Title

Diffusion imaging in dementia with Lewy bodies: associations with amyloid burden, atrophy, vascular factors and clinical features

Author names and affiliations

*Paul C Donaghy[1] PhD, Michael Firbank[1] PhD, George Petrides[2] MBBS, Jim Lloyd[2] PhD, Nicola Barnett[1] MSc, Kirsty Olsen[1] MSc, Alan J Thomas[1] PhD, John T O'Brien[4] DM

1: Translational and Clinical Research Institute, Newcastle University, UK

2: Nuclear Medicine Department, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

3: Department of Psychiatry, University of Cambridge, UK

*Corresponding Author: Dr Paul Donaghy; Level 3 Biomedical Research Building, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL. Tel: +44191 208 1318. E-mail: paul.donaghy@ncl.ac.uk

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Abstract

Introduction

White matter disruption in dementia has been linked to a variety of factors including vascular disease and cortical pathology. We aimed to examine the relationship between white matter changes on diffusion tensor imaging (DTI) in DLB and factors including vascular disease, structural atrophy and amyloid burden.

Methods

Participants with DLB (n=29), Alzheimer's disease (AD, n=17) and healthy controls (n=20) had clinical and neuropsychological assessments followed by structural and diffusion tensor 3T MRI and ^{18}F-Florbetapir PET-CT imaging. Voxelwise statistical analysis of white matter fractional anisotropy (FA) and mean diffusivity (MD) was carried out using Tract-Based Spatial Statistics with family-wise error correction ($p<0.05$).

Results

DLB and AD groups demonstrated widespread increased MD and decreased FA when compared with controls. There were no differences between the DLB and AD groups.

In DLB, increased MD and decreased FA correlated with decreased grey matter and hippocampal volumes as well as vascular disease. There was no correlation with cortical florbetapir SUVR. The relationship between DTI changes and grey matter/hippocampal volumes remained after including Cumulative Illness Rating Scale-Geriatric vascular score as a covariate.

Conclusions

Widespread disruption of white matter tracts is present in DLB and is associated with vascular disease, reduced hippocampal volume and reduced grey matter volume, but not with cortical amyloid deposition. The mechanism behind the correlation observed between hippocampal volume and white matter tract disruption should be investigated in future cohorts using tau imaging, as hippocampal atrophy has been shown to correlate with tau deposition in DLB.

Introduction

White matter changes, visualised as white matter hyperintensities on structural T2 MRI, are associated with dementia with Lewy bodies and Alzheimer's disease [1, 2]. Diffusion tensor imaging (DTI) is a means of measuring white matter integrity by examining the movement of water molecules. White matter disruption has been observed in DLB using DTI, particularly in parieto-occipital areas [3-5]. White matter disruption in dementia has been linked to a variety of factors including vascular disease, cortical amyloid and tau deposition and cortical atrophy. White matter hyperintensities (WMH) on MRI are often attributed to microvascular disease [6]. However, a large cohort study found that WMH correlated with cortical atrophy in addition to vascular risk factors [7]. Medial temporal lobe atrophy has been shown to correlate with white matter hyperintensities in both DLB and AD [8]. Low CSF amyloid (indicative of greater cerebral amyloid pathology) is associated with the accumulation of WMH on MRI in healthy older people [9]. However, DTI alterations during life were found to correlate with neurofibrillary tangle stage but not neuritic amyloid plaque stage in AD [10]. White matter hyperintensities on post-mortem MRI have been found to correlate with cortical amyloid and tau deposition, though on linear regression, only tau was independently related to WMH score [11]. In AD, these lesions are not associated with the same degree of ischaemia as is observed in those of healthy controls [12]. These findings suggest that white matter changes may be associated with neurodegeneration, in addition to vascular risk factors.

