Using atrophy as a marker of disease severity to understand the evolution of DTI changes in Alzheimer’s disease
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Introduction
DTI is a neuroimaging technique that is being applied widely in Alzheimer’s disease (AD) research to identify microstructural alterations in white matter (WM) tracts. Several neurodegenerative processes – modelled in vitro or by computer simulations – have successfully been captured by diffusion MRI (Beaulieu NMR Biomed, 2002) but results have sometimes been inconsistent and such models are, by definition, reductionist and therefore can never fully represent the complexity of neurodegenerative mechanisms. In order to better understand how DTI parameters might reflect neuronal loss in AD, the relationship of tensor metrics to a measure of grey matter atrophy (i.e. hippocampal volume) was explored in this study using an unbiased whole-brain method and a regional approach.

Methods
Forty-three patients (age: 70±6; MMSE: 23.7±3.6) with early-stage probable AD according to NINCDS-ADRDA criteria and 26 matched controls (CTL, age: 68±6) were recruited from the memory clinic at Addenbrooke’s Hospital. MRI scans were performed on a Siemens Trio 3T system with a 12-channel TIM head-coil using a twice-refocused, single-shot EPI pulse sequence: 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, and was then followed by the application of diffusion gradients along 63 non-collinear orientations (b=1000 s/mm²); the total scan time was 8’44” (GRAPPA=2). FSL’s diffusion toolbox was used to correct for eddy currents, fit the tensor and compute λ₁, RD, MD and FA maps. Anatomical T₁-weighted images were also acquired in the same session using MPRAGE: TR/TE/TI=2300/2.86/900 ms, flip angle 9°, 144 slices, 192x192 matrix and 1.25x1.25x1.25 mm³ voxel size; scan time was 7’23”.

Results
Voxel-wise regressions showed that left hippocampal volumes in AD patients are strongly related to (increased) RD and (reduced) FA bilaterally and confluently in mesial parietal, temporo-parietal and caudal temporal WM, with strongest coefficients along the caudal CC. Significant RD correlations were slightly more extensive than those for FA along the posterior cingulum and in superior temporal areas. MD results overlapped with those for RD but overall they were less extensive and more left lateralised (data not shown). λ₁ statistical maps did not survive the applied significance level. The regional study revealed that RD, MD and FA in the splenium of the CC – but not in the truncus or the genu – are strongly related to left mesial temporal lobe atrophy. λ₁ was found to be independent of hippocampal shrinkage. Note that data for the right hippocampus (not shown) presented with a similar behaviour albeit correlations were less marked.

Discussion
In a previous study, we found that RD/FA – but not λ₁ – correlated with dementia severity as measured by global cognition, implying that whatever these two metrics capture, it is likely to be related to neuronal loss (Acosta-Cabronero et al. PLoS ONE, 2012). The current study further explored this question using atrophy as an independent marker of disease severity and demonstrated that RD/FA also co-vary with mesial temporal lobe atrophy; whereas λ₁, which is the most sensitive marker of AD degeneration in incipient clinical stages, behaves independently of both cognitive deficits and hippocampal volume reductions. The results in this study, therefore, provide additional supporting evidence that suggests that early λ₁ alterations in AD, which precede those for RD/FA in the same neural network (Acosta-Cabronero et al. PLoS ONE, 2012), may be capturing an upstream event to axonal degeneration.