Longitudinal Tract Atrophy in Normal Aging and 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 examine tract atrophy in normal-aged and AD subjects undergoing serial diffusion MRI scans 1 year apart.

Methods MRI images were acquired approximately 1 year apart on a 3.0 Tesla scanner (Philips Medical Systems, Best, The Netherlands) at the F.M. Kirby Research Centre for Functional Brain Imaging at the Kennedy Krieger Institute. DTI images were acquired using a SENSE head coil. An eight-element RF coil, converted to six-channel to be compatible with the six-channel receiver, was used. DTI acquisitions were made using a single-shot spin echo–echo planar sequence (SE-EPI), with diffusion gradients applied in 32 non-collinear directions and $b = 700$ s/mm^2. Five additional reference images with least diffusion weighting ($b = 33$ s/mm^2) were also acquired. Sixty axial slices were acquired to cover the entire cerebrum and cerebellum, parallel to the AC-PC line. The field of view/size of the acquisition matrix/slice thickness were 212 × 212 mm^2/96 × 96/2.2 mm. Other imaging parameters were: TR > 7000 ms and TE = 80 ms; and SENSE reduction factor = 2.5. To improve the signal-to-noise ratio, two datasets were acquired, leading to a total acquisition time of 7 min. A follow up scan was also acquired 12 months later. After processing the acquired data using constrained spherical deconvolution (CSD) [1], to determine probability density functions of multiple fibre orientations in every voxel [2], the *PICo* multi-fibre probabilistic tractography method [3,4] was used to extract the uncinate fasciculus (UF), inferior and superior longitudinal fasciculi (ILF and SLF) from both hemispheres of ten normal-aged and eight AD subjects at both visits. Using an automated thresholding algorithm [5], study specific *PICo* connection probability threshold values of 0.07, 0.07 and 0.6 were identified as optimum for the UF, ILF and SLF respectively. As previously reported in [6], an adapted implementation of the electric field model described by [7] 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 vertex of triangulated tract representations through this electrostatic vector field until a skeleton voxel was reached. Using the generated curve-skeletons, the half-widths of the tracts were computed as a function of position along the tract (Figure 1).

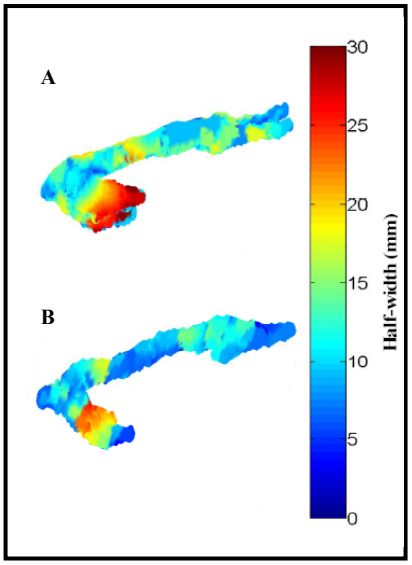

Figure 1

A) Right UF of an AD subject extracted from the initial scan data colour-coded by half width-values.

B) Right UF of the same AD subject extracted from the follow up scan data colour-coded by half-width values.

Results For the UF, in the normal-aged group 7 out of 10 subjects demonstrated a statistically significant ($P<0.05$) hemisphere lateralisation with the right UF having a greater average half-width than the left. This pattern was reduced to 6 out of 10 subjects in the follow-up scan. The SLF showed statistically significant lateralisation, with 8 out of 10 subjects having greater left average half-width than the right. This pattern was maintained in the follow-up scan. For the ILF, there was no clear pattern of lateralisation in both scans. In the AD group, there was no statistically significant pattern of lateralisation in all three tracts.

When comparing the mean half-width values longitudinally (initial scan vs. follow up), for the normal-aged and AD groups using Wilcoxon paired non-parametric tests, all tests show significant differences. The tests also point to a difference in the rates of the progression of atrophy in the two groups, with a consistently more rapid rate of atrophy in the AD group. Table 1 illustrates the various comparisons that were made.

Table 1 The results of inter-group tests along with the mean half-width reduction values. Inter-hemispheric differences where tested for using two tailed *t*-tests, taking unequal variances into account. Longitudinal differences were tested for using Wilcoxon paired non-parametric tests.

	Normal-Aged						AD					
	UF		ILF		SLF		UF		ILF		SLF	
Comparison	p-value	Difference (mm)	p-value	Difference (mm)	p-value	Difference (mm)	p-value	Difference (mm)	p-value	Difference (mm)	p-value	Difference (mm)
* $L_1 \leftrightarrow R_1$	0.021	r:4.21±3.95	0.792	2.24±1.47	0.006	l:1.9±0.95	0.368	1.13±1.14	0.904	1.53±1.06	0.139	2.94±2.17
$L_2 \leftrightarrow R_2$	0.055	r:3.98±3.69	0.742	2.27±1.31	0.005	l:2.19±0.94	0.768	2.13±1.68	0.337	2.05±1.38	0.053	2.58±1.89
$R_1 \leftrightarrow R_2$	0.002	-1.5±0.45	0.002	-0.72±0.2	0.002	-0.96±0.48	0.008	-2.23±1.25	0.008	-1.14±0.9	0.008	-1.53±1.05
$L_1 \leftrightarrow L_2$	0.002	-0.92±0.21	0.002	-0.77±0.26	0.002	-0.72±0.18	0.008	-1.63±2.07	0.008	-1.96±1.71	0.008	-0.93±0.37

* L_1/R_1 denotes the hemisphere from which the tract was extracted from: L=Left, R=Right; l=left-lateralisation; r=right lateralisation. The subscript numbers indicate the scan: 1 is the initial scan and 2 is the follow up.

Discussion & Conclusions This work demonstrates that it is possible to identify the effect of progression of Alzheimer's disease on tracts via the measurement of tract width. The evidence for right hemisphere lateralisation for the UF in the Normal-Aged group is comparable to published *in vitro* work [8], which found right hemisphere lateralisation in the UF in 80% of their subjects and is compatible with previous cross-sectional tractography findings [5]. The lack of lateralisation of the UF in the AD group is also compatible with this previous work [5]. The higher rate of atrophy of UF and SLF over 1 year in the right hemisphere that we have observed in both noarmal-aged and AD subjects indicates possible hemisphere-specific atrophy processes that are accelerated in the presence of AD and is comparable to previously reported findings [9]. The findings of this study indicate that our method is sensitive to both longitudinal changes and inter-hemispheric differences in tract width and may have future use as a biomarker in clinical trials to assess the performance of therapeutic intervention on the rate of atrophy.

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