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 tied spatial normalisation [10] and longitudinal high-dimensional warps were then estimated. Analyses involved univariate and multivariate data derived from the longitudinal 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

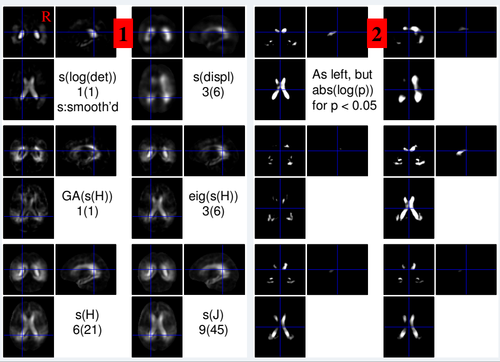
Two-stage inter- and intra-subject registration provided deformation fields between the serial images in an average atlas space (approximating the procedure of [9]). At each voxel, the three components of this displacement can be analysed directly [6]; more commonly, the spatial gradient of the transformation is taken (the 3x3 Jacobian matrix) and its univariate determinant is analysed. The measures are spatially smoothed with an 8mm full-width at half-maximum Gaussian. Here we compare these standard approaches to other multivariate measurements derived from J. The singular value decomposition J=USV' gives the polar decomposition J=(UV')(VSV') =(R)(T), with rotation R and T=sqrtm(J'J) encoding shape. Several strain tensors derived from T are known in solid-mechanics, including the Hencky Tensor H= logm(T)=logm(J'J)/2 [1]. H can also be motivated by a desire to perform Log-Euclidean analysis of a positive definite symmetric tensor derived from J [8].

Searchlight Morphometry

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

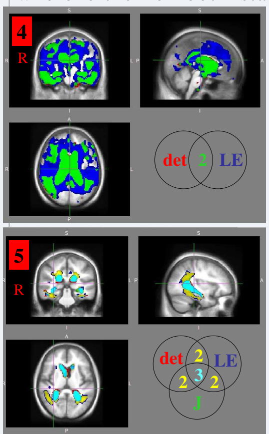
Statistical Analysis

The two-sample Cramér 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 dimensionalities 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 most of the alternative statistics, 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 pFDR<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 to focus on 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 the best 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.

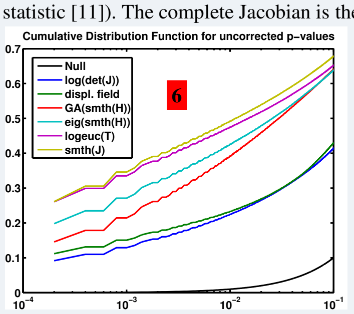
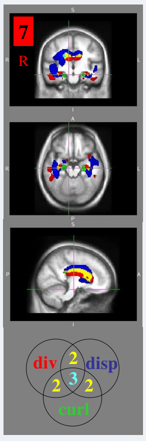
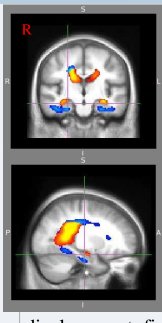
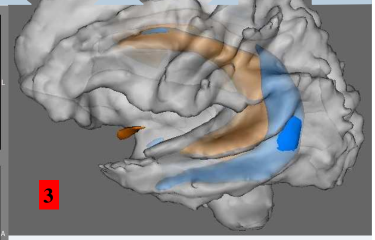


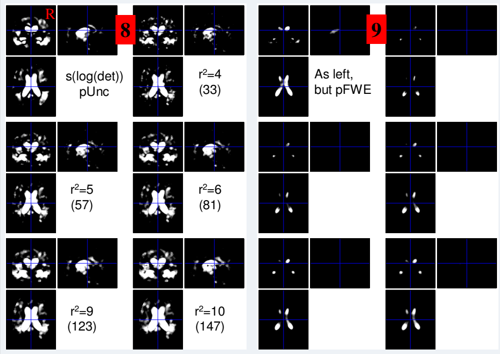
Figure **7** explores the complementarity of different measures, as in [6], the divergence and curl of the vector displacement field are considered alongside its 3 components. There is evidence that different measures might be best used in combination.







[6] shows div(disp) approximates det(J), and they chose it in preference due to its statistical independence from the actual displacement field components. However, we found this approximation to have inferior power to log(det(J)).



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 pUnc. 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.

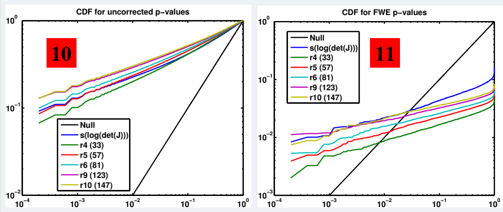
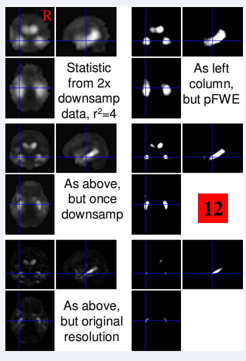


Figure **12** attempts to increase the spatial range of searchlight analysis without unduly large numbers of voxels, by using spline-pyramid resampling [4] but results are not improved. Multivariate analyses have been shown to have potential benefits, but further work is required to understand and overcome certain drawbacks. It is likely that more precise spatial normalisation [5] will improve both Tensor and Searchlight Morphometry.



References: **[1]** Ashburner & Friston (2004) Ch.6 in Human Brain Function, 2nd ed. **[2]** Baringhaus & Franz (2004) J Multivar Anal 88:190-206 **[3]** Belmonte & Yurgelun-Todd (2001) IEEE TMI 20:242-8 **[4]** Brigger et al (1999) IEEE TIP 8:1254-64 **[5]** Chu et al (2008) OHBM14 499-T-AM **[6]** Chung et al (2001) Neuroimage 14:595-606 **[7]** Kriegeskorte et al (2006) PNAS 103:3863-8 **[8]** Lepore et al (2008) IEEE TMI 27:129-41 **[9]** Rao et al (2004) IEEE TMI 23:1065-76 **[10]** Ridgway et al (2007) OHBM13 **[11]** Schwartzman et al (2005) MRM 53:1423-31

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gsk GlaxoSmithKline
CMIC