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Magnetic Resonance Imaging in Lewy Body Dementias

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Key Words
Magnetic resonance imaging · Lewy bodies · Parkinson's disease dementia · Dementia · Alzheimer's disease

Abstract
Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) share common clinical, neuropsychological and pathological features. In clinical diagnosis, distinguishing between these conditions and other dementia subtypes such as Alzheimer's disease (AD) can be difficult. Despite the development of consensus diagnostic criteria, sensitivity for diagnosis remains low, especially outside specialist centres. Neuroimaging techniques using magnetic resonance (MR) can assess changes in structure, microstructure through diffusion tensor imaging and metabolism using spectroscopy and cerebral perfusion. Identification of such changes may contribute to our understanding of the disease process, assist in refining ante-mortem diagnosis and allow disease progression to be measured. This may be both clinically useful and a tool for assessing outcome in therapeutic trials. DLB and PDD share a similar pattern of MRI changes including global brain volume loss, a predominantly subcortical pattern of cerebral atrophy and structural preservation of the medial temporal lobe compared to AD. This review summarises the application and findings from MR studies in DLB and PDD to provide further insight into the similarities between the conditions, highlight the potential for the clinical application of MR techniques and outline promising areas for further research.

Introduction

Lewy body dementias (LBD) include dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) and share common clinical and pathological features [1]. DLB is one of the most common forms of dementia, accounting for approximately 15% of all cases at autopsy [2]. The development of dementia in Parkinson's disease (PD) is a frequently recognised complication of a relatively common neurodegenerative disease. The risk of progression to dementia in PD increases with age and has been shown to affect over 70% of PD patients in an 8-year prospective longitudinal study, 6 times the rate in healthy control subjects [3].

DLB and PDD are differentiated from other dementia subtypes by the presence of Lewy body pathology: α-synuclein fibrillary aggregates which form neuronal in-

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clusion bodies (Lewy bodies) and Lewy neurites. Brain stem nuclei are usually affected in varying degrees; other affected areas include limbic and neocortical areas [4].

DLB and PDD have a similar clinical phenotype; features include spontaneous motor parkinsonism, recurrent visual hallucinations and fluctuating cognitive impairment. Neuropsychiatric changes include prominent attentional dysfunction and impairment of executive function, visuospatial function, and aspects of language and memory retrieval. Other common symptoms relate to autonomic dysfunction and neuroleptic sensitivity reactions [4]. Given the similarities between DLB and PDD, the separation between the 2 conditions has been determined by consensus based on the duration of Parkinsonian features relative to the development of dementia the requirement being less than 12 months for DLB [2]. Whilst PDD and DLB are not necessarily the same disorder, they may represent different points on the same and possibly continuous spectrum of Lewy body disorders [1]. The currently available treatment options such as the cholinesterase inhibitors, the provision of prognostic information and the avoidance of potentially life-threatening neuroleptic medication highlight the importance of early recognition and accurate diagnosis of LBD.

Clinically differentiating DLB from other dementia subtypes such as Alzheimer's disease (AD) and vascular dementia (VaD) can be equally difficult. Consensus criteria for DLB were developed to assist with the ante-mortem diagnosis [4]. Although the criteria have a high specificity (79–100%), the sensitivity is low, so that the diagnosis will be missed in many cases during life [5]. These criteria were revised in 2005 in an attempt to improve case detection, but the accuracy of the new criteria has not yet been systematically assessed [4].

In light of the poor sensitivity of the consensus criteria, it is important to establish additional markers which, when combined with clinical assessment, can improve diagnostic accuracy. Neuroimaging is a clear choice to obtain additional information on brain changes. MRI provides excellent soft tissue discrimination without using ionising radiation. Advanced MR techniques provide a wealth of information including structural changes, microstructural changes through diffusion tensor imaging, tissue energetics and metabolism through spectroscopy and cerebral perfusion. MR neuroimaging in LBD may assist in providing pathophysiological information as well as increasing the accuracy of ante-mortem diagnosis.

This paper reviews the MRI literature in DLB and PDD to determine whether there are characteristic imaging changes that may assist with the diagnosis, and given the clinical and pathological similarities between the conditions, how imaging changes may provide further insights into the relationship between DLB and PDD.

Methods

The literature search was completed using the computer database MEDLINE accessed via the Web of Knowledge. Two separate searches for relevant papers published from January 1966 to July 2009 were completed concurrently. They included the key words: (1) Lewy and Mag* Res* and (2) Parkinson, dementia and Mag* Res*. Papers were then limited to those published in English and related to human studies. The search produced a total of 406 papers which were screened individually by title and abstract searching for information pertaining to MR in DLB or PDD. The bibliographies of relevant papers were also hand searched for additional references. Finally, only studies including 5 or more subjects were considered as providing representative data. Fifty original research papers were identified. No previous review of MR techniques in DLB and PDD was identified.

Structural Magnetic Resonance Imaging

Conventional MRI data has been used extensively in the study of neurodegenerative disorders to examine regional changes in tissue volume. Several methods are routinely used to analyse MRI data including visual inspection, region of interest (ROI) analysis or voxel based morphometry (VBM).

Visual rating and ROI analysis methods depend on the appropriate a priori choice of structures to be analysed while VBM performs a point by point analysis of each voxel within the image across whole data sets allowing unbiased and largely operator-independent data analysis. All 3 methods have been used to investigate structural imaging changes in LBD. Table 1 summarises the findings of the structural MRI studies.

Cortical Atrophy

A common finding in structural MR studies in dementia is whole brain atrophy when compared with control subjects with widespread grey matter reduction in the frontal, temporal and parietal areas [6–9].

