correlations were significant when left hemisphere superior temporal ROI/mean slice glucose correlations were examined, although hallucinations fell below statistical significance. Of 22 ROI correlations, 18 were positive and 8 significant.

It is interesting that no BPRS scale correlated significantly with whole slice glucose metabolic rate and no BPRS scale correlated significantly with absolute glucose metabolic rate for the superior temporal ROI; only relative or left/right ratios related to clinical features.

Table 3. BPRS Scale Correlations with Temporal Lobe Relative Metabolic Rate

	L/R ratios				Left side ratios to whole slice			
	ROI superior	Outline lobe	Peel L2	Peel L3	ROI superior	Outline lobe	Peel L2	Peel L3
BPRS total	0.52[a]	0.15	0.41	0.54	0.66[a]	−0.06	0.62[a]	0.22
Suspicion	0.36	−0.26	0.37	0.35	0.59[a]	−0.01	0.73[a]	0.15
Depression	0.46	0.00	0.32	0.16	0.51[a]	−0.17	0.59[a]	−0.16
Thought content	0.45	0.12	0.49[a]	0.52[a]	0.49[a]	0.05	0.37	0.31
Anxiety/tension	0.41	0.28	0.34	0.26	0.38	−0.06	0.33	0.09
Disorganized speech	0.40	0.27	0.29	0.54[a]	0.60[a]	−0.25	0.45	0.30
Hallucinations	0.47[a]	0.27	0.18	0.28	0.40	−0.13	0.36	0.15
Emotional withdrawal	0.32	0.04	0.33	0.61[a]	0.54[a]	0.08	0.54[a]	0.35
Motor hyperactivity	−0.03	0.21	0.03	−0.21	−0.01	−0.05	−0.18	−0.04
Blunted affect	0.26	0.25	0.41	0.60[a]	0.40	0.23	0.47[a]	0.11
Elated mood	−0.19	0.15	0.07	−0.10	−0.18	0.19	0.22	−0.23

[a] $p < 0.05$, two-tailed.

Cortical Peel Analysis

The anterior and posterior temporal sectors (Figures 4 and 5) were examined. Patients with schizophrenia had a higher glucose metabolic rate (25.2 ± 5.9) than normals (20.8 ± 7.0) when compared by three-way repeated measures ANOVA (diagnostic group by hemisphere by anteroposterior position; main effect of group, $F = 4.95$, df = 1,38, $p = 0.03$). The anterior (2) segment had higher metabolic rate (24.4) than the posterior (3) segment (22.2) by the main effect for position ($F = 43$, $p < 0.0001$), but no interactions with group or hemisphere were observed. The schizophrenics showed greater left than right hemisphere glucose levels in contrast to normals, who showed exactly equal levels, but this difference was not statistically confirmed (hemisphere by group interaction, $F = 1.98$, df = 1,38, $p = 0.168$). The left/right ratios for the posterior sector, 1.05 in schizophrenics and 1.03 in normals, were not significantly different ($t = 0.80$, $p < 0.10$). For the anterior sector, the left/right ratios were 1.05 in schizophrenics and 0.99 in normals and were significantly different ($t = 2.33$, $p < 0.05$). Sector/whole slice ratios also did not distinguish normals from schizophrenics.

Neither left/right ratios nor left-sided sector/whole slice ratios correlated significantly with BPRS hallucinations. However, other BPRS scales did correlate significantly. As with the ROI analysis, all significant correlations were positive, and for the posterior temporal sector, they were higher for left/right than left/whole slice ratios. Also similar was the almost complete absence of any correlation between absolute metabolic rate and BPRS (the single exception being left anterior temporal and disorganized speech).

Discussion

We report here increased temporal lobe glucose metabolic rate in schizophrenic patients compared with controls. This increase was significantly higher on the left than on the right in some analyses and appeared to be correlated with several aspects of psychopathology. More detailed anatomic delineation revealed that the increases in glucose metabolic rate and asymmetry were greatest in the anterior and superior temporal region.

In cerebral blood flow studies, most emphasis recently has been on evaluating frontal lobe flow. However, Ingvar and Franzen (1974) did note high flows in the temporo-occipital region in cases with evidence of hallucinating activity.

The increased temporal lobe glucose use in schizophrenia reported here could be consistent with the increased fast waves observed on temporal lobe EEG reported by others (Flor-Henry 1976; 1983; Morihisa et al. 1983). Flor-Henry and Koles (1984) also describe a left lateralization to the temporal lobe of 8–13 cycles/sec EEG differences between schizophrenic and normal individuals during the eyes-closed condition. Morihisa et al. (1983) reported increased fast waves on EEG in schizophrenic patients in left temporal-parietal regions (their Figure 2A), and similar left anterior findings were reported by Morstyn et al. (1983). Abrams and Taylor (1979), on the other hand, found abnormal left temporal lobe slowing, which was significantly correlated with the severity of formal thought disorder and emotional blunting in schizophrenic patients.

