

# Regional Gray Matter, White Matter, and Cerebrospinal Fluid Distributions in Schizophrenic Patients, Their Siblings, and Controls

Tyrone D. Cannon, PhD; Theo G. M. van Erp, MA; Matti Huttunen, MD, PhD; Jouko Lönqvist, MD; Oili Salonen, MD, PhD; Leena Valanne, MD; Veli-Pekka Poutanen, MSc; Carl-Gustav Standertskjöld-Nordenstam, MD; Raquel E. Gur, MD, PhD; Michelle Yan, PhD

**Background:** Cortical gray matter volume reductions and cerebrospinal fluid (CSF) volume increases are robust correlates of schizophrenia, but their sources have not been established conclusively.

**Methods:** Structured diagnostic interviews and magnetic resonance imaging scans of the brain were obtained on 75 psychotic probands (63 with schizophrenia and 12 with schizoaffective disorder), ascertained so as to be representative of all such probands in a Helsinki, Finland, birth cohort; 60 of their nonpsychotic full siblings; and 56 demographically similar control subjects without a personal or family history of treated psychiatric morbidity.

**Results:** Patients with schizophrenia and their siblings exhibited significant reductions in cortical gray matter volume and significant increases in sulcal CSF volume compared with controls. The patients, but not their siblings, also exhibited significant reductions in white mat-

ter volume and significant increases in ventricular CSF volume. Regional effects were most robust when component volumes were expressed as percentages of overall regional volumes; in this case, for patient and sibling groups, gray matter volume reductions and sulcal CSF volume increases were significantly more pronounced in the frontal and temporal lobes than in the remainder of the brain. None of the group differences varied significantly by sex or hemisphere.

**Conclusions:** Structural alterations of the cerebral cortex, particularly in the frontal and temporal lobes, are present in patients with schizophrenia and in some of their siblings without schizophrenia; such changes are thus likely to reflect genetic (or shared environmental) effects. Ventricular enlargement is unique to the clinical phenotype and is thus likely to be affected primarily by nonshared causative factors.

*Arch Gen Psychiatry.* 1998;55:1084-1091

From the Departments of Psychology (Dr Cannon and Mr van Erp) and Psychiatry (Drs Cannon, Gur, and Yan), University of Pennsylvania, Philadelphia; and the Department of Mental Health, National Public Health Institute of Finland (Drs Huttunen and Lönqvist), and the Department of Radiology, University of Helsinki (Drs Salonen, Valanne, and Standertskjöld-Nordenstam and Mr Poutanen), Helsinki, Finland.

**S**TRUCTURAL CEREBRAL abnormalities are robust correlates of schizophrenia, but their causes have not been established conclusively.<sup>1,2</sup> Family studies can be informative in this regard.<sup>3</sup> A structural or functional abnormality that is expressed in probands with schizophrenia and some of their relatives without schizophrenia is likely to reflect genetic processes that confer vulnerability to the disorder.<sup>4</sup> Although shared environmental effects could also account for this pattern, results of twin and adoption studies<sup>5,6</sup> show that such effects have a negligible contribution to the cause of schizophrenia overall and are thus unlikely to have a substantial effect on biologic markers of the disorder. Conversely, an abnormality that is expressed in probands with schizophrenia but not their relatives could reflect nonshared (genetic or individual-specific environmental) causative factors or pro-

cesses secondary to the manifestation of psychosis or its treatment.

The most consistently observed anatomical findings in imaging studies of schizophrenia are reduced gray matter volumes and enlargement of the cerebrospinal fluid (CSF) spaces.<sup>1,7</sup> Gray matter volume is reduced in the neocortex generally and in a variety of subcortical structures; CSF volume is increased in the third and lateral ventricles and cortical sulci. In a computed tomographic study of offspring of parents with and without schizophrenia in Denmark, evidence of disassociation in the causative antecedents of cortical and subcortical abnormalities was found.<sup>8-10</sup> Sulcal CSF-brain ratios varied with participants' degree of genetic loading but not with obstetric effects, whereas ventricular CSF-brain ratios varied with an adverse obstetric history, but only among those with a high genetic risk for schizophrenia.<sup>8-10</sup> The interpretability of this evidence is restricted, however, by the

## PARTICIPANTS AND METHODS

### SAMPLE ASCERTAINMENT

Participants were drawn from the total population of individuals born in Helsinki, Finland, in 1955 and all their full siblings ( $N = 7840$  and  $N = 12\,796$ , respectively) who (along with their parents) were screened in national case registries for psychiatric morbidity using methods described previously.<sup>5</sup> A total of 267 members of this population (1.3%) had a registered diagnosis of 295.x (schizophrenia, schizoaffective disorder, or schizophreniform disorder) according to the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*, 8th ed,<sup>18</sup> numbering scheme. Proband were recruited at random from this total pool. We attempted to recruit at least 1 sibling without schizophrenia of each studied proband, but this was possible for only 62 of 80 patients. Dual-echo magnetic resonance imaging data for 7 participants (5 probands and 2 siblings) had to be excluded because of movement artifact and other technical problems, leaving 75 probands and 60 siblings forming 60 proband-sibling pairs. Studied probands were equivalent to the remainder of the proband population in terms of year of birth ( $1954 \pm 5.3$  vs  $1953 \pm 4.6$ ,  $t = 1.2$ ;  $P = .23$ ), nuclear family size (ie, parents and siblings) (mean  $\pm$  SD,  $5.1 \pm 1.7$  vs  $5.1 \pm 1.6$ ,  $t = 0.5$ ;  $P = .64$ ), sex (56% vs 57% male,  $\chi^2 = 0.1$ ;  $P = .76$ ), history of inpatient admissions (98% vs 94%,  $\chi^2 = 1.6$ ;  $P = .20$ ), age at first inpatient admission (mean  $\pm$  SD,  $25.6 \pm 6.7$  vs  $25.7 \pm 6.1$  years,  $t = -0.1$ ;  $P = .94$ ), history of comorbid substance abuse disorders (14% vs 13%,  $\chi^2 = 0.1$ ;  $P = .81$ ), and work disability (75% vs 76% receiving a pension,  $\chi^2 = 0.0$ ;  $P = .88$ ), but the studied group had more hospital admissions than the nonstudied group (mean  $\pm$  SD,  $8.9 \pm 8.2$  vs  $6.4 \pm 7.3$ ,  $t = 2.6$ ;  $P = .01$ ).

