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Computed Tomographic Evidence for Generalized Sulcal and Ventricular Enlargement in Schizophrenia

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• Quantification of ventricular and sulcal volumes from the computed tomographic (CT) scans of 45 schizophrenic patients and 57 normal controls was carried out using a semi-automated computerized approach. The sizes of all cerebrospinal fluid spaces measured were significantly related to age in the control population. An age regression model was used to compare patients and controls. Schizophrenics had slightly larger ventricles and considerably larger sulci than controls. Enlargement of the ventricles and sulci was not correlated with measures of negative symptoms or neuropsychological impairment. The CT scans of eight very ill chronically institutionalized schizophrenics were also analyzed. Their CT findings did not differ significantly from the larger group of schizophrenics studied. Our results show that the cerebral atrophy found in schizophrenia is diffuse in nature and does not relate clearly to measures of disease severity or chronicity.

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Johnstone et al[1] first reported computed tomographic (CT) evidence of lateral ventricular enlargement in schizophrenic patients in 1976. Earlier in this century there had been much interest in similar findings based on pneumoencephalography. With the advent of CT, a readily available, noninvasive, and relatively sensitive means of assessing gross cerebral pathology, there has been a renewed interest in investigating structural evidence of cerebral damage in schizophrenia. These investigations have been the focus of a number of recent reviews.[2-5]

Ventricular enlargement has been the most consistent finding in CT studies of schizophrenic patients. The proportion of schizophrenic patients whose ventricular size has been 2 SDs higher than the mean of normal controls (in those studies that have found a difference) have ranged from 3% to 35%.[2] In general, there has been a great deal of overlap between the values obtained for schizophrenic patients and those obtained for controls. It is therefore not surprising that there have been a substantial number of studies in which statistically significant differences between schizophrenics and controls were not found. Ventricular enlargement in schizophrenic patients is a nonspecific finding; similar differences have been described in Alzheimer's disease,[2] Huntington's chorea,[6] Parkinson's disease,[7] alcoholism,[8] bipolar disorder,[9,10] delusional depression,[11] and anorexia nervosa.[12,13] Ventricular size has been the most commonly investigated measure in CT studies. This is likely due to a number of factors. Ventricular enlargement was the most frequently reported abnormality in pneumoencephalographic studies of schizophrenia[5] and it was the first reported CT abnormality in schizophrenic patients.[1] In addition, the ventricles are large structures that are easily visualized and can be quantitated with a reasonably low degree of measurement error by linear or planimetric techniques. However, neuropathological studies of schizophrenic patients to date have more commonly reported cortical changes than the periventricular or subcortical changes implied by ventricular enlargement.[5]

The first two groups involved in this research, Johnstone et al[1] and Weinberger et al,[14,15] also investigated the possibility of cortical changes in schizophrenia. Their results were divergent on this issue; Weinberger et al[15] reported evidence of enlarged cortical sulci in 32% of their sample, whereas Johnstone et al[16] found no evidence of sulcal enlargement. Subsequent studies of sulcal enlargement have also been inconsistent. Measurement of sulcal size on CT poses more of a problem than measurement of ventricular size. The two commonly employed methods of

quantitating sulcal size are (1) linear measurement of the largest sulci[15] and (2) use of a visual rating scale. When sulci can be seen, it is difficult to define precisely where the fluid-tissue and brain-skull boundaries lie because of partial voluming effects and spectral shift artifact.[17,18] These artifacts can seriously limit the validity of linear measurements and visual ratings of the cortical sulci.

Similar problems have confounded the assessment by CT of other small cerebral structures, such as the third ventricle and sylvian fissures. These structures have been of specific interest because of the theoretical involvement of deep gray matter structures and temporal areas in the pathogenesis of schizophrenia. Reports of third ventricular enlargement to date have also been inconsistent, with some studies reporting significant differences between schizophrenics and controls[19-22] and others reporting no significant differences.[23,24] Sylvian fissure size has been studied by Weinberger et al,[15] who have reported significant differences between schizophrenics and controls using linear measurements. Okasha and Madkour,[25] however, were unable to find significant sylvian fissure enlargement in their sample of schizophrenic patients.

Jernigan et al[26] developed a computerized method of analyzing ventricular and sulcal volume from brain CT scans. In an earlier study from this center, they studied CT measures in schizophrenic patients and found no significant differences in lateral ventricular and sulcal measures between patients and normal volunteer controls. When planimetric methods were used to check this new method, there were still no differences detected between patients and controls. The current study was undertaken to reexamine this question with a second-generation CT scanner and a new measurement method.

There is now good evidence that the ability to find differences between schizophrenic patients and controls depends on both the choice of patient group[27] and choice of control group.[28] Luchins and Meltzer[27] showed that patients from a long-term hospital setting had more evidence of ventricular enlargement than those from an acute-care hospital setting, suggesting that more severely impaired schizophrenics were more likely to show ventricular enlargement. However, it is not yet clear which particular clinical manifestations of severe impairment are most clearly associated with ventricular enlargement.

Despite widespread acceptance of the notion that patients with negative symptoms are more likely to have enlarged ventricles, the current literature does not support a definite relationship. Pearlson et al[9] found a significant correlation between negative symptom scores and ventricle-brain ratio (VBR) in a sample of 19 schizophrenic patients. Williams et al[29] also found that patients with negative symptoms had significantly larger VBRs, and that patients whose VBRs were greater than 1 SD above normal were significantly more likely to have negative symptoms. Andreasen et al[30] looked explicitly at this question and found that when they divided their schizophrenic patients into those with large ventricles (>1 SD from the control mean) and those with small ventricles, no statistically significant differences in the severity of negative symptoms were detected, though the patients with large ventricles tended to have a preponderance of negative symptoms. Other studies[31-35] have not found a relationship between negative symptoms and VBR magnitude.

