Local tissue volume changes in early MS are most strongly reflected in non-peripheral grey matter

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INTRODUCTION Multiple Sclerosis (MS) is a chronic degenerative disease of the nervous system, broadly sub-categorized by the temporal profile of the clinical symptoms: relapse-remitting (RRMS), primary- or secondary-progressive (PPMS, SPMS). MS is characterized by white matter (WM) lesions throughout the brain, and has previously been considered a disease primarily of the WM. However, there is evidence to suggest that there are also significant grey matter (GM) changes associated with MS [1]. At present, however, it is unclear whether cortical or subcortical GM degeneration is more pronounced. Furthermore, the age of onset of MS is relatively varied, and it is yet unknown whether GM degeneration is influenced by age of onset of disease.

PURPOSE OF STUDY (i) Establish whether cortical or subcortical GM atrophy dominates in early MS; (ii) investigate whether the degree of GM atrophy varies in young and older-onset MS patients of matched clinical status; (iii) propose an image analysis work-flow for reproducible and standardized quantification of the required imaging endpoints for such analysis.

METHODS T1-weighted 1mm isotropic 3D and T2-FLAIR volumes [2,3] were acquired on a Siemens 3T Verio using a 12-channel head coil and neck array in two cohorts of MS patients (Young: n=21, 2M/19F, aged 30.4±3.2yrs, all RRMS; Older: n=17, 5M/12F, aged 48.7±3.3yrs; 15 RRMS/2 SPMS) matched for disease duration and other clinical scores (such as number of relapses, EDSS), and two groups of correspondingly age-matched healthy controls (Young: n=31, 18M/13F, aged 31.9±3.5yrs; Older: n=21, 12M/9F, aged 47.3±4.0yrs). MRI data processing followed the workflow in Figure 1. GM and WM lesions were segmented using Jim 6.0 (Xinapse), afterwards FSL tools were used [4]: FLIRT (with 6 DOF) for co-registrations; SIENA and FIRST for global and local (subcortical) tissue volumes, respectively, with lesion filling using the manually drawn GM and WM lesion masks [5]. An analysis of variance was used on the global and local tissue volumes with a p-value of 0.01 considered statistically significant.

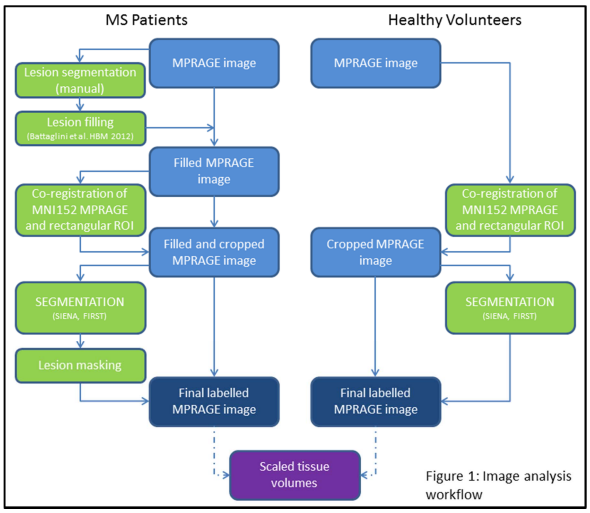

Figure 1: Image analysis workflow

RESULTS Comparing all MS patients to controls, irrespective of age group, revealed a significant decrease in global GM and non-peripheral GM (npGM) volume, but not in WM or peripheral GM (pGM). The percentage decrease in mean GM volume (-6.19%) was over twice that of WM (-2.74%), and the decrease in npGM (-13.34%) was more than triple that of the pGM (-4.08%). When considering age-group effects (Figure 2), similar percentage decreases in all global tissue volumes were observed for the young and older MS groups. Analysis of the local (subcortical) tissue volumes then revealed the specific locality of the npGM changes: both young and older MS patients had significantly reduced volumes in the thalamus ($P<=0.001$ for both), putamen ($P<0.001$ for both) and the nucleus accumbens ($P<0.001$ and $P=0.005$) compared to the age-matched controls, and no change in the volumes of the brain stem, the amygdala or the pallidum; only the younger MS group had significantly reduced volume in the caudate and the hippocampus ($P<0.001$ for both), although the caudate was close to significance for the older MS group ($P=0.012$).

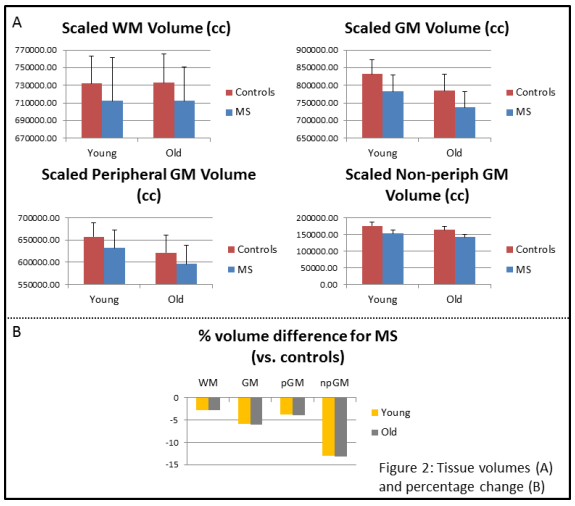

Figure 2: Tissue volumes (A) and percentage change (B)

DISCUSSION A few studies have previously identified subcortical GM atrophy in MS patients [1], but we believe that this is the first study to directly compare the relative atrophy in both global and local tissue structures in young and older-onset MS. We find the npGM degeneration dominates over that of the periphery, and in the first 2-3 years of disease (i.e., the typical disease duration of this data cohort) there is much less WM atrophy than GM (as previously described [6]). Furthermore, whilst both young and older-onset MS patients have significant atrophy in several subcortical regions, only the young MS patients show significant atrophy of the caudate and the hippocampus, suggesting that either the older-onset MS patients have inherently larger regional volumes here or that there is slower degeneration of these two subcortical regions in the older MS patients within the first few years of disease. We have also demonstrated an image analysis workflow for future analysis of these measures in larger MS studies.

References: [1] Bakshi R. et al., J Neuroimaging 2005; 15:30S-45S; [2] Jack CR, Jr. et al., JMRI 2008;27(4):685-691; [3] Mugler J, at al. MRM 1990;15:152-157; [4] FMRIB Software Library (FSL version 5.0, http://fsl.fmrib.ox.ac.uk/fsl) [5] Battaglini, et al. HBM 2012; 33 (9) 2062-71. [6] Chard DT et al., JNNP 2003;74:1551-1554.