In dementia with Lewy bodies, Alzheimer's disease pathology may be a factor in the development of white matter disruption in addition to vascular disease and Lewy body pathology. Amyloid and tau deposition are frequently observed in DLB, [13, 14]. Multi-modal imaging can help to establish which factors are most important in the development of white matter changes in different types of dementia. This study investigated these associations in DLB, comparing findings in diffusion weighted imaging to vascular risk factors, structural imaging and PET amyloid imaging.

Aims and hypotheses

We aimed to examine correlation between WM changes on DTI in DLB with factors that may be associated with white matter damage, including vascular factors, structural atrophy and amyloid burden. Hippocampal volume was investigated in addition to overall grey matter volume, as hippocampal atrophy has been shown to correlate with tau deposition in DLB [15]. We included comparison groups of healthy similarly aged controls and an AD dementia group.

We hypothesised that DLB and AD subjects would have lower fractional anisotropy and greater mean diffusivity than healthy older people. In DLB, we hypothesised that these changes would be related to cortical pathology and cell damage, and that therefore, changes in white matter diffusion would be associated with lower grey matter volume, lower hippocampal volume and greater cortical amyloid deposition as well as increased vascular disease.

Methods

Participants

Participants with dementia were recruited prospectively between June 2013 and February 2016 from secondary care services in the North of England. All participants were ≥60 years old and had a diagnosis of probable AD or probable DLB confirmed by two clinicians based on contemporaneous diagnostic criteria [16, 17], with an MMSE ≥12. Participants were recruited prior to the publication of the 2017 diagnostic criteria for DLB [18], but all DLB participants met the updated criteria for a diagnosis of probable DLB. Post-mortem diagnosis was used where available. Control participants were recruited through a research case register or were partners of participants.

Participants were excluded if they had a major concurrent psychiatric illness; severe physical illness; contraindications to PET-CT imaging or MRI; a history of other significant neurological illness including stroke or previous experimental treatment with an amyloid-targeting agent.

Participants with capacity gave their written informed consent to take part in the study. For those who lacked capacity, their participation in the study was discussed with a consultee in accordance with the UK Mental Capacity Act. The study received ethical approval from the National Research Ethics Service Committee North East - Newcastle & North Tyneside 2 (13/NE/0064).

Baseline cognitive and clinical assessment

Participants had a clinical and cognitive assessment carried out at baseline and 1 year. This included the Addenbrooke's Cognitive Examination-Revised (ACE-R), and the Bristol and Instrumental Activities of Daily Living Scales (BADL, IADL) [19, 20]. IADL domains were given ordinal scores, with higher scores indicating greater impairment [21]. IADL and BADL scores were combined to make a composite function z-score for Tract-Based Spatial Statistics (TBSS) analysis in the DLB group. Comorbidities, including vascular disease, were assessed using the Cumulative illness Rating Scale for Geriatrics (CIRS-G) [22].

Imaging

Imaging was performed at baseline. Details of the MRI and PET acquisition and analysis have been published elsewhere [23] and will briefly be summarised here.

Brain MRI scans were acquired using a 3T MR scanner (Achieva scanner; Philips Medical Systems), with body coil transmission and eight channel head coil receiver. Images acquired included a 3D sagittal magnetisation-prepared rapid gradient echo (MPRAGE) sequence (repetition time 8.3ms, echo time 4.6ms, flip angle 8°, inversion delay 1250ms, imaging time 4.5mins, sagittal acquisition matrix 216x240, voxel size 1x1x1mm) and echo planar imaging spin echo (EPI-SE) diffusion tensor imaging (TR 6126ms, TE 70ms, 124x120 matrix ; 270x270 FOV; 59 slices with slice thickness 2.11mm). Diffusion weighting was in 64 directions with a b value of 1000s/mm^2 along with 6 images with b value of 0 s/mm^2.