In addition, a control group of 56 subjects without schizophrenia (28 sibling pairs) was recruited from the same study population after excluding any individual with a personal or family history of treated psychiatric morbidity.

### DIAGNOSTIC EVALUATION

All participants (ie, probands, siblings, and controls) were interviewed using the Structured Clinical Interview for DSM-III-R Disorders, Patient or Non-Patient edition.<sup>19</sup> Any participant with an Axis I psychotic condition was also rated using the Scale for the Assessment of Positive Symptoms<sup>20</sup>

and the Scale for the Assessment of Negative Symptoms.<sup>21</sup> All other participants were interviewed and rated on the Cluster A items from the Personality Disorder Examination.<sup>22</sup> A standard coding form was used to summarize details of the illness and treatment history of any participant with a history of inpatient admissions. The interviewer assigned diagnoses according to DSM-III-R<sup>23</sup> criteria using all available information. Clinical case summaries were generated, stripped of identifying and diagnostic information, and independently evaluated by another diagnostician. Reliability of the primary diagnosis was excellent (ie,  $\kappa = 0.94 \pm 0.02$ ).<sup>24</sup> Diagnostic disagreements were flagged, and another independent diagnostician rated those cases for consensus diagnoses. Of the 75 probands studied, 63 were diagnosed as having schizophrenia and 12 as having schizoaffective disorder. The 75 probands had a mean  $\pm$  SD age at first symptoms of  $21.5 \pm 5.2$  years, average Scale for the Assessment of Positive Symptoms global rating of  $2.7 \pm 0.9$ , and average Scale for the Assessment of Negative Symptoms global rating of  $1.9 \pm 1.1$ .

As shown in **Table 1**, the proband, sibling, and control groups were balanced in terms of age, sex, handedness, social class, nuclear family size (ie, parents and siblings), and history of any DSM-III-R substance use or dependence disorder (primarily alcohol-related disorders). The sibling and control groups were also balanced in terms of percentage of group with a DSM-III-R diagnosis of depression or anxiety disorder. Six siblings and no controls had a Cluster A personality disorder diagnosis ( $P < .05$ ).

### IMAGING PROCEDURES

#### Acquisition

Magnetic resonance imaging scans were performed on a 1.0-T scanner (Siemens Medical Systems, Iselin, NJ) in the Department of Radiology, University of Helsinki. An average of 29 interleaved, 5-mm-thick transaxial slices were acquired using a conventional dual-spin echo sequence, with a repetition time of 2800 milliseconds, echo times of 20 and 80 milliseconds, a flip angle of 90°, and no interslice gap. The matrix size was  $256 \times 256$  pixels, corresponding to a field of view of 23 cm and an inplane resolution of  $0.9 \times 0.9$  mm. Digitized images were analyzed on computer workstations (SUN, Sun Microsystems, Mountain View, Calif).

Continued on next page

limited diagnostic specificity and localizing significance of CSF-based anatomical measures<sup>2</sup> and by the possibility that the mothers had unusually severe forms of schizophrenia.<sup>11</sup> Furthermore, with 1 exception,<sup>12</sup> the other previous family studies<sup>13,14</sup> that examined differences between individuals at high and low genetic risk for schizophrenia found increased ventricular CSF-brain ratios in relatives of patients with schizophrenia, leaving open the possibility of a direct genetic contribution to markers of subcortical pathologic features. (The other published family studies<sup>15-17</sup> did not use control groups at low genetic risk for schizophrenia.) However, because ventricular CSF-brain ratio confounds 2 potentially dissociable anatomical features of schizophrenia (ie, decreased cortical gray matter volume and increased ventricular CSF vol-

ume), the possible causative segregation of these features has not yet been adequately tested.

In the present study, we performed magnetic resonance imaging scans of the brain on a representative sample of patients with schizophrenia, their siblings without schizophrenia, and a demographically balanced sample of control subjects at low genetic risk for schizophrenia. We hypothesized that reduced cortical gray matter volume and increased sulcal CSF volume mark the degree of genetic loading for schizophrenia and thus should be present in patients with schizophrenia and in some of their siblings without schizophrenia, whereas increased ventricular CSF volume reflects nonshared causative effects or presence of the clinical phenotype and thus should be present in patients with schizophrenia but not in their siblings.

## Segmentation and Reslicing

After deleting pixels corresponding to the skull and meninges, the remaining pixels were classified into 3 tissue types (gray matter, white matter, and CSF) using an adaptive Bayesian algorithm for 3-dimensional tissue segmentation.<sup>25</sup> This algorithm is more robust to field inhomogeneities and shading artifact than other approaches currently in use, with an absolute measurement error of 1% to 3% for a given tissue compartment based on phantom and repeated-scanning studies.<sup>26</sup> To control for differences in head tilt during acquisition, images were resliced parallel to the anterior commissure–posterior commissure axis.

## Anatomical Tracings

All tracings were performed on resliced axial images using a standard set of operationally defined criteria of the regions of interest (ROIs).<sup>27</sup> The left and right hemisphere ROIs included all brain tissue except the pons, medulla, cerebral peduncles, and cerebellum. The ventricular ROIs included the lateral and third ventricles but not the fourth ventricle or cerebral aqueduct. On inferior slices, the borders of the frontal lobe ROIs were the interhemispheric fissure and the cortical perimeter. Above the mamillary bodies, the posterior border was defined by a horizontal line from the most anterior extent of the sylvian fissure to the interhemispheric fissure. Tracings were continued in this fashion until the slice immediately preceding the splenium of the corpus callosum, where a new posterior border was defined by a horizontal line touching the most anterior part of the caudate nucleus. At the level of the midbrain, the posteromedial border of the temporal lobe ROIs was delineated by the pons and cerebellum. The sylvian fissure was used to separate the temporal lobe from adjacent frontal regions. The posterior boundary was defined by drawing a line extending from the contralateral cerebral peduncle to the anterior tip of the cerebellum. Above the mamillary bodies, the sylvian fissure and the diencephalon structures served as the medial borders. The posterior edge was formed by a horizontal line from the most posterior tip of the posterior fossa to the lateral perimeter. The slice preceding the splenium of the corpus callosum represented the superior extent of the temporal lobe tracings. In addition, a “posterior” region was defined as all tissue exclusive of the frontal and temporal lobe regions.

