Morphometric Brain Abnormalities in Schizophrenia in a Population-Based Sample: Relationship to Duration of Illness


Abstract

A variety of structural brain abnormalities have been documented in schizophrenia in magnetic resonance imaging (MRI) studies. The most consistent findings in previous region of interest (ROI) studies have been enlargement of lateral and third ventricles and cortical sulci and volume reductions in temporal and frontal lobes. Consistent with these findings, newer, voxel-based morphometry (VBM) schizophrenia studies have frequently reported regional differences in parts of the frontal and temporal lobes. In all, 50% of studies in the meta-analysis by Honea et al reported gray matter deficits in schizophrenia in the left medial temporal lobe; superior temporal, parahippocampal, inferior, and medial frontal gyri; and in the right superior temporal gyrus. Reductions in other lobes have also been reported, although less often.

However, there has been considerable variability in results of schizophrenia MRI studies. A number of factors may contribute to this variability, including differences in analysis methods, variability in the disorder itself, and also due to variations in sampling selection and recruitment biases concerning both patient and control samples. Many imaging studies have drawn nonrandom samples, which can constrain generalizability of their findings. Many studies consist of chronic or hospitalized patients, with a disproportionate number of severe cases with long duration of illness and heavy antipsychotic drug exposure. Such patients may have more prominent cerebral abnormalities. Population-based studies are

Introduction

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more robust to recruitment biases than other research methodologies; thus, as Lawrie and Abukmeil and Glahn et al have previously argued, there is a clear rationale for population-based neuroimaging studies in schizophrenia. As far as we are aware, only one previous population-based sample, a Helsinki birth cohort, has reported case-control structural brain results in schizophrenia: Cannon et al reported significant reductions in cortical gray and white matter volume and significant increases in subcortical cerebrospinal fluid (CSF) volume especially in the frontal and temporal lobes in their ROI study in schizophrenia.

Whether structural brain abnormalities in schizophrenia are progressive in nature or not remains unclear. Some studies suggest that there are morphometric brain abnormalities even before the illness onset or at the onset in first-episode patients, and there is evidence that at least some of the schizophrenic brain abnormalities are developmental in nature. Nevertheless, some longitudinal studies suggest progressive changes in the disorder, and increased duration of illness has been associated with reduced gray matter in frontotemporal regions.

We investigated if morphometric brain abnormalities would exist in a truly representative sample of patients with schizophrenia and determined the regional gray and white matter and CSF differences in schizophrenia in relation to nonpsychotic general population control subjects using brain activation and morphological mapping (BAMM) software to perform BAMM-VBM, a VBM style analysis. Furthermore, we investigated the relationship between brain structure and duration of illness within the group of patients with schizophrenia.

Materials and Methods

The Northern Finland 1966 Birth Cohort

The Northern Finland 1966 Birth Cohort of 12 058 live-born children (96% of those eligible) is an unselected, general population cohort ascertained during mid-pregnancy in the provinces of Lapland and Oulu with an expected date of birth during 1966. The great majority of the cohort members are Finns (white Caucasians), with less than 1% being Roma people and Lapps. The present study is based on 11 017 individuals who were living in Finland at the age of 16 years. Of these, 83 denied the use of their data, resulting in 10 934 subjects. Permission to gather data was obtained from the Ministry of Social and Health Affairs, and the study design has been approved by and is under review of the Ethical Committee of the Northern Ostrobothnia Hospital District. The “Materials and Methods” section is described in detail by Isohanni et al., Ridler et al., and Tanskanen et al.

Ascertainment and Sampling of People With Psychosis

The Finnish Hospital Discharge Register (FHDR) was used to identify cohort members with psychosis. All cohort members over 16 years appearing on the FHDR until 1997 for any mental disorder (ICD-8 (International Classification of Diseases) 290–309, ICD-9 290–316, and ICD-10 Foo-F69, F99) were identified. Case records were scrutinized, and diagnoses were validated using Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised (DSM-III-R) criteria.

