Decreased Apparent Fibre Density in the optic pathways correlates with Glaucoma disease severity

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Target Audience: Clinicians and neuroscientists with an interest in white matter degeneration in Glaucoma, and researchers that perform diffusion-weighed MRI and analysis.

Purpose: To investigate white matter degeneration in Glaucoma patients compared to healthy controls, and to investigate correlations between white matter loss and Glaucoma severity.

Introduction: Glaucoma is the second leading cause of blindness worldwide with 8.4 million bilaterally blind people[1]. It is a progressive neurodegenerative disease characterised by retinal ganglion cell and optic nerve fibre loss[2]. White matter (WM) microstructure abnormalities in glaucoma have been reported using diffusion tensor imaging (DTI). Tensor-derived parameters (fractional anisotropy and diffusivity) have been used to investigate correlations with disease severity[3] in glaucoma, as well as the topographic relationship between retinal ganglion cell loss and changes in the optic radiation[4].

In this work, we performed the first diffusion MRI study of glaucoma disease using the relatively new quantitative measure Apparent Fibre Density (AFD)[5]. AFD is derived from the Fibre Orientation Distribution (FOD), and is proportional to the intra-cellular volume of axons (i.e. density). Unlike diffusion tensor-derived measures, each AFD measurement can be associated with a specific population of fibres within a single voxel and is therefore robust in regions with crossing fibres. Herein we use the word *fixel* to refer to specific *fibre population* within a single *voxel*.

Methods: We recruited 88 subjects including 42 Glaucoma (18 male; 45 to 87 years; mean age 57.2) and 46 healthy controls (18 male; 40 to 80 years; mean age 64.9). For the purposes of AFD group comparisons, we separated Glaucoma patients into two groups (mild and advanced) based on results of a visual field test performed using the Advanced Glaucoma Intervention Study (AGIS) criteria[6]. Patients with an AGIS score of 0 to 5 were classified as mild Glaucoma (23 cases), and those with score of 6 to 20 were classified as advanced Glaucoma (19 cases).

Diffusion-weighted images were acquired on a 3T Siemens Trio (60 directions, b-value 3000 s/mm^2). Pre-processing was performed as described in[8]. FODs were computed by Robust Spherical Deconvolution[9] using MRtrix[10]. A population-specific FOD template was generated from a subset of data (mix of 10 healthy controls, 10 mild and 10 advanced glaucoma subjects) and all FOD images were registered to that template[11]. AFD modulation was applied in the final transform to account for axonal loss that manifests as fibre bundle atrophy[8]. Fixels were defined by identifying peaks in each FOD lobe, and the AFD computed as the integral of the FOD lobe[12].

We performed several whole-brain fixel-based analyses using a recently developed method called connectivity-based fixel enhancement (CFE)[5]. We compared the AFD in corresponding fixels between: all Glaucoma vs controls, advanced Glaucoma vs controls, mild Glaucoma vs controls, and mild vs advanced Glaucoma. In the Glaucoma patients only, we performed fixel-based correlations of AFD with two different measures of disease severity, namely the AGIS visual field score[6], and Pattern Standard Deviation (PSD). The PSD is derived from the adjusted thresholds in the pattern deviation probability plot[7], and is a measure of the focal loss. For statistical inference, we assigned both family-wise error (FWE) corrected and uncorrected p-values to each fixel using non-parametric permutation testing (5000 permutations). To visualise results, each fixel is rendered as a line within the appropriate voxel, and colour-coded according to the fixel orientation (red: R-L, blue: I-S, green: A-P) or p-value.

Results: As shown by Fig. 1a, a significant decrease in AFD was identified in the optic tract and optic radiation in Glaucoma patients compared with controls (FWE corrected p<0.05). Note that all significant fixels in the entire brain are displayed (*i.e.* a 'glass brain'). The same fibre tracts were identified in the advanced Glaucoma vs controls (Fig. 1b), with a slightly larger spatial extent. When comparing mild Glaucoma vs controls and mild vs advanced Glaucoma no fixels were significant at the FWE-corrected level. However when we investigated the uncorrected p-values (Fig. 1c & d), the optic tract was significant at p<0.001, as was parts of the optic radiation in the mild vs advanced comparison. In the AFD correlations with AGIS and PSD (Fig. 1e & f respectively), no fixels were significant at the FWE-corrected level, however at p<0.001 uncorrected the optic tract and radiation were significant.

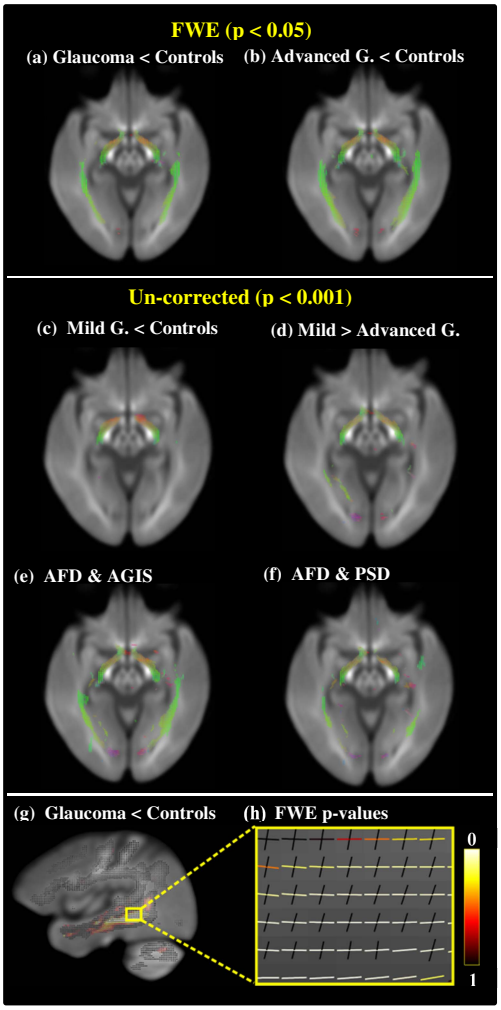

Figure 1. *Apparent fibre density (AFD) group differences and correlations. Statistically significant fixels (fibre populations within a voxel) are overlaid on the mean AFD template and coloured by direction Red:L-R, blue:I-S, green: A-P. Significant AFD decreases in Glaucoma compared to controls* ***(a),*** *advanced Glaucoma cases compared to controls* ***(b),*** *mild Glaucoma compared to controls* ***(c)*** *and mild compared to advanced Glaucoma* ***(d)*** *AFD negative correlation with* ***(e)*** *AGIS and* ***(f)*** *PSD.* ***(g)*** *Sagittal view of all fixels coloured by p-value.* ***(h)****Zoomed in region of (g), illustrating fixel-specific p-values of the optic radiation within voxels containing crossing fibres.*

Discussion and Conclusion: We have performed the first whole-brain fixel-based analysis of Glaucoma disease and observed decreased AFD in Glaucoma patients that was shown to correlate with disease severity. We note that previous DTI studies have also found group differences in the optic tract and radiation, however the AFD is a more biologically interpretable measure that is fibre bundle specific in regions with crossing fibres (as seen in Fig. 1h). In addition to the direct information provided regarding glaucoma, the tract specificity of these findings provides encouraging corroboration for both previous and future AFD fixel-based analysis where pathology exists in pathways that contain a larger proportion of voxels with crossing fibres.

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