Cerebral Gray Matter Volume Deficits in First Episode Psychosis

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**Background:** Structural brain differences including decreased gray matter and increased cerebrospinal fluid volumes have been observed in the brains of chronically ill patients with schizophrenia. We hypothesized that deficits in gray matter volume would be present in patients presenting with a first episode of nonaffective psychosis.

**Methods:** We used magnetic resonance imaging to compare the brains of 77 patients assessed as having a first episode of psychosis (meeting DSM-III-R criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified) with those of 61 healthy controls matched for age, sex, race, and parental socioeconomic status. Axial, dual-echo scans of the whole brain were segmented into gray matter, white matter, and cerebrospinal fluid compartments using a computerized volumetric approach. These measures were corrected for the significant effects of intracranial volume and age prior to performing between-group comparisons.

**Results:** The first episode psychosis group had significantly smaller gray matter volume ($t_{136} = -2.2; P = .03$) and greater cerebrospinal fluid volume ($t_{136} = 2.5; P = .02$) than normal controls. In the patient group, gray matter volumes were positively correlated with estimates of IQ but not with age of onset, duration of illness, or measures of premorbid functioning.

**Conclusions:** Deficits in gray matter volume are present in patients experiencing first episode nonaffective psychosis. The magnitude of these differences is smaller than has been described in more chronically ill patients.

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**INDIVIDUALS** suffering from schizophrenia have been shown to have larger intracranial cerebrospinal fluid (CSF) volume and smaller cerebral gray matter volume, though some studies have failed to detect such differences. There is much interest in establishing when these differences arise and whether they progress over the course of the illness. It is also unclear whether these differences in brain structure are associated with clinical features of the illness such as presence of a family history of schizophrenia, response to treatment, duration of illness, cognitive deficits, exposure to antipsychotic medication, or long-term outcome.

The difficulties in establishing such relationships in part may be due to design limitations of previous studies. Difficulties arise in choosing optimal patient and control samples, in eliminating the possible confounding effects of substance abuse and antipsychotic medication, and in measurement of brain structures from magnetic resonance imaging (MRI) scans.

Clinical correlates of brain structures in schizophrenia may be more readily identified in samples of patients experiencing their first episode of psychosis. The chance of identifying relationships between brain structures and outcome may be limited in studies of patients with chronic schizophrenia by the skewed range in outcome. As all patients with schizophrenia will have a first episode, the broadest range in outcome should be found in samples of patients identified at the time of their first episode.

This study was undertaken to determine whether structural brain abnormalities could be identified in patients experiencing first episode of nonaffective psychosis and to investigate whether significant clinical correlates could be identified.

**RESULTS**

**BRAIN MEASURES**

The group with first episode psychosis had significantly smaller total gray matter volume ($t_{136} = -2.2; P = .03$) and significantly greater total CSF volume ($t_{136} = 2.5; P = .02$) when compared with the age-matched, normal control group.
SUBJECTS AND METHODS

This study involved 3 subject groups: (1) a group of patients experiencing first episode psychosis, (2) a large control group used to calculate the correction factors for the effects of intracranial volume (ICV) and age on brain measures, and (3) a subset of this large control group selected as a matched comparison group for the patients who had first episode psychosis.

Consecutive referrals to the inpatient and outpatient services of the First Episode Psychosis Program at the Clarke Institute of Psychiatry were invited to participate in this study. The Clarke Institute is a tertiary care, university teaching hospital located in Toronto, Ontario. The protocol was approved by the Human Subjects Committee of the University of Toronto School of Medicine; all subjects provided written consent to participate. Patients were enrolled if they were experiencing a first episode of psychosis and were aged between 16 and 50 years. For this study, patients were considered to have a first episode of psychosis if they were receiving treatment for the first time for an episode of psychosis. Efforts were made to study as many patients as possible prior to any exposure to antipsychotic medication.

Patients were excluded if the psychosis was determined to be due to an identifiable medical illness, drug use, or an underlying mood disorder; if they had a history of significant medical or neurological illness; or if they had ever met DSM-III-R17 criteria for substance dependence or abuse (other than for nicotine or caffeine). Subjects were also screened for any medical contraindications for MRI scanning.

