Similar cortical lesion distribution and cortical atrophy location in patients with relapsing-remitting multiple sclerosis.

M. Battaglini[1], M. Calabrese[2], M. L. Stromillo[1], A. Favaretto[2], A. Giorgio[1], F. Rinaldi[2], P. Gallo[2], and N. De Stefano[1]
[1]Neurological and Behavioral Sciences, University of Siena, Siena, Toscany, Italy, [2]Multiple Sclerosis Center of Veneto Region, University of Padua, Padova

Introduction Pathological mechanisms leading cortical tissue loss in Multiple Sclerosis (MS) are largely unknown. Nevertheless cortical lesions (CLs) are detectable in MS by using novel sequences as the double inversion recovery (DIR) and their anatomical location and spatial distribution can be assessed by generating a CL probability map (CLPM). Voxel based Morphometry (VBM) has been successfully used in MS studies to assess anatomical and spatial localization of GM volume decreases. Against this background, we aimed here to ascertain the spatial relationship between CLs distribution and GM atrophy.

Methods ***Study Population and MRI examination*** We consecutively selected 103 patients with a diagnosis of Relapsing-Remitting MS and 30 healthy controls age and sex matched. All patients underwent the same brain MRI protocol performed to the MS Center in Padova and were assessed clinically with the Expanded Disability Status Scale (EDSS) on the day of scanning. All images were on a 1.5-T scanner (Achieva, Philips Medical Systems, Best, the Netherlands) with a maximum gradient strength of 33 mT/m, using a 16-channel head coil. The following images were acquired from each subject: 1 DIR, 3 consecutive 3-dimensional fast-field echo (FFE) T1-weighted (T1W) sequence and 1 fast fluid-attenuated inversion recovery (FLAIR).***MR data analysis***. ***Creation of Cortical and WM Lesion masks.*** For each patient, CL were identified on the DIR image, manually outlined and segmented into a binarized CL mask using a thresholding technique based on Fuzzy C-mean algorithm. Creation of FLAIR WM binarized lesion mask was obtained in each patient by a single observer, unaware of subjects' identity, employing a segmentation technique based on user-supervised local thresholding ***Creation of "unbiased" T1-W images*** To improve the signal-to-noise ratio, the 3 distinct T1-W images were co-aligned and averaged by using the mri_motion_correct.fsl included into the FreeSurfer softwares library. To make the segmentation and non-linear registration steps better performing, the WM lesion mask of each subject was linearly registered to the averaged T1-W by using FLIRT, the linear registration tool of the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk) and there each single lesion was refilled with intensities similar to the intensities of voxels surrounding it, generating an "unbiased" T1-W image. ***Volume Measurements*** For each subject, Normalized Cortical Volume (NCV) was assessed from the "unbiased" T1-W image using the SIENAx method. A VBM-FSL procedure was carried out with FSL tools. 30 "unbiased" T1-W images for each subjects group were affinely registered to the MNI152 standard brain and averaged to create a symmetric study-specific template. All the "unbiased" T1-W images were segmented using FAST4 and the resulting grey-matter partial volume images were then non-linearly registered to the study template previously created. Finally the registered partial volume GM images were modulated by dividing by the Jacobian of the warp field and smoothed with an isotropic Gaussian kernel with a sigma of 2.5 mm. Localization was assessed by using the MNI and the Harvard-Oxford atlases provided by FSL. ***Creation of cortical lesion probability maps.*** cLPM was created following steps previously described[1]: 1) CL masks were firstly linearly aligned to the respective "unbiased" T1W image and after non-linearly registered to the same VBM symmetric study-specific template created using the transformation parameters derived by registering each "unbiased" T1W image on the template. 2) Finally a cLPM was created by averaging all the standard-space CL masks. In this map, voxel intensity represents the probability of that voxel being lesion. Localization was assessed by using the MNI and the Harvard-Oxford atlases provided by FSL.***Statistical analysis*** Differences between HS, patient with presence of CL (CL-p) and with absence of CL (CL-a patients) were assessed using analysis of variance (ANOVA) followed by pairwise post hoc comparison using Tukey's HSD procedure to account for multiple comparisons. Data were considered significant at the 0.05 level. ***Voxelwise analysis*** To test for differences in GM local density, Randomise program within FSL was used to perform an ANOVA analysis between the above mentioned 3 groups (Clusters at t>2, p significant at p<0.05 after multiple comparisons).