There has also been much interest in whether patients with enlarged ventricles are more cognitively impaired. The literature to date has been inconsistent on this issue as well.[3] A number of studies have found associations between measures of cerebral atrophy (enlarged ventricles

or sulci) and measures of cognitive functioning such as the Folstein Mini-Mental State Examination, the Halstead-Reitan Battery, the Wechsler Adult Intelligence Scale, and the Luria-Nebraska Battery.[16,36-39] However, others have not found such differences.[14,29,33]

Significant changes in brain structure are seen with aging. To assess accurately the magnitude of CT differences in schizophrenic patients, the contribution of age needs to be controlled for rigorously. Earlier work by Zatz et al[40] using a computerized approach to measuring cerebrospinal fluid (CSF) volumes suggested that there were no significant changes in ventricular or sulcal measures with normal aging until the age of 60 years. More recent work from this laboratory using a different computerized approach to measuring CSF volumes[18] has shown that there are significant changes in lateral ventricular and sulcal volumes with age throughout the adult age range. Given this finding, the most valid approach to controlling for age in a patient sample is to express the CT measures in terms of deviation from normal age-expected values.[41] We have expressed deviations from normal as z scores, which are derived by subtracting the age-expected CT value from the patient's CT value and dividing by the age-predicted SD.

Smith and Iacono[28] have also made the point that whether a study of VBR in schizophrenia is positive or not tends to be more closely related to the VBRs of the control group than those of the patients. The VBRs of controls in positive studies have been smaller than those in negative studies. In general, control scans drawn from a pool of medically ill patients with "normal scans" have had smaller VBRs than scans from normal community volunteer controls. This finding underscores the need to use normal volunteer controls whenever possible.

In the present study we applied a computerized volumetric approach for measuring CT scans to a sample of psychiatric inpatients with schizophrenia. Use of this computerized method has also allowed measurement of lateral and third ventricular volumes as well as cortical sulcal volumes in more specific brain regions. The relationships between CT measures and clinical variables have also been investigated in this patient group. The CT results were then compared with those of a smaller group of much more severely impaired chronically institutionalized schizophrenic patients.

SUBJECTS AND METHODS
Subjects

The study subjects consisted of 45 male inpatients at the Palo Alto (Calif) Veterans Administration Medical Center who were hospitalized between 1982 and 1984. All but one of these subjects were patients on the clinical research wards. All subjects were veterans who qualified for Veterans Administration psychiatric benefits. Patients on the research wards were recruited from the hospital's outpatient psychiatric evaluation unit if they had a provisional diagnosis of schizophrenia, were being hospitalized voluntarily or as part of a legal conservatorship, and could be appropriately cared for on an unlocked inpatient unit. Consecutive admissions to the research wards were considered for involvement in this study if they had a Research Diagnostic Criteria (RDC) diagnosis of probable or definite schizophrenia and did not meet any of the exclusion criteria. Patients were excluded if they had any major medical illnesses or past or present neurological illness. Those patients who satisfied the above criteria and were willing to provide informed consent were included in this study.

All subjects met RDC for definite or probable schizophrenia as determined through evaluation by a psychiatric resident. The diagnosis of schizophrenia was further subtyped as chronic in 38 patients, subchronic in six patients, and subacute in one patient. Patients ranged in age from 22 to 61 years (mean±SD, 34±9 years). Age at onset (age at first period of illness) and duration of
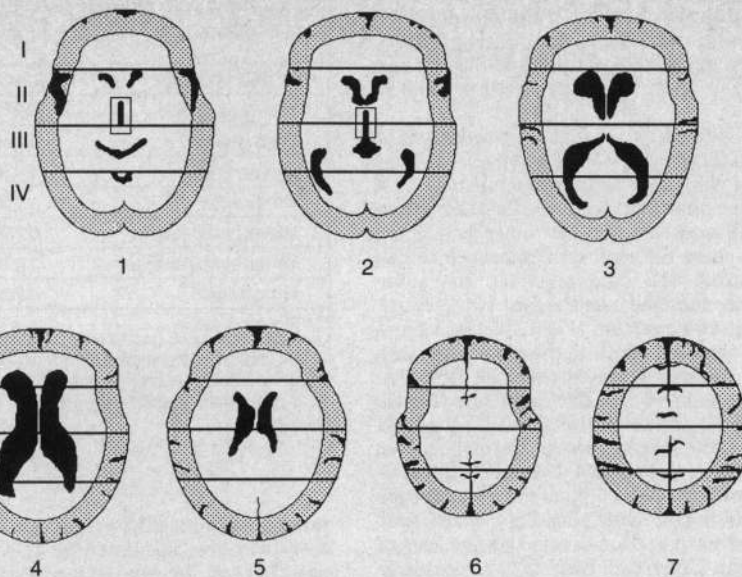
Fig 1.—Schematic representation of seven computed tomographic sections used for data analysis. Fluid-tissue threshold was determined for each section (see text). Each section was divided into central 55% area and peripheral 45% area (stippled) to facilitate quantification of lateral ventricular and cortical sulcal volumes, respectively. Each section was also divided into quarters of equal area (anterior to posterior) to provide regional measurements of cortical sulcal volume. Third ventricle was localized using rectangular region of interest on sections 1 and 2.

illness were determined for all but one of the patients using RDC. Mean age at onset of schizophrenia was 23 ± 4 years, and mean duration of illness was 11 ± 9 years. As a part of other protocols on the research ward, attempts were made to evaluate patients free of psychotropic medications. Sixteen of the patients were free of psychotropic medications other than chloral hydrate for at least two weeks at the time of the CT scan.

An additional eight male schizophrenic patients who had CT scans done for a previously reported study[42] were reanalyzed with the computerized method. This population is described in detail elsewhere.[42] Briefly, an attempt was made to find a group of patients who would represent the most severely and chronically ill schizophrenic patients. It was hypothesized that they would be more likely than other schizophrenic patients to have CT measures that differed from controls and that the magnitude of their CT changes would also be greater than those of less severely and chronically affected schizophrenic patients. All were inpatients at the Menlo Park division of the Palo Alto Veterans Administration Medical Center. One of us (S.M.S.) examined all those inpatients (n=20) at the Menlo Park division of the Palo Alto Veterans Administration Medical Center who had a diagnosis of schizophrenia and who had been hospitalized more or less continuously for the past ten years. Of these patients, eight met the criteria for this study. All had RDC diagnoses of chronic schizophrenia and no known history of chronic alcoholism, other drug abuse, diagnosable organic brain disorders, or lobotomies. The eight patients from Menlo Park were between 35 and 55 years old (mean, 49.6 years), had an average length of hospitalization of 27.3 years, and had an average Brief Psychiatric Rating Scale (BPRS) score of 57.9.

