Heritability of Corpus Callosum Anisotropy in Elderly Twin Men

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Introduction

Recently, we reported that the midsagittal area of the corpus callosum is genetically determined even into old age (1). In other studies we observed that callosal macrostructural size does not decline with age (2), despite notable age-related decline in its microstructural integrity (3, 4). This dissociation of genetic and aging effects on callosal macrostructure versus its microstructure raises the question of the extent to which the intrinsic components of white matter structure, measurable with diffusion tensor imaging (DTI), is heritable. A method that permits the estimation of the relative contribution of genetic and nongenetic influences on a phenotype, such as brain morphology, is the twin design, which compares the phenotypic expression in monozygotic (MZ) twin pairs, who share all their genes, with dizygotic (DZ) twin pairs, who share half their genes.

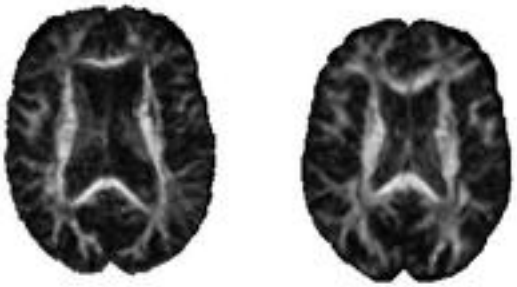
Methods

The subjects were 14 MZ and 18 DZ twin pairs of community-dwelling men, age 70 to 82 years old (MZ: 76±2.6; DZ: 76±2.9). All 64 men were World War II veterans, participating in the National Heart, Blood, and Lung Institute longitudinal study of cardiovascular risk factors.

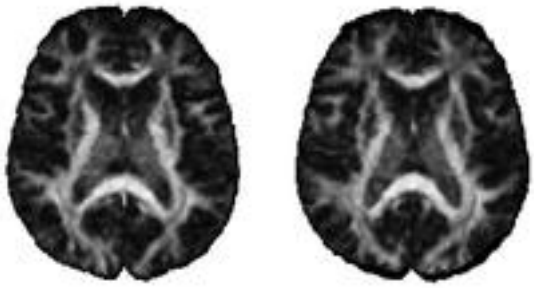
DTI used a single shot echo-planar imaging technique (5mm thick slices, 0mm gap, TR=6000ms, TE=106ms, 128x128 zerofilled to 256x256 acquisition matrix). The amplitude of the diffusion-sensitizing gradients was 1.4 Gauss/cm with 32 ms duration and 34 ms separation. Diffusion was measured along six non-collinear directions. The diffusion tensor carries information about the predominant direction of diffusion and was expressed as fractional anisotropy (FA), which reflects the deviation from isotropic diffusion on an intravoxel basis.

For tissue segmentation (5), a fast spin-echo (FSE) sequence was collected in the axial plane (5mm thick slices, 0mm slice gaps, TR=2500ms, TE=20/80ms, echo train length=8, 256x256 acquisition matrix). DTI and FSE data were acquired at the same 18 slice locations beginning 2 cm below and aligned with the AC-PC line.

Echo-planar DTI acquisition can cause spatial distortion, which can be minimized with spatial warping (3). Here, we applied a 5th order (42-parameter), 2D polynomial warping function in order to map the echo-planar images (b=0) onto the corresponding FSE images. This approach allowed anatomical regions of interest to be identified on FSE images and coregistered with diffusion data. Because the warping function was derived from nondiffusion-weighted echo-planar data, the dependent diffusion measures were not used to determine spatial correction.



Fractional Anisotropy images of a DZ twin pair.



Fractional Anisotropy images of an MZ twin pair.

Regions of interest—the genu and splenium of the corpus callosum—were indexed separately and manually drawn on three contiguous, native FSE images. Slice selection was done on FSE images on a twin-pair basis and blind to zygosity.

We estimated genetic and nongenetic contributions to individual differences in regional FA by comparing twin-pair similarities of FA for MZ and DZ twin pairs. The extent to which MZ twin pairs are more similar to each other than DZ twin pairs are to each other on a given measure is considered an indicator of genetic influence on that measure.

Results

Within each zygosity group, intraclass correlations (ICCs) were calculated separately for genu and splenium FA. The comparison of the MZ and DZ ICCs provides a descriptive statistic for the presence of genetic effects. The ICCs for splenium FA were .73 in MZ and .25 in DZ twin pairs, and for genu FA the ICCs were .54 in MZ and .22 in DZ twins.

Maximum likelihood estimation of the genetic and nongenetic components of variance was carried out on calculated averages of 100 bootstrap computations of the observed variance-covariance matrices for MZ and DZ twins. Estimates of the genetic components of variance for splenium FA were 71% genetic and 29% nongenetic (model fit χ^2 = .29, df=4, P=.96); for genu FA these estimates were 53% genetic and 47% nongenetic (model fit χ^2 = .13, df=4, P=.98). The goodness of fit of a genetic model was significantly better than a purely nongenetic model; the differences between the genetic and nongenetic model were significant for both splenium (χ^2 =7.18, df=1, p<.01) and genu (χ^2 =5.10, df=1, p<.03).

Discussion

Like macrostructure, the microstructure of the corpus callosum is under substantial genetic control, even when examined in late life. Both the genu and the splenium showed significant heritability of FA, and the genetic contribution was greater in the splenium than the genu, suggesting that interhemispheric connections in frontal regions may be more influenced by nongenetic factors than those in parietal regions.

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References

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