Voxel-Based Analysis of Alzheimer's Disease using Apparent Fibre Density

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Introduction: Alzheimer's disease (AD) is the most common cause of dementia and is pathologically characterised by the build up of amyloid plaques and neurofibrillary tangles in the brain. Previous diffusion-weighted imaging (DWI) studies have detected significant changes in several white matter pathways in AD. Regions that are reported to be affected across DWI studies include the corpus callosum, cingulum, uncinate fasciculus and superior longitudinal fasciculus (SLF) [1]. The majority of previous DWI studies have investigated scalar measures of the diffusion tensor (DT) such as Fractional Anisotropy (FA) [2]. However, since the diffusion tensor cannot appropriately model voxels with crossing fibres, differences in FA are difficult to interpret biologically in terms of individual fibre bundles [3].

In this paper we investigate AD using a recently developed measure called Apparent Fibre Density (AFD) [4]. The AFD measure is derived from Fibre Orientation Distributions (FOD) computed from high angular resolution DWI. Numerical simulations suggest that the AFD (the FOD amplitude) along a given orientation can be interpreted as being proportional to the intra-axonal volume of axons aligned with the respective orientation [4]. Voxel-based analysis of AFD permits population differences to be localised in both the spatial *and* orientation domains. Therefore unlike existing measures such as FA, AFD differences can be attributed to a single fibre bundle within a region containing multiple fibres. In this work we demonstrate the first use of AFD to detect voxel-wise changes in AD patients, and identify the specific pathways involved.

Methods: Data were acquired from 39 AD subjects and 91 age-matched healthy volunteers recruited as part of the Australian Imaging Biomarkers & Lifestyle Flagship Study of Ageing (3T Siemens Trio, 60 DW directions, b=3000 s/mm^2, 2.3mm isotropic). Pre-processing involved mask-based motion correction [4], DW bias field correction based on a b=0 image [5], and mean DW intensity normalisation across subjects (based on the mean b=0 cerebral spinal fluid intensity). The DW image resolution was up-sampled by a factor of 2 using cubic b-spline interpolation, since in our experience this improves image alignment during the registration process. FODs were computed by Constrained Spherical Deconvolution [6] using MRtrix [7], using the group average single fibre response function. To establish voxel-wise correspondence between subjects, we first computed a population-specific FOD template from 20 randomly chosen AD subjects and 20 healthy controls, using an iterative update approach [8]. FOD images from all subjects were subsequently registered to the population FOD template. This was performed using the FOD spherical harmonic (SH) L$_2$ norm metric with a maximum SH degree (l_{max}) of 4 [8]. During registration, the Jacobian matrix at each point in the displacement field was used to reorient the FODs using apodised Point Spread Function (PSF) reorientation [9]. Because the non-linear registration process alters a fibre bundle's total volume and therefore its total AFD, when applying the final transformations the AFD is modulated by an amount proportional to the corresponding change in cross-sectional area (and hence in axonal density) [4]. Spatially normalised, reoriented, modulated FODs were sampled along 200 equally distributed orientations within each voxel. AFD was then compared across corresponding voxels and directions. As described in [4], 'non'-fibre directions were excluded from analysis using a 4D mask. As each AFD comparison is associated with both a voxel and a direction, statistical analysis (and multiple comparison correction) must be performed over both the spatial and angular domains. This was achieved using the supra-threshold cluster-based permutation testing approach outlined in [4]. In this method, supra-threshold t-values are clustered with neighbours defined in both space and orientation. We chose a cluster-forming threshold of t>3.36 (corresponding to an uncorrected p-value of 0.001), a neighbour angular threshold of 15 degrees, and 5000 permutations. Cluster significance was obtained by comparing the cluster size (defined as the number of supra-threshold directions, summed over all voxels within the cluster) to the maximal-cluster-size permutation distribution [10]. Significant clusters were visualised by computing a PSF along each direction in the cluster, which were averaged within each voxel [4].

