

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 2×2×2 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 λ_1 , 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, 192×192 matrix and 1.25×1.25×1.25 mm³ voxel size; scan time was 7'23''. Left and right hippocampi were manually traced on coronal slices and their volumes were normalised by total intracranial volume or TIV (Jack *et al.* Neurology, 1989). TIV was determined for each subject using a previously validated method (Pengas *et al.* J Neuroimaging, 2009). For the regional study, we extracted DTI data from 3 callosal subdivisions (splenium, truncus and genu) of equal length along the axis that connects the most distal midsagittal corpus callosum (CC) boundaries. The regional DTI relationships with hippocampal atrophy were tested using Pearson's correlations. TBSS v1.2 was used to perform whole-brain linear regressions with 10,000 permutations of the data and threshold-free cluster enhancement (TFCE). Statistical maps were thresholded at P_{TFCE}<0.05.

Results

Voxel-wise regressions showed that left hippocampal volumes in AD patients are strongly related to (increased) RD and (reduced) FA bilaterally and confluent 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). λ_1 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. λ_1 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 λ_1 – 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 λ_1 , 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 λ_1 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.