Fifty-seven volunteers were recruited by newspaper advertising and by word of mouth from the community to serve as controls for a previously reported study on the effects of aging as measured by CT.[18] They were initially screened by telephone interview and then by questionnaire to exclude individuals with significant psychiatric and neurological histories, recent use of psychoactive drugs, or alcohol consumption exceeding 50 g/d for a period of one month or longer. The final sample of community volunteers included 29 men and 28 women. They ranged in age from 20 to 82 years. Their CT scans were used to generate age-normalized regression curves for all measures used. All CT data were expressed as percent fluid in the regions of interest (ie, fluid/[fluid + tissue]).[18]

CT Scans

Computed tomographic scans were obtained with an EMI 1010 scanner with eight to 14 contiguous tomographic sections, 8 mm thick, obtained at $+15°$ to the canthomeatal line. This angle was used to avoid exposing the eyes to x-radiation. Informed consent was obtained from all subjects. Scans were filmed for routine radiological evaluation and also stored on magnetic tape as 160×160-pixel images with a CT number resolution of one count per Hounsfeld unit. Analysis was performed with a general-purpose laboratory computer (VAX 11-730) equipped with a graphics display system (AED-767) using procedures described in detail previously.[18] Briefly, the data were initially passed through a two-dimensional high- and low-pass digital filter to minimize spectral shift artifact, and all CT numbers were corrected for intracranial area. A threshold CT number, below which all pixels are classified as fluid and above which all pixels are classified as tissue, was then chosen by a trained rater for each section of each scan. This was accomplished at the computer console, where all sections of the original scans were displayed using a 7-bit gray scale on the upper row of the console, with the corresponding filtered cranial area–corrected sections displayed using a 1-bit scale (either black or white) on the lower row. A trained rater adjusted this scale until black and white areas on the lower row corresponded to fluid and tissue areas in the upper row. Percent fluid values obtained by the trained rater and by one of us (A.P.) were highly correlated (Pearson product-moment correlation) both for the ventricular measure ($r = .97$) and for the sulcal measure ($r = .98$).[18]

CT Regions of Interest

For image analysis, sections above those with significant sphenoid or petrous bone interrupting the "roundness" of the skull were used. An index section was identified for each scan that included the anterior horns of the lateral ventricles, the third ventricle, and the quadrigeminal cistern and was below the posterior horns of the lateral ventricles. The index section and the next six sections superior to it were used for data analysis (Fig 1). Each section was divided empirically by area into a medial 55% segment and a peripheral 45% segment. This division generally separated the ventricles and the centrum semiovale from the cortex. Using this division, the following regions of interest were

defined: lateral ventricles—the percent fluid in the inner 55% of the first five sections beginning with the index section (Fig 1, sections 1 through 5); and vertex sulci—the percent fluid in the outer 45% of the sixth section above the index section (Fig 1, section 7).

Each CT section was also divided by area into four quarters of equal area, anterior to posterior (Fig 1). The lines dividing quarters were drawn by the computer to be perpendicular to a regression line drawn from five points chosen to define the midline of each section. Using these quarters and the inner and outer areas, the following regions were defined with reference to the index section: sylvian fissures—the fluid pixels in the outer segments of the second quarter summed over the first two sections and divided by the area of the two quarters (Fig 1, sections 1 and 2, quarter II); frontal sulci—the fluid pixels in the outer segments of the first (most anterior) quarter summed over the first five sections and divided by the area of the five quarters (Fig 1, sections 1 through 4, quarter I); parieto-occipital sulci—the fluid pixels in the outer segments of the fourth (most posterior) quarter summed over the fifth and sixth sections and divided by the area of the two quarters (Fig 1, sections 5 and 6, quarter IV); anterior vertex sulci—the fluid pixels in the outer segments of the first and second quarters of the seventh section divided by the area of the two quarters (Fig 1, section 7, quarters I and II); and posterior vertex sulci—the fluid pixels in the outer segments of the third and fourth quarters of the seventh section divided by the area of the two quarters (Fig 1, section 7, quarters III and IV).

A measure of the third ventricle was also developed. The third ventricle was identified only at or below the level of the anterior horns. Anteriorly, the third ventricle was not measured beyond the posterior border of the anterior horns. Posteriorly, it was not considered to extend beyond the pineal gland. The third ventricle was considered to be a narrow fluid space whose lateral walls are parallel for most of their length. Care was taken not to mistake the third ventricle for the quadrigeminal and interpeduncular cisterns. For each of the first two CT sections, a rectangular area was defined such that the only fluid pixels present fell within the boundaries of the third ventricle (Fig 1, sections 1 and 2). These third ventricular areas were summated and divided by the sum of the areas of both sections to give the third ventricular measure.

Computerized measurements of the third ventricle done by the trained rater and one of us (R.B.Z.) were highly correlated ($r = .97$, Pearson product-moment correlation). To validate this computerized measure of the third ventricle, a more conventional manual linear measurement of the third ventricle was made. The third ventricle was identified on the index section and the section above the index section; the section where the third ventricle was largest was chosen for this linear measurement. Since the third ventricle is a structure with parallel sides for most of its course, diverging only at the anterior and posterior extremes, width was measured along the parallel course (narrowest point), rather than at either extreme, which would have been a much less reliable measure. Measurements were made to the nearest millimeter with a millimeter ruler on images expanded to twice actual size and displayed on a computer console. The two measures of the third ventricle were highly correlated ($r = .83$, Spearman rank correlation). This manual measurement of the third ventricle was used only for validation purposes and was not used for any of the analyses of the study data.