One hundred and forty-six living subjects (84 men) were found to have a history of a psychotic episode and were invited to participate the present study; 92 (63%, 52 men) attended and gave written informed consent. Three subjects did not fulfill the criteria of psychosis. Two subjects were excluded after MRI scan due to structural lesions (hydrocephalus). Altogether 87 participants (49 men) with a history of psychosis were sampled, of whom 61 people (36 men) met DSM-III-R criteria for schizophrenia. Other psychoses (n = 26) consisting of bipolar disorder, schizoaffective disorder, schizophreniform psychosis, and other forms of psychosis including delusional disorders were not included in the sample for analysis.

The control subjects without a psychotic episode were randomly selected from the cohort members living in Oulu area. In total, 187 control subjects were invited; 104 (62 men) consented to participate. There was no major demographic difference between participating and nonparticipating subsets of nonpsychotic subjects.

Subjects who did not consent to imaging or had images of inadequate quality were excluded from the analysis (7 schizophrenia patients, 4 controls). Adequate MRI scans were obtained from 54 schizophrenia subjects (33 men) and 100 control subjects (60 men). Three schizophrenia subjects were hospitalized at the time of scanning (there was missing data concerning hospitalization of 2 patients). Duration of Illness

The onset of illness was ascertained from medical records and defined as the age when having the first evident psychotic symptoms. Duration of illness was calculated in years by deducting the age at onset of illness from the age at the date of MRI.

The age at onset of illness did not differ between the participants (n = 54, mean 23.1 years [SD 4.3]) and nonparticipants with schizophrenia (n = 40, mean 21.8 years [SD 4.1]). The hospital treatment periods of nonparticipants were longer (median 378 days) than those of participants (167 days).

Antipsychotic Medication and Urine Drug Screen

During the 3-month period prior to scanning, 20 subjects with schizophrenia were taking atypical antipsychotic medication and 26 subjects typical antipsychotic medication. Seven of them had taken both atypical and typical medication. Fourteen subjects had not taken antipsychotic medication (there was missing data concerning the medication status of 1 patient).
An analysis of urine drug screen was performed on all subjects at the time of scanning. One subject with schizophrenia tested positive for methadone and 1 for opiates. Two control subjects tested positive for opiates. No patients or controls tested positive for cannabis, cocaine, or amphetamine.

Image Acquisition, Image Analysis, and Data Processing
MRI was conducted in 1999–2001 when participants were aged 33–35 years. Data were acquired using a GE Signa system (General Electric, Milwaukee, WI) operating at 1.5 T in Oulu University Hospital, Finland. Dual echo fast spin echo (T2 and proton density (PD) weighted) images of the whole brain were acquired in the coronal plane with slice thickness = 3 mm, repetition time (TR) = 4000 ms, and echo time (TE) = 24 and 96 ms. All subjects were scanned on the same scanner using the same protocol.

The MRI data were segmented and probabilistic maps of gray matter, white matter, and CSF were created for each subject by using BAMM software.39,40 Voxels representing extracerebral tissue were automatically identified and set to 0 using a linear scale-space set of features obtained from derivatives of the Gaussian kernel.41 Manual editing of the segmented images was necessary only to remove the brain stem below a line parallel to the base of cerebellum. The probability of each intracerebral voxel belonging to each of 4 possible tissue classes (gray matter, white matter, CSF, or dura/vasculature) was then estimated by a modified fuzzy clustering algorithm in the 2-dimensional feature space formed by the PD and T2 intensities.40 The coronal in-plane voxel size was 0.86 x 0.86 mm². Total brain, gray matter, white matter, and CSF volumes in milliliters were calculated from segmented images in native space.