Using VBM, Burton et al. [10] compared subjects with PD (n = 24), PDD (n = 31), DLB (n = 20), AD (n = 35) and controls (n = 39). They observed a diffuse pattern of grey matter atrophy affecting the temporal, parietal, middle and inferior frontal gyri and the occipital lobe in PDD when compared with control subjects, with no significant

Table 1. Structural MRI studies

Author	Year	Control	DLB	PDD	AD	MRI	MRI findings
Cortical atrophy							
Huber et al. [69]	1989	10	0	10 (10) [b]	0	1.5 T visual image analysis	PDD: brain surface area, ventricular measurements, supra- and infra-tentorial lesions were not significantly different from PD
Middelkoop et al. [19]	2001	24	23	0	25	1.0 T semi-automated segmentation	DLB: occipital lobe – no difference in raw or normalised volume compared with controls and AD
Burton et al. [7]	2002	25	25	0	30	1.0 T VBM	DLB: grey matter atrophy – diffuse involving temporal, frontal, parietal lobes and insular cortices. Occipital lobe – no grey matter loss
Ballmaier et al. [8]	2004	38	16	0	29	1.5 T cortical pattern matching	DLB: temporal lobe and orbitofrontal cortices – relative preservation compared with AD
Burton et al. [10]	2004	36	17	26 (31) [b]	28	1.5 T VBM	PDD: no significant differences to DLB. Grey matter atrophy: widespread, temporal lobes, occipital lobes, right frontal and left parietal lobe. Occipital grey matter atrophy compared with PD
Ramirez-Ruiz et al. [70]	2005	0	0	16/8 (13/11) [b]		1.5 T VBM	PDD: progressive grey matter loss predominantly in the hippocampal, temporal and occipital lobes
Summerfield et al. [29]	2005	13	0	16 (16) [b]	0	1.5 T VBM	PDD: cortical and subcortical grey matter atrophy – hippocampus, thalamus and anterior cingulate most affected compared with controls. Left superior temporal gyrus and right hippocampus atrophy compared with PD
Beyer et al. [9]	2007	20	18	15	21	1.5 T VBM	PDD: grey matter atrophy – diffuse, less than DLB
Whitwell et al. [15]	2007	72	72	0	72	1.5 T VBM and ROI	DLB: grey matter atrophy – dorsal midbrain, hypothalamus and substantia innominata. Relative sparing of the hippocampus and temporoparietal cortex
Beyer and Aarsland [13]	2008	0	0	15	0	1.5 T VBM, segmented images modulated and smoothed	PDD: group that developed dementia early had more areas of atrophy than the late dementia group-medial frontal gyrus, right precuneus, left inferior parietal lobule, superior frontal gyrus and middle temporal gyrus. In the late dementia group, there was atrophy in the inferior frontal gyrus and in unmodulated images, reduced grey matter in the insula
Rate of cerebral atrophy							
O'Brien et al. [21]	2001	20	10	0	9 (9) [a]	1.0 T longitudinal, quantification of boundary shift integral	DLB: 12-month whole brain atrophy rate increased (1.4% per year) compared with controls (0.5–0.7% per year), no significant difference between dementia groups: AD (2.0% per year), VaD (1.9% per year)
Burton et al. [20]	2005	24	0	13 (18) [b]	0	1.5 T boundary shift integral	PDD: 12-month whole brain atrophy greater (1.12 ± 0.98% per year) compared with PD (0.31 ± 0.69% per year) and controls (0.34 ± 0.76% per year)
Whitwell et al. [22]	2007	25	9	0	12 (13+12+5+5) [a]	1.5 T semi-automated segmentation and manual tracing	DLB: whole brain atrophy rate: 0.4% per year, ventricular expansion rate 4.8% per year, not significantly different from controls and less than AD
Medial temporal lobe							
Laakso et al. [32]	1996	34	0	8 (12) [b]	50 (9) [a]	1.5 T ROI hippocampus	PDD: hippocampus – raw volume smaller than AD but not significantly
Hashimoto et al. [6]	1998	27	27	0	27	1.5 T semi-automated segmentation and manual tracing	DLB: hippocampal formation – relative preservation compared with AD
Barber et al. [23]	1999	26	26	0	28 (24) [a]	1.0 T MTA visual rating scale	DLB: MTL – relative preservation. Temporal lobe atrophy correlates with memory impairment and age
Harvey et al. [25]	1999	0	9	0	11	0.5 T visual rating and volumetric analysis	DLB: MTL – relative preservation

Table 1 (continued)