Amyloid imaging was carried out using a Siemens Biograph-40 PET-CT scanner. Participants were given a 370MBq intravenous injection of ^{18}F-Florbetapir (Amyvid) followed by a 15 minute scan starting 30-50 minutes after injection to image amyloid distribution. Images were reconstructed using iterative reconstruction (4 iterations, 16 subsets), with a 168x168 matrix size, 2.04x2.04mm pixel size, 3mm slice thickness, and 3mm post-reconstruction Gaussian filter. Attenuation correction was performed utilising CT scan data.

Image processing

Data were processed with the FSL toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) [24]. The DTI images were processed to correct for subject motion and eddy current distortion with eddy software. Voxelwise statistical analysis of the FA and MD data was carried out using TBSS [25]. For each subject we calculated the mean FA and MD over all the pixels on the skeleton.

The 3D structural MR images were segmented into white matter, grey matter and CSF using SPM 8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/); total intracranial volume defined as the sum of these. White matter hyperintensity (WMH) segmentation was carried out using the FLAIR and T1 structural images using a semi-automated threshold-based algorithm employing SPM8 functions (www.fil.ion.ucl.ac.uk/spm) in an in-house written Matlab package (Matlab R2013a, Mathworks, Inc., Natick, MA, USA) as described previously [26]. The resulting WMH masks were manually edited using ITK-SNAP (www.itksnap.org) to correct for minor errors. Hippocampal volumes were calculated

using an automated technique [27]. Grey matter volume (GMV), hippocampal volume and white matter hyperintensities (WMH) were expressed relative to total intracranial volume. There was a positive skew in the WMH data (Shapiro-Wilk statistic=0.85, p=0.001), therefore the log of WMH was used to make the data more normally distributed (Shapiro-Wilk statistic=0.96, p=0.34).

The amyloid PET image was co-registered with the native space MRI. A mean cortical standardised uptake value ratio (SUVR) was derived from the unweighted mean of frontal, temporal, parietal and cingulate regions relative to the whole cerebellum [28].

Statistical Analysis

Statistical analysis was completed using IBM SPSS Statistics software (version 22; http://www-03.ibm.com/software/products/en/spss-statistics). Demographic comparisons were carried out using t-tests or Mann-Whitney tests. χ^2 or Fisher's Exact tests were used for categorical variables. Age and sex were included as covariates in the TBSS analyses. Years in education was also included in correlations with cognitive scores. Statistical analysis in FSL was carried out using the randomise tool with 5000 permutations. Family-wise error correction was applied using threshold free cluster enhancement (TFCE) to identify significant clusters ($p<0.05$). The anatomical location of significant clusters was determined using the John Hopkins University White Matter Labels Atlas. Subjects with missing data were excluded from each analysis. The sample size was calculated to investigate amyloid imaging in DLB, AD and controls as previously reported [23].

Results

Recruitment and attrition

A total of 69 participants completed baseline assessment and DTI imaging. One AD participant was subsequently excluded due to poor scan quality. Two DLB participants were excluded following a post-mortem diagnosis of non-DLB dementia (one AD, one mixed pathology). Five DLB cases and one AD case were confirmed by post-mortem diagnosis. Sixty-six participants were included in the baseline comparison (Table 1). Correlation between baseline DTI measures and clinical progression was analysed for DLB participants, 23/29 of whom completed follow-up assessment (four died, one had a severe stroke and one withdrew).

Comparison between diagnostic groups at baseline

DLB (n=29), AD (n=17) and Control (n=20) groups were well matched for age and sex. DLB participants had greater levels of physical comorbidity measured by the CIRS-G. DLB and AD participants were well matched for cognitive impairment, though DLB cases were more functionally impaired. DLB and AD both had lower mean FA and higher mean MD than controls. There were no differences between the two dementia groups in mean FA or mean MD.

