Genetic Influences on White Matter Architecture in Twins: A Diffusion Tensor Tractography Study

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Introduction: Advances in brain imaging have provided investigators with new ways to probe the white matter architecture of the brain through diffusion tensor imaging (DTI). Prior studies have shown that white matter is under tight genetic control during embryonic development [1]. Neuroimaging studies have shown that white matter brain volume and fiber architecture are strongly heritable and are linked to IQ through common genes [2-5]. Using imaging measures of fiber characteristics and genetic data from identical and fraternal twins, we fitted quantitative genetic models to fiber tracts to determine where common genes underlie fiber integrity and the expression of IQ.

Methods: 23 monozygotic and dizygotic young adult twin pairs (92 subjects) received DTI scans, genotyping, and neurocognitive evaluations. DTI data were acquired using an optimized diffusion sequence with 94 non-collinear gradient directions. After diffusion tensor reconstruction, mean diffusivity, lattice index, and fractional anisotropy were computed for each voxel. Segmentation of major white matter tracts, including the corpus callosum, cingulum, and corticospinal tracts, was performed using a fluid mechanics based tractography method [6]. We assessed fiber integrity by calculating the average DTI scalar metric along the segmented fiber tracts. Using the ACE model for genetic analysis, we fitted a structural equation model to the twin covariances for each tract's scalar measures with the subjects' IQ data to estimate the relative contributions of genetic and environmental factors to variance in fiber integrity measures and intelligence scores.

Results: The ACE model showed a significant additive genetic component ($p < .05$; Figure 1) for mean diffusivity (MD), which suggests that fiber integrity of the corpus callosum is genetically influenced. By contrast, we did not detect genetic influences on the lattice index (LI), a measure of spatial coherence of a fiber tract.
We used a bivariate form of the ACE genetic model ('cross-trait' design) to reveal that common genes mediate CC mean diffusivity and IQ, extending prior findings that corpus callosum fiber integrity (MD) is heritable. Mean diffusivity was correlated ($p < .05$; Figure 2) with all forms of IQ tested - full-scale, performance and verbal IQ (FIQ/PIQ/VIQ) -, which suggests that the structural heritability of the corpus callosum has a genetic correlation to the expression of intelligence. Initial results for the other fiber tracts show similar genetic trends.

Conclusions: Using diffusion tensor tractography, we identified genetic factors that affect brain fiber architecture and its link to intelligence. Based on diffusion imaging scans of 92 twins, we fitted quantitative genetic models in fine spatial detail across the brain. Our results suggest the fiber integrity of the corpus callosum is predominantly genetically controlled. These same measures of fiber integrity showed a strong link to the expression of intelligence. In contrast to previous studies [4], we did not find the size (LI) of the corpus callosum to be heritable. However, prior studies suggesting callosum size was heritable did not assess 3D fiber coherence, an advantage of LI. In future studies, we hope to clarify the causative genetic factors that underlie white matter development across the entire brain.

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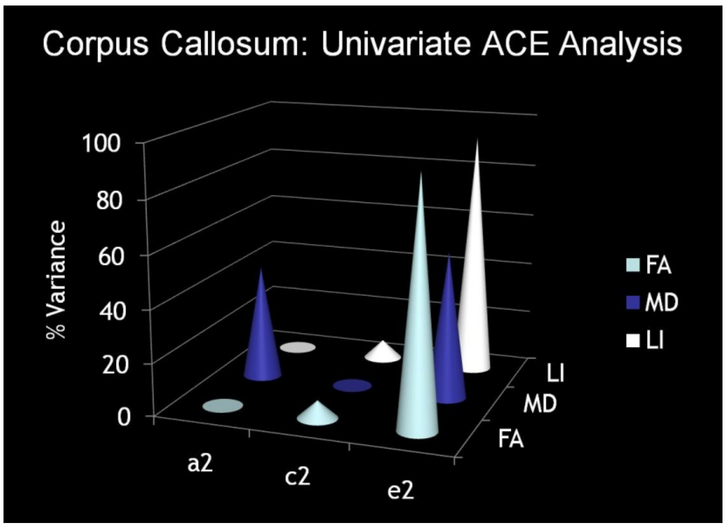

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