Author	Year	Control	DLB	PDD	AD	MRI	MRI findings
Barber et al. [28]	2000	26	27	0	25 (24) [a]	1.0 T ROI analysis semi-automated segmentation	DLB: larger temporal lobe, hippocampal and amygdala volume compared to AD
Barber et al. [24]	2000	26	26	0	22	1.0 T ROI analysis	DLB: MTL – relative preservation
Burton et al. [7]	2002	25	25	0	30	1.0 T VBM	DLB: MTL – relative preservation compared with AD
Camicioli et al. [30]	2003	12	0	10 (10) [b]	11	volumetric	PDD: reduced hippocampal volume (control > PD > PDD > AD)
Ballmaier et al. [8]	2004	38	16	0	29	1.5 T cortical pattern matching	DLB: temporal lobe – relative preservation (hippocampus, parahippocampus and amygdala) compared with AD
Burton et al. [10]	2004	36	17	26 (31) [b]	28	1.5 T VBM	PDD: no significant differences to DLB. MTL – relative preservation compared with AD
Hanyu et al. [37]	2005	18	17	0	31	1.5 T magnetisation transfer ratios ROI	DLB: lower hippocampal MTR than controls, higher hippocampal MTR than AD (controls > DLB > AD DLB)
Junque et al. [31]	2005	16	0	16 (16) [a]	0	1.5 T manual tracing ROI	PDD: hippocampal (20%) atrophy compared with controls. PD: hippocampal atrophy (10%) compared with controls (not statistically significant)
Summerfield et al. [29]	2005	13	0	16 (16) [b]	0	1.5 T VBM	PDD: cortical and subcortical grey matter atrophy – hippocampus, thalamus and anterior cingulate most affected compared with controls. Left superior temporal gyrus and right hippocampus atrophy compared with PD
Tam et al. [26]	2005	39	25	31 (33) [b]	31	1.5 T visual rating scale	PDD: MTA – relative preservation compared with AD, similar to DLB
Beyer et al. [9]	2007	20	18	15	21	1.5 T VBM	PDD and DLB: MTL – relative preservation, compared with AD
Whitwell et al. [15]	2007	72	72	0	72	1.5 T VBM and ROI	DLB: relative sparing of the hippocampus and temporoparietal cortex
Bouchard et al. [34]	2008	44	0	13 (44) [b]	0	1.5 T manual tracing of hippocampus, amygdala and intracranial volume	PDD: hippocampal atrophy predominantly in the head of the hippocampus
Ibarretxe-Bilbao et al. [35]	2008	56	0	9 (16+19) [b]	0	1.5 T VBM, ROI	PDD: grey matter loss involving entire hippocampus compared with controls. PD + visual hallucinations: hippocampal loss confined to the head of the hippocampus
Sabbatoli et al. [33]	2008	28	14	0	28	1.0 T manual tracing, radial atrophy mapping	DLB: hippocampus – 10–20% volume loss (compared with controls) affecting regions CA1, dorsal midline aspect CA2–3 and subiculum and presubiculum. Atrophy less than AD
Kenny et al. [36]	2008	37	20	30 (31) [b]	26	1.5 T manual segmentation	DLB and PDD: total normalised entorhinal cortex volumes smaller in dementia (AD, PDD and DLB) compared with controls. Smaller entorhinal cortex volume in DLB compared with PD
Burton et al. [27]	2009	0	23	0	11 (12) [a]	1.0 T (20 subjects) 1.5 T (26 subjects) Scheltens standardised visual rating scale	DLB: less hippocampal atrophy than AD on MRI in pathologically confirmed cases
Subcortical structures							
Hashimoto et al. [6]	1998	27	27	0	27	1.5 T semi-automated segmentation and manual tracing	DLB and AD: amygdala atrophy comparable
Barber et al. [28]	2000	26	27	0	25 (24) [a]	1.0 T ROI analysis semi-automated segmentation	DLB: larger amygdala volume compared to AD. Ventricular volume increased compared with controls, although whole brain volume was relatively preserved

Table 1 (continued)

Author	Year	Control	DLB	PDD	AD	MRI	MRI findings
Hanyu et al. [71]	2001	12	0	6 (11) [b]	(6) [a]	1.5 T MTR, ROI	PDD: lower MTR in the subcortical white matter including frontal and genu of the corpus callosum compared with controls
Barber et al. [43]	2002	25	26	0	21 (18) [a]	1.0 T ROI volumetric caudate nucleus	DLB: caudate nucleus – no significant volumetric difference between dementia groups
Almeida et al. [42]	2003	35	0	20	27	1.5 T volumetric segmentation whole brain and caudate nucleus	PDD: caudate nucleus volume – no significant difference between controls and PD
Cousins et al. [41]	2003	37	14	0	27	1.5 T volumetric, semi-automated and manual segmentation	DLB: putamen – smaller compared with controls but not AD. When normalised to total intracranial volume reduced compared with controls and AD
Brenneis et al. [45]	2004	10	10	0	10	1.5 T VBM	DLB: basal forebrain atrophy compared with AD. Lateral prefrontal cortex and left premotor cortical atrophy compared with controls
Burton et al. [10]	2004	36	17	26 (31) [b]	28	1.5 T VBM	PDD: no significant differences to DLB. Grey matter atrophy: widespread, subcortical regions include right caudate tail and putamen and bilateral thalamus
Junque et al. [31]	2005	16	0	16 (16) [a]	0	1.5 T manual tracing ROI	PDD: amygdala (21%) atrophy compared with controls. PD: amygdala atrophy (11%) compared with controls, not statistically significant
Summerfield et al. [29]	2005	13	0	16 (16) [b]	0	1.5 T VBM	PDD: cortical and subcortical grey matter atrophy – hippocampus, thalamus and anterior cingulate most affected compared with controls
Wiltshire et al. [72]	2005	27	0	25 (24) [b]	16	1.5 T ROI	PDD (and PD): callosal atrophy not significantly different from controls or AD
Hanyu et al. [44]	2007	28	31	0	122 (34) [a]	1.5 T substantia innominata thickness measured	DLB: substantia innominata – smaller than AD
Whitwell et al. [15]	2007	72	72	0	72	1.5 T VBM and ROI	DLB: grey matter atrophy – dorsal midbrain, hypothalamus and substantia innominata. Relative sparing of the hippocampus and temporoparietal cortex
White matter hyperintensities							
Barber et al. [48]	1999	26	27	0	28 (25) [a]	1.0 T semi-quantitative visual rating scale	DLB: PVH increased compared with controls. WMH decreased compared with controls
Barber et al. [47]	2000	0	27	0	25	1.0 T semi-automated segmentation	DLB: PVH increase associated with ventricular dilatation. DWMH associated with history of hypertension
Beyer et al. [50]	2007	20	0	16 (19) [b]	0	1.5 T semi-quantitative visual rating scale	PDD: more WMH in the deep white matter and periventricular areas compared with PD subjects, however, not increased compared with controls
Burton et al. [49]	2006	33	14	13	23	1.5 T volumetric analysis	DLB: WMH baseline similar to controls, no significant increase in progression rate over 12 months. PDD: WMH increased progression rate compared with controls