Clinical Measures

Determinations were made of age at onset using RDC criteria and duration of illness for all but one of the study patients. Cognitive functioning was measured by the Luria-Nebraska Neuropsychological Battery in 34 of these patients. Eleven patients were not tested with the Luria-Nebraska Battery because they were discharged, were transferred to a locked ward, or refused testing. The number of scales on which a patient scored in the impaired range was summed to form a Global Score. Of 45 schizophrenic patients, 44 had had a BPRS completed while on the inpatient unit. Twenty-three patients had had a BPRS completed while they had been free of all psychotropic medications other than chloral hydrate for two weeks or longer. The last BPRS score obtained medication free in these 23 subjects was used for analysis. In addition, 35 subjects had had a BPRS completed while

Table 1.—CT Measures for 45 Schizophrenic Patients*

CT Measure	z Score, Mean ± SEM	t	P<
Lateral ventricles	0.317 ± 0.185	1.710	.05
Third ventricle	0.376 ± 0.148	2.538	.02
Sylvian fissures	0.436 ± 0.161	2.707	.01
Vertex sulci	1.200 ± 0.240	5.003	.001
Vertex sulci, anterior	0.785 ± 0.223	3.521	.002
Vertex sulci, posterior	1.129 ± 0.238	4.740	.001
Frontal sulci	0.722 ± 0.144	5.006	.001
Occipital sulci	1.093 ± 0.164	6.648	.001

*CT indicates computed tomography. P values are two-tailed, except for lateral ventricles where the P value is one-tailed. The schizophrenic patients as a group had significantly enlarged ventricles and sulci on all measures studied.

taking psychotropic medications; the mean final medicated BPRS score was also calculated for this sample, but this datum was not used for any further data analysis. Combined scores for positive and negative symptoms were calculated from the BPRS in a manner consistent with the cluster analysis of Overall.[43] The positive symptom cluster includes hallucinations, unusual thought content, grandiosity, and suspiciousness. The negative symptom cluster includes blunted affect, emotional withdrawal, and mannerisms and posturing. The following predictions were made based on the existing literature: (1) BPRS negative symptom scores would be positively correlated with age-corrected measures of ventricular and sulcal size and (2) Luria Global scales would be positively correlated with age-corrected measures of ventricular and sulcal size.

Statistical Analysis

The percent fluid CT measures from each region of interest for the 57 community controls were each plotted against age to form age regression curves.[18] To best fit the regression lines to the percent fluid data, the age term was in some cases squared or cubed. In addition, the percent fluid values were arcsine transformed to stabilize the variance with respect to age. As it was expected that the variance in CT measures would increase with age, the SE of the regression (ie, SD with the effect of age removed) was calculated to take this into account.[41] Age-corrected z scores were calculated for each of the CT measures for each patient in the following way: the percent fluid measure expected for a given patient (as derived from the appropriate regression curve) was subtracted from the patient's observed percent fluid measure, and this difference was then divided by the SD expected for the patient's age. Testing for statistical significance between the z scores of patients and controls was done using the single-sample t test. The z scores of the two patient groups were compared using the Mann-Whitney U test. Differences in z scores among different areas of the brain in schizophrenics were assessed by the paired-sample t test.

Correlations between age and percent fluid measures were calculated using the Pearson product-moment correlation coefficient. Correlation between percent fluid measures within patients and within controls was calculated with the Spearman rank correlation test. Correlations between clinical measures and CT measures were also calculated using the Spearman rank correlation test.

RESULTS
Correlations of CT Measures With Age

All CT measures correlated significantly with age in the control population at the $P \le .001$ level. Correlations were optimized for all CT measures by correlating them with age squared with two exceptions: the third ventricle measure was most highly correlated with age and the occipital measure was most highly correlated with age cubed. The 28 female community volunteers did not differ significantly from the 29 male community volunteers on any of the age-corrected CT measures.
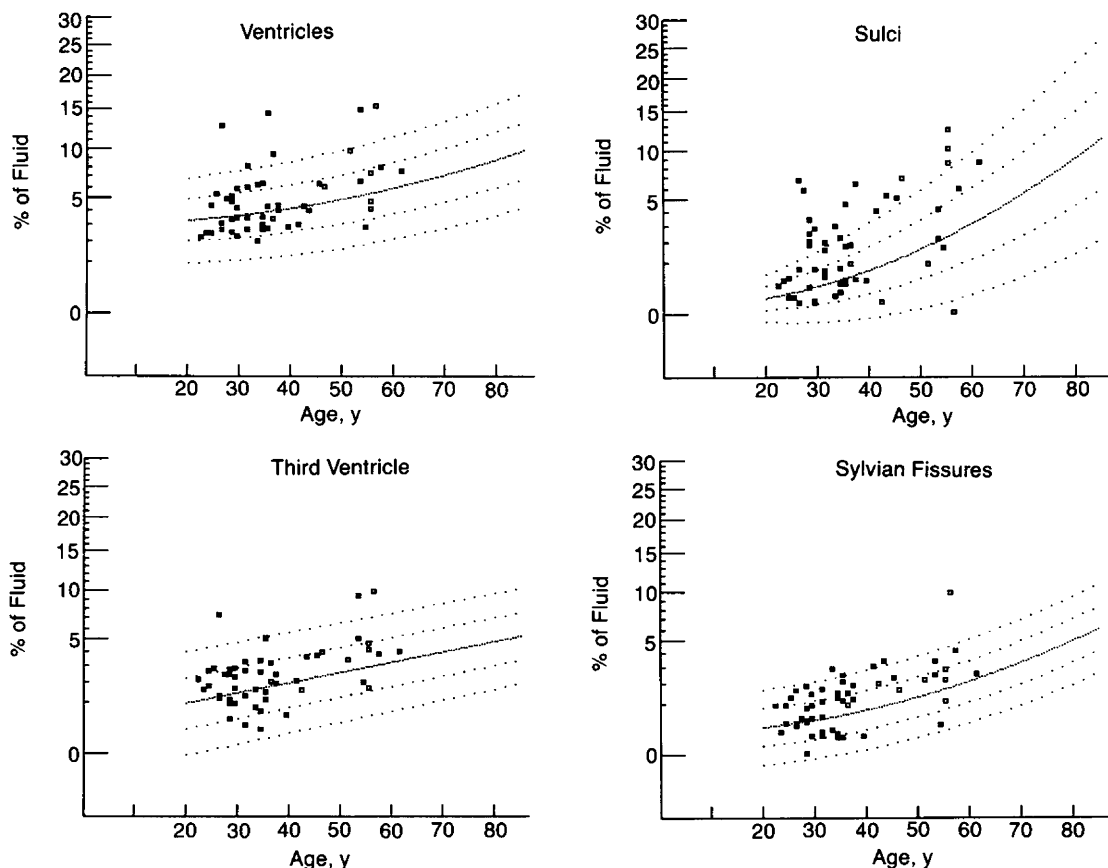
Fig 2.—Age vs percent fluid computed tomographic measures for lateral ventricles, vertex sulci, third ventricle, and sylvian fissures. Data for 45 schizophrenic inpatients (closed squares) and eight chronically institutionalized schizophrenic patients (open squares) are superimposed on mean regression line and SD lines derived from 57 community volunteers.

