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ABSTRACT

Background: The nosologic relationship between dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD) is continuously being debated. We conducted a study using voxel-based morphometry (VBM) to explore the pattern of cortical atrophy in DLB and PDD.

Methods: Seventy-four patients and healthy elderly were imaged (healthy elderly n = 20, PDD n = 15, DLB n = 18, and Alzheimer dementia [AD] n = 21).Three dimensional T1-weighted MRI were acquired, and images analyzed using VBM. The following diagnostic criteria were used: criteria proposed by the third report of the DLB Consortium for DLB, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Diseases Association criteria for AD, and Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria for dementia in PDD.

Results: Overall dementia severity was similar in the dementia groups. We found more pronounced cortical atrophy in DLB than in PDD in the temporal, parietal, and occipital lobes. Patients with AD had reduced gray matter concentrations in the temporal lobes bilaterally, including the amygdala, compared to PDD. Compared to DLB, the AD group had temporal and frontal lobe atrophy.

Conclusion: We found that despite a similar severity of dementia, patients with dementia with Lewy bodies (DLB) had more cortical atrophy than patients with Parkinson disease with dementia (PDD), indicating different brain substrates underlying dementia in the two syndromes. Together with previous studies reporting subtle clinical and neurobiologic differences between DLB and PDD, our findings support the hypothesis that PDD and DLB are not identical entities, but rather represent two subtypes of a spectrum of Lewy body disease. ***Neurology*® 2007;69:747–754**

The most common Lewy body diseases are dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD), which are distinguished by a differential sequence of parkinsonism and dementia.[1] Although clinical and neurobiologic changes are similar in DLB and PDD,[2,3] subtle differences have been reported. More executive dysfunction[4,5] and more frequent psychoses have been found in DLB than in PDD,[2] as well as differences in the pattern and severity of parkinsonism,[6] and levodopa responsitivity.[7]

Morphologic studies have indicated that Alzheimer-type and Lewy body pathology is more pronounced in DLB than in PDD.[8,9]

In contrast, in the only study comparing structural MRI in PDD and DLB using voxel based morphometry (VBM), DLB and PDD differed from Alzheimer dementia (AD) but there were no differences between DLB and PDD.[10]

We conducted a study using VBM to further explore the pattern of atrophy in DLB and PDD. Patients with PDD and DLB, as well as patients with AD and healthy elderly, were imaged and compared to test the following hypotheses: 1) there are no significant differences between DLB and PDD regarding gray matter atrophy; 2) the regional pattern of atrophy in DLB and PDD differs from that in AD. Specifically, gray matter atrophy is more marked in AD than in DLB/PDD.

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METHODS

Case-finding and diagnostic procedures. Patients were consecutive referrals to the Departments of Neurology, Geriatric Medicine, and Geriatric Psychiatry at Stavanger University Hospital, Norway. In addition, some of the patients with PD were participants in a prospective epidemiologic study of patients with PD in Rogaland, Norway,[11] and were recruited at their annual follow up visit.

Diagnosis of PD and dementia. A diagnosis of PD was made according to explicit criteria.[12] A minimum requirement for a diagnosis of PD was two or more of the four cardinal signs for PD (i.e., resting tremor, bradykinesia, rigidity, and postural instability), and the response to a dopaminergic agent should be at least moderate.

Diagnosis of PDD was made in a patient fulfilling PD criteria who also fulfilled criteria for dementia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for dementia[13] and cognitive assessment. Patients were examined by a psychiatrist and a research nurse, both with special training in neuropsychiatry. A clinical medical examination was also performed. Cognitive tests and caregiver-based rating scales (see below) were administered by a research nurse. Patients with a notable cognitive impairment before or within 1 year after onset of PD were not included in the PDD group.

Diagnosis of AD and DLB. AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Diseases Association (NINCDS–ADRDA) criteria for a diagnosis of probable AD,[14] and probable DLB was diagnosed according to the criteria suggested by the third report of the DLB Consortium.[15] Dementia diagnoses were made after a clinical interview with the patient and a caregiver and supported by neuropsychological testing. Eleven patients with DLB underwent iodine I 123-radiolabeled 2beta-carbomethoxy-3beta-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT. In 10 cases the diagnosis was supported by a pathologic scan. Of note, all patients in this geographic area who are referred to a dementia specialist for evaluation are referred to one of these three clinics. The records of all patients included were re-evaluated by an experienced old age psychiatrist (D.A.) for verification of the diagnosis before inclusion in the VBM analysis.

