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Magnetic Resonance Imaging Abnormalities in Lenticular Nuclei and Cerebral Cortex in Schizophrenia

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• **Neuropathologic and brain imaging studies have produced evidence of brain abnormalities in schizophrenic patients, often within the cerebrum's limbic lobe, and, less frequently, within basal ganglia. In the present study we used magnetic resonance imaging morphometric techniques to estimate volumes of specific cerebral structures in schizophrenic patients and age- and sex-matched normal controls. Estimates of the volume of mesial temporal lobe structures were reduced and estimates of the volume of the lenticular nucleus were increased in the schizophrenic patients. There was also evidence of reduced cranial volume in some schizophrenics. The magnitude of the lenticular abnormality, but not the temporal lobe abnormality, was associated with age at first psychiatric contact; earlier onset was associated with larger lenticular nuclei. The possible relevance of these results to neurodevelopmental hypotheses about the pathogenesis of schizophrenia is discussed.**

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Recent neuropathologic studies have produced converging evidence of brain pathologic changes in schizophrenic patients, often within the cerebrum's limbic lobe, and, less frequently, within the basal ganglia. Some of the first abnormalities noted in these regions include disorganization of cells in the neuropil[1,2] and other cytoarchitectonic irregularities[3-6] and increased gliosis,[7-9] although the latter could not be confirmed in some studies.[4,10-14] Several investigators have measured reduced volumes of and/or decreased cell numbers in mesial temporal lobe structures, including amygdala, hippocampus, parahippocampal gyrus, and entorhinal cortex.[13,15-19] Benes and colleagues[5,6] found smaller, more widely spaced neurons and excessive vertical axons in the cingulate cortex of schizophrenic patients. Abnormalities of basal forebrain nuclei of the substantia innominata were also found in several studies.[7,9,20]

Bogerts and colleagues[15] reported a reduction in the volume of the internal pallidum in addition to mesial temporal lobe volume reductions; however, Rosenthal and Bigelow[21] found no volume differences in basal ganglia structures. In contrast to these results, significant *increases* in striatal and pallidal volumes were found in a recent study.[22] The methods of the latter study may have been more sensitive than those of earlier studies since individual corrections for tissue shrinkage and pairwise matching for age and gender were used.

Although excessive mineralization in the pallidum (a putative marker for dysfunction in that structure) had been noted on neuropathologic examination of some schizophrenic brains,[9] a recent study revealed no significant increase in iron deposition in the internal segment.[23] Another basal ganglia structure that has received scrutiny, partly because of its strong connection with the limbic system, is the nucleus accumbens, in which some neurons were found to have decreased diameter.[24] However, the volume of this structure appeared to be unaltered in a recent morphometric study.[15] A slight overall reduction in brain weight and volume in schizophrenic patients has also been noted in some neuropathologic studies.[16,25,26] In another study, however, brain size in schizophrenic patients was equivalent to that in controls.[21]

Magnetic resonance imaging (MRI) provides the anatomical resolution necessary for in vivo detection of some of the structural abnormalities revealed in pathologic studies. This technique has been applied in a number of recent studies of schizophrenia. In addition to increases in cerebrospinal fluid volume,[27,28] other anomalies have been observed, such as reduced cerebral size,[29-31] temporal horn abnormalities,[32] corpus callosum and adjacent septum pellucidum abnormalities,[33-35] and volume reductions in the thalamus[28] and temporal lobe.[36-38]

Unfortunately, some studies have already reported findings that are inconsistent with the MRI studies cited above. For example, no increased ventricular volume was found in two studies,[39,40] and Kelsoe et al[27] were unable to

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detect differences in limbic or basal ganglia volumes or corpus callosum measurements. The results of a study of corpus callosum measurements in schizophrenic patients by Mathew et al[33] did not confirm an expected width increase, but their results did suggest increased callosal length and increased size of the septum pellucidum, which was correlated with the duration of illness. Uematsu and Kaiya[35] reported increased septum size, and the increases were associated with a positive family history of the disorder, but not duration of illness. Hauser et al[41] could not confirm any morphologic differences in the corpus callosum between schizophrenics and controls. Finally, decreased brain size could not be confirmed in several MRI studies.[27,28,42-45]

In summary, anatomical studies of schizophrenic patients, while somewhat inconsistent, have revealed numerous abnormalities, some of which are consistent with degenerative changes (such as ventricular enlargement and gliosis), but several of which suggest neurodevelopmental anomalies (such as small brain size, callosal anomalies, increased volume of basal ganglia structures, and reduced limbic volumes unaccompanied by gliosis). In the present study, we used MRI morphometric techniques to estimate volumes of specific cerebral structures in schizophrenic patients and age- and sex-matched normal controls. In addition to overall cerebral size and the sizes of CSF spaces, we examined nuclei of the basal ganglia, diencephalic structures, regional cortical structures, and the presence of signal hyperintensity in the white matter. Of primary interest, of course, were measures of limbic and basal ganglia structures, and abnormalities were detected in both of these regions in the present study. These results were interpreted in light of recent neurodevelopmental hypotheses about the pathogenesis of schizophrenia.

PATIENTS, MATERIALS, AND METHODS

Patients

Patients were selected from the University of California, San Diego (UCSD) Outpatient Psychiatric Research Center (OPCRC). Each patient underwent an extensive diagnostic workup, including the Structured Clinical Interview for *DSM-III-R* (SCID-P).[46] Patients were excluded if they had a history of significant medical or neurologic illnesses, including significant loss of consciousness from any cause. Patients all met *DSM-III-R* criteria for schizophrenia. A schizophrenic subtype was assigned for each of the chronic schizophrenic patients on the basis of *DSM-III-R* criteria. The patients designated as having the paranoid subtype of the disease did not have prominent disturbances of affect or conceptual disorganization. Patients who had a predominance of conceptual disorganization were classified as having the disorganized subtype, and the remaining patients were classified as having the undifferentiated subtype.[47] Age at onset of the disorder was estimated by recording the age at which the first contact was made with a mental health professional.

