Brain Deficits Visualized in Fragile X Syndrome using Elastic Matching and Riemannian Tensor-Based Morphometry

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Background:
Fragile X syndrome (FRX) is the most common inherited form of mental retardation, affecting 1 in 2000 men and 1 in 4000 women. Caused by mutation of the *FMR1* gene on the X chromosome, FRX leads to developmental and neuropsychiatric abnormalities, including atypical social development, tactile defensiveness, impaired visuospatial memory, attention deficits and language dysfunction. Here, we used high-dimensional elastic registration of MRI scans, and tensor-based morphometry (TBM), to map the profile of structural brain abnormalities in FRX.

Method:
3D volumetric T1-weighted structural brain MR images were acquired from 36 FRX subjects (mean age: 14.7 yrs.±1.6SD; 18M/18F) and 32 healthy controls (14.7 yrs.±2.2SD; 16M/16F) and analyzed using TBM.

Scans were aligned to a high-resolution single-subject average MRI scan in ICBM space (the Colin27 brain template), using 9-parameter registration to adjust for individual brain scale differences (no group differences were detected in overall brain scale). The Colin27 template was then nonlinearly registered to each individual in the study, by computing an inverse-consistent 3D elastic deformation vector field to deform one 3D image to match the other, maximizing the mutual information between the images (Leow et al. IPMI2005: 493-503). A minimal deformation target (MDT) was then generated by applying the inverse of the mean displacement fields from all subjects to the Colin27 brain (Kochunov et al. HBM2005 24:325-331). Every scan was elastically re-registered to the MDT. Maps of the local Jacobian determinant (expansion factor) were computed from the spatial derivatives of the deformation fields. Group differences in regional volumes were detected by applying multiple regression to the log-transformed Jacobian maps.

Because Jacobian matrices are positive definite symmetric tensors, we also computed distances between them in a Riemannian framework that accounts for the curvature of the associated matrix Lie group. Rather than average the Jacobian determinants, we compared the Riemannian means (Pennec et al. MICCAI2005: 943-950) of the deformation tensors at each voxel, defined for each group as:

$$\bar{\sum}(x) = \exp(\bar{W}(x)),\ \ with \bar{W} = \frac{1}{N}\sum_i \log(D_i(x)) \ \&\ D_i(x) = \nabla\psi_i^T \nabla\psi_i\,,$$

$$\psi_i(x) = transformation,\ \ D_i(x) = Deformation\ Tensor$$

Permutation testing provided corrected *p*-values for group differences overall and in predefined regions-of-interest.

Results:

Figure 1a shows the profile of local volumetric differences between the two groups (FRX divided by control). FRX subjects had larger volumes bilaterally for the caudate (p=0.002), and lateral ventricle volumes (p=0.002). After (but not before) adjusting for individual brain volume differences, parietal and temporal white matter volumes were greater in FRX - by 2.9% (p=0.027) and 1.4% (p=0.038). Significance maps are shown in **Figure 1b**. Group differences assessed using Riemannian tensor averaging did not differ from those computed by conventional scalar averaging of the Jacobian determinants. Log-transformation did not significantly alter the effects found the scalar Jacobian maps.

Conclusion:

TBM visualizes the profile of structural deficits in the brain without time-consuming specification of regions-of-interest. Caudate nuclei and temporal/parietal white matter were enlarged in FRX; differences were detected automatically. Future longitudinal analyses will monitor the degree of hypertrophy over time and correlate it with measures of social functioning and cognition. Further correlations between IQ, clinical scores and these abnormalities will help in understanding the neurological underpinnings of FRX and its treatment.

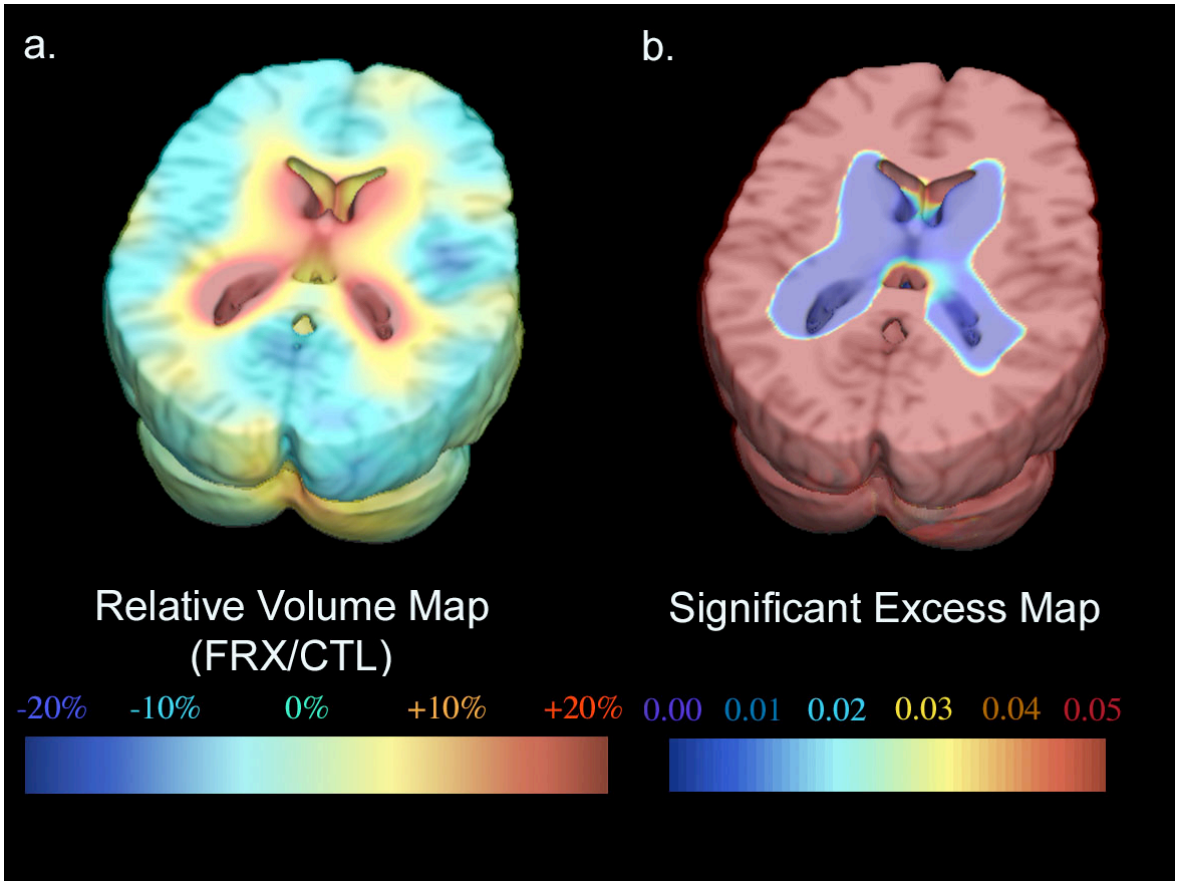

Figure 1. a. Ratio map shows mean volumetric differences between groups. Tissue volumes are ~20% greater in the caudate and white matter. b. FRX subjects show significant volume excesses subcortically.