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White matter integrity in dementia with Lewy bodies: a voxel-based analysis of diffusion tensor imaging

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ABSTRACT

Many patients with dementia with Lewy bodies (DLB) have overlapping Alzheimer's disease (AD)–related pathology, which may contribute to white matter (WM) diffusivity alterations on diffusion tensor imaging (DTI). Consecutive patients with DLB ($n = 30$), age- and sex-matched AD patients ($n = 30$), and cognitively normal controls ($n = 60$) were recruited. All subjects underwent DTI, 18F 2-fluoro-deoxy-D-glucose, and ^{11}C Pittsburgh compound B positron emission tomography scans. DLB patients had reduced fractional anisotropy (FA) in the parietooccipital WM but not elsewhere compared with cognitively normal controls, and elevated FA in parahippocampal WM compared with AD patients, which persisted after controlling for β-amyloid load in DLB. The pattern of WM FA alterations on DTI was consistent with the more diffuse posterior parietal and occipital glucose hypometabolism of 2-fluoro-deoxy-D-glucose positron emission tomography in the cortex. DLB is characterized by a loss of parietooccipital WM integrity, independent of concomitant AD-related β-amyloid load. Cortical glucose hypometabolism accompanies WM FA alterations with a concordant pattern of gray and WM involvement in the parietooccipital lobes in DLB.

1. Introduction

Diffusion tensor imaging (DTI) provides information on white matter (WM) microstructure, using the anisotropic nature of water diffusion, which is impeded perpendicularly to WM fibers. Fractional anisotropy (FA) is a robust DTI-derived measure (Pierpaoli and Basser, 1996) of the directionality of water diffusion, which decreases with the degeneration of WM. Hence, FA is often used as a proxy of WM integrity (Carmichael and Lockhart, 2012; Douaud et al., 2011).

DTI studies in dementia with Lewy bodies (DLB) have reported varying extents of WM involvement, ranging from widespread reduced FA in the corpus callosum, frontal, parietal, occipital, and temporal WM (Bozzali et al., 2005; Lee et al., 2010) to involvement confined to temporoparietal limbic and occipital pathways (Firbank et al., 2007, 2011; Kiuchi et al., 2011; Watson et al., 2012). Reduced FA in the occipital WM, specifically in the inferior longitudinal fasciculus, a pathway important for visuospatial processing, was a common finding in DLB patients (Bozzali et al., 2005; Kantarci et al., 2010; Kiuchi et al., 2011; Lee et al., 2010; Ota et al., 2008; Watson et al., 2012). Many DLB patients who fulfill the clinical criteria for probable DLB have overlapping Alzheimer's disease (AD)–related pathology, which may have contributed to the variation in WM diffusivity alterations in DLB.

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^{11}C Pittsburgh compound B (PiB) on positron emission tomography (PET) imaging traces β-amyloid (Aβ) plaques which are present in both AD and DLB patients (Foster et al., 2010; Rowe et al., 2007). Although PiB binds to Aβ in both the neuritic and diffuse plaques (Klunk et al., 2001; Mathis et al., 2002), it has a higher affinity to neuritic plaques. Further, PiB does not bind to α-synuclein in Lewy bodies (Burack et al., 2010; Fodero-Tavoletti et al., 2007; Kantarci et al., 2012c). Therefore, PiB uptake on PET can serve as a marker of AD-related Aβ pathology in DLB.

[18F]2-fluoro-deoxy-D-glucose (18F-FDG) PET findings in DLB are characterized by hypometabolism in the occipital and posterior temporoparietal cortex (Imamura et al., 1997; Minoshima et al., 2001). However, cortical atrophy has not been observed in these posterior brain regions, neither in cross-sectional magnetic resonance imaging (MRI) studies in clinically diagnosed DLB patients (Middelkoop et al., 2001; Whitwell et al., 2007), nor in a longitudinal MRI study that investigated the pattern of cortical atrophy rates on antemortem MRI in an autopsy-confirmed cohort (Nedelska et al., 2014). Since DLB patients show a specific pattern of reduced cortical metabolism, FDG-PET is particularly useful to examine the neurodegenerative changes in the cortical gray matter, and to assess whether hypometabolism in the cortex relates to a loss of WM integrity in DLB.

It remains unknown whether AD-related Aβ pathology is responsible for the alterations in WM microstructure in patients with DLB. Further, it is unclear whether the WM alterations on DTI topographically coincide with cortical hypometabolism observed on FDG-PET in DLB. First, we determined the pattern of WM diffusivity alterations in DLB compared with cognitively normal controls (CN) and AD patients using voxel-based analysis (VBA) across the WM of the entire brain. Second, we examined the contribution of Aβ load to the disruption of WM integrity in patients with DLB, and finally, we compared the pattern of WM alterations on DTI and cortical glucose hypometabolism on FDG-PET in DLB.