Controls were selected from a pool of normal volunteers who had participated in various neuropsychiatric brain imaging studies. The age range of the controls (19 to 42 years) was similar to that of the patients (18 to 46 years). All controls underwent medical and psychiatric screening, the extent of which varied from a single interview to assess medical and psychiatric history to screening that consisted of medical history, physical examination, and structured psychiatric examination.

Other demographic characteristics of the two groups are as follows. The mean (SD) age of controls was 32.2 (6.4) years and for patients, 30.0 (7.9) years. Five (21%) of the 24 controls were women and 19 (79%) were men, while 14 (33%) of the 42 patients were women and 28 (67%) were men. The mean (SD) education for controls was 15.0 (2.4) years and for patients, 13.2 (2.0) years.

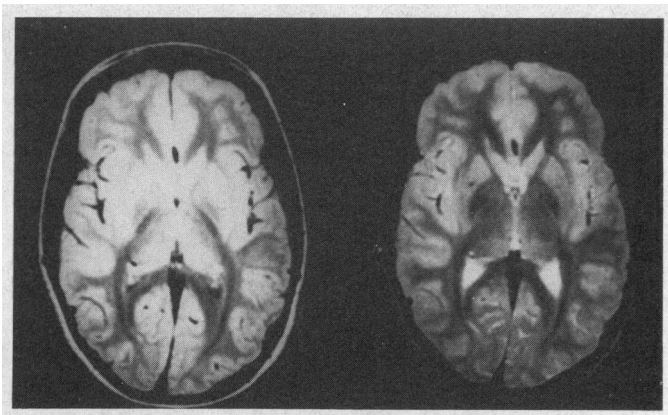

Fig 1.—*Representative images from the standard protocol. Left, Axial section, spin echo, 2000/25 milliseconds. Right, Axial section, SE, 2000/70 milliseconds. Sections are 5 mm thick. A 256 × 256 matrix with 2.5-mm gaps between images and a 24-cm field of view was used.*

Subjects were classified as substance abusers if they met one or more of the following criteria[48]: (1) consumption of at least five alcoholic beverages per day for a minimum of 90 days; (2) inhalation of marijuana at least 5 days per week for a minimum of 90 days; or (3) use of several substances of abuse (excluding alcohol and marijuana) on 30 or more occasions. The most commonly abused substances in this population of outpatient schizophrenics were alcohol and marijuana. Other psychoactive substances were less common and had usually been accompanied by use of multiple substances. All schizophrenic subjects denied use of any psychoactive substance in the 6 months prior to undergoing their baseline clinical assessments or MRI.

Twenty-three (55%) of the 42 chronic schizophrenic patients and none of the controls were classified as substance abusers. Ten schizophrenic patients had disorders classified as disorganized subtype, 24 had undifferentiated subtype, and eight had paranoid subtype. Seventy-four percent of the schizophrenic subjects had been hospitalized, and 90.5% had been treated with neuroleptic medication. The mean (SD) age of patients at first psychiatric contact was 19.4 (5.5) years. The mean (SD) number of psychiatric hospitalizations was 2.9 (3.6), and the mean duration of hospitalizations was 3.5 (6.5) months. The mean (SD) neuroleptic use in chlorpromazine equivalents was 656 (1008) mg.

MRI Protocol

Magnetic resonance imaging was performed with a 1.5-T super-conducting magnet (Signa, General Electric, Milwaukee, Wis) at the UCSD/AMI Magnetic Resonance Institute, San Diego, Calif. Two spatially registered images (Fig 1) were obtained simultaneously for each section using an asymmetrical, multiple-echo sequence (repetition time, 2000 milliseconds; echo time, 25 and 70 milliseconds) to obtain images of the entire brain in the axial plane. Section thickness was 5 mm with a 2.5-mm gap between successive sections in all instances. A 256 × 256 matrix and 24-cm field of view were used. For the following discussion of image analysis, the term *pixel* will be used to refer to a single picture element (or signal value) from the image matrix. The term *voxel* will be used to refer to the corresponding three-dimensional volume from which the signal value for a pixel arises.

Image Analysis

Detailed descriptions of the image-analytic approach used in the present study are contained in several articles.[49-52] Image data sets were assigned random numeric codes, and all analyses were conducted blind to any subject characteristics. Briefly, each pixel

location within a section of the imaged brain was classified on the basis of its signal values in both original images (echo time, 25 and 70 milliseconds) as most resembling CSF, gray matter, white matter, or signal hyperintensity (tissue abnormality). This was accomplished in two steps. First, two new linear combinations of the pixel values were computed to optimize tissue contrast (ie, CSF/brain and gray matter/white matter). Classification criteria that were adjusted separately for each section were then applied to these computed values. The full series of axial images was analyzed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex.

Consistently identifiable landmark points and structural boundaries were designated on the pixel-classified images by trained image analysts, as described below. The processed image data were then transformed spatially so that all locations within the brain images could be identified relative to a common anatomical coordinate system. Cerebral regions were then defined relative to this coordinate scheme (ie, stereotactically).

Definition of Subcortical Structures

To delineate subcortical structures, the operators circumscribed pixels classified as gray matter that were visually determined to be in caudate nuclei, lenticular nuclei, and diencephalic gray-matter structures (which included, but did not separately delineate, mammillary bodies, hypothalamic gray, septal nuclei, and thalamus). Further subdivisions of the structures could not reliably be visually determined. The operators did not trace the edges of the structures, but defined polygons that included all gray-matter pixels within the structures and excluded those gray-matter pixels associated with other structures. In some cases, when the subcortical nuclei were contiguous with other areas classified as gray but clearly not in the structures, boundaries were manually constructed using the filmed images as a guide. Estimates of the volumes of the subcortical structures were made by summing the designated gray-matter pixels across all sections.

