Brain Volume Changes in First-Episode Schizophrenia

A 1-Year Follow-up Study

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Background: Imaging studies of patients with schizophrenia have demonstrated that brain abnormalities are largely confined to decreases in gray matter volume and enlargement of the lateral and third ventricles. Global gray matter volume has been reported to progressively decrease in childhood-onset and chronic schizophrenia. Global gray matter volumes have not been examined longitudinally in patients with first-episode schizophrenia. One would expect global gray matter to decrease progressively, particularly in first-episode patients, because clinical deterioration is greatest in the early stages of the disease.

Methods: Patients with first-episode schizophrenia who had taken antipsychotic medication for 0 to 16 weeks (n = 34) and matched healthy comparison subjects (n = 36) were included in the study. For all subjects, magnetic resonance imaging scans of the whole brain were obtained at inclusion and after 1 year (mean [SD], 12.7 [1.1] months). Outcome was measured 2 years after inclusion. To compare morphological changes over time between patients and healthy comparison subjects, multiple repeated-measures analyses of variance were conducted with intracranial volume as a covariate. Outcome and cumulative antipsychotic medication were related to changes in patients’ brain volumes.

Results: Total brain volume (~1.2%) and gray matter volume of the cerebrum (~2.9%) significantly decreased and lateral ventricle volume significantly increased (7.7%) in patients. The decrease in global gray matter volume significantly correlated with outcome and, independently of that, with higher cumulative dosage of antipsychotic medication.

Conclusions: The loss of global gray matter in schizophrenia is progressive, occurs at an early stage of the illness, and is related to the disease process and antipsychotic medication.

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Brain imaging studies have consistently demonstrated brain abnormalities in patients with schizophrenia. These changes are largely confined to decreases in gray matter volumes and enlargement of the lateral and third ventricles. Although the origin of schizophrenia is still unknown, schizophrenia has recently been considered to result from abnormalities in neurodevelopment. The neurodevelopmental theories of schizophrenia are based on neurocognitive and motor problems observed in high-risk children and the apparent lack of progression in brain abnormalities over the course of the illness according to computed tomography (but see Kemali et al) and magnetic resonance imaging (MRI) studies. Some studies report that enlarged ventricles and decreases in brain volumes are already present at disease onset, which is consistent with the notion of a neurodevelopmental origin for the brain abnormalities found in schizophrenia.

However, schizophrenia has long been thought to be a progressive or degenerative, not developmental, disorder. Indeed, Kraepelin considered progressive clinical deterioration to be the hallmark of the disorder, naming it dementia praecox to reflect this particular aspect. Lately, others have reemphasized that the decline in functioning in schizophrenia is an important clue to its pathogenesis and that the brain abnormalities in schizophrenia could be expected to reflect this clinical progression. If brain changes progress over time, one would expect the changes to be particularly pronounced in the first (symptomatic) years of the schizophrenic illness because it is then that the most rapid clinical changes, including deterioration in functioning, are seen. Indeed, it has been suggested that the 5 years after the first psychotic episode are char-
characterized by the largest decline in functioning, followed by a relatively stable clinical period.\textsuperscript{32,33} Significantly, recent longitudinal imaging studies have reported that brain abnormalities increase over time in patients with schizophrenia.\textsuperscript{17,24-36}

A few longitudinal MRI studies have examined brain structures in first-episode patients and their changes over time.\textsuperscript{17,24,25,30,31,34,35} Volume decreases in the total brain,\textsuperscript{17} frontal lobe,\textsuperscript{24} right cerebellum,\textsuperscript{25} and superior temporal gyrus\textsuperscript{34} (but see Keshavan et al\textsuperscript{31}) have been reported, as have increases in ventricular volume,\textsuperscript{17} at least in a subgroup of poor-outcome patients.\textsuperscript{35} Moreover, changes may be caused by decreases in focal gray matter, as suggested by findings in the superior temporal gyrus.\textsuperscript{34}

In patients with chronic schizophrenia, prospective studies using computed tomography and MRI have found that lateral ventricle volume increases\textsuperscript{26,29,35} and temporal and frontal lobe gray matter volume decreases\textsuperscript{36} over time. Global gray matter volume has only been examined prospectively in childhood-onset schizophrenia.\textsuperscript{36} Progressive decline in gray matter volume has been found in this rare form of the disorder.\textsuperscript{32} Thus, longitudinal imaging studies have reported that brain changes and outcome\textsuperscript{17,24,25} or even reported an inverse relationship.\textsuperscript{31}

