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Longitudinal diffusion tensor imaging in dementia with Lewy bodies and Alzheimer's disease

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ABSTRACT

Objective: Changes in the white matter of dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) have been reported using diffusion weighted MRI, though few longitudinal studies have been done.
Methods: We performed diffusion weighted MRI twice, a year apart on 23 AD, 14 DLB, and 32 healthy control subjects. Mean diffusivity (MD) and fractional anisotropy (FA) were calculated.
Results: In AD, there were widespread regions where the longitudinal MD increase was greater than in controls, and small areas in the parietal and temporal lobes where it was greater in AD than DLB. In AD, decrease in brain volume correlated with increased MD. There were no significant differences in progression between DLB and controls.
Conclusions: In AD the white matter continues to degenerate during the disease process, whereas in DLB, changes in the white matter structure are a relatively early feature. Different mechanisms are likely to underpin changes in diffusivity.

1. Objective

Dementia with Lewy bodies (DLB) is a common form of neurodegenerative dementia in older people, second to Alzheimer's disease (AD). Studies of DLB have found relatively less overall brain atrophy than AD, particularly in the temporal lobes [1]. A number of studies have investigated the structural integrity of the white matter in DLB using MR diffusion tensor imaging (DTI) and have found mixed results, but generally, DLB subjects have DTI changes in parieto-occipital regions, whilst AD changes are more widespread, and have been reported to particularly involve the medial temporal lobe and limbic pathways [1,2].

In a previous study, we found widespread reductions of fractional anisotropy (FA) in AD, with DLB changes more restricted to parieto-occipital regions, along with generally increased mean diffusivity (MD) in both groups [3]. In this study, we report the longitudinal change in MD and FA measured over 1 year in these subjects.

2. Methods

2.1. Subjects

Seventy-one individuals aged over 60 (36 subjects with probable AD [4] and 35 with probable DLB [5]) were recruited from a community-dwelling population of patients referred to local old age psychiatry, geriatric medicine, or neurology services. Thirty-five control subjects were recruited from relatives and friends of subjects with dementia or volunteered via local advertisements. All subjects underwent clinical and neuropsychological evaluations with diagnostic procedures as previously described [3]. MR scanning was done on all subjects at baseline and was repeated after 1 year on those subjects who consented for repeat scanning. The

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research was approved by the local ethics committee. All subjects or, where appropriate, their nearest relative, provided written informed consent.

Of the 36 AD subjects, 23 were included after 11 were unable to participate in the follow-up assessment, one AD was excluded due to excessive motion on the repeat DT images, and DTI data were not available on another. Of the 35 DLB subjects, 14 were included after 12 declined to participate due to ill health, and 9 subjects had died. Of the 35 HC subjects, 32 were included in the present analyses after 2 declined to participate, and DTI data were not available on one control.

Assessment of global cognitive measures in all subjects (those with AD or DLB and controls) involved use of the Cambridge Cognitive Examination (CAMCOG), which incorporates the Mini-Mental State Examination (MMSE) [6]. Verbal episodic memory and visual episodic memory were assessed with the Hopkins Verbal Learning Test (HVLT) and Brief Visual Memory Task–Revised (BVMT), respectively, and a composite z-score of episodic memory (verbal and visual) relative to control group performance was derived to incorporate all aspects of the memory task, as described previously [3].

Verbal fluency was assessed with the Delis Kaplan letter fluency task (FAS). Motor parkinsonism was assessed with the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) [7].

2.2. Imaging

Subjects underwent MRI scanning on a 3T MRI system (Intera Achieva scanner, Philips Medical Systems, Eindhoven, Netherlands) with an 8-channel receiver head coil within 2 months of the baseline cognitive study assessment, and at 1 year after the initial scan.

DTI images were acquired using a Pulsed Gradient Spin Echo (PGSE) sequence and multi-slice single shot EPI readout, with 24 slices. TE = 71 ms and TR = 2524 ms with 2 mm in-plane resolution, 6 mm slice thickness and matrix size of 128 × 128. Diffusion weighting was in 16 directions with a b value of 1000 s mm^{-2} and a single measurement at b = 0 s mm^{-2}.