Exclusion criteria. We excluded patients with any neurologic or psychiatric disorder other than PD, AD, or DLB that could be etiologically related to dementia. We checked the standard sequences of the MRI scans before inclusion of a patient or control person. Those who had structural abnormalities in the brain affecting gray matter were excluded from VBM analysis. Subjects with marked tremor which interfered with the imaging session were also excluded. One patient fulfilling the criteria for probable DLB but with a normal FP-CIT SPECT was excluded.

Clinical assessment. For motor symptoms, staging of PD and DLB was carried out according to the Hoehn & Yahr scale.[16]

For cognition, all patients performed a Mini-Mental State Examination (MMSE), a brief cognitive screening test.[17] In addition, patients completed the Dementia Rating Scale[18] or the CAMCOG, the cognitive battery of the CAMDEX.[19]

For psychiatric symptoms, the purpose of the psychiatric assessment was twofold: first to elicit information for the diagnosis of DLB, i.e., visual hallucinations, and second to differentiate between depression-induced cognitive impairment and dementia. Psychiatric symptoms were assessed using The Neuropsychiatric Inventory (NPI),[20] a structured caregiver-based clinical interview designed to elicit psychiatric symptoms in subjects with brain damage and cognitive impairment. Depression was assessed by a psychiatrist or a research nurse using either the Montgomery Åsberg Depression Rating Scale (MADRS)[21] or NPI.

Control group. Healthy elderly control persons were recruited among elderly people from local clubs for retired people, from relatives of patients with PD or dementia, and other volunteers after information about the project. The controls had no active neurologic or psychiatric disorder. They had no cognitive complaints, and were not taking any medication that could affect their cognition. A minimum MMSE score of 28 was required. Informed consent was obtained from all patients and control subjects, and the study has the approval of the Regional Committee for Medical Research Ethics, University of Bergen.

MRI. Patients and controls were scanned at the Department of Radiology, Stavanger University Hospital, in the period from December 2001 to June 2005 with a 1.5 T Phillips Gyroscan NT intra, Release 8.1 MRI machine. A software upgrade of the machine was done in fall 2003, to Release 10. This has not affected the quality of the images, which has been stable throughout the study. We performed a structural MRI series with a T1-weighted three-dimensional fast spoiled gradient recalled echo (FSPGR) (repetition time [TR] 12.4 msec, echo time [TE] 4.2 msec, inversion time [TI] 650 msec, matrix 256 × 192, slice thickness 1.6 mm).

Image analysis. Standard sequences (T1, dual fast field echo [FFE], T2 fluid attenuation inversion recovery [FLAIR]) were done to visualize focal lesions of white or gray matter that might lead to exclusion from the study. These sequences were not used for statistical image analysis in this study.

VBM preprocessing. VBM[22] including the optimized VBM protocol of Good et al.[23] was applied for the preprocessing of the images, including creating a study-specific T1 template image (based on all the patients and controls in our study), and a study-specific gray matter template/prior probability map. The preprocessing steps are already described in detail by others.[10,23] The first preprocessing steps include the creation of customized templates. T1 images of each patient were normalized to the T1 template of SPM2 using an affine only cut-off. After normalizing, images were averaged and then smoothed with an 8 mm kernel, creating the T1 template. We then normalized the original images to the customized T1 template using a 25 mm cut off. The normalized images were then segmented and smoothed with an 8 mm kernel. The smoothed gray matter images were then averaged creating the study-specific gray matter template. These templates were used in the optimized VBM protocol in the following manner; the original images were segmented and the gray matter images were normalized to the customized gray matter template. The resulting deformations from the normalization of gray matter to the gray matter template were used to normalize the original T1 images before the final segmentation. Segmented images were then smoothed