Progressive brain volume changes in schizophrenia may be related to outcome. However, results have been inconsistent. A relationship among poor outcome, increases in ventricle volume,\textsuperscript{26,29,35} and decreases in regional gray matter volume\textsuperscript{36} has been reported. In contrast, other studies failed to find a relationship between brain changes and outcome\textsuperscript{17,24,35} or even reported an inverse relationship.\textsuperscript{30}

Antipsychotic medication may also influence brain volume changes over time. A larger cumulative dosage of antipsychotic medication was related to progressive decreases in frontal lobe ventricle volume in patients with first-episode schizophrenia.\textsuperscript{30,37,38} In patients with chronic\textsuperscript{30} or childhood-onset\textsuperscript{35} schizophrenia no such relationship was found. One study of first-episode schizophrenia reported an inverse relationship between antipsychotic medication and progressive ventricular changes, suggesting that antipsychotic medication could prevent pathologic ventricular enlargement.\textsuperscript{39}

No study has examined global gray matter volumes prospectively in first-episode schizophrenia. Therefore, we examined global gray matter volumes in the MRIs of 34 patients with first-episode schizophrenia at baseline and after 1 year. To control for the brain volume changes observed in normal aging,\textsuperscript{39,43} patients were compared with 36 carefully matched healthy subjects. Healthy comparison subjects were scanned twice at the same interval as patients. The Camberwell Assessment of Need (CAN) was used to assess outcome, and the cumulative dosage of antipsychotic medication was calculated.

### METHODS

Patients with first-episode schizophrenia (n=34), recruited from the First-Episode Schizophrenia Research Program at the University Medical Center Utrecht, Utrecht, the Netherlands, and healthy comparison subjects (n=36) were included in the study (Table 1). All subjects provided written informed consent prior to participation. For all subjects, MRI scans of the whole brain were obtained at inclusion (T0) and after 1 year (T1) (scan interval, mean [SD], 12.7 [1.1] months).

At baseline, all subjects were physically healthy and did not have a history of head injury or a diagnosis of drug or alcohol abuse or dependence. At 1-year’s follow-up, all subjects remained physically healthy.

At inclusion, patients were assessed with the Comprehensive Assessment of Symptoms and History\textsuperscript{44} by 2 trained raters who independently determined the diagnosis and achieved consensus afterward. The onset of prodromal symptoms and the duration of untreated psychosis was measured by a shortened version of the Interview for the Retrospective Assessment of the Onset of Schizophrenia.\textsuperscript{45} Severity of illness was measured with the Positive and Negative Syndrome Scale (PANSS).\textsuperscript{46} Of the 34 patients, 24 had never received antipsychotic medication. The remaining 10 patients had been prescribed antipsychotics for less than 16 weeks before the first scan (T0).

At T1, all 34 patients were reassessed for diagnosis and severity of illness using the Comprehensive Assessment of Symptoms and History and the PANSS; 29 patients then met DSM-IV

### TABLE 1. Demographic Data for 34 Patients With First-Episode Schizophrenia and 36 Healthy Controls\textsuperscript{*}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
<th>Controls</th>
<th>t or (\chi^2) Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>30</td>
<td>(\chi^2 = 0.05)</td>
<td>.82</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handedness, No. of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>31</td>
<td>31</td>
<td>(\chi^2 = 2.23)</td>
<td>.33</td>
</tr>
<tr>
<td>Left</td>
<td>2</td>
<td>5</td>
<td>(t = -1.23)</td>
<td>.22</td>
</tr>
<tr>
<td>Mixed</td>
<td>0</td>
<td>0</td>
<td>(t = 1.11)</td>
<td>.27</td>
</tr>
<tr>
<td>Age, mean ± SD (range), y</td>
<td>26.2 ± 5.31 (19-37)</td>
<td>24.5 ± 5.8 (17-40)</td>
<td>(t = -1.61)</td>
<td>.11</td>
</tr>
<tr>
<td>Weight, mean ± SD (range), kg, T0</td>
<td>73.0 ± 12.2 (52-100)</td>
<td>76.1 ± 11.4 (57-100)</td>
<td>(t = 0.80)</td>
<td>.43</td>
</tr>
<tr>
<td>Height, mean ± SD (range), cm, T0</td>
<td>177.2 ± 9.0 (160-193)</td>
<td>184.1 ± 7.5 (170-199)</td>
<td>(t = 3.49)</td>
<td>.001</td>
</tr>
<tr>
<td>Parental educational level, mean ± SD, y</td>
<td>13.47 ± 3.24</td>
<td>14.03 ± 2.56</td>
<td>(t = 1.13)</td>
<td>.26</td>
</tr>
<tr>
<td>Education, mean ± SD, y</td>
<td>11.50 ± 2.72</td>
<td>12.28 ± 3.05</td>
<td>(t = 1.1)</td>
<td>.27</td>
</tr>
<tr>
<td>MRI interval, mean ± SD, mo</td>
<td>12.85 ± 1.15</td>
<td>12.44 ± 0.94</td>
<td>(t = -1.61)</td>
<td>.11</td>
</tr>
</tbody>
</table>

