Voxel-Based Analysis of Global and Neocortical Progression of Brain Atrophy in RR MS

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Introduction. Global atrophy estimation has become widely accepted as a useful marker for disease progression or response to therapy in multiple sclerosis (MS). Due to the increasing interest in assessing and monitoring brain atrophy, computed methods for estimation of brain volumes have gained attention. By using these methods, global brain volume changes can be estimated with great precision. Recently, attention has focused on defining the tissue compartments and regions within which atrophy occurs. In this longitudinal study, we used the extension of our automated method for brain atrophy estimation allowing voxel-based, regional, cross-subject analysis over time (the regional version of the SIENA method, SIENAr, and SIENA-VBM) to assess regional brain volume changes of a group of relapsing remitting (RR) MS patients in a mean period of three years.

Material and Methods. We studied 59 patients with RR-MS plus 25 age and gender matched healthy controls. In the whole group of patients, identical clinical and MR procedures were performed at baseline and repeated after a mean follow-up time of 3 years (range 2-4.8 years). In each MR exam, the protocol included a transverse dual-echo, turbo spin-echo sequence, yielding proton density (PD) and T_2-weighted images and transverse T_1-weighted images. These sequences yielded image volumes of 50 slices, 3 mm thick. Classification of T_2 lesion volume (LV) was performed in each patient by a single observer employing a segmentation technique based on user-supervised local thresholding and unaware of subject identity.

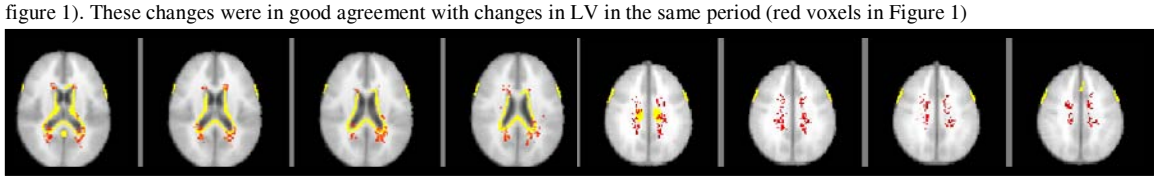
SIENAr. Analysis of the longitudinal data was based on SIENA (Structural Image Evaluation, using Normalisation, of Atrophy – a part of FSL, FMRIB's Software Library at www.fmrib.ox.ac.uk/fsl [1]). Each subject's two-time point pair of T_1 images was analysed with SIENA, giving an output "flow" image which is zero everywhere except at brain/non-brain edge points (including internal edges such as at the edge of the lateral ventricles). At these edge points is encoded the between-time-point edge motion in mm. Each subject's flow image was first normalised by inter-scan interval. It was then dilated spatially using non-binary dilation and then resampled to MNI152 space using FLIRT. It was then masked by a standard-space brain/non-brain edge. This process means that voxel-wise comparisons are possible, as each subject's edge image has effectively been deformed to match the standard-space brain edge image. The images were then smoothed by a Gaussian filter of HWHM 10mm (for increased sensitivity to local change) and remasked.

SIENA-VBM. Analysis was performed by using SIENA with a voxel-based morphometry approach. On T_1-W, we i) extracted the brain by using BET (part of FSL); ii) non-linearly registered the images (by using the MNI152 template), obtaining a group template by averaging all transformed images iii) obtained partial volume estimation (PVE) images of gray matter (GM), white matter (WM) and CSF using FAST (part of FSL) iv) applied to these images the optimised normalization parameters coming from our group template v) smoothed by a Gaussian filter of HWHM 10mm and corrected for volume changes by dividing by the Jacobian determinants obtained from the normalization.