## Volumetric Measurements and Reliability

Pixel counts were integrated within ROIs and across slices to yield volumes. Interrater reliabilities of the defined measurements based on 10 randomly selected images were excellent (intraclass correlations, >0.93). The measurements used in the study were generated by 1 image analyst (T.V.E.) who was unaware of the clinical status of the participants (ie, patient, sibling, or control). **Table 2** shows the mean  $\pm$  SD regional gray matter, white matter, and CSF volumes of the 3 diagnostic groups separately by sex.

## STATISTICAL ANALYSES

Brain morphologic data were analyzed using repeated-measures analysis of variance and covariance models. This approach controls the type I error rate (ie, maintains the hypothesis-wise  $\alpha$  level at  $P \leq .05$ ) by requiring that a predictor have a significant multivariate (main or interaction) effect before examining its contribution to particular dependent variables. For analyses of gray matter, white matter, and sulcal CSF, hemisphere and region (frontal, temporal, and posterior) served as within-subject independent variables; for analysis of ventricular CSF, hemisphere was a within-subject variable. In all models, overall intracranial volume and age at scanning served as continuously scaled covariates, and sex, history of substance abuse, diagnosis group (patient, sibling, or control), and the interactions of diagnosis group with sex and substance abuse served as predictors. Significant multivariate main effects of group were followed by pairwise group contrasts using the independent sample *t* statistic for the patient-control and sibling-control comparisons and the matched-pair *t* statistic for the patient-sibling comparisons. Significant interactions of group with hemisphere or region were followed up with univariate analyses of covariance collapsing across any nonsignificant within-subject dimensions. All analyses used type III (regression) sums of squares, which tests the significance of each predictor while accounting for all other model terms simultaneously. The primary analyses used the absolute volumetric data as dependent variables. Another set of analyses used ratio measures of the relative regional proportions of each tissue type (eg, frontal gray matter volume divided by overall frontal volume).

## RESULTS

### GROUP DIFFERENCES IN ABSOLUTE VOLUME

Results of repeated-measures analyses of regional gray matter, white matter, and CSF volumes are shown in **Table 3**. **Figure 1** gives the mean  $\pm$  SEM volumes by group collapsing across any nonsignificant within-subject dimensions. The data shown are adjusted for intracranial volume, age, sex, and history of substance abuse and *z* transformed such that the control group has a mean of 0 and an SD of 1 on all measures. The mean  $\pm$  SEM proband minus sibling differences and matched-pair *t* test results are given parenthetically in the text below.

In the analysis of gray matter volume, there was a significant overall main effect of group, with probands and siblings having significantly less gray matter volume than controls but no difference between probands and siblings ( $0.11 \pm 0.21$ ,  $t_{59} = 0.54$ ;  $P = .59$ ). Group did not interact significantly with hemisphere or region. For white matter, there was also a significant overall main effect of group, with probands having significantly less white matter than controls but not siblings ( $-0.08 \pm 0.29$ ,  $t_{59} = -0.28$ ;  $P = .78$ ) and no difference between siblings and controls. The hemisphere  $\times$  group and hemisphere  $\times$  region  $\times$  group interactions were not significant, but group did interact significantly with region. Probands had significantly less white matter volume than controls in the posterior region but not

**Table 1. Demographic Characteristics of the 3 Comparison Groups\***

Characteristic	Probands (n = 75)	Siblings (n = 60)	Controls (n = 56)	F or $\chi^2$ Statistic	P
Age, mean $\pm$ SD, y	40.5 $\pm$ 5.5	40.7 $\pm$ 5.8	40.8 $\pm$ 3.1	0.0	.96
Sex					
Male	40 (53)	27 (45)	25 (45)	1.3	.52
Female	35 (47)	33 (55)	31 (55)		
Handedness					
Right	69 (92)	57 (95)	50 (89)	1.3	.52
Left/mixed	6 (8)	3 (5)	6 (11)		
Parental social class, mean $\pm$ SD	3.3 $\pm$ 1.4	3.4 $\pm$ 1.5	3.6 $\pm$ 1.3	0.9	.40
Family size, mean $\pm$ SD	5.2 $\pm$ 1.7	5.6 $\pm$ 2.1	5.0 $\pm$ 1.2	1.8	.16
Substance disorder					
Yes	21 (28)	8 (13)	14 (25)	4.4	.11
No	54 (72)	52 (87)	42 (75)		
Other Axis I disorder					
Yes	...	12 (20)	12 (21)	0.0	.85
No	...	48 (80)	44 (79)		
Cluster A disorder					
Yes	...	6 (10)	0 (0)	5.9	.02
No	...	54 (90)	56 (100)		
Intracranial volume, mean $\pm$ SD, mL	1287 $\pm$ 153	1281 $\pm$ 145	1293 $\pm$ 132	0.1	.89

\*Values are number (percentage) unless otherwise indicated. Ellipses indicate data not applicable.

in the frontal or temporal regions, with no significant differences between probands and siblings or between siblings and controls. In the analysis of sulcal CSF volume, there was a significant main effect of group, with probands and siblings having significantly greater sulcal CSF volume than controls but no difference between probands and siblings ( $0.25 \pm 0.16$ ,  $t_{59} = 1.6$ ;  $P = .12$ ). Group also interacted significantly with region, but the hemisphere  $\times$  group and hemisphere  $\times$  region  $\times$  group interactions were not significant. Probands had significantly greater sulcal CSF volume than controls in the frontal and temporal regions but not in the posterior region; probands also had significantly greater sulcal CSF volume than siblings in the frontal and temporal lobes but not in the posterior region ( $0.47 \pm 0.16$ ,  $t_{59} = 3.0$ ,  $P = .004$ ;  $0.45 \pm 0.18$ ,  $t_{59} = 2.5$ ,  $P = .01$ ;  $0.05 \pm 0.16$ ,  $t_{59} = 0.3$ ,  $P = .73$ , respectively); and siblings had significantly greater sulcal CSF volume than controls in all regions. For ventricular CSF, there was a significant main effect of group, with patients having significantly larger ventricles than siblings ( $0.46 \pm 0.17$ ,  $t_{59} = 2.6$ ;  $P = .01$ ) and controls, who did not differ. Group did not interact significantly with hemisphere.