Definition of Cortical Regions

Visual determination of specific cortical structures on MRI depends on the presence of visible gross morphologic features relative to which the boundaries of the cortical regions can be defined. Standard regional divisions for the cortex are based to a large extent on cortical gyral patterns, but the accurate localization of particular gyri or sulci throughout a series of images is often impossible. Even when attempts are made to standardize head positioning, rotation of the head (relative to the imaging plane) occurs in all three planes. Careful inspection indicates that relatively small rotations substantially change the appearance of brain structures in the image plane, further complicating their visual identification. Thus, manually tracing the structures in the sections in which they are best visualized often leads to inaccurate boundary determinations and volume assessments. The stereotactic techniques described below are designed to address these problems.

To define anatomically consistent cortical regions, a method was adopted for making subdivisions of the cerebrum relative to the centromedial structural midline and two consistently identifiable, operator-designated points: the most anterior midline point in the genu and the most posterior midline point in the splenium of the corpus callosum. By calculating estimated rotation angles using these landmarks, it was possible to perform a three-dimensional rotation of the images, thus correcting each individual's image data for rotation out of the optimal imaging plane. Regions could then be constructed that resulted in highly consistent placement of regional boundaries relative to gross anatomical landmarks.

The midsagittal plane was considered to pass through the two corpus callosum points. The orientation of this plane was then determined by computing a regression line through a series of visually selected brain-stem midline points. The division of the cerebrum was then based on two major planes (Fig 2): an *axial* plane, which is perpendicular in orientation to the midsagittal plane and passes through the two corpus callosum points, and a *coronal* plane, which is defined as perpendicular to the first plane and passes through the midpoint between the two corpus callosum points. By computing new coordinates for the center point of each voxel relative to these planes, each voxel was assigned to one of four zones: (1) inferior to the axial plane and anterior to the coronal plane (IA); (2) inferior to the axial plane and posterior to the coronal plane (IP); (3) superior to the axial plane and anterior to the coronal plane (SA); and (4) superior to the axial plane and posterior to the coronal plane (SP).

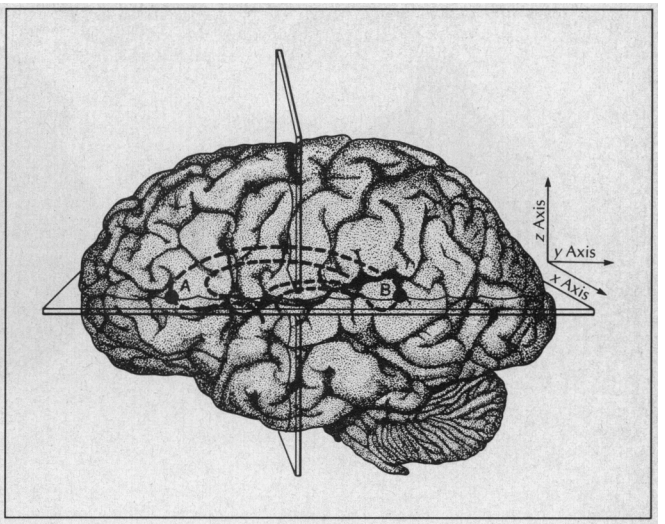

Fig 2.—*Cerebral regions are defined as follows. Points A and B in the corpus callosum are the most anterior midline point in the genu and the most posterior midline point in the splenium, respectively. An axial plane passing through these two points is defined as perpendicular to the midsagittal plane. A coronal plane is defined as perpendicular to the axial plane and passing through the midpoint between points A and B. Four cerebral zones are defined: inferior anterior, inferior posterior, superior anterior, and superior posterior. Anterior temporal, orbitofrontal, and some dorsolateral and mesial frontal cortex lie in the inferior anterior zone. Posterior temporal and inferior occipital cortex fall in the inferior posterior zone. Most of the remaining parts of the frontal lobe fall into the superior anterior zone, and the superior posterior zone contains primarily parietal cortex and superior occipital cortex.*

These defined planes are independent of the image plane, since a three-dimensional rotation is first applied based on the positions of the landmarks described above. It should be noted that the accuracy of the estimated rotation angle for z axis rotation is lower than that for x and y axis rotation since the image data sets are anisotropic. Anterior, temporal, orbitofrontal, and some dorsolateral and mesial frontal cortex lie in the inferior anterior zone. Posterior temporal and inferior occipital cortex fall in the inferior posterior zone. Most of the remaining parts of the frontal lobe fall into the superior anterior zone, and the superior posterior zone contains primarily parietal lobe and a small portion of the superior occipital cortex.

To further separate mesial from peripheral cortical regions, an ellipsoid volume was defined within the supratentorial cranial vault. This volume constitutes 30% of the supratentorial volume and has cardinal dimensions proportional to those of the supratentorial vault (ie, the z axis extent of the ellipsoid is proportional to the maximum z axis extent of the supratentorial cranium, the y axis extent of the ellipsoid is proportional to the maximum y axis extent of the supratentorial cranium, and the x axis extent of the ellipsoid is proportional to the maximum x axis extent of the supratentorial cranium).

The ellipsoid is centered slightly behind but in the same axial plane as the origin of the coordinate system described above, at a point 60% of the distance from the genu to the splenium ref-

