In Vivo Neuropathology of Cortical Changes in Elderly Persons with Schizophrenia

Giovanni B. Frisoni, Annapaola Prestia, Andrea Adorni, Paul E. Rasser, Maria Cotelli, Andrea Soricelli, Matteo Bonetti, Cristina Geroldi, Panteleimon Giannakopoulos, and Paul M. Thompson

Background: Elderly schizophrenia patients frequently develop cognitive impairment of unclear etiology. Magnetic resonance imaging (MRI) studies revealed brain structural abnormalities, but the pattern of cortical gray matter (GM) volume and its relationship with cognitive and behavioral symptoms are unknown.

Methods: Magnetic resonance scans were taken from elderly schizophrenia patients (n = 20, age 67 ± 6 SD, Mini-Mental State Examination [MMSE] 23 ± 4), Alzheimer’s disease (AD) patients (n = 20, age 73 ± 9, MMSE 22 ± 4), and healthy elders (n = 20, age 73 ± 8, MMSE 29 ± 1). Patients were assessed with a comprehensive neuropsychological and behavioral battery. Cortical pattern matching and a region-of-interest analysis, based on Brodmann areas (BAs), were used to map three-dimensional (3-D) profiles of differences in patterns of gray matter volume among groups.

Results: Schizophrenia patients had 10% and 11% lower total left and right GM volume than healthy elders (p < .001) and 7% and 5% more than AD patients (p = .06 and ns). Regions that had both significantly less gray matter than control subjects and gray matter volume as low as AD mapped to the cingulate gyrus and orbitofrontal cortex (BA 30, 23, 24, 32, 25, 11). The strongest correlate of gray matter volume in elderly schizophrenia patients, although nonsignificant, was the positive symptom subscale of the Positive and Negative Syndrome Scale, mapping to the right anterior cingulate area (r = .42, p = .06).

Conclusions: The orbitofrontal/cingulate region had low gray matter volume in elderly schizophrenia patients. Neither cognitive impairment nor psychiatric symptoms were significantly associated with structural differences, even if positive symptoms tended to be associated with increased gray matter volume in this area.

Key Words: Alzheimer’s disease, Brodmann areas, gray matter, MRI, schizophrenia

The presence of structural brain changes in the brain of elderly schizophrenia patients, as well as their relationship with the cognitive/behavioral symptoms of this disorder, are still matters of debate. Postmortem studies have shown various abnormalities in all cerebral lobes (1,2), including cortical neuropil volume reduction (3), and imaging studies have identified decreased volume in several cortical, subcortical, and infratentorial brain structures (4,5). Brain volume losses may result partly from neurodevelopmental pathogenetic core in schizophrenia (6,7) but may also be related to the long-term use of neuroleptics (8,9), concomitant presence of Alzheimer’s disease (AD) or vascular dementia, or still unknown interactions between aging and disease (2).

Patterns of cognitive impairment involving attention, memory, executive functions, sensory-visceromotor multimodal integration, motivation, and decision making have been repeatedly reported in elderly schizophrenia patients (10,11), although neuropathological changes of AD and cerebrovascular lesions have been found to be remarkably rare (12). In this line, greater right-sided neuropsychological impairment and brain structural damage, as well as hippocampal and amygdalar 10% volume reduction, have been reported in elderly schizophrenia patients (1,2). In contrast, a retrospective research of magnetic resonance (MR) scans of psychotic patients from 45 to 87 years of age did not reveal significant differences in structural abnormalities between patients and normal subjects or between early-onset and late-onset schizophrenia patients (13). Similarly, Nesvåg et al. (14) found that prefrontal and temporal cortical thinning in schizophrenia patients from 17 to 57 years of age was equal in older and younger subjects even after antipsychotic medications. While recently, Meda et al. (15) showed alterations of gray matter concentration in a large sample of first-episode and chronic schizophrenia patients with a voxel-based morphometry approach, to the best of our knowledge a study of the whole cortical mantle with a technique providing high spatial accuracy in elderly schizophrenia persons has, so far, never been carried out.

