Psychological Medicine, 1999, **29**, 181–187. Printed in the United Kingdom

Magnetic resonance imaging differences between dementia with Lewy bodies and Alzheimer's disease: a pilot study

G. T. HARVEY, J. HUGHES, I. G. McKEITH, R. BRIEL, C. BALLARD, A. GHOLKAR, P. SCHELTENS, R. H. PERRY, P. INCE AND J. T. O'BRIEN[1]

From Cherry Knowle Hospital, Sunderland; Institute for Health of the Elderly, Castleside Unit, Department of Radiology, Department of Neuropathology and MRC Neurochemical Pathology Unit, Newcastle General Hospital and Newcastle University Department of Psychiatry, Royal Victoria Infirmary, Newcastle-upon-Tyne; and Department of Neurology, Academisch Ziekenhuis VU, Amsterdam, The Netherlands

ABSTRACT

Background. Temporal lobe atrophy on magnetic resonance imaging (MRI) has been suggested as a specific diagnostic marker for Alzheimer's disease (AD). No previous comparison with dementia with Lewy bodies (DLB) has been reported.

Method. T1-weighted MRI scans were performed on 11 subjects with AD (nine with NINCDS/ADRDA probable AD and two with neuropathologically proven AD) and nine subjects with DLB (four with probable DLB diagnosed by clinical criteria and five with neuropathologically proven DLB). Groups were matched for age, duration of illness and cognitive test score. Two raters, blind to diagnosis and neuropathological findings, measured the volumes of the frontal lobes, temporal lobes, hippocampi, parahippocampal gyri, amygdalae, and caudate nuclei using a computerized volumetric analysis system. Scans were also rated for medial temporal atrophy on a four-point scale by an experienced rater.

Results. AD subjects had significantly smaller left temporal lobes and parahippocampal gyri than those with DLB. Medial temporal atrophy was present in 9/11 AD cases (82%) and absent in 6/9 (67%) of DLB cases. Two neuropathologically confirmed cases of DLB had severe medial temporal atrophy; both had concurrent AD-type pathology in the temporal lobe (Braak stage 4).

Conclusions. This pilot study supports the hypothesis that a greater burden of pathology centres on the temporal lobes in AD compared with DLB, except in DLB cases with concurrent Alzheimer pathology. A larger study is needed to confirm these findings and to determine whether MRI has a role in assisting with the clinical differentiation between DLB and AD.

INTRODUCTION

Generalized cerebral atrophy is well recognized to occur in dementia (Jacoby & Levy, 1980) and atrophy of the medial temporal lobe structures, especially the hippocampus, is particularly marked in Alzheimer's disease (AD) (De la Monte, 1989; O'Brien, 1995; De Leon *et al.* 1997). It has been suggested that this pattern of atrophy may be useful in the distinction between AD and normal ageing (Jack *et al.* 1992; Jobst *et al.* 1997), benign senescent forgetfulness (Soininen *et al.* 1994) and late life depression and other causes of cognitive impairment (O'Brien *et al.* 1997). In a study of neuropathologically confirmed cases, Jobst *et al.* (1997) found that the width of the medial temporal lobe as measured by computerized tomographic (CT) scanning could distinguish AD from normal controls and those with other dementias with a sensitivity of 85% and specificity of 78%. However, the study included only four subjects with dementia with Lewy

[1] Address for correspondence: Dr J. T. O'Brien, Institute for the Health of the Elderly, Newcastle General Hospital, Newcastle-upon-Tyne NE4 6BE.

bodies (DLB), two of whom had atrophy of the medial temporal lobe. Atrophy of medial temporal lobe structures has also been reported in some patients with Parkinson's disease, both with and without dementia, in vascular dementia (Laasko *et al*. 1996) and in diffuse Lewy body disease (DLB) (Double *et al*. 1996). As such, the usefulness of temporal lobe atrophy in distinguishing AD from DLB remains to be determined.

Dementia with Lewy bodies has relatively recently been described as a common cause of dementia in old age, accounting for up to 20% of cases (McKeith *et al*. 1996), with characteristic neuropathological and clinical features. Intracytoplasmic, neuronal inclusion bodies (Lewy bodies) are found in the brainstem, subcortical nuclei, limbic cortex and neocortex, and clinical features include fluctuating cognitive impairment, visual hallucinations and parkinsonism. Consensus criteria for the clinical and neuropathological diagnosis of probable and possible DLB have been published (McKeith *et al*. 1996).

There have been no previously published studies of MRI appearances in DLB. Using CT scanning, Forstl *et al*. (1993) examined eight cases of NINCDS/ADRDA (McKhann *et al*. 1984) probable AD where Lewy body type pathology was present at post-mortem (designated as Lewy body variant of Alzheimer's disease). They found that these cases had more marked frontal cerebral atrophy than those with pure Alzheimer type pathology. In a neuropathological study, Double *et al*. (1996) reported frontal lobe atrophy in DLB, though did not study an AD group for comparison. In contrast, Mann & Snowden (1995) found no differences in atrophy of either the frontal or the temporal lobes in a neuropathological study comparing AD and DLB.

We compared regional patterns of atrophy on structural MRI in cases of AD and DLB. Our hypothesis was that frontal atrophy be significantly greater in patients with DLB, while atrophy of temporal lobe structures would be more prominent in patients with AD.

METHOD

Subjects

We included 20 subjects with dementia who had been referred to Newcastle University Department of Old Age Psychiatry. All subjects were clinically diagnosed by an experienced rater (I.G.M.) using the NINCDS/ADRDA criteria for AD (McKhann *et al*. 1984) and the Consensus criteria for DLB (McKeith *et al*. 1996). The clinical diagnoses were made using information from a thorough clinical assessment, which involved informant history, dementia blood screen and cognitive testing including the Mini-Mental State Examination (MMSE) (Folstein *et al*. 1975). Post-mortem neuropathological data subsequently became available for seven cases. Pathological diagnosis was made in accordance with CERAD criteria for AD and consensus guidelines for DLB (McKeith *et al*. 1996). Final diagnoses were: nine probable, two definite AD and four probable and five neuropathologically confirmed DLB (3 predominantly neocortical DLB, 2 predominantly limbic DLB). Demographic data (including length of history) was obtained from the casenotes by a rater blind to the final diagnosis and to the MRI findings.

MRI scanning

Each patient was scanned on a 0.5 Tesla IGE MV MAX imager. Initially localizers were obtained in two planes to correct for asymmetry of position. Sagittal localizers were obtained using a T1-weighted (TR 620, TE 21) sequence. Axial images were obtained using a dual echo (TR 2080, TE 40/80) sequence. Coronal images were then obtained using an inversion recovery sequence (TR 2000, TI 600 and TE 25). In each patient 14 coronal images were obtained perpendicular to the long axis of the temporal lobe and were of 5 mm thickness with 1 mm gap. These images were displayed with 1·2 magnification on a standard film format. Anatomical structures to be measured were defined with reference to a MRI anatomical atlas (Truwit & Lempert, 1995). In each subject a reference slice was identified as the image in which the temporal and frontal lobes become contiguous and in which the optic chiasm was seen. The areas of the lateral ventricles and the right and left caudate were measured on this slice. Right and left frontal lobes were measured on the three slices anterior to the reference slice (slices 1, 2 and 3). The right and left amygdalae were measured on the reference slice and one slice posteriorly (slices 0 and -1). Five slices posterior to the reference slice (slices -1, -2, -3, -4

and −5) were used to measure the right and left parahippocampal gyri, the most posterior slice coinciding with the pulvinar of the thalamus; slices −2 to −5 were used to measure the right and left hippocampi. Slices 3, 2, 1, 0 −1, −2, −3, −4 and −5 were used to measure the right and left temporal lobes, the intracranial area and the whole brain area, excluding the medulla and brainstem. This approach was adopted because the coronal slices did not extend to the very anterior surface of frontal lobe in all cases. However, all cases had at least three slices anterior to the reference slice allowing a comparable segmented frontal lobe volume to be calculated for every patient.

Anatomical regions were outlined by visual cursor tracing and image intensity thresholding and volumes calculated using a commercially available, computerized, software package (SEESCAN, Cambridge, UK). This was done by two independent raters who were blind to the clinical diagnosis. Five randomly selected cases were evaluated on three separate occasions to measure intra-rater reliability. In addition, hard copies of the coronal series were rated for medial temporal atrophy (MTA) on the right and left using a previously described 5-point scale (Scheltens *et al.* 1992), which assesses MTA on the basis of increasing width of the choroidal fissure and temporal horn and decreasing height of the hippocampal formation (0 = normal, 4 = severe MTA). Scores for right and left were summed to give a total score of MTA for each subject (0–8).

Statistical analysis

Intra-rater reliability was assessed using the coefficient of variation (standard deviation/mean). Inter-rater reliability was calculated using the Pearson's correlation coefficient (r). The ventricle to brain ratio (VBR) was calculated as the ratio of the area of the lateral ventricle to the whole brain area on the reference slice (slice 0). Anatomical volumes were calculated by multiplying regional areas by slice thickness and summing across the relevant slices. Volumes were normalized to control for head size by dividing by total intracranial volume and multiplying by 10^3. Groups comparisons were performed using t tests with the Statistical Package for the Social Sciences (SPSS; Norušis, 1990). Because of the small sample size results were confirmed using non-parametric (Mann–Whitney) tests, which did not alter any of the results presented. Correlations between normalized temporal and frontal lobe volumes and clinical variables (age, length of history, MMSE score) were performed using Pearson's correlation coefficient.

RESULTS

There were no significant differences between groups in age, length of history of dementia or MMSE score at the time of the scan (Table 1). The VBR was similar in the two groups; the mean VBR in the DLB group was 0·066 (S.D. = 0·036), and in the AD group was 0·087 (S.D. = 0·036), ($P = 0{\cdot}21$). Intra-rater reliability was very good with coefficient of variation as follows: frontal lobes 1·3%, temporal lobes 3·0%, parahippocampal gyrus 3·2%, hippocampus 7·5%, amygdala 6·8% and caudate 8·5%. Inter-rater reliability as indicated by correlation coefficients between raters was also good; frontal lobe $r = 0{\cdot}93$, temporal lobe $r = 0{\cdot}93$, parahippocampal gyrus $r = 0{\cdot}51$, hippocampus $r = 0{\cdot}89$, amygdala $r = 0{\cdot}78$, and caudate $r = 0{\cdot}62$ (all $P < 0{\cdot}05$). Mean volume differences between raters were less than 5% for all areas except hippocampus (9% for left, 10% for right) and caudate (18% for left, 12·5% for right).

Comparison between the diagnostic groups (Table 2) showed a significantly smaller left temporal lobe volume in AD subjects compared to those with DLB. The mean corrected volume of left temporal lobe in the AD subjects was 59·21 (S.D. = 9·36), and in those with DLB was 68·00 (S.D. = 6·78) ($P = 0{\cdot}03$). There was also a difference in the volume of the left parahippocampal gyrus, again the AD group showing a volume reduction compared to DLB. The mean corrected volume of parahippocampal gyrus in

Table 1. *Demographic characteristics of patients with Alzheimer's disease* (*AD*) *and dementia with Lewy bodies* (*DLB*)

	AD ($N = 11$)	DLB ($N = 9$)
Age in years (mean ± S.D.)	78·8 ± 5·9	74·8 ± 6·5
Sex (m/f)	4/7	4/5
MMSE (mean ± S.D.)	18·3 ± 2·8	19·1 ± 6·5
Duration of dementia in months (mean ± S.D.)	38·2 ± 19·7	42·7 ± 25·2

Table 2. *Normalized regional brain volumes in Alzheimer's disease (AD) and dementia with Lewy Bodies (DLB)*

	AD ($N = 11$)	DLB ($N = 9$)	P
Hippocampus			
Right	2·70 ± 0·87	3·06 ± 0·92	0·38
Left	2·68 ± 0·78	3·13 ± 0·92	0·24
Parahippocampus			
Right	4·99 ± 0·62	5·23 ± 1·28	0·58
Left	4·70 ± 0·42	5·36 ± 0·62	0·02*
Amygdala			
Right	3·13 ± 0·69	3·40 ± 0·66	0·39
Left	2·80 ± 0·73	3·38 ± 0·74	0·09
Caudate			
Right	1·43 ± 0·27	1·37 ± 0·37	0·71
Left	1·43 ± 0·29	1·46 ± 0·39	0·86
Frontal lobe			
Right	67·89 ± 7·23	69·27 ± 7·00	0·67
Left	66·41 ± 6·72	67·96 ± 7·84	0·64
Temporal lobe			
Right	65·48 ± 11·91	71·07 ± 5·87	0·19
Left	59·21 ± 9·36	68·00 ± 6·78	0·03*

Volumes expressed as mean ± standard deviation and calculated as volume of region divided by intracranial volume and multiplied by 1000). P values refer to independent t tests (2-tailed).
* $P < 0·05$.

