

## Dynamic diffusion tensor behaviour in the evolution of Alzheimer's disease

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**Introduction:** Conflicting results have been reported in Alzheimer's disease (AD) using diffusion tensor imaging (DTI). Some studies show stronger axial diffusion (L1) differences; some report stronger radial or mean diffusion (RD/MD) effects; and some studies show, in addition, widespread fractional anisotropy (FA) reductions. Although such variability may be influenced by differences in diffusion time and post-processing methodology, in this study we explored the hypothesis that in AD, there is a differential impact on the diffusion tensor at different disease stages. To try to resolve what alterations are more prominent early, and how they differ from those that are more apparent later, we contrasted 3T DTI data from two AD groups: (a) patients typically diagnosed with mild-cognitive impairment or MCI-stage AD—i.e. patients scanned at the MCI stage who were subsequently shown to have AD—and (b) moderately-impaired AD subjects, both compared cross-sectionally. We then assessed a cohort that was followed up longitudinally in a transition from mild to moderate stages, and regressed DTI data against a global measure of cognitive status. We performed whole-brain analyses and also assessed a directly-visualised white matter (WM) tract that is known to be severely damaged in AD *i.e.* the corpus callosum (CC). **Methods:** Forty-three patients (age:  $70 \pm 6$ ) and 26 matched controls (CTL, age:  $68 \pm 6$ ) were recruited. Addenbrooke's cognitive examination—revised (ACE-R) (Mioshi et al, Int Ger Psych 2006) 100-point scale scores were obtained for all participants; hence enabling a median split into mild (best 50% ACE-R:  $81 \pm 4$ ,  $N=21$ ) and moderate AD cohorts (worse 50% ACE-R:  $62 \pm 9$ ,  $N=22$ ). In addition, a subgroup of 16 AD subjects was followed up with scans and neuropsychology tests taking place 12 months apart (ACE-R at baseline/12 months:  $70 \pm 14$ / $78 \pm 7$ ). 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 to transmit/receive r.f. signals from a twice-refocused, single-shot EPI pulse sequence: TR/TE=7800/90 ms; matrix,  $96 \times 96$ ; 63 axial slices and voxel resolution of  $2 \times 2 \times 2$  mm<sup>3</sup>. The sequence was first run once without diffusion weighting ( $b=0$  s/mm<sup>2</sup>,  $b_0$ ), and was followed by the application of diffusion gradients along 63 non-collinear orientations ( $b=1000$  s/mm<sup>2</sup>); the total scan time was 8'44''. Anatomical T<sub>1</sub>-weighted images were also acquired in the same session using MPRAGE: TR/TE/TI=2300/2.86/900 ms, flip angle 9°, 144 slices,  $192 \times 192$  matrix and  $1.25 \times 1.25 \times 1.25$  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 L1, RD, MD and FA maps. For the region of interest study,  $b_0$  images were coregistered to structural images, where the CC was individually traced. We then segmented the CC into three regions (splenium, body and genu) of equal length along the axis that connects the most distal (caudal and rostral) points from the CC's centre-of-mass. Mean subject values were statistically compared against the CTL population using nonparametric Mann-Whitney *U* tests; pairwise Pearson's linear correlations against cognitive profiles

were also computed. The TBSS approach (Smith et al., Neuroimage 2006) was used to perform voxelwise statistics at the WM tract centres (FA>0.2), with 10,000 permutations of the data and enhancing cluster-like structures (Smith and Nichols, Neuroimage 2009). Statistical maps were inspected at three different threshold levels: both corrected (family-wise error,  $P<0.005$  and 0.05) and uncorrected for multiple comparisons ( $P<0.01$ ). **Results and Discussion:** The CC study showed that the body and genu were relatively preserved throughout the course of the disease (not shown). As expected from prior knowledge, analysis of the splenium (Fig. 1), however, revealed significant ( $P<0.01$ ) tensor profile changes that can be summarised as follows: in the mild group (blue), only increased L1 featured prominently, whereas RD and FA were found to change more significantly than L1 in later disease stages (magenta). In addition, RD and FA alterations were found, therefore, to be good predictors of cognitive decline, whereas L1 was found to remain relatively stationary. These results suggest that, in the splenium, (i) L1 is the most sensitive DTI marker to detect early AD abnormalities; and that (ii) RD, and hence FA also, are more sensitive metrics for tracking disease progression. If this behaviour extended beyond the mid-sagittal splenium, in turn, it would explain the variability observed in metric sensitivity between AD studies. To test this, we inspected TBSS maps (FWE,  $P<0.05$ ) and found extensive L1/RD/FA abnormalities in the moderate group that were mostly bilateral and confluent in superior temporal and parietal WM areas including the posterior cingulum bundle and splenium fibres (not shown). Concordant, though less extensive results were also found for the mild AD group at the same threshold level. In this latter analysis, however, we were particularly interested in the most prominent early alterations, hence we explored a more stringent statistical threshold (FWE,  $P<0.005$ ), at which only L1 clusters survived (blue, Fig. 2); the most affected tracts included interhemispheric projections through the splenium to the posterior cingulate cortex (and possibly to other parietal and superior temporal areas). Note that spatially concordant clusters of significance were also found for RD and FA at less stringent threshold levels; and also in the longitudinal assessment, where RD/FA—but not L1—changed significantly (in these same areas) in the transition from mild to moderate AD (not overlaid to avoid confusion). Also in agreement with the regional plots and concordant with previous results, we found that FA was strongly correlated with ACE-R along the same WM tracts (red, Fig. 2). **Conclusions:** This study demonstrated that there is a dynamic evolution of diffusion tensor change with evolving AD; specifically an abrupt L1 increase is the most statistically prominent early alteration but this then remains stable (in other words a 'state-specific' marker), while RD (and therefore FA) become increasingly abnormal as the disease progresses (a 'stage-specific' marker).

