Volumes of Brain Structures in Twins Discordant for Schizophrenia

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Background: The study was designed to examine the relative contributions of genetic and nongenetic factors to structural brain abnormalities in schizophrenia and subjects at risk to develop the disorder.

Methods: The brains of 15 monozygotic and 14 same-sex dizygotic twins discordant for schizophrenia (patients) and 29 healthy twins pair-wise matched for zygosity, sex, age, and birth order were studied using high-resolution magnetic resonance imaging scans.

Results: Intracranial and whole-brain corrected frontal lobe volumes were smaller (4.6% and 2.7%, respectively) in discordant monozygotic twins as compared with healthy monozygotic twins. Irrespective of zygosity, discordant twins had smaller whole-brain (2%), parahippocampal (9%), and hippocampal (8%) volumes than healthy twins. Moreover, patients had smaller whole-brain volumes (2.2%) than their nonschizophrenic cotwins, who in turn had smaller brains (1%) than healthy twins. Lateral and third-ventricle volumes were increased in discordant dizygotic twins as compared with healthy dizygotic twins (60.6% and 56.6%, respectively). Finally, within discordant twins, lateral ventricles were larger (14.4%) in patients than in their nonschizophrenic cotwins.

Conclusions: Smaller intracranial volumes in the monozygotic patients and their cotwins suggest that increased genetic risk to develop schizophrenia is related to reduced brain growth early in life. The additional reduction in whole-brain volume found in the patients suggests that the manifestation of the disorder is related to (neurodegenerative) processes that are most likely nongenetic in origin.

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CHRONIC LEUKOCYTOSIS is a severe chronic psychiatric disorder that affects around 1% of the general population.1 Although its cause is unknown, family, twin, and adoption studies have established the importance of genetic factors. Indeed, the risk to develop schizophrenia increases with the degree of kinship and is highest (48%) in monozygotic (MZ) twins, who share the same genome.2 Environmental factors, such as intrauterine and perinatal factors, are involved as well.3-5 However, the relative contributions of genetic and environmental factors to the cause of schizophrenia remain equivocal.6

Pathophysiological, schizophrenia is understood as a brain disease. Postmortem studies7 and studies using in vivo imaging techniques such as computed tomography and magnetic resonance imaging (MRI) scanning have convincingly demonstrated morphological abnormalities in the brains of patients with schizophrenia.8,9 However, it is unclear whether the brain abnormalities associated with schizophrenia are genetic or environmental in origin. A genetic component is suggested by increased sulcal cerebrospinal fluid and reduced gray matter volumes,10 smaller thalamic volumes,11 and enlarged ventricles12,13 in patients with schizophrenia as well as in their nonschizophrenic siblings (who share, on average, 50% of the genes) as compared with healthy controls. Furthermore, enlarged ventricles and increased sulcal cerebrospinal fluid have been found in subjects with an increased genetic risk to develop schizophrenia, such as obligate carriers, subjects with a schizotypal personality disorder, and offspring of mothers with schizophrenia.14,15 However, not all studies found a familial component or increased genetic risk related to increased ventricle size.2,13,16 The involvement of nongenetic factors is emphasized by studies researching monozygotic twins discordant for schizophrenia, in which the ill twins were found to have smaller brain and hippocampal volumes and larger ventricles than their nonschizophrenic...
SUBJECTS AND METHODS

SUBJECTS

Twenty-nine pairs of twins, 15 MZ and 14 same-sex DZ discordant for schizophrenia, and 15 MZ and 14 DZ healthy control twins pair-wise matched on zygosity, sex, age, and birth order took part in the study (Table 1). Subjects were recruited in collaboration with psychiatric services and by advertisements in national newspapers. All subjects gave written informed consent to participate in the study after full explanation of the study aims and procedures. Zygosity was determined by DNA fingerprinting using either the polymorphic markers D06S474, D07S1804, D07S1870, D12S811, D13S119, D13S126, D13S788, D20S119, D22S683, DXS1001, and ELN, or D13S317, VWA, D74520, D35138, TH01, TPOX, CSF1PO, and D53818. Except for 1 control twin pair, all twins were reared together. The 1 control twin pair was separated at age 12 years when both their parents died.

