DTI measures at the midline corpus callosum in patients with incipient and mild Alzheimer's disease

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Introduction: Diffusion tensor imaging (DTI) can be used to identify white matter (WM) tract changes, and several DTI measures have previously been proposed as markers of demyelination, axonal damage and neuronal loss [1]. It is unclear, however, how these measures relate to atrophy and global cognition in neurodegeneration; and whether in region-of-interest (ROI) studies, changes in diffusivity are due to true microstructural abnormalities in WM tracts or if, in contrast, they are generated by the artefactual inclusion of adjacent tracts due to atrophy. To try to answer some of these questions and to minimise measurement errors, we performed a DTI study of the midline corpus callosum (CC) in incipient and mild Alzheimer's disease (AD) patients. Several DTI measures were compared to CC area as a marker of atrophy and global cognitive data for evaluation of cognitive status.

Methods: Twenty-four subjects, 13 patients diagnosed with mild cognitive impairment or MCI (age: 70±6), 7 mild AD patients (age: 66±6) and 4 healthy controls (age: 66±3) took part in this study. When scanned, the control, MCI and AD group's mean mini-mental state examination (MMSE) scores were 29.0/30 (σ=1.4), 26.0/30 (σ=2.4) and 24.0/30 (σ=1.7), respectively. Addenbrooke's cognitive examinations (ACEs) were also performed on all participants; ACE is a 100-point global cognitive screening instrument [2] that is sensitive to the cognitive deficits of early AD. MRI scans were performed on a Siemens Trio 3T system with a gradient set capable of 45 mT/m and 200 T/m/s, and a 12-channel TIM head-coil. T_1-weighted anatomic images were acquired using a 3D magnetisation-prepared rapid gradient-echo (MPRAGE) pulse sequence (TR/TE/TI=2300/2.86/900 ms, flip angle 9°, 1 average, 144 slices, 192×192 matrix size, 1.25×1.25×1.25 mm^3 voxel size). DTI was performed using a single-shot echo-planar imaging (EPI) pulse sequence (TR/TE=7800/90 ms, b-value=1000 s/mm^2, 62 non-collinear diffusion sensitising gradient orientations, 1 average, 63 slices, 96×96 matrix, voxel size: 2-mm isotropic), and one EPI volume acquired without diffusion gradients (b=0 s/mm^2). FMRIB's Diffusion Toolbox (FDT) was used to correct for eddy currents, fit the diffusion tensor and compute diagonal elements (λ_1 or axial diffusivity, λ_2 and λ_3), mean diffusivity (MD) and fractional anisotropy (FA) at each brain voxel. $(\lambda_2+\lambda_3)/2$, known as radial diffusivity (RD), were also calculated. The volumetric scans were coregistered to diffusion space (FA image) and manual tracings of the CC in the mid-sagittal slice were taken with special care to avoid partial volume effects. These ROIs were then used to mask the parametric maps and calculate the CC areas in the midline. Due to varying degrees of cortical atrophy and brain sizes, the cross-sectional areas were normalised (A_r) to the total inter-cranial volumes (TIVs), which were calculated using a previously described method [3].

Results and Discussion: Although axial diffusivities appear to increase slightly with disorder progression, Fig. 1(a) reveals that neurodegenerative disease is not strongly associated with λ_1 variations in the CC. It is conceivable that axonal damage may not reflect drastic changes in axial diffusivity; however, it is plausible that the increase in diffusivities perpendicular to the main diffusion direction (λ_2 and λ_3) is more significant when axons degenerate. The histogram plots of MD, RD and FA in Fig. 1(b)-(d) show an evident change in parametric values, characterised by an increase in mean and radial diffusivity, and a decrease in anisotropy with disease progression. It becomes apparent from the MD and RD histograms that disease causes certain intra-voxel diffusivities to increase above a critical value ($1.1\cdot10^{-3}$ and $6.5\cdot10^{-4}$ for MD and RD, respectively). This behaviour was quantified by high mean, and radial, diffusivity integrals (HMDI and HRDI); with lower and upper integration limits at the empirically-defined critical value and maximum diffusivity value, respectively, and computed as a percentage of the total integral. Table 1 lists normalised CC areas, mean ACE scores, mean λ_1, MD, RD and FA values, and diffusivity integrals in the CC ROI for each participant's group. In summary, the results are in agreement with previous findings [4-7], suggesting that there is a progressive change in cognitive performance, brain atrophy and tissue microstructure during neurodegenerative decline towards AD. Next, an evaluation was made of the linear relationship between normalised CC area, diffusion parameters and global cognition of 20 patients using Pearson's correlation. Table 2 shows the correlation coefficients, $r(18)$, of each pair, which indicates that there is a statistically significant linear relationship between all diffusion coefficients (except axial diffusivity) and normalised CC area (p<0.05). Poor λ_1 prediction for A_r caused MD and FA to exhibit worse correlation to brain atrophy than RD. We found a very strong relationship (p<0.001) between HRDI and A_r. In contrast, the correlation with ACE scores was stronger for MD compared to RD. This, however, did not translate into a better FA prediction, which surprisingly appeared to be totally independent of global cognition. HMDI presented the best correlation to ACE score (p<0.001). Importantly, it was observed that the high diffusivity integrals systematically improved correlation with both CC area and ACE score compared to that of mean ROI values. In particular, RD's relationship with ACE (p»0.1) turned into significant (p<0.05) by using the high diffusivity integral measure. Finally, it is important to note that although global cognition showed a very poor correlation with brain atrophy (p»0.1), the removal of two noisy data points resulted in $r(16)$=0.58, p≈0.01.