Tissue classification maps were resliced in the axial orientation and coregistered with a customized template image in standard stereotactic space52 by using an affine transformation and trilinear interpolation implemented in FSL (FMRI Software Library) software.43–45 These procedures resulted in maps of the density of gray matter, white matter, and CSF at each voxel; density is here defined as the probability that a voxel represents tissue of a particular class.40,46

Transformed images were smoothed with a standard 4-mm full-width half-maximum kernel.40 Voxels-level statistic maps, representing group differences in density in gray matter, white matter, or CSF maps, were tested for statistical significance by using a nonparametric permutation test of the mass or sum of suprathreshold voxel clusters. For whole-brain maps, the size of each clusterwise test was set such that the expected number of false-positive tests in each map was <1: for gray and white matter maps, clusterwise $P < .003$. $T$ tests at each voxel were performed and measured against the null distribution calculated from permutations of the original data set and thresholded at $P < .05$ to form spatially contiguous clusters of suprathreshold voxels. The cluster statistics were then performed on this data such that the total $t$ statistic from each of these suprathreshold regions is calculated and a new null distribution is created from the permuted thresholded data and then statistically thresholded at the defined error clusters per image, based on a false discovery rate theory of statistical inference.47

We analyzed the relationship between duration of illness and total brain, gray matter, white matter, and CSF volumes in patients using correlation analysis. Furthermore, having established areas where brain structure differed in patients with schizophrenia and controls in this data set, we investigated the correlation between tissue density in those regions and duration of illness.

Results
Analyses of Whole-Brain Volume, Total Gray Matter Volume, Total White Matter Volume, and Total CSF Volume
In analyses without controlling for total intracranial volume (ICV), there were no significant between-group differences in whole-brain volume ($−2.4\%$: schizophrenia 1266 ± 120 ml, controls 1297 ± 117 ml [2-sample $t$ test, $df = 152$, $t = 1.55$, $P = .123$]), gray matter volume ($−2.2\%$: schizophrenia 682 ± 58 ml, controls 697 ± 57 ml [$t = 1.50$, $P = .136$]), white matter volume ($−2.7\%$: schizophrenia 584 ± 67 ml, controls 600 ± 66 ml [$t = 1.46$, $P = .146$]), or CSF volume ($+6.5\%$: schizophrenia 196 ± 41 ml, controls 184 ± 35 ml [$t = −1.85$, $P = .066$]). After controlling for ICV, between-group differences in whole-brain volume (univariate analysis of variance, total $df = 153$, $F = 8.20$, $P = .005$) and total CSF volume ($F = 8.20$, $P = .005$) were significant, and there were trends toward significant differences in total gray matter volume ($F = 3.44$, $P = .066$) and total white matter volume ($F = 3.10$, $P = .080$).

Regional Differences in Gray Matter
Significant gray matter density deficits were identified in patients with schizophrenia in 7 large clusters (table 1). As several clusters span different regions, the results are also depicted graphically (figure 1); purple and blue regions denote areas of gray matter deficit; red and yellow regions denote areas of gray matter excess in subjects with schizophrenia relative to the controls. The left side of each panel represents the right side of the brain; the z coordinate for each axial slice in the standard space of Talairach and Tournoux42 is given in millimeters. Clusterwise probability of type 1 error: $P = .003$, at this size of test less than 1 false-positive test was expected over the whole map.

Regional gray matter density deficits were found bilaterally in the cerebellum, brain stem, hypothalamus, thalamus, claustrum, middle frontal gyrus, inferior frontal gyrus, precenral gyrus, insula, superior temporal...
gyrus, fusiform gyrus, parahippocampal gyrus, cuneus, and lingual gyrus; in the left putamen, posterior cingulate, superior frontal gyrus, transverse temporal gyrus, precuneus, and in the right caudate and postcentral gyrus. Overall within these regions, gray matter density was reduced by 7% in subjects with schizophrenia (2-sample t test, \(t = 7.990, \text{df} = 152, P < .001\)).

Significant gray matter density excesses in subjects with schizophrenia (figure 1) were found bilaterally in the caudate, anterior cingulate, and medial orbitofrontal cortex and in the left putamen and pallidus; density in these regions was increased by 10% (\(t = 7.385, \text{df} = 152, P < .00001\)).