INSERT TABLE 1 HERE

Comparison of TBSS findings between diagnostic groups

All TBSS results are presented following correction for family-wise error (FWE) using TFCE. There was widespread decreased fractional anisotropy and increased mean diffusivity in DLB compared with controls, including in the corona radiata, superior longitudinal fasciculus, corpus callosum, sagittal stratum and internal capsule (Figure 1). Similar changes were also observed in AD compared with controls, including the in the corona radiata, superior longitudinal fasciculus, corpus callosum, internal capsule and fornix. There were no differences between the DLB and AD groups.

After including WMH as a covariate in the comparison between DLB and controls, the widespread differences in FA remained; the differences in MD were restricted to the right fornix, posterior limb of the internal capsule and sagittal stratum. The widespread differences in both FA and MD remained in AD with WMH included as a covariate (Supplementary Figure 1).

INSERT FIGURE 1 HERE

Correlation between TBSS and imaging/vascular measures in DLB

There was no significant association between FA/MD and amyloid deposition measured by Florbetapir SUVR or visual rating in the DLB group.

Global white matter hyperintensity burden was associated with reduced FA and increased MD, in widespread areas including the corona radiata and superior longitudinal fasciulus (Supplementary Figure 2).

There was a small area of negative correlation between CIRS-G vascular score and FA in the right posterior corona radiata and widespread positive correlation with MD in areas including the superior and anterior corona radiata, superior longitudinal fasciulus, fornix and sagittal stratum (Supplementary Figure 3).

There was no correlation between grey matter volume and FA. There was negative correlation between grey matter volume and mean diffusivity in the anterior corona radiata and corpus callosum (Figure 2).

INSERT FIGURE 2 HERE

There was positive correlation between FA and hippocampal volume in widespread areas including the corona radiata, superior longitudinal fasciulus, corpus callosum, internal capsule, external capsule, fornix and sagittal stratum. Negative correlation between MD and hippocampal volume was observed in areas including the superior and anterior corona radiata, corpus callosum, right superior longitudinal fasciculus and right sagittal striatum within the DLB group (Figure 3).

INSERT FIGURE 3 HERE

Correlations between TBSS and clinical measures in DLB

There was no significant correlation between FA/MD and baseline ACE score, baseline function z-score, change in ACE score over 1 year or change in function z-score over 1 year.

Correlations between TBSS and imaging measures in DLB with CIRS-G vascular score as a covariate

Following the observation of correlation between CIRS-G vascular score and DTI measures, the TBSS analyses were repeated with CIRS-G vascular score as a covariate to ensure the results were not due to confounding due to vascular disease. Significant correlations were still present in all the analyses presented in Figures 2, 3 and Supplementary Figure 2. The correlation between WMH and FA (negative) and MD (positive) remained, but was restricted to posterior areas (Supplementary Figure 4). The negative correlation found between MD and GMV remained present, and was more

widespread (Supplementary Figure 5). The correlation between hippocampal volume and FA (positive) and MD (negative) was highly similar (Supplementary Figure 6).

Discussion

We found significant decreased mean fractional anisotropy and increased mean diffusivity in both DLB and AD when compared with controls. This is in keeping with damage to white matter tracts that is known to occur in both these diseases [29] and previous studies using DTI [3, 4]. We found more widespread areas of reduced FA and increased MD in DLB compared with controls than these previous studies, which found predominantly posterior changes. The most prominent changes were seen in the corona radiata, corpus callosum, superior longitudinal fasciculus, sagittal stratum and internal capsule. This is in keeping with some previous region of interest studies [30, 31] though others have not found changes in these areas [32]. Previous region of interest studies have also reported decreased FA in regions including the uncinate and inferior occipitofrontal fasciculi in DLB compared with controls [5, 32, 33].

There were no differences between AD and DLB following FWE correction, again in keeping with some previous studies [3, 4].

There was correlation between CIRS-G vascular score and FA/MD in DLB. However, vascular disease does not appear to explain the differences between DLB and healthy controls in DTI measures. The control group had similar rates of smoking and similar scores on CIRS-G heart and vascular scales and higher resting systolic blood pressure than DLB cases. This is consistent with the hypothesis that white matter changes in dementia are not explained by vascular pathology alone and are associated with neurodegenerative disease processes [12].

