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# Mapping Genetic Influences on Brain Fiber Architecture and Intellectual Performance - A High Angular Resolution Diffusion Imaging (HARDI) Study

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**Introduction:** A key neuroscientific question is how strongly the white matter (WM) architecture of the brain is determined by genetic versus environmental factors. To address this question, we analyzed HARDI data from 92 twins and fitted quantitative genetic models to model individual variations in white matter integrity between monozygotic (MZ) and dizygotic (DZ) twins. We used a cross-trait cross-twin design to determine (1) where in the brain fiber integrity was linked with intellectual performance; and (2) to what extent genetic factors mediated this correlation.

**Methods:** 30-gradient HARDI data were acquired from 23 MZ twin pairs (22M/24F; age = 25.1±1.5 years) and 23 same-sex DZ twin pairs (20M/26F; age: 23.5±2.1 years) on a 4T Bruker Medspec MRI scanner, as 27 diffusion-weighted ($b$ = 1132 s/mm$^2$) and 3 non-diffusion weighted volumes per subject: gradient directions were uniformly distributed on an imaginary sphere. Imaging parameters were: 21 axial slices (5 mm thick; 0.5 mm gap), 23 cm FOV, TR/TE 6090/91.7 ms, 1.8x1.8 mm$^2$ in-plane resolution; scan time: 3.05 minutes. HARDI data were registered by fluidly matching their corresponding diffusion tensor images (DTI), using an information-theoretic overlap measure (the symmetrized Kullback-Leibler divergence). We then computed 3D maps of WM integrity based on the generalized fractional anisotropy (GFA), which generalizes the FA concept from single-tensor DTI to HARDI [1]. To analyze genetic influences on WM integrity, we fitted structural equation models (SEM), to estimate the additive genetic (A), shared environmental (C) and unique environmental (E) components of variance in GFA at each voxel. The significance of genetic effects on GFA was evaluated by comparing the full ACE versus the reduced CE models. We then tested whether any regional correlations between WM integrity and intellectual performance were mediated by common genetic factors, by fitting cross-trait cross-twin models at every voxel.

**Results:** The first column in **Fig. 1** shows that there are highly significant genetic influences on fiber integrity (GFA), using the false discovery rate method (FDR <0.05) to correct for multiple comparisons. The other three columns present the percentage contributions of A, C, and E components to the variance in GFA. White matter integrity in regions of high diffusion anisotropy (FA > 0.3) was under strong genetic control, especially in the corpus callosum, the left cerebral peduncle, inferior longitudinal fasciculus/inferior fronto-occipital fasciculus, left posterior thalamic radiation/optic radiation, the superior longitudinal fasciculus, and the superior and posterior *corona radiata* bilaterally. In these regions, the strong correlation between GFA and intellectual performance was mediated by common genetic factors (**Fig. 2;** $r_a$ denotes the genetic correlation coefficient). Similar patterns were

noted for full-scale IQ (FIQ), performance IQ (PIQ), and object assembly (OBJ, a component sub-test of PIQ).

**Conclusions:** Measures of white matter integrity derived from HARDI are highly heritable. Higher GFA is linked with better intellectual performance, especially with performance IQ, and this linkage is of genetic origin. These heritable traits will expedite the search for specific genes influencing cognition and white matter integrity in the brain.

**References:**

Tuch, DS (2004), 'Q-ball imaging', *Magn Reson Med*, vol. 52, no. 6, pp. 1358-1372.