THE MULTIVARIATE VARIANCE-COMPONENTS ANALYSIS IN DTI

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INTRODUCTION

The intraclass correlation (ICC) is a common measure to quantify the degree of resemblance within pairs for a quantitative trait. In imaging genetics - a relatively new field that examines genetic effects on brain images - ICCs must commonly be estimated from twin data. Here we extend the commonly used Pearson’s correlation to a more appropriate definition using a restricted maximum likelihood method (REML). This gives unbiased ICC estimation, even for small sample sizes. The method may be used for both univariate and multivariate data. We applied our analysis to both univariate and multivariate (tensor) measures derived from diffusion tensor images (DTI) of 25 monozygotic (MZ) and 25 dizygotic (DZ) twin pairs.

METHODS

SUBJECTS and IMAGE ACQUISITION:
We acquired 3D structural brain MRI scans and DT-MRI scans from 100 subjects: 25 pairs of MZ twins (25.1±1.55D years old) and 25 pairs of DZ twins (23.08±2.1 years) on a 4T Bruker Medspec MRI scanner. Imaging parameters: 21 axial slices (5 mm thick), FOV = 23 cm, TR/TE 6090/91.7 ms, 0.5 mm gap, with a 128x100 acquisition matrix; 30 directional gradients; The reconstruction matrix: 128×128, yielding a 1.8x1.8 mm2 in-plane resolution; Total scan time: 3.05 minutes.

INTRACLASS CORRELATION FOR UNIVARIATE MEASURES:

\[ ICC_{\text{univ,REML}} = \max(0, \frac{1}{N} \frac{MS_{\text{between}} - MS_{\text{within}}}{MS_{\text{between}} + MS_{\text{within}}}) \]

where MSbetween and MSwithin are mean square differences between and within pairs N= number of pairs

INTRACLASS CORRELATION FOR MULTIVARIATE MEASURES:

\[ \Gamma = \Sigma^{-1/2} \Omega \Sigma^{-1/2} \]

\[ \Sigma = \begin{bmatrix} (t_1 - \mu) (t_2 - \mu) \end{bmatrix} \]
\[ \Omega = \begin{bmatrix} (t_1 - \mu) (t_1 - \mu) \end{bmatrix} \]
\[ \mu = \text{the sample mean of total } t_1 \text{ & } t_2 \text{ vectors} \]
\[ t_1 \text{ & } t_2 \text{ = 60 vectors defined at each voxel containing deviation of the DTs of twin 1 and twin 2 from the mean of DT} \]

Defining random variables: \( \xi = \frac{1}{2} (t_1 - t_2) \) \& \( \eta = \frac{1}{2} (t_1 + t_2) \)

We can also define: \( G = \frac{1}{N} \sum \xi \xi^T \) \& \( H = \frac{1}{N} \sum \eta \eta^T \)

Since \( E(G) = \frac{1}{2} (\Sigma - \Omega) \) \& \( E(H) = \frac{1}{2} (\Sigma + \Omega) \)

the components of unbiased estimate for intraclass correlation are:

\[ \hat{\Sigma} = \frac{N}{N-1} H + G \]
\[ \hat{\Omega} = \frac{N}{N-1} H - G \]

FALCONER’S HERITABILITY STATISTICS:

\[ h^2 = 2(\hat{r}_{\text{MZ}} - \hat{r}_{\text{DZ}}) \]

RESULTS

Figures 1 a-h show ICC maps of MZ and DZ pairs for the FA, GA, tanh(GA), and full DT measures. In MZ twins, who share the same genes, all deep white matter regions show very high intra-pair correlations (resemblance). These correlations are highly significant in a broadly distributed deep white matter region, including the corpus callosum and some anterior temporal regions. Correlations detected for the full diffusion tensors are generally higher than those for the three DT-derived scalar measures. Also, correlations are higher among the MZ pairs than for the DZ pairs, as expected for a genetically influenced trait. However, unlike the univariate ICC values for FA, GA, and tGA, the multivariate ICC values for the full diffusion tensor measures are derived from the largest eigenvalue of the computed matrix. For the multivariate intraclass correlation, we found empirically that the maximum eigenvalue has a mean value of around 0.5 in null data: intraclass correlations are always non-negative by definition. Thus, univariate and multivariate ICC values are not inherently comparable. Maps of Falconer’s heritability statistics (h2) are also shown in Figures 1 i-l.

Although the r-values for univariate and multivariate ICC maps are not directly comparable, p-value maps in Figure 2 show that the significance of the correlations (obtained from a permutation-based null distribution) is much higher for the full diffusion tensor in the MZ twin group, probably because more information on fiber microstructure is retained. These methods suggest that the full diffusion tensor is a promising target for genetic studies.

REFERENCES:
