Genetic Influences on White Matter Microstructure in 280 Twins Scanned with 4 Tesla High Angular Resolution Diffusion Imaging (HARDI)

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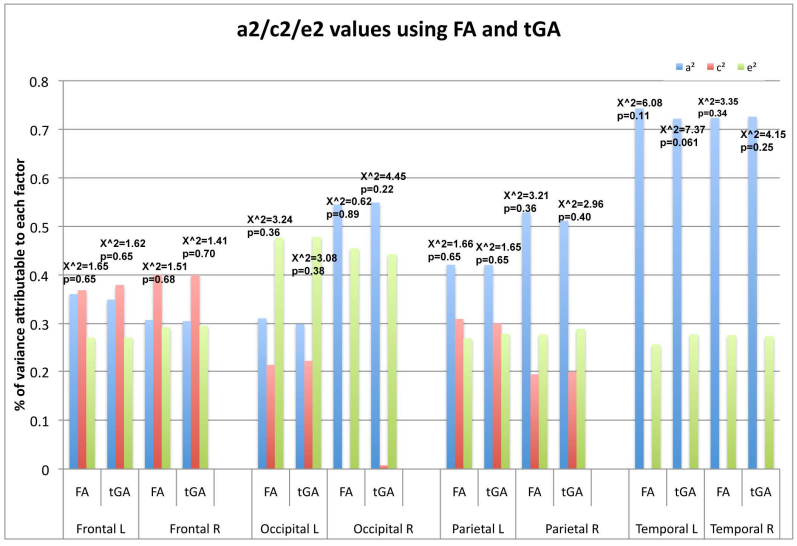
Introduction:

High angular resolution diffusion imaging (HARDI) reveals white matter microstructure in remarkable detail. By scanning 280 young adult twins with 105-gradient HARDI at 4 Tesla, we set out to compute the relative contributions of genetics and environmental factors to white matter. For each individual, we computed fractional anisotropy (FA) and geodesic anisotropy (GA) from which we estimated genetic and environmental contributions to the population variances in four ROIs (frontal, occipital, parietal and temporal lobes). We hypothesized that we would see greater genetic influences on early-developing regions, such as visual areas of the occipital lobes, and greater environmental influences on frontal lobe regions, which have a more protracted period of maturation.

Methods:

We acquired 105-gradient high angular resolution diffusion imaging (HARDI) data and corresponding 3D T1-weighted MR images from 63 same-sex MZ twin pairs and 77 DZ twin pairs on a 4 T Bruker Medspec MRI scanner. An optimized HARDI sequence [3] was used, with gradients uniformly distributed with respect to spherical angle. The MZ twin pairs (mean age: 23.0 +/- 2.00SD yrs) included 82 women (24.2+/-2.1 yrs) and 44 men (23.4+/-2.11 yrs). The DZ pairs (23.3 +/- 2.0 yrs) included 29 same-sex female pairs (23.1+/-1.8 yrs), 14 same-sex male pairs (22.2+/-1.5 yrs), and 34 opposite-sex pair twins (23.8 +/- 2.1 yrs).Diffusion weighted images, after manual removal of extra-cerebral tissues, were corrected for EPI distortion: the corresponding T1-weighted scans were 1) linearly registered to the standardized Colin27 brain template using a 9-parameter registration with FLIRT software [2] and 2) nonlinearly aligned using nonlinear elastic registration [4]. Diffusion tensors were computed using the MedINRIA software (http://www.sop.inria.fr/asclepios/software/MedINRIA) and were rotated, based on the deformation tensor obtained from the fluid registration to the common template, to maintain the coherence of the principal eigenvector field. For each individual, we computed voxelwise fractional anisotropy (FA) and geodesic anisotropy (GA) from the preprocessed tensors. We fitted an A/C/E structural equation model, using both MZ and DZ twin pairs to determine the variance components attributable to additive genetic (A), common environmental (C), and unique environmental factors (E) [5]. Using Mx software [5], we also estimated genetic and environmental contributions to the population variances in four ROIs (frontal, occipital, parietal and temporal lobes). We estimated the proportional contribution of the A, C and E components to the lobar summaries.



Results & Discussion:

The plots show the estimated contributions of A, C and E to FA and tanh(GA) in the four ROIs. Hemispheric measures were not pooled to allow for any lateralized effects. In all lobes, genetic influences were accounted for between 30 and 75% of the variance. As hypothesized, strong shared environmental effects (C) were detected in the frontal regions and genetic effects (A) were dominant in the occipital regions, especially in the right hemisphere, consistent with our work showing a L/R asymmetry in frontal and occipital FA [1]. . In this A/C/E model, a probability (p) greater than 0.05 indicates that the model is a *good* fit. The model is rejected if $p<0.05$.

In conclusion, (1) HARDI measures reveal relatively strong genetic effects on white matter; and (2) both FA and GA, especially in temporal lobes, may be promising targets from genome-wide genetic association analysis.

Reference

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