A diagnosis was generated for each subject in the following way: A Structured Clinical Interview for DSM-III-R (SCID)18 was completed for each subject based on an interview and review of clinical information by a trained research assistant, research fellow, or psychiatrist. The OPCRIT system19 was then used to document diagnostic criteria: to complete the OPCRIT forms, a process of consensus was used which included the principal investigator (R.B.Z.) and a research assistant or research fellow who had reviewed all clinical and research data. The OPCRIT program was then used to generate DSM-III-R diagnoses. This process was completed after each subject had undergone scanning as all efforts were made to study patients prior to antipsychotic treatment or as soon as possible in their treatment course.

In addition to the SCID, patients were also administered the Premorbid Adjustment Scale,20 the Family Interview for Genetic Studies,21 the National Adult Reading Test (NART)22,23 and the Quick Test24 to estimate intellectual ability. An estimate of lifetime alcohol consumption was obtained using the method described by Skinner.25 Total lifetime exposure to antipsychotic medication was estimated for all patients using medical records and patient self report. Dose for each antipsychotic agent received was multiplied by a conversion factor26 to yield dose expressed in milligrams of haloperidol per day and then multiplied by the number of days that dose was received; the sum of all antipsychotic medication ever received was then used as a measure of total lifetime antipsychotic exposure expressed in haloperidol equivalents. Age of onset was defined using the OPCRIT criteria . . . the earliest age at which medical advice was sought for psychiatric reasons or at which symptoms began to cause subjective distress or impair functioning.27 Duration of illness was defined as the difference between the age at the MRI scan and the age of onset.

Eighty-four patients were recruited and underwent MRI scanning for this study. Seven patients were excluded from the analysis for the following reasons: 6 for a history of substance abuse and 1 in whom the diagnosis of bipolar disorder became clear shortly after the MRI scan was obtained. The analysis included 77 patients experiencing first episode psychosis (Table 1). DSM-III-R diagnoses were as follows: 46 of the patients met criteria for schizophrenia, 16 for schizoaffective disorder, 10 for delusional disorder, 3 for psychotic disorder not otherwise specified, and 2 for schizoaffective disorder–depressive type. At the time of the MRI scan, 28 patients were neuroleptic-naive.

A group of 82 healthy control subjects (Table 1) were used to calculate the correction factors for the effects of ICV and age on the brain measures. Control subjects were administered the nonpatient version of the SCID and were excluded if they had a lifetime history of any major psychiatric disorder or a family history of schizophrenia. All other exclusion criteria were the same for controls as for patients. Eighty-five control subjects underwent MRI scanning and 3 were subsequently excluded from further study—1 subject for movement artifact, 1 for a positive family history of schizophrenia, and 1 for large patches of demyelination that subsequently led to a diagnosis of multiple sclerosis after the scan was read as being abnormal by a neuroradiologist (D.J.M.). These individuals were recruited from the community as normal control subjects for this study (n = 52) and for concurrent studies in our program that involved an MRI scan (n = 30).

From the large control group, 61 healthy adults were selected to form a comparison group, similar in sex, race, age, and parental socioeconomic status distribution to the group with first episode psychosis (Table 1). Parental socioeconomic status was determined using the 2-factor index (educational level and occupation) of social position developed by Hollingshead.27 The subject’s father’s educational level and occupation were used to calculate parental socioeconomic status unless the subject reported growing up with a single mother in the household.

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Analysis of covariance was then used to test for main effects of ICV, age, sex, and diagnosis on each of the brain measures, as well as interactions between diagnosis and the effects of these variables. Intracranial volume and age each yielded significant main effects consistent with the age regression model described later. Because sex did not, it was removed from the ANCOVA, as were the nonsignificant interaction terms between diagnosis and ICV, diagnosis and age, and diagnosis and sex. Group differences as assessed by ANCOVA were used to confirm the results from the age regression approach described later.

An age regression approach was adopted to assess group differences and to facilitate investigation of clinical correlates. In the large control group, ICV was significantly correlated with total CSF volume (r[81] = 0.54, P < .001), sulcal CSF volume (r[81] = 0.52, P < .001), ventricular CSF volume (r[81] = 0.23, P < .05), total gray matter volume (r[81] = 0.93, P < .001), and total white matter volume (r[81] = 0.91, P < .001). After correcting for the effects of ICV on these measures, age remained significantly correlated with total CSF volume (r[81] = 0.37, P < .001), sulcal CSF volume (r[81] = 0.36, P < .001), total gray matter volume (r[81] = 0.41, P < .001) (Figure 1) but not ventricular volume (r[81] = 0.20, P > .10). ICV- and age-corrected residuals were calculated for all the brain measures based on linear regression analysis of the large control group. The z-scores were then calculated by dividing these residuals by the SD of the large control group.

