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MRI volumetric study of dementia with Lewy bodies

A comparison with AD and vascular dementia

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Article abstract—*Objective:* To compare global and regional atrophy on MRI in subjects with dementia with Lewy bodies (DLB), AD, vascular dementia (VaD), and normal aging. In addition, the relationship between *APOE*-ϵ4 genotype and volumetric indices was examined. *Method:* MRI-based volume measurements of the whole-brain, ventricles, frontal lobe, temporal lobe, hippocampus, and amygdala were acquired in elderly subjects with DLB (n = 27; mean age = 75.9 years), AD (n = 25; 77.2 years), VaD (n = 24; 76.9 years), and normal control subjects (n = 26; 76.2 years). *Results:* Subjects with DLB had significantly larger temporal lobe, hippocampal, and amygdala volumes than those with AD. No significant volumetric difference between subjects with DLB and VaD was observed. Compared with control subjects, ventricular volumes were increased in all patients with dementia, though those with DLB showed a relative preservation of whole-brain volume. There were no significant differences in frontal lobe volumes between the four groups. *APOE*-ϵ4 status was not associated with volumetric indices. *Conclusion:* The findings support the hypothesis that DLB is associated with a relative preservation of temporal lobe structures. In the differentiation of DLB and AD, this may have important implications for diagnosis. **Key words:** Dementia with Lewy bodies—Alzheimer's disease—Vascular dementia—MRI—Temporal lobe—Frontal lobe.

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Dementia with Lewy bodies (DLB) is characterized by fluctuating cognitive impairment, persistent visual hallucinosis, and parkinsonism. It is the second most common form of degenerative dementia and may account for up to 20% of cases of late-life dementia.[1] Ante mortem diagnosis of DLB and its differentiation from other common forms of late-onset dementias, particularly AD and vascular dementia (VaD), is important for a number of reasons. Some patients with DLB may have an accelerated disease progression and approximately 50% of subjects experience life-threatening adverse reactions to antipsychotic medications (neuroleptic sensitivity).[2] In contrast, subjects with DLB may have an enhanced therapeutic response to treatment with cholinesterase inhibitors.[3]

Volumetric MRI may provide important supplementary information that could support or counter a

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Table 1 *Subject characteristics*

Characteristic	DLB (n = 27)	AD (n = 25)	VaD (n = 24)	Control (n = 26)	*p* Value
Age, y	75.9 ± 7	77.2 ± 5	76.9 ± 7	76.2 ± 5	NS
M:F	19:8	9:16	15:9	14:12	NS
Education, y	9.2 ± 1	9.8 ± 3	9.9 ± 1	10.1 ± 2	NS
Length of history, mo	39.6 ± 18	42.4 ± 25	41.0 ± 25	NA	NS
MMSE score (max 30)	13.8 ± 8	15.6 ± 5	18.4 ± 5	28.1 ± 2	<0.001*
CAMCOG score (max 107)	47.3 ± 26	56.2 ± 16	62.5 ± 13	97.2 ± 5	<0.001*

Values expressed as mean ± standard deviation.

* Post hoc Scheffe test showed significant differences between control and AD, control and VaD, control and DLB ($p < 0.001$) and between VaD and DLB ($p < 0.05$).

VaD = vascular dementia; DLB = dementia with Lewy bodies; MMSE = Mini-Mental State Examination; CAMCOG = Cambridge Cognitive Examination; NS = not significant; NA = not applicable.

clinical diagnosis of DLB. A recent volumetric study[4] and initial work from our group[5,6] indicate that there may be less atrophy of temporal lobe structures on MRI in DLB compared with AD. Information regarding other structural features that may differentiate DLB from AD are inconclusive and there has been no detailed volumetric comparison of DLB and VaD to date.

A number of recent studies reported an association between the *APOE*-ϵ4 genotype and specific morphologic changes identified on neuroimaging in subjects with AD.[7-11] No consistent link has been identified, and the relationship between volumetric indices on MRI and *APOE*-ϵ4 status in DLB has not been characterized.

The purpose of this study was to compare the extent of global and regional atrophy on MRI in patients with DLB, AD, and VaD, and age-comparable normal control subjects. We also examined the relationship between *APOE*-ϵ4 status and volumetric indices in these subjects. We hypothesized that subjects with DLB would have less temporal lobe atrophy than those with AD and VaD.

