

Tensor-Based Morphometry of the Corpus Callosum in Williams Syndrome

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Williams syndrome (WS) is a disorder associated with a genetic deletion in the 7q11.23 region of the genome. WS patients exhibit mild to moderate mental retardation, but are relatively proficient in language and musical ability. A complex pattern of gray/white matter reductions has been observed in prior studies of WS, and improved techniques are required to map their spatial profile. We therefore mapped white matter thickness reductions in the corpus callosum (CC) in WS, with a new approach based on fluid image warping and tensor-based morphometry (TBM).

Methods: 3D T1-weighted brain MRIs of 42 WS subjects (age: 29.2±9.0SD years, 19M/23F) and 40 age-matched healthy controls (age: 27.5±7.4 years; 16M/24F) were rigidly aligned to ICBM standard space. The CC was traced at midline with a standardized anatomical protocol. Each individual CC was fluidly registered to an average contour derived by averaging the boundary coordinates of the discretized contours of all controls. For fluid image registration, driving forces were applied throughout the deforming image to maximize the Jensen-Renyi divergence between it and the target CC (both were represented as binary images, with values of 1 inside the CC). The resulting partial differential equation was solved iteratively, by convolving the applied force field with the Green's function of the linearized Cauchy-Navier fluid operator. This guaranteed smooth, one-to-one, deformation mappings, while achieving perfect boundary registration.

The Jacobian of the deformation field indicates local tissue expansion (Jacobian > 1) or shrinkage (Jacobian < 1) relative to the healthy control mean shape. Shape differences between diagnostic groups were tested pixelwise by multiple regression, by fitting coefficients β_i in the following general linear model:

$$\log(\text{Jacobian}) = \beta_0 + \beta_1 * \text{diagnosis} + \beta_2 * \log(\text{total cerebral volume}) + \beta_3 * \text{age}.$$

Here *diagnosis* was coded as a binary covariate, *total cerebral volume* and *age* were detrended as confounds. Data were log-transformed to reduce skew in the Jacobian distribution. To avoid assuming normality, the design matrix was permuted 5,000 times, yielding a non-parametric *F* distribution for assessing effects of each covariate. A corrected probability map for the group differences was derived from the permutation distribution.

Results & Discussion: CC thinning was highly significant in the *splenium* and *isthmus* ($p < 0.01$), but not the *genu* ($p = 0.05$; Figs. 1-3). Figure 1 shows the mean log(Jacobian) is below zero for the WS subject group, and Figure 3 shows the significance of these group differences. Fig. 4 shows the log(Jacobian) map for an illustrative case: values below zero visualize local reductions.

Conclusions: Tensor-based morphometry (i.e., shape analysis) better visualizes the profile of white matter reductions in WS, agreeing with prior work parcellating the CC into sectors (Schmitt et al., *Dev Med Child Neuro*, 2001). The reduced white matter volumes in the *splenium/isthmus* and parietal/occipital white matter may underlie the visuospatial deficit in WS. By contrast, frontal/temporal fibers, carried in the *genu*, are relatively preserved, consistent with the relative sparing of frontal lobe volumes and of affective and language functions in WS.

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