### Regional Differences in White Matter

Significant white matter density deficits were identified in subjects with schizophrenia (figure 2) bilaterally in the cerebellum, brain stem, corpus callosum, capsula interna, corona radiata, centrum semiovale, subgyral frontal white matter, inferior frontal gyrus, medial frontal gyrus, middle frontal gyrus, cingulate, subgyral temporal white matter, superior temporal gyrus, parahippocampal gyrus, and subgyral parietal white matter; in the left capsula externa and cuneus; and in the right middle temporal gyrus, transverse temporal gyrus, supramarginal gyrus, and inferior parietal lobule. Density in these regions was decreased by 7% (\(t = 8.297, \text{df} = 152, P < .00001\)).

### Regional Differences in CSF

Significant CSF density excesses were identified in patients with schizophrenia, relative to control subjects (figure 3) bilaterally in the lateral ventricles, third ventricle, frontal interhemispheric fissure, and left Sylvian fissure. These regions were increased by 13% (\(t = 5.078, \text{df} = 152, P < .00001\)). A small region of significant

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**Table 1. Coordinates of the Center of Mass of the 7 Clusters in Which We Detected Deficits in Schizophrenia Relative to the Control Group**

<table>
<thead>
<tr>
<th>Region</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Maximum z</th>
<th>Minimum z</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum</td>
<td>9</td>
<td>-45</td>
<td>-14</td>
<td>-8</td>
<td>-24</td>
<td>489</td>
</tr>
<tr>
<td>Left insula (BA13)</td>
<td>-39</td>
<td>4</td>
<td>1</td>
<td>16</td>
<td>-24</td>
<td>884</td>
</tr>
<tr>
<td>Right precentral gyrus (BA44)</td>
<td>44</td>
<td>9</td>
<td>7</td>
<td>35</td>
<td>-16</td>
<td>902</td>
</tr>
<tr>
<td>Thalamus</td>
<td>2</td>
<td>-13</td>
<td>2</td>
<td>20</td>
<td>-12</td>
<td>1065</td>
</tr>
<tr>
<td>Left middle frontal gyrus (BA10)</td>
<td>-32</td>
<td>51</td>
<td>11</td>
<td>35</td>
<td>-4</td>
<td>446</td>
</tr>
<tr>
<td>Posterior cingulate gyrus (BA31)</td>
<td>-4</td>
<td>-63</td>
<td>14</td>
<td>35</td>
<td>4</td>
<td>440</td>
</tr>
<tr>
<td>Left inferior frontal gyrus (BA45)</td>
<td>-46</td>
<td>16</td>
<td>21</td>
<td>35</td>
<td>4</td>
<td>248</td>
</tr>
</tbody>
</table>

*Note:* BA, Brodmann’s area. The anatomical label of the centroid of each cluster is provided, along with BA for cortical regions. Some of the clusters are very large and extend into many different regions (displayed in figure 1 and described in the text). The maximum and minimum z values of the clusters, and size in number of voxels, are listed, in order to indicate of the extent of the clusters.

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**Fig. 1. Regional Gray Matter Differences Between Subjects With Schizophrenia and Controls.** Gray matter deficits (purple/blue): bilaterally in the cerebellum, brain stem, hypothalamus, thalamus, claustrum, middle frontal gyrus, inferior frontal gyrus, precentral gyrus, insula, superior temporal gyrus, fusiform gyrus, parahippocampal gyrus, cuneus, and lingual gyrus; in the left putamen, superior frontal gyrus, posterior cingulate, transverse temporal gyrus, and precuneus; and in the right caudate and postcentral gyrus. Gray matter excesses (red/yellow): bilaterally in the caudate, anterior cingulate, and medial orbitofrontal cortex and in the left putamen and pallidus.
CSF deficit was identified in the quadrigeminal cistern. This region was decreased by 10% ($t = 2.566$, $df = 152$, $P < .013$).

