Structural Brain Changes in Parkinson Disease With Dementia

A Voxel-Based Morphometry Study

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Background: Parkinson disease with dementia (PDD) results from neuropathological changes in cortical and subcortical brain regions. Voxel-based morphometric analysis of magnetic resonance images can contribute to in vivo identification of the cerebral regions predominantly involved in PDD.

Objective: To identify structural cerebral regions most closely related to the presence of PDD.

Design: Magnetic resonance images were obtained from 16 patients who had PDD, 13 patients with PD without dementia, and 13 age-matched healthy control subjects. Gray matter volumes were compared using optimized voxel-based morphometric analyses.

Results: Compared with healthy controls, patients with PDD showed gray matter volume decreases in several of the following regions: bilateral putamen, accumbens nuclei, left side of the thalamus, bilateral hippocampus, parahippocampal region, and anterior cingulate gyrus. Patients with PD also showed gray matter reductions compared with healthy controls in the right side of the hippocampus, left anterior cingulate gyrus, and left superior temporal gyrus.

Conclusions: The hippocampus, thalamus, and anterior cingulate are the regions most affected in PDD. Our results agree with recent neuropathological findings suggesting the involvement of the limbic and cortical areas in PD.


Parkinson disease (PD) is among the most frequent chronic neurodegenerative diseases. The estimated prevalence of PD with dementia (PDD) is approximately 30% and the risk of dementia in patients with PD is almost 6 times higher than in the general elderly population.

The neuropathological basis responsible for the presence of PDD remains controversial. Degeneration in the subcortical structures, notably the medial part of the substantia nigra; the basal ganglia, amygdala, and thalamus; nucleus basalis of Meynert; and locus coeruleus have variously been implicated in PDD. However, recent studies also emphasize the importance of cortical changes. An association has been observed between dementia and the presence of cortical Lewy bodies. The presence of Alzheimer-type neuropathology in PD is another likely contributor to dementia.

Magnetic resonance imaging (MRI) allows in vivo identification of global and regional atrophy. Studies have shown PDD to be associated with volumetric changes in the substantia inominata, the hippocampus, and total cerebral volume. Voxel-based morphometry (VBM) allows the determination of brain density and/or volume changes without a priori region of interest selection. This technique has been used in degenerative disorders such as Alzheimer disease, dementia with Lewy bodies (DLB), and mild cognitive impairment. In PD, it has been used to determine the structures involved in the generation of parkinsonian resting tremor.

The aim of this study was to use VBM to examine more closely the structural brain changes responsible for PDD. We, therefore, compared brain changes in patients with PDD, in patients with PD without dementia, and in healthy age-matched control subjects.

METHODS

SUBJECTS

Forty-two subjects between the ages of 54 and 84 years participated in this study as well as...
having been in a previously published study. Three groups of patients (16 patients with PDD, 13 patients with PD, and 13 controls) were recruited from the Parkinson Disease and Movement Disorders Unit, Hospital Clinic, Barcelona, Spain, during a 9-month period (Table 1). The study was approved by the local ethics committee. Written informed consent was obtained from the patient or the patient’s caregiver.

### DIAGNOSTIC CRITERIA AND SELECTION

Idiopathic PD was diagnosed using the criteria of the Parkinson’s Disease Society Brain Bank, London, England. All patients had a good or an excellent initial response to levodopa treatment. Dementia was assessed using 3 standardized instruments: the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), the Clinical Dementia Rating scale, and the Mini-Mental State Examination. Subjects needed a Clinical Dementia Rating scale score of 1, a Mini-Mental State Examination score of less than 23, and both HDRS and MMSE scores of less than 23, and both Hoehn and Yahr stages of 2 or 3.

### MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging was obtained in all subjects using a 1.5-T scanner (GE Medical Systems Co, Milwaukee, Wis) and the head coil. A strict imaging protocol was used, including a 3-dimensional inversion recovery preparation spoiled gradient recalled echo sequence of the entire brain in the axial plane, and the following parameters: repetition time, 17 milliseconds; echo time, 5 milliseconds; inversion time, 300 milliseconds; section thickness, 1.5 mm; field of view, 24 × 256 cm; and number of excitations, 1.

