Longitudinal Multivariate Tensor- and Searchlight-Based Morphometry Using Permutation Testing

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Abstract
Tensor based morphometry [1] was used to detect statistically significant regions of neuroanatomical change over time in a comparison between 36 probable Alzheimer’s Disease patients and 20 age- and sex-matched controls. Baseline and twelve-month repeat Magnetic Resonance images underwent their spatial normalisation [10] and longitudinal high-dimensional warps were then estimated. Analyses involved univariate and multivariate comparisons of the three deformation fields. The most prominent findings were expansion of the fluid spaces, and contraction of the hippocampus and temporal region. Multivariate measures were notably more powerful, and have the potential to identify patterns of morphometric difference that would be overlooked by conventional mass-univariate analysis.

Tensor-Based Morphometry
Two-stage inter- and intra-subject registration provided deformation fields between the serial images in an average atlas space (cortical and sub-cortical) procedure of [9]. At each voxel, the three components of this displacement can be analysed directly [6]; more commonly, the spatial smoothing combines noisy voxel-wise data to below a statistical threshold [23]. At each voxel, the three components of the displacement field were notably more powerful, and have the potential to identify patterns of morphometric difference that would be overlooked by conventional mass-univariate analysis.

Searchlight Morphometry
Spatial smoothing combines noisy voxel-wise data to increase the chance of detecting smooth signals. An alternative approach [7] is to cluster neighbouring unsmoothed measurements into a multivariate summary. For example, in the spherical (searchlight) kernel around each voxel, Multivariate statistics on these data can potentially detect signals with more complex spatial patterns of information.

Statistical Analysis
The two-sample Cramer test [2] is based on Euclidean distances between multivariate observations and does not require sufficient observations to estimate the covariance matrix. We determine p-values corrected for Family Wise Error using a new multivariate version of the step-down methodology of [3], with 5000 unique random permutations, thresholding at pFWE<0.05.

Results
Figure 1 shows statistics, and figure 2, images of significance (FWE p-values, on a logarithmic scale from p=0.05-0.0005), for six different measurements (their covariances and corresponding number of unique covariance matrix elements are shown below the names). To the right are cross-sectional views and a 3D rendering of the significant voxels from log-Euclidean analysis of the smoothed strain tensor, colour-coded by the sign of the two group mean of trace(smoothed(H)), which without smoothing, would be equal to the conventional log Jacobian determinant. Findings include ventricular expansion, reduced temporal lobe gray matter, and some white matter differences. Quite similar patterns were found with another alternative statistic, but to differing extents. We explore these differences in greater detail below. First, we note that if more lenient False Discovery Rate correction is used in place of FWE (as in [8]), we find the differences appear more dramatic. Figure 4 below compares the smoothed log determinant with the smoothed log-Euclidean strain tensor elements, showing regions where either or both statistics were significant.

The 6-element H promotes many voxels to FDR<0.05, while almost no voxels are found exclusively with the scalar determinant. Though visually less spectacular, FWE correction still shows advantages for multivariate data. In figure 5 we include also the full Jacobian matrix, (not considered in [6,8], possibly because its high dimensionality can be problematic with a standard statistic). More voxels meet FWE significance with the full Jacobian than with H.

In order to more accurately quantify the differences in power, we plot curves of the cumulative distribution of the uncorrected voxel-wise p-values [8] (with a log-scale on the x-axis) for the most significant p-values. The displacement field components are found to outperform the standard log Jacobian determinant, but other multivariate measurements offer more dramatic improvements. The Geodesic Anisotropy [8] was found to be of several “orientational” measures (not shown) including curl(disp) and the major eigenvector of the strain tensor, which we analysed with novel permutation testing of the Watson statistic [11]). The complete Jacobian is the most powerful.

The figures above compare smoothed log(det(J)) to results from searchlight analyses of unsmoothed data, in spherical kernels with a range of squared radii (in voxels, number of voxels in kernel shown in parentheses). Interestingly, the uncorrected results appear to show a slightly better trade-off between sensitivity and localisation than for Gaussian smoothing. This carries over to FDR adjusted p-values (used in [7]), as they are monotonically related to p(unc). However, FWE corrected results (9) actually favour the standard analysis. Considering cumulative distributions of uncorrected and FWE p-values, the results are similar: without correction, a 57-voxel searchlight roughly matches the power of smoothing; with correction, 123 or 147 voxels are required, but such kernels have inadequate resolution. This trend for increasingly multivariate measurements to be relatively more penalised by FWE correction is also apparent in the multivariate TBM analyses; the corrected version of figure 5 (not shown) is much less clear-cut.

Figure 7 explores the complementarity of different measures, as in [6], the divergence and curl of the vector displacement field are considered alongside its 3 components. There is evidence that different measures might be best used in combination.

References: