Diffusivity changes are predominantly proportional along all axes with early neurodegeneration in Alzheimer's disease

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Introduction: Diffusion tensor imaging (DTI) is broadly used to identify white matter (WM) tract abnormalities in neurodegenerative diseases such as Alzheimer's disease (AD)[1, 2]. To date, several DTI measures have been proposed as markers of demyelination, axonal damage, neuronal loss, increase in membrane permeability, destruction of intra-cellular compartments or glial pathology[3]. However, the vast majority of studies have only focused on changes in *mean diffusivity* (MD) and *fractional anisotropy* (FA) without reporting results for their component *eigenvalues* in isolation (*i.e.* λ_1, λ_2 & λ_3). Using changes in FA to measure loss of WM tract integrity assumes that degeneration will give rise to changes in the anisotropy of the *diffusion ellipsoid*. This is true if, for instance, radial diffusivity (RD=λ_2+λ_3/2) increased and *axial diffusivity* (λ_1) remained constant, as is typically hypothesised to explain loss of myelin sheath and/or nerve fibres[4]. Conversely, if longitudinal and transverse diffusion increased proportionally, then FA, which is a function of their ratio, would remain relatively unchanged. We hypothesised that this might be the case in early-stage AD *i.e.* that changes in the diffusion tensor may be primarily isotropic as a result of the complex interaction between several neurodegenerative processes.

Methods: Thirty-eight subjects, 25 patients diagnosed with mild AD (age: 70±6) and 13 sex- and age-matched controls (age: 67±6) took part in this study. When scanned, the control and AD groups mean mini-mental state examination (MMSE) scores were 29.0/30 (σ=1.2) and 22.9/30 (σ=4.1) respectively. MRI scans were performed on a Siemens Trio 3T system equipped with gradient coils capable of 45 mT/m (slew rate, 200 T/m/s) and a 12-channel TIM head-coil. The diffusion tensor was acquired using a conventional *single-shot echo-planar imaging* (EPI) pulse sequence with diffusion-gradient orientations along 63 non-collinear directions (b=1000 s/mm^2, TR/TE/NEX 7.8 s/90 ms/1, 63 axial slices, 96×96 matrix, voxel size: 2-mm isotropic), and one scan without diffusion weighting (b=0 s/mm^2). *FMRIB's diffusion toolbox*[5] (FDT v2.0) was used to correct for *eddy currents*, fit the tensor and compute the diagonal elements, MD, RD and FA at each brain voxel. Warping errors due to anatomical discrepancies and brain atrophy were minimised by taking advantage of the *tract-based spatial statistics* (TBSS v1.1) approach[6]; this method allows voxel-wise statistics to be applied only at the centre of each major fibre bundle defined by a study-specific *WM tract skeleton*. Nonparametric *t*-tests of reduced/increased DTI indices in patients were performed using *randomise* v2.1[7]; we generated 5000 permutations of the data to test against. Correcting for multiple testing and choosing a meaningful threshold level is also a perennial dilemma in voxel-wise statistics; although there is a mathematical rationale for using *false-discovery rate* (FDR) or *family-wise error* (FWE), determining a critical value for "clinical" significance is much more problematic. We therefore compared three increasingly conservative significance levels: (i) p<0.01 uncorrected for multiple comparisons, (ii) FDR-corrected p<0.05 and (iii) FWE-corrected p<0.05. Cluster-like structures were enhanced using the *threshold-free cluster enhancement*[8] (TFCE) algorithm.

Results and Discussion: TBSS results for increased FA and reductions in diffusivities did not show any statistically significant difference at p<0.01 (uncorrected threshold). Results for reduced FA and increased λ_1, RD and MD (**Fig. 1**) however, highlighted concordant clusters of significance for all three diffusivity indices, unlike FA for which there was an overall lack of sensitivity. Anisotropy changes not only were less extensive, but also were not significant when we controlled the rate of *type I errors*. In contrast, diffusivity differences were highly significant as they largely survived FDR and FWE correction. These observations are consistent with the hypothesis that early neurodegeneration in AD is associated with proportional changes in any plane of the diffusion ellipsoid. Abnormalities were bilateral and confluent involving the posterior cingulum bundle, parahippocampal gyrus and spreading into lateral posterior temporoparietal WM areas; significant differences were also found in the fornix and the splenium of the corpus callosum. Hypometabolism in adjacent grey matter areas is an established feature in AD[9, 10]; it is believed that these areas degenerate as part of a functionally and anatomically integrated network[10, 11] and that there would be relative sparing of caudal occipital lobe, temporal pole and prefrontal WM. The findings for λ_1, RD, and MD, but not for FA, identified precisely this distribution of WM changes.