### VOXEL-BASED MORPHOMETRY

The MRIs were analyzed using SPM99 (WDCN, London or http://www.fil.ion.ucl.ac.uk/spm). All the automated image processing was done by a single masked investigator (C.S.). One subject with PD was excluded from VBM analysis because visual inspection of the MRI revealed marked hypointensities consistent with basal ganglia calcifications.

All MRI processing was carried out in accord with the optimized VBM protocol. Briefly, the processing steps outlined by this protocol are (1) the creation of a customized anatomical T1-weighted template and prior probability images separately for each group, by normalizing the brain images to the default SPM T1-weighted template; (2) normalization of the structural brain images in each group using these customized templates, segmenting and cleaning the original T1-weighted images, normalizing the brain images to the customized templates, segmentation and cleaning of normalized brain images, and modulation of gray matter images by the determinant of the Jacobian matrix derived from the spatial normalization step. This procedure has been previously described in detail.

Differences in gray matter were examined using analysis of variance with post hoc comparisons (controls>patients with PD; controls>patients with PDD; patients with PD>patients with PDD). Statistical thresholds were corrected for the 3 post hoc comparisons used here, using the SPM99 compare-populations 1 scan per subject. Exclusive masking was used to determine which voxel differences were specific to one disease process. Results were thresholded for the group being studied at P<.001 (uncorrected for multiple comparisons). Only those clusters exceeding a size of 10 voxels were included in the analysis.

Owing to the characteristics of our acquisition protocol and head size differences among subjects, the most superior and/or inferior regions were absent in some subjects or not clearly visible after reorientation. Therefore, we restricted the volumetric analysis to a region of interest comprising the temporal lobes, caudate, lentiform nuclei, cingulate gyrus, anterior cingulate, thalami, insula, extranuclear region, amygdala, hippocampus, and parahippocampus gyri. This was achieved by means of the Wake Forest University–PickAtlas software (available at: http://www.fmri.wfubmc.edu).

### Table 1. Demographic and Clinical Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With PD</th>
<th>Patients With PDD</th>
<th>Healthy Control Subjects</th>
<th>( \chi^2 ) Test or F Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72.77 ± 4.90</td>
<td>70.06 ± 7.88</td>
<td>70.08 ± 7.17</td>
<td>0.70</td>
<td>.51</td>
</tr>
<tr>
<td>Education attainment, y</td>
<td>8.15 ± 5.27</td>
<td>6.62 ± 4.53</td>
<td>9.31 ± 4.48</td>
<td>3.58</td>
<td>.17</td>
</tr>
<tr>
<td>HDRS score</td>
<td>1.83 ± 2.25</td>
<td>2.94 ± 4.55</td>
<td>0.61 ± 1.19</td>
<td>3.29†</td>
<td>.19</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.54 ± 1.05</td>
<td>17.33 ± 5.51</td>
<td>29.23 ± 1.17</td>
<td>30.9†</td>
<td>&lt;.001‡</td>
</tr>
<tr>
<td>Duration of evolution of PD, y</td>
<td>10.61 ± 7.41</td>
<td>12.94 ± 5.36</td>
<td>NA</td>
<td>2.11†</td>
<td>.15</td>
</tr>
<tr>
<td>Hoehn and Yahr stages</td>
<td>2.73 ± 0.72</td>
<td>3.37 ± 1.02</td>
<td>NA</td>
<td>3.64</td>
<td>.07</td>
</tr>
<tr>
<td>UPDRS II</td>
<td>1.89 ± 1.83</td>
<td>5.83 ± 4.61</td>
<td>NA</td>
<td>4.31†</td>
<td>.04§</td>
</tr>
<tr>
<td>UPDRS II</td>
<td>9.64 ± 5.70</td>
<td>22.92 ± 12.69</td>
<td>NA</td>
<td>8.22†</td>
<td>.004‡</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>24.50 ± 12.04</td>
<td>36.33 ± 13.81</td>
<td>NA</td>
<td>5.00</td>
<td>.04§</td>
</tr>
<tr>
<td>Levodopa dose, mg</td>
<td>604.17 ± 215.80</td>
<td>679.17 ± 211.55</td>
<td>NA</td>
<td>0.74</td>
<td>.40</td>
</tr>
</tbody>
</table>