[a] Number of subjects in another dementia comparison group. [b] PD comparison group.

difference between the cortical atrophy profile in PDD and DLB. A VBM study by Beyer et al. [9] in PDD (n = 15), DLB (n = 18), AD (n = 21) and healthy controls (n = 20) also found reduced grey matter in the temporal, parietal and occipital lobes. However, in contrast to Burton et al. [10] the changes were more pronounced in DLB than PDD. The authors suggest several explanations for the differing result: (1) the clinical criteria for PDD used by Burton et al. [10] required the presence of visual hallucinations or cognitive fluctuations, so the PDD subjects selected had a clinically similar phenotype to the DLB subjects, possibly increasing the likelihood of similar cerebral changes and (2) a shorter duration of illness in the PDD group than in the previous study which may be associated with more severe morphological changes. The DLB group included by Beyer et al. [9] was also older; and, although not significant, may have influenced the differing results. However, the increased cortical amyloid deposition in DLB compared to PDD, reported in pathological and amyloid positron emission tomography (PET) studies, would be consistent with the finding of greater structural cortical change in DLB [11, 12]. Interestingly, a recent VBM study in PDD has reported greater cortical atrophy in patients who developed dementia early in the course of their disease (<8 years) compared with those who developed dementia later in the course of their illness (>8 years) [13]. Although they did not include a DLB comparison or control group, this finding is consistent with neuropathological data which found more severe plaques and cortical α-synuclein pathology in the group with shorter duration of PD prior to dementia [14] and reinforces the heterogeneity amongst patients with PDD which in small sample sizes would influence the MR study findings.

Whitwell et al. [15] described what they term a signature MR pattern in DLB. Using both VBM and ROI analysis they studied subjects with DLB (n = 72), AD (n = 72) and controls (n = 72) with careful matching for age, education and dementia severity. They found very little cortical grey matter loss, in contrast to the relatively diffuse pattern of grey matter loss observed by others [7, 9, 10]. However, they report scattered regions of cortical loss in frontal and parietal lobes which is in keeping with other studies, but to a lesser degree. There was also a region of grey matter loss identified around the third ventricle which may represent hypothalamus. These findings were in contrast to AD where a widespread pattern of grey matter loss was found, involving the medial temporal and temporoparietal regions. As with other MR studies there was a large degree of overlap in the results between individual subjects, precluding the use of those MR methods as diagnostic scans. However, the study contributes useful information to patterns of cerebral atrophy in DLB as detected by MR and particularly how they differ from AD.

Occipital hypometabolism and hypoperfusion in DLB have been documented in PET and single-photon emission computed tomography (SPECT) studies, respectively [16–18]. This led to interest into whether there were associated structural MR changes. Most volumetric studies using ROI analysis [19] and VBM [7, 10] did not find a significant occipital structural change in DLB. However, a VBM study comparing PD and PDD found that there was significant grey matter loss of the left occipital lobe [10]. The left occipital gyrus was also found to have more atrophy in DLB compared with control subjects using VBM [9].

Rate of Cerebral Atrophy

The rate of cerebral atrophy in DLB has been assessed in several longitudinal MR studies [20–22]. The overall brain atrophy rate in DLB has been reported to be 1.4% per year, slightly less than in AD (2% per year), but still 3 times the rate in similarly aged controls [21]. Whitwell et al. [22] reported a longitudinal MR study with pathologically confirmed cases of DLB (n = 9), AD (n = 12), mixed AD/DLB (n = 13), controls (n = 25) and other dementia subtypes. Although there was a large amount of overlap in individual patient brain atrophy rates between the groups, a lower atrophy rate (0.4% per year) and ventricular expansion rate (4.8% per year) was reported in DLB compared with AD (atrophy 1.1% per year with a ventricular expansion rate of 8.3% per year). The group with mixed AD/DLB pathology also had a greater atrophy rate than the DLB group (1.3% per year, ventricular expansion 7.2% per year), a similar rate to that previously reported in DLB. Interestingly, the rate of atrophy in the pure DLB was not significantly different from the control group. The authors suggest that the subject group clinically diagnosed with DLB may contain subjects with mixed pathology and conclude that the technique may help to differentiate DLB from AD and be valuable for future disease modifying treatment trials [22]. In a longitudinal study [20] comparing PD (n = 18), PDD (n = 13) and controls (n = 24), whole brain atrophy rates were higher in PDD (1.12% per year) than PD (0.31% per year) and controls (0.34% per year), similar to the rate in DLB reported by O'Brien et al. [21] yet higher than reported in DLB by Whitwell et al. [22]. It is possible that the atrophy reflected in the sample of PDD may be partly due to Alzheimer pathology rather than Lewy-related pathology [20].

