

The diffusion ellipsoid loses planarity in early Alzheimer's disease

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Introduction: Diffusion tensor imaging (DTI) is a neuroimaging technique that has extensively been used in the context of Alzheimer's disease (AD) research to identify microstructural alterations in white matter (WM) pathways. Earlier results showed that both primary (axial and radial) diffusion components (L1 and RD) are abnormally increased in a spatial pattern that involves parietal and superior temporal WM tracts connecting the so-called circuit of Papez (Acosta-Cabronero et al., Brain 2010). This scenario, whereby the abnormal diffusion ellipsoid expands in all directions, renders fractional anisotropy (FA) relatively insensitive because both L1 and RD increase in concert. A recent study clarified that in the clinical evolution of AD primary diffusivities increase in varying degrees: L1, early and abruptly, remaining then relatively unchanged over time; and RD, linearly predicting cognitive decline – this leads to FA reductions that are only apparent in later disease stages (abstract submitted to ISMRM 2012). This result helped explain why FA abnormalities in AD have been inconsistently reported; more importantly, it highlighted that the earliest diffusion changes are not highly anisotropic as measured by FA. In the present study, we explored a range of other anisotropy measures in a cohort of mildly-impaired subjects to shed new light on the profile of the early diffusion tensor behaviour characterising AD. **Methods:** Twenty-one patients (age: 72±5) diagnosed with early-stage probable AD according to Dubois criteria (Lancet Neurol 2007) and 26 matched controls (CTL, age: 68±6) were recruited. When scanned, the CTL and AD group's mean mini-mental state examination (MMSE) scores were 29.1/30 (σ=0.8) and 25.9/30 (σ=1.6), respectively. Experiments were performed on a Siemens Trio 3T system with gradient coils capable of 45 mT/m, and a 12-channel TIM head-coil. We used a twice-refocused, single-shot EPI pulse sequence with TR/TE=7800/90 ms; matrix, 96 x 96; 63 axial slices and voxel resolution of 2x2x2 mm³. The sequence was first run without diffusion weighting (b=0 s/mm², b₀), and then diffusion gradients were applied along 63 non-collinear orientations (b~1000 s/mm²) to feed the single-tensor model; the total scan time was 8'44". The FMRIB's diffusion toolbox was used to correct for eddy currents, fit the tensor and compute the diagonal elements; negative eigenvalues were set to 0. In addition to those for primary diffusivities, we also computed maps for all indices shown in the list. TBSS (Smith et al., Neuroimage 2006) was used to perform voxelwise analyses of skeletonised WM tract centres; we ran 10,000 permutations of the data using 'randomise' and enhanced cluster-like structures (Smith and Nichols, Neuroimage 2009). All statistical maps were family-wise error corrected (P<0.05). **Results and Discussion:** The thresholded statistical maps for all primary diffusivities were mostly

bilateral and confluent in superior temporal and parietal WM areas including the posterior cingulum and the splenium. Overall, in this study, we found that the derived metric radial diffusion (RD) and its component eigenvalues (L2 and L3), were spatially concordant, though we noted that L3 appeared to be slightly more sensitive to neurobiological changes, particularly in left parietal WM areas. MD results, unsurprisingly, also overlapped with those from its components and therefore, they did not reveal new abnormalities (hence not shown). FA, in contrast, suffered a noticeable reduction in sensitivity compared to all primary and derived diffusivity metrics. Similar results to those for FA, though even less extensive, were found for other 6 anisotropy metrics (not shown). It should be noted, however, that geodesic anisotropy (GeoA) showed slightly more extensive clusters of significance than FA. This result is in agreement with previous simulations (Correia et al., Neuroimage 2011) that suggested that GeoA should perform better than FA for the typical diffusion anisotropy regimes present in the human brain. Taken together, these observations suggest that overall, absolute diffusivities are more sensitive to the underlying neurodegenerative processes that drive the characteristic diffusion-weighted features of early AD; which therefore, make them more meaningful to detect early WM alterations than standard measures of diffusion anisotropy. FA or GeoA, for instance, have in common that they are weighted by disproportionate changes in diffusivity that may occur along any of the three orthogonal orientations defined by the