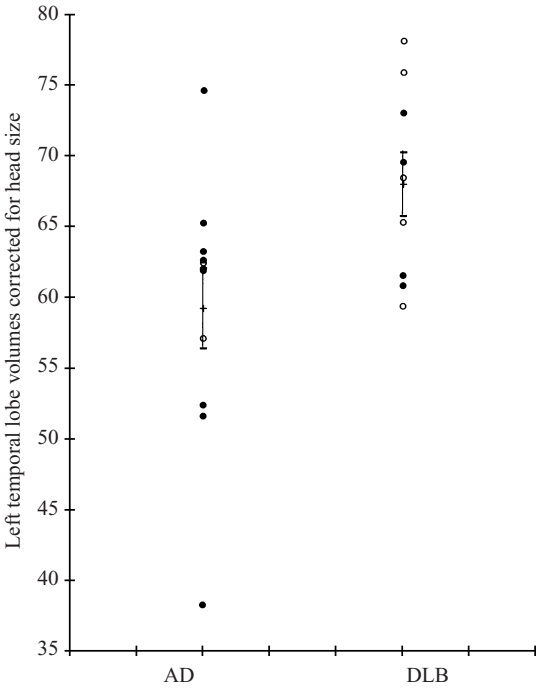

FIG. 1. Scatter plot of left temporal lobe volumes corrected for headsize, in Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). (Mean and S.E.M. indicated; ○, neuropathologically confirmed cases.)

the AD group was 4·70 (S.D. = 0·42) and in the DLB group was 5·36 (S.D. = 0·62), ($P = 0·02$). No differences were found in the frontal lobe volumes. A scatter plot of the left temporal lobe size by diagnosis is shown in Fig. 1.

MTA ratings for the AD subjects were as follows: 2, 2, 6, 6, 6, 6, 7, 7, 8, 8, 8. For the DLB subjects they were: 0, 2, 2, 4, 5, 5, 6, 8, 8. Using a cut-off of six or more to denote severe MTA, 9/11 AD subjects had severe MTA compared with only 3/9 DLB subjects. This difference just failed to reach statistical significance (Fisher's exact test, 2-tailed, $P = 0·065$). Two of the three DLB cases with severe MTA have come to post-mortem (one limbic, one neocortical DLB) and both had concurrent Alzheimer-type pathology in the temporal lobes in the form of tangles (Braak stage 4). Of the three DLB cases who did not show severe MTA, two had neocortical DLB and one limbic DLB. Both AD cases that had post-mortem confirmation had severe MTA (scores 6 and 8). Examples of scans are shown in Fig. 2.

Examination of the relationship of the frontal and temporal lobe sizes with the clinical variables of age, length of history and cognitive test score showed a significant positive correlation between the size of the right temporal lobe and MMSE score in the AD group, ($r = 0·61$, $P = 0·05$). This correlation was not present on the left side, ($r = 0·36$, $P = 0·23$). There was no equivalent relationship found in the DLB group, (right temporal lobe and MMSE score, $r = -0·03$, $P = 0·94$; left temporal lobe and MMSE score, $r = -0·01$, $P = 0·98$). No other correlations were found to be significant.

DISCUSSION

This is the first study to compare MRI appearances in DLB with AD. Our first hypothesis, that AD subjects would have greater atrophy of temporal lobe structures than those with DLB, was supported using both volumetric and visual assessment. This fits with previous reports that suggest selective patterns of atrophy in AD (De la Monte *et al.* 1989; Jack *et al.* 1992; O'Brien, 1995; Jobst *et al.* 1997). The occurrence of medial temporal lobe atrophy early in the course of AD is consistent with the observation that amnesia is a central and early clinical feature of the disease, because of the known importance of