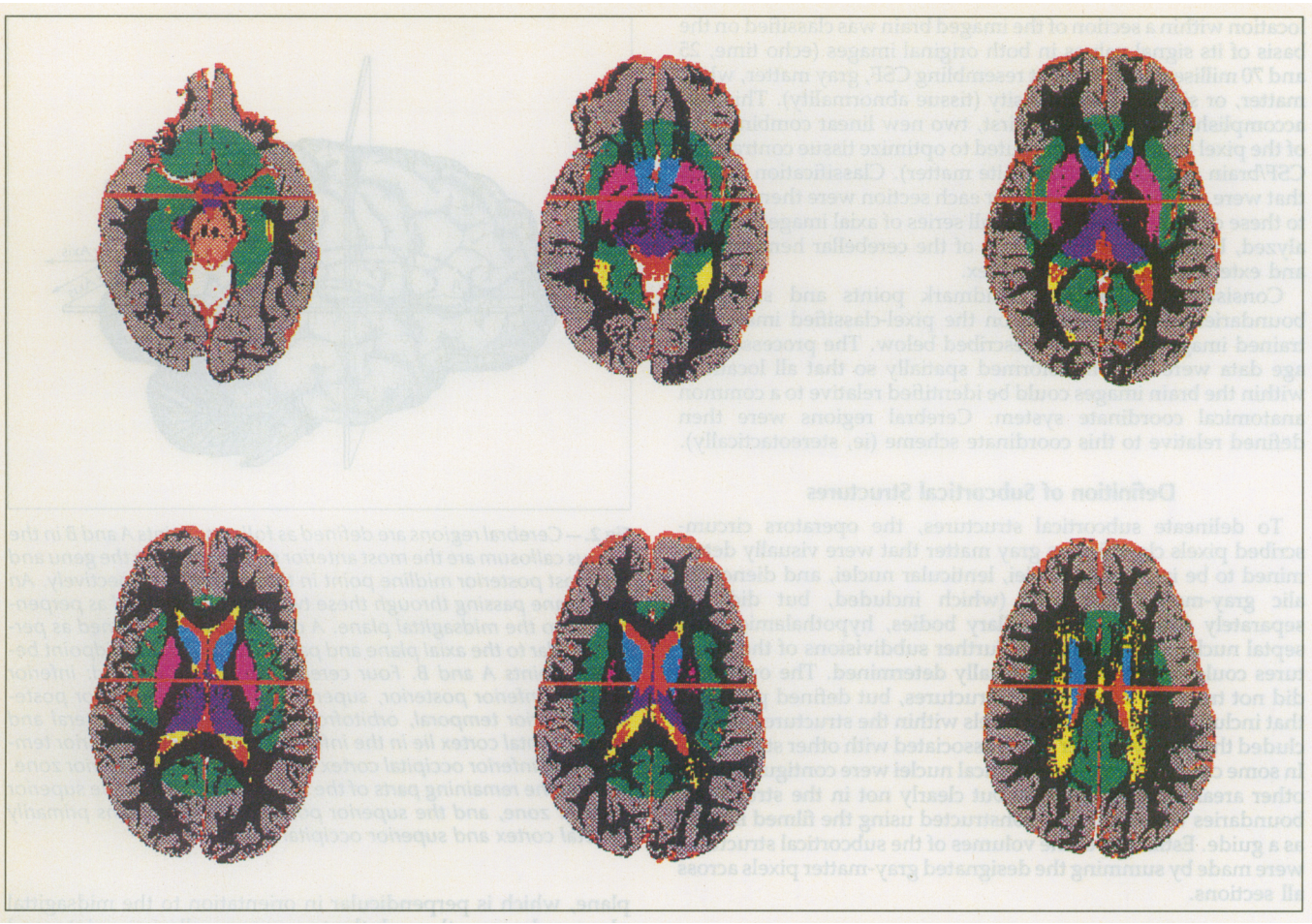

Fig 3.—*Representative, fully processed images. Pixels are classified and zones have been manually designated. The gray-matter pixels have been color coded to display the zone designations: gray indicates peripheral cortex; green, mesial cortex; blue, caudate; magenta, lenticular nucleus; and purple, diencephalon. Cerebrospinal fluid and white-matter pixels in all zones are displayed in red and black, respectively; however, these pixels are coded separately by zone so that regional measures may be computed. The yellow pixels within the subcortical zone are white matter with the signal characteristics of gray matter. Top row, Sections completely classified as inferior to the dividing plane. Bottom row, Sections completely classified as superior to the dividing plane. For both inferior and superior zones, the red line shown within the sections indicates the position of the coronal dividing plane. The ellipsoid defining the mesial cortex has cardinal dimensions proportional to those of the supratentorial cranium and occupies 30% of its volume.*

erence point along the line connecting them. The size and center point of the volume were chosen empirically to isolate as well as possible the medial cortical surfaces of the limbic lobe while excluding the more lateral neocortical surfaces. The choice of these parameters for the ellipsoid was based on the examination of 25 normal control brains of different ages and with different degrees of head rotation. The area designated as mesial with this method is shown in green in Fig 3. It consistently includes the most posterior parts of the orbital frontal lobe (including the anterior perforated substance and related basal forebrain structures), the amygdala, the hippocampus and most of the parahippocampal gyrus, the insula, and most of the cingulate gyrus. The ellipsoid defines mesial and peripheral zones within each of the four original cerebral zones defined above.

The fully processed images are illustrated in Fig 3. The different pixel classes are color coded as follows: diencephalic areas are purple, caudate nuclei are blue, and lenticular nuclei are magenta. Within the subcortical white matter are some voxels with signal values that fall not within the criterion range for white, but within the range of gray-matter values (ie, they demonstrate lengthened T_2 relative to other white-matter voxels). These voxels have been coded separately and are shown in Fig 3 in yellow.

The red line running through each section indicates the position of the coronal dividing plane. Because this plane passes through the diencephalic gray-matter regions and divides the functionally distinct hypothalamic and septal structures (lying anteriorly) from the bulk of the thalamus (lying posteriorly), the corresponding anterior and posterior diencephalic areas were examined separately. It should be noted that areas within the lenticular nucleus containing significant iron deposits, particularly in globus pallidus, do not meet the signal criteria for gray matter and are thus not included in this region. Fluid is shown in red and white matter in black; however, subcortical fluid and cortical fluid are measured separately.

Volume of the supratentorial cranium was estimated by summing supratentorial voxels (including CSF, hyperintensities, and gray and white matter) over all sections. The gray-matter voxels within each of the subcortical structures and the cortical gray-matter voxels within each of the eight cerebral zones were summed separately. Eight regional volumes were also computed by summing all supratentorial voxels (including CSF, hyperintensities, and gray and white matter) within each region. Those diencephalic structures falling within the anterior cerebral zone (ie, before the defined *coronal* plane), including septal nuclei, hypothalamic midline gray, and some basal forebrain regions (Fig 3), and those falling within the posterior cerebral zone (almost entirely thalamus) were volumed separately. Finally, an index of signal alterations in the white matter was constructed by summing voxels within the subcortical white-matter regions having signal characteristics meeting criteria for "gray matter" or for "signal hyperintensities"; ie, they had longer T_2 values.

