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

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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 matter 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.

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STRUCTURAL CEREBRAL abnormalities are robust correlates of schizophrenia, but their causes have not been established conclusively. Family studies can be informative in this regard. 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. Although shared environmental effects could also account for this pattern, results of twin and adoption studies 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 processes 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. 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 a dissociation in the causative antecedents of cortical and subcortical abnormalities was found. 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. 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 1935 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. A total of 267 members of this population (1.3%) had a registered diagnosis of 295.x (schizophrenia, schizoaffective disorder, or schizoaffective disorder) according to the Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, 8th ed, numbering scheme. Probands 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 (1934 ± 5.3 vs 1935 ± 4.6, t = 1.2; P = .23), nuclear family size (ie, parents and siblings) (mean ± SD, 5.1 ± 1.7 vs 5.1 ± 1.6, t = 0.5; P = .64), sex (56% vs 57% male, χ² = 0.1; P = .76), history of inpatient admissions (98% vs 94%, χ² = 1.6; P = .20), age at first inpatient admission (mean ± SD, 25.6 ± 6.7 vs 25.7 ± 6.1 years, t = –0.1; P = .94), history of comorbid substance abuse disorders (14% vs 13%, χ² = 0.1; P = .91), and work disability (75% vs 76% receiving a pension, χ² = 0.0; P = .88), but the studied group had more hospital admissions than the nonstudied group (mean ± SD, 8.9 ± 8.2 vs 6.4 ± 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. Any participant with an Axis I psychotic condition was also rated using the Scale for the Assessment of Negative Symptoms. All other participants were interviewed and rated on the Cluster A items from the Personality Disorder Examination. 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 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, κ = 0.94 ± 0.02). 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 ± SD age at first symptoms of 21.5 ± 5.2 years, average Scale for the Assessment of Positive Symptoms global rating of 2.7 ± 0.9, and average Scale for the Assessment of Negative Symptoms global rating of 1.9 ± 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, 3-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 × 256 pixels, corresponding to a field of view of 23 cm and an inplane resolution of 0.9 × 0.9 mm. Digitized images were analyzed on computer workstations (SUN, Sun Microsystems, Mountain View, Calif).

Continued on next page
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 ± 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 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).

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 ($0.11\pm0.21$, $t_{59}=0.54$, $P=.59$). 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 ($-0.08\pm0.29$, $t_{59}=-0.28$, $P=.78$) 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
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 ± 0.16, $t_{59} = 1.6; P = .12$). Group also interacted significantly with region, but the hemisphere × group and hemisphere × region × 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 had significantly smaller gray matter–brain ratios than siblings in the frontal region ($−0.39 ± 0.15, t_{59} = −2.62; P = .01$) but not in the temporal or posterior region ($−0.26 ± 0.16, t_{59} = −1.6, P = .11; 0.13 ± 0.15, t_{59} = 0.8, P = .41$, respectively). Overall, white matter–brain ratio was significantly smaller in probands compared with siblings ($−0.35 ± 0.15, t_{59} = −2.4; P = .02$) and controls, who did not differ. The results of all other group contrasts and of the tissue type × 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

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<th>MS</th>
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<td>13.6</td>
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<td>19.2†</td>
</tr>
<tr>
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<td>478.1</td>
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<td>1231.1</td>
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<td>475.7</td>
<td>6.9†</td>
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<td>6.9†</td>
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<td>955.8</td>
<td>9.3§</td>
<td>2209.2</td>
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<td>100.6</td>
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<td>68.6</td>
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<td>19.2†</td>
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<td>3.9§</td>
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<tr>
<td>Error (region)</td>
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<td>134.4</td>
<td>...</td>
<td>89.3</td>
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<td>67.6</td>
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<tr>
<td>Hemisphere × region × group</td>
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<td>3.7</td>
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<td>0.8</td>
<td>...</td>
<td>...</td>
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*MS indicates mean squares; ellipses, data not applicable.
†P < .001.
‡P < .01.
§P < .05.
**Figure 1.** Mean ± 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 ± 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, but the mode of inheritance is complex, involving many genes and certain types of neurally disruptive environmental risk exposures. Because transmission of predisposing genes for this disorder does not depend on overt manifestation of schizophrenia in first-degree relatives, 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 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. 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 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, 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, 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).

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 deviation 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 and another recent family study, 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-
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.

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