All subjects underwent extensive psychiatric assessment procedures using the Comprehensive Assessment of Symptoms and History interview,20 the Schedule for Affective Disorders and Schizophrenia: Lifetime Version,21 the Structured Interviews for DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition),22,23 the Family Interview for Genetic Studies,24 and a medical history inventory. Psychiatric diagnosis was established according to criteria of DSM-IV. Diagnostic assessments were conducted by trained and experienced psychologists and psychiatrists at the Department of Psychiatry of the University Medical Center, Utrecht, the Netherlands. Consensus was reached in presence of a senior psychiatrist. The following subtypes were diagnosed in the twins with schizophrenia: paranoid (7 MZ; 4 DZ), disorganized (3 MZ; 3 DZ), undifferentiated (2 MZ; 5 DZ), residual (2 MZ; 2 DZ), and catatonic (1 MZ). Furthermore, 3 MZ patients and 1 DZ patient had an additional diagnosis of depressive disorder not otherwise specified. Diagnoses in nonschizophrenic cotwins included paranoid personality disorder (2 MZ: 1 of which also had a schizoid personality disorder and a recurrent major depressive disorder; 1 DZ), schizotypal personality disorder (2 MZ), schizoid personality disorder (1 DZ), major depressive disorder (4 MZ: 1 recurrent and 3 single episodes [1 with psychotic symptoms and 1 with agoraphobia]; 2 DZ: single episode), avoidant personality disorder (2 DZ: 1 with social phobia and 1 with partial epilepsy), generalized anxiety disorder with a dependent personality disorder (1 MZ), and no psychiatric diagnoses (5 MZ; 6 DZ). Moreover, 5 MZ and 4 DZ patients and 1 MZ and 1 DZ cotwin had histories of substance or alcohol abuse. Healthy control twins had no psychiatric illness, no schizophrenic spectrum disorders, no first-degree relatives with a history of psychiatric illness, and no second-degree relatives with a psychotic disorder. Two patients had never been on antipsychotic medication. Six patients used atypical antipsychotic medications (mean daily dose, 438.33 chlorpromazine equivalents; SD, 206.56) and 21 patients received typical antipsychotic medications (mean daily dose, 641.67 chlorpromazine equivalents; SD, 821.71).

ACQUISITION OF MAGNETIC RESONANCE IMAGES

Magnetic resonance imaging scans were obtained using a 1.5-T and a 0.5-T (13 discordant twin pairs, 7 MZ and 6 DZ) Philips Gyroscan scanner (Philips Medical Systems, Best, the Netherlands). Eight controls were scanned on both scanners to evaluate the effect of scanner type. For volumetric analysis on the 1.5-T scanner a 3-dimensional (3-D) T1-weighted, coronal, spoiled gradient echo scan (FFE) of the whole head (echo time [TE], 4.6 ms; time to repeat [TR], 30 ms; flip angle, 30°; 170-180 contiguous slices; 1×1×1.2-mm³ voxels), and a coronal dual-contrast turbo spin echo of the whole brain (TE₁, 14 milliseconds; TE₂, 80 milliseconds; TR, 6350 milliseconds; 120 contiguous slices; 1×1×1.6-mm³ voxels) were acquired. Scans on the 0.5-T scanner included a 3D T1-weighted, coronal FFE scan of the whole head (TE, 13 milliseconds; TR, 30 milliseconds; flip angle, 30°; 170-180 contiguous slices; 1×1×1.2-mm³ voxels) and an inversion recovery (IR) scan (TE, 30 milliseconds; TI, 300 ms; TR, 2720 milliseconds; 36 contiguous slices; 1×1×3.6-mm³ voxels, frontal and occipital poles not included).

IMAGE ANALYSIS

Raters were blind to subject identification and status and cerebral hemisphere. Image volumes were Talairach corrected (no scaling25) and corrected for magnetic field inhomogeneities.26,27 Total intracranial, whole-brain lateral ventricle and third ventricle volumes were measured automatically. The medial temporal structures (amygdala, hippocampus, and parahippocampal gyrus) and frontal lobes, were delineated manually by 1 and 2 raters, respectively (Figure 1).Automatically segmented volumes of interest (VOI) were visually checked by 1 rater and edited if necessary.