Methods. *Recruitment of subjects.* Seventy-six subjects over age 60 years who fulfilled Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM- IV)[12] criteria for dementia were recruited from a community-dwelling population of patients with an informant in regular contact. Seventy-two of these subjects were prospectively chosen from a clinical case register[13] of consecutive referrals to old age psychiatry services. All potential subjects on the register (n = 199) were assessed for their suitability to take part in the study: whether they met the entry criteria; could give consent and were willing to take part in the study; could cooperate and tolerate having an MRI scan; and exhibited the absence of medical contraindications for MRI. An additional four subjects were recruited from a specialist dementia clinic. Twenty-six age-matched controls were recruited from among spouses and friends of dementia subjects. The local ethics committee approved the research and all subjects, as well as the nearest relative for patients, gave informed consent after the nature of the procedures had been fully explained.

Assessments and diagnosis. All dementia subjects were assessed as previously described.[6] Cognitive function was measured using the Cambridge Cognitive Examination (CAMCOG),[14] which incorporates the Mini-Mental State Examination (MMSE),[15] within 3 months of the MRI scan. Depressive symptoms were also rated using the Montgomery Asberg Depression Rating Scale (MADRS).[16]

Standardized clinical diagnostic criteria were used to characterize the type of dementia. Diagnosis of AD, VaD, and DLB were made in accordance with National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association,[17] National Institute of Neurological Disorders and Stroke/Association International pour la Recherche el l' Enseignement en Neuroscience,[18] and DLB consensus criteria[1] by consensus agreement between three experienced raters (J.O., C.B., I.M.). Diagnosis was made blind to MRI scan findings. Pathologic confirmation of diagnosis has since been acquired in seven patients.

Subjects with dementia. The total sample size consisted of 27 subjects with consensus criteria DLB (probable in 26, possible in 1, with autopsy confirmation in 4), 25 subjects with NINCDS/ADRDA AD (definite in 3, probable in 21, and possible in 1) and 24 subjects with National Institute of Neurological Disorders and Stroke/AIREN VaD (probable in 14 and possible in 10). Subject characteristics are summarized in table 1.

Normal control subjects. Control subjects were recruited after a detailed assessment to exclude evidence of dementia (from history or score <80 on the CAMCOG), depression (from history or score >10 on the MADRS), and a history of any other significant neurologic, physical, or psychiatric disorder including drug and alcohol abuse.

MRI scan acquisition. All scans were performed on a 1.0-tesla Siemens Magnetom Impact Expert MRI Scanner (Siemens Medical, Munich/Erlangen, Germany). T1-weighted three-dimensional MPRAGE (magnetization-prepared rapid-acquisition gradient echo) turbo flash sagittal sequence was used to acquire whole-brain images (repetition time = 11.4 msec, time to echo = 4.4 msec, inversion time = 400 msec, time delay = 50 msec, matrix 256 × 256, slice thickness = 1 mm). Standard head positioning was used.

Table 2 *Summary of mean normalized ratios* and raw volumes by diagnostic group*

Structure	DLB (n = 27)	AD (n = 25)	VaD (n = 24)	Controls (n = 26)	Differences between dementia groups	Differences between controls and dementia groups
Whole brain						
Ratio	70.47	66.74	67.27	71.58	NS	AD and VaD†
Raw volume	1,120 cm^3	1,017 cm^3	1,043 cm^3	1,102 cm^3		
Ventricles						
Ratio	3.47	4.01	4.54	1.83	NS	AD and VaD,‡ DLB*
Raw volume	55.1 cm^3	61.9 cm^3	71.4 cm^3	28.4 cm^3		
Frontal lobes						
Ratio	4.21	3.85	3.81	4.15	NS	NS
Raw volume	66.8 cm^3	58.5 cm^3	59.1 cm^3	63.8 cm^3		
Temporal lobes						
Ratio	3.66	3.22	3.50	4.04	DLB > AD*	AD and VaD,‡ DLB*
Raw volume	58.2 cm^3	49.3 cm^3	54.2 cm^3	62.3 cm^3		
Hippocampus						
Ratio	0.14	0.10	0.12	0.18	DLB > AD‡:VaD > AD*	AD, VaD and DLB‡
Raw volume	2,296 mm^3	1,572 mm^3	1,927 mm^3	2,717 mm^3		
Amygdala						
Ratio	0.08	0.05	0.07	0.09	DLB > AD‡	AD and VaD‡
Raw volume	1,208 mm^3	832 mm^3	1,035 mm^3	1,340 mm^3		

Normalized to intracranial area (volume of structure in mm^3/midsagittal intracranial area in mm^2). *p* Values are post hoc Scheffe adjusted for MMSE score. For hippocampal volumes n = 22 for AD and n = 20 for VaD; for amygdala volumes n = 19 for both groups.