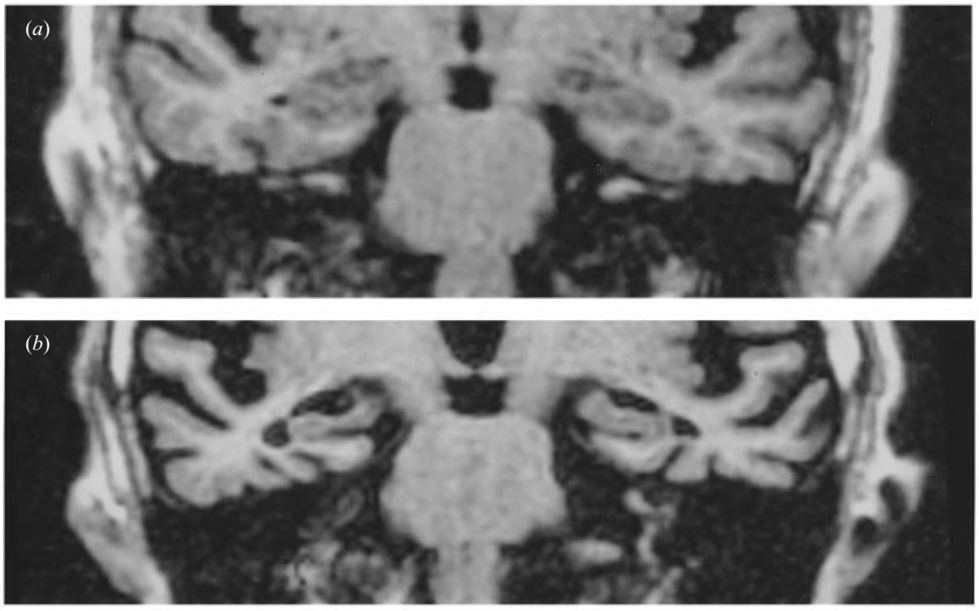

FIG. 2. Sample coronal MRI scans of medial temporal lobe showing : (*a*) relative absence of medial temporal atrophy (combined visual rating 0) in a subject with dementia with Lewy bodies; and (*b*) severe MTA (combined visual rating 6) in a patient with Alzheimer's disease. Post-mortem confirmation of diagnosis has been obtained in both these cases.

hippocampus and temporal lobe in mnemonic function in humans. In contrast to AD, cognitive impairment in DLB has a different profile, with impairments in visuospatial function and attention as prominent features, while memory disturbance often appears only later (McKeith *et al*. 1996). Differences have been found also in the neuropathology of the medial temporal lobe between DLB and AD, showing significantly lower numbers of neurofibrillary tangles in the CA/2 and CA/3 hippocampal regions of patients with DLB (Ince *et al*. 1991). This, together with our findings of relative sparing of temporal lobe structures on MRI, may explain some of the differences in cognitive profile of the two dementias. However, it should be noted that reports of selective medial temporal lobe atrophy in AD are not consistent and that studies have shown atrophy in this area in cases of dementia with Lewy body pathology (Double *et al*. 1996; Laasko *et al*. 1996; Jobst *et al*. 1997). Our results may provide an explanation for such discrepant results as the two DLB cases that had severe medial temporal atrophy on visual ratings had concurrent Alzheimer pathology. Although based on only five cases, it appeared to be the presence of Alzheimer-type pathology, rather than limbic *versus* neocortical Lewy body pathology, which is associated with temporal lobe atrophy in DLB subjects. This requires confirmation in a larger series, though if confirmed MRI may have a role in identifying *in vivo* DLB subjects with concurrent Alzheimer pathology. In support of this, both Huesgen *et al*. (1993) and Nagy *et al*. (1996) found a strong correlation between temporal lobe volume loss on MRI and tangle count at post-mortem. It is also interesting that we found a significant correlation between MMSE score and temporal lobe volume in the AD but not the DLB group. This further supports the view that the initial basis for cognitive decline in DLB lies outside atrophic change and Alzheimer-type pathology in the temporal lobe.