Results ***Clinical Demographic of Study Subjects*** No differences for age and gender between the 3 groups were detected, while CL-p showed significant higher WM LV (CL-p: 13.8 ±10.46; CL-a: 2.4 ±2.7; p < 0.0001) and EDSS (CL-p: 2.5 (1-6); CL-a: 1.8 (1-4.5); p < 0.0001) than CL-a, but similar disease duration. ***Volume Assessment*** 3 CL-p patients were excluded for technical problems. NCV was similar in HC and CL-a (615±36 and 618±33 cm3, p=0.97) and higher in both groups than in CL-p (589±43 cm3, p<0.01). (See Figure 1). At the VBM analysis, no differences were detected between HC and CL-a (Figure 2A).Cortical GM volume was lower (p <0.0002) in CL-p than in HC, but with a prominence in the Frontal (with 3851 significant decreased voxels selectively located in Superior, Precentral, Cingulate and Paracingulate Gyri) Parietal (with 2445 significant decreased voxels selectively located in the post-central gyrus and Precuneous Cortex) and Temporal lobes (Inferior and Superior Temporal Gyri involved with 1361 GM decreased voxels) (See Figure 2B).

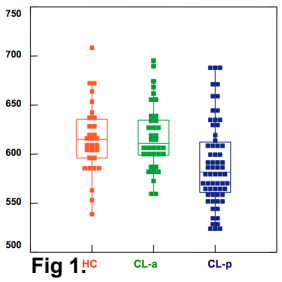


Fig 1.

Cortical GM volume was similarly lower (p < 0.0004) in CL-p than in CL-a. Frontal (with 2301 significant decreased voxels selectively located in Superior, Precentral, Cingulate and Paracingulate Gyri) and Parietal (with 726 significant decreased voxels selectively located in the post-central gyrus and Precuneous Cortex) lobes were the most affected (Figure 2C).

Fig 2.

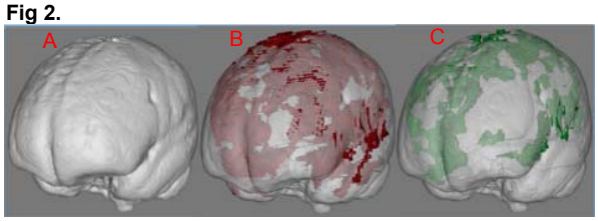
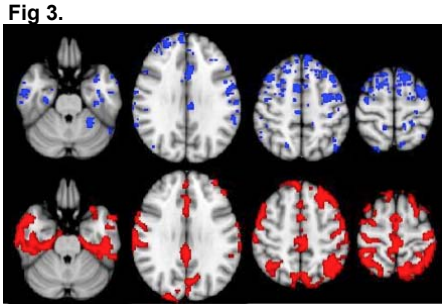


Fig 3.



Cortical lesion features and spatial distribution. A total of 689 in 64 out of 100 (64%) RR patients were identified. The bigger incidence of CLs was found in the frontal (51.8%) and temporal (30.4%) lobes and lower in the parietal (13.2%) and occipital (4.6%) lobes. More specifically, CLs were mostly distributed across 10 cortical regions of the reference atlas. Cortical motor area (defined here by the superior and middle frontal gyrus, precentral gyrus, and supplementary motor cortex) showed the highest presence of CLs (37.2%), followed by the anterior cingulate cortex (defined here by the anterior cingulate and paracingulate gyri) (9.2%). Fig 3 shows a similar spatial distribution pattern of cortical atrophy measured between CL-p and groups and CLs in Frontal and temporal lobes. Conversely, cortical atrophy is more widespread in the parietal lobe with respect to the CLs.

Conclusion Both the SIENAX and VBM methods show that MS patients with CLs have lower cortical volumes than both patients without CLs and HC. The VBM analysis suggests that these differences are meanly focused in the frontal, parietal and temporal lobes, where the CL distribution and the location are prevalent. These findings are indicative of a crucial role of CLs in development of GM atrophy.