Conclusion: The analysis proposed in this pilot study indicated that CC degeneration in AD is significantly correlated with specific diffusion parameters. Fibre loss in the CC is particularly associated with increased diffusion perpendicular to the axonal direction; this was reflected by the strong relationship between radial diffusivity and normalised CC area. ACE score, in contrast, was better predicted by mean diffusivity in all three directions, which may indicate that global cognitive performance could be associated with the way axons are rearranged in the CC as axonal degeneration occurs. It was striking, however, to observe that FA changes were independent of global cognition when a single bundle of axons (the CC) was studied in isolation. Furthermore, it was found that high diffusivity integrals may be more biologically meaningful/sensitive than mean ROI values.

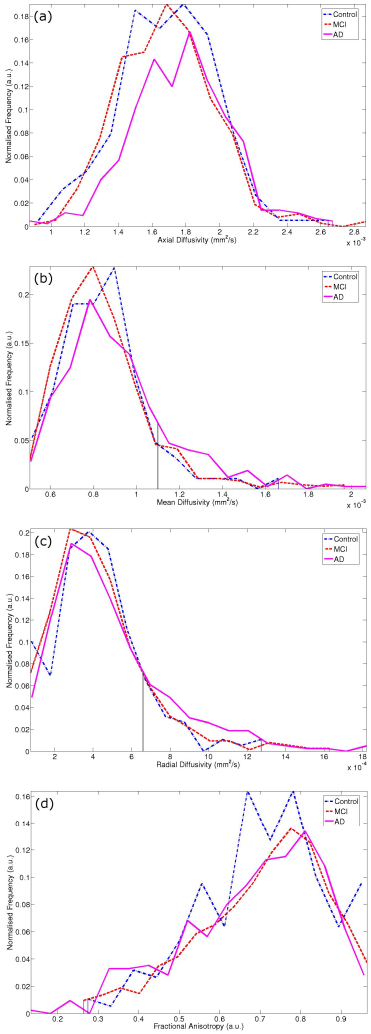

Fig. 1: CC (a) λ_1, (b) MD, (c) RD and (d) FA histogram plots.

Table 1: Mean normalised CC areas, ACE scores, ROI diffusion parameter values and high diffusivity integrals.

	Control	*MCI*	*AD*
A_r ($\cdot10^{-4}$ a.u.)	3.63	3.35	3.12
ACE (%)	89.5	81.2	70.9
λ_1 ($\cdot10^{-3}$ mm^2/s)	1.68	1.69	1.77
MD ($\cdot10^{-4}$ mm^2/s)	8.42	8.47	9.13
RD ($\cdot10^{-4}$ mm^2/s)	4.21	4.27	4.86
FA (a.u.)	0.709	0.708	0.689
HMDI (%)	8.99	10.25	17.84
HRDI (%)	12.70	14.91	22.30

Table 2: Correlation coefficients (*p<0.05 uncorrected for multiple contrasts).

	A_r	*λ_1*	*MD*	*RD*	*HMDI*	*HRDI*	*FA*
A_r	---	0.24	-0.49*	-0.62*	-0.59*	-0.69*	0.58*
ACE	0.21	0.39	-0.51*	-0.28	-0.71*	-0.45*	0.08

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