Automatic segmentation software included histogram analysis algorithms and series of mathematical morphological operators to connect all voxels of interest. Intracranial volume was segmented on dual contrast turbo spin echo and IR scans. Voxels inferior to the cerebellum midway of the foramen magnum were excluded. Frontal and occipital poles were added manually to the IR intracranial volumes by overlaying the IR intracranial volume over the corresponding 0.5-T

cotwins.17-19 The present study was designed to examine the neuroanatomical correlates of a (possible) genetic predisposition to develop schizophrenia and the relative contributions of genetic and nongenetic factors to these structural brain abnormalities. High-resolution MRI scans of the brain were obtained from MZ and dizygotic (DZ) twins discordant for schizophrenia and healthy twin pairs who were pair-wise matched on zygosity, sex, age, and birth order. The study of twins discordant for schizophrenia significantly enhances the sensitivity to detect brain abnormalities because shared genetic and prenatal and postnatal environmental factors that contribute to the variation in brain morphology are controlled for. Importantly, discordant MZ twin pairs, unlike discordant DZ twin pairs, have the same genetic predisposition to develop schizophrenia. A genetic role is suggested when MZ patients and their cotwins differ from healthy MZ twins but do not differ from each other, and the finding is more
Table 2 presents absolute volumetric data. Estimates of within–twin-pair similarity are presented in Table 3.

The intraclass correlations for volumes of interest, except for parahippocampal volume in discordant twin pairs, were higher for MZ twin pairs than for DZ twin pairs. In particular, intracranial, whole-brain, frontal lobe, and hippocampal volumes in both discordant and healthy twin pairs, and lateral ventricle volume in healthy twin pairs only seemed to be under a high degree of genetic control. Intraclass correlation coefficients for the parahippocampal gyrus and third ventricle were substan-

pronounced in discordant MZ than in discordant DZ twin pairs. The degree to which brain structure is genetically controlled can be estimated by comparing the within-pair similarity of the MZ twins with that of the DZ twins.

DATA ANALYSIS

Statistical analyses were performed with the SPSS package for Windows version 6.1 (Statistical Product and Service Solutions 6.1; SPSS Inc, Chicago, Ill). The data were normally distributed, except for the lateral ventricles, the third ventricle, and the hippocampus. These variables were successfully normalized using a logarithmic transformation. Within–twin-pair similarity for VOIs was estimated by calculating ICCs on standardized residuals corrected for age and sex for discordant and healthy MZ and DZ twin pairs. Fisher r to z transformations were used for statistical testing and to calculate 93% confidence intervals. Volume measurements and variables such as age, height, parent education, and subject education were pair-wise analyzed using repeated measures multivariate analysis of covariance (rm-MANCOVA). Zygosity (monozygotic, dizygotic) was entered as a between-subjects factor. Group (Discordant twin pairs, healthy twin pairs), twin (1=patient with schizophrenia or matched healthy control twin, 2=nonschizophrenic cotwin or matched healthy control twin), and side (left, right) were analyzed as matched samples. The following main and interaction effects were tested: zygosity, group, twin, zygosity × group; zygosity × twin; and zygosity × group × twin. Second, any interaction with the side factor was evaluated. To evaluate the effect of substance abuse and organic brain syndromes within discordant families twin pairs in which 1 or both twins had a history of substance abuse (9 twin pairs: 8 patients and 3 cotwins) and organic brain syndrome (1 twin pair: 1 cotwin) at some point during their lives were compared with twin pairs without such histories using a rm-MANCOVA, with history (positive, negative) as a between-subject factor and twin (patient, nonschizophrenic cotwin) as a within-subject factor. Intracranial volume was used as a covariant for whole-brain, extracerebral CSF (intracranial volume – whole-brain and ventricle volumes) and ventricle volumes whereas whole-brain volume was a covariant for the frontal lobes and the medial temporal structures. Significant interactions were followed up with a priori special contrasts. All tests were 2-tailed. The level of significance was .05.

3-D data volume, which was resampled to fit IR scan dimensions. Whole-brain volume was segmented on the 3-D FFE scans. Whole-brain volumes contained gray and white matter tissue only. In lateral ventricle segmentation, automatic decision rules bridged connections not detectable and prevented ‘leaking’ into cisterns. The third ventricle was limited by coronal slices, clearly showing the anterior and posterior commissures. The upper boundary was a plane through the plexus choroidae ventriculi tertii in the mid-sagittal slice perpendicular to this slice.

