Multivariate Analysis of Diffusion Tensor Data Using the Hotelling T2 Statistic

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Introduction Despite its intrinsically multivariate nature, most statistical analyses of diffusion tensor imaging (DTI) data utilize massively univariate approaches such as statistical parametric mapping (SPM). We show here that a multivariate approach using the Hotelling T^2 statistic can make more efficient use of the data in regions where significant differences in two or more parameters occur. This statistic represents the data at each voxel as a vector in an N dimensional space and tests the length of the difference between the means of the vectors for each condition. This approach is demonstrated by analyzing maps of fractional anisotropy (FA) and apparent diffusion coefficient (ADC). We test the assumption of normality for both FA and ADC and compute appropriate transformations to ensure that it is met.

Methods DTI data was acquired on a 3T scanner (GE Signa) using a 2D cardiac gated DW EPI pulse sequence with 12 uniform diffusion-encoding directions and diffusion-weighting = 1114s/mm^2. Other imaging parameters included 240 mm FOV, 120x120 matrix, 39 contiguous 3mm thick slices and 3 NEX. Forty-five subjects were imaged (13 controls and 32 with closed head injuries 8 to 12 weeks post injury). All had sustained at least a moderate injury, with an initial Glasgow Coma Scale score of 13 or below. They were studied within a longitudinal project of neurobehavioral outcome following brain injury. The controls were healthy adults recruited by advertisement from the university. All provided written informed consent. Diffusion tensor images were spatially normalized to a common reference in the MNI space using a deformable registration method implemented in the Insight Toolkit [1] before maps of the FA and the ADC were computed individually. The normality assumption was tested by computing normal probability plots (not shown) and plotting histograms of the unsmoothed white-matter data after transformation to a Fisher Z statistic. The Box-Cox transformation [2] was computed by minimizing the correlation coefficient of the normal probability plots. The corrected data were smoothed with a Gaussian filter to a 6mm FWHM and were then used to compute the Hotelling T^2 statistic and univariate F-statistics for ADC and FA at each voxel. The resulting maps were then corrected for multiple comparisons [3] using an F threshold of 15 and an extent threshold of 64.

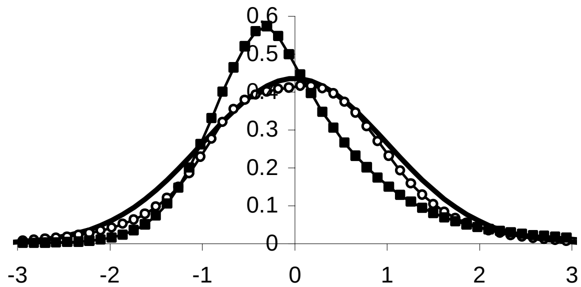

Figure 1. Histogram of normalized white matter values.

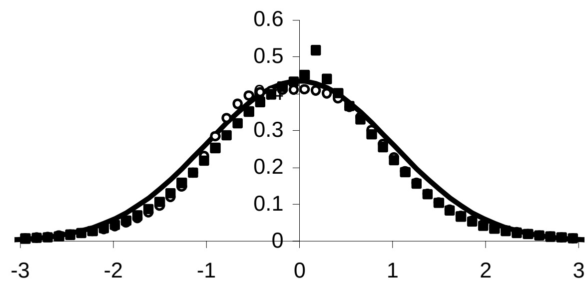

Figure 2 Histogram of transformed white matter values.

Results Both normality tests showed that FA was nearly normal but that ADC was significantly skewed and tail-heavy in white matter as shown in Figure 1 Applying the Box-Cox transformation significantly improved the validity of the normality assumption as shown by the histograms in Figure 2. Examination of the statistical maps in Figure 3 show that significant group differences in FA and ADC largely occurred in disjoint regions of the brain. As shown by the upper pair of arrows in Figure 3, the Hotelling T^2 statistic detected regions that were not seen in either the FA or ADC maps.

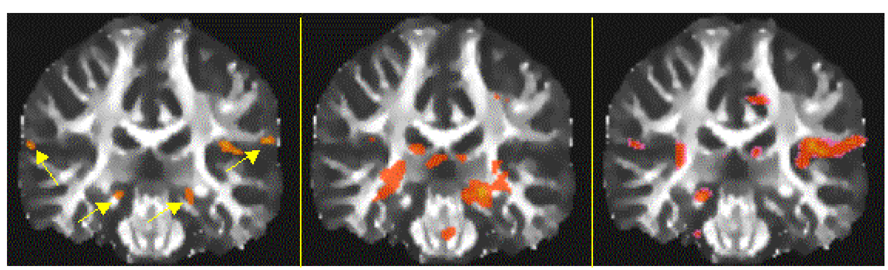

Figure 3. Hotelling T^2 map (left), F statistic map of FA (center), and F statistic map of ADC (right). The upper pair of arrows indicates regions that were detected by the multivariate test but not by the univariate tests. The lower pair indicates regions that were detected on either the FA or ADC maps but not on both.

Discussion The failure of the normality assumption can lead to decreased sensitivity if the distribution is tail-heavy, as is the case here. Appropriate transformations can be applied to ease this problem. The Hotelling T^2 statistic decreases sensitivity to differences where only one of the two variates shows an effect because the addition of the second variable increases the variance in the test but does not increase the mean difference. It is, however, capable of improving sensitivity in regions where the combined contribution of both variables to the signal difference outweighs the increase in variance.

References **1**. G Box and D Cox, 1964,J. Royal Stat Soc B, 26(2):211-252. **2**. J. Cao, 1999, Advance in Applied Prob., 31:579-595. **3.** TS Yoo. 2004 Insight into Images. A K Peters.