Follow-up analyses examining the group interaction with tissue type confirmed that siblings were significantly more deviant from controls in terms of a combined index of gray matter volume reduction and sulcal volume enlargement than in terms of a combined index of white matter volume reduction and ventricular volume enlargement ( $F_{1,108} = 4.1$ ;  $P = .04$ ). The corresponding effects contrasting the sibling-control differences on gray matter vs white matter volume and on sulcal vs ventricular CSF volume did not reach statisti-

cal significance ( $F_{1,108} = 1.5$ ,  $P = .22$ ;  $F_{1,108} = 2.1$ ,  $P = .15$ , respectively).

## GROUP DIFFERENCES IN PROPORTIONAL VOLUMES

The repeated-measures analyses using the ratio measures as dependent variables yielded results nearly identical to those reported above except that the group  $\times$  region interaction term became significant for gray matter ( $F_{4,360} = 6.5$ ;  $P < .001$ ) and was no longer significant for white matter ( $F_{4,360} = 1.0$ ;  $P = .39$ ). **Figure 2** plots the mean  $\pm$  SEM ratio measures by group collapsing across any nonsignificant within-subject dimensions. The data shown again represent  $z$  scores corrected for intracranial volume, age, sex, and history of substance abuse. In univariate analyses, probands and siblings had significantly smaller gray matter-brain ratios than controls in the frontal and temporal regions but not in the posterior region; probands had significantly smaller gray matter-brain ratio than siblings in the frontal region ( $-0.39 \pm 0.15$ ,  $t_{59} = -2.62$ ;  $P = .01$ ) but not in the temporal or posterior region ( $-0.26 \pm 0.16$ ,  $t_{59} = -1.6$ ,  $P = .11$ ;  $0.13 \pm 0.15$ ,  $t_{59} = 0.8$ ,  $P = .41$ , respectively). Overall, white matter-brain ratio was significantly smaller in probands compared with siblings ( $-0.35 \pm 0.15$ ,  $t_{59} = -2.4$ ;  $P = .02$ ) and controls, who did not differ. The results of all other group contrasts and of the tissue type  $\times$  group interaction tests were the same as those observed on the absolute volume measures.

## COVARIATES

Overall intracranial volume was significantly positively related to nearly all the anatomical measures in this study, with markedly stronger relationships (ie, effect sizes 6 to 10 times greater) with the volumetric compared with the ratio measures. When examined by itself, sex had a significant effect on variability in the anatomical measures, which disappeared entirely after accounting for differences in overall intracranial volume. There was not a significant interaction of diagnostic group with sex on any of the anatomical measures. Age was significantly positively related to CSF volume and brain ratio measures and was significantly negatively related to gray matter volume and brain ratio measures, but did not correlate significantly with white matter measures. There were no significant (main or interaction) effects involving substance disorder on the anatomical measures in this study.

## SUBGROUP CONTRASTS

There were no significant differences on the anatomical measures between probands with diagnoses of schizophrenia and schizoaffective disorder, between siblings with and without other Axis I disorders (ie, depression or anxiety), or between siblings with and without Cluster A disorders. Furthermore, the overall pattern of results was identical to that reported above when schizoaffective probands and their siblings were excluded and when siblings with Cluster A or other Axis I disorders were excluded.

**Table 2. Regional Gray Matter, White Matter, and Cerebrospinal Fluid Volumes by Group and Sex\***

	Probands		Siblings		Controls	
	Males (n = 40)	Females (n = 35)	Males (n = 27)	Females (n = 33)	Males (n = 25)	Females (n = 31)
Frontal lobe						
Gray matter						
Left	68.5 ± 7.6	58.8 ± 7.4	69.2 ± 8.1	60.9 ± 5.5	70.1 ± 5.5	62.5 ± 6.5
Right	69.9 ± 8.3	60.4 ± 7.6	71.7 ± 9.3	62.5 ± 6.1	71.7 ± 5.1	64.3 ± 6.5
White matter						
Left	47.6 ± 5.6	36.7 ± 5.5	47.1 ± 6.8	38.7 ± 3.9	47.7 ± 5.8	40.5 ± 6.2
Right	48.6 ± 6.2	37.3 ± 5.3	47.7 ± 7.5	38.8 ± 3.7	48.6 ± 5.7	40.5 ± 6.0
Sulci						
Left	16.8 ± 8.2	13.3 ± 7.2	13.7 ± 7.2	10.6 ± 3.5	12.1 ± 4.1	9.8 ± 3.2
Right	16.7 ± 7.8	13.0 ± 6.5	13.8 ± 6.8	11.0 ± 3.9	12.2 ± 4.2	10.0 ± 3.0
Temporal lobe						
Gray matter						
Left	75.0 ± 7.8	64.8 ± 7.5	74.8 ± 8.1	66.3 ± 6.9	75.4 ± 7.8	67.7 ± 6.2
Right	78.4 ± 10.1	68.1 ± 7.5	78.8 ± 8.4	68.9 ± 6.8	79.7 ± 10.0	70.5 ± 6.8
White matter						
Left	40.2 ± 5.5	31.0 ± 4.9	40.0 ± 5.0	32.6 ± 4.1	38.9 ± 6.0	32.7 ± 4.6
Right	41.2 ± 5.9	31.8 ± 5.8	39.7 ± 5.2	33.5 ± 3.9	39.9 ± 5.8	33.7 ± 4.3
Sulci						
Left	10.2 ± 6.7	7.4 ± 4.9	7.2 ± 5.5	5.7 ± 3.1	5.9 ± 3.2	4.0 ± 1.4
Right	9.9 ± 6.6	6.8 ± 4.2	7.4 ± 5.2	5.7 ± 3.6	5.3 ± 1.7	4.0 ± 1.6
Posterior region						
Gray matter						
Left	223.6 ± 20.9	195.2 ± 17.9	223.3 ± 24.4	200.8 ± 18.1	227.2 ± 15.3	205.8 ± 16.9
Right	217.9 ± 20.7	190.4 ± 16.2	221.1 ± 24.1	196.6 ± 18.5	222.7 ± 16.9	200.1 ± 14.4
White matter						
Left	168.4 ± 20.7	139.9 ± 19.7	174.5 ± 22.4	147.3 ± 16.9	176.4 ± 17.4	153.1 ± 18.1
Right	168.5 ± 19.2	142.1 ± 21.1	175.3 ± 23.9	148.8 ± 17.6	176.9 ± 18.3	155.4 ± 18.2
Sulci						
Left	32.7 ± 14.8	25.5 ± 15.6	31.3 ± 18.1	24.1 ± 10.1	28.9 ± 12.3	23.4 ± 8.0
Right	30.1 ± 13.8	23.5 ± 14.4	30.5 ± 17.1	22.8 ± 10.4	28.1 ± 11.9	22.4 ± 7.1
Ventricles						
Left	14.9 ± 9.1	10.8 ± 7.1	10.8 ± 7.1	8.7 ± 7.3	11.9 ± 7.5	7.7 ± 2.8
Right	12.8 ± 7.6	10.3 ± 7.2	10.3 ± 5.4	8.3 ± 7.1	10.1 ± 4.5	7.0 ± 2.4