Statistical Analysis

Before comparing the measures from patients with those from controls, additional analyses were conducted to remove irrelevant variability due to head size and age from the estimated volumes of gray-matter structures, CSF, and white-matter abnormality. These adjustments were based on analyses conducted earlier within a larger group of 107 normal controls. Most, but not all, of the present controls were in this larger group. The magnitudes of normal age-related changes and effects of cranium (or cranial region) size were estimated for each measure with multiple regression analyses.

Previous studies[53,54] have suggested that some relationships between brain structural volumes and age or cranial volume are not linear. For this reason, polynomial regressions were performed to detect significant deviations from linearity. If the simple correlation (linear component) of age with a morphologic measure was statistically significant, a quadratic term (age squared) was added to the regression. Similarly, if a linear term for the cranial measure contributed significantly, a quadratic term was included. If the addition of such terms significantly increased the multiple correlation coefficient (R^2), the function was considered to be nonlinear, and the function with both terms was used in the correction formula.

On the basis of these analyses, new measures were computed for each normal control that expressed the original values as deviations from the values predicted from the subjects' ages and cranium sizes. Similar analyses were then conducted to estimate any age-related change in the variance of the new deviation scores. Finally, formulas were constructed for estimating a subject's deviation from age- and cranium-predicted values in SD units appropriate for the subject's age.

This rather complex data reduction method was used because the resulting measures are considered to have numerous advantages over the simple volumes. In the present study, the volumes of brain structures were measured in an attempt to detect abnormalities such as atrophy, hypoplasia, or hyperplasia of the structures. Within normal subjects, brain size variability, presumably related to body size variability, is a large contributor to the volume variability of most brain structures; yet, by definition, it is not related to any of these abnormal processes. Thus, if such variability can be removed, a larger proportion of the remaining variability should be related to abnormal processes. A similar argument applies to the volume variability within normal subjects that is associated with age. The present method produces measures of structural volume that are independent of cranium size variations and age.

It should be noted that a deviant score on such a measure has a different meaning than a deviant score on a more conventional volume measure. Such a score suggests that a structural volume has an anomalous (or improbable) relationship to cranial size, ie, it is too large or too small, given the subject's age. The degree to which results using these measures are comparable with those from neuropathologic studies is not clear. A further advantage of the measures presented here, however, is that since they represent estimated z scores, they are expressed on roughly equivalent scales; thus, it is possible to make gross comparisons of the magnitude of change in one structure with that in another. Since the z scores may not have equal sensitivity in all age ranges and do not correct for other demographic factors, we have conservatively compared the mean z scores of the schizophrenic sample with those of the matched control group, rather than with the larger control group of 107 children and adults.

Group means of the cerebral volumes and z scores were compared with results of Student's *t* tests. Because of concerns about the effects of substance abuse within the patient sample, the abusing and nonabusing subgroups were compared in separate analyses. Because of the small sample sizes, differences between the schizophrenia subtype groups were examined with nonparametric Kruskal-Wallis analyses of variance. Age at first psychiatric contact was correlated with selected brain structural measures using Pearson's product-moment correlation coefficient. Post hoc covariance analyses were conducted to ensure that group differences on structural measures were not attributable to education differences between the groups. Finally, post hoc analyses were conducted in which the sample was separated into male and female subsamples.

Table 1.—Intracranial Volumes

	Mean (SD) Intracranial Volume, Voxels*	
	Controls	Patients
Supratentorial cranium	196819 (19208)	192645 (21746)
Inferior zone	76318 (7655)	78558 (11537)
Superior zone	120501 (14634)	114085 (13146)†

*The mean (SD) inferior-superior ratio for controls was 0.64 (0.08) and for patients, 0.69 (0.09). $P<.05$.
†$P<.10$.

RESULTS

The mean volume of the supratentorial cranial vault was only slightly smaller in patients than in controls (Table 1). Inspection of the separate volumes for the inferior (infracallosal) and superior (supracallosal) regions suggests that there may have been a slight reduction of the superior zone in patients ($P<.10$), and that this zone was significantly reduced relative to the inferior zone ($P<.05$).

Group comparisons of the adjusted volumes (z scores) for white-matter abnormalities, ventricular CSF, and cortical sulcal CSF are shown in Table 2. All measures show increases in patients relative to controls, although the difference on the ventricular measure falls just short of significance ($P<.06$).

No significant reductions in the measures of subcortical gray-matter structures were observed in patients (Table 3). However, the lenticular nucleus measure shows a highly significant volume *increase* ($P=.001$). Follow-up analyses of this structure confirmed that in spite of a tendency for the cranial vault to be smaller in the schizophrenic patients, the absolute volume (simple sum of the designated voxels) of the lenticular nucleus is larger ($P<.01$). The increase is slightly more prominent on the left side ($P<.01$) than on the right side ($P<.05$), but the left-right asymmetry is not itself significantly different between the groups.

Analyses of regional cortical gray-matter measures are summarized in Table 4. Significant volume reductions in the patients were observed in mesial temporal and orbitofrontal regions. There were no significant differences in any of the superior regions or in the neocortical temporo-occipital area.

To ensure that the observed morphologic abnormalities were not associated with a history of substance abuse, the 19 nonabusing patients were compared on all measures with the 23 patients with a history of substance abuse. The results are summarized in Table 5. Only two significant differences emerged. The superior cranial volume was significantly smaller in the nonabusing group ($P<.05$). Inspection of the subgroup means on the remaining measures provided no evidence of greater volume loss in the patients with a history of substance abuse. The means are generally very similar within the two groups. The second difference between the groups was a decreased volume of mesial temporal lobe gray matter in the *nonabusing* group ($P<.05$). It should be noted that the lenticular nucleus was significantly increased in size relative to the 24 controls in both the substance-abusing ($P<.01$) and nonabusing ($P<.01$) subgroups.

