HERITABILITY OF WHITE MATTER (WM) FIBRES BASED ON FIBRE ORIENTATION DISTRIBUTION (FOD) MEASUREMENTS ON HARDI DATA

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Purpose We aim to estimate the genetic influence on WM structures using Fibre Orientation Distrubution (FOD) based measurements [1]. We hypothesize that because FOD resolves the crossing fibres, it will allow measuring genetic influence on intra-voxel fibre structures. We estimated the heritability of FOD measures over a twin cohort, by projecting the heritability of FOD onto fibre tracks, and estimating the genetic influence along fibre tracks.

Method Materials The datasets used in this paper were acquired from *N*=328 subjects (118M, 210F) with average age of 22.7(2.3) years old. Among the subjects, there are 71 pairs (*N*=142, 48M, 94F) of monozygotic twins (MZ) with average age of 22.8(2.2) years old, and 90 pairs (N=180, 69M, 111F) of dizygotic twins (DZ) with average age of 22.6(2.4) years old. High Angular Resolution Diffusion Imaging (HARDI) data were acquired using a 4T Bruker Medspec MRI scanner. Each dataset consists of 11 images without diffusion sensitization (b=0), and diffusion weighted images (DWI) with 94 gradient directions at b = 1159 s/mm^2.

Data Processing DWI images were corrected for eddy current distortion and subject motion [2, 3]. N4 bias-field correction was performed [4]. Image intensity was normalized across the subjects. Constrained spherical deconvolution was used to reconstruct the FOD with up to 4th-order spherical harmonics, describing the distribution of the underlying fibre population with respect to spatial orientation at each voxel. A population average template was created to spatially normalize the FOD images. FOD images were registered to the template using a symmetric diffeomorphic non-rigid registration, with the FOD descriptors reoriented and modulated by the deformation field [5]. For the average FOD template, 3 peaks in the FOD profile with maximal amplitudes were identified using the MRtrix package [6] and in each registered FOD image, the peaks were match to the peaks identified on the FOD template.

Statistical Analysis We estimated both the reliability and the heritability of FOD peaks. The reliability of FOD peaks in terms of intra-class correlation (ICC) was estimated on a subset of 39 subjects scanned repeatedly with 3-month interval [7]. The measurements of FOD peak was modelled using an ACE model, in which the measurement is subjected to the influence of additive genetics A, common environment C, and residual E due to unique environment and measurement errors which are independent between individuals FODpeak = $A + C + E$. The measurements of FOD peak amplitude made on twin sample were used to fit the covariance structure of the ACE model. A non-negative least square estimation [8] was used to estimate the variance of each component, and the heritability index estimates of genetic influence within the total variance h^2=Var(A)/Var(FOD$_{peak}$).

Track-based Analysis We performed the whole brain probabilistic fibre tracking [9] on the population average FOD template. When generating fibre tracks, the fibre tracking algorithm was restricted to keep only the tracks connecting various cortices, linking cerebral cortex with subcortical nuclei, such as corticostriatal and corticothalamic tracts, and those travelling through the brain stem. Tracks ending in the WM without reaching cerebral cortex, subcortical nuclei, or passing through the brain stem were excluded since they do not represent anatomically plausible axons. As FOD peaks characterise the underlying fibre structure in each voxel, the heritability FOD peak measure describes genetic influence on the fibre tracks travelling through the voxel along the direction of the FOD peak. This allowed us to project the heritability index h^2 of FOD peaks onto the fibre tracks in the tractogram. For each point on a given track produced by the fibre tracking algorithm, we obtained its reliability and heritability by interpolating, respectively, the reliability and heritability estimates of the FOD peaks in the voxels surrounding the given point. We first located the point within a cell of eight surrounding voxels. In the surrounding voxels with two FOD peaks, we chose one peak that formed a smaller angle with the tangent of the track at the given point. The interpolating weight for each peak was determined in the same manner as in bilinear image interpolation. In case the angles between the tangential direction of the track at a point and all peak directions in one of the neighbouring voxels were greater than 45 degrees, we assigned zero reliability and zero heritability to the peak in the interpolation. This penalised the tracks deviating from the FOD peak directions by lower interpolated reliability and heritability. In addition, we set the less reliable heritability estimates to zero. A binary mask was created by thresholding the test-retest reliability ICC of FOD peaks at 0.6. We applied this mask to the voxel-wise peak heritability estimates, such that the heritability estimate for FOD peaks within the reliability mask is kept, while those without (reliability ICC < 0.6) were regarded as 0. The trimmed mean of the heritability calculated over the entire stretch of each track excluding the 5% highest and the 5% lowest values was calculated over the given track.