Student t tests were used to assess significance when the z-scores for total gray matter, total CSF, and total white matter volumes were compared between the group with first episode psychosis (n = 77) and the age-matched control group (n = 61). As the primary objective of this study was to determine whether patients experiencing a first episode of psychosis had deficits in brain gray matter volume, this hypothesis was tested at the P = .05 level of statistical significance, 2 tailed. All other analyses were considered exploratory.

Within the group with first episode psychosis, we used Pearson product moment correlations to test for significant relationships between the gray matter z-scores and each of the following: age at onset, duration of illness, Premorbid Adjustment Scale subscales, NART scores, and Quick Test scores. Because we also had Quick Test and NART IQ measures for many (n = 46) of the controls, we used ANCOVA to test for an interaction between the effects of diagnosis and IQ on the corrected gray matter volumes. IQ measures were only available for subjects who were proficient at English. Brain measures for patients considered to have a definite family history of schizophrenia in a first- or second-degree family member (n = 13) were compared with those of patients with a negative family history (n = 63) using the Student t test.

In the patient group, there was a significant correlation between Quick Test IQ and the gray matter z-scores (r[52] = 0.39, P = .004). Among the controls, however, we found no such correlation (r[45] = −0.13, P = .38). Analysis of covariance revealed a significant interaction between

P = .002) but sulcal volume did not differ significantly.

White matter volume did not differ between the 2 groups (t[105] = .25, P = .8).

Significant differences in gray matter and CSF volumes but not white matter volume were confirmed using ANCOVA for both the total patient group and the subgroup diagnosed with schizophrenia.
Table 1. Characteristics of the Patient and Control Samples

<table>
<thead>
<tr>
<th>Variable</th>
<th>With First Episode Psychosis (n = 77)</th>
<th>With First Episode Schizophrenia† (n = 46)</th>
<th>Matched (n = 61)</th>
<th>All (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at MRI, y</td>
<td>26.0 ± 6.6</td>
<td>26.2 ± 6.1</td>
<td>26.6 ± 6.6</td>
<td>28.9 ± 8.0</td>
</tr>
<tr>
<td>Range</td>
<td>17-46</td>
<td>17-46</td>
<td>17-45</td>
<td>17-51</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>43/34</td>
<td>25/21</td>
<td>34/27</td>
<td>41/41</td>
</tr>
<tr>
<td>Race, No. of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>50</td>
<td>25</td>
<td>43</td>
<td>64</td>
</tr>
<tr>
<td>Asian</td>
<td>16</td>
<td>14</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Black</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Parental socioeconomic status (n)</td>
<td>3.2 ± 1.5 (76)</td>
<td>3.0 ± 1.5 (45)</td>
<td>3.0 ± 1.5 (48)</td>
<td>3.0 ± 1.5 (53)</td>
</tr>
<tr>
<td>Range</td>
<td>9-19 (76)</td>
<td>9-19 (45)</td>
<td>11-21 (61)</td>
<td>10-21 (82)</td>
</tr>
<tr>
<td>Quick test IQ (n)‡</td>
<td>92.0 ± 10.7</td>
<td>92.8 ± 12.2</td>
<td>100.0 ± 12.2</td>
<td>100.7 ± 11.9</td>
</tr>
<tr>
<td>Range</td>
<td>70-125 (53)</td>
<td>70-125 (30)</td>
<td>80-125 (41)</td>
<td>80-125 (46)</td>
</tr>
<tr>
<td>Lifetime alcohol consumption, kg (n)</td>
<td>10.1 ± 15.7</td>
<td>8.9 ± 13.7</td>
<td>17.6 ± 29.9</td>
<td>20.9 ± 32.8</td>
</tr>
<tr>
<td>Range</td>
<td>0-74.5 (75)</td>
<td>0-68.5 (45)</td>
<td>0-120.0 (38)</td>
<td>0-120.0 (43)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>23.7 ± 6.5</td>
<td>23.1 ± 5.5</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Range</td>
<td>14-45</td>
<td>14-43</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Duration of illness, y</td>
<td>2.3 ± 2.7</td>
<td>3.3 ± 2.9</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Range</td>
<td>0.04-15</td>
<td>0.5-15</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lifetime antipsychotic exposure, haloperidol equivalents</td>
<td>102 ± 215</td>
<td>94 ± 188</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Range</td>
<td>0-1360</td>
<td>0-909</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

* Values expressed as mean ± SD, unless otherwise indicated. Ellipses indicate not applicable.
† First episode schizophrenia subjects are a subset of the first episode psychosis group.
‡ English-proficient subjects only.

