Callosal size and curvature variation in 22q11.2 syndrome: A factor analytic study

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Introduction

The 22q11.2 deletion syndrome is a group of disorders that share a common genetic basis but present diverse phenotypic manifestations. Recently, special interest has been devoted to the morphometric characterization of the corpus callosum in the 22q11.2 syndrome and evidence of volumetric differences in the isthmus and splenium have been reported [1,2]. In this paper, we present a factor analysis approach for studying volumetric and morphometric variation in structures of interest and a case study based on the 22q11.2 deletion syndrome. The method is based on the analysis of high-dimensional sets of vector variables obtained from non-rigidly registering a template image so as to align its anatomy with the subject anatomy of a sample. The result of registration is a set of displacement fields from which the amount of point-wise volume enlargement or reduction of the image can be statistically analyzed with the purpose of extracting a reduced set of latent variables. In the case of the 22q11.2 deletion syndrome, we hypothesize that the corpus callosum of patients presents, on average, higher curvature for the anterior half of the structure.

Methods and Materials

Factor analysis is a statistical method that explores the data with the purpose of discovering underlined connections among the variables that can be used to support hypothesis on the morphology and functionality of structures. A vector of original variables $\mathbf{y}$ (e.g. volumetric information) may be represented by a much smaller set of factor scores $\mathbf{f}$, based on the linear transformation $\mathbf{y} = \mathbf{A}\mathbf{f} + \mathfrak{d}$, where $\mathbf{A}$ is a matrix with the correlations between variables and factors (loadings) and $\mathfrak{d}$ is the error term. A fundamental feature of factor analysis is that, in addition to data reduction, it may favor data interpretation. In the study of the callosal anatomy in the 22q11.2 syndrome, we show how the factors can be associated to specific regions of the corpus callosum, evidencing morphological differences between populations.

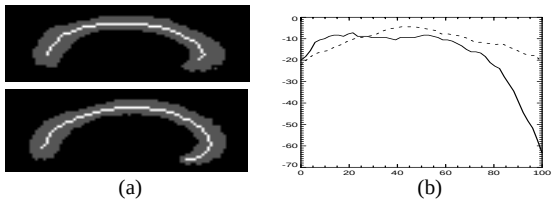
The sample used in the experiments was composed of T1-weighted MRI volumes of 18 patients (age=118±17 mo) and 18 matched controls (age=125±24 mo), as described in [2]. The midsagittal slices were extracted and the callosa segmented by supervised thresholding and manual delineation. The boundaries of the callosa were registered to the template by matching their curvature [3]. The displacement fields representing the deformation of the template contour required to conform to the subjects were interpolated within the entire callosal body. The average displacement field for normal controls and patients were used to display the average shape of the callosal structure in each group. Fig. 1 shows the average shape and medial axis of the corpus callosum for the normal controls and patients. The curvature plot reveals a major difference in the anterior part of the structure, for which the patients present more curved anatomy.

Analysis of volumetric variability

The Jacobian determinants of the corpus callosum were computed so as to quantify the point-wise amount of dilatation or compression needed to register the template to each image in the sample. The t-statistics for the Jacobian determinants are shown in Fig. 2. The regions in blue represent the parts of the structure in which there is more statistical confidence to reject the null hypothesis of equal means between patients and controls. The differences between the Jacobians of normal and pathological populations were investigated in a factor-analytic study. The input to factor analysis was a vector containing the Jacobian determinants at each voxel and the diagnosis variable. Loadings were computed from the eigenvectors of the correlation matrix and rotated based on the quartimax algorithm [4,5], allowing the observation of regions in the callosal structure that vary in size in a correlated way and are concomitantly correlated to the pathology. Fifteen factors explained 84.67 % of the sample variance. Fig. 2 shows the regions related to each factor. Colors represent the absolute correlation of each factor with diagnosis, which are greater at the anterior regions of the callosum and at the isthmus. The sample was further represented in the factor space by computing the factor scores of each subject. The strength of the scores as a reduced representation of the original data was investigated through a classification study using cross-validation. A Bayesian classifier, a discriminant function and a least squared error fit of the data were applied and determined the number of factors that yielded the best classification rates. The best rate (80.6%) was obtained with the least-squared-error classifier, using 2 out of 15 factors. The discriminant function and Bayes classifier obtained, respectively, 77.8% and 72.2% hit rates. The statistical significance of the classification results was analyzed based on randomized tests [6]. At each of the 1000 simulations, the whole cross-validation process was repeated using randomly-chosen values for the diagnosis variable. The test subjects were classified and the hit rate registered so as to characterize its distribution. The probability that the hit rates would have been obtained by chance was 0.006.

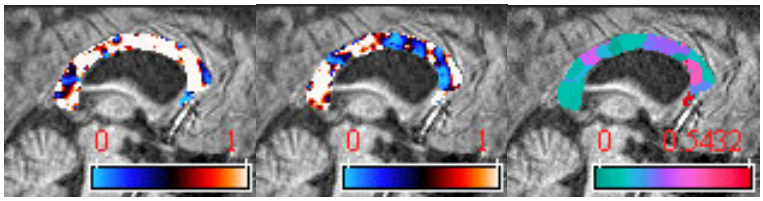
Analysis of shape variability

Shape variability was also investigated in a factor-analytic study, now considering the *x* and *y* displacement components of the medial axis voxels. Five factors explained 89.52% of the sample variance. The ones with largest absolute correlation with the disease are related to the displacement of the middle body in y direction (loading=0.40) and the one related to the displacement of the lower posterior body in x direction (loading=-0.42). These factors can explain the difference between the curvature of the anterior part of the callosa in patients and controls. The strength of the displacement-related scores as a reduced representation of the original data was also investigated through a classification study using cross-validation and randomized tests. The best classification rate (77.8%) was obtained with the least-squared-error classifier and the discriminant function, using 2 out of 5 factors. The statistical significance was 0.004.



(a) (b)

Fig.1 (a) The average shape and medial axis of the corpus callosum for normal controls (top) and patients (bottom). (b) The plot shows the curvature of the medial axis as a function of boundary length, from splenium to rostrum (patients in solid line).



(a) (b) (c)

Fig.2 (a) Regions in which the Jacobians are greater in the patients, (b) regions greater in the normal controls. The colors represent the statistical confidence of the results (p-values). (c) Regions of the corpus callosum assigned to each factor. The color is proportional to the absolute correlation (loading) to diagnosis.

Conclusion

We presented a method to describe the volumetric and morphometric variability of the corpus callosum in pathology, with an application to the 22q11.2 deletion syndrome. The factor analysis of the displacement fields obtained from registration of a template shape was able to determine the major pathological differences in anatomy. The isthmus and anterior half of the callosa are larger in controls and the curvature of the anterior half more accentuated in patients, on average.

References

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