Results The average of estimated test-retest ICC in the WM (ROI defined by FA>0.3) was 0.670 for the first FOD peak measure and 0.547 for the second peak (in ROI defined by FA>0.3 and FOD > 0.1). The heritability of the first FOD peak averaged over the WM region was 0.204. The average heritability of the second FOD peak measurement in the WM was 0.252. The results of FOD peak heritability estimation is shown in Figure 1. The heritability estimated for fibre tracks is shown in Figure 2, in which spatially separated fibre connections are shown to have different heritability.

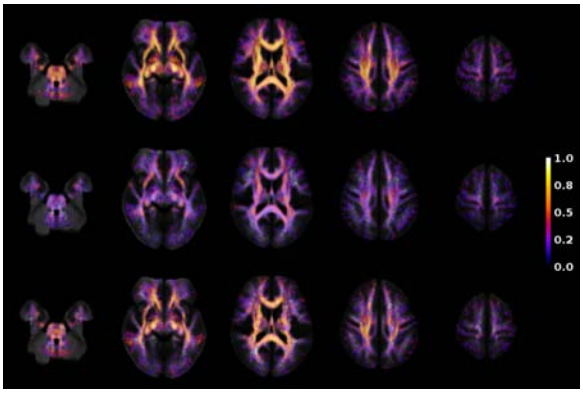

Figure 1. Heritability of the first peak in FOD measurement of diffusion MR in white matter overlaid on the average FA map. From top to bottom: ICC in MZ twins; ICC in DZ twins; heritability index h^2.

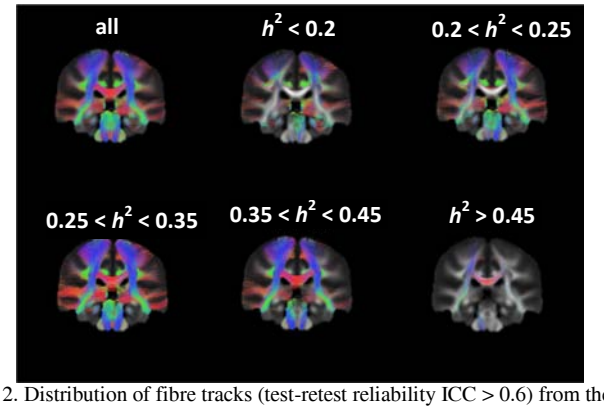

Figure 2. Distribution of fibre tracks (test-retest reliability ICC > 0.6) from the fibre tracking results according to heritability, coronal slice of the tractogram. The sample tracks are separated by thresholding their track-average heritability index.

Discussion and Conclusion We presented a new method of estimating the genetic influence on WM using FOD-based measurements. We used the FOD peak measure to quantify the fibre structure in each voxel, and estimated the heritability of WM fibres based FOD peak measure. We found that the FOD peak is strongly heritable across major WM tracts. In particular, the commissural fibres connecting contralateral hemispheres show strong heritability. By thresholding based on fibre heritability, we found spatially separated fibre population have different heritability.

References [1] Tournier *et al*., *Neuroimage* 35(4):1459-1472, 2007. [2] Raffelt *et al*., ISMRM 2012, 3555. [3] Rohlfing *et al*., MICCAI 2008, LNCS 5241:798-806. [4] Tustison *et al*., *IEEE TMI* 29(6) 1310-1320, 2010. [5] Raffelt *et al*., *NeuroImage* 59(4) 3976-3994, 2012. [6] Tournier *et al*., *Int J Imaging Syst Technology* 22(1):53–66, 2012. [7] Shen *et al*., ISMRM 2013, 2119. [8] Chen *et al*., "Voxel-wise cluster-based heritability inferences of fMRI data," OHBM 2013. [9] Tournier *et al*., ISMRM 2010, 1670.