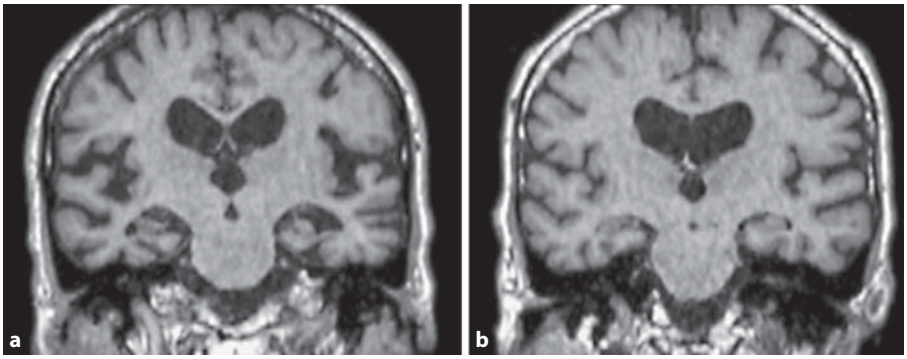

Fig. 1. Coronal view illustrating relative preservation of the MTL and hippocampus in DLB (**b**) compared with Alzheimer's disease (**a**).

Medial Temporal Lobe

A robust MR finding in DLB and PDD is that of relative preservation of the medial temporal lobe (MTL) when compared with Alzheimer's disease [7, 15, 23–26] (fig. 1). Barber et al. [23] used a standardised visual rating scale to grade medial temporal atrophy (MTA) in patients with DLB (n = 26), AD (n = 28), VaD (n = 24) and healthy volunteers (n = 26) and found that whilst MTA occurred more in all dementia groups compared with controls, there was less MTA in DLB compared with AD and VaD. The absence of MTA was highly specific for separating DLB from AD (100%) and VaD (88%), with a much lower sensitivity (38%). This finding has been consistent in both ROI [6, 21, 24, 25] and VBM [7, 9, 10] studies. This was supported by a prospective MRI study with pathological verification which found the pathological correlates of MTA include senile plaques and neurofibrillary tangles but not Lewy body-associated pathology [27].

The hippocampus itself, which forms part of the MTL, is less atrophic in DLB than in AD [6, 15, 24, 28]. Using VBM [10, 29] and manual volumetric measurement techniques [26, 30, 31] subjects with PDD have been found to have less hippocampal atrophy than subjects with AD but more than controls, a finding that is also consistent with the pathological overlap between PDD and DLB. A single study has reported contrary findings, with hippocampal volumes in PDD patients smaller than in AD patients [32], although the differences were not statistically significant. The authors suggest that this may in part be due to coexistent AD pathology in the PDD group and this finding has not been replicated in other larger studies.

Sabattoli et al. [33] studied hippocampal morphology using manual tracing of hippocampal boundaries and computer assisted post processing in DLB (n = 14), AD (n = 28) and healthy control subjects (n = 28). They found that in DLB subjects there was global hippocampal volume loss of 10–20% compared with the control group, less than in AD. The pattern of hippocampal change was also different in DLB compared with AD with prominent changes in the anterior sector of CA1 and along the midline and ventral surface (CA2–3 field, subiculum and presubiculum) in DLB [33]. The authors conclude that the differing pattern of hippocampal atrophy in DLB may be related to the underlying neuropathology [33]. Using manual tracing [34] and VBM [35], hippocampal atrophy in PDD was found to primarily affect the head of the hippocampus with a similar pattern being observed in the older PD group [34].

The entorhinal cortex which forms part of the MTL was found to be smaller in DLB, PDD and AD compared to control subjects using a manual segmentation technique [36]. The percentage volume reduction was 14.7% in the PDD group, 19.9% in the DLB group and 21.9% in the AD group. Although the entorhinal cortex volume was the smallest in AD, it was not significantly smaller than in other dementia groups, suggesting this may reflect a common mechanism [36].

Hanyu et al. [37] used the MR technique of magnetisation transfer ratios (MTR) to detect regional differences in the white matter between AD, DLB and controls. The MTR measurement reflects the degree of interaction between mobile tissue water and macromolecular structures such as myelin. They found a significant difference in the hippocampal MTR, with the MTR of those with dementia being significantly lower (controls > DLB > AD) than in healthy controls. Interpretation of this reduction in MTR is consistent with loss of myelin and/or increased tissue water content associated with changes in cellular structure and may contribute to a differential diagnosis between DLB and AD [37].

Subcortical Structures

DLB and PDD are characterised by a pattern of subcortical structural changes. Nigrostriatal degeneration

and dopaminergic loss, particularly of the dopamine transporter in the striatum, occurs in LBD but not to a significant extent in AD [38]. This can be visualised using specific imaging ligands; using FP-CIT SPECT imaging, for example, reductions of 40–50% were documented in striatal structures in LBD [39]. These changes were found to have a sensitivity of 78% and specificity of 90% in distinguishing DLB primarily from AD in a multicentre study and have been incorporated in the latest revision of the consensus criteria for DLB [4, 40]. It is important to consider how these functional dopaminergic changes may be related to structural and other MR changes. Striatal atrophy has been documented in LBD: putamen atrophy has been reported in PDD [10, 29] and in DLB, relative to AD [41]. Although no significant structural differences were detected in the caudate nucleus in DLB [41–43], atrophy of the right caudate tail was reported in PDD in one VBM study [10]. However, it seems very unlikely that the magnitude of atrophy seen (5–10% reduction in volume) is sufficient to explain the highly significant (up to 50%) FP-CIT SPECT reductions observed.

Atrophy of the substantia innominata and dorsal midbrain in DLB [15, 44, 45] has been documented, findings which are supported by the pathological involvement of the areas, including the nucleus basalis of Meynert (contained in the substantia innominata) [46].

