Voxel-Level Cross-Subject Statistical Analysis of Brain Atrophy in early Relapsing Remitting MS patients

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The estimation of global atrophy rate is gaining popularity as a sensitive measure of brain volume change, for example as a marker for disease progression or effectiveness of disease treatment. In this abstract we extend our automated method of atrophy estimation to allow for voxel-wise cross-subject statistical analysis – i.e. to allow the investigation of different atrophy rates in different parts of the brain, without the need to pre-specify regional ROIs. This new method is tested in a group of early relapsing remitting (RR) multiple sclerosis (MS) patients. Results show significant regional brain volume changes over 1 year follow-up.

Introduction
Automated global atrophy estimation is becoming widely accepted as a useful marker for disease progression or response to therapy [1]. However, although brain atrophy is constantly demonstrated in chronic neurological disorders such as (MS), there has been very little work on the regional or local analysis of such temporal change in MS. Here we show regional brain volume changes in a group of MS patients. We have carried out cross-subject analysis of atrophy rate at the voxel level, by transforming atrophy edge images into standard space and effectively deforming into a standard brain-edge space.

Data
Conventional MR images were acquired at 1.5T (Philips NT Gyroscan) in 38 RR MS patients at early disease stages (median disease duration = 2.9 years, median age =35, median Expanded Disability Status Scale (EDSS)=1.5). The whole group of MS patients was scanned at two time points with a mean inter-scan interval of 1.3 years. The MR protocol included transverse T_1-W gradient echo images (TR/TE=35ms/10, 256x256 matrix, 1 signal average, 250x250 mm field of view), which yielded image volumes of 50 slices, 3 mm thick that were used for the regional analysis of brain change.

Methods
Analysis of the longitudinal data was based on SIENA [2] (part of FSL – FMRIB's Software Library – www.fmrib.ox.ac.uk/fsl). Each subject's T1-weighted image was analysed with SIENA, giving an output 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-points edge motion in mm; it is negative for estimated atrophy and positive for "growth". Each subject's flow image was first normalised by inter-scan interval to give mm change per year. It was then dilated spatially using non-binary dilation [3] and then resampled to standard space (MNI152) using FLIRT [4]. It was then masked by a standard-space brain/non-brain edge mask (derived from the MNI152). 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 and remasked. Next, all subjects' resulting standard space flow images were analysed voxel-wise with multiple regression to find voxel-wise trends, dependent on various factors (mean group effect, patient age, EDSS, disease duration). Resulting Z-statistic maps were thresholded at $P<0.05$, Bonferroni-corrected for multiple comparisons (over voxels). Colour overlay images were created on top of the MNI152 standard brain, to allow interpretation.

Results
The figure shows voxels with significant group mean effect. Brain atrophy was found in several brain regions in the 1 year follow-up. This is most pronounced around the lateral ventricles, but is significantly evident around the brainstem, in the cerebellum and in the cortex of frontal, temporal and occipital lobes.
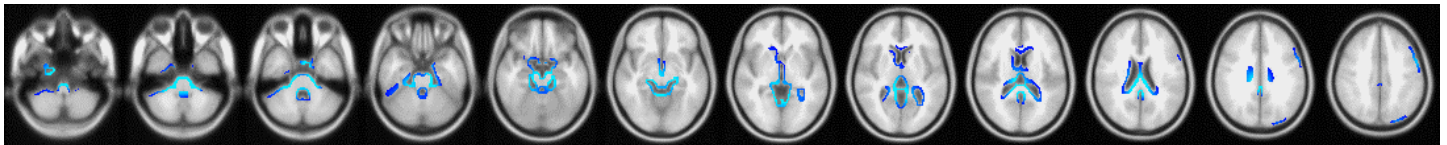
Discussion
We have shown that regional brain volume changes can occur in patients with very early stages of MS even in only 1 year. That we can find significant changes locally after multiple comparison correction is of great interest, as global measures (i.e. pooling across all voxels) only just reach significance in early MS. As expected, brain volume changes are most pronounced around lateral ventricles, but can be significantly evident in other brain regions including cortex. Voxel-level cross-subject analysis of brain volumes can provide an accurate and sensitive regional estimation of brain atrophy.

References
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