\*T0 indicates baseline; MRI, magnetic resonance imaging.
criteria for schizophrenia, and 5 patients met criteria for schizo-affective disorder. The number of days spent in the hospital between T0 and T1 was recorded and used as a measure of 1-year outcome. In addition, every patient was monitored carefully for the amount and type of medication prescribed between T0 and T1. Patients were prescribed typical (n=5) or atypical (n=15) antipsychotics, and a number of patients (n=14) were prescribed typical and atypical antipsychotics, although not simultaneously, at various times during the first year of follow-up. To calculate the cumulative dosage of typical antipsychotics, a table from the Dutch National Health Service was used to derive the haloperidol equivalents.47 For atypical antipsychotics, the respective pharmaceutical companies suggested how to convert the dosage into haloperidol equivalents.49 and corrected for inhomogeneities in the magnetic field.50 Intracranial, total brain, cerebral gray and white matter, lateral ventricle, third ventricle, and cerebellum volumes were then automatically measured with histogram analysis algorithms and a series of mathematical morphological operators to connect all voxels of interest.51 Intracranial volume was segmented on the dual-contrast turbo spin-echo scans (second echo). Using mathematical morphological operators the intracranial volumes were segmented automatically, with the foramen magnum being used as the inferior boundary. The dual-contrast turbo spin-echo scans and the intracranial region segmentations on them were registered to the 3-dimensional FFE images using a mutual information maximization algorithm.51 The 3-dimensional FFE images were masked with the binary intracranial volumes. This was done to remove tissues such as extracranial fat. Total brain volumes were segmented on the T1-weighted scans and contained gray and white matter tissue only. Gray and white matter segmentation was done based on intensity histogram shape analysis of the 3-dimensional FFE images and had been calibrated and validated on a set of 80 human brain images.51 In lateral ventricle segmentation, automatic decision rules bridged connections that were not detectable and prevented “leaking” into cisterns. The third ventricle was limited by coronal slices that clearly showed the anterior and posterior commissures; the upper boundary was a plane through the plexus choroiditis ventriculi tertii in the midsagittal slice perpendicular to this slice. The cerebellum was limited by the tentorium cerebelli and the brainstem. All images were checked after the measurements and corrected manually, if necessary. The interrater reliability of the measurements, determined

### MRI PROCEDURES AND MEASUREMENTS

Magnetic resonance images were acquired with a Philips NT scanner (Philips Medical Systems, Best, the Netherlands) operating at 1.5 T. A T1-weighted 3-dimensional fast field echo (FFE) scan (echo time [TE], 4.6 milliseconds; repetition time [TR], 30 milliseconds; flip angle, 30°; and field of view, 256 mm) with 160 to 180 contiguous coronal 1.2-mm slices and a T2-weighted dual-echo turbo spin-echo scan (TE1, 14 milliseconds; TE2, 80 milliseconds; TR, 6350 milliseconds; flip angle, 90°; and field of view, 256 mm) with 120 contiguous coronal 1.6-mm slices of the whole head were used for the quantitative measurements. In addition, a