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.

DLB = dementia with Lewy bodies; VaD = vascular dementia; NS = no significant difference.

Analysis of regions of interest. Images were transferred to a workstation (SPARCSTATION, Tatung, Telford, UK) and analyzed using ANALYZE software[19] (Version 7.5.5, Mayo Foundation, Rochester, MN). The data were first reformatted into coronal slices perpendicular to the long axis of the left hippocampus (slice thickness = 1 mm, cubic voxels of 1 mm), correcting for any malalignment when necessary.

Six regions of interest (ROI) were measured: two indices of global atrophy, whole-brain and ventricular volumes; two indices of lobar atrophy, frontal and temporal lobe volumes; and two indices of medial temporal atrophy, hippocampal and amygdala volumes. The right and left sides of bilateral ROIs were measured on each slice in accordance with the anatomic boundaries described below (in mm^3). CSF spaces were excluded from all parenchymal measurements. To control for variation in head size, volume for each ROI were normalized to the midsagittal intracranial area. Final volumes were expressed as a normalized ratio (units mm^3/mm^2).

All ROIs, except whole-brain volumes, were measured sequentially, slice-by-slice (1 mm). The frontal lobes, temporal lobes, and ventricles were measured using a combination thresholding (between CSF and brain) and automatic edge-finding techniques. The hippocampus, amygdala, and intracranial area were manually traced using a mouse-driven cursor. Whole-brain volumes were determined using a semiautomated segmentation process.

The same trained rater (R.B.) conducted all measurements blind to diagnosis. Intrarater reliability was assessed by measuring seven subjects on three occasions. The mean coefficient of variation for the volumetric indices was between 1% and 4%.

Anatomic borders of regions of interest. Whole-brain volume was measured from above the level of the foramen magnum. Ventricular volume (lateral and third ventricles) was measured across the entire length and defined by the CSF–brain boundary. Frontal lobes were measured from the first cortical gyrus to the slice anterior to the optic chiasm using in accordance with previous studies.[20] The average length measured (equivalent to the number of slices) was 43.6 mm (SD = 3.4).

Temporal lobes were measured throughout their length from the first cortical gyrus rostrally to the slice showing the longest length of fornix separating from the hippocampus caudally. The average length measured was 66.3 mm (SD = 2.9).

Standard anatomic boundaries were used to define the hippocampus.[21,22] The measurement included the hippocampus proper, dentate gyrus, subicular complex, alveus, and fimbria. The hippocampus was measured from the first slice identifying the head to the slice showing the

Table 3 *Differences between controls and dementia subjects*

Region of interest	DLB	AD	VaD
Whole brain	NS	↓	↓
Ventricles	↑	↑	↑
Frontal lobes	NS	NS	NS
Temporal lobes	↓	↓	↓
Hippocampus	↓	↓↓	↓
Amygdala	NS	↓↓	↓

↓ = significantly smaller volume in dementia subjects compared to control subjects (two arrows indicate a difference of over 40%); ↑ = significantly larger volume in dementia compared to control subjects; VaD = vascular dementia; DLB = dementia with Lewy bodies; NS = no significant difference.

longest length of fornix.[22,23] The average length measured was 38.1 mm (SD = 2.6). In two subjects with AD and four with VaD, the hippocampus could not be reliably identified due to movement artifacts.

The anatomic boundaries of the amygdala were defined according to standard criteria.[22] The anterior margin was arbitrarily defined from the first slice at the closure of the lateral sulcus. The average length measured was 13.6 mm (SD = 1.8). In six subjects with AD and five with VaD, the amygdala could not be reliably identified due to movement artifacts.