\*Values are mean ± SD cubic centimeters.

**Table 3. Repeated-Measures Analysis of Variance Results for Gray Matter, White Matter, and Cerebrospinal Fluid (CSF) Volumes\***

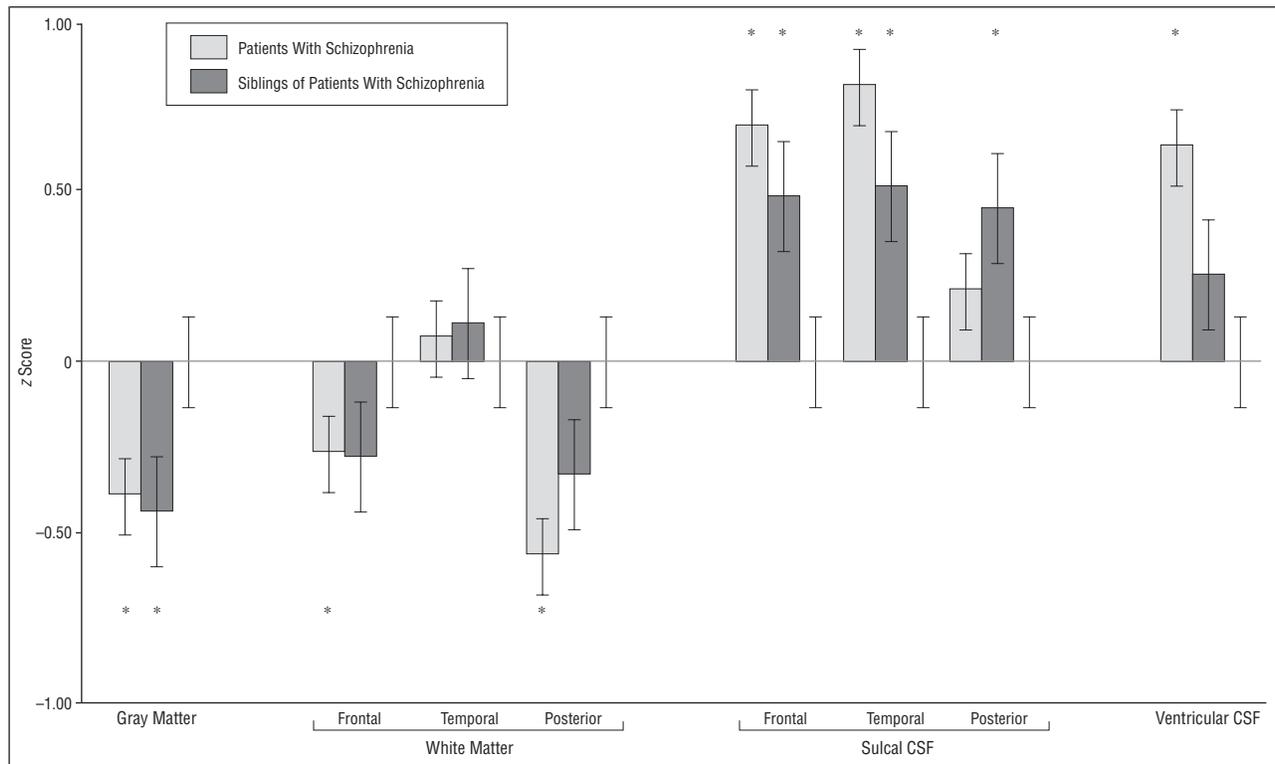
Source of Variation	df	Gray Matter		White Matter		Sulcal CSF		Ventricular CSF	
		MS	F	MS	F	MS	F	MS	F
Intracranial volume	1	52 294.8	232.9†	67 322.8	669.0†	3756.2	13.4†	1628.0	23.7†
Age at scan	1	2977.1	13.3†	16.3	0.2	1467.8	5.2‡	1238.8	18.1†
Sex	1	95.8	0.4	130.9	1.3	14.6	0.1	13.6	0.2
Substance abuse	1	717.4	3.2	2.7	0.0	743.0	2.7	4.1	0.1
Group	2	708.9	3.2‡	478.1	4.8§	1321.1	4.7§	475.7	6.9†
Probands vs controls	1	1126.5	5.0‡	955.8	9.5§	2209.2	7.9‡	922.0	13.4†
Siblings vs controls	1	983.7	4.4‡	247.4	2.5	1699.9	6.1‡	104.4	1.5
Group × sex	2	12.0	0.1	12.2	0.1	1.9	0.0	48.6	0.7
Group × substance abuse	2	372.4	1.7	85.7	0.9	649.7	2.3	78.6	1.1
Error	180	224.5	...	100.6	...	279.9	...	68.6	...
Hemisphere × group	2	17.5	2.0	6.4	1.1	5.7	1.6	2.9	0.6
Error (hemisphere)	180	8.8	...	5.9	...	3.7	...	5.3	...
Region × group	4	98.7	0.7	353.2	3.9§	158.0	2.3‡	...	...
Error (region)	360	134.4	...	89.3	...	67.6	...	...	...
Hemisphere × region × group	4	3.7	0.2	5.5	0.6	2.7	0.8	...	...
Error (hemisphere × region)	360	15.8	...	9.9	...	3.3	...	...	...

\*MS indicates mean squares; ellipses, data not applicable.