### Table 2. Clinical Data for 34 Patients With First-Episode Schizophrenia*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DSM-IV diagnosis, No. of patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>23</td>
<td>29</td>
<td>...</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>2</td>
<td>5</td>
<td>...</td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>7</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Psychotic episode, not otherwise specified</td>
<td>2</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Prodromal phase, mo</td>
<td>37.8 ± 51.3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Psychosis, mo</td>
<td>17.2 ± 30.3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Duration of hospitalization between the 2 scans, d</td>
<td>78.9 ± 42.5</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>PANSS positive symptoms</td>
<td>17.0 ± 4.8</td>
<td>12.9 ± 4.5</td>
<td>...</td>
</tr>
<tr>
<td>PANSS negative symptoms</td>
<td>17.9 ± 6.3</td>
<td>15.67 ± 5.2</td>
<td>...</td>
</tr>
<tr>
<td>PANSS psychopathology</td>
<td>35.6 ± 10.2</td>
<td>29.0 ± 6.7</td>
<td>...</td>
</tr>
<tr>
<td>Total antipsychotic medication (cumulative lifetime)</td>
<td>65.9 ± 157.6</td>
<td>2077.5 ± 962.7</td>
<td>...</td>
</tr>
<tr>
<td>in haloperidol equivalents, mg</td>
<td>...</td>
<td>...</td>
<td>0.3 ± 0.2</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise indicated. T0 indicates baseline; T1, 1 year after study inclusion; T2, 2 years after study inclusion; PANSS, Positive and Negative Syndrome Scale; CAN, Camberwell Assessment of Need; and ellipses, not applicable.
STATISTICAL ANALYSES

Brain volume measurements and clinical data were normally distributed. To examine whether brain volumes changed more in patients with first-episode schizophrenia than in the healthy comparison subjects during the 1-year follow-up, multiple repeated-measures analyses of covariance (MANCOVA) with intracranial volume as a covariate were conducted with total brain, cerebellum, gray and white matter of the cerebrum (total brain, excluding cerebellum and brainstem), and lateral and third ventricles as dependent variables and group (patients or healthy comparison subjects) and time (T0 or T1) as independent variables. To examine whether changes in brain asymmetry occurred over 1 year in patients compared with healthy comparison subjects, a MANCOVA was performed with total brain, gray and white matter, and lateral ventricles as dependent variables and group, time, and side (left or right) as independent variables (group × time × side interaction). In case of a significant finding, post hoc paired t tests were conducted separately for patients and healthy comparison subjects.

To assess the effect of diagnosis, the same analysis was performed excluding patients with a diagnosis of schizoaffective disorder at T1. Moreover, to examine the effect of prior antipsychotic medication use, Pearson product-moment correlations were calculated with intracranial volume as a covariate. To control for baseline scores the same analyses were done with T0 scores added as a covariate.

Exploratory analyses were performed to assess the effect of different types of antipsychotic medication (atypical, typical, or clozapine) on brain morphology using Pearson product-moment correlations. The Statistical Product and Service Solutions statistical package for Windows, version 9.0 (SPSS Inc, Chicago, Ill) was used for these analyses, with a 2-tailed α level of .05.

To control for scanner software upgrades, the same analyses were conducted with the date of the scan added as a covariate.

RESULTS

DEMOGRAPHIC DATA

As seen in Table 1, patients and healthy comparison subjects did not significantly differ with regard to sex, handedness, age, weight, parental education, and scan interval. Although not matched for education, they did not differ from healthy comparison subjects on years of education.

Patients and healthy comparison subjects did significantly differ in height, but because intracranial volume was used as a covariate, the results presented here are uncontrolled for height. However, results did not change when height was used as a covariate.

BRAIN VOLUME CHANGES

Differences Between and Within Groups Over Time

Significant group × time interactions were found for total brain (F1,62=25.64; P<.001), gray matter of cerebrum (F1,62=20.55; P<.001), and lateral ventricle (F1,62=11.58; P=.001) volumes (Table 3). No significant interaction effects of group × time × side were found for any of these measurements. Changes in volume (scan T1 – scan T0) for total brain, gray matter, and lateral ventricles are provided in Figure 1. When patients with a schizoaffective disorder were excluded, the results did not change, except for a significant increase in third ventricle volume over time (F1,62=4.89; P=.03). Including only pa-
patients who had not taken antipsychotics did not change the results, except for another significant increase in third ventricle volume ($F_{1,57} = 10.89; P = .002$).

In patients, paired $t$ tests (scan T0 vs scan T1) revealed a significant decrease in total brain ($t_{53} = 3.15; P = .004$) and gray matter ($t_{53} = -4.65; P < .001$) and an increase in lateral ventricle volume ($t_{53} = 3.23; P = .003$) over 1 year. In healthy comparison subjects, a significant increase in total brain was found over time ($t_{53} = 4.76; P < .001$). The results did not change when the date of scanning was added as a covariate.