Table 1 Characteristics of participants

	PDD	AD	DLB	Controls	*p* Value
Subjects	15	21	18	20	—
Female/male	5/10	16/5	9/9	10/10	0.064
Mean age, y	73.3 (6.5)	75.1 (9.2)	78.3 (5.8)*	73.6 (6)	0.145
MMSE score	19.3 (4.7)	20.0 (5.0)	19.4 (4.9)	29.6 (0.7)†	<0.001
Education, y	9.9 (3.6)	8.2 (2.2)	8.3 (2.1)	12.1 (4.3)‡	0.001
H&Y stage	3 (0.5)	—	2.4 (1.6)	NA	0.423
Duration of dementia, y	1.9 (1.1)	2.9 (1.4)	3.7 (2.2)¶	NA	0.013

Values are mean (SD).
*DLB significantly older than PDD ($p = 0.036$) and controls ($p = 0.028$).
†Not different between dementia groups, but significantly higher in normal controls.
‡Longer education in controls than AD ($p < 0.001$) and DLB ($p = 0.002$).
§Longer duration of dementia in AD than PDD ($p = 0.03$).
¶Longer dementia duration in DLB than PDD ($p = 0.007$).
PDD = Parkinson disease with dementia; AD = Alzheimer dementia; DLB = dementia with Lewy bodies; MMSE score = Mini-Mental State Examination; H&Y stage = Hoehn & Yahr stage; NA = not applicable.

with a 12 mm kernel. The resulting smoothed images were used in the statistical analysis.

Statistical analyses. Smoothed images from the preprocessing steps were analyzed using statistical parametric mapping (SPM2) (Wellcome Department of Cognitive Neurology, London, UK [http://www.fil.ion.ucl.ac.uk/spm]). Data were analyzed on a PC using windows XP professional, version 5.1 and Matlab 6.5.2 (Mathworks, Natick, MA). The following voxel-based analyses of gray matter were performed.

Differences in gray matter between groups were assessed statistically using one-way analysis of variance (ANOVA). We also performed analyses where age and education were included as covariates either using analysis of covariance or in the single subjects conditions and covariates option in SPM. In all analyses the whole brain was analyzed. Significance levels for *t* statistics were set at $p < 0.001$ uncorrected for multiple comparisons. All results are presented at the voxel level.[24] The coordinates obtained for the peak voxels, i.e., the anatomic location with maximal gray matter loss within each significant cluster, were transferred into Talairach space using Matthew Brett's mni2tal routine (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). The anatomic locations of the peak voxels were found using The Talairach Daemon Client.[25] The results given by the Talairach daemon were verified by the Co-planar Stereotaxic Atlas of the Human Brain.[26] When discrepancies in the location of peak voxels were found, the manually detected anatomic locations were reported.

Group statistics were done using SPSS for Windows, version 12.0.1 (SPSS for Windows, Release 12.0.1, SPSS Inc.). Differences between groups on continuous variables with normal distribution were assessed using one-way ANOVA with post hoc Scheffe test to determine group differences. For the nonparametric data a Kruskal Wallis test was used followed by a post hoc Mann-Whitney *U* test, or a χ^2 test was used when appropriate, using $p < 0.05$ as significant.

RESULTS

The total study group comprised 74 subjects: PDD (n = 15), DLB (n = 18), AD (n = 21), and healthy controls (n = 20). The demographic and clinical characteristics of the four groups are presented in table 1. The patient groups were well balanced with regards to overall cognitive functioning as measured with the MMSE. All patients with DLB fulfilled the criteria for probable DLB according to the third report of the DLB Consortium.[15] Patients with DLB were older than healthy controls and patients with PDD. Control persons had longer education than patients with AD and DLB. In the DLB and AD groups the mean duration of dementia was longer than in the PDD group (table 1). All patients with PDD were taking L-dopa medication, compared to only 55% of patients with DLB. The use of a cholinesterase inhibitor (CEI) was 53% in the PDD group, 81% in the AD group, and 83% in the DLB group. The percentage of patients taking antipsychotic medication in the three groups were PDD 47%, AD 5%, and DLB 17%. Antidepressant medication was prescribed in 33% of patients with PDD, 19% in the AD group, and 50% of patients with DLB.