Manual segmentation was performed in an anterior-posterior direction on whole-brain volumes using ANALYZE (Biomedical Imaging Resource, Mayo Foundation Clinic, Rochester, Minn). A volume-rendered 3D representation of the brain and simultaneous visualization and manipulation of coronal, transverse, and sagittal slices enabled accurate localization of landmarks. The frontal pole, the lateral fissure, and the interhemispheric, circular inner, precentral, and cingulate sulci limited the frontal lobes. Amygdala segmentation started in the coronal slice, above which the optic tract lies. The lateral border was defined by the gray matter of this nucleus until the gray matter of the parahippocampal gyrus was reached. From then on, the border was continued as a straight line in direct continuation with the inferior and medial border of the amygdala. Segmentation of the hippocampus started in the coronal slice in which the characteristic oval shape of mammillary bodies was visible for the first time, and stopped when the fornix was visible as a continuous tract. The border of the hippocampus was defined by its gray matter. Parahippocampal gyrus segmentation began simultaneously with the amygdala. The posterior commissure was its posterior border. The lateral border was defined by the collateral sulcus, and the superior border was defined by a straight line from the most superolateral point of the collateral sulcus to the most superior point of the mediotemporal cortex in the crural cistern. The amygdala and hippocampus were then excluded from the parahippocampal gyrus segmentation. Although the collateral sulcus has considerable interindividual variability making it prone to bias, we considered it adequate, as there was no reason to assume differences in variability between groups.

Intrarater reliabilities, expressed as intraclass correlation coefficients (ICC), for intracranial, whole-brain, and lateral and third ventricle volumes calculated on 22, 14, and 18 scans, respectively, were all 0.99. For the amygdala, hippocampus, parahippocampus, and frontal lobes, intrarater reliabilities calculated on 14 scans were 0.49, 0.82, 0.84, and 0.99, respectively. Interrater reliability for the frontal lobes was 0.98. Because of low reliabilities, the amygdala volumes were excluded from further analysis.

The intraclass correlations for volumes of interest, except for parahippocampal volume in discordant twin pairs, were higher for MZ twin pairs than for DZ twin pairs. In particular, intracranial, whole-brain, frontal lobe, and hippocampal volumes in both discordant and healthy twin pairs, and lateral ventricle volume in healthy twin pairs only seemed to be under a high degree of genetic control. Intraclass correlation coefficients for the parahippocampal gyrus and third ventricle were substan-

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tially lower in discordant MZ twin pairs as compared with healthy MZ twin pairs.

### INTRACRANIAL VOLUME

A significant zygosity × group interaction \( F(1,27)=4.43; P<.05 \) was found. This was attributable to discordant MZ twin pairs having smaller intracranial volumes than healthy MZ twin pairs and the discordant DZ twin pairs not differing from their controls. Monozygotic patients and their cotwins did not differ from each other. Intracranial volumes were not significantly different between MZ and DZ patients.

### WHOLE-BRAIN VOLUME

A significant main effect for group \( F(1,26)=15.71; P<.001 \), with both the patients and their cotwins having significantly smaller brains than the healthy twin pairs \( F(1,27)=15.72; P<.001 \) and \( F(1,27)=4.35; P<.05 \), respectively, and a group × twin interaction \( F(1,26)=12.82; P<.001 \) were found (Figure 2). The group × twin interaction was attributable to patients having significantly smaller brains than their cotwins \( F(1,27)=7.06; P<.05 \) and the healthy twins not differing significantly from each other.

### FRONTAL LOBES

A significant zygosity × group interaction was found \( F(1,26)=6.01; P<.05 \). This was attributable to discordant MZ twin pairs having smaller frontal lobes than healthy MZ twin pairs and discordant DZ twin pairs not differing from their controls.

### HIPPOCAMPUS

A significant main effect for group \( F(1,26)=4.92, P<.05 \) was found, with discordant twin pairs having smaller hippocampal volumes than healthy twin pairs. For parahippocampal gyrus, a significant main effect for group \( F(1,26)=4.77; P<.05 \) was found, with discordant twin pairs having smaller parahippocampal volumes as compared with healthy twin pairs.

### EXTRACEREBRAL VOLUME

A significant group effect \( F(1,26)=13.98; P<.001 \), with discordant twins having larger extracerebral volume than control twins, and a group × twin interaction \( F(1,26)=12.97; P<.001 \) were found. The group × twin interaction was attributable to patients having significantly larger extracerebral volumes than their cotwins and healthy twins not differing from each other.