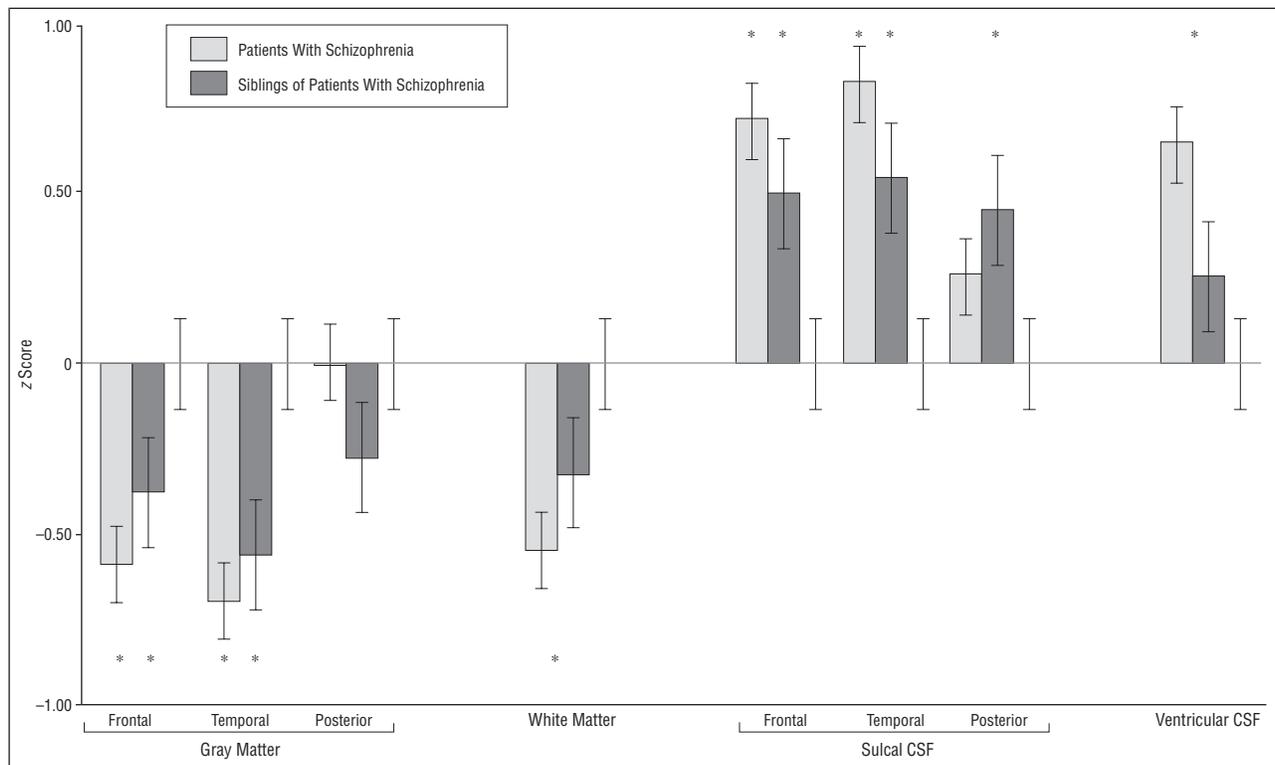
†P < .001.

‡P < .01.

§P < .05.



**Figure 1.** Mean  $\pm$  SEM z scores for volumetric measures of overall gray matter, regional white matter, regional sulcal cerebrospinal fluid (CSF), and overall ventricular CSF in patients ( $n = 75$ ), siblings ( $n = 60$ ), and control subjects (error bars;  $n = 56$ ). The data shown are corrected for total intracranial volume, age, sex, and history of substance abuse and are collapsed across any nonsignificant within-subject dimensions (ie, hemisphere or region). Asterisks above and below error bars indicate statistically significant differences from controls. Results of the matched-pair  $t$  tests contrasting patients and their siblings are given in the text.



**Figure 2.** Mean  $\pm$  SEM z scores for ratio measures of regional gray matter, overall white matter, regional sulcal cerebrospinal fluid (CSF), and overall ventricular CSF in patients ( $n = 75$ ), siblings ( $n = 60$ ), and control subjects (error bars;  $n = 56$ ). The data shown are corrected for total intracranial volume, age, sex, and history of substance abuse and are collapsed across any nonsignificant within-subject dimensions (ie, hemisphere or region). Asterisks above and below error bars indicate statistically significant differences from controls. Results of the matched-pair  $t$  tests contrasting patients and their siblings are given in the text.

The principal findings of this study are that patients with schizophrenia and their siblings without schizophrenia show reduction in cortical gray matter volume compared with a demographically balanced sample of controls at low genetic risk for schizophrenia, whereas patients with schizophrenia (but not their siblings without schizophrenia) show ventricular enlargement and reduced white matter volume. This pattern is consistent with the hypothesis that cortical gray matter volume reduction in schizophrenia reflects, at least in part, factors associated with the disorder's genetic basis (or shared environmental effects), whereas ventricular volume enlargement (and thus presumably reduced volumes of subcortical structures) reflects primarily nonshared causative effects or factors secondary to the illness or treatment.

The role of genetic effects in schizophrenia is substantial,<sup>5</sup> but the mode of inheritance is complex, involving many genes and certain types of neurally disruptive environmental risk exposures.<sup>28</sup> Because transmission of predisposing genes for this disorder does not depend on overt manifestation of schizophrenia in first-degree relatives,<sup>5,29</sup> identification of an underlying biologic or behavioral trait that marks the degree of genetic predisposition could enhance efforts to locate such genes chromosomally. It was previously demonstrated that unaffected siblings of probands with schizophrenia show neuropsychological deficits resembling those observed in probands<sup>4</sup> and that offspring of parents with schizophrenia manifest cortical sulcal volume enlargement to a degree correlated with their level of genetic risk for the illness.<sup>8-10</sup> The present findings extend this work by demonstrating that the absolute and relative amount of gray matter in the cerebral cortex is reduced in individuals at genetic risk for schizophrenia. Cortical gray matter volume deficits thus become candidates to explain evidence of functional brain compromise in high-risk individuals and for use as quantitative endophenotypic indicators in genetic studies.