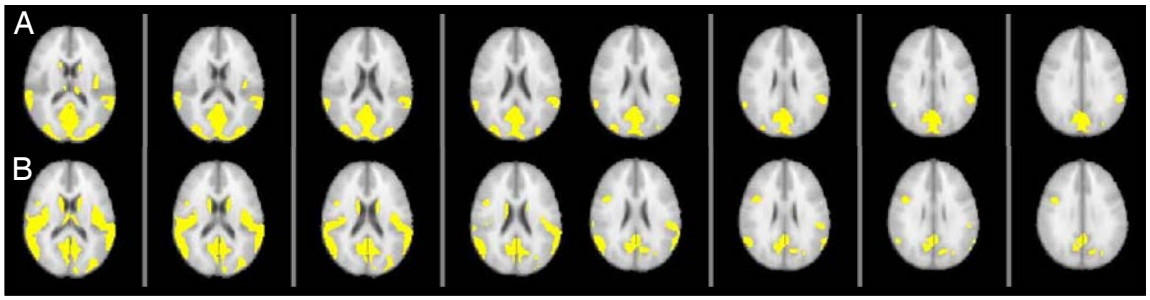
SPM5. An additional analysis was performed by using optimised VBM protocol of SPM5 (2). This was performed only to assess differences in GM between MS patients and normal controls, in comparison with the homologous analysis performed with SIENA-VBM.

Statistical Analysis: We performed the statistical analysis using Randomise (part of FSL) permutation testing. In SIENAr, all subjects' resulting standard space flow images were analysed with multiple regressions across the number of voxels within the edge mask in custom template space by using null distributions of maximum cluster size {Pseudo-t}-test statistics. In SIENA-VBM, group analysis was performed relative to i) GM differences between MS patients and normal controls ii) GM changes of MS patients over time (two time points). Analysis was restricted to a standard space averaged GM PVE mask and differences were assessed by using null distributions of maximum cluster size {Pseudo-t}-test statistics. Resulting Z-statistic maps were thresholded at $p<0.05$ (corrected).

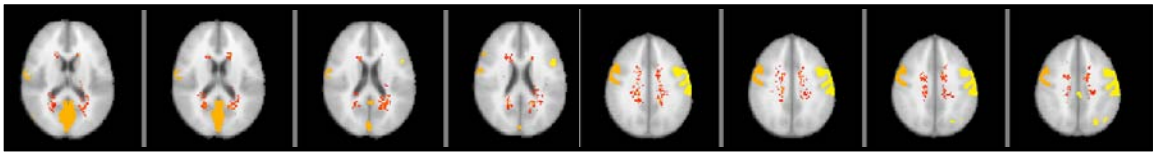
Results SIENAr analysis of regional brain edge shifts showed changes ($p<0.001$) along the lateral and third ventricles and across the cortical surface (yellow voxels in figure 1). These changes were in good agreement with changes in LV in the same period (red voxels in Figure 1)



To test whether GM changes account for a major proportion of the global brain atrophy, we performed a SIENA-VBM analysis selectively on the GM tissue volumes. First, differences in GM tissues were assessed between MS patients and normal controls. Analysis of both SIENA-VBM and SPM5 showed similar, diffuse GM loss in MS patients (figure 2: A results of SIENA-VBM; B: results of SPM05-VBM; yellow voxels have $p<0.05$).



We also used SIENA-VBM in the 2 MR time points to assess specific brain GM regions that have high probability to progress over time. In this case, LV changes were used as covariate. As shown in figure 3 (red to yellow voxels, $p<0.05$), GM changes were significant in regions very similar to that reported in the SIENAr analysis (see figure 1) and also in this case were in good agreement with the changes in LV in the same period



Conclusions

Our study has explored regional and global brain atrophy and their relation to T_2-W LV in RR MS patients. The results provide evidence that substantial GM atrophy is found in RR MS patients even over such a relatively short follow-up period. Both the SIENAr and SIENA-VBM approach suggest that atrophy rates vary across the cortex, with the greatest rate of changes in the frontal, temporal and midline cortices.

References. 1. Smith et al NeuroImage 2004; 2.Good NeuroImage 2001