To address this issue, we used an image analysis method (cortical pattern matching [CPM]) capable of mapping profiles of volumetric changes in three dimensions with a few millimeters spatial accuracy to define the patterns of increased/decreased gray matter volume in 20 patients with long-term schizophrenia evolution compared with 20 patients with AD and 20 age-matched control subjects.

From the LENITEM–Laboratory of Epidemiology Neuroimaging and Telemedicine (GBF, AP, AA, CG) and Psychogeriatric Ward (GBF, AA, CG), IRCCS Centro San Giovanni di Dio FBF, the National Centre for Research and Care of Alzheimer’s and Mental Diseases, Brescia, Italy; Schizophrenia Research Institute (PER), Sydney, and Priority Centre for Brain and Mental Health Research and School of Design, Communication, I.T. (PER), University of Newcastle, Newcastle, Australia; Cognitive Neuroscience Section (MC), IRCCS S. Giovanni di Dio FBF, Brescia, Italy; SDN Foundation and Institute of Diagnostics and Nuclear Development and University of Naples Parthenope (AS), Naples, Italy; Service of Neuroradiology (MB), Istituto Clinico Città di Brescia, Brescia, Italy; Division of Geriatric Psychiatry (PG), University Hospitals of Geneva, Geneva, and Division of Old Age Psychiatry (PG), University Hospitals of Lausanne, Lausanne, Switzerland; and Laboratory of Neuro Imaging (PMT), UCLA School of Medicine, Los Angeles, California.

Address reprint requests to Giovanni B. Frisoni, M.D., Centro San Giovanni di Dio FBF, The National Centre for Research and Care of Alzheimer’s and Mental Diseases, via Pilastri 4, 25125 Brescia, Italy; E-mail: gfrisoni@fatebenefratelli.it.

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Methods and Materials

Study Subjects and Assessment

The schizophrenic patients were selected from those staying at the Psychiatric Unit of the IRCCS Centro San Giovanni di Dio Fatebenefratelli in Brescia, Italy, from December 2006 to April 2008. The ward is a 40-bed long-term unit where patients are referred from community services or, less frequently, acute psychiatry units. The length of stay is generally 12 months to 24 months but may occasionally extend to 36 months.

The selection criteria included old age (60 years and older) and a DSM-IV diagnosis of schizophrenia with onset before age 40. Exclusion criteria included history of substance dependence, other diseases of the central nervous system, and unstable medical conditions. Vascular risk factors such as hypertension, diabetes, and smoking were systematically ascertained. The symptoms of schizophrenia were assessed with the Positive and Negative Syndrome Scale (PANSS), comprising 30 items rated on a 7-point scale (1 = absent, 7 = extreme) assessing positive and negative symptoms and general psychopathology. Poor outcome was ascertained through an interview with the patients and caregivers conducted by a psychiatrist and defined as less than 10 years of continuous regular working activity during the patient’s life.

Twenty patients with National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) probable AD were recruited from among those coming for observation at the Outpatient Memory Clinic from the same institution and matched with twenty patients with schizophrenia at the Psychogeriatric Ward of the IRCCS Centro San Giovanni di Dio Fatebenefratelli. The selection criteria included old age (60 years and older) and a DSM-IV diagnosis of schizophrenia with onset before age 40. The ward is a 40-bed long-term unit where patients are referred from community services or, less frequently, acute psychiatry units. The length of stay is generally 12 months to 24 months but may occasionally extend to 36 months.

As a voxel-based technique, CPM has some affinities with the widely used voxel-based morphometry (VBM) but also important peculiarities. Although both methods may be used to analyze the distribution of cortical gray matter, the explicit modeling of the cortex in the CPM approach allows the cortical surfaces of all subjects in the groups to be aligned precisely, using a warping approach that precisely matches the sulcal and gyral landmarks of all experimental subjects. As such, deficits that selectively affect one or two gyri or specific lobes of the brain will be correctly localized on the cortex. Voxel-based morphometry is relatively more automated but does not permit precise matching of cortical anatomy, as the cortex is not explicitly modeled, and matching of anatomy across subjects has to rely on automated matching of image intensities, which is not generally a reliable guide to sulcal homologies at the cortex.