**Effect of Duration of Illness**

Duration of illness was not correlated with total brain volume ($r = -0.003$, $P = .983$), gray matter ($r = -0.096$, $P = .491$), white matter ($r = 0.077$, $P = .580$), or CSF ($r = 0.151$, $P = .276$) within the schizophrenia group. We also examined the association between duration of illness and tissue density in ROIs defined by case-control differences. Density in gray matter–deficit areas was significantly negatively correlated with duration of illness: thus, the longer the duration of illness, the less gray matter density in deficit areas ($r = -0.473$, $P < .001$, figure 4a).

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**Fig. 2. Regional White Matter Differences Between Subjects With Schizophrenia and Controls.** White matter deficits (purple/blue): bilaterally in the cerebellum, brainstem, corpus callosum, capsula interna, corona radiata, centrum semiovale, subgyral frontal white matter, inferior frontal gyrus, medial frontal gyrus, middle frontal gyrus, cingulate, subgyral temporal white matter, superior temporal gyrus, parahippocampal gyrus, and subgyral parietal white matter; in the left capsula externa and cuneus; and in the right middle temporal gyrus, transverse temporal gyrus, supramarginal gyrus, and inferior parietal lobule.

**Fig. 3. Regional CSF Differences Between Subjects With Schizophrenia and Controls.** CSF excesses (red/yellow): bilaterally in the frontal horns and bodies of lateral ventricles, atrium of the right lateral ventricle, third ventricle, frontal interhemispheric fissure, and left Sylvian fissure. CSF deficit (blue): in the quadrigeminal cistern.
Duration of illness was also negatively correlated with bilateral white matter density deficits ($r = -.284$, $P = .038$, figure 4b). Duration of illness was neither correlated with gray matter density excess ($r = .223$, $P = .105$) nor with CSF excess ($r = .029$, $P = .834$).

Discussion

Main Findings

Morphometric brain abnormalities were found in subjects with schizophrenia compared with controls in a general population-based sample of the same age. In the frontal lobe, we observed bilateral gray matter deficits in the dorsal and lateral prefrontal cortex and in the premotor and motor cortices (middle, inferior, and superior frontal gyri and precentral gyri). There were gray matter deficits in the insula bilaterally and in the left posterior cingulate. In the temporal lobe, we noted some medial temporal lobe abnormalities (reductions in gray matter density in the parahippocampal gyrus bilaterally) and reductions in the superior temporal gyrus and fusiform gyrus bilaterally and left transverse temporal gyrus. We also noted some deficits in the parietal (postcentral gyrus and precuneus) and occipital lobes (cuneus and lingual gyri). There were reductions bilaterally in the cerebellum, thalamus, and basal ganglia. Relative gray matter excesses were found bilaterally in the basal ganglia, medial orbitofrontal cortex, and anterior cingulate cortex. There were white matter deficits in an extensive network including inter- and intrahemispheric tracts in frontal and temporal lobes and subcortical structures. Gray and white matter densities in ROIs defined by case-control differences were negatively associated with duration of illness.

Comparison With Earlier Studies

The total brain, gray matter, white matter, or CSF volume differences (unadjusted for ICV) were not significant in subjects with schizophrenia compared with controls in this sample, though some differences emerged after controlling for ICV. We found similar trends for volume reductions as in the meta-analysis on MRI studies by Wright et al,1 who reported brain volume to be 2%, gray matter 4%, and white matter 2% smaller in subjects with schizophrenia than in control subjects. The total CSF volume increase in our study was less than in previous studies.1

Meta-analysis of VBM studies by Honea et al11 reported gray and white matter deficits in patients with schizophrenia, relative to controls, in a total of 50 brain regions; the most consistent findings were gray matter deficits in the left medial temporal lobe, superior temporal, parahippocampal, inferior, and medial frontal gyri and in the right superior temporal gyrus. A recent meta-analysis of VBM studies in schizophrenia by Ellison-Wright et al18 detected gray matter decreases in the thalamus, the left uncus/amygdala region, the insula bilaterally, and the anterior cingulate. Morphometric brain abnormalities especially in the frontal and temporal lobes and basal ganglia have been observed even in first-episode patients.6,18–21 Meda et al7 reported similar findings in their recent large-scale ($n = 400$) multicenter study.