2. Methods

2.1. Subjects and clinical evaluations

We identified 30 consecutive patients with probable DLB (McKeith et al., 2005) from a prospective, longitudinally followed cohort at the Mayo Clinic Alzheimer's Disease Research Center (ADRC; a dementia clinic-based cohort) in Rochester, MN during a 3-year period 2010–2013. For comparison, we included 30 patients with probable AD (McKhann et al., 1984) and 60 CN either from the ADRC or from the Mayo Clinic Study on Aging (a community-based cohort) who were (1:1 or 2:1, respectively) age- and sex-matched with DLB patients. Eligibility was defined as the absence of any major abnormality on structural MRI that could confound the results such as tumors or large hemispheric infarcts, the absence of primary neurological illness affecting cognition other than DLB or AD, and sufficient scan quality to conduct analysis. The study was approved by the Mayo Clinic Institutional Review Board. All subjects or their proxies provided the informed consent on study participation.

Global measures of Clinical Dementia Rating Sum of Boxes (CDR-SOB; Hughes et al., 1982), Mini-Mental State Examination (MMSE; Folstein et al., 1975), and Dementia Rating Scale (DRS; Morris, 1993) were used to assess clinical disease severity at the time of the study. The presence, duration, and severity of DLB clinical features, and the duration of dementia were ascertained. Visual hallucinations (VH) had to be fully formed, recurring, and unlikely to be the consequence of causes other than DLB. VH severity was coded as mild, moderate, or severe. Fluctuations were considered present if patients scored 3 or 4 points on the Mayo Clinic Fluctuations questionnaire (Ferman et al., 2004). Motor impairment was scored using motor subscale of the Unified Parkinson's Disease Rating Scale (Fahn, 1987). Probable rapid eye movement sleep behavior disorder (pRBD) was diagnosed using the International Classification of Sleep Disorders-II diagnostic criteria B for pRBD (AASM, 2005).

2.2. MRI acquisition

MRIs were performed at 3T using an 8-channel phased array coil (GE, Milwaukee, WI, USA) and parallel imaging with an acceleration factor of 2. A 3D T1-weighted high-resolution magnetization prepared rapid gradient echo acquisition with repetition time = 7 ms, echo time = 3 ms, inversion time = 900 ms, flip angle = 8°, a slice thickness of 1.2 mm, and in plane resolution of 1.0 mm was obtained for anatomic segmentation and labeling. DTI was acquired using a single-shot echo-planar T2-weighted sequence in the axial plane with the following acquisition parameters: TR = 10,200 ms;

Table 1
Subjects' characteristics

	CN $n = 60$	DLB $n = 30$	AD $n = 30$	p-Value[a]
Females (%)	10 (17)	5 (17)	5 (17)	1.0
Age (y)	68.5 (63, 76)	69 (63, 76)	72.5 (64, 79)	0.48
Education (y)	15.5 (12.5, 18)	15 (12, 18)	16 (12, 18)	0.69
APOE ε4 carriers (%)	11 (18)	13 (43)	23 (77)	<0.001
CDR sum of boxes	0.0 (0.0, 0.0)	5.75 (4.0, 7.0)	4.75 (2.5, 7.0)	<0.001
MMSE	29 (28, 29)	20.5 (15, 24)	21 (14, 23)	<0.001
DRS	—	125.5 (114, 131)	111 (85, 127)	0.03
PiB SUVR	1.31 (1.27, 1.37)	1.43 (1.30, 1.88)	2.35 (2.17, 2.52)	<0.001
VH present (%)	—	23 (77)	2 (8)	<0.001
Fluctuations present (%)	—	27 (90)	2 (8)	<0.001
Motor UPDRS	—	12 (7, 14)	0 (0, 2)	<0.001
RBD present (%)	—	28 (93)	4 (15)	<0.001
Dementia duration (y)	—	5.04 (3.75, 7.17)	5.21 (3.50, 7.00)	0.88
VH duration (y)	—	1.91 (0.75, 3.59)	—	—
Fluctuations duration (y)	—	2.25 (1.49, 3.67)	—	—
Parkinsonism duration (y)	—	3.50 (1.17, 5.75)	—	—
RBD duration (y)	—	9.21 (4.16, 14.08)	—	—

Medians (interquartile ranges) are listed for the continuous and the proportions (%) are for the categorical variables.
Key: AD, Alzheimer's disease; APOE, apolipoprotein; CDR, Clinical Dementia Rating; CN, cognitively normal control; DLB, dementia with Lewy bodies; DRS, Dementia Rating Scale; MMSE, Mini-Mental State Examination; PiB, ^{11}C Pittsburgh compound B; RBD, rapid eye movement sleep behavior disorder; SUVR, standardized uptake value ratio; UPDRS, Unified Parkinson's Disease Rating Scale; VH, visual hallucinations (probable and definite combined together).
[a] p-Values are from the Wilcoxon rank sum for the continuous variables, and a χ^2 test for differences in proportions.