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.


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.24 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.25 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),26 the Clinical Dementia Rating scale;27 and the Mini-Mental State Examination.28 Subjects needed a Clinical Dementia Rating scale score of 1, a Mini-Mental State Examination score of less than 23, and both DSM-IV items to fulfill dementia criteria. The Clinical Dementia Rating scale and DSM-IV were administered by a trained clinician (J.M. or Francesc Valldeoriola, MD), and the Mini-Mental State Examination by an experienced neuropsychologist (C.S.). Where required for the Clinical Dementia Rating scale, collateral information was drawn from the patient’s spouse or caregiver. The control group was matched for sex and number of excitations, 1.

### 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, 24X256 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).30 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.18 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, segmenting, averaging, and smoothing the averaged brains in each group; (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.16 Differences in gray matter were examined using analysis of variance with post hoc comparisons (controls>paitients with PD; controls>paitients with PDD; patients with PD>paitients 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, hippocampi, and parahippocampus gyrus. This was achieved by means of the Wake Forest University-PickAtlas software31 (available at: http://www.fmrip.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>χ² 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>30.01</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</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</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>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>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 χ² statistic.

†Indicates calculated using the χ² test.

‡Denotes significant (P<.05) 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

PATIENTS WITH PDD VS CONTROLS

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).

PATIENTS WITH PD 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 gyri (Table 2).

PATIENTS WITH PDD VS PATIENTS WITH PD

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.13,32 Hippocampal reductions may be due to both Lewy body and Alzheimer-type changes.10,33,34

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,33 and an earlier study of neuropathology and dementia in PD also identified volumetric loss in the thalamus as a predictor of dementia.3 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 PDD36 and DLB.38 Volumetric reduction of the anterior cingulate may be involved in the attentional deficits described in PDD.37

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.39 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.32

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.30 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