The finding of significant deficits in gray matter volume in patients with first episode nonaffective psychosis adds further support to the finding that deficits in gray matter volume may underlie the CSF volume increase reported in earlier computed tomography and pneumoencephalography studies. The finding of smaller gray matter volume has been reported by many independent research groups in chronically ill samples.6,7,9,10,11 Using postmortem samples, Pakkenburg46 has described cortical volume deficits and Seleson et al41 have recently reported evidence for reduced cortical thickness (in the absence of reduced neuron number).

Significant deficits in gray matter volume in patients with a first episode of psychosis have also been described in recent reports by Lim et al12 and Keshavan et al.13 This study differs in important ways from the study by Lim et al for clinical and MRI considerations. Lim et al12 studied a smaller group of patients (n = 22), included comparison subjects who underwent MRI scanning for neurological complaints, and did not include neuroleptic-naïve patients. Their image analysis was restricted to 7 noncontiguous MRI sections of 5 mm thickness. Keshavan et al13 studied patients with first episode nonaffective psychosis who were treatment-naïve but the sample included only 13 patients.

Gray matter volume deficits were found to be correlated with 2 independent estimates of intellectual ability, the Quick Test and the NART, in the patient group. Further, we found significant diagnosis-by-Quick Test and diagnosis-by-NART interactions on gray matter z-scores suggesting that the relationship between cognitive functioning and gray matter volume is substantially different in patients from...
controls. It should be kept in mind that the NART and Quick Test provide only estimates of cognitive ability and do not provide information about specific deficits which may be of importance in schizophrenia. In keeping with our finding, Sullivan et al44 have also reported that gray matter z-scores in patients with chronic schizophrenia were significantly correlated with regional and global measures of cognitive function. Whether similar associations are present in healthy controls remains controversial.45

We did not detect other significant clinical correlates of gray matter deficits in this study. Deficits in gray matter volumes did not differ in those with a family history of schizophrenia or a history of major psychiatric illness compared with those without. In this study, family history was obtained whenever possible by interviewing a single first-degree family member; it would have been optimal to have interviewed all first-degree family members directly. However, studies relating the presence of a family history of schizophrenia to structural brain

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Table 2. Brain Measures for Patients With First Episode (FE) Psychosis and Age-Matched Controls Before and After Correction for Intracranial Volume (ICV) and Age

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 61)</th>
<th>FE Psychosis (n = 77)</th>
<th>FE Schizophrenia (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICV</td>
<td>1108 ± 132</td>
<td>1097 ± 120</td>
<td>1087 ± 114</td>
</tr>
<tr>
<td>Total CSF</td>
<td>107 ± 23</td>
<td>113 ± 22</td>
<td>113 ± 23</td>
</tr>
<tr>
<td>Sulcal CSF</td>
<td>82 ± 18</td>
<td>85 ± 16</td>
<td>84 ± 17</td>
</tr>
<tr>
<td>Ventricular CSF</td>
<td>15 ± 5</td>
<td>17 ± 7</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>Gray matter</td>
<td>559 ± 72</td>
<td>549 ± 66</td>
<td>540 ± 62</td>
</tr>
<tr>
<td>White matter</td>
<td>442 ± 61</td>
<td>435 ± 57</td>
<td>434 ± 56</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± SD. Negative values for age- and ICV-corrected measures and for effect sizes indicate volumes that are smaller than expected for a given age and ICV. CSF indicates cerebrospinal fluid; ellipses, not applicable.

†z-scores.
‡P < .05.
§P < .01 (compared with the age-matched control group).

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Figure 1. Age vs cerebrospinal fluid (CSF) (A), gray matter (B), and white matter (C) volumes corrected for the effects of intracranial volume (ICV) for 82 healthy controls. The regression line (solid) for controls is shown together with lines demarcating 1 and 2 SDs above and below the regression line.