Twelve patients were recruited for the study but were excluded from the VBM analysis for various reasons. Three patients became agitated during scanning, three withdrew from the study after being scheduled for MRI, two were excluded because of movement artifacts due to tremor, three had structural lesions affecting gray matter, and one patient was unable to be scanned in the correct head position. One control was excluded because of claustrophobia. Average time between clinical testing and MRI scanning was 28.1 (25.5) days.

Comparison of patients with PDD and DLB. When comparing patients with PDD and DLB (*p* uncor-

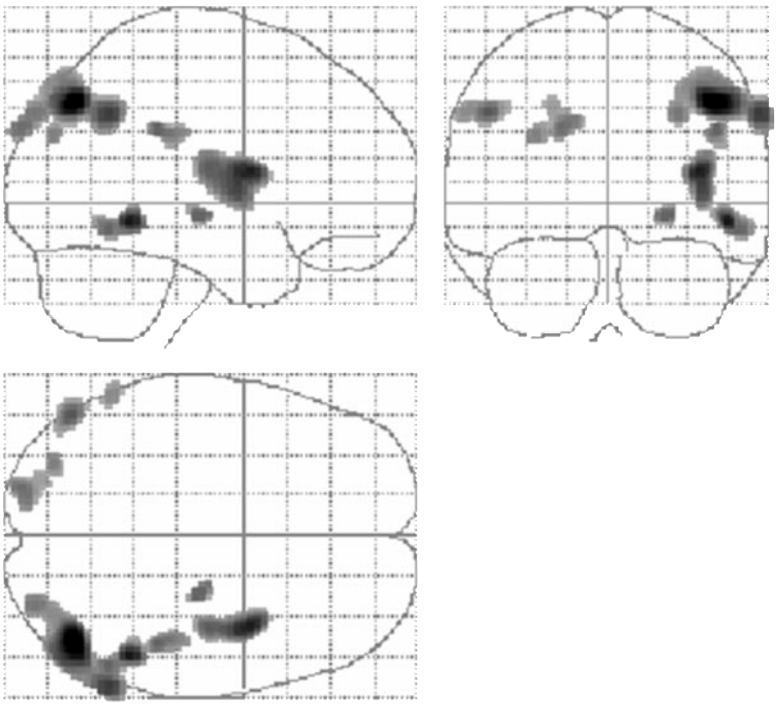
Table 2 Anatomic location of areas of reduced gray matter in dementia with Lewy bodies compared with Parkinson disease with dementia

Talairach coordinate					
x	y	z	Structure	Cluster size	Z score
44	−67	42	R Inferior parietal lobule	1,869	4.38
29	−83	39	R Precuneus		3.49
−49	−68	38	L Angular gyrus	209	3.67
−58	−51	38	L Inferior parietal lobule	82	3.35
38	4	13	R Insula	915	4.03
39	−7	8	R Insula		3.67
−30	−76	31	L Superior occipital gyrus	73	3.43
−20	−88	34	L Cuneus	254	3.54
−23	−79	42	L Precuneus		3.24
53	−56	−6	R Inferior temporal gyrus	302	3.60
26	−20	−3	R Lentiform nucleus	67	3.60

Age was covariate in the analysis. The coordinates x, y, and z refer to the anatomic location, referring to standard stereotactic space as defined by Talairach and Tournoux.[35] Only clusters larger than 200 mm^3/60 voxels are shown. In this table all reported voxels are p uncorrected < 0.001.

rected < 0.001), using age as a covariate, there were areas of reduced gray matter in the temporal, parietal, and occipital lobes, with increased atrophy in patients with DLB relative to PDD. Changes were found bilaterally in the inferior parietal lobule and in the precuneus. Areas with increased atrophy only in the right hemisphere were in the insula, inferior temporal gyrus, and in the lentiform nucleus. Areas of increased atrophy found only in the left hemisphere were in the angular gyrus, cuneus, and in the superior occipital gyrus (table 2, figure 1). To further adjust for the effect of age, the analyses were performed after excluding the three oldest patients with DLB, and the age of this DLB group did not differ from the PDD group. This left the results practically unchanged (data not shown). We found no areas where patients with PDD had more gray matter atrophy than patients with DLB (p uncorrected < 0.001).