### LATERAL VENTRICLES

Significant interactions were seen for zygosity × group \( F(1,26)=6.24; P<.05 \), with discordant DZ twins having larger lateral ventricles than control DZ twins and MZ twins not differing from control MZ twins; for group × twin \( F(1,26)=6.48, P<.05 \), with patients having larger lat-

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**Table 1. Demographic Data**

<table>
<thead>
<tr>
<th></th>
<th>Discordant Twin Pairs</th>
<th>Healthy Twin Pairs†</th>
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</thead>
<tbody>
<tr>
<td>MZ (N = 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>35.11 (10.31) [18.5-51.75]</td>
<td>35.62 (11.35) [19.44-55.84]</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>6/9</td>
<td>6/9</td>
</tr>
<tr>
<td>Parent education, y</td>
<td>11.20 (3.26) [6-16]</td>
<td>11.64 (2.31) [10-15]</td>
</tr>
<tr>
<td>DZ (N = 14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>35.67 (10.77) [20.39-50.52]</td>
<td>35.12 (10.26) [21.75-51.46]</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>6/8</td>
<td>6/8</td>
</tr>
<tr>
<td>Parent education, y</td>
<td>12.07 (2.97) [6-16]</td>
<td>11.50 (2.35) [10-16]</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Cotwin</th>
<th>NC1</th>
<th>NC2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, m</td>
<td>1.76 (0.11) [1.55-1.94]</td>
<td>1.76 (0.11) [1.55-1.92]</td>
<td>1.75 (0.07) [1.63-1.84]</td>
<td>1.76 (0.06) [1.65-1.88]</td>
</tr>
<tr>
<td>Handedness, R/L/both</td>
<td>13/2</td>
<td>11/4</td>
<td>11/4</td>
<td>13/2</td>
</tr>
<tr>
<td>Education, y</td>
<td>11.5 (3.02) [7-16]</td>
<td>13.1 (2.53) [7-16]</td>
<td>12.7 (2.29) [8-16]</td>
<td>13.0 (2.10) [9-16]</td>
</tr>
<tr>
<td>Age at first symptoms, y</td>
<td>22.2 (6.91) [9-33]</td>
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<td>...</td>
</tr>
<tr>
<td>Age at first hospitalization, y</td>
<td>23.5 (4.40) [15-33]</td>
<td>...</td>
<td>...</td>
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</tr>
<tr>
<td>DZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, m</td>
<td>1.76 (0.11) [1.56-1.91]</td>
<td>1.77 (0.09) [1.58-1.87]</td>
<td>1.74 (0.10) [1.56-1.89]</td>
<td>1.75 (0.09) [1.59-1.87]</td>
</tr>
<tr>
<td>Handedness, R/L/both</td>
<td>12/2</td>
<td>13/1</td>
<td>13/0/1</td>
<td>9/4/1</td>
</tr>
<tr>
<td>Education, y</td>
<td>11.1 (3.18) [6-16]</td>
<td>13.6 (2.43) [8-16]</td>
<td>13.9 (1.42) [10-16]</td>
<td>12.9 (2.21) [10-16]</td>
</tr>
<tr>
<td>Age at first symptoms, y</td>
<td>19.5 (6.37) [8-34]</td>
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<tr>
<td>Age at first hospitalization, y</td>
<td>24.5 (8.88) [14-44]</td>
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</tbody>
</table>

* All values are presented as a mean (SD) [range], unless otherwise indicated. For “parent education” and “height,” affected and healthy monozygotic (MD) and dizygotic (DZ) twin pairs did not differ significantly from each other \( P>.51 \) and \( P>.36 \), respectively. For “education,” patients with schizophrenia had significantly fewer years of education than their cotwins and healthy twins \( P<.01 \). Ellipses indicate not applicable.
† One subject was never hospitalized \( N=13 \).
‡ NC1 indicates healthy control twins matched by zygosity, age, sex, and birth order to the patient with schizophrenia; NC2, healthy control twins matched by zygosity, age, sex, and birth order to the nonschizophrenic cotwin.
eral ventricles than their cotwins; and for zygosity × side (F<sub>1,27</sub> = 18.42; P < .01), with MZ but not DZ twins having larger left than right lateral ventricles.