This study used a random population-based sampling method that resulted in excellent correspondence between studied and nonstudied probands in terms of the major demographic and clinical history variables. We can thus rule out that the evidence of gray matter volume reduction in the sibling group is a consequence of selecting probands of especially high severity or with an otherwise unusual clinical presentation. Furthermore, because the sibling and control groups were well balanced in terms of demographic variables and the expression of nonpsychotic Axis I disorders, and because the sibling-control differences in gray matter persisted after excluding patients with psychiatric illness of any kind, we can rule out that the present findings are because of an excess of nonspecific mental illness in the sibling group. That cortical gray matter volume is reduced in patients and their first-degree relatives not clinically affected with schizophrenia and never treated with antipsychotic drugs also clearly indicates that such changes in the patients cannot be accounted for entirely by factors secondary to illness expression or treatment<sup>30</sup> and are thus likely to be present, at least in part, before illness onset.

Because the proband-sibling pairs in this study were reared in the same homes, we cannot entirely rule out a shared

environmental contribution to the gray matter volume reductions observed in the patient and sibling groups. However, there is little reason to suspect a role of shared environmental effects in the cause of schizophrenia overall,<sup>5,6</sup> and it is difficult to imagine a systematic environmental effect on brain structure that would be shared by siblings discordant for schizophrenia but not by age-, sex-, handedness-, and parental-social class-matched controls. Obstetric effects represent the most plausible such candidate, but results of epidemiological studies demonstrate that obstetric complications are no more common among unaffected relatives of schizophrenics than in the general population,<sup>28</sup> and a history of such complications has been found to predict outcomes of schizophrenia in discordant cotwins and sibling pairs (ie, obstetric complications represent a unique rather than a shared environmental effect).<sup>28,31,32</sup>

This study used a multivariate approach to analysis that permitted examination of regional and hemispheric differences among the diagnostic groups. Contrary to the view that neuropathologic changes in schizophrenia are focused in the left hemisphere, we detected no significant hemispheric differences between patients and controls or between siblings and controls in any of the tissue types. Significant regional variation was present in absolute white matter volume, in which patient-control differences were greater in posterior than anterior regions, and in absolute sulcal CSF volume, in which patient-control and sibling-control differences were greater in anterior than posterior regions, but there was not a significant regional distribution to the group differences in absolute gray matter volume. A regional effect emerged when gray matter volumes were expressed as percentages of overall regional volumes such that the patient-control and sibling-control differences were more pronounced in the temporal and frontal regions than in the posterior regions. This pattern probably reflects a sensitivity difference between ratio measures compared with absolute volume measures in this context because reduced gray matter volume and increased sulcal CSF volume aggregate in producing deviance in the former but not the latter and because the proband and sibling groups show abnormalities on both of these component measures. In any case, these regional effects must be interpreted against the background of generalized pathologic features in the cerebral cortex of patients with schizophrenia and some of their first-degree relatives.

Our model predicts that cortical pathologic change is a vulnerability characteristic that is probably necessary but not sufficient for the manifestation of schizophrenia, whereas ventricular enlargement is a disease-specific marker that could reflect factors involved in illness expression among those genetically predisposed. Consistent with the Danish computed tomographic findings<sup>8-10</sup> and another recent family study,<sup>12</sup> ventricular enlargement was present in patients with schizophrenia but not in their siblings without schizophrenia. This pattern suggests that nonshared genetic or individual-specific environmental causative factors or effects secondary to the clinical manifestation of schizophrenia or its treatment contribute to variability in ventricular volume in this population. We are currently examining the contributions of perinatal hypoxia and other obstetric risk factors in relation to the morphologic data. If the ventricular findings are found not to be secondary phenomena, it is possible that subcortical pathologic fea-

tures (ie, reduced hippocampal and thalamic volumes), which are correlated with enlargement of the third and lateral ventricles in patients with schizophrenia at autopsy,<sup>33,34</sup> contribute to the expression of formal psychotic signs among those genetically predisposed. It will be necessary to compare patient, sibling, and control groups on subcortical volume measures from high-resolution magnetic resonance imaging scans to test this implication.

This study has several limitations. First, the use of relatively gross anatomical divisions could have obscured a stronger pattern of underlying regional variation than was detected. In particular, because subcortical structures were not delineated separately from nonfrontal and nontemporal cortex, group differences in subcortical gray or white matter volume could have been obscured by the absence of group differences in occipital-parietal cortex volume (which accounts for approximately 85% of the volume of the "posterior" region). Second, the small number of siblings with Cluster A personality disorders limited our ability to test whether cortical gray matter volume deficits are more severe in siblings with schizophrenia spectrum diagnoses, a hypothesis that would seem to follow from the genetic association between schizophrenia and Cluster A personality disorders.

In summary, we found evidence consistent with the view that cortical gray matter volume reduction in schizophrenia reflects, at least in part, genetic effects that predispose to the disorder (or shared environmental factors), whereas ventricular volume enlargement reflects primarily nonshared causative effects or factors secondary to the illness or its treatment. These findings suggest an anatomical basis for evidence of neuropsychological deficits in first-degree relatives of schizophrenics and encourage the use of neuroimaging measures as endophenotypic indicators in genetic linkage studies.

Accepted for publication August 7, 1998.

This research was supported by grant MH48207 from the National Institute of Mental Health, Bethesda, Md.

We thank Ulla Mustonen, MSW, and Liisa Varonen, PhD, for their contributions to subject recruitment and assessment; Antti Tanskanen, MS, for his contributions to the register searches and database structures; Mary O'Brien, PhD, for her contributions to the diagnostic procedures and reliability assessment; and Bruce Turetsky, MD, and other investigators in the Mental Health Clinical Research Center, Department of Psychiatry, University of Pennsylvania, Philadelphia (grant MH43880) for their contributions to the development of the image analysis procedures used in this study.

Corresponding author: Tyrone D. Cannon, PhD, Department of Psychology, University of Pennsylvania, 3815 Walnut St, Philadelphia, PA 19104-6196 (e-mail: cannon@hirisk.psych.upenn.edu).