Figure 1 Areas of reduced gray matter in patients with dementia with Lewy bodies compared with Parkinson disease with dementia



Age as covariant in the analysis. Results shown on glass brain, where significant areas of atrophy are shown as gray and black clusters. Atrophy was found bilaterally in the inferior parietal lobule and in the precuneus, and on the right side: insula, inferior temporal gyrus, and in the lentiform nucleus. Left side: angular gyrus, cuneus, and in the superior occipital gyrus.

Comparison of patients with PDD and AD. Compared with patients with PDD, patients with AD had reduced gray matter concentrations in the amygdala and middle temporal gyrus bilaterally (p uncorrected < 0.001). There were also reduced gray matter concentrations in the right insula and postcentral gyrus. Left sided gray matter reductions were found in the hippocampus and middle occipital gyrus (table 3, figure 2). There were no areas where patients with PDD had more gray matter atrophy than patients with AD.

Comparison of patients with DLB and AD. When age and education were entered as covariates in the analysis, patients with AD had reduced gray matter concentration with peak voxels in the right hippocampus, uncus, and parahippocampal gyrus (p uncorrected < 0.001). On the left side the area of reduced gray matter also included the hip-

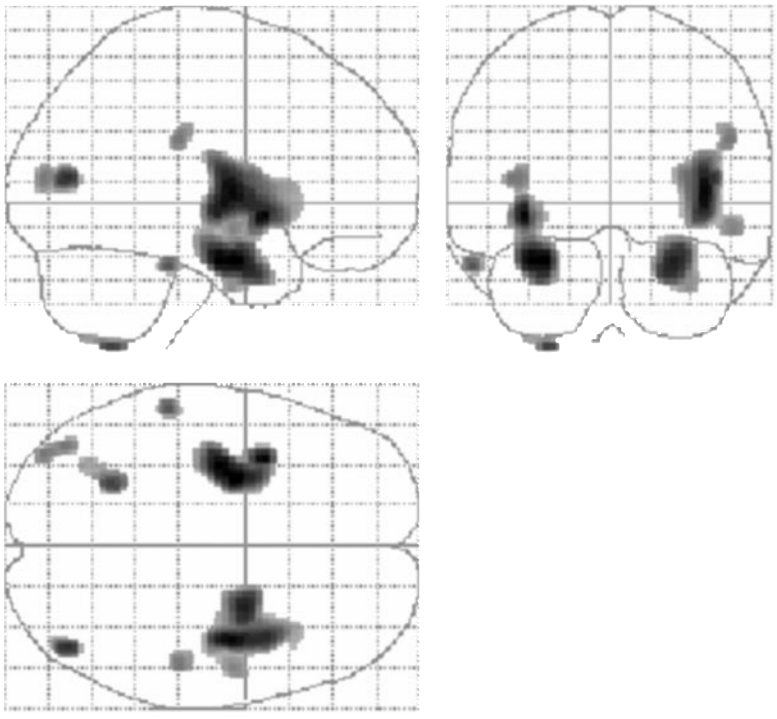
Table 3 Anatomic location of areas of reduced gray matter in Alzheimer disease compared with Parkinson disease with dementia

Talairach coordinate					
x	y	z	Structure	Cluster size	Z score
−33	−12	−20	L Hippocampus	1,989	4.01
−27	−6	−19	L Amygdala		3.98
39	−6	5	R Insula	2,422	3.96
38	8	−3	R Insula		3.79
26	−1	−20	R Amygdala	1,085	3.84
42	−71	14	R Medial temporal gyrus	141	3.76
−56	−32	−20	L Medial temporal gyrus	75	3.57
−41	−72	14	L Middle occipital gyrus	150	3.42
−38	−81	14	L Middle occipital gyrus		3.41
50	−25	26	R Postcentral gyrus	82	3.42

The coordinates x, y, and z refer to the anatomic location, referring to standard stereotactic space as defined by Talairach and Tournoux.[35] Only clusters larger than 200 mm^3/60 voxels are shown. In this table all reported voxels are p uncorrected < 0.001.

pocampus, but there was no local maximum in the hippocampus. There were frontal areas of atrophy in the right rectal gyrus, and in the left middle and inferior frontal gyrus.