We found gray matter deficits in several of these frontal and temporal regions. In the frontal lobe, we observed bilateral deficits in the dorsal and lateral prefrontal cortex and premotor cortex (middle and inferior frontal gyri,
left superior frontal gyrus), and motor cortex (precentral gyrus). There were gray matter deficits in the insula bilaterally. Our findings of reductions in frontal lobe gyri converge mostly with previous large VBM studies, meta-analysis of ROI-based MRI studies, and recent VBM meta-analyses. Hulshoff Pol et al found deficits in inferior, middle, and superior frontal gyri, in addition to orbitofrontal deficits. Shenton et al reported frontal reductions in 60% of the reviewed 50 MRI studies, and Honea et al reported that 50% of studies found gray matter deficits in left inferior and medial frontal lobe gyri. Honea et al also reported that 40% of the studies had found insular gray matter deficits, in accordance with our bilateral finding.

In the temporal lobe, we noted bilateral superior temporal gyrus reductions, which is in accordance with meta-analyses by Honea et al and Shenton et al. Additionally, we noted fusiform gyrus and left transverse temporal gyrus reductions and some medial temporal lobe abnormalities. We observed gray matter reduction in one medial temporal lobe structure—the parahippocampal gyrus, where we found bilateral gray matter reduction, in accordance with previous studies. However, we did not find reductions in the hippocampus or amygdala, although volume reductions in these regions have been frequently reported previously in ROI-based studies. The result of our prior, ROI study of hippocampus was a borderline case: hippocampal volume was reduced 2%, but adjustment for total brain volume diminished the effect. In that study, we did not find amygdalar volume changes either. Even though many VBM studies and some meta-analyses have reported volume reductions in hippocampus or amygdala, it is not a universally reported finding: eg, the largest study published to date, an international multicenter study, consisting of 200 patients, did not find hippocampal reductions.

Surprisingly, besides the deficits in the prefrontal, premotor, and motor cortices and posterior cingulate, we observed gray matter excesses in the medial orbitofrontal cortex and anterior cingulate, whereas many previous studies have found deficits in these regions. The interpretation of these results is challenging. One implication of this anatomical distinction is that these parts of the frontal cortex have different cognitive functions, with dorsal and lateral prefrontal cortex being strongly associated with executive, attentional, and working memory function, and the orbitofrontal cortex playing a more critical role in affective decision making. Likewise, the anterior cingulate cortex has different functions according to anatomical subdivisions, with more rostral sections subtending emotional processing and more caudal sections suberving attentional and cognitive control functions. Our finding of subgenual anterior cingulate gray matter excess is not in direct discrepancy with meta-analysis by Ellison-Wright et al, who reported deficits mostly in pregenual and dorsal anterior cingulate. Additionally, anterior cingulate increases in schizophrenia are not entirely unprecedented, as at least 2 previous studies have reported similar findings, which have been interpreted as possibly stemming from medication effects. Finally, there is 1 more possible explanation for our anterior cingulate results; interindividual variability in sulcal and gyral anatomy of this region has been shown in control populations as well as in schizophrenia patients. Our finding of gray matter density excess in the anterior cingulate may present true density difference, or difference in shape, which may cause the apparent density differences in this sample.

In addition to the deficits in frontal and temporal cortices described above, we observed widespread gray matter deficits, which extended into parietal lobe (postcentral gyri or sensory cortex and precuneus), the occipital lobe (cuneus and lingual gyri), and the cerebellum. While parietal or occipital lobes have perhaps been somewhat neglected in schizophrenia research in comparison with studies focusing on frontal and temporal pathology, in fact 60% of the MRI studies of the parietal and 44% of studies of the occipital lobe have reported volume reductions. Some of the more recent VBM studies and meta-analyses report volume reductions in parietal or occipital lobes. In addition, we found gray matter excesses in parts of the basal ganglia (bilaterally in the caudate and left putamen) in accordance with meta-analyses by Shenton et al and by Wright et al. It has been suggested that these basal ganglia excesses could be secondary to neuroleptic medication.