Results: A significant decrease in AFD was observed in AD compared to healthy subjects within voxels *and* orientations corresponding to the left and right cingulum (Fig. 1b), left and right uncinate fasciculus (Fig. 1c-d), and the anterior commissure (Fig. 1c), corpus callosum (Fig. 1e) and SLF (Fig. 1f). No significant increases in AFD were detected in AD. Note that the uncinate fasciculus and parts of the anterior commissure were detected within a single cluster due to overlapping end points in the temporal lobes (Fig. 1e).
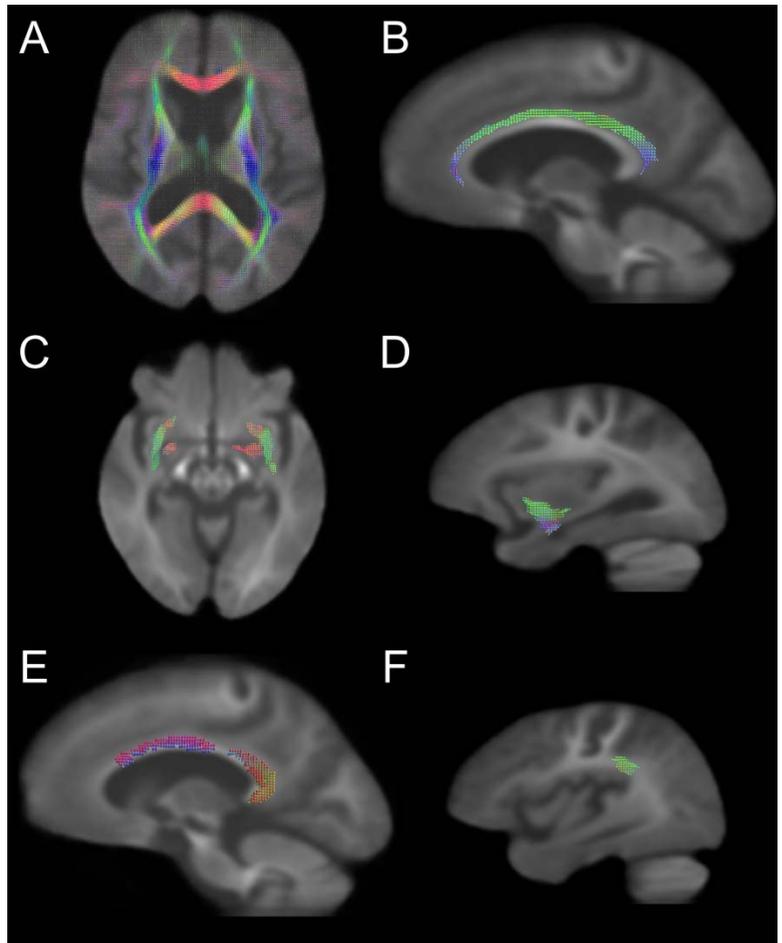

Figure 1. A) Population average image after FOD registration of all 130 subjects. FODs (l_{max} =4) overlaid on the l =0 SH coefficient image. **B-F)** show significant voxels and directions within a cluster (AD vs controls), visualised using the SH PSF method [4], colour coded for direction (green:anterior-posterior, red:left-right, blue:inferior-posterior), and overlaid on the group mean l=0 coefficient. **B)** Left cingulum (p<0.0002) **C)** Left (p<0.0004) and right (p<0.001) uncinate fasciculus, and anterior commissure. **D)** Right uncinate fasciculus (p<0.001). **E)** Corpus-callosum (p<0.0001) **F)** Superior longitudinal fasciculus (p<0.032). Note that all clusters displayed are more extensive than can be appreciated from a single slice. All p-values are corrected for multiple comparisons using the method in [4].

Discussion and Conclusion: We report the first use of AFD to detect changes in AD and the affected anatomy is consistent with previous findings [1]. Both the corpus callosum and SLF clusters contain significant voxels and directions within the centrum semiovale – a region known to contain many fibre crossings. This study demonstrates the advantage of AFD voxel-based analysis by assigning pathology-related changes to individual fibre bundles within regions containing multiple fibre orientations. Future work will investigate the ability of AFD to discriminate between mild cognitive impairement, AD and healthy subjects.

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