MAPPING GENETIC INFLUENCES ON LATERAL VENTRICLES USING MULTI-ATLAS FLUID IMAGE ALIGNMENT IN TWINS

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Introduction

Imaging genetics is a new field of brain mapping in which genetic influences on brain structure can be quantified and mapped in entire populations. Here we fitted genetic models to computational maps of anatomy in an imaging database, to study the fundamental causes of anatomic variation in a population. To assess the relative influence of genes and environment on brain structure, we developed an algorithm pipeline to analyze lateral ventricular shape and volume in 28 MZ and 28 DZ twin pairs (112 scans) by automatically extracting surface-based 3D anatomical models. The overall goal of this work is to zero in on promising phenotypes to screen for effects of candidate genes that may influence brain morphology.

Methods

T1-weighted volumetric MRIs of 112 twins (56 identical, 56 fraternal) were aligned to the ICBM-53 average brain template with a 6-parameter rigid-body transformation. We applied our automated segmentation approach ("Multi-Atlas Fluid Image Alignment" [1]) to fluidly propagate hand-labeled parameterized surface meshes into the 112 scans, labeling the lateral ventricles. Mesh surfaces were averaged within subjects to minimize segmentation error. We fitted quantitative genetic models at each of 30,000 surface points to measure the proportion of shape variance attributable to genetic differences, unique environmental influences and shared environmental effects.

Quantitative genetic analysis at each surface vertex computed maps of several standard genetic parameters, such as Falconer's heritability estimate, and variance proportions attributable to additive genetic (A), shared (C) and unshared (E) environmental effects. To determine the proportion of variance attributable to genetic influences, we performed (1) classical heritability analyses (using Falconer's method) for lateral ventricle shape and volume, and (2) maximum likelihood estimation (MLE) using path analysis. We compared different surface-based maps of genetic statistics using fields of chi-squared statistics to (1) rank the models, (2) ascribe significance values to the model parameters at each surface vertex, and (3) visualize regions where each model (genes, environment, or both) best explained anatomical variance in the population. Permutation testing on these ACE coefficient maps was performed as proposed in [2], to give corrected P-values for maps of genetic effects, corrected for multiple comparisons.

Results and Discussion

Color-coded maps (**Fig. a, b**) show local intraclass correlations and associated significance maps for radial ventricular thickness at each vertex. Falconer's heritability estimate h^2 is plotted at each surface point (**Fig. c)**. Genetic control of structure is greatest in the mid-portion of anterior horn and in the posterior horn. **Table 1** shows estimates of a^2, c^2 and e^2 derived from the ACE model, and their χ^2-distributed goodness-of-fit statistic (*df* denotes degrees of freedom). *Large P*-values indicate a good model fit to the data.

Conclusions

Consistent with earlier work using volumes [3], these 3D genetic brain maps demonstrate a significant influence of common environmental factors but minimal contribution of genetic factors to lateral ventricular volumes, accounting for 21.3% and 0% of variance respectively.

References:

[1] Chou YY et al. Neuroimage (2008).

[2] Chiang MC et al. ISBI 2008.
[3] Schmitt E et al. NeuroImage (2007): 70-82.