Most of the subcortical findings in our study are in agreement with previous studies. We observed bilateral thalamic volume reduction, which has also been reported in meta-analyses by Wright et al, Konick and Friedman, Honea et al, and Ellison-Wright et al. In addition, we found gray matter excesses in parts of the basal ganglia (bilaterally in the caudate and left putamen) in accordance with meta-analyses by Shenton et al and by Wright et al. It has been suggested that these basal ganglia excesses could be secondary to neuroleptic medication.
and thus, white matter should not be overlooked in future morphometric studies.

Our data suggest an effect of duration of illness on brain structure because the duration of illness correlated with the gray and white matter deficits in the areas identified in the case-control comparison. Increased duration of illness has previously been associated with reduced gray matter volumes in temporal or frontal cortices. Longitudinal studies have shown progressive total brain and gray matter volume loss, lateral ventricle enlargement, as well as progressive regional gray or white matter volume decreases and sulcal CSF enlargement in fronto-temporal regions, though negative results have also been reported. The combination of evidence of progressive effects and the reports of gray or white matter reductions in first-episode patients suggest a dual process model of psychosis: the pathological process of schizophrenia effects brain structure at various neurodevelopmental stages and may continue as neurodegenerative gray matter loss over time.

However, there is another possible explanation for our results relating duration of illness to increased gray and white matter deficits. Given that all our participants were of the same age, duration of illness is inversely correlated with age at onset in this cohort, so that patients who had the longest duration of illness also were younger when they first became unwell. Thus, an important alternative interpretation of our findings is that patients with a young age of onset are characterized by greater brain structural deficits. This could be interpreted as secondary to neurodevelopmental processes, namely that the putative pathological process which causes an early age of onset also causes more marked neuropathology in terms of abnormal gray and white matter density.

Finally, an additional reason contributing to the correlation of deficits with duration of illness could be the chronic effect of antipsychotic drugs because as preliminary evidence suggests that chronic exposure to haloperidol and olanzapine may decrease brain weight and volume in monkeys. Despite preliminary studies in humans, it remains unclear how antipsychotic drugs effect brain morphology in schizophrenia. The effect of drug treatment is not easy to disentangle in an observational study, and only a randomized placebo-controlled treatment study, which could be unethical, could finally resolve this issue.

**Strengths and Limitations of the Study**

The major strength of the study is the epidemiologically representative general population sample. Large effect sizes from initial studies in a field often disappear in subsequent work with larger, more representative samples. The present study has these features and yet yields significant results. The epidemiological nature of the sample makes it more representative than most imaging studies and support generalization of the findings to the population of patients with schizophrenia. Our study is the first VBM study of schizophrenia where cases and controls are sampled in a population-based manner. This study is the second case-control study of brain morphology in schizophrenia where all participants are drawn from a population-based birth cohort. To our knowledge, only one population-based birth cohort sample has previously reported structural brain abnormalities in schizophrenia, that is the study by Cannon et al. Their study was ROI based, and most analyses from that sample have focused on genetics (sibling and twin studies) and fetal hypoxia.

As age has previously been shown to be related to brain morphology (quite possibly differently in cases and controls), the fact that all our subjects, being drawn from a birth cohort, are of the same age is an additional advantage, which eliminates the possibility of confounding by this factor. We were also able to exclude the effect of ethnic differences in brain structure because the subjects were the same ethnic background representing the general population of the whole Finland. Additionally, we had approximately 2 control subjects in both genders for each schizophrenia subject to strengthen the statistical power. In contrast to a number of previous schizophrenia studies, our cases are not overrepresented by men: we had a representative sample of women with psychosis (39%), a group often neglected. The sample of subjects is not overrepresented by severe cases of psychosis: at the time of scanning, there were only 3 hospitalized patients.