$$\begin{aligned} \text{RD} &= \frac{\lambda_2 + \lambda_3}{2} \\ \text{MD} &= \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \\ \text{FA} &= \frac{\sqrt{\frac{3}{2} \left[(\lambda_1 - \text{MD})^2 + (\lambda_2 - \text{MD})^2 + (\lambda_3 - \text{MD})^2 \right]}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \\ \text{RA} &= \frac{\sqrt{\frac{1}{3} \left[(\lambda_1 - \text{MD})^2 + (\lambda_2 - \text{MD})^2 + (\lambda_3 - \text{MD})^2 \right]}}{\text{MD}} \\ \text{VR} &= \frac{\lambda_1 \lambda_2 \lambda_3}{\text{MD}^3} \\ \text{VF} &= 1 - \text{VR} \\ \text{UA}_{\text{surf}} &= 1 - \frac{\sqrt{(\lambda_1 \lambda_2 + \lambda_2 \lambda_3 + \lambda_3 \lambda_1) / 3}}{\text{MD}} \\ \text{UA}_{\text{vol}} &= 1 - \frac{(\lambda_1 \lambda_2 \lambda_3)^{1/3}}{\text{MD}} \\ \text{UA}_{\text{vol,surf}} &= 1 - \frac{(\lambda_1 \lambda_2 \lambda_3)^{1/3}}{\sqrt{(\lambda_1 \lambda_2 + \lambda_2 \lambda_3 + \lambda_3 \lambda_1) / 3}} \\ \text{LI} &= \frac{\text{FA} + \text{FA}^2}{2} \\ \text{GeoA} &= \sqrt{\sum_{i=1}^3 \log^2 \left(\frac{\lambda_i}{\text{MD}} \right)} \\ \text{C}_l &= \frac{\lambda_1 - \lambda_2}{\lambda_1 + \lambda_2 + \lambda_3} \\ \text{C}_p &= \frac{2(\lambda_2 - \lambda_3)}{\lambda_1 + \lambda_2 + \lambda_3} \\ \text{C}_s &= \frac{3\lambda_3}{\lambda_1 + \lambda_2 + \lambda_3} \\ \text{C}_a &= \frac{\lambda_1 + \lambda_2 - 2\lambda_3}{\lambda_1 + \lambda_2 + \lambda_3} \end{aligned}$$

diffusion eigenvectors. In other words, unless the diffusion ellipsoid stretches only axially or transversely, or along more than one axis but in opposite directions, primary diffusivities will be more sensitive to change than these derived measures. We now know that early WM abnormalities in AD are characterised by an early increase in L1, accompanied by a slower—but more steady—change in RD (submitted to ISMRM 2012). In addition, in this cross-sectional study of mild AD, we also observed that L3 changes may overpower those for L2. Thus it seems appropriate in this context, to dissect diffusion anisotropy into components that render more specifically a wider variety of geometric changes. The family of geometric anisotropy measures (Peled et al. Brain Research 1998) attempt to relate measures of anisotropy to the underlying structural geometry of the tensor. These indices split diffusion behaviours into three basic cases: linear (C_l), planar (C_p), and spherical (C_s or C_a). In the linear case, C_l will be large for diffusion that is highly restricted along the transverse orientation; it may therefore be indicative of tract-orientation uniformity within a voxel. The planar anisotropy metric (C_p) is highly sensitive to deviations from the plane spanned by the two eigenvectors corresponding to the two largest eigenvalues. The spherical measures (C_s and C_a), in contrast, are specifically sensitive to disproportionate changes along the most restricted diffusion orientation i.e. that of L3. Note that C_s and C_a are similar, hence only results for the former are shown here. In this study, the distribution of C_p reductions (i.e. loss of tensor planarity) was found to be much more widespread than that of C_l reductions (i.e. loss of linearity) or increased C_s/C_a (i.e. gain of sphericity), and is spatially concordant with changes in both L1 and RD, which suggests that the diffusion ellipsoid, overall, becomes less planar in mild AD subjects. Less planar, in this scenario, means primarily that L3 takes values closer to L2, but also that L1 diverges from L2; note that the perfectly-oblate case is described by L1 ≈ L2 » L3. FA or GeoA are therefore only effective to detect linear and spherical changes in AD, whereas absolute diffusivities are highly effective in the detection of the more widespread loss of tensor planarity. Note that these results are in agreement with the increased sensitivity observed for L1 and L3 relative to that for L2. **Conclusion:** Loss of planarity appears to be the most biologically-meaningful description of the anisotropic changes in the mild AD's diffusion tensor.