Figure 2. Intracranial (ICV)-corrected brain measures for all 77 patients superimposed on control regression line (solid) and lines demarcating 1 and 2 SDs above and below the regression line. The patient group differed significantly from the control group on total cerebrospinal fluid (CSF) (A) and total gray matter (B) volumes, but not total white matter volume (C).
We did not find any associations between duration of illness or age of onset and the magnitude of gray matter deficits. Lim et al also failed to find these associations in a recent study that involved state hospital patients with a very broad range in the age at onset and duration of illness. Rapaport et al, however, have found that during a 2-year period ventricular size increased to a greater extent in children and adolescents with schizophrenia than in healthy controls of similar age. Given the large sample size and the considerable range of durations of illness in both this study and the Lim et al study, it is unlikely that the magnitude of the deficits in gray matter volume increase during the long-term course of the illness. That some limited degree of change might occur in the early years of the illness cannot be ruled out.

Most patients in this study had little or no antipsychotic exposure and yet had brain abnormalities qualitatively similar to those reported in patients who have been treated for many years. Among those patients who met criteria for schizophrenia, those who were neuroleptic-naive had a mean gray matter effect size of − 0.42. It is, therefore, unlikely that the gray matter volume deficits and CSF volume increases reported in patients with schizophrenia are a consequence of antipsychotic treatment. The range of antipsychotic exposure in this study was, however, very limited. To conclusively rule out the possibility that antipsychotic exposure contributes to the magnitude of structural brain abnormalities, one would need to carry out a prospective longitudinal follow-up MRI study of patients with a first episode of psychosis as it is critical in addressing this question that there be both brain measures prior to any exposure as well as substantial variance in total antipsychotic exposure.

The magnitude of the gray matter deficits in this sample was much smaller than the effect sizes reported in patients with more chronic forms of the illness. The results from this study of a mean gray matter effect size of − 0.4 for all patients and − 0.6 for those meeting DSM-III-R criteria for schizophrenia is consistent with the recent MRI findings of Lim et al who found a gray matter effect size of approximately − 0.5 in a group of first episode patients who later had a diagnosis of schizophrenia confirmed. Zipursky et al found a gray matter effect size of − 1.15 in 22 patients with chronic schizophrenia from an American Veteran's Administration Medical Center; the results of this study were replicated by Lim et al who found an effect size of − 1.18. These findings suggest that more chronically ill patients have greater deficits in gray matter volume. Whether this reflects a process of deterioration or a selection bias in studies of patients with chronic schizophrenia remains to be clarified.

There are many considerations that limit the interpretation of this study. While none of the patients met criteria for a primary mood disorder at the time of the study, longitudinal follow-up is necessary to confirm the diagnoses. Longitudinal follow-up of these patients (in progress) will determine whether variability in diagnoses over time might also explain the smaller gray matter effect size reported in this sample. That those subjects who did not meet diagnostic criteria for schizophrenia had smaller gray matter deficits than those with schizophrenia is consistent with this possibility. Establishing the age of onset and in turn the duration of illness is an undertaking fraught with uncertainty; the error inherent in this determination may have contributed to our inability to detect associations between these variables and MRI measures. However, even when the duration of illness was calculated using the onset of the prodrome or the onset of psychotic symptoms as criteria, no associations with gray matter z-scores were detected. Measures of clinical symptoms were excluded in this analysis as patients were studied at different times in their treatment course ranging from acutely psychotic and untreated to fully recovered with treatment. It remains unclear how to meaningfully assess the relationship between clinical symptoms that are highly variable over short periods with brain measures that are relatively fixed over the same time span. Finally, this study does not provide information about the regional distribution of gray matter deficits. Previous studies have reported deficits in multiple cortical areas with a gradient in the magnitude of deficits reflecting more striking deficits in frontal and temporal areas. This is being explored using MRI that acquired from this sample of subjects using a 3-dimensional radiofrequency spoiled gradient recalled echo sequence.

This study confirms the presence of significant deficits in cerebral gray matter volume and increases in CSF volume in patients presenting with a first episode of non-affective psychosis. It is unlikely that this finding can be attributed to either antipsychotic treatment or to the duration of time the illness has gone untreated. This finding is most consistent with the view that the structural brain abnormalities found in schizophrenia predate the onset of psychosis.

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