A T1 weighted volumetric sequence (3D MPRAGE, sagittal acquisition, 1 mm isotropic resolution and matrix size of 240 × 240 × 180; TR = 9.6 ms; TE = 4.6 ms; flip angle = 8°; SENSE factor = 2) was also acquired. Additionally, we acquired quantitative images using a fast quantitative T1 measurement based on a custom inversion recovery prepared EPI sequence (axial slices, 2 mm isotropic resolution, matrix 128 × 128 × 72, TR = 15 s, TE = 24 ms, inversion time TIR = 0.25–2.5 s in 12 uniform steps); and a fast quantitative multi-echo T2 measurement based on a Gradient and Spin Echo Imaging sequence (2 mm isotropic resolution, matrix 128 × 128 × 72, TR = 4.7 s, 8 spin echoes at 20 ms spacing, EPI factor 5).

2.3. Image processing

Data were processed with the FSL toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). The DTI images were processed to correct for subject motion and eddy current distortion, and fractional anisotropy (FA) and mean diffusivity (MD) calculated. The baseline and 1 year FA images were spatially registered together, by calculating the transform from base to 1 year, and vice versa, and resampling both images to the space halfway between them. The average of the baseline and 1 year FA maps was then calculated, along with the difference of the two MD and FA maps. We then used the TBSS package in FSL to align the average FA maps for each subject to the standard template, and to create a mean FA skeleton representing the centres of all tracts common to the cohort. Each subject's difference FA and MD data were then projected onto the mean FA skeleton. Voxelwise statistics on the skeleton were then performed on the difference images to look for longitudinal increases or decreases in FA and MD between groups. This was done as an ANOVA, without covariates, and also with the addition of age, sex, and WMH (white matter hyperintensity) score to the model. We used the TFCE (threshold-free cluster enhancement) [8] to find regions of significant difference between groups correcting for multiple comparisons. We also calculated the mean (and SD) of change in FA and MD within the entire skeleton for each group. Reported clusters are all $p < 0.05$ corrected for multiple comparisons.

In addition, we used the FSL SIENA package to determine longitudinal brain atrophy from the 3D T1 weighted images, as described in our previous publication [9].

In order to visualise white matter hyperintensities, an image with contrast resembling a FLAIR (fluid attenuated inversion recovery) sequence was calculated from the quantitative T1 and T2 maps [10] and the standard image contrast for inversion recovery [11]. The resulting images (see supplementary figure e1 for examples) were reviewed by two experienced raters (RB, SJC) who rated the white matter hyperintensities according to the Fazekas scale [12]. We took the deep WMH score as representative of vascular disease and included it in the analysis of the DTI data.

3. Statistics

We used SPSS (version 22, IBM, New York, USA) for analysis of non imaging data. Group comparisons were performed with ANOVA or Chi square. Comparison of mean FA and MD controlling for covariates was done with the general linear model, with fixed factors of group and sex, and covariates of age and deep WMH rating. Correlations were performed with Pearson correlation.

4. Results

Table 1 shows the subject demographics of the study participants with repeat DTI data. AD and DLB were well matched for overall cognitive impairment, though as expected, AD subjects performed worst on baseline episodic memory. The DLB subjects showed significant progression of motor features as assessed by increased UPDRS ($p = 0.045$). There were no significant differences between groups in WMH rating score. WMH score was significantly correlated ($p < 0.001$) with both mean FA and MD in the whole white matter at baseline, controlling for group and age.

Since a number of subjects had dropped out since our original baseline DTI study [3], we repeated analysis of the baseline FA and MD, but including only the subjects in the present report. The results from subjects with followup data were similar to those in the whole group, with FA decreased, and MD increased, in both AD and DLB (suppl. Figures e2 & e3).

We found regions throughout the white matter where MD increased longitudinally in AD relative to controls [Fig. 1]. There were also small regions in the left parietal and temporal lobe where the MD increases in AD were greater than DLB. No regions of significant change in MD were found in DLB or controls, or in FA in any group. Addition of covariates of age, sex and WMH rating did not qualitatively change these results. The mean increase in MD in the whole skeleton was significantly different between groups, (control 0.0044 SD 0.009 × 10^{-3} mm^2 s^{-1}; AD 0.0139 SD 0.016 × 10^{-3} mm^2 s^{-1}; DLB 0.0056 SD 0.019 × 10^{-3} mm^2 s^{-1}) $F_{2,66} = 3.2$, $p = 0.047$, with post hoc AD > control (Tukey $p = 0.045$). The group difference was still significant after including age, sex and WMH in the model ($F_{2,63} = 3.3$, $p = 0.038$). Neither age, sex, nor baseline WMH rating significantly predicted change in MD ($p > 0.1$). Overall change in mean FA in the whole skeleton was not