Figure 2 Areas of reduced gray matter in patients with Alzheimer disease (AD) compared with patients with Parkinson disease with dementia



Results shown on glass brain, where areas of atrophy are presented as gray and black clusters. Patients with AD had atrophy in the amygdala and middle temporal gyrus bilaterally, right side: insula and postcentral gyrus. Left side: hippocampus and middle occipital gyrus. p Uncorrected < 0.001.

Comparison of dementia groups with normal controls. The results from comparison of patients with PDD to healthy controls have recently been reported.[27]

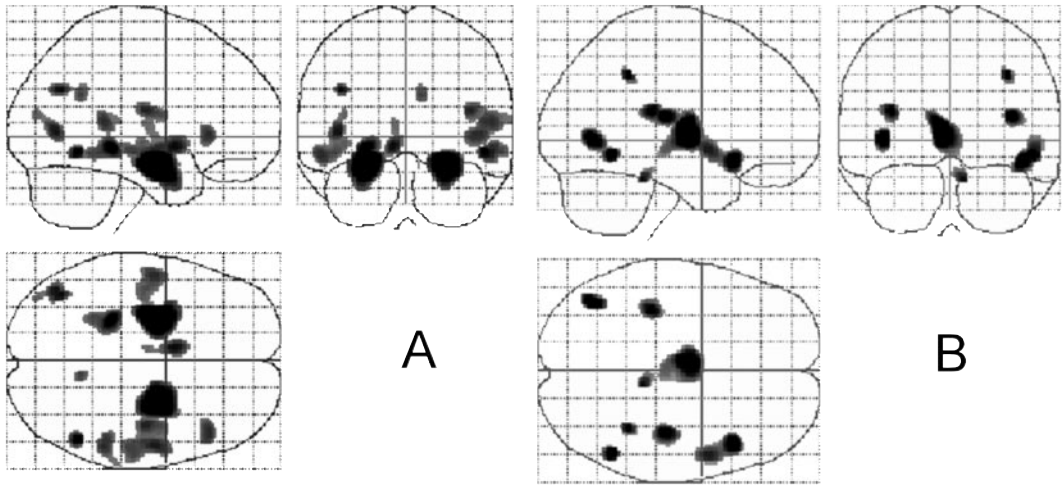
After adjusting for age and education, patients with DLB had reduced gray matter concentrations (p uncorrected < 0.001) bilaterally in the insula, and thalamus compared with controls. Right sided atrophy was found in the inferior parietal lobule, superior temporal gyrus, and the inferior temporal gyrus. On the left side patients with DLB had atrophy of the red nucleus and middle occipital gyrus (figure 3).

After adjusting for education, patients with AD had areas of gray matter concentrations reduction (p FWE < 0.05) in the amygdala and hippocampus bilaterally, and on the left side in the middle and superior temporal gyrus, and uncus, while on the right side in the inferior frontal gyrus (figure 3).

DISCUSSION The main finding in this VBM study was the more pronounced cortical atrophy in DLB than in PDD. Patients with DLB had more atrophy in temporal, parietal, and occipital lobes. These differences occurred despite similar level of overall dementia. In no area was there more atrophy in patients with PDD than in patients with DLB. As expected, patients with AD had more marked atrophy than DLB and PDD, in particular in the medial temporal lobes. Widespread cortical atrophy was found in all patient groups compared to healthy elderly.

The finding of more atrophy in DLB than in

Figure 3 Areas of atrophy and regional changes



(A) Areas of atrophy in patients with Alzheimer disease compared with healthy control subjects. (B) Areas of atrophy in patients with dementia with Lewy bodies compared with healthy control subjects. Results shown on glass brain, where areas of atrophy are presented as gray and black clusters. (A) Regional changes in gray matter found in amygdala and hippocampus bilaterally, left: middle and superior temporal gyrus, and uncus, right side: inferior frontal gyrus. We show only those areas surviving a family wise error (FWE) correction for multiple comparisons p FWE < 0.05. (B) Regional changes in gray matter, compensated for differences in age and education: bilaterally in the insula, and thalamus. Right side: inferior parietal lobule, superior temporal gyrus, and inferior temporal gyrus. Left side: red nucleus and middle occipital gyrus p uncorrected < 0.001.