Correlation of CT Measures With Each Other

All percent fluid CT measures were significantly correlated with one another within the schizophrenic population, and all but one correlation (third ventricle vs occipital sulci) were significant in the control population.

CT Measures in Schizophrenic Patients

The z scores for the schizophrenic patients were greater than those for the community volunteers in all regions of interest (Table 1 and Fig 2). The lateral ventricles were slightly enlarged compared with controls. The most striking differences were for the sulci as measured on the highest of the seven sections analyzed. The mean area for this section did not differ significantly between patients and controls. There was no significant difference between the sulcal enlargement measured in the anterior half of this section compared with the posterior half of the section. Sulci were enlarged in both the frontal and occipitoparietal areas; there was no statistically significant difference between the amount of sulcal enlargement measured in these two areas. There were small but significant differences between the sizes of the third ventricle and the sylvian fissures in schizophrenics compared with controls.

Clinical Measures

Age at onset and duration of illness did not correlate significantly with the z scores for the lateral ventricles, third ventricle, vertex sulci, or frontal sulci. The Luria Global scores had a mean ± SD of 2.9 ± 3.0 (n = 34). There were no significant associations between the Luria Global scores and the lateral ventricle z scores (r = −.04) and vertex sulcal z scores (r = .03). The mean final unmedicated BPRS score for 23 subjects was 40.2 and the mean final medicated BPRS score for 35 subjects was 37.8. The BPRS scores (unmedicated values only) for the negative symptom cluster (mean ± SEM, 2.6 ± 0.5, n = 23) and for the blunted affect

Table 2.—CT Measures for Eight Chronically Institutionalized Schizophrenic Patients*

CT Measure	z Score, Mean ± SEM	t
Lateral ventricles	0.604 ± 0.486	1.242
Third ventricle	0.547 ± 0.403	1.344
Sylvian fissures	0.957 ± 0.538	1.778
Vertex sulci	0.893 ± 0.809	1.104

*CT indicates computed tomography. The z scores for these patients did not differ significantly from the larger group of schizophrenic patients presented in this study or from normal control values.

item alone (3.11 ± 0.27, n = 23) did not correlate significantly (one-tailed) with the lateral ventricle, third ventricle, frontal sulci, or vertex sulci z scores.

CT Measures in Chronic Cohort

The mean z scores for this group of patients are listed in Table 2. They did not differ significantly from the larger group of schizophrenic patients on any of the CT measures. They also did not differ significantly from the control population on any of the CT measures. The magnitudes of the effect size (ie, the mean z) for all CT measures except the vertex sulcal measure were greater than those of the larger schizophrenic sample. This result was strongly influenced by one patient whose CT measures, with the exception of the vertex sulcal measure, were much larger than normal (Fig 2).

COMMENT

The results of the analysis of CT scans from 45 inpatient schizophrenics support previous reports of small but sig-

nificant CT differences in schizophrenic patients as a group. Most emphasis in the earlier literature has focused on lateral ventricular enlargement in schizophrenic patients. The current study using a computerized method of analyzing CT data suggests that the differences apparent in the cerebral cortex are more prevalent and of greater magnitude than the differences detectable in either the lateral or third ventricles. This was the case for both the larger inpatient sample and the chronically institutionalized sample. This may not have been appreciated by most earlier studies because of the inherent limitations in using rating scales and linear measurements to quantitate cortical sulcal size.

Our findings are in close agreement with the study by Weinberger et al,[15] who reported that 32% of their schizophrenic patients had evidence of sulcal enlargement as assessed by linear measurements. In the present study, 15 (33%) of 45 patients had cortical sulcal measures that were beyond 2 SDs from their age-predicted values. On the other hand, we found that significant ventricular enlargement (ie, >2 SDs) could be identified in only four (9%) of 45 patients. Weinberger et al[15] did *not* find that ventricular and sulcal size were correlated in their schizophrenic patients, whereas we found a significant association between these two measures ($r = .620$, $P \leq .001$, Spearman rank correlation). This discrepancy is likely related to the differences in the measurement techniques and in the subsequent statistical analysis utilized. The CT measures of ventricles and sulci in the Weinberger et al study were dichotomized into a classification of with/without enlarged ventricles and with/without cortical atrophy and then tested by a 2×2 χ^2 analysis. Due to the more precise quantitation of sulci afforded by the computerized volumetric measurements, we have analyzed the ventricular and sulcal measures as continuous variables whose association can best be assessed with a Spearman rank correlation test.

Work by Doran et al[44] has suggested that there was evidence of specific frontal atrophy on CT in schizophrenic patients. Our work supports the finding of frontal sulcal enlargement. However, we have also found evidence of significant sulcal enlargement in the temporal and occipitoparietal areas. We did not find evidence of increased frontal atrophy relative to occipitoparietal atrophy but rather a trend in the opposite direction. In this respect, the current study does *not* support the notion of relative structural hypofrontality in schizophrenic patients.

One still needs to account for the observation that many symptoms of schizophrenia have similarities with "frontal lobe" symptoms. It is conceivable that even if the atrophic process is generalized, certain regions of the brain may be more vulnerable to the effects of this degree of tissue loss. Alternatively, it may be that the cortical changes are a secondary, generalized response to cellular changes in deeper brain structures and that the clinical symptoms cannot be correlated with these secondary changes.