THIRD VENTRICLE

A significant main effect was found for group (F<sub>1,26</sub> = 4.66; P < .05), with discordant twins having larger third ventricles than control twins, and for a zygosity × group interaction (F<sub>1,26</sub> = 6.44; P < .05), with discordant DZ twins having larger third ventricles than control DZ twins and discordant MZ twins not differing from control MZ twins.

SUBSTANCE ABUSE

There was no main effect for history of substance or alcohol abuse for any of the total VOIs (F value range, 0.04-0.92; P value range, .35-.84). When data were analyzed...
This study compared brain structure in MZ and same-sex DZ twins discordant for schizophrenia with those of healthy twins pair-wise matched on zygosity, age, sex, and birth order. Most VOIs, particularly intracranial, whole-brain, and frontal lobe volumes, seemed highly genetically controlled. Intracranial and frontal lobe volumes were decreased in discordant MZ twin pairs, whereas whole-brain, and parahippocampal volumes were reduced in discordant pairs irrespective of zygosity. In addition to the decrements found in their cotwins, patients showed additional reductions in whole-brain volume. Lateral and third ventricle volumes were increased in discordant DZ twin pairs. Compared with their cotwins, patients showed increased lateral ventricle volume.

The first major finding is that of reduced intracranial volumes in discordant MZ twin pairs as compared with healthy MZ twin pairs, with intracranial volume being highly genetically controlled. Notably, MZ patients and their cotwins were affected to a similar degree. Since they share the same genetic vulnerability to develop schizophrenia, and since this finding was more pronounced in the discordant MZ twin pairs than in the discordant DZ twin pairs, smaller intracranial volumes may reflect a neuroanatomical correlate of a genetically based vulnerability to develop schizophrenia. Brain growth is the main factor determining cranial growth in early development; consequently, these findings suggest that brain growth in schizophrenia is stunted early in life. Although the finding of smaller intracranial volumes is consistent with the result of a recent meta-analytic study of cranial size in schizophrenia,33 our results suggest that this volume reduction may reflect a genetic vulnerability to developing schizophrenia, rather than being related to the illness itself. However, an alternative explanation is that an interaction between genetic vulnerability and environmental events occurring predominantly in MZ (and not DZ) twin pairs leads to abnormal brain growth, resulting in smaller intracranial volumes.

The second major finding is that whole-brain volume was reduced in discordant twin pairs irrespective of zygosity. Since both patients and their cotwins displayed decrements in total brain volumes, this probably reflects shared factors that may be either genetic and/or environmental in origin. The finding is consistent with those of a recent family study reporting decreased gray matter volumes in patients with schizophrenia and their nonpsychotic siblings.10 The additional decrease in whole-brain volume in the patients as compared with their cotwins suggests that schizophrenia itself is expressed by further reductions in brain tissue, which are most likely attributable to nongenetic factors. Similarly, a study in discordant MZ twins showed significant brain volume reductions in patients as compared with their healthy cotwins.17,33 Our finding of reduced brain volume in schizophrenia is consistent with the results of several other studies.8,17,33

Frontal lobe volumes were decreased in discordant MZ twin pairs as compared with healthy MZ twin pairs in excess of the overall decrement in brain volume. This

**Table 3. Brain Structure Similarity Measures in Twins**

<table>
<thead>
<tr>
<th></th>
<th>Discordant Twin Pairs</th>
<th>Healthy Twin Pairs</th>
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<tbody>
<tr>
<td></td>
<td>MZ (n = 15)</td>
<td>DZ (n = 14)</td>
</tr>
<tr>
<td></td>
<td>MZ (n = 15)</td>
<td>DZ (n = 15)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.93 (0.80-0.98)</td>
<td>0.45 (0.00-0.79)</td>
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<tr>
<td>Whole brain</td>
<td>0.86 (0.62-0.95)</td>
<td>0.08 (0.00-0.59)</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>0.84 (0.58-0.95)</td>
<td>0.26 (0.00-0.70)</td>
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<tr>
<td>Hippocampus</td>
<td>0.68 (0.26-0.88)</td>
<td>0.00 (0.00-0.53)</td>
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<tr>
<td>Parahippocampal gyrus</td>
<td>0.34 (0.00-0.73)</td>
<td>0.37 (0.00-0.75)</td>
</tr>
<tr>
<td>Lateral ventricle</td>
<td>0.67 (0.24-0.88)</td>
<td>0.18 (0.00-0.65)</td>
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<td>Third ventricle</td>
<td>0.36 (0.00-0.74)</td>
<td>0.17 (0.00-0.64)</td>
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<td>0.86 (0.62-0.95)</td>
<td>0.35 (0.00-0.74)</td>
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<td>0.93 (0.80-0.98)</td>
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<td>0.73 (0.35-0.90)</td>
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<td>0.70 (0.29-0.89)</td>
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<td>0.73 (0.35-0.90)</td>
<td>0.00 (0.00-0.53)</td>
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<tr>
<td></td>
<td>0.71 (0.31-0.90)</td>
<td>0.27 (0.00-0.70)</td>
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</table>