PDD is new and contrasts with the only previous VBM study of MRI in PDD and DLB.[10] There are several possible explanations for this difference. Most importantly, patients with PDD in the previous study[10] had shorter duration of disease than those in our study. An association between more severe morphologic changes and shorter duration between onset of PD and dementia has recently been reported.[9] Thus, our patients with PDD may have less severe morphologic cortical changes, which may explain a less pronounced cortical atrophy compared to subjects with DLB. In addition, either VH or FC was required for a diagnosis of PDD in the previous study. Thus, patients with PDD with a clinical phenotype similar to DLB were selected in that study, which probably increases the likelihood of similar brain changes.

More cortical atrophy in DLB than PDD is consistent with several recent clinical and pathologic studies that report differences between the two dementias. Psychotic symptoms are more common in DLB than in PDD[2,28,29] and more pronounced executive[4,5] and visuoconstructional[30] and spatial[31] dysfunction in patients with DLB compared to patients with PDD have been reported. Furthermore, several studies have reported more morphologic changes in DLB compared to PDD, both Alzheimer-type changes[8] and a higher density of Lewy bodies,[32,33] although another study reported no differences.[34] Finally, recent evidence suggests different patterns of amyloid-beta peptides in the CSF in DLB and PDD.[35] Thus, although methodologic limitations preclude firm conclusions, emerging clinical and neurobiologic research indicates different pathophysiologic pathways for DLB and PDD.

The posterior parietal association cortex is involved in the convergence of different sensory information. Thus possible clinical implications of the differences in atrophy between PDD and DLB found in our study could be related to differences in visual perception. In both PDD and DLB hypoperfusion of parietal and occipital areas has been found,[36,37] and results showing impaired visuoconstructional skills in DLB compared to PDD[30] could be related to differences in atrophy. Further studies are needed to address this issue.

Patients with AD had more atrophy of the medial temporal lobes bilaterally including the amygdalae compared to patients with PDD and DLB. This is in line with previous studies[10,38] although minor differences between the studies exist. Patients with DLB had more widespread atrophy in temporal, parietal occipital, and frontal regions than healthy controls, i.e., many of the same significant areas as a previous report,[38] although these investigators present volume differences while we present differences in gray matter concentrations.

There are methodologic factors that may have influenced our findings. Although the sample size was larger than many other studies, and care was

taken to select patients from different sources, the number of patients in each group is small. Given the marked clinical heterogeneity in PDD and DLB, our findings may not fully be generalized to the entire population of patients with PDD and DLB.

There were demographic and clinical differences between the groups. We attempted to adjust for this in the statistical analyses by including age and education as a covariates where the groups differed. In addition, we reanalyzed the data after removing the oldest patients with DLB, leaving the groups with similar age. The finding of more cortical atrophy in DLB than in PDD remained significant, indicating that these are robust findings. We chose not to include dementia duration as a covariate, although this is a possible confound, since there could be differences in the measurement of dementia duration between the PDD and AD/DLB groups due to recall bias and masking of early cognitive deficit due to motor symptoms in the PDD group. Most importantly the groups were matched for dementia based on the MMSE. No generally accepted method exists for matching dementia severity when comparing different dementia types, but MMSE is the most widely used cognitive screening scale in dementia.

Another issue concerns the diagnostic accuracy. The diagnosis of PD was made according to international standards, but there are no overall accepted clinical criteria for PDD, and no biomarkers available. Thus the diagnosis of PDD was based on clinical evaluation only and some patients may have been misdiagnosed. However, a proportion of the patients with PDD have been followed for 10 years or more by the same movement disorder research neurologist and diagnosed according to standardized criteria. In an autopsy study at our hospital there has been a 100% accuracy rate of Lewy body–PD in the subset of the 22 patients who have come to autopsy so far.[39]

The most recent international consensus criteria for DLB were used.[15] Although some studies have reported low sensitivity to the previous consensus criteria for clinical DLB diagnosis (report of the Consortium on DLB International Workshop),[40] a high specificity has generally been reported.[41] Fifty-five percent of patients with DLB had functional imaging of the nigrostriatal dopamine system using FP-CIT SPECT performed which confirmed dopamine transporter loss, a method that has shown high specificity to distinguish between DLB and AD,[42] providing further support for the diagnostic accuracy.

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