We investigated this hypothesis using three markers of cortical pathology – amyloid deposition, grey matter volume and hippocampal volume. Hippocampal volume was included as this has been shown to correlate with tau deposition in DLB [15]. We found no correlation between amyloid deposition and FA or MD using TBSS. This is in keeping with post-mortem findings in AD, where tau has been identified as the pathological correlate of white matter disruption [10, 11]. The inclusion of amyloid deposition measured by PET in a previous study reduced the areas of significant reduction in fractional anisotropy in DLB and controls, though the difference was not felt to be substantial [4]. An independent relationship between amyloid and FA was not reported. As such, at present there is no clear evidence for a link between amyloid deposition and DTI measures in DLB.

We found that decreased grey matter volume was associated with higher mean diffusivity in frontal areas. Relationships between white matter changes and grey matter volume loss in corresponding cortical areas have been reported in a previous DTI study [33]. More strikingly, decreased hippocampal volume was associated with widespread increases in mean diffusivity and decreases in fractional anisotropy. Correlation remained present when vascular risk was accounted for using CIRS-G vascular score. These findings are in keeping with previous studies that found correlation between visually rated hippocampal atrophy and increased WMH [8] and decreased FA in the fornix, stria terminalis and corpus callosum [34]. In the present study, using quantitative measurement of hippocampal size, more widespread correlation was identified. It may seem surprising that atrophy in a small brain region should be linked to global changes in cerebral white matter to a greater extent than global grey matter volume. An explanation for this may be that hippocampal atrophy is a marker for co-existing pathological processes such as tau deposition. Hippocampal atrophy is known to correlate with neurofibrillary tangle Braak stage correlates in DLB (Pearson's r=-0.63) [15]. Neurofibrillary tangle Braak stage is known to be associated with DTI changes in AD [10]. The link between hippocampal volume and white matter disruption in our cohort may therefore be explained by tau pathology as the causative factor for both findings. With the advent of tau imaging, it will be possible to test this hypothesis in future studies.

We found no correlation between DTI measures and baseline cognition or functional impairment, or progression in cognitive or functional impairment. An absence of correlation with global measures of cognition and function has previously been reported, though correlation has been found with measures of memory, verbal fluency, motor parkinsonism, and visual hallucinations in DLB [3, 4]. The lack of correlation with global measures of cognition and function may be due to a lack of power to detect such associations. This is a particular issue with longitudinal associations, due to attrition. Our data suggests that changes in FA and MD are associated with both the dementia process (as evidenced by differences between DLB and controls) and vascular changes (as demonstrated by correlation with CIRS-G vascular). Therefore, FA and MD may not track or predict the progression of the dementia process accurately. Despite this, the evidence presented here that white matter changes are related to measures of cortical pathology is worthy of further attention and further supports the hypothesis that not all white matter changes in dementia are related to vascular disease.

Strengths and weaknesses

This study reports a relatively large cohort of DLB participants with multimodal imaging and clinical assessment. TBSS results are presented with FWE correction to avoid false positive findings. A range of demographic factors were available to assess for confounding, such as smoking history, blood pressure measurement and vascular history. The degree of vascular disease in this cohort is limited by the exclusion of participants with clinical stroke. Therefore, vascular disease and vascular risk factors may play a greater role in white matter disruption in some cases of DLB, where severe vascular disease is present. The CIRS-G vascular sub-scale is an imprecise tool to measure vascular disease, but it did demonstrate correlation with FA and MD in DLB. We chose to use this scale to correct for vascular risk rather than WMH volume, as there is evidence that WMH reflects dementia pathology in addition to vascular pathology [7, 9, 12, 35].