The differences in CT measures between the larger sample of schizophrenic patients and controls achieved statistical significance for all measures used. In the case of the smaller, more chronically ill sample, no statistically significant differences from controls were achieved, even though on all measures, except the vertex sulcal measure, this group had larger mean z scores than the larger sample. This was likely greatly influenced by the contribution of one outlier whose CT measures, other than the vertex sulcal measure, were all beyond the second SD of normal. In the case of the vertex sulci, however, four of the eight chronically ill patients had sulci that were more than 2 SDs

larger than the control mean. This is consistent with our finding of more striking sulcal changes than ventricular changes in the larger patient group. The tendency to have enlarged ventricles and sulci is comparable for the more chronically ill sample; the failure to achieve statistically significant differences for these measures is most likely related to the small sample size. A previously published analysis of these eight scans based on a simple rank ordering by blind qualitative neuroradiological assessment did show that the third ventricular and frontotemporal sylvian-sulcal rankings, but not the lateral ventricular or vertex sulcal rankings, were greater in this group compared with eight age-matched controls.[42] That these two analyses yielded different results for the same patient group is due to sampling differences for the control comparison groups.

The failure to find large differences in ventricular size between these two groups of schizophrenics is at odds with the previous report of Luchins and Meltzer.[27] In their study, the acutely ill and chronically ill ward patients were matched for age with mean ages of 28.6 and 27.8 years, respectively. In the present study, the chronically ill sample had a mean age that was 16 years greater than the mean age for the larger sample. It is possible that the differences between the older, more chronically ill sample and controls may have been obscured by concomitant CT changes related to aging per se, thus diminishing the effect size for the chronically ill patients. To pursue this possibility further, we compared the percent fluid CT measures of the eight chronically ill patients with eight blindly age-matched patients from the larger group of patients. No statistically significant differences between these two groups were found using this approach. Our results suggest that older, more chronically and severely ill schizophrenic patients have structural brain findings on CT that are comparable, in the magnitude that they deviate from age-expected values, with those of younger, less severely ill patients.

We have used an age regression model to correct CT measures for the effects of age throughout the adult age range.[41] The correlations with age were all highly significant, which further underscores the need for carefully controlling for the effects of age in both the patient and control samples.

It is possible that factors not directly related to the etiology of schizophrenia may have contributed to the CT differences observed. We have shown in an earlier study of CT changes in alcoholics[45] that there were significant correlations between lifetime alcohol consumption and ventricular and sulcal z scores. One of our patients met the RDC for alcoholism as well as for schizophrenia; unfortunately, we do not have quantitative data to assess more fully the contribution of alcohol consumption to the CT findings in this group of schizophrenics. Most CT studies in schizophrenia have not found a relationship between CT changes and a history of alcohol abuse, although most of these studies have not used quantitative estimates of alcohol consumption. A recent study that did use a more quantitative estimate did report a significant correlation between amount of alcohol consumed and VBR.[46] It is unlikely that alcohol consumption can explain the differences found between schizophrenics and controls in this and other studies. However, it is likely that alcohol consumption would affect the magnitude of the differences detected. It will be important in future studies of structural brain changes in schizophrenic patients to more carefully separate out the effects of alcohol.

We were not able to find significant correlations between CT measures and clinical measures of cognitive impair-

ment. This is not unusual, in that CT–cognitive function studies often produce few correlations.[45] Our patient sample also had a relatively low (ie, nonpathological) mean Luria Global score; thus, there was little range of cognitive performance to create a correlation. Eleven patients were not tested on the Luria-Nebraska battery for reasons outlined in the "Subjects and Methods" section. There was a trend for the ventricular and sulcal z scores of those who were not tested to be larger than the scores of those who were tested, but these differences failed to reach statistical significance. It is possible that clinical factors that precluded testing some of these patients led to the exclusion of some patients with more striking CT findings. Such a bias would have made it more difficult to find a relationship between cognitive impairment and ventricular and sulcal enlargement.

We did not find significant correlations between CT measures and ratings of negative symptoms. In fact, there was a trend for the frontal z scores to be inversely correlated with negative symptom scores. Recent CT studies by Owens et al[33] and Farmer et al[35] also failed to find significant positive correlations between these two variables. The literature to date does not appear to support the earlier suggestion that there may be a link between the presence of CT differences and negative symptoms.

The previous study of CT measures in schizophrenia from our center[26] was unable to detect significant differences between schizophrenics and controls. There are a number of possible explanations for the conflicting results generated by these two studies. The two studies differ in a number of important ways: patient and control sample characteristics, sample size, CT scanner, and computer algorithms for distinguishing tissue and fluid.

In the present study, all but one of the patients were inpatients on a psychiatric research ward. The study by Jernigan et al[26] included outpatients as well as inpatients from our research ward and other wards. Of the research ward patients included in that study, only those who were able to be medication free for over two weeks were included. This criterion and the inclusion of outpatients may have led to the selection of a group of patients who were less likely to differ from controls on CT measures. In the current sample of patients, those who were able to be medication free for greater than two weeks had cortical sulci that were significantly smaller (mean $z = 0.75$, n = 23) than those who were never medication free (mean $z = 1.67$, n = 22) during the index admission ($t = 1.978$, $P \le .05$, one-tailed). There was a nonsignificant trend in the same direction for the lateral ventricles, with the unmedicated group having a mean z of 0.11 and the medicated group having a mean z of 0.53. These two groups of patients did not differ significantly in age or on Luria Global scores. The differences found between the CT measures of these two groups are not likely related to the effects of the medications themselves. Of those patients who were medication free for greater than two weeks during the index admission, 16 were scanned while not taking medications. The CT measures for these patients did not differ from those of ten patients who had been taking medications for greater than two weeks at the time of their scans. This finding suggests that patients who are able to discontinue medications may be a distinct subgroup of patients who differ on biological measures. It is not clear how this group differs clinically from the group that could not be assessed free of medications.

The present study also employed larger sample sizes than the Jernigan et al study[26]: 45 compared with 30 schizophrenics and 57 vs 33 controls. With our larger patient and control samples, we had additional power to detect small differences between the two groups. Had we had only 30 patients in our sample with the same effect size, the difference in the size of the lateral ventricles would not have been statistically significant. Unfortunately, we do not have comparable clinical ratings available for the earlier group of patients, so it is not possible to compare the groups directly.