## REFERENCES

- Cannon TD. Abnormalities of brain structure and function in schizophrenia: implications for etiology and pathophysiology. *Ann Med*. 1996;28:533-539.
- Buchanan RW, Carpenter WT. The neuroanatomies of schizophrenia. *Schizophr Bull*. 1997;23:367-372.
- Cannon TD, Marco E. Structural brain abnormalities as indicators of vulnerability to schizophrenia. *Schizophr Bull*. 1994;20:89-102.
- Cannon TD, Eyer Zorrilla LT, Shtasel DL, Gur RE, Gur RC, Marco EJ, Moberg P, Price RA. Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. *Arch Gen Psychiatry*. 1994;51:651-661.
- Cannon TD, Kaprio J, Lonnqvist J, Huttunen MO, Koskenvuo M. The genetic epidemiology of schizophrenia in a Finnish twin cohort: a population-based modeling study. *Arch Gen Psychiatry*. 1998;55:67-74.
- Kendler KS, Gruenberg AM, Kinney DK. Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish Adoption Study of Schizophrenia. *Arch Gen Psychiatry*. 1994;51:456-468.
- Pfefferbaum A, Marsh L. Structural brain imaging in schizophrenia. *Clin Neurosci*. 1995;3:105-111.
- Cannon TD, Mednick SA, Parnas J. Genetic and perinatal determinants of structural brain deficits in schizophrenia. *Arch Gen Psychiatry*. 1989;46:883-889.
- Cannon TD, Mednick SA, Parnas J, Schulsinger F, Praestholm J, Vestergaard A. Developmental brain abnormalities in the offspring of schizophrenic mothers, I: contributions of genetic and perinatal factors. *Arch Gen Psychiatry*. 1993;50:551-564.
- Cannon TD, Mednick SA, Schulsinger F, Parnas J, Praestholm J, Vestergaard A. Developmental brain abnormalities in the offspring of schizophrenic mothers, II: structural brain characteristics of schizophrenia and schizotypal personality disorder. *Arch Gen Psychiatry*. 1994;51:955-962.
- Parnas J, Cannon TD, Jacobsen B, Schulsinger H, Schulsinger F, Mednick SA. Lifetime DSM-III-R diagnostic outcomes in offspring of schizophrenic mothers: results from the Copenhagen High-Risk Study. *Arch Gen Psychiatry*. 1993;50:707-714.
- Silverman JM, Smith CJ, Guo SL, Mohs RC, Siever LJ, Davis KL. Lateral ventricular enlargement in schizophrenic probands and their siblings with schizophrenia-related disorders. *Biol Psychiatry*. 1998;43:97-106.
- Weinberger DR, DeLisi LE, Neophytides AN, Wyatt RJ. Familial aspects of CT scan abnormalities in chronic schizophrenic patients. *Psychiatry Res*. 1981;4:65-71.
- Reveley AM, Reveley MA, Clifford CA, Murray RM. Cerebral ventricular size in twins discordant for schizophrenia. *Lancet*. 1982;1:540-541.
- DeLisi LE, Goldin LR, Hamovitz JR, Maxwell ME, Kurtz D, Gershon ES. A family study of the association of increased ventricular size with schizophrenia. *Arch Gen Psychiatry*. 1986;43:148-153.
- Suddath RL, Christison GW, Torrey EF, Casanova MF, Weinberger DR. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N Engl J Med*. 1990;322:789-794.
- Waldo MC, Cawthra E, Adler LE, et al. Auditory sensory gating, hippocampal volume, and catecholamine metabolism in schizophrenics and their siblings. *Schizophr Res*. 1994;12:93-106.
- World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*. 8th ed. Geneva, Switzerland: World Health Organization; 1969.
- Spitzer RL, Williams JB, Gibbon M. *Instruction Manual for the Structured Clinical Interview for DSM-III-R (SCID)*. New York: Biometrics Research Department, New York State Psychiatric Institute; 1987.
- Andreasen NC. *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City: University of Iowa; 1984.
- Andreasen NC. *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City: University of Iowa; 1983.
- Loranger AW, Sussman VL, Oldham JM, Russakoff LM. *Personality Disorder Examination: A Structured Interview for Making Diagnosis of DSM-III-R Personality Disorders*. White Plains, NY: Cornell Medical College; 1985.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association; 1987.
- Cohen JA. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20:37-46.
- Yan MXA, Karp JS. An adaptive Bayesian approach to three-dimensional MR brain segmentation. In: Bizais Y, Barillot C, Di Paola R, eds. *Information Processing in Medical Imaging*. New York, NY: Kluwer Academic Publishers; 1995:201-213.
- Goldszal A, Davatzikos C, Pham DL, Yan MX, Bryan RN, Resnick SM. An image-processing system for qualitative and quantitative volumetric analysis of brain imaging. *J Comput Assist Tomogr*. 1998;22:827-837.
- Turetsky BT, Cowell PE, Gur RC, Grossman RI, Shtasel DL, Gur RE. Frontal and temporal lobe brain volumes in schizophrenia: relationship to symptomatology and clinical subtype. *Arch Gen Psychiatry*. 1995;52:1061-1070.
- Cannon TD. On the nature and mechanisms of obstetric influences in schizophrenia: a review and synthesis of epidemiologic studies. *Int Rev Psychiatry*. 1997;9:387-397.
- Gottesman II, Bertelsen A. Confirming unexpressed genotypes for schizophrenia: risks in the offspring of Fischer's Danish identical and fraternal discordant twins. *Arch Gen Psychiatry*. 1989;46:867-872.
- Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon TD, Bilker W, Gur RC. A follow-up magnetic resonance imaging study of schizophrenia: relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry*. 1998;55:145-152.
- Eagles JM, Gibson I, Bremner MH, Clunie F, Ebmeier KP, Smith NC. Obstetric complications in DSM-III schizophrenics and their siblings. *Lancet*. 1990;335:1139-1141.
- McNeil TF, Cantor-Graae E, Torrey EF, Sjostroum K, Bowler A, Taylor E, Higgins ES. Obstetric complications in histories of monozygotic twins discordant and concordant for schizophrenia. *Acta Psychiatr Scand*. 1994;89:196-204.
- Brown R, Colter N, Corsellis JAN, Crow TJ, Frith CD, Jagoe R, Johnstone EC, Marsh L. Postmortem evidence of structural brain changes in schizophrenia: differences in brain weight, temporal horn area and parahippocampal gyrus compared with affective disorder. *Arch Gen Psychiatry*. 1986;43:36-42.
- Lesch A, Bogerts B. The diencephalon in schizophrenia: evidence for reduced thickness of the periventricular grey matter. *Eur Arch Psychiatr Neurol Sci*. 1984;234:212-219.