The thalamus has also been reported to be smaller in PDD [10, 29]. Atrophy of the amygdala in DLB was similar to AD in one study [6] and 2 other studies found no difference between DLB and controls [7, 28]. A significant reduction in amygdala volume in PDD compared with controls has been reported in 2 studies using manual volumetric techniques [31, 34].

White Matter Hyperintensities

Damage to the white matter is particularly evident in the ageing brain appearing as focal punctuate areas of hyperintense signal on T2-weighted MRI. Using a standardised visual rating scale, white matter hyperintensities (WMH) were shown to be more extensive in DLB when compared with control subjects but were similar to AD [47, 48]. However, using automated volumetric analysis, Burton et al. [49] found no significant difference between the amount of WMH in the DLB, PDD and control subjects and greater amounts in AD. The authors suggest that differing results may relate to a smaller sample size in their study and to the use of a different analysis technique. After 1 year they showed that WMH increase significantly in patients with AD, PDD and healthy controls, but not in those with DLB, and that the amount of WMH at baseline predicts progression possibly indicating baseline susceptibility in subjects [49]. Interestingly, Beyer et al., [50] using a visual rating scale, also found that there was no significant difference in WMH between PDD (n = 16) and control (n = 20) subjects. However, in contrast to other studies, they also included a PD group (n = 19) who had significantly lower WMH score than both the PDD and control group. The reason for the difference is not entirely clear and may in part reflect the heterogeneous nature of PD combined with a small sample size. The authors raise the possibility of lower neurotransmitter levels in PD compared to controls leading to fewer WMH [50]. Still, this would presumably apply to both PD and DLB and would not necessarily explain the lack of progression of WMH observed by Burton et al. [49] in DLB contrasting with the progression of WMH observed in PDD.

WMH can be further divided into periventricular hyperintensities (PVH) which are adjacent to the ventricles and deep white matter hyperintensities (DWMH). The relationship between WMH and brain atrophy was studied by Barber et al. [47] and they found that PVH rather than DWMH in AD and DLB correlated with increasing ventricular dilatation, suggesting that PVH are associated with atrophy rather than cerebral ischaemia [47].

MR Diffusion Tensor Imaging

Diffusion-weighted MR imaging measures the diffusional displacement of water molecules within the tissue on a timescale of milliseconds. Water movements at this level are dictated by true diffusion but also by interaction between moving water molecule and tissue structures at the cellular level, such as cell membranes and intracellular organelles [51]. Diffusion measurements can also provide detail on tissue microstructure via measures of anisotropy of water movement. In brain tissue, this anisotropy is defined by the direction of the white matter tracts [51]. Strictly, the diffusion properties of water are described mathematically by a tensor, a matrix of values which correspond to the gradient and cell orientation. Accurate assessment of the diffusion properties therefore requires measurement using diffusion tensor MRI (DT-MRI). From this tensor measures of anisotropy can be derived: the mean diffusivity ($\overline{D}$) or Apparent Diffusion Coefficient (ADC) and fractional anisotropy (FA) [52]. Microstructural changes that occur in LBD can po-

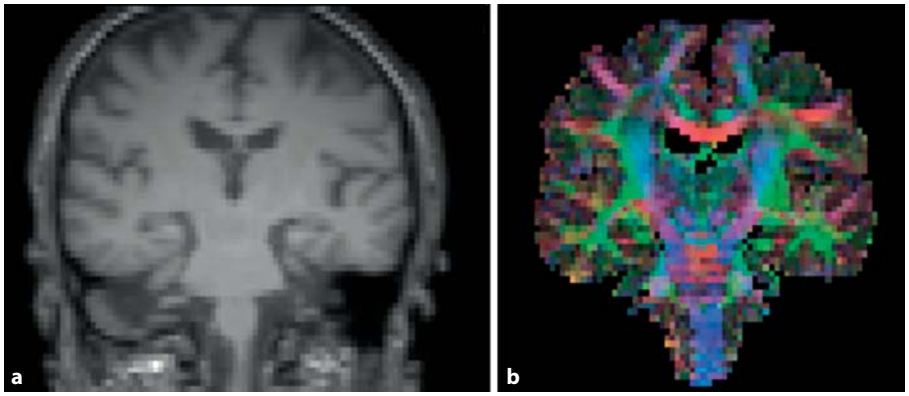

Fig. 2. Coronal view illustrating DT-MRI in DLB. Direction of brain water diffusion within white matter is highly restricted (anisotropic) with movement primarily along the direction of the white matter tracts. **a** Structural scan. The colour-coded fractional anisotropy (FA) map (**b**) encodes the degree of anisotropy by image intensity, while pixel colour shows the primary direction of diffusion (red: left–right, green: anterior–posterior, blue: superior–inferior.

tentially be detected as reflected in alterations in these measures.

Bozzali et al. [53] used this technique to investigate DLB (n = 15) compared with a control group (n = 36). They report DT-MRI changes in the corpus callosum and pericallosal areas (increased $\overline{D}$ and decreased FA values). White matter was also affected in the frontal, parietal and occipital areas in DLB patients with less prominent involvement of the temporal white matter. The caudate nucleus had DTI changes with increased $\overline{D}$ without an associated FA reduction. The authors suggest that the white matter changes found in DLB may reflect the pathophysiological process that eventually affects neurons in the association cortex [53]. Findings were somewhat limited by the small sample size and lack of another type of dementia as a comparison group [53].