* Values are presented as intraclass correlations (95% confidence intervals) calculated on standardized residuals after correcting for age and sex. A genetic component is indicated when intraclass correlations are higher in monozygotic (MZ) twins, who share 100% of their genes, than in dizygotic (DZ) twins, who share, on average, 50% of their genes. Note that confidence intervals are rather large, indicating that these similarities measures are rough estimates of the degree to which brain structure is genetically controlled.

† For MZ vs DZ twins within discordant and healthy twin pairs separately, P < .05.

Figure 2. Whole-brain volume. All values are means ± SEMs. A significant group effect (A: F1,26 = 15.71; P < .001) indicated that twins discordant for schizophrenia had significantly smaller whole-brain volumes than healthy twins. Patients (B: F1,27 = 15.72; P < .001) as well as their cotwins (C: F1,27 = 4.35; P < .05) had reduced whole-brain volumes. Moreover, patients had significantly smaller brains than their cotwins (D: F1,27 = 7.06; P < .05).

COMMENT

This study compared brain structure in MZ and same-sex DZ twins discordant for schizophrenia with those of healthy twins pair-wise matched on zygosity, age, sex, and birth order. Most VOIs, particularly intracranial, whole-brain, and frontal lobe volumes, seemed highly genetically controlled. Intracranial and frontal lobe volumes were decreased in discordant MZ twin pairs, whereas whole-brain, and parahippocampal volumes were reduced in discordant pairs irrespective of zygosity. In addition to the decrements found in their cotwins, patients showed additional reductions in whole-brain volume. Lateral and third ventricle volumes were increased in discordant DZ twin pairs. Compared with their cotwins, patients showed increased lateral ventricle volume.

The first major finding is that of reduced intracranial volumes in discordant MZ twin pairs as compared
Hippocampal and parahippocampal volumes were reduced in discordant twin pairs irrespective of zygosity, which may thus be secondary to genetic or shared environmental effects. Parahippocampal reductions are most likely of environmental origin because ICCs for this structure were substantially lower in discordant MZ twin pairs than in healthy MZ twin pairs. Hippocampal volume reductions in schizophrenia have been found in siblings of patients, while in MZ twins, hippocampal reductions were reported in the MZ twins with schizophrenia as compared with the cotwins, suggesting additional environmental influences. Importantly, our finding that both genetic as well as common environmental factors may be involved in the medial temporal lobe decrease in schizophrenia seems to be supported by these findings.

Lateral and third ventricular volumes were increased in discordant DZ twin pairs as compared with control DZ twin pairs, and comparable in discordant MZ twin pairs as compared with control MZ twin pairs. Our finding that discordant MZ twins did not differ from healthy controls is in agreement with reported findings. Lateral ventricles were enlarged in patients as compared with their cotwins, suggesting that the enlargement is mainly due to environmental events. The finding is in agreement with those for discordant MZ twin and sibling pairs. Third ventricle enlargement also seems to be environmental in origin because ICCs were substantially lower in discordant MZ twin pairs as compared with healthy MZ twin pairs.

A limitation of this study was that by not including MZ twins discordant for schizophrenia, a group was selected where environmental factors are important in the development of the disorder, hereby preventing estimation of the true genotypic population variance. Furthermore, although attempts were made to ensure comparability of volumetric measures across scanning platforms, we cannot rule out the possibility that the use of 2 different scanners influenced our results. Finally, it is not known to which extent physiological factors such as medication intake may have contributed to volume differences between twins with schizophrenia and non-schizophrenic twins.

In conclusion, findings from this study suggest that increased genetic risk to develop schizophrenia may lead to impaired brain development, possibly early in life. The manifestation of the disorder itself appears related to additional (perhaps degenerative) processes that are, at least partly, nongenetic in origin.

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