Where the current study differs most strikingly from the Jernigan et al[26] study is not in the measurement of lateral ventricles, which are only marginally different in this study, but in the large number of patients in the current study who had evidence of enlarged cortical sulci. The measurement of the cortical sulci is likely affected to a great extent by both the different scanners used and the different software algorithms for analyzing the data. The Syntex scanner used in the Jernigan et al study was an earlier-generation scanner than the EMI 1010 used in the current study; there was much less resolution of the cortical sulci because of spectral shift artifact at higher brain levels. The EMI 1010 also has a high degree of spectral shift artifact; however, steps were taken to filter out this artifact so that sulci could be assessed in a more accurate way.[18] The Jernigan et al study also differed in the method of designating pixels located in the "grayish," partially volumed areas at the edges of the ventricles and sulci. The current approach was to identify a threshold level for the CT number above which it would be anatomically correct to identify all pixels as tissue and below which all pixels would be identified as fluid.

The relationship between severity of illness and the magnitude of ventricular and sulcal size in schizophrenics does not appear to be straightforward. Although the two samples of schizophrenic patients presented herein (the Palo Alto patients and the Menlo Park patients) differed greatly in degree of functional impairment and on BPRS scores, there were no striking differences apparent between their respective measures of ventricular and sulcal size. As previously discussed, these differences may have been obscured by the age differences in the two samples. In addition, no significant relationships were found between measures of cognitive dysfunction or negative symptoms and ventricular and sulcal measures. It was puzzling, therefore, that those patients who were able to be assessed medication free should have smaller vertex sulci than those patients who were not able to discontinue their medications. It is conceivable that there might be some clinically meaningful way in which these groups do differ that might be related to the CT differences found. With the data available, however, these two groups could not be distinguished clinically.

CONCLUSION

Our results suggest that patients with schizophrenia, as a group, do have slightly enlarged ventricles and sulci. The differences between schizophrenics and normal controls were small but statistically significant for all measures studied. The sulcal changes were more prominent than the ventricular changes. The sulcal enlargement found was generalized in nature, with no particular predilection for the frontal lobes. Measures of ventricular and regional sulcal enlargement were significantly intercorrelated in the patient population, suggesting that the underlying pathological process is not merely affecting different areas in different individuals. One interpretation is that generalized increases in CSF space volumes (and attendant decreases in the surrounding tissue volumes) may not be

the primary abnormality in schizophrenia but rather may be secondary to changes occurring in more specific subcortical structures.[47] Recent neuropathological studies[48,49] have implicated the medial temporal structures of the hippocampus, parahippocampal gyrus, and amygdala. The limitations of CT in visualizing these areas are such that this question will need to be addressed by magnetic resonance imaging studies.

References

1. Johnstone E, Crow T, Frith C, Husband J, Kreel L: Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet* 1976;2:924-926.

2. Jernigan T: Anatomical and CT scan studies of psychiatric disorders, in Berger P, Brodie HKH (eds): *American Handbook of Psychiatry.* New York, Basic Books Inc Publishers, 1986, vol 8, pp 213-235.

3. Goetz K, van Kammen D: Computerized axial tomography scans and subtypes of schizophrenia: A review of the literature. *J Nerv Ment Dis* 1986;174:31-41.

4. Seidman L: Schizophrenia and brain dysfunction: An integration of recent neurodiagnostic findings. *Psychol Bull* 1983;94:195-238.

5. Weinberger D, Wagner R, Wyatt R: Neuropathological studies of schizophrenia: A selective review. *Schizophr Bull* 1983;9:193-212.

6. Sax D, O'Donnell B, Butters N, Menzer L, Montgomery K, Kayne H: Computed tomographic, neurologic, and neuropsychological correlates of Huntington's disease. *Int J Neurosci* 1983;18:21-36.

7. Sroka H, Elizan T, Yahr M, Burger A, Mendoza M: Organic mental syndrome and confusional states in Parkinson's disease. *Arch Neurol* 1981;38:339-342.

8. Ron M: The alcoholic brain: CT scan and psychological findings. *Psychol Med Monogr Suppl* 1983;3:1-33.

9. Pearlson G, Garbacz D, Breakey W, Ahn H, DePaulo J: Lateral ventricular enlargement associated with persistent unemployment and negative symptoms in both schizophrenia and bipolar disorder. *Psychiatry Res* 1984;12:1-9.

10. Nasrallah H, McCalley-Whitters M, Jacoby C: Cortical atrophy in schizophrenia and mania: A comparative CT study. *J Clin Psychiatry* 1982;43:439-441.

11. Scott M, Golden C, Ruedrich S, Bishop R: Ventricular enlargement in major depression. *Psychiatry Res* 1983;8:91-93.

12. Artmann H, Grau H, Adelmann M, Schleiffer R: Reversible and non-reversible enlargement of cerebrospinal fluid spaces in anorexia nervosa. *Am J Neuroradiol* 1985;2:23-27.

13. Enzemann D, Lane B: Cranial computed tomography findings in anorexia nervosa. *J Comput Assist Tomogr* 1977;1:410-414.

14. Weinberger D, Torrey E, Neophytides A, Wyatt R: Lateral cerebral ventricular enlargement in chronic schizophrenia. *Arch Gen Psychiatry* 1979;36:735-739.

15. Weinberger D, Torrey E, Neophytides A, Wyatt R: Structural abnormalities in the cerebral cortex of chronic schizophrenic patients. *Arch Gen Psychiatry* 1979;36:935-939.

16. Johnstone E, Crow T, Frith C, Stevens M, Kreel S, Husband J: The dementia of dementia praecox. *Acta Psychiatr Scand* 1978;57:305-324.

17. Maser J, Keith S: CT scans and schizophrenia: Report on a workshop. *Schizophr Bull* 1983;9:265-283.

18. Pfefferbaum A, Zatz L, Jernigan T: Computer-interactive method for quantifying cerebrospinal fluid and tissue in brain CT scans: Effects of aging. *J Comput Assist Tomogr* 1986;10:571-578.

19. Boronow J, Pickar D, Ninan P, Roy A, Hommer D, Linnoila M, Paul S: Atrophy limited to the third ventricle in chronic schizophrenic patients. *Arch Gen Psychiatry* 1985;42:266-271.