There are limitations to the use of TBSS in dementia subjects. Voxels compared between subjects may not be from the same anatomical position and changes in the size and shape of white matter tracts in different diseases can result in alignment errors [36]. Therefore, the differences noted between healthy controls and the dementia groups may be influenced by morphological changes in the brain and scan misalignment rather than actual differences in FA and MD in specific white matter tracts. This manuscript predominantly focuses on comparisons within the DLB group. For these analyses, a specific FA skeleton for the DLB group was created. Group specific skeletons have been suggested by some authors to reduce the risk of misalignment [37]. That said, the association of morphological changes (such as grey matter volume and hippocampal volume) with FA and MD in DLB could be influenced by misalignment in those with greater atrophy. However, this does not explain the greater associations observed with hippocampal volume compared with global grey matter volume, as the latter might be expected to have a greater influence on overall brain morphology.

Correlation between hippocampal volume and white matter disruption could be influenced by hippocampal white matter loss, as white matter changes causing loss of volume in the hippocampus could be associated with white matter disruption in other brain areas. However, we do not believe that this will have significantly impacted on our results, as the volume of white matter in the hippocampus is small and the automated segmentation of the hippocampus used seeks to exclude white matter [27].

The finding of widespread correlation between hippocampal volume and white matter disruption cannot be explained with certainty by the data available here. We have presented an evidenced-based hypothesis to explain the data i.e. that tau pathology may mediate the findings. This will need to be tested in future studies using tau imaging.

Conclusions

Widespread disruption of white matter tracts is present in DLB, evidenced by reduced FA and increased MD on TBSS. There are no significant differences observed between DLB and AD following FWE correction. White matter tract disruption is correlated with vascular factors, hippocampal volume and grey matter volume, but not with cortical amyloid deposition. The mechanism behind the correlation observed between hippocampal volume and white matter tract disruption should be investigated in future cohorts using tau imaging.

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Author Contributions

PCD – 1 A,B,C; 2 A, B, C; 3A

MF – 1 A,B; 2 A,C; 3B

JL – 1 A; 2 C; 3 B

GP - 1 A; 2 C; 3 B

NB – 1 B,C; 3 B

KO – 1 B,C; 3 B

AJT – 1 A,B; 2 C; 3 B

JTO'B – 1 A,B; 2 A,C; 3B

Key: 1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

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Figure Legends (colour)

Figure 1. Comparisons between DLB, AD and control groups. A: Clusters of reduced FA in DLB v Control. B: Clusters of increased MD in DLB v Control. C: Clusters of reduced FA in AD v Control. D: Clusters of increased MD in AD v Control. Green (FA) and red (MD) areas denote clusters with significant difference between groups ($p<0.05$ FWE corrected) with age and sex as covariates. White matter skeleton in white.

Figure 2. TBSS correlation with grey matter volume (GMV) in DLB. Clusters of negative correlation between GMV and MD. Red areas show correlation $p<0.05$ (FWE corrected) with age and sex as covariates. White matter skeleton in white.

Figure 3. TBSS correlation with hippocampal volume. A: Clusters of positive correlation between hippocampal volume and FA. B: Clusters of negative correlation between hippocampal volume and MD. Green (FA) and red (MD) areas show correlation $p<0.05$ (FWE corrected) with age and sex as covariates. White matter skeleton in white.

Figure Legends (black and white)

Figure 1. Comparisons between DLB, AD and control groups. A: Clusters of reduced FA in DLB v Control. B: Clusters of increased MD in DLB v Control. C: Clusters of reduced FA in AD v Control. D: Clusters of increased MD in AD v Control. Shaded areas on white matter skeleton denote clusters with significant difference between groups ($p<0.05$ FWE corrected) with age and sex as covariates. White matter skeleton in white.

Figure 2. TBSS correlation with grey matter volume (GMV) in DLB. Clusters of negative correlation between GMV and MD. Shaded areas on white matter skeleton show correlation $p<0.05$ (FWE corrected) with age and sex as covariates. White matter skeleton in white.

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