Studies of frontal lobe pathology in DLB are also inconclusive; Forstl *et al*. (1993) found greater frontal atrophy in DLB, but this was not supported by Mann & Snowden (1995) who found no differences post-mortem between AD and DLB. In addition, Lippa *et al*. (1994) report that neuronal counts in the frontal cortex do not differ in DLB and AD cases coming to autopsy. We found neither a significant frontal volume difference nor trend towards a difference, be-

tween groups. We may have failed to find a difference because of the differing imaging modalities and different patient selection. Subjects included by Forstl *et al*. had all fulfilled NINCDS criteria for probable AD during life but had unsuspected DLB at post-mortem. In contrast our subjects all fulfilled clinical criteria for DLB. Another possibility is that we failed to find a significant difference either because of insufficient power of the study or because frontal lobe volume could not be fully assessed as the imaging protocol did not include the most anterior part of the frontal lobes in all subjects. However, major strengths of this study are the use of two blind raters who demonstrated excellent intra and inter-rater reliability, the use of rigorous standardized diagnostic criteria and the similarity of the groups with respect to the important variables of age, MMSE score and length of history.

We anticipate the clinical diagnosis to be accurate in an estimated 90% of our cases, based on studies of the sensitivity and specificity of similar standardized diagnostic criteria used previously (Boller *et al*. 1989; McKeith *et al*. 1994). This is supported by our clinical diagnoses, which were correct in six of the seven cases for which we had neuropathological data. One subject was re-allocated to the AD group from the DLB group after post-mortem. Of interest, his MRI scan had shown severe MTA on visual inspection.

Using the optimum cut-off level which separated groups (Fig. 2), temporal lobe volume would have correctly identified nine of the 11 AD subjects and six of the nine DLB subjects, with exactly the same discrimination obtained using visual ratings of MTA. Clearly, these figures must be regarded as very preliminary given the very small numbers studied and the arbitrary selection of an optimal cut-off for both volumetric and visual rating data. However, they raise the possibility that temporal lobe MRI may be useful in differentiating AD from DLB. Our finding of differences in temporal lobe volumes in the absence of differences in VBR or frontal lobe volumes shows some specificity for this result. Timing of the scans in relation to disease severity may be important, since Jobst *et al*. (1997) have suggested that medial temporal lobe atrophy may be an early feature in AD, yet occur in other dementias later in the course However, this cannot be the explanation in this study since groups were matched for severity of dementia. An *in vivo* investigation which may assist with diagnosis would be a major advance, since the accurate clinical diagnosis of DLB is important since such patients show a more rapid cognitive decline and may have serious adverse reactions to antipsychotics (McKeith *et al*. 1996). Further study of the usefulness of MRI in differentiating between AD and DLB is required, with the assessment of a larger number of subjects with larger magnet strength, thinner slice thickness and autopsy confirmation of diagnosis in more cases.

REFERENCES

Boller, F., Lopez, O. L. & Moossy, J. (1989). Diagnosis of dementia: clinicopathologic correlations. *Neurology* **39**, 76–79.

De la Monte, S. (1989). Quantification of cerebral atrophy in preclinical and end-stage Alzheimer's disease. *Annals of Neurology* **25**, 450–459.

De Leon, M. J., George, A. E., Golomb, J., Tarshish, C., Convit, A., Kluger, A., De Santi, S., McRae, T., Ferris, S. H., Reisberg, B., Ince, C., Rusinek, H., Bobinski, M., Quinn, B., Miller, D. C. & Wisniewski, H. M. (1997). Frequency of hippocampal formation atrophy in normal aging and Alzheimer's disease. *Neurobiology of Aging* **18**, 1–11.

Double, K. L., Halliday, G. M., McRitchie, D. A., Reid, W. G., Hely, M. A. & Morris, J. G. (1996). Regional brain atrophy in idiopathic Parkinson's disease and diffuse Lewy body disease. *Dementia* **7**, 304–313.

Folstein, M. F., Folstein, S. E. & McHugh, P. R. (1975). 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* **12**, 189–198.

Forstl, H., Burns, A., Luthert, P., Cairns, N. & Levy, R. (1993). The Lewy body variant of Alzheimer's disease: clinical and pathological findings. *British Journal of Psychiatry* **162**, 385–392.

Huesgen, C. T., Burger, P. C., Crain, B. J. & Johnson, G. A. (1993). In vitro microscopy of the hippocampus in Alzheimer's disease. *Neurology* **43**, 145–152.

Ince, P., Irving, D., MacArthur, F. & Perry, R. (1991). Quantitative neuropathological study of Alzheimer-type pathology in the hippocampus: comparison of senile dementia of Alzheimer type, senile dementia of Lewy body type, Parkinson's disease and non-demented elderly control patients. *Journal of the Neurological Sciences* **106**, 142–152.