Images were reoriented along the anterior commissure-posterior commissure (AC-PC) line, voxels below the cerebellum were removed, the anterior commissure was set as the origin of the spatial coordinates, and normalization was carried out through 12-parameter affine transformation on a customized template (18). Individual brain masks were extracted, visually inspected, and manually corrected with Display, a three-dimensional visualization program (http://www.bic.mni.mcgill.ca/software/Display/Display.html) developed at the McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada) that allows the manual correction of errors in regions of interest (or “masks”) differentiating brain and non-brain tissues. The resulting masks were then applied to normalized images to obtain “skull-stripped” images of each hemisphere (18). After automated 3-D hemispheric reconstruction using an intensity threshold that best differentiated gray matter from extracerebral cerebrospinal fluid (CSF), 39 sulcal lines for each hemisphere were manually traced (17 sulci on the lateral and 12 sulci on the medial surfaces and 10 lines to outline interhemispheric gyral limits) by a single tracer (anterior-posterior [AP] (http://users.loni.ucla.edu/~khayashi/Public/medial_surface/; http://www.loni.ucla.edu/~esowell/new_sulcvar.html) (19).

The reliability of manual outlining was assessed before experimental subject tracing with a standard protocol requiring the same rater to trace all lateral and medial sulci of six test brains (19). At the end of the reliability phase, the mean 3-D difference of the tracer from the gold standard (19) was <3 mm for all medial and lateral sulci.

Individual sulcal maps were averaged to create a common average sulcal map for all subjects in the study; then individual cortical surfaces were parameterized, flattened, and warped and image voxels were classified using a partial volume classifier algorithm (20). The gray matter was extracted and mapped onto the corresponding parametric hemispheric model in exact spatial correspondence. Gray matter density was computed at each cortical point as the proportion of tissue classified as gray matter in a sphere centered at that point with a radius of 15 mm and then averaged within each group to obtain the mean gray matter density.

A deformable Brodmann area atlas (21) was applied to the left and right hemisphere average cortical surface models (17).

Statistical Analysis

Cortical pattern matching analyses were carried out assessing the relationship between gray matter density and diagnosis to identify cortical gray matter loss in patients between groups. Maps of the average percentage gray matter reduction were computed and classified as gray matter, white matter, and cerebrospinal fluid (CSF) with a partial volume classifier (PVC) for each experimental subject. The distributions of cortical gray matter, white matter, and CSF were then averaged within each group to obtain the mean gray matter density.
computed based on the voxel-by-voxel ratio between the mean gray matter density value in patients and healthy elders.

A surface point significance threshold of \( p < .05 \) was used to map gray matter changes. Correction for multiple comparisons was carried out by permutation testing at threshold of \( p < .05 \). Maps of Pearson’s \( r \) correlations of clinical variables with cortical gray matter density were computed, as well as the associated \( p \) value maps thresholded at \( p < .05 \).

Results

The study groups (Table 1) were well-matched for gender and education (\( p > .39 \) on analysis of variance [ANOVA] and chi-square test). The schizophrenia patients were about 5 years younger than both the AD and control subjects (\( p = .064 \) on ANOVA), while cognitive performance and disability were similar between AD and schizophrenia (\( p > .31 \) on Tukey post hoc comparisons). It should be noted that elderly schizophrenia patients achieved MMSE scores as low as 14 out of 30, but none of the latter satisfied DSM-IV criteria for alcohol abuse.

Table 1. Sociodemographic, Cognitive, and Clinical Features of the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Healthy Elderly (( n = 20 ))</th>
<th>Elderly Schizophrenia Patients (( n = 20 ))</th>
<th>Alzheimer’s Disease Patients (( n = 20 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Years (Range)</td>
<td>72.5 ± 7.6 (58–85)</td>
<td>67.4 ± 6.2 (60–78)</td>
<td>72.7 ± 9.1 (58–81)</td>
</tr>
<tr>
<td>Sex, Female</td>
<td>14 (70%)</td>
<td>10 (50%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Education, Years</td>
<td>8.8 ± 4.2</td>
<td>7.8 ± 3.5</td>
<td>7.0 ± 5.1</td>
</tr>
<tr>
<td>Mini-Mental State Examination (Range)</td>
<td>29.1 ± .9 (27–30)</td>
<td>22.8 ± 4.4 (14–30)</td>
<td>22.0 ± 4.3 (13–28)</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>100 ± 0</td>
<td>89 ± 15</td>
<td>94 ± 13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (20%)</td>
<td>5 (25%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0 (0%)</td>
<td>4 (20%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2 (10%)</td>
<td>9 (45%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>9 (45%)</td>
<td>4 (20%)</td>
<td>10 (50%)</td>
</tr>
</tbody>
</table>

Values denote mean ± SD or number (%).

