Fixel-Based Morphometry: Whole-Brain White Matter Morphometry in the Presence of Crossing Fibres

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Target Audience: Researchers and clinicians interested in performing white matter morphometry using diffusion-weighted MRI (DWI).

Purpose: To develop a novel method for whole-brain white matter morphometry that gives fibre tract-specific information in voxels with crossing fibres.

Introduction: Voxel-based morphometry (VBM) and tensor-based morphometry (TBM) are commonly used methods for whole-brain morphometric population analysis. Both methods exploit information derived from the spatial warps computed during image registration of all subjects towards a common template. At each voxel in the non-linear warp, the local affine is defined by the spatial derivative (Jacobian matrix, **J**), and local volumetric change is described by the determinant of **J**. When investigating grey matter, differences in the Jacobian determinant imply a difference in the number of neuronal cells. However when investigating white matter (WM), the determinant does not necessarily reflect a difference in the number of axons, since the direction of the expansion or contraction relative to the fibre orientation is important. Expansion or contraction parallel to the fibre orientation implies a difference in axon length. However a change to the cross sectional area in the perpendicular plane implies a difference in the number of axons (Fig. 1a), which is potentially more relevant when investigating pathology.

A previous method for WM morphometry uses the diffusion tensor to estimate the fibre orientation (and therefore the cross-sectional plane) [1], however only a single fibre orientation can be derived from the tensor and this estimate is not robust in regions with crossing fibres. In this work we propose a novel method that uses Fibre Orientation Distributions (FOD) to resolve multiple *populations of fibres* within each *voxel* ('fixels'). We perform whole-brain statistical comparisons of fixels across groups in a method called fixel-based morphometry (FBM).

Method: To demonstrate the proposed method we compared 20 epilepsy patients (all with hippocampal sclerosis) with 80 age- and sex-matched controls. DWIs were acquired on a 3T Siemens Trio (60 directions, b=3000 s/mm^2, 2.5mm). Pre-processing involved motion correction and up-sampling by a factor of 2. FODs were computed by Robust Spherical Deconvolution[2]. Individual FOD images were flipped left-right to align the epileptic side and registered towards a symmetrical population-specific FOD template[3] (Fig. 1b). To identify fixels of interest (i.e. a fixel mask), we segmented each individual FOD[4] in the population template image and removed spurious fixels using a FOD 'lobe' integral threshold of 0.15.

For each fixel, *f*, in the template fixel mask we computed a measure, *c*, that reflects the change in perpendicular cross-sectional area: $c_f = \log\left(\det(\mathbf{J})/\left\|\mathbf{J}\hat{\mathbf{v}}_f\right\|\right)$, where det is the matrix determinant, **J** is the Jacobian matrix of a warp that maps from template to subject, $\hat{\mathbf{v}}_f$ is the Cartesian unit vector defining the orientation of fixel *f*. Similar to TBM, we perform the log transform to ensure data are zero centred and normally distributed. We compared *c* over all fixels between the epilepsy patients and controls. Statistical analysis was performed with connectivity-based fixel enhancement[5], using a whole-brain group average tractogram computed with the iFOD2 probabilistic streamlines algorithm[6] (Fig. 1c). Corrected p-values were assigned to each fixel using permutation testing (5000 permutations)[5]. Age, gender, ipsilateral side, and intra-cranial volume were considered as covariates of no interest.

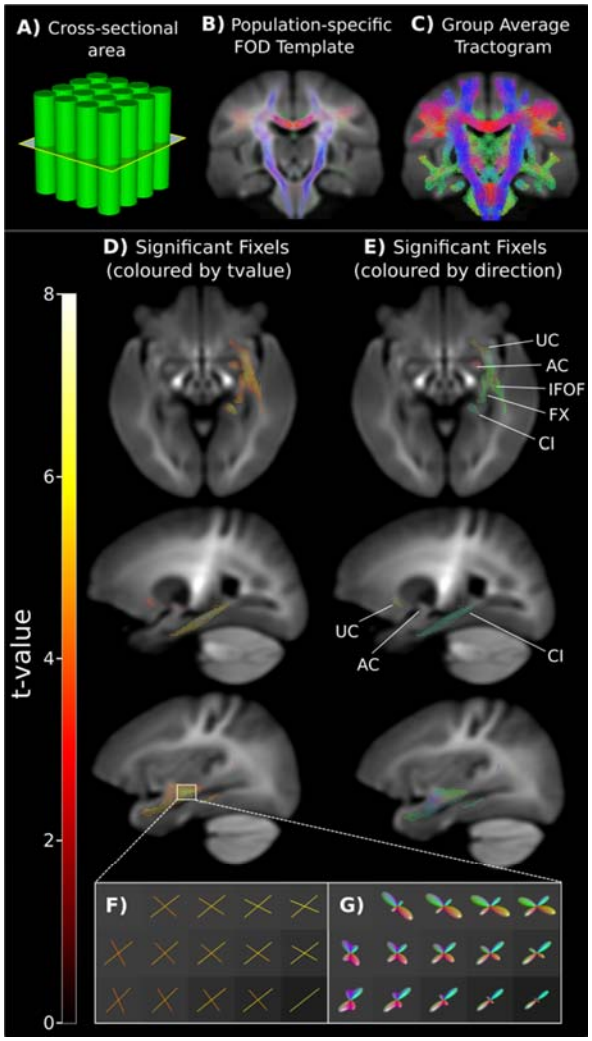

Figure 1. A) A population difference in cross-sectional area implies a difference in the number of axons. **B)** Unbiased population-specific FOD template. **C)** Group average tractogram used to define fixel-fixel connectivity in the statistical analysis. **D)** Fixels with a significantly reduced cross-sectional area in hippocampal sclerosis. Fixels are displayed as unit vectors, colour-coded by t-value. **E)** Significant fixels, colour-coded by direction (Red: L-R, Blue: I-S, Green: A-P). **F)** Significant fixels in a region containing crossing fibres. Each fixel is assigned a separate t-value. **G)** FODs from the population-specific template used to identify fixels of interest (corresponds to F).

Results: We observed a significant reduction in cross-sectional area in fixels within WM tracts projecting from the ipsilateral temporal lobe (Fig. 1d & e). Tracts include the uncinate fasciculus (UC), anterior commissure (AC), inferior frontal occipital fasciculus (IFOF), fornix (FX) and parahippocampal cingulum (CI). As shown by the crossing fibre region in figure 1f, each fixel has a separate t-value and therefore results are fibre tract specific.

Discussion: In this work we have developed a novel method called fixel-based morphometry (FBM). Unlike standard VBM and TBM, FBM is fixel specific, uses only the relevant information contained in the Jacobian matrix by considering the fibre orientation, and employs FOD images to drive accurate white matter registration. We note that FODs were also used for morphometry analysis in related work [7]; however FBM is a whole-brain approach not restricted to a tract of interest. Also note that while we used FODs for image registration and to define the fixels of interest, FBM can be performed using other higher-order diffusion models.

References: **[1]** Zhang et al. Proc MICCAI 2:466-473 (2009) **[2]** Tournier D et al., Proc. ISMRM 21, 0773 (2013), **[3]** Raffelt D et al. (2011) NeuroImage 56(3):1171-80 **[4]** Smith RE et al., Neuroimage 67, 298–312 (2013), **[5]** Raffelt D et al., Proc. ISMRM 21, 841 (2013), **[6]** Tournier D et al., Proc. ISMRM 18, 1670 (20) **[7]** Raffelt D et al., Proc ISMRM 19, 671 (2011)