Jack, Jr, C. R., Petersen, R. C., O'Brien, P. C. & Tanlelos, E. C. (1992). MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. *Neurology* **42**, 183–188.

Jacoby, R. J. & Levy, R. (1980). Computed tomography in the elderly. 2. Senile dementia: diagnosis and functional impairment. *British Journal of Psychiatry* **136**, 256–269.

Jobst, K. A., Lin, P. D. & Shepstone, B. J. (1997). Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, x-ray CT, and apo E4 in medial temporal lobe dementias. *International Psychogeriatrics* **9** (suppl. 1), 191–223.

Laakso, M. P., Partanen, K., Riekkinen Jr, P., Lehtovirta, M., Helkala, E. L., Hallikainen, M., Hanninen, T., Vainio, P. & Soininen, H. (1996). Hippocampal volumes in Alzheimer's disease,

Parkinson's disease with and without dementia, and in vascular dementia; an MRI study. *Neurology* **46**, 678–681.

Lippa, C. F., Smith, T. W. & Swearer, J. M. (1994). Alzheimer's disease and Lewy body disease; a comparative clinicopathological study. *Annals of Neurology* **35**, 81–88.

McKeith, I. G., Fairbairn, A. F., Bothwell, R. A., Moore, P. B., Ferrier, I. N., Thompson, P. & Perry, R. H. (1994). An evaluation of the predictive validity and inter-rater reliability of clinical diagnostic criteria for senile dementia of Lewy body type. *Neurology* **44**, 872–877.

McKeith, I. G., Galasko. D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., Salmon, D. P., Lowe, J., Mirra, S. S., Byrne, E. J., Lennox, G., Quinn, N. P., Edwardson, J. A., Ince, P. G., Bergeron, C., Burns, A., Miller, B. L., Lovestone, S., Collerton, D., Jansen, E. N., Ballard, C., de Vos, R. A., Wilcock, G. K., Jellinger, K. A. & Perry, R. H. (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* **47**, 1113–1124.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. & Stadlan, E. (1984). Clinical diagnosis of Alzheimer's disease; report of the NINCDS/ADRDA work group under the auspices of the Department of Health and Human Task Force in Alzheimer's disease. *Neurology* **34**, 939–944.

Mann, D. M. A. & Snowden, J. S. (1995). The topographic distribution of brain atrophy in cortical Lewy body disease: comparison with Alzheimer's disease. *Acta Neuropathologica* **89**, 178–183.

Nagy, Z., Jobst, K. A., Esiri, M. M., Morris, J. H., King, E. M., MacDonald, B., Litchfield, S., Barnetson, L. & Smith, A. D. (1996). Hippocampal pathology reflects memory deficit and brain imaging measurements in Alzheimer's disease: clinicopathologic correlations using three sets of pathologica diagnostic criteria. *Dementia* **7**, 76–81.

Norušis, M. J. (1990). *Statistical Package for the Social Sciences* SPSS: Chicago.

O'Brien, J. T. (1995). Is hippocampal atrophy on magnetic resonance imaging a marker for Alzheimer's disease? *International Journal of Geriatric Psychiatry* **10**, 431–435.

O'Brien, J. T., Desmond, P., Ames, D., Schweitzer, I. & Tress, B. (1997). The differentiation of depression from dementia by temporal lobe magnetic resonance imaging. *Psychological Medicine* **27**, 1267–1275.

Scheltens, P., Leys, D., Barkhof, F., Huglo, D., Weinstein, H. C., Vermersch, P., Kuiper, M., Steinling, M., Walters, E. & Valk, J. (1992). Atrophy of the medial temporal lobes on MRI in 'probable' Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *Journal of Neurology, Neurosurgery and Psychiatry* **55**, 967–972.

Soininen, H. S., Partanen, K., Pitkanen, A., Vainio, P., Hanninen, Y., Koivisto, K. & Riekkinen, P. J. (1994). Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment; correlation to visual and verbal memory. *Neurology* **44**, 1660–1668.

Truwit, C. L. & Lempert, T. E. (1995). *High Resolution Atlas of Cranial Neuroanatomy*. Williams & Wilkins: Maryland.