Table 2 shows that half of the patients had poor outcome. Although the duration of working activities approached 13 years on average, this was lower in those with poor outcome than good outcome (2 ± 3 years vs. 25 ± 14 years, \( p < .0001 \) on two-tailed \( t \) test). Disease severity was comparable with other series of geriatric schizophrenia patients previously described (22). Almost all schizophrenia patients (19/20) were taking either first- or second-generation antipsychotics, 65% were treated for anxiety symptoms, and none were taking antidepressants. The neuropsychological performance of the schizophrenia group (Table 3) was significantly lower than that of healthy elderly persons but not significantly different from that of AD patients.

Figure 1 shows that cortical volumetric patterns were quantitatively remarkably different in the two patient groups. Gray matter loss in AD mapped to the temporoparietal, frontal, posterior cingulate/retrosplenial, and medial temporal regions, while in elderly schizophrenia patients, it mapped to more restricted areas that included the cingulate and orbitofrontal regions and superior and middle temporal gyri. Figure 2 shows that areas with specifically decreased gray matter volume in Alzheimer’s disease were distributed across widespread neocortical areas. In elderly schizophrenia patients, areas with lower gray matter volume than in AD were confined to the posterior part of the anterior cingulate gyrus and few small and scattered foci were detected in the temporal poles bilaterally, right rectal gyrus, and right primary motor cortex (Figure 2).

Having identified the cingulate gyrus as a potentially critical area in elderly schizophrenia patients, volume increased/decreased in its BAs when studied in relation to volume changes in the others. Supplement 1 shows that elderly schizophrenia patients had 10% and 11% lower total cortical gray matter volumes than healthy subjects in the left and right hemispheres, respectively, and marginally greater gray matter volume (±7% and +5%) than Alzheimer’s disease patients. The sensorimotor area was remarkably spared in elderly schizophrenia patients (−3% and −7%) compared with the healthy control subjects. Region-of-interest analysis of individual BAs indicated that a number of Bas, including the cingulate gyrus, had low gray matter volume in elderly schizophrenia patients (BA 11, 21, 23, 24, 25, 30, 31, 32, 38, 40, 43) (Supplement 1). Of these, cingulate/orbitofrontal BAs (BA 11, 23, 24, 25, 30, 32) had in elderly schizophrenia patients similar or lower gray matter...
volume than in AD (Figure 3A). If low gray matter volume was arbitrarily defined as below the threshold of −13% of control subjects, BAs with low gray matter volume in schizophrenia patients largely overlapped with those found using the ROI analysis of individual BAs (BA 11, 21, 22, 23, 24, 25, 30, 31, 32, 38, 43) and still included all BAs in the cingulate/orbitofrontal regions (Figure 3B).

The effect of sex on GM volume of the cingulate/orbitofrontal BAs in elderly schizophrenia patients (23) was tested by comparing the volumes in the 10 women versus 10 men. There were no sex-related differences in the GM volume of this area. The effect of first- and second-generation antipsychotics in elderly schizophrenia patients (24) was tested by comparing the volumes in the 4 patients who were treated with first-generation antipsychotics and the 11 patients treated with second-generation antipsychotics, but no statistically significant differences were found.

