# TRACT ATROPHY IN ALZHEIMER'S DISEASE MEASURED USING PROBABILISTIC TRACTOGRAPHY

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**Introduction** The quantitative characterisation of atrophy can provide useful biomarkers for assessing the evolution of neurological conditions such as Alzheimer's disease (AD). While current literature has mainly focused on measuring the atrophy of whole brain, global grey and/or white matter (WM), specific lobes or grey matter structures (e.g. the hippocampus), it is likely that atrophy caused by such conditions also affects WM tracts via degenerative processes. If specific tract systems are more prone to atrophy than others, then tractography-guided atrophy measurements may be more sensitive than less targeted methods. For this purpose, in this work we apply a novel method for quantifying the width of WM tracts to look for evidence of tract atrophy in mild cognitive impairment (MCI) and AD subjects.

**Methods** High angular resolution diffusion-weighted imaging (HARDI) was performed on subjects using a reversed k-space distortion-corrected protocol [1]. Acquisition: 3T Philips Achieva scanner; 8 element SENSE head coil; SENSE factor 2.5; phase-encoding in L-R orientation; PGSE EPI sequence with $TE$ = 54 ms, $TR$ = 11884 ms, $G$ = 62 mTm$^{-1}$, 112 × 112 matrix, reconstructed resolution 1.875 x 1.875 mm$^2$, slice thickness 2.1 mm, 60 slices, $b$ = 1200 smm$^{-2}$ ($\Delta$, $\delta$ = 29.8, 13.1 ms), and 1 $b$ = 0 image. After processing the acquired data using $q$-ball and model-based residual bootstrapping [2,3], to determine multiple fibre orientations in every voxel, the *PICo* multi-fibre probabilistic tractography method [4,5] was used to extract the uncinate fasciculus (UF) and inferior longitudinal fasciculus (ILF) from both hemispheres of eight Normal-Aged, eight MCI and seven AD subjects. The superior longitudinal fasciculus (SLF) was also extracted successfully in the healthy group but proved impossible to extract reliably in the AD group and is therefore not considered further here. Using an automated thresholding algorithm, connection probability threshold values of 0.09 and 0.08 were identified as optimum for the UF and ILF respectively. This algorithm starts by randomly selecting a tract from a given subject as the target tract and using affine registration with 12 degrees of freedom to register all the tracts from the same hemisphere of other subjects to this target tract to create an initial average tract of the population. The initial average is then used to again register all the individuals' tracts from their native space into the initial average tract's space, resulting in a secondary average tract. The secondary average tract is manually thresholded by the user in order to have an estimate of the true topology of the tract of interest; this is the only manual intervention in the algorithm. The secondary average tract is then used as the template for determining the optimum group threshold. The algorithm successively applies a threshold value within the connection probability range [0,1] with a step of 0.01 and applies each threshold to each individual's tract. At each step, using Dice's similarity coefficient [6], the algorithm computes the overlap between the thresholded tract and the thresholded template in 3D space. The overlap scores at each threshold step are averaged over all subjects and the threshold value with the highest average overlap score is identified as the group optimum. The tract masks were then up-sampled by a factor of 3 and subsequently smoothed using a box kernel of size 3x3x3. As we previously reported in [7] an adapted implementation of the electric field model described by [8] was used to generate the curve-skeletons of the extracted tracts. Using the electrostatic vector field computed as part of the electric field model, the geodesic surface-skeleton distance was calculated by tracking from every boundary voxel through this electrostatic vector field until a skeleton voxel is reached. The mean geodesic distance at every skeleton voxel, referred to as the half width, was calculated by averaging all the streamlines tracking to that voxel. Using the generated curve-skeletons, the half widths of the tracts were computed as a function of position along the skeleton (Fig 1).