Firbank et al. [54] compared subjects with DLB (n = 16), AD (n = 15) and a healthy older control group (n = 15) using a DT-MRI technique with fluid-attenuated inversion recovery (FLAIR) to suppress confounding signals from CSF. They found that the DLB group had reduced FA in the precuneus area on ROI analysis. Given that hypoperfusion in this area has previously been found in DLB using SPECT [55], the authors hypothesised that the disrupted connectivity as demonstrated by a reduced FA in the area of the precuneus may result in medial parietal hypoperfusion [54]. Diffuse white matter changes found by Bozzali et al. [53] were not replicated in this study. The authors suggested that the results by Bozzali et al. [53] may have been influenced by brain atrophy as the use of diffusion sequence without FLAIR. CSF suppression results in high ADC values from the CSF, potentially increasing white matter ADC due to partial volume effects. Firbank et al. [54] included subjects with moderate WMH which may also have contributed to the differing results.

Further analysis of the same patient group [54] found bilateral clusters adjacent to the posterior cingulate with reduced FA [56] (see fig. 2). This correlated with global atrophy in AD and DLB. Given that the hippocampus, anterior and posterior cingulate and lateral parietal regions show functional connectivity, the authors conclude that dementia progression as measured by global atrophy is associated with disruption of the white matter connecting the regions [56].

Matsui et al. [57] reported a reduction in the FA in the posterior cingulate (ROI) in a DT-MRI study of PDD subjects (n = 11) compared with PD (n = 26) and healthy controls (n = 10). This finding, along with Firbank et al. [56], supports the notion that the posterior cingulate may play an important role in the pathological process of LBD.

Proton Magnetic Resonance Spectroscopy

Proton MR spectroscopy (^{1}H-MRS) provides information relating to brain metabolism by measuring the signal originating from protons attached to key biomolecules [58]. The MRS signal is much weaker than MRI due to the lower concentration of these biomolecules (in millimolar concentrations compared to water protons at 110 M). To gain sensitivity, MRS voxels are typically 1–8 cm^3 in volume [58, 59] and are usually only collected from a few pre-selected regions, limiting information about true regional differences. The brain proton spectrum includes metabolite peaks for 5 important compounds: (1) N-acetyl aspartate (NAA) is regarded as a marker of neuronal integrity and is reduced in neuronal dysfunction or loss; (2) creatine (Cr) is related to general metabolism and is assumed to be relatively constant and is therefore often taken as an internal reference level; (3)

Table 2. ^{1}H-MRS studies

Author	Year	Controls	Patient number			Area (voxel of interest)	DLB				PDD			
			DLB	PDD	AD		NAA/Cr	Cho/Cr	Glx/Cr	mI/Cr	NAA/Cr	Cho/Cr	Glx/Cr	mI/Cr
Molina et al. [61]	2002	11	12	0	0	WM: centrum semiovale GM: parasagittal parietal cortex	↓ ↔	↓ ↔	↓↔ ↔	NA NA				
Summerfield et al. [65]	2002	13	0	14	0	lentiform/caudate nucleus bilateral occipital cortices					↔ ↓	↔ ↔	NA NA	↔ ↔
Kantarci et al. [60]	2004	206	20	0	121 (41/8)[a]	right and left posterior cingulate gyrus and inferior precunei	↔	↑↔	↔	↔				
Griffith et al. [62]	2008	12	0	12 (12)[b]	0	posterior cingulate gyrus					↓	↔	NA	↔
Griffith et al. [63]	2008	61	0	12	22	posterior cingulate gyrus					↓	↔	↓	↔
Xuan et al. [64]	2008	8	8	0	0	bilateral hippocampi	↓	↔	NA	NA				

↔ = Unchanged; ↓ = reduced; ↑ = increased; WM = white matter; GM = grey matter; NA = not applicable.
[a] Number of subjects in another dementia comparison group. [b] PD comparison group.

choline (Cho) is seen as an indicator of membrane activity; (4) myo-inositol (mI) is mainly contained in glial cells; and (5) glutamine/glutamate (Glx) metabolism occurs in neurons and glial cells and reduction may reflect glial cell or axonal impairment [58, 59]. Table 2 summarises the findings of 6 ^{1}H-MRS studies identified in LBD.

Using a single voxel spanning the right and left posterior cingulate gyri and inferior precunei, Kantarci et al. [60] studied proton MRS in subjects with AD (n = 121), DLB (n = 20), VaD (n = 8), frontotemporal lobar degeneration (n = 41) and healthy controls (n = 206). NAA/Cr levels were reduced in all dementias except for DLB, suggesting posterior cingulate neuronal integrity in DLB as compared with other dementia subtypes [60]. This is however in contrast to the DTI findings [56]. Molina et al. [61] also found that there was no change in the NAA/Cr in DLB (n = 12) compared to healthy controls (n = 11) using the parasagittal parietal cortex as a VOI. They acknowledged the limitation of using a single VOI potentially obscuring larger inter-group sized differences.

Griffith et al. [62] compared the spectroscopic profiles in PD (n = 12), PDD (n = 12) and controls (n = 12) using a VOI located in the posterior cingulate gyrus. The PDD group had significantly reduced NAA/Cr when compared with both the PD and control groups with no detected change in Cho/Cr or mI/Cr. The same group also compared the proton MRS in PDD and AD, again using a VOI located in the posterior portion of the posterior cingulate gyrus [63]. A reduction in NAA/Cr was found in both PDD and AD suggesting neuronal dysfunction, a finding which contrasted with the Kantarci et al. [60] data in DLB subjects. A reduced Glx/Cr was also reported in PDD, differing from an increased mI/Cr in AD [63].

In a proton MRS study by Xuan et al. [64] in DLB (n = 8) and healthy controls (n = 8), the right and left hippocampi were chosen as VOI, an area that has been previously studied in AD, and a significant decrease in the NAA/Cr ratio was observed.