Comparisons between disorganized, undifferentiated, and paranoid groups were made. Only one difference emerged; the cranial volume was significantly smaller in disorganized patients relative to the other groups. The difference was somewhat larger in the superior region ($P<.02$) than in the inferior ($P<.08$) region.

Within the schizophrenic sample, correlations were computed between age at the time of first psychiatric contact and the three

Table 2.—Global Measures: Volumes and Age- and Cranium-Adjusted, *z* Scores

Measure	Controls		Patients	
	Mean (SD) Volume*	Mean (SD) *z* Score	Mean (SD) Volume†	Mean (SD) *z* Score
White-matter abnormality	2670 (843)	0.58 (1.2)	3077 (1499)	1.39 (1.6)†
Cortical cerebrospinal fluid	14756 (4656)	0.12 (1.2)	17654 (5081)	0.85 (1.4)†
Ventricles	2751 (1033)	0.05 (1.2)	3305 (1279)	0.77 (1.5)‡

*Summed voxels.
†$P<.05$.
‡$P<.10$.

Table 3.—Subcortical Gray-Matter Structures: Volumes and Age- and Cranium-Adjusted *z* Scores

Structure	Controls		Patients	
	Mean (SD) Volume*	Mean (SD) *z* Score	Mean (SD) Volume*	Mean (SD) *z* Score
Anterior diencephalon	424 (123)	0.57 (1.0)	379 (148)	0.20 (1.2)
Thalamus	1870 (351)	0.08 (1.0)	1824 (442)	–0.00 (1.4)
Lenticular nucleus	1985 (303)	–0.34 (0.9)	2250 (440)	0.55 (1.1)†
Caudate nucleus	1906 (290)	–0.11 (1.1)	1886 (268)	–0.15 (0.8)

*Summer voxels.
†$P<.01$.

Table 4.—Regional Cortical Gray-Matter Volumes: Volumes and Age- and Cranium-Adjusted *z* Scores

Region*	Controls		Patients	
	Mean (SD) Volume†	Mean (SD) *z* Score	Mean (SD) Volume†	Mean (SD) *z* Score
IAM	4806 (821)	0.27 (1.1)	4382 (781)	–0.57 (1.3)‡
IPM	5549 (1052)	0.36 (1.2)	5069 (859)	–0.52 (1.2)‡
IAL	10804 (1828)	0.38 (0.9)	10579 (2408)	–0.20 (1.4)§
IPL	16327 (3831)	0.11 (0.9)	16814 (3524)	–0.17 (1.0)
SAM	3195 (550)	–0.15 (0.8)	3104 (677)	–0.28 (1.1)
SPM	5179 (720)	–0.05 (1.1)	5061 (938)	–0.24 (1.7)
SAL	18605 (3264)	–0.21 (1.0)	17530 (2782)	–0.49 (1.0)
SPL	26448 (4231)	–0.15 (1.0)	25183 (4103)	–0.38 (1.2)

*I indicates inferior; A, anterior; M, mesial; P, posterior; L, lateral; and S, superior.
†Summed voxels.
‡$P<.01$.
§$P<.10$.

volume measures distinguishing schizophrenics from controls: the mesial temporal lobe measure (IPM), the orbitofrontal/temporal pole measure (IAM), and the lenticular volume measure. Only the latter yielded a significant correlation ($r=-.38$; $P<.01$). The other two measures showed no association with age at onset ($r=-.03$ for IPM; $r=.11$ for IAM).

To rule out the possibility that group differences might be related to demographic differences reflected in the higher educational achievements of the controls, correlations were computed between years of education and the brain structural measures. No significant correlations occurred, either within controls or within patients. Furthermore, analyses of covariance, controlling for years of education, were performed for the lenticular volume and the two limbic volumes (IPM and IAM), showing significant group differences. In all cases, the group differences remained significant and the regression coefficients for the education variable were very small.

Table 5.—Comparison of Substance Abuse Subgroups on Brain Measures

	Nonabusing Patients	Abusing Patients
Mean (SD) intracranial volumes, voxels		
Supratentorial cranium	186820 (23550)	197455 (19340)
Inferior zone	77813 (12894)	79173 (10543)
Superior zone	109006 (12629)	118281 (12285)*
Mean (SD) global measures, *z* scores		
White-matter abnormality	1.53 (1.6)	1.27 (1.7)
Cortical cerebrospinal fluid	0.80 (1.6)	0.88 (1.4)
Ventricles	0.86 (1.8)	0.70 (1.3)
Mean (SD) subcortical gray-matter structures, *z* scores		
Anterior diencephalon	0.10 (1.2)	0.29 (1.2)
Thalamus	0.04 (1.5)	–0.03 (1.4)
Lenticular nucleus	0.51 (1.1)	0.57 (1.2)
Caudate nucleus	–0.04 (0.7)	–0.24 (1.0)
Mean (SD) regional cortical gray-matter volumes, *z* scores		
IAM	–0.79 (1.4)	–0.38 (1.1)
IPM	–0.95 (0.9)	–0.17 (1.3)*
IAL	–0.31 (0.9)	–0.12 (1.7)
IPL	–0.33 (0.8)	–0.04 (1.1)
SAM	–0.24 (1.3)	–0.31 (1.0)
SPM	–0.42 (1.9)	–0.08 (1.5)
SAL	–0.57 (1.0)	–0.41 (1.1)
SPL	–0.49 (1.0)	–0.29 (1.3)

*$P<.05$.
†The mean (SD) inferior-superior ratio for nonabusing patients was 0.71 (0.1) and for abusing patients, 0.67 (0.1).
‡I indicates inferior; A, anterior; M, mesial; P, posterior; L, lateral; and S, superior.