We then tested the hypothesis that volumetric differences in the cingulate/orbitofrontal regions may be related to the clinical features of elderly schizophrenia patients. The relationship of gray matter volume with neuropsychological tests and the behavioral scale were examined with the voxel-based approach. Individual models were fitted for each neuropsychological test and PANSS scale. The model with the highest, albeit nonsignificant, value on permutation test was the PANSS positive symptom scale ($p = .06$). Figure 1 in Supplement 1 shows a rich pattern of cortical areas significantly correlated to performance on the letter fluency test (predictably mapping to the dorsal frontal and lateral

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**Table 3. Neuropsychological Features of the Study Groups**

<table>
<thead>
<tr>
<th></th>
<th>Healthy Elderly</th>
<th>Elderly Schizophrenia Patients</th>
<th>Alzheimer’s Disease Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score</td>
<td>$p$ vs. Healthy Elderly Score</td>
<td>$p$ vs. Alzheimer’s Disease Patients Score</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey-Osterreith’s Complex Figure—Recall</td>
<td>10.9 ± 3.4</td>
<td>&lt;.0001</td>
<td>2.5 ± 3.0</td>
</tr>
<tr>
<td>Auditory Verbal Learning Test—Immediate Recall</td>
<td>42.3 ± 7.0</td>
<td>&lt;.0001</td>
<td>10.6 ± 13.6</td>
</tr>
<tr>
<td>Auditory Verbal Learning Test—Delayed Recall</td>
<td>8.6 ± 3.1</td>
<td>&lt;.0001</td>
<td>1.2 ± 2.1</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Token Test</td>
<td>31.8 ± 3.0</td>
<td>.015</td>
<td>25.9 ± 4.6</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>28.8 ± 8.2</td>
<td>&lt;.0001</td>
<td>13.0 ± 8.6</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>33.3 ± 8.4</td>
<td>&lt;.0001</td>
<td>20.2 ± 10.8</td>
</tr>
<tr>
<td><strong>Frontal-Executive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>53 ± 16</td>
<td>.005</td>
<td>127 ± 83</td>
</tr>
<tr>
<td><strong>Visuospatial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey-Osterreith’s Complex Figure—Copy</td>
<td>30.4 ± 7.2</td>
<td>&lt;.0001</td>
<td>15.0 ± 11.2</td>
</tr>
</tbody>
</table>

Values indicate mean ± SD.

ns, nonsignificant.

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Figure 1. Voxel-based gray matter loss in 20 elderly schizophrenia patients and 20 Alzheimer’s disease patients with comparable cognitive deterioration compared with 20 healthy elderly persons. Significance on permutation test is reported on top of each hemisphere.

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temporal cortex mainly in the left hemisphere), while PANNS positive score was associated with gray matter volume changes in small scattered areas mapping to the frontal, temporal, and parietal neocortex.

The association of regional gray matter differences in the elderly schizophrenia group was also investigated with a number of clinical features, such as poor versus good outcome, ever versus never electroconvulsive therapy (ECT) administered, and age at onset before versus after 25 years, by testing the significance on permutation test of group differences, but none reached significance ($p > .18$). The age-adjusted correlations of gray matter volume with medication history (ever vs. never use of first-generation neuroleptics and ever vs. never use of second generation-neuroleptics) and number of years of treatment with first- and second-generation neuroleptics were also not significant ($p > .30$).

**Discussion**

These results indicate that sections of the right cingulate/orbitofrontal cortex show selectively low gray matter volume in our group of chronic elderly schizophrenia inpatients. Although our sample of chronic schizophrenia inpatients may not be representative of other groups of schizophrenia patients, their pattern of low gray matter volume is remarkably uncommon in AD and is consistent with neuropathological studies indicating that their cognitive impairment may be due to causes other than AD ($25,26$).

**The Neurodegenerative Versus the Neurodevelopmental Hypotheses**

The finding of structural changes in the brains of our elderly schizophrenia patients raises the old question (27) of whether these are recent and possibly due to neurodegeneration or long standing and possibly due to neurodevelopment. Ample evidence supports the notion that neurodevelopmental factors play a key role in the pathogenesis of the disease, and imaging studies have shown a peculiar alteration of brain maturation in adolescents with young-onset schizophrenia (6).

However, evidence is also present suggesting that this early component may in a subgroup of patients be followed in later years by a late component of possibly neurodegenerative etiology. Recent MR studies in adult schizophrenia patients have found ventricular enlargement over 10 years of follow-up (28), whole brain volume shrinkage over 4 years (29), and decrement of frontal gray and white matter volumes (30,31). Interestingly, the patients of the above were similar to those of the present study in that their age at onset of first psychiatric symptoms was between 21.2 years and 24.0 years and they had a chronic course.