20. Dewan M, Pandurangi A, Lee S, Ramachandran T, Levy B, Boucher M, Yozawitz A, Major L: Central brain morphology in chronic schizophrenic patients: A controlled CT study. *Biol Psychiatry* 1983;18:1133-1140.

21. Tanaka Y, Hazama H, Kawahara R, Kobayashi K: Computerized tomography of the brain in schizophrenic patients: A controlled study. *Acta Psychiatr Scand* 1981;63:191-197.

22. Pandurangi A, Dewan M, Boucher M, Levy B, Ramachandran T, Bartell K, Bick P, Phelps B, Major L: A comprehensive study of chronic schizophrenic patients: II. Biological, neuropsychological, and clinical correlates of CT abnormality. *Acta Psychiatr Scand* 1986;73:161-171.

23. Gluck E, Radu W, Mundt C, Gerhardt P: A computed tomographic prolective trohoc study of chronic schizophrenics. *Neuroradiology* 1980;20:167-171.

24. Nyback H, Wiesel F, Berggren B, Hindmarsh T: Computed tomography of the brain in patients with acute psychosis and in healthy volunteers. *Acta Psychiatr Scand* 1982;65:403-414.

25. Okasha A, Madkour O: Cortical and central atrophy in chronic schizophrenia: A controlled study. *Acta Psychiatr Scand* 1982;65:29-34.

26. Jernigan T, Zatz L, Moses J, Berger P: Computed tomography in schizophrenics and normal volunteers: I. Fluid volume. *Arch Gen Psychiatry* 1982;39:765-770.

27. Luchins D, Meltzer H: A comparison of CT findings in acute and chronic ward schizophrenics. *Psychiatry Res* 1986;17:7-14.

28. Smith G, Iacono W: Lateral ventricular size in schizophrenia and choice of control group. *Lancet* 1986;1:1450.

29. Williams A, Reveley A, Kolakowska T, Ardern M, Mandlebrote B: Schizophrenia with good and poor outcome: II. Cerebral ventricular size and its clinical significance. *Br J Psychiatry* 1986;146:239-246.

30. Andreasen N, Olsen S, Dennert J, Smith M: Ventricular enlargement in schizophrenia: Relationship to positive and negative symptoms. *Am J Psychiatry* 1982;139:297-302.

31. Nasrallah H, Kuperman S, Hamra B, McCalley-Whitters M: Clinical differences between schizophrenic patients with and without large cerebral ventricles. *J Clin Psychiatry* 1983;44:407-409.

32. Luchins D, Lewine R, Meltzer H: Lateral ventricular size, psychopathology, and medication response in the psychoses. *Biol Psychiatry* 1984;19:29-44.

33. Owens D, Johnstone E, Crow T, Frith C, Jagoe J, Kreel L: Lateral ventricular size in schizophrenia: Relationship to the disease process and its clinical manifestations. *Psychol Med* 1985;15:27-41.

34. Losonczy M, Song I, Mohs R, Small N, Davidson M, Johns C, Davis K: Correlates of lateral ventricular size in chronic schizophrenia: I. Behavioral and treatment response measures. *Am J Psychiatry* 1986;143:976-981.

35. Farmer A, Jackson R, McGuffin P, Storey P: Cerebral ventricular enlargement in chronic schizophrenia: Consistencies and contradictions. *Br J Psychiatry* 1987;150:324-330.

36. Golden C, Moses J, Zelazowski R, Graber B, Zatz L, Horvath T, Berger P: Cerebral ventricular size and neuropsychological battery. *Arch Gen Psychiatry* 1980;37:619-623.

37. Jeste D, Kleimman J, Potkin S, Luchins D, Weinberger D: Ex uno multi: Subtyping the schizophrenic syndrome. *Biol Psychiatry* 1982;17:199-222.

38. Rieder R, Donnelly E, Herdt J, Walkman I: Sulcal prominence in young chronic schizophrenic patients: CT scan findings associated with impairment on neuropsychological tests. *Psychiatry Res* 1979;1:1-8.

39. Donnelly E, Weinberger D, Walkman I, Wyatt R: Cognitive impairment associated with morphological brain abnormalities on computed tomography in chronic schizophrenic patients. *J Nerv Ment Dis* 1980;168:305-308.

40. Zatz L, Jernigan T, Ahumada A: Changes on computed cranial tomography with aging: Intracranial fluid volume. *Am J Neuroradiol* 1982;3:1-11.

41. Jernigan T, Zatz L, Ahumada A, Pfefferbaum A, Tinklenberg J, Moses J: CT measures of cerebrospinal fluid volume in alcoholics and normal volunteers. *Psychiatry Res* 1982;7:9-17.

42. Stahl S, Jernigan T, Pfefferbaum A, Zatz L: Brain computerized tomography in subtypes of severe chronic schizophrenia. *Psychol Med* 1988;18:73-78.

43. Overall J: The Brief Psychiatric Rating Scale in psychopharmacology research. *Mod Probl Pharmacopsychiatry* 1974;7:67-78.

44. Doran A, Pickar D, Boronow J, Breier A, Wolkowitz O, Goodwin F: CT scans in schizophrenic patients, medical and normal controls: Replication and new findings, abstracted (p 140). American College of Neuropsychopharmacology Annual Meeting: Abstracts of Panels and Posters, 1985.

45. Pfefferbaum A, Rosenbloom M, Crusan K, Jernigan T: Brain CT changes in alcoholics: The effects of age and alcohol consumption. *Alcoholism Clin Exp Res* 1988;12:81-87.

46. Turner S, Toone B, Brett-Jones J: Computerized tomographic scan changes in early schizophrenia: Preliminary findings. *Psychol Med* 1986;16:219-225.

47. Weinberger D: Computed tomography (CT) findings in schizophrenia: Speculation of the meaning of it all. *J Psychiatr Res* 1984;18:477-490.

48. Bogerts B, Meertz E, Schonfeldt-Bausch R: Basal ganglia and limbic system pathology in schizophrenia. *Arch Gen Psychiatry* 1985;42:784-791.

49. Brown R, Colter N, Corsellis N, Crow T, Frith C, Jagoe J, Johnstone E, Marsh L: Postmortem evidence of structural brain changes in schizophrenia. *Arch Gen Psychiatry* 1986;43:36-42.