**Differences Between Groups at Both Time Points**

At the T0 scan, third ventricle volume was significantly larger in patients than in healthy comparison subjects ($F_{2,67} = 11.51; P = .01$). No other group effects for the different brain volumes were found at scan T0. At scan T1, total brain volume ($F_{2,67} = 4.41; P = .04$) and cerebral gray matter volume ($F_{2,67} = 5.70; P = .02$) were found to be smaller in patients compared with healthy comparison subjects. At scan T1, a nonsignificant trend was present for larger lateral ventricles in patients ($F_{2,53} = 2.94; P = .09$). Third ventricle volumes remained significantly larger in patients at scan T1 ($F_{2,67} = 21.54; P < .001$). No significant group × side interaction effects were found for any of these measures at T0 and T1.

**Correlations With Clinical Variables and Outcome**

Decreases in cerebral gray matter volume over 1 year correlated significantly with cumulative dose of antipsychotic medication between T0 and T1 ($r_{51} = -0.45; P = .009$) (Figure 3). This finding was not related to a specific type of antipsychotic medication (atypical, typical, or clozapine). Cumulative antipsychotic medication did not significantly correlate with CAN score ($r_{20} = 0.12; P = .57$).

This longitudinal study compared brain volume changes in 34 patients with first-episode schizophrenia with those of 36 healthy comparison subjects over a 1-year period. Volumes of total brain, gray and white matter, cerebellum, and lateral and third ventricles were measured. Our main finding is that global gray matter volume significantly declined and lateral ventricle volume increased over this 1-year period in patients compared with healthy comparison subjects. Moreover, these volume changes were significantly related to outcome and, independently of that, to cumulative antipsychotic medication used over the first year of treatment. White matter volume was not different between the 2 groups. Third ventricle volume did not significantly increase over time, but it was already enlarged at baseline. Our findings strongly suggest that gray matter loss is progressive, occurs in the early stages of schizophrenia, and is related to both antipsychotic medication use and outcome.

To our knowledge, no other study has examined global gray matter volume in first-episode schizophrenia during 1 year. Our finding of a progressive global gray matter decrease is consistent with studies of patients with chronic and childhood-onset schizophrenia. In these studies, gray matter changes were examined over an average of 2 to 4 years, whereas our study examined global gray matter changes during the first year of treatment. The progressive decrease in total brain volume is in concordance with 1 previous longitudinal study of first-episode schizophrenia. In that study, in addition to the finding of decreased total brain volume, an increase in...
The left lateral ventricle volume was reported. In our sample, a bilateral increase in ventricle volume was found over time. Our finding of total brain volume decreases differs from a first-episode study examining patients for an average of 18 months, in which no progressive change in total brain volume was found. In that study, the number of healthy comparison subjects included was small, and the healthy comparison subjects were also older than the patients. Interestingly, however, progressive ventricular enlargement was found in patients with poor outcomes. Similarly, total brain volume did not decline in another study examining 40 patients with schizophrenia (first-episode and chronic) for 2 years. Nevertheless, patients did show a more rapid decline in left hemisphere volume compared with the healthy comparison subjects.

In the present study, positive and negative symptoms, as rated with the PANSS, were not found to be associated with the changes in brain volumes over time. Associations between symptoms and progressive brain volume changes have been inconsistently reported. Our study is in agreement with some studies but not with others, including those specifically designed to examine gray matter volumes over time. These inconsistencies could be the result of different groups being examined (ie, patients with chronic vs first-episode vs childhood-onset schizophrenia) or the use of different rating scales. Moreover, it has also been suggested that changes in mental state might affect brain volume measurements. Thus, the differences between this and other studies could be secondary to differences in patients' mental states.

Duration of hospitalization was not found to be associated with brain volume changes over time. This is consistent with 1 study in patients with first-episode schizophrenia but not with another. The latter study reported an inverse relationship between duration of hospital stay and ventricular volume because a greater ventricular volume change was found to be associated with a shorter amount of time spent in the hospital. The failure to find an association was also in contrast to a study in patients with chronic schizophrenia that reported an association between a decrease in prefrontal gray matter and total duration of hospitalization. In fact, hospitalization may not be a good outcome measure in patients with chronic schizophrenia that reported an association between a decrease in prefrontal gray matter and total duration of hospitalization. In this study, 1-year changes

**Figure 2.** Change during 1 year in gray matter (A), total brain (B), and lateral ventricle (C) volumes and total number of needs, as measured by the Camberwell Assessment of Need, in patients with schizophrenia.