Our three methods of analysis in the PET studies have different advantages and drawbacks but produced similar results. The lower slice (14% above CM line) lobe method has the advantage of clearly delineating the temporal lobes and functionally related region of interest, but may suffer from partial volume dilution, with skull and tissues lying below the pole. This is somewhat compensated for by using whole lobe areas, but intersubject variation in lobe shapes may still markedly affect mean values, as brain areas thin in the vertical direction could be included. The use of maximum values partly may avoid this problem by selecting a value in the center of the lobe further from the rim. In contrast, the 21% slice atlas method identifies small individual regions within the temporal lobe and is less affected by partial volume dilution, as temporal brain tissue is known to underlie this slice. However, stereotaxic placement based on proportional height, width, and length adjustments will involve some individual variation. Note that the lobe outline technique could not easily be applied to the 21% cut, as the boundary-finding program could not delineate the medial margins of the temporal lobe at our PET resolution. The atlas box technique could be faulted on the 14% slice, as the variation in position of whole slice outline is greatest here. Thus, a direct comparison of the two methods in the identical slice is not wholly appropriate. However, we could test our ROI by applying them to published atlases. The temporal lobe boxes fit well the orbitomeatal slice in Salomon and Huang (1980; p 86). The "superior hippocampal" box sits on the region labeled uncus and the inferior near the "parahippocampal gyrus." As these details are below our resolution, we have avoided a terminology more detailed than superior or inferior hippocampus. A larger box (5 × 5 pixels) yields values correlated over 0.92 with the 3-pixel box for all areas.

Unlike the small ROI, the cortical peel technique uses a voxel nearly five times as large. This technique yielded no correlation with hallucinations, but generally showed relatively high metabolic rates on the left associated with symptom expression and a great paucity of right-sided or absolute metabolic rate correlations. Thus, its results resembled the small ROI technique.

No large differences in variance were observed among the three methods. The means and standard deviations for metabolic rates for the left temporal outline (22.8 ± 4.5), superior temporal ROI (24.5 ± 5.2), and posterior temporal sector (24.8 ± 6.1) are all quite similar, not demonstrating marked artifacts of partial voluming in the two non-ROI techniques.

Our finding of left greater than right (L > R) glucose metabolic rate in schizophrenia is similar to, but not identical to, the Sheppard et al. (1983) ^{15}O study. They used a

technique derived from our cortical peel method and examined a slice at 40 mm above the orbitomeatal line. Our slice was parallel to the CM line and situated lower, averaging 35 mm above CM. Our lateral reconstruction places our second sector, where left/right differences were significant, in the middle temporal region. Sheppard et al. (1983) sum the third and fourth sectors so that middle temporal and occipital regions are included. Both methods may include some activity in the inferior portions of the inferior parietal lobule. Despite these differences, the direction of finding, L > R in schizophrenia, was consistent.

The finding of higher metabolic rates in left temporal cortex of patients with schizophrenia links the symptoms of verbal hallucinations and disturbed, disorganized speech to the language localization in this region. Other symptoms of schizophrenia, including suspiciousness, disturbed thought content, hostility, and emotional withdrawal, also showed correlations with this area. Bear's (1979) contrast of epileptics with foci in the left versus the right temporal lobe is of interest in this regard. He found that self-report of psychopathological items, such as suspiciousness and anger, were higher in left temporal patients. Bear suggests that exaggerated availability of emotional associations in verbal form may underlie these symptoms and other aspects of personality (including religiosity, circumstantiality, and humorless sobriety).

It should be noted that our patients were not performing a verbal task, but were receiving brief electrical stimuli. The finding of the highest observed correlation (0.73) with suspiciousness may relate to the setting; detailed examination of the left temporal and inferior parietal lobes during controlled verbal tasks may emphasize other smaller regions of specific deficit and reveal stronger or different lateralization effects. It is also possible that differences in the rate of habituation to electric shocks between schizophrenics and normals could explain the observed differences, although typically, patients with schizophrenia have shown more rapid habituation (e.g., Bernstein 1970).

It is of interest that by measuring ^{15}O consumptions with PET, Gallhofer et al. (1983) found that temporal lobe epileptic patients with nuclear schizophreniform disorders had predominantly left temporal cortical dysfunction. However, lower regional blood flow was found in left as compared to right temporal regions. This finding was interpreted as being consistent with temporal and limbic dysfunction.

Taken together, the previous publications cited and our present study further support the hypothesis that some schizophrenic symptomatology may be related to the left temporal lobe pathology. We acknowledge, however, that other reasonable evaluations of these data can be made. No convincing correlation with relative hypofrontality was found, suggesting some independence of elevated temporal and reduced frontal abnormalities. Whether or not these represent two types of schizophrenia with distinctive etiologies and symptoms will require larger samples of subjects and perhaps specific behavioral probes of temporal and frontal cortex. As positron-emitting substances with the ability to bind specific receptors become available, more extensive evaluation of temporal lobe dysfunction not possible with 18-[F]-2-deoxyglucose may further clarify these findings.

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