Abbreviations: HDRS, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination; NA, not applicable; PD, Parkinson disease; PDD, Parkinson disease with dementia; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Data are given as mean ± SD. For normally distributed variables with homogeneity of variance, we have used an analysis of variance. For nonnormally distributed variables, and/or in the case of inhomogeneity of variance, we have used the nonparametrical Kruskal-Wallis test that provides a \( \chi^2 \) statistic.†Indicates calculated using the \( \chi^2 \) test.‡Denotes statistically significant differences between healthy controls and patients with PDD and between patients with PD and patients with PDD.§Denotes statistically significant differences between patients with PD and patients with PDD.
RESULTS

When patients with PDD were compared with normal age-matched controls, several cortical and subcortical areas showed gray matter differences. **Table 2** summarizes the brain areas in which we observed voxels that differed significantly between patients with PD and controls, the size of the cluster of statistically significant voxels, the Talairach coordinates of the peak voxel, and the z scores. In the basal ganglia we observed bilateral gray matter loss in the putamen, nucleus accumbens, and the left side of the thalamus (Figure, center row). In the limbic region, both sides of the hippocampus were reduced in size (Figure, top row), as was the left parahippocampal region. In the cortical region the anterior cingulate gyrus was also bilaterally decreased (Figure, bottom row).

**Table 2. Brain Areas Showing Significant Differences Between Groups***

<table>
<thead>
<tr>
<th>Talairach Coordinate†</th>
<th>Structure</th>
<th>Cluster Dimension, mm³</th>
<th>z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients With PDD vs Healthy Controls Subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32 −27 −8</td>
<td>R hippocampus*</td>
<td>8040</td>
<td>4.82</td>
</tr>
<tr>
<td>−28 −35 −4</td>
<td>L hippocampus</td>
<td>248</td>
<td>3.64</td>
</tr>
<tr>
<td>−34 −20 −18</td>
<td>L parahippocampal gyrus</td>
<td>4848</td>
<td>3.84</td>
</tr>
<tr>
<td>−16 −22 0</td>
<td>L thalamus*</td>
<td>1128</td>
<td>4.35</td>
</tr>
<tr>
<td>18 14 4</td>
<td>R putamen</td>
<td>448</td>
<td>3.47</td>
</tr>
<tr>
<td>−20 12 10</td>
<td>L putamen</td>
<td>536</td>
<td>3.56</td>
</tr>
<tr>
<td>4 4 −8</td>
<td>Bilateral accumbens and hypothalamus</td>
<td>264</td>
<td>3.45</td>
</tr>
<tr>
<td>−6 2 −6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−8 27 28</td>
<td>R anterior cingulate gyrus (BA 32)*</td>
<td>1824</td>
<td>4.99</td>
</tr>
<tr>
<td>−8 34 26</td>
<td>L anterior cingulate gyrus (BA 32)*</td>
<td>1976</td>
<td>4.79</td>
</tr>
<tr>
<td><strong>Patients With PD vs Controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 −35 −4</td>
<td>R hippocampus</td>
<td>160</td>
<td>3.51</td>
</tr>
<tr>
<td>−8 20 44</td>
<td>L anterior cingulate gyrus (BA 32)</td>
<td>152</td>
<td>3.40</td>
</tr>
<tr>
<td>−44 −12 −28</td>
<td>L superior temporal gyrus (BA 38)</td>
<td>136</td>
<td>3.33</td>
</tr>
<tr>
<td><strong>Patients With PDD vs Patients With PD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 −16 −16</td>
<td>R hippocampus</td>
<td>416</td>
<td>3.69</td>
</tr>
<tr>
<td>−64 −24 8</td>
<td>L superior temporal gyrus</td>
<td>336</td>
<td>3.48</td>
</tr>
</tbody>
</table>

Abbreviations: BA, Broadmann area; PD, Parkinson disease; PDD, Parkinson disease with dementia.