The population-based nature of the research means that our study is less susceptible to sampling biases than most schizophrenia neuroimaging research. The controls are representative of the population from which the cases arise and are not "supernormal," as previous evidence suggests that selection of supernormal control participants may have enormous influence on results of neuroimaging studies, which is why we selected our control participants from the Oulu region general population truly at random (constrained only by gender stratification). The lifetime absence of a clinical diagnosis of any psychotic disorder in the nonpsychotic group was confirmed, but because they were drawn truly randomly from the population, there were some cases of other psychiatric or somatic diseases.

Illicit drug use is high in samples of schizophrenia in many countries, and chronic use is known to affect brain structure. Patients with schizophrenia who continue to use cannabis after illness onset show larger increases in ventricular volume than schizophrenia patients who abstain from cannabis after illness onset. An advantage of our cohort, due to its location in Northern Finland and the time the study was conducted, is that very few patients were exposed to illicit drugs: on analysis of urine drug screens performed on all subjects, none
tested positive for cannabis, cocaine, or amphetamine at the time of scanning.

An advantage of our methodology is that we employ permutation-based methods of statistical testing, which require less assumptions than parametric analyses and also allow for the use of a smaller amount of smoothing of the original data (parametric statistics may often require greater smoothing to meet the assumptions of Gaussian random field theory). This is important as the amount of smoothing has been shown to be important in determining the results of morphological studies in schizophrenia research.11

With a total of 154 participants (combined cases and controls), our sample is larger than most schizophrenia neuroimaging studies, which typically include under 50 participants,7 though it is considerably smaller than the very largest studies to date, such as Hulshoff Pol et al3 and Meda et al7; therefore, the possibility of type 2 error remains.

Another limitation was the moderate nonparticipation in the psychosis group. Even though we were able to identify a total of 146 subjects with psychosis who were born in Northern Finland in 1966, our final sample of schizophrenia patients whose imaging data passed quality control standards consisted of 54 individuals. The rationale for inviting all cohort subjects with previously identified psychosis on national registers (as opposed to identifying all subjects with previously identified schizophrenia) was in order to capture individuals who had been previously misdiagnosed or who had recently converted to meet criteria for schizophrenia. This approach was successful in identifying a number of additional cases of schizophrenia who would otherwise have been missed. However, it is a limitation of our study that there were a number of schizophrenia patients who we could identify from national records, but who did not agree to participate in the study, or who could not be contacted. The clinical course of the participants was more advantageous than among the nonparticipants with psychosis.13,35 Our sample may, therefore, be slightly biased toward the less severe cases of psychosis with a consequent reduction in power to detect brain changes related to severity of illness.

A technical limitation of our study relates to our scanning parameters. Although an advantage of our study is that all participants were scanned in the same magnet using the same software, a limitation is that we collected 3-mm thick slices, which is less than optimal and which could limit our sensitivity to detect small differences between groups.

A limitation in investigating the relationship of brain structure to illness duration is that, in our study, all patients are of the same age and, in an early middle age, typical to birth cohort studies.83 As age has been shown to be a predictor of brain abnormality in schizophrenia,79 this confers the advantage that age is not a con-founder as regards the case-control analysis, but for the within-patients analysis, it is a limitation because there is a reciprocal relationship between illness duration and age at onset of illness. Thus, the longer the duration of illness, the earlier the age of onset; it is impossible to separate these issues in this study. Moreover, the only way to truly study the course of brain structure changes in the illness is to perform repeated measurements of brain structure over time.

Conclusion

Morphometric brain abnormalities in frontotemporal regions and basal ganglia were confirmed in this epidemiological sample. Furthermore, gray matter density deficits were observed in brain regions which have previously received less scrutiny in schizophrenia research. White matter reductions were bilateral and widespread. Subjects with longer duration of illness, and younger age at onset, showed more prominent brain abnormalities suggesting either that developmental brain deficits relate to an earlier age of onset or that brain abnormalities in schizophrenia are progressive in nature.

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