Finally, because earlier reports have suggested that brain morphologic abnormalities may be more prevalent in male than in female schizophrenic patients, separate comparisons of the diagnostic groups were conducted for male and female subjects. Unfortunately, this resulted in rather small samples; the female control group consisted of only five subjects. Therefore, the results must be interpreted with great caution. Nevertheless, there was little evidence for less abnormality in the female subjects. Despite the small sample sizes, the female patients showed significantly smaller cranium sizes and significantly increased lenticular and anterior diencephalic volumes relative to their controls. The reduction in volume of mesial temporal lobe structures and the increase in white-matter abnormality approached significance. There were, however, no increases in CSF volumes. In contrast, male patients showed highly significant increases in ventricular and sulcal CSF volumes, significant increases in lenticular nucleus volume, and significant decreases in mesial temporal and orbitofrontal cortical volumes. However, there was no evidence of decreased cranium volumes in the male patients.

COMMENT

These results support several earlier studies indicating structural brain abnormalities in schizophrenic patients. They confirm that evidence of brain volume loss is often present in these patients in the form of increased CSF

spaces, although it should be noted that the increases observed in the present study were quite subtle. They also suggest that this volume loss is associated with mild, diffuse, signal hyperintensity in white matter. The analyses of brain volume lend some support to earlier findings of reduced brain size in at least some schizophrenic patients.[16,25,26,29,32] The cortical analyses yield results that are consistent with earlier studies showing reduced volume of the temporal limbic system in schizophrenic patients.[13,15-19]

The structures within the regions implicated in the present study (IAM, IPM, and, possibly, IAL) include mesial and lateral orbitofrontal cortex, uncus, amygdala, hippocampus, parahippocampal gyrus, and a small portion of the inferior insula and temporal pole (Figs 2 and 3). These cortical gray-matter volume reductions are beyond those attributable to overall cranial volume reductions, since they have been adjusted for cranial volume. Unfortunately, it is not possible to determine with the present methods whether the reductions are distributed evenly across the structures within these regions or if they are present in only a few specific structures. Unfortunately, we could not confirm previous findings of decreased volume of the thalamus in our schizophrenic sample.

To our knowledge, this is the first report of increased lenticular nucleus volume in living schizophrenic patients, although we are aware of preliminary observations in another laboratory of increased putamen size (T.L.J. and Nancy Andreassen, MD, PhD, oral communication, December 1990). Since no reports of increased volume in basal ganglia studies had emerged when we began our data analysis, this must be considered a post hoc result. However, our original comparison included only nonabusing subjects. The lenticular increase in this subgroup relative to controls is statistically significant. Later, we compared the separate group of substance-abusing patients with controls and found again that the lenticular nucleus was significantly increased in volume. This second analysis, then, constitutes a partial replication of the result.

Our lenticular structure included globus pallidus, putamen, and parts of the nucleus accumbens (ie, if the latter was contiguous with putamen in an axial section it was included in the lenticular measure). As noted above, mineralization in these structures, especially in the globus pallidus, affects the signal values on MRI and leads to underestimation of the structural volume with our methods. Thus, a group difference could result if there was significantly *less* mineralization in these structures in schizophrenics. However, previous reports have indicated either increases[9] or no differences[23] in basal ganglia mineralization, so this seems an unlikely explanation.

These results are consistent with the recent postmortem findings by Heckers et al,[22] in which striatal and pallidal structures were larger in the brains of schizophrenic subjects than in the brains of controls with no neuropsychiatric diagnoses. Kelsoe et al[27] did not observe increased volumes of lenticular nuclei on MRI; however, the nuclei were measured on a single coronal section with 1-cm thickness and fewer subjects were examined. Thus, the group comparison of lenticular volumes in that study may simply have lacked power and measurement sensitivity.

Abnormal function of the lenticular nucleus has been observed in several positron emission tomography studies of schizophrenic patients, either in the form of altered metabolic rate,[55,56] higher lentricular metabolism relative to cortical metabolism,[57] or abnormal functional asymmetry (left greater than right) of the striatum.[58,59] Recently, increased blood flow in the left globus pallidus was observed in a group of first-episode schizophrenics,[60] suggesting that this abnormality is not attributable to effects of neuroleptic treatment. Our finding suggests that such abnormal function may be accompanied by *structural* anomalies, and raises questions about the relationship between the two factors.

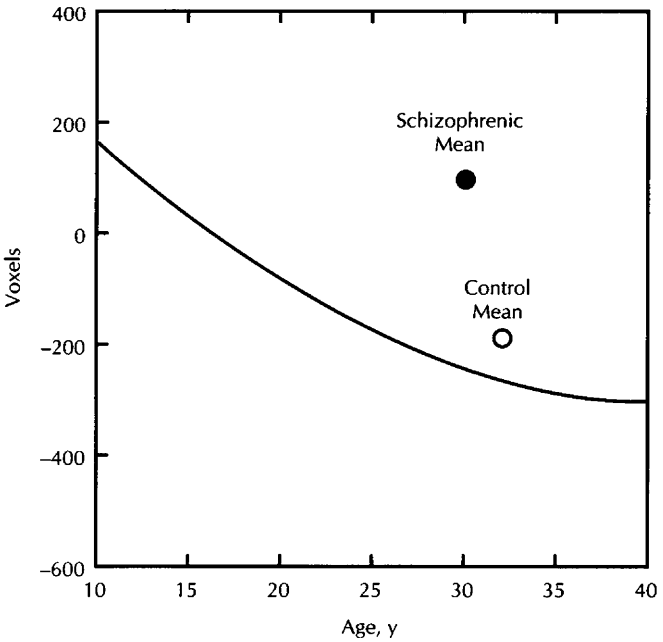

Fig 4.—*The curve shows the decline in lenticular nucleus volume (adjusted linearly for the volume of the supratentorial cranial vault) over the age range from 10 to 40 years in normal volunteers (Jernigan et al.* Brain. *In press.). The means of the adjusted volumes for the two samples in the present study were plotted for comparison. While the mean for the controls lies near the curve, as expected, the mean for the schizophrenic patients is more similar to that observed in younger nonschizophrenic subjects.*

