Multivariate asymmetry analysis (MVAA): applications in temporal lobe epilepsy

Diego Cantor-Rivera[1], Terry M. Peters[2], and Ali R. Khan[2]
[1]*Biomedical Engineering Graduate Program, Western University, London, ON, Canada,* [2]*Medical Biophysics, Western University, London, ON, Canada*

Introduction: Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy and is commonly treated with surgical resection of the anterior temporal lobe [1]. Better understanding of the structural abnormalities and their relationship with seizure onset can help tailor resections to improve surgical outcomes and minimize functional deficits. Recent work using region-based methods has shown that hemispherical asymmetry in quantitative relaxometry and DTI [2,3] is useful in classifying and lateralizing TLE. A limitation of these methods however is that they employ a static set of atlas regions, and they do not exploit the complementary information that multivariate measures of asymmetry can provide. We have thus developed a novel voxel-based image analysis technique that incorporates intrinsic tissue parameters along with morphometry to efficiently generate sensitive whole brain maps of asymmetry and applied it to investigate focal structural abnormalities in temporal lobe epilepsy.

Materials & Imaging: TLE patients (N=16) who were candidates for anterior temporal lobectomy (ATL) surgery were recruited for this study, along with age-matched healthy control subject (N=21). All subjects underwent imaging (relaxation mapping and diffusion-tensor imaging) on a 3T Discovery MR750 scanner (General Electric, Milwaukee, WI, USA) with a 32 channel head coil. We used DESPOT1-HIFI [4] for T1 mapping, and DESPOT2-FM [5] for T2 mapping, acquiring images at 1 mm isotropic resolution. Diffusion tensor imaging (DTI) was performed using 41 gradient directions (b-value=1000, 6 B0) and 2.5 mm isotropic resolution.

Multivariate Asymmetry: Synthetic T1-weighted images with inherent bias-field correction were generated from the T1 maps and used in place of T1-weighted images for segmentation and registration. Brain masking and tissue segmentation were performed with FSL [6,7], and registration to a symmetric template was performed with non-rigid B-spline registration, with affine initialization (NiftyReg,[8]). Co-registered FA and MD maps were transformed to this symmetric template space, along with Jacobian-modulated gray matter density maps. Spherical neighbourhoods were then systematically compared between the left and right hemisphere in the symmetric template space, using *regional asymmetry*, defined as the result of a two-sample Kolmogorov-Smirnov test (Figure 1). This procedure created a set of asymmetry maps (A_{T1}, A_{T2}, A_{FA}, A_{MD}, A_{GM}) for each subject. From these, a single map for each subject was obtained by evaluating the voxel-wise Mahalanobis distance with respect to the multivariate distribution of asymmetry observed in a control group (Figure 2). Linear support vector machines (SVM) were trained to discriminate between patients and controls using these Mahalanobis distance maps (MDMs) and evaluated with leave-one-out cross-validation. To measure the improvement on classification accuracy attributable to the asymmetry measurement, we also performed SVM classification on Mahalanobis maps obtained directly from the spatially-normalized T1, T2, FA, MD and modulated GM data (without asymmetry measurement) and their performance was compared.

Results & Discussion: The cross-validated performance metrics for the proposed method (asymmetry images) and the baseline experiment (original images) are shown in Table 1. Our approach identified correctly 15 out of 16 TLE patients (sensitivity = 94%). The multivariate examination of brain asymmetry integrates heterogeneous signals in a standardized estimation of asymmetry. The Kolmogorov-Smirnov test reports asymmetry in the [0,1] range (0: complete symmetry, 1: complete asymmetry) regardless of the original units (e.g. relaxation times, diffusion coefficients).

Conclusion: This work describes a novel and general computational framework for investigating focal asymmetry in multi-parametric MRI. Pattern analysis of these asymmetry maps reveals that hemispherical asymmetry in structural and diffusion images play a significant role in detection of abnormalities in TLE. This method can also be applied to further our understanding of asymmetry and hemispheric specialization in the developing brain or in the quantification of diseases characterized by focal pathological changes such as stroke or cancer.

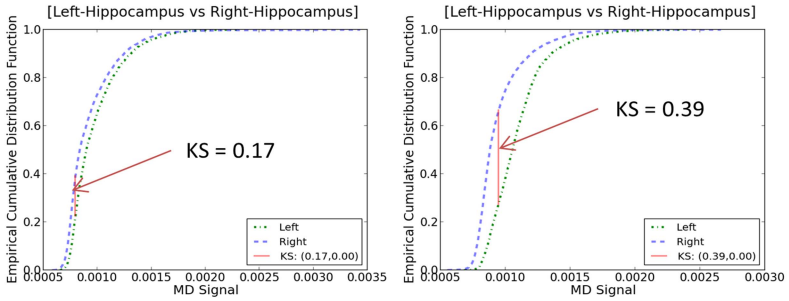

Figure 1: Example of KS-based asymmetry in the hippocampus of a healthy control (left), and a patient (right)

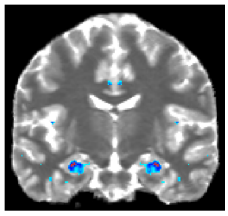

Figure 2: Mahalanobis distance map (thresholded) in a patient with hippocampal sclerosis

SVM	Asymmetry images	Original images
Accuracy	**84%**	65%
Sensitivity	**94%**	75%
Specificity	**76%**	57%

Table 1: Classification performance (SVM) using multi-parametric MRI with and without asymmetry

References:

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