**The Cingulate/Orbitofrontal Area in Schizophrenia**

A recent meta-analysis has reported macrostructural abnormalities in the right anterior cingulate gyrus (BA 24 and 32) are present in about 50% of studies on schizophrenia patients (4), and microstructural alterations of the cingulate white matter tracts have been demonstrated to correlate with positive symptoms (32). More specific to the population of our study is a meta-analysis (33) indicating lower volume of the anterior cingulate gyrus in chronic versus acute schizophrenia patients. The involvement of this gyrus is plausible considering the involvement of thalamocorticostriatal circuits repeatedly invoked in the pathophysiology of schizophrenia (34). The thalamus receives input from the striatum and sends projections to the prefrontal and cingulate cortex, and functional neuroimaging studies suggest that executive functioning deficits in schizophrenia may be mediated by basal ganglia-thalamocortical circuitry disruption (35).

The posterior cingulate (BA 23 and 31) and retrosplenial (BA 26, 29, 30) areas are typically affected in AD (18) but less typically...
Figure 3. Pattern of mean ROI-based volume changes in elderly schizophrenia patients compared with Alzheimer’s disease patients (based on data shown in Supplement 1). Yellow are Brodmann areas (BAs) where the volume of the gray matter in elderly schizophrenia patients is lower than in healthy elders, light blue are BAs where the volume in elderly schizophrenia patients is lower than in AD patients, and violet BAs are those where both conditions are satisfied. (A) and (B) show the patterns of low gray matter volume under two different definitions of volume difference. (A) depicts a decrease of mean BA volume higher than 13%, and (B) depicts significantly lower volume after correction for multiple comparisons (Supplement 1). In both (A) and (B), the region where both conditions are met corresponds to the orbitofrontal/cingulate area. AD, Alzheimer’s disease; BA, Brodmann area; ROI, region of interest.

Temporal Volume Reductions in Schizophrenia

In our elderly schizophrenia group, we found reduced volume of some areas in the lateral temporal (BA 21, 22) and temporopolar (BA 38) cortex. This is not surprising, as those areas are relatively more affected in young and adult schizophrenia patients (1,40). Lower volume of the superior temporal gyrus correlates with severity of thought disorders and auditory hallucinations in schizophrenia (41), and in one case the neuropil of the temporopolar cortex contained a disproportionately high number of unusually asymmetrical synapses (42). However, it should be underlined that also within the frontal and temporal lobes some areas did not show significant structural damage after decades of disease and drug treatment, possibly suggesting that these may not be involved in the disease pathophysiology (8). This is the case of the middle (BA 46) and left superior frontal gyrus (BA 6, 8, 9) involved in sustained attention and working memory and inferior temporal (BA 20) and fusiform gyri (BA 37) involved in processing of colors information, faces, bodies, words, and numbers recognition. Less surprising is the sparing of some occipital and parietal regions, such as the visual (BA 17) and the largest part of the somatosensory cortex (BA 1, 2, 3, 4).

Limitations

Some peculiarities of the schizophrenia patients in the present study suggest caution in the generalizability of the results. The patients were taken from a long-term facility, and seeing as hospitalized elderly schizophrenia patients who are in general less functional than the nonhospitalized, our results may thus not be generalizable to the whole population of elderly schizophrenia patients. Moreover, the educational level of our patients was relatively low, again prompting caution in the generalization of the results.

The cortical pattern-matching algorithm used can detect and map structural differences in the cortical mantle but does not model subcortical, infratentorial, or white matter changes. Abnormalities have indeed been found in the gray matter of the striatum, thalamus, hippocampus, amygdala, and cerebellum and widespread in the white matter of schizophrenia patients.
Future studies will need to characterize the local differences in these structures with appropriate tools.

The structural increased/decreased gray matter volumes that we found might be due to a number of confounding variables. While we have explicitly avoided a confounding effect of age-associated changes by matching experimental groups by age, we have tried to rule out the effect of others (poor outcome, ECT, and age at onset) by disaggregated analyses. However, the small groups resulting from disaggregation suggest caution in drawing definitive conclusions. Future efforts will need to study much larger patient groups to disentangle the effect of these and other factors such as drug treatment that might affect brain structure in elderly schizophrenia patients.

All authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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