Summerfield et al. [65] compared ^{1}H-MRS in subjects with PDD (n = 14), PD (n = 12) and controls (n = 13). Using a single voxel technique, they selected an area of the basal ganglia and the occipital cortex. Subjects with PDD showed lower NAA/Cr values than in PD or controls without an associated change in mI/Cr in the occipital cortex suggesting neuronal dysfunction without glial involvement. The results are in contrast to those of AD: decreased NAA/Cr and increased mI/Cr in the occipital area [58].

In summary, some but not all studies found relatively normal NAA/Cr ratios in DLB while in PDD, similar reductions to AD are seen. The differing voxels of interest, comparison groups and small sample size currently limit the generalisabilty of results. Therefore, further ^{1}H-MRS studies are needed as they may contribute to our understanding of the pathological process in LBD.

Functional MRI

Functional MRI (fMRI) can be used to image regional brain activity. This technique relies on the fact that the magnetic state of haemoglobin (Hb) is oxygen dependent and changes from diamagnetic to paramagnetic as oxyhaemoglobin is deoxygenated [66]. The increased consumption of oxygen by neurons during activation is accompanied by a disproportionate supply of oxygenated blood so that there is a net reduction in deoxy-Hb downstream from the area of activation which leads to an increase in the MR signal (T2 or T2* weighting), a process described as blood oxygenation level-dependent (BOLD) contrast [66].

As previously noted, SPECT and PET studies have reported changes in occipital blood flow and glucose metabolism, respectively, in DLB compared with AD [16–18]. However, the cause of this is not clear and may not relate to structural changes [7, 19]. Greater deficits have been observed in the lateral occipitotemporal cortex compared with ventral and medial areas [16]. In an exploratory fMRI study, Sauer et al. [67] looked at task-related brain activity using a visual motion task as the lateral occipitotemporal probe and a colour and face discrimination task as the ventral occipitotemporal probe in 32 subjects: AD (n = 10), DLB (n = 9) and controls (n = 13). Subjects were given task-related instructions and asked to respond using an alternative key press as quickly and as accurately as possible. The motion task resulted in reduced activation in the lateral occipitotemporal area in DLB subjects compared with AD and controls and in a trend toward a slower reaction time. Deficits were also evident in the face task (discriminating gender) with reduced ventral occipitotemporal activation and accuracy in the DLB group compared with AD and controls. The superior temporal sulcus is known to be atrophied in AD and, to a lesser extent, in DLB [68], and a greater resting blood flow in the right MTL has also been documented in a SPECT study [16]. Sauer et al. [67] found greater motion-related superior temporal sulcus activation in DLB than AD, suggesting that the slower reaction time in the motion task was less likely to be a result of non-specific effects such as fatigue. Since these fMRI studies rely on indirect detection of activity (the BOLD effect), any underlying changes in the microvasculature at the capillary level may confound the interpretation of changes in activity measured in these studies [67].

Conclusions

MR changes in DLB and PDD are similar and are characterised by a profile of atrophy predominantly affecting the subcortical structures with relative preservation of the MTL structures which are very consistent with the characteristic clinical and cognitive features of the disease. These structural imaging similarities provide support for the view that DLB and PDD represent points along a spectrum of Lewy body disorders. Relative preservation of the MTL compared with AD shows promise as a diagnostic marker in differentiating AD from DLB and has been incorporated into the revised criteria for the clinical diagnosis of DLB [4]. The rate cerebral atrophy has potential as an outcome measure in therapeutic trials of putative disease modifying agents. However, further longitudinal studies looking at serial rates of atrophy are required before this can be fully established. In particular as with the validation of any surrogate marker, a link between atrophy rate and some clinically significant outcome needs to be established for DLB as has been done for AD [21]. It is not yet possible to form robust conclusions about the utility of other MR measures. A combination of inconsistent results reported between studies, and a degree of overlap in MR measures between dementia subtypes currently limits the diagnostic utility of some imaging techniques. There are many factors which may contribute to the varying results including the heterogeneity in study populations with differing levels of education, age range and cognitive and functional deficits, all of which are inherent to any clinical study in dementia. Other factors may include differing MR techniques and analysis methods, recruitment strategies and the fact that clinical research, despite the application of well-validated clinical diagnostic criteria, remains limited by a level of diagnostic uncertainty. It is also possible that a number of subjects have more than one type of dementia pathology, for example, PDD or DLB subjects may also have varying degrees of Alzheimer pathology, possibly diluting the differences between the conditions. However, there is little doubt that DLB and PDD are different clinicopathological entities from AD. The challenge is discovering the link between the clinical presentation and a relatively non-invasive in vivo technique to refine the ante-mortem diagnosis thereby allowing patients to access appropriate prognostic information and treatment strategies. MR techniques offer a non-invasive method to study cerebral changes in more detail. MR studies to date have been single modality studies, mostly looking at only structural change. Advanced MR techniques such as

DTI, perfusion imaging and spectroscopy offer more sensitive measures for detecting early and potentially preclinical changes. Areas of interest would include the visuoperceptual association areas, in particular the posterior cingulate/precuneus region and the ventral and dorsal visual streams (occipitotemporal and occipitoparietal pathways). With advances in MR technology including higher field strengths and shorter scanning times, the development of a multimodal MR protocol, incorporating structural imaging changes, microstructural changes through DTI, metabolism through spectroscopy and measurement of perfusion, may assist in better understanding the inconsistencies between studies and provide new insights into the differences between DLB, PDD, AD and age matched controls. This, in turn, may help refine the ante-mortem diagnosis and assessment of disease progression.

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