*Each reported anatomical location exceeds a voxelwise statistical uncorrected P<.001 threshold level. Asterisk denotes significance at the P<.05 (corrected for multiple comparisons) level. The cluster size denotes the extent of the cluster of significant voxels in cubic millimeters.

†The Talairach coordinate refers to the location of the most statistically significant voxel in the cluster.

**PATIENTS WITH PDD VS CONTROLS**

Patients with PD showed a gray matter reduction in the following 3 regions compared with the controls: the right side of the hippocampus, the left anterior cingulate, and the left superior temporal gyrus (Table 2).

**PATIENTS WITH PD VS PATIENTS WITH PDD**

The comparison of patients with PDD and patients with PD showed statistically significant differences in the left superior temporal gyrus and right side of the hippocampus.

**COMMENT**

This study aimed to identify structural brain changes in PDD using VBM. Our results showed that volumes of the following several structures were reduced in patients with PDD relative to age-matched controls: hippocampus, putamen, accumbens and thalamic nuclei, parahippocampal regions, and anterior cingulate gyrus.
Hippocampal atrophy has been consistently described as a feature in dementia. In our study, VBM results showed a bilateral hippocampal reduction in patients with PDD, which was more pronounced in the right hemisphere. Previous studies have observed hippocampal degeneration in PD. Hippocampal reductions may be due to both Lewy body and Alzheimer-type changes.

We also found a relationship between reduction of the left side of the thalamus and dementia. The thalamus has also recently been identified as a major target for neuropathological inclusions such as Lewy bodies in patients with PD, and an earlier study of neuropathology and dementia in PD also identified volumetric loss in the thalamus as a predictor of dementia. Because in our study, the patients with PDD had greater motor impairment than patients with PD, it is possible that tissue loss observed in the thalamus and putamen may reflect motor as well as cognitive impairment in PDD.

Analysis of cortical regions with VBM showed a marked volume decrease in the anterior cingulate in patients with PDD compared with controls. The anterior cingulate has been shown to be particularly vulnerable to Lewy body inclusions in PDD and DLB. Volumetric reduction of the anterior cingulate may be involved in the attentional deficits described in PDD.

We also found extensive volumetric reduction in the parahippocampal gyrus. In DLB, cases with well-formed visual hallucinations exhibited high densities of Lewy bodies in the amygdala and parahippocampus. Several subjects with dementia in our sample had a history of visual hallucinations.

Patients with PD but without dementia also differed from controls in the hippocampus and anterior cingulate, although reductions were less marked than for patients with PDD. Further, the comparison between patients with PDD and patients with PD revealed differences in the right side of the hippocampus and the left superior temporal regions. Together these results suggest that there may be a gradient of neuropathology affecting cingulate and medial temporal lobe structures in parkinsonism. Consistent with this idea, postmortem studies have demonstrated that all patients with PD have some degree of cortical Lewy body pathology.

Our study has the limitations implicit to VBM procedures. One should be cautious when using automated image processing packages for investigations in degenerative diseases because the software was not specifically designed to measure atrophy. We attempted to solve this problem by creating a local template comprising both patients with PDD, patients with PD, and controls. Also, our sample was exclusive to patients from a clinical population and may not be representative of patients with PD and patients with PDD in the wider community. We also used criteria for enrollment in the PDD group that excluded patients with questionable or early-onset dementia and that focused on memory impairment rather than visuospatial or attentional deficits. Our results may, thus, pertain more to patients in the more-advanced stages of dementia, and further studies with patients exhibiting a spectrum of dementia severity may be required to establish whether MRI is a useful technique for differential diagnosis of PDD.

Voxel-based morphometric methods were used to examine structural brain changes in PDD; gray matter loss at both cortical and subcortical sites was observed. Results revealed volumetric reductions in thalamic, hippocampal, and anterior cingulate regions, corroborating previous neuropathological findings in PDD.

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REFERENCES


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CONCLUSIONS