Determination of APOE *genotype.* Genomic DNA was isolated from whole blood and *APOE* genotypes were determined using standard PCR.[24]

Statistical analysis. The statistical package SPSS for Windows (release 7.5; SPSS, Chicago, IL) was used for data analysis. Volumetric comparisons were made using the normalized ratio (volume of structure in mm^3 divided by midsagittal intracranial area in mm^2). Differences between diagnostic groups on volumetric indices were assessed using analysis of variance adjusting for MMSE score, followed by post hoc Scheffe test to correct for multiple comparisons. Linear regression was used to explore the relationship between volumetric findings, diagnosis, and variables which may influence brain size. Independent Student's *t*-tests were used to examine volume differences between subjects with and without *APOE*-ϵ4 allele. For nonparametric data, Kruskal-Wallis analysis of variance was used. (All statistical tests were two-tailed and regarded as significant at $p < 0.05$.)

Table 4 *Differences between subjects with DLB and other dementia subjects*

Region of interest	DLB versus AD	DLB versus VaD
Whole brain	NS	NS
Ventricles	NS	NS
Frontal lobes	NS	NS
Temporal lobes	↑	NS
Hippocampus	↑	NS
Amygdala	↑	NS

↑ = significantly larger volume in subjects with dementia with Lewy bodies (DLB) compared with AD; VaD = vascular dementia; NS = no significant difference.

Results. As shown in table 1, groups were comparable for age, gender ($\chi^2 = 6.7$, $df = 3$, $p = 0.08$), length of history and years of education. Ninety-five percent of subjects were right-hand dominant with no group differences. As would be expected, CAMCOG and MMSE scores were lower in all dementia groups compared with control subjects ($p < 0.001$). Subjects with DLB were more impaired than those with VaD on MMSE (13.8 versus 18.4; $p < 0.05$) and CAMCOG (47.3 versus 62.5; $p < 0.05$) scores.

Mean normalized and raw volumes for each ROI are shown in table 2. Differences between control and dementia subjects are summarized in table 3, and between subjects with DLB and other dementia subjects in table 4.

Measured volumes. Control subjects had larger normalized whole-brain volumes compared with AD ($p < 0.01$) and VaD ($p < 0.01$), but not DLB ($p = 0.919$) patients. There was a trend for DLB subjects to have larger whole-brain volumes than those with AD ($p = 0.051$) but not VaD ($p = 0.106$).

Ventricular volume was smaller in contrast compared to all dementia groups ($p < 0.001$).

There were no differences between dementia subjects. There were no significant differences in normalized frontal lobe volumes between control and dementia subjects.

Control subjects had larger normalized temporal lobe volumes compared to all dementia groups ($p < 0.001$). Subjects with DLB had larger temporal lobe volumes compared to those with AD (3.66 versus 3.22, $p < 0.05$).

Control subjects had larger hippocampi compared to all dementia groups ($p < 0.001$). Subjects with DLB had larger hippocampi than those with AD ($p < 0.001$), but not VaD ($p = 0.107$). AD subjects also had smaller hippocampi than those with VaD ($p < 0.05$).

Controls had larger amygdalae compared to subjects with AD and VaD ($p < 0.001$), but not DLB ($p = 0.273$). Subjects with DLB had larger left and right amygdalae than those with AD ($p < 0.001$).

Stepwise linear regression was used to examine the relationship between hippocampal volume, the different dementia subtypes, and factors that may influence brain volume (age, gender, MMSE score, *APOE*-ϵ4 status, or history of hypertension). Significant variables were a diagnosis of AD (Beta = −0.516, $p < 0.01$), MMSE score (Beta = 0.436, $p < 0.01$), and a diagnosis of VaD (Beta = −0.311, $p < 0.01$). Together these variables predicted 59% of the variance ($r^2 = 0.592$).

APOE-*ϵ4 and volumetric indices.* There were no significant differences in volumetric indices between ϵ4-negative and -positive subjects for all dementia groups. Within each dementia group, there were no significant differences in age, duration of illness and cognitive impairment between ϵ4-negative and -positive subjects. In addition, *APOE*-ϵ4 status did not predict atrophy for any volumetric indices in dementia subjects using linear regression.

Discussion. This study examined MRI volumetric differences in subjects with DLB, AD, VaD, and normal subjects. Subjects with DLB had significantly larger temporal lobe, hippocampal, and amygdala volumes than those with AD, with a trend toward larger whole-brain volumes. Overall, there were no significant volumetric differences between subjects with DLB and VaD and in frontal lobe volumes be-

tween all subjects. Total ventricular volumes were nonspecifically increased in all subjects with dementia. Atrophy was not associated with presence of *APOE*-ϵ4.