Evidence from earlier anatomical studies of schizophrenic patients suggests that damage to the brain may occur before maturation of the nervous system is complete. Reduced brain size and focally decreased volumes of limbic structures, in the absence of associated gliosis, have been interpreted as indirect evidence of hypoplasia.[12,13,18,26] Kovelman and Scheibel[2] speculated that the cell disorganization they observed in the limbic system may be due to defective cell migration. In 1982, Feinberg[61,62] advanced the hypothesis that the typical peripubertal onset of the disorder may be due to the role of late brain maturation in its pathogenesis. According to his model, programmed synaptic elimination[63] in early adolescence could be delayed or decreased in at least some schizophrenic patients, perhaps involving dopaminergic endocrine interactions during puberty. It is of interest in this regard that Benes et al[6] reported excessive vertical axons in anterior cingulate cortex of schizophrenics, a condition that could be due to an interruption of the normal process by which supernumerary axons are eliminated in development.

The present findings suggest that cranial volume is reduced in some schizophrenics, and that reductions in the

superior zone may be more prevalent than those in the inferior zone. These results provide further support for the role of neurodevelopmental factors. Jernigan et al[64,65] recently described cerebral morphologic changes during adolescence using the MRI methods used in the present study. The superior cranial vault showed continuing growth in adolescence, while the inferior vault did not. Also, the volumes of subcortical and cortical (especially superior cortical) structures showed definite peripubertal reduction.

Among the subcortical structures, the lenticular nucleus showed the most dramatic volume reduction. Superior cerebral volume reductions in some schizophrenics may indicate a disturbance of this late brain growth in supracallosal brain regions. Similarly, increased lenticular nucleus volume in schizophrenic patients could be related to a failure of those late processes of maturation that normally result in its volume reduction. Figure 4 shows schematically the decrease in lenticular volume during adolescence. The mean volumes obtained in the present samples are plotted for comparison.

In this context, it is important to note that failures of stimulus filtering and gating in schizophrenic patients probably involve abnormalities of cortico-striato-pallido-thalamic circuitry,[66,67] which includes lenticular structures. Thus, our observed lenticular abnormalities may have important functional implications for the cognitive deficits seen in schizophrenic patients.

Separate analyses of subgroups of the schizophrenic sample led to some unexpected results. For example, structural abnormalities were, if anything, more prominent in the nonabusing than abusing subgroup. Specifically, the cranial volume reductions were less prominent in the patients with a history of substance abuse, and there was evidence that the limbic abnormalities might also be milder in this group. This counterintuitive result is, at first, difficult to explain. The subtype analysis offers a possible clue regarding the discrepancy in cranial measures. The present analysis suggested that the disorganized patients had the greatest reductions in cranial volume. Eight (73%) of the 11 disorganized patients were nonabusers. Perhaps disorganized patients, rather than nonabusing patients *per se*, are more likely to have reduced brain size. It is possible that these disorganized patients are too asocial and generally impaired even to obtain and abuse drugs.

Another possibility is that the substance-abusing patients have a neurologically milder disorder, but the action of the abused substances exacerbates the symptoms, resulting in superficially similar illnesses in these patients. In particular, the substance abuse may exacerbate what would otherwise be milder limbic dysfunction in this group, thus functionally equating these patients with the nonabusing patients who have significant structural abnormalities in both basal ganglia and limbic systems. If so, then the structural lenticular abnormality, and any associated abnormal cortico-striato-pallido-thalamic circuitry, may be more central to the disorder, since this feature is present in equal magnitude in both groups. It is of interest that the sample of schizophrenics examined after death by Heckers et al[22] in whom the basal ganglia were enlarged did not have statistically significant limbic reductions,[68] again suggesting that the basal ganglia abnormalities may be at least as prevalent among schizophrenics as are the limbic abnormalities.

Weinberger[69] recently advanced the hypothesis that a static structural lesion early in development, probably in midline limbic and diencephalic structures, interferes with the maturation of meso-cortical dopamine systems in the brains of schizophrenic patients. This leads to deafferentation of the prefrontal dopamine system, which has the effect of increasing mesolimbic dopamine activity. This view links psychosis with functional overactivity of mesolimbic systems, and the defect state with limbic and prefrontal abnormalities. Thus, the primary etiologic factor is the structural limbic lesion, which produces symptoms through its interaction with processes of maturation and the unopposed, but normal, function of spared systems. The present findings can, to some extent, be placed in the context of this thesis.

Structural damage is present in limbic and orbitofrontal structures and evidence suggests that in at least some cases alterations of late brain maturation may have led to reduced volume of superior prefrontal and parietal areas. It is possible that these effects on maturation extend to lenticular structures as well, by impeding normal regressive changes. Surprisingly, the limbic and prefrontal changes appear to be less consistent in the present sample than are the lenticular changes. This could simply be due to a lack of sensitivity of the present MRI methods to the specific alterations that exist in the limbic system. Another possibility, however, is that structural alterations of lenticular nuclei (or changes for which the lenticular increases are a marker) are themselves the primary psychotogenic factors. Further evidence of the importance of the lenticular abnormality in the pathogenesis of the disorder comes from the significant association of the magnitude of the lenticular increase with the age at which the disorder emerged (ie, the earlier the onset, the more dramatic the lenticular volume increase). This pattern is consistent with the idea that earlier onset is associated with greater interference with late maturation within the cortico-striato-pallido-thalamic system. Nevertheless, as Weinberger suggested, varying degrees of limbic and frontocortical abnormality may accompany the lenticular changes, and these may indeed be related to the defect state.

Studies are under way that may provide further insight into these issues. These studies will examine in greater detail the substructures of the limbic system and basal ganglia, and will combine sensitive morphometric techniques with functional imaging methods and detailed clinical analysis.

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