**Figure 3.** Change in gray matter volume and cumulative dosage of antipsychotic medication from baseline (T0) to 1 year after study inclusion (T1) in patients with schizophrenia.
in volumes of total brain, gray matter, and lateral ventricles were significantly correlated with outcome after 2 years, suggesting that brain volume changes are related to the disease process.

Independent of the association between outcome and progressive gray matter changes, an association was found between higher cumulative dosage of antipsychotic medication and gray matter volume decreases. We did not find an association between gray matter decreases and various types of antipsychotic medication. However, a type II error cannot be excluded because the subject groups were small, especially in the typical antipsychotic medication group (n = 5). The finding of an association between progressive gray matter change and cumulative antipsychotic medication has not been reported previously in patients with schizophrenia (no such relationship was found in patients with childhood-onset schizophrenia). Although it has been suggested that antipsychotics might prevent pathological ventricular enlargement, it has also been documented that antipsychotics produce morphological changes, most clearly in the striatum, with atypical antipsychotics decreasing and typical antipsychotics increasing caudate nucleus volume. Moreover, progressive decreases in frontal lobe volumes in first-episode patients have been associated with higher dosage of antipsychotic medication. Indeed, that we did not find differences in brain volumes (except for third ventricle enlargement) between patients and healthy comparison subjects at baseline, which is in disagreement with other studies examining global gray matter in first-episode schizophrenia.

An underlying neurodegenerative process in schizophrenia has long been disputed. The lack of fibrillary gliosis in postmortem studies of the schizophrenic cortex was the primary argument against it. Currently, it is believed that the absence of gliosis does not necessarily preclude schizophrenia from being a neurodegenerative disorder because gliosis is not always demonstrable or permanent after neuronal injury. Possibility, psychosis itself could be “toxic” through abnormal excitatory amino acid neurotransmission in glutamatergic systems. Increased glutamatergic activity has been suggested to cause cellular damage and death through excitotoxic effects. Additionally, antipsychotics may have a neurotoxic effect and cause a decrease in neuronal density in the striatum and prefrontal cortex, although it is unlikely that these subtle changes in neurotransmitters and their systems, due to the disease itself and/or antipsychotic medication, would be sufficient to trigger gliosis or show other signs of ongoing neurodegeneration in the postmortem brain. Excessive neuronal apoptosis could possibly cause the progressive changes found in schizophrenia. Apoptosis does not lead to inflammation or necrosis and subsequently gliosis. Interestingly, haloperidol by itself may also cause cortical cell death through apoptosis. Other processes resulting in atrophy, such as abnormal neurite pruning, have also been proposed in relation to the progressive changes found in schizophrenia. Therefore, in this study, the gray matter decreases found on MRI over 1 year could be explained by either (programmed) cell death and/or atrophy.

The increased total brain volume in the healthy comparison group was surprising because the findings of cross-sectional studies conducted in healthy subjects suggest that decreases in total brain volume begin in early adolescence. This could be an artifact of the scan procedure or a measurement error. However, this is the first prospective imaging study over 1 year in young healthy adults. A prospective study of healthy children, including adolescents aged 22 years and older, suggested decreases in some but increases in other areas (occipital lobe) of gray matter. Moreover, evidence is accumulating that white matter increases into the fifth decade of life, which suggests that the adult brain is in a constant state of change.

There are limitations to this study. First, a selection bias may have affected the results. This is reflected in the patients and healthy comparison subjects having similar years of education at baseline. One could speculate that this may have contributed to the failure to find baseline morphological differences, except for third ventricle enlargement, between patients and healthy comparison subjects. Indeed, gray matter volume has been reported to be related to IQ. Second, because this study only examined overall changes in global gray matter volume, some brain areas such as the subcortical and limbic structures may contribute more to the effect than others. Third, there was a preponderance of men in the sample. Although the sample was small, women with schizophrenia lost less gray matter volume (−1.6%) than did men (−3%). Other limitations concern antipsychotic medication, such as the use of different types of medication, the lack of standardized haloperidol equiva-
lents for atypical antipsychotics, and inclusion of 10 patients who were not antipsychotic naive.

In summary, the gray matter decrease of nearly 3% in patients with schizophrenia during their first year of treatment, which is associated with outcome and cumulative antipsychotic medication, suggests that the loss of gray matter in patients with schizophrenia is progressive, occurs at an early stage of the illness, and is related to the disease process and antipsychotics.

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