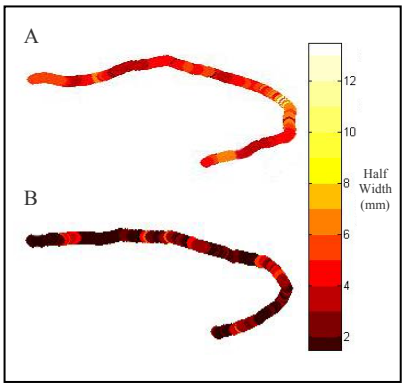


Figure 1: A) UF skeleton of a Normal-Aged subject colour-coded by half width values. B) UF skeleton of an AD subject colour-coded by half width values.

**Results** For the UF, in the Normal-Aged group seven out of eight subjects demonstrated right hemisphere lateralization where the right UF had a greater average half width than the left (paired $t$-test p = 0.0054). In the MCI group seven out of eight subjects also demonstrated right hemisphere lateralization, which was also significant at group level (paired $t$-test p = 0.0057). In the AD group there was no such clear pattern of lateralization (paired $t$-test p = 0.6815). For the ILF, there was no clear pattern of lateralization or statistical significance between the left and right ILF tracts in all three groups.

Figure 2 illustrates the normalized histograms of half width values of the left (blue) and the right (red) UF for the Normal-Aged, MCI and AD groups. The cross group comparisons using unpaired $t$-tests showed that there was a statistically significant difference between the average half width values of the right UF of the Normal-Aged group and the AD group (p = 0.0071); and between the average half width values of the right UF of the MCI group and the AD group (p = 0.015). However, the cross group comparisons for the left UF, and the left and right ILF average values did not demonstrate any significance.

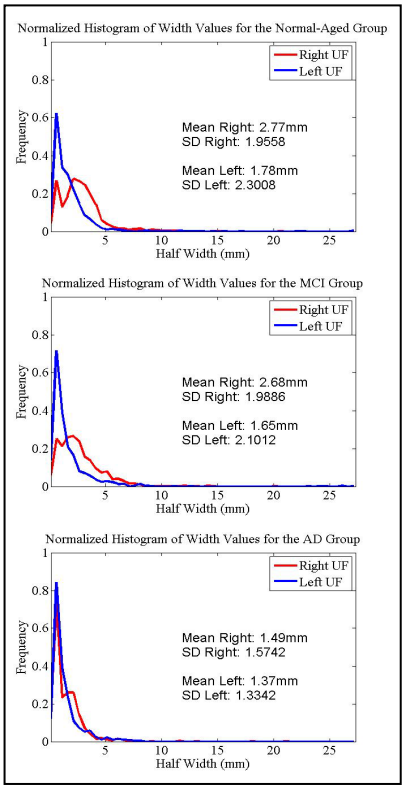


Figure 2: Normalized histograms of the half width values of the Left and Right UF tracts of all the subjects in the Normal-Aged (Top), MCI (Middle) and AD (Bottom) groups.

**Discussion & Conclusions** This work demonstrates that it is possible to identify the effects of Alzheimer's disease on tracts via the use of a novel measurement of tract width. The evidence of possible right hemisphere lateralization for the UF in the Normal-Aged and MCI groups is comparable to published *in vitro* work [9], which found right hemisphere lateralization in the UF in 80% of their subjects. Interestingly this lateralization was not detected in the AD group, perhaps indicating hemisphere-specific atrophy processes involving the uncinate fasciculus. Longitudinal studies using our method are now required in order to assess if it may have future use as a biomarker in clinical trials to assess the performance of a given treatment on the rate of atrophy.

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**References** [1] Embleton *et al*, *HBM*, in press, 2009, [2] Tuch, *Magn. Reson. Med*., 52, 1358, 2004, [3] Haroon *et al*, *IEEE Trans Med Imaging*, 28, 535, 2009, [4] Parker *et al*, *Lect. Notes Comput. Sci.*, 2732, 684, 2003, [5] Parker *et al*, *Phil. Trans. Roy. Soc. Series B*, 360, 893, 2005, [6] Shattuck *et al, Neuroimage*, 45, 431, 2009. [7] Azadbakht *et al*, *Proc ISMRM*, 4957, 2009. [8] Cornea *et al*, *The Visual Computer*, 21, 945, 2005, [9] Highley *et al*, *Cerebral Cortex*, 12, 1218, 2002.