Summary and Conclusions: In this study, we analysed changes in the anisotropic properties of the diffusion ellipsoid (FA) and the underlying driver for these differences (i.e. changes in λ_1, RD and MD) in mild AD patients compared to elderly controls. Results for increased diffusivities were concordant, more sensitive and therefore, more biologically plausible than those for FA. These findings suggest that current models of axonal integrity simply explained by FA reductions do not suffice to describe WM deterioration in early-stage AD and possibly in neurodegenerative diseases in general.

References: 1. Damoiseaux, J.S. et al. *Hum Brain Mapp* (2008); 2. Fellgiebel, A. et al. *Neuropsychologia* 46, 1698 (2008); 3. Beaulieu, C. *NMR Biomed* 15, 435 (2002); 4. Song, S.K. et al. *Neuroimage* 17, 1429 (2002); 5. Smith, S.M. et al. *Neuroimage* 23 Suppl 1, S208 (2004); 6. Smith, S.M. et al. *Neuroimage* 31, 1487 (2006); 7.Nichols, T.E. et al. *Hum Brain Mapp* 15, 1 (2002); 8. Smith, S.M. et al. *Neuroimage* (2008); 9. Nestor, P.J. et al. *Nat Med* 10 Suppl, S34 (2004); 10. Nestor, P.J. et al. *Ann Neurol* 54, 343 (2003); 11. Nestor, P.J. et al. *Neuroimage* 30, 1010 (2006).

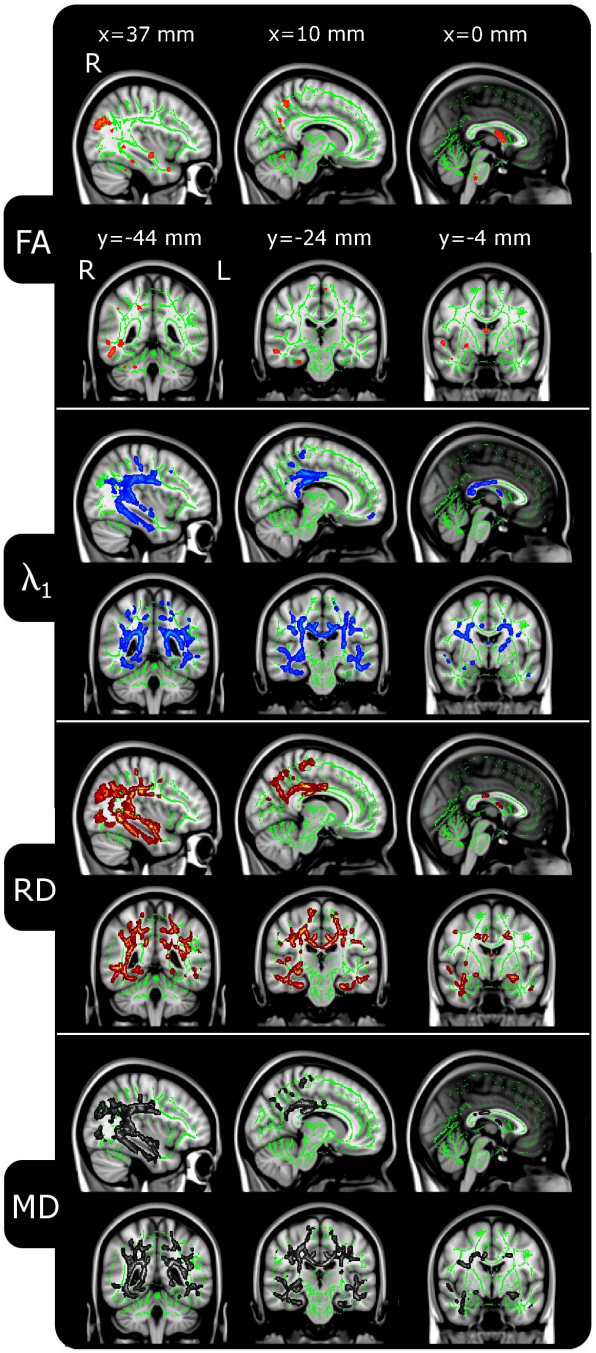

Figure 1. Thresholded (uncorrected p<0.01) statistical maps for reduced FA and increased λ_1, RD and MD in AD patients overlaid onto the MNI152 template and the WM tract skeleton. All images are displayed in "radiological" convention.