AN ESTIMATION OF METHOD-INHERENT AND PATHOLOGY-ASSOCIATED VARIABILITY OF GM MEASURES IN MS USING DUAL SAMPLING

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Abstract: Cortical grey matter (GM) atrophy has been described in multiple sclerosis (MS) before (1). However, little information exists about the inherent variability of measures of grey matter within individual MS patients. Here we estimate the variability of GM measures by employing a longitudinal dual sampling study protocol and two different analysis techniques: voxel-based morphometry (VBM) and surface-based morphometry (SBM). We also contrast the scan-to-scan variability with the pathological changes occurring during the course of a year within the same patients.

Introduction: Although MS has been traditionally thought to be a white matter disease, GM involvement is increasingly implicated. Previous studies of GM volume loss in MS patients highlighted a potential role for tissue-specific measures of atrophy (1). It is, however, unknown how reliable measures of GM are in a standard clinical setting. Quantifying the variability of GM measures would help to determine the degree of noise that obscures underlying change over time. VBM is a more sensitive technique, but it has been shown that SBM analysis with FreeSurfer can produce more interpretable measures by dissociating thickness from surface area and curvature changes (3). In this study, repeated scans allow for estimates of the variability of the methods (by comparing scans 2 weeks apart) as well as their sensitivity to the pathological changes (by comparing scans 52 weeks apart). This work sets out to study the evolution of tissue-specific brain atrophy in patients with progressive multiple sclerosis (PPMS). Its applications are two-fold : firstly, to obtain the measurement variability within individual patients, and secondly to assess change over time in cortical GM.

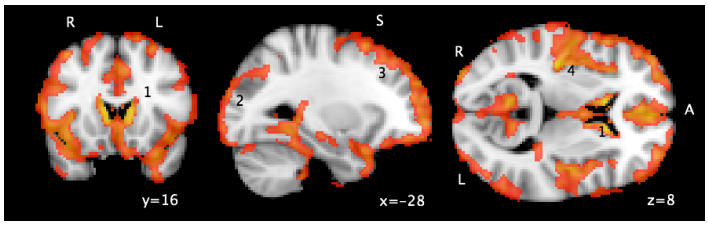

Figure 1: GM density decreased significantly ($p<0.0002$) over a year in cortical and subcortical GM. caudate nucleus (1), parietal and occipital areas (2), the frontal lobes (3) and the planum temporale (4). (red:t=3 to yellow:t>6)

Region	mean %	std %
Insular_Cortex	-3.45	(3.19)
Superior_Frontal_Gyrus	-4.57	(5.37)
Occipital_Fusiform_Gyrus	-2.03	(2.45)

Table 1: Mean and standard deviation of the differences between scans two weeks apart averaged across subjects for specific regions.

Methods: *Patients.* Scans from 17 PPMS patients and 7 healthy controls were analysed. The mean age of the patients was 49.5 years (range 32-55) and 47 years (range 39-55) in controls. MS patients had mean disease duration of 7.2 ± 2.1 years and median EDSS score of 3.5 (0-6.5) *Acquisition.* High resolution 3D-T1 weighted images (MPRAGE) were obtained on a 1.5T scanner (Siemens Sonata). Each patient and each control was scanned four times, at baseline (t=0) and 2, 50, and 52 weeks after the first scan. *Image Analysis:* VBM: We optimized VBM (as implemented in FSL, www.fmrib.ox.ac.uk/fsl) for a longitudinal study design, by first registering the four scans belonging to the same subject to a subject-specific bias-free template using an affine registration (12 degrees of freedom). These templates were then registered to a study-specific template generated from all subjects using a non-linear transformation. Individual scans were segmented, smoothed (7 mm FWHM), and transformed to the study-specific template using the above transformation path. Permutation-based statistics were carried out and cluster-based tresholding at $t > 3$ to determine longitudinal changes over a year. In addition, the mean and standard deviation of the differences between scans 2 weeks apart were calculated within subjects. SBM: We used an optimized version of FreeSurfer (surfer.nmr.mgh.harvard.edu/fswiki) for longitudinal deformable surface modelling. The two week separated scans were averaged to increase the contrast to noise of the GM/WM boundary definition. The first time point was fit and its surface model was brought into affine alignment with the second scan and deformed to match its intensities gradients. Reliability (or reproducibility) of cortical thickness measurements was evaluated by calculating the mean and standard deviation of the differences between separate surface estimates within subjects (6).

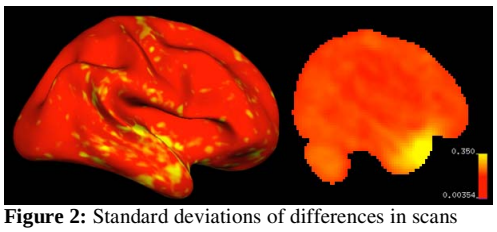

Figure 2: Standard deviations of differences in scans two weeks apart. Left, the standard deviation of differences in thickness estimates [mm]. Right, the standard deviation of GM partial volume estimates [%].

Results: *Longitudinal Changes.* GM density decreased significantly ($p<0.0002$) in MS patients over a year (Fig. 1,2). GM changes were found all over the cortical surface. In addition, grey matter density decreased in subcortical structures such as the caudate nucleus. Both methods show their variability between two week scans to be less than the size of the estimated pathological changes that took place over a year. VBM: GM measures of the pathological changes were on the order of 2-5% whereas the method's variability between the two week scans was less than 1%. SBM: The quantitative measurement of thickness derived from the surface fits was found to have a variability of no more than ~0.3 mm between two week scans. Longitudinal results need to be recomputed as a problem with FreeSurfer's approach was discovered during the analysis stage of this study. A new version has been released with fixes for these problems. Previous work in Alzheimer's disease shows cortical thinning of up to 1.25 mm in longitudinal SBM (5).

Discussion and Conclusion: PPMS is a useful model to investigate the evolution of atrophy as the potential confounding factors of inflammation and oedema play a lesser role (4). The use of dual sampling is useful in assessing reproducibility of measures and can be a useful adjunct in clinical trials. Although there are several causes for variability in imaging measures that need consideration, optimising segmentation techniques for instance, the ability to assess test-retest variability is important before the sensitivity of longitudinal estimates can be evaluated. We have shown that GM measures of longitudinal change are highly reproducible in a clinical population. VBM measures are more sensitive in general than SBM measures (3) both are capable of detecting longitudinal pathological changes. Our results show that GM density changes are much larger than the method inherent variability. VBM is therefore a useful and practical method for clinical assessment of GM changes. Future research will show if it is sensitive to correlations of cortical measures with neurobehavioual and cognitive measures (e.g. EDSS).

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4. Thompson AJ et al. Ann Neurol 1991;29:53-62. 5. Lerch J et al. Cerebral Cortex, 2005; 15(7):995-1001. 6. Han X et al. NeuroImage, 2006; 32(1):180-94.