The strengths of this study included the recruitment of community-based elderly subjects with late-life dementia, with comparable age, sex, education, and duration of illness. Volumetric differences between groups were therefore unlikely to be related to differences in age or gender. A potential criticism of this study would be the reliance on clinical, rather than pathologic, diagnoses. However, as previously discussed[6] clinical diagnoses were made after detailed assessments and in accordance with standardized criteria.

A major finding of this study was that subjects with DLB had significantly larger whole-temporal lobes, hippocampi, and amygdalae than those with AD. This is consistent with and further extends our previous observation using visual rating of medial temporal lobe atrophy in the same sample.[6] A similar pattern of differential hippocampal atrophy in AD and DLB has been reported,[4] although the volume loss in dementia subjects was less extensive; in addition, there was no difference in amygdala volume. These discrepancies need to be explored further, but may reflect variations in methodology and sample selection, as our subjects were an average of 4 to 5 years older, had had dementia for a longer period, and had lower MMSE scores.

Importantly, the differential pattern of temporal lobe atrophy in DLB and AD during life is consistent with autopsy studies.[25-29] The convergence of findings suggest that in the differentiation of DLB from AD, the preservation of temporal lobe structures, especially the hippocampus, is supportive of a clinical diagnosis of DLB. Pathologically, this may be explained by the relative absence of AD-type pathology in DLB, especially neurofibrillary tangles.

All three dementia groups had more extensive temporal lobe and hippocampal atrophy when compared with age-matched controls. In relation to AD, this is highly consistent with well-established findings[23,30] and may relate to the extent of tangle pathology.[31,32] Previous studies have also reported increased atrophy of temporal lobe structures in both subjects with Lewy body pathology[33,34] and VaD[33] when compared with normal controls. The pathologic basis of these findings is less clear. Further neuropathologic studies are necessary in order to clarify the relationship, if any, between concurrent AD-type pathology and temporal lobe atrophy on MRI in subjects with DLB and VaD. It would be important to determine whether MTA in life is a marker of AD-type pathology not only in AD, but also in other disorders where comorbid processes may be interacting.

Measures of global atrophy demonstrated significant enlargement of ventricles in dementia subjects compared with control subjects. Patients with DLB, however, had relatively well-preserved whole-brain parenchyma volume. Autopsy studies indicating relative preservation of synapse integrity[35] and neuronal counts in subjects with DLB[36] may explain this relative conservation of overall brain volume.

Frontal lobe volumes were similar in all three dementia groups. In relation to DLB and AD, this replicates the finding of autopsy reports[26,37] and our MRI pilot study[5] using a different cohort of subjects. As such, the results did not confirm previous reports of an association between frontal lobe atrophy and Lewy body pathology[34,38] although once again, comparisons between studies are complicated by differences in methodology, patient selection, and the relative small number of subjects.

There were no significant differences in frontal lobe volumes between control and dementia subjects. This may reflect the limitations of our measurement, which was restricted to the anterior third of the frontal lobe. Alternatively, it could indicate that changes in frontal lobe volume are a relatively normal feature of successful aging, or that in subjects with dementia atrophy may only emerge at a late stage in the progression of the illness. This could account for the discrepancies between ante mortem and post mortem studies noted above.

Overall, we observed no MRI volumetric differences between DLB and VaD. This suggests other structural changes, in particular cerebral infarcts, possibly in conjunction with white matter changes,[39] are likely to be more useful in discriminating these conditions. Given that subjects with VaD performed better on tests of cognitive function, it raises the possibility that differences in neurochemical substrates may underlie the cognitive impairment in DLB.

The role of *APOE* in the pathogenesis of dementias remains to be determined. In particular, studies examining the relationship between the *APOE*-ϵ4 allele and neuroimaging changes have so far produced contrasting findings.[7-11,40] Our results accord with those of Jack et al.,[9] as we found no association between volumetric indices and the presence of the *APOE*-ϵ4 allele. Further, this finding was observed in subjects with AD as well as those with DLB and VaD. Although still controversial, this finding suggests atrophic processes are not directly linked to the presence of *APOE*-ϵ4 allele.

There is a growing body of evidence from both in vivo MRI and autopsy studies to suggest that the consensus criteria for DLB[1] should be modified to emphasize the relative preservation of temporal lobe structures in DLB compared with AD.

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