

# DTI measurements of neurodegeneration in early Alzheimer's disease: A corpus callosum study

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**Introduction:** Although diffusion tensor imaging (DTI) can be used to identify microstructural abnormalities in white matter tracts<sup>1,2</sup>, it is unclear what tensor changes represent in neurobiological terms and how they relate to global cognition in neurodegeneration. To explore these questions while minimising measurement errors caused by tract boundary uncertainty, we performed a reductionist DTI study in a directly visualized tract –the midline corpus callosum (CC)– in mild Alzheimer's disease (AD) patients. Several DTI measures were investigated in detail and compared to cognitive status. **Methods:** Forty-two patients (age: 70±6) diagnosed with early-stage probable AD according to Dubois criteria<sup>3</sup> and 29 sex-, age- and education-matched healthy volunteers (age: 68±7) were explored in this study. When scanned, the control (CN) and AD group's mean mini-mental state examination (MMSE) scores were 29.0/30 ( $\sigma=1.5$ ) and 23.8/30 ( $\sigma=3.6$ ), respectively. Addenbrooke's cognitive examination – revised<sup>4</sup> (ACE-R) scores were also obtained for all participants. MRI scans were performed on a Siemens Trio 3T system with gradient coils capable of 45 mT/m and 200 T/m/s slew rate. A 12-channel TIM head-coil was used with twice-refocused single-shot EPI: TR/TE=7800/90 ms; matrix, 96 x 96; 63 axial slices and voxel resolution of 2x2x2 mm<sup>3</sup>. The diffusion tensor was acquired with diffusion gradients along 63 non-collinear directions ( $b=1000$  s/mm<sup>2</sup>), and one scan without diffusion weighting ( $b=0$  s/mm<sup>2</sup>,  $b_0$ ); the total scan time was 8'44". T<sub>1</sub>-weighted anatomic images were also acquired using a 3D MPRAGE pulse sequence: TR/TE/TI=2300/2.86/900 ms, flip angle 9°, 144 slices, 192x192 matrix and 1.25x1.25x1.25 mm<sup>3</sup> voxel size; scan time was 7'23". The FMRIB's diffusion toolbox was used to correct for eddy currents, fit the diffusion tensor and compute diagonal elements (L1 or axial diffusivity, L2 and L3), mean diffusivity (MD) and fractional anisotropy (FA) at each brain voxel.  $(L2+L3)/2$ , known as radial diffusivity (RD), were also calculated. Each  $b_0$  image was coregistered to match its corresponding structural image, and the CC in the mid-sagittal slice was manually traced to extract the diffusion parameters from each DTI map. The CC's cross-sectional area normalised to the total intra-cranial volume was not statistically different between ADs and CNs. The lack of atrophy allowed us to divide the CC automatically in three regions (splenium, body and genu) of equal length along the axis connecting the furthest point in each direction from the CC's centre-of-mass. **Results and Discussion:** AD patients showed significantly increased mean L1, RD and MD in both splenium (L1:  $p=0.035$ ; RD:  $p=0.048$ ; MD:  $p=0.018$ ) and genu (L1:  $p=0.031$ ; RD:  $p=0.046$ ; MD:  $p=0.031$ ) compared to the mean values in the CN population using nonparametric Mann-Whitney  $U$  tests. L1 and MD changes in AD were found to be the most sensitive metrics, which is in agreement with a previous investigation<sup>5</sup>. Mean FA, however, although not significantly, decreased in the splenium, whereas it remained unchanged in the body and genu. The results confirmed that the splenium and genu of the CC are involved in AD, whereas the body of the CC remains relatively intact. The figure below shows probability density functions (*pdfs*) of L1, RD, MD and FA in the splenium and genu; voxel values were binned into 11 equally spaced containers and error bars were derived from the variability between subjects. L1 exhibited narrow *pdfs* that could be approximated to normal distributions. RD *pdfs*, however, were more dispersed and positively skewed. As a result, MD *pdfs* were also slightly positively skewed and FA *pdfs*, negatively skewed. An important feature of L1 is that it not only increases in AD patients, but also its variability remains constant during the early stages of the disease. This is illustrated by the symmetry of the L1 integral differential between control and patient populations (coloured bars in figure). The very narrow distribution of positive and negative differentials in the splenium suggests that L1 does not change as a function of cognitive performance; instead, it seems to be sensitive to early neurodegeneration in a discrete manner. The integrals over positive (or negative) integral differentials also revealed that changes in MD (12% of the splenium and 7.5% of the genu), L1 (11%/8%) and RD (10%/7%) are more widespread in AD than FA reductions (8%/6.5%). Besides, it is important to note the large distribution of RD positive differentials in contrast with the narrow negative differential. This can be seen as radial diffusion taking a large range of values in neurodegeneration. This characteristic makes RD a suitable marker of cognitive decline, which is reflected by the significant Pearson's correlation coefficient resulting from testing the strength of the linear relationship between mean RD in the splenium and MMSE ( $p=0.018$ ), and the non-significant trend with ACE-R ( $p=0.060$ ). FA is even more dispersed than RD, and although is the least sensitive metric to detect abnormalities in AD, its pattern of change in the splenium predicts cognitive performance more accurately (MMSE:  $p=0.010$ ; ACE-R:  $p=0.034$ ). FA correlations with MMSE/ACE-R scores can be improved using low-anisotropy integrals (MMSE:  $p=0.004$ ; ACE-R:  $p=0.016$ ) instead of mean FA values. We found that global cognition is highly correlated with the concentration of voxels in the splenium with FA lower than the total mean in the patient population. Note that total FA and RD means in the splenium present the largest positive integral differences between patients and controls. RD correlations with cognitive scores were also improved using high-diffusivity integrals (MMSE:  $p=0.015$ ; ACE-R:  $p=0.056$ ). Another interesting result, not necessarily evident from these plots, is that mean L1 is significantly correlated with mean RD –but not FA– in the splenium ( $p=0.002$ ) and genu ( $p=2 \cdot 10^{-4}$ ) –but not in the body– of control subjects. The linear relationship between diffusivities along orthotropic orientations may suggest that axonal and/or glial densities are inherently variable in these two structures across the elderly population. MD and FA were also found to be inversely correlated in splenium ( $p=2 \cdot 10^{-7}$ ) and genu ( $p=0.016$ ) –but not in the body–, which reinforces the idea of a scenario with uneven neuronal structures. **Conclusions:** The results indicate that the splenium is involved in the cognitive decline of early AD patients; this is in agreement with the hypothesis that the posterior association cortex<sup>6</sup> is selectively vulnerable in AD. The genu is also abnormal, although it possibly follows a different pattern of abnormality to that in the splenium. This is not an implausible scenario, since the genu contains tracts connecting ventral frontal cortex regions where amyloid plaques are known to deposit pre-clinically in AD<sup>7</sup>. However, the differences observed in the parametric *pdfs* suggest that the neurodegenerative processes involved in the genu may be somewhat different to those in the splenium. **References:** 1. J Mol Neurosci 34:51 (2008); 2. NMR Biomed 15:435 (2002); 3. Lancet Neurol 6:734 (2007); 4. Neurology 55:1613 (2000); 5. Brain (in press; doi:10.1093/brain/awp257); 6. Ann Neurol 54:343 (2003); 7. J Neurosci 25:7709 (2005).

