A VOXEL-BASED MORPHOMETRY STUDY OF GREY AND WHITE MATTER DENSITY CHANGES IN MS PATIENTS WITH DIFFERENT CLINICAL PHENOTYPES

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Introduction

Brain atrophy is a well-known feature of multiple sclerosis (MS) and involves both the white matter (WM) and the grey matter (GM) (cortex and subcortical nuclei) [1]. It may develop early in the disease course and there is evidence that the rate and the topographical distribution of brain atrophy may vary according to the different MS phenotypes [2]. Brain atrophy in MS is only partially associated to the extent of T2 lesions, but it seems reflect and predict the clinical manifestations of the disease better than T2 lesion load [1]. To date, only a few studies [3, 4, 5] used voxel-based morphomentry (VBM) to assess regional GM loss in patients with relapsing remitting (RR) and primary progressive (PP) MS. These studies demonstrated that cortical GM reduction preferentially involves structures in the frontal and temporal lobes and deep GM in RRMS [3, 4] and deep GM structures in PPMS [5]. In the present study, we applied VBM analysis [6] to a large cohort of MS patients to assess whether the topographical distribution of GM and WM volume changes varies in the different disease phenotypes. We also interrogated the correlations between regional GM and WM volume changes with clinical disability and total lesion volume (TLV).

Methods

Using a 1.5 Tesla scanner, the following sequences of the brain were obtained from 134 patients with MS [7] (31 with clinically isolated syndromes (CIS) suggestive of MS, 37 with RRMS, 23 with PPMS and 43 with secondary progressive (SP) MS) and 29 healthy controls: a) dual-echo turbo spin-echo (TSE): TR/TE = 3300/16-98 ms, ETL = 5, slice thickness = 5 mm, matrix size = 256x256, FOV = 250x250 mm, 24 contiguous axial slices; b) 3D T1-Weighted MP-RAGE sequence: TR/TE = 11.4/4.4 ms, TI= 300 ms, flip angle = 15°, matrix size = 256x256, FOV = 256x256 mm; slab thickness = 160 mm, voxel size 1x1x1 mm. TLV was measured on PD-weighted scans using a local thresholding segmentation technique [8]. On MP-RAGE images, normalized brain volume (NBV) and total intracranial volume (ICV) were measured using SIENAx software [9]. After coregistration of MP-RAGE images with the corresponding PD-weighted images, PD-visible lesions were masked out (using MRIcro software), in order to avoid missclassification of WM lesions as GM. For the analysis of WM atrophy, lesions were not removed. Customized GM and WM templates were created from MP-RAGE scans of both healthy controls and MS patients using SPM2 software [10]. An optimized version of VBM analysis [11] was used to assess between-group differences in GM and WM volumes on MP-RAGE scans, using SPM2. The resulting GM and WM images were modulated to retain pre-normalization volume information and stored in the intensity of voxels. Prior to statistical analysis, the scans were thresholded at 20% of global intensity to reduce the influence of any remaining non-GM and non-WM tissue. An Ancova model, with age, disease duration and ICV as nuisance covariates, was used to compare GM and WM volumes between groups. Basic models and linear regression analysis (SPM2) were used to correlate GM and WM density changes with EDSS and TLV. SPM maps were thresholded at $p<0.001$, uncorrected for multiple comparisons.

Results

Compared to controls, CIS patients had WM density reduction around the left (L) lateral ventricle, the splenium of corpus callosum, the L middle frontal gyrus (MFG), the right (R) middle temporal gyrus, the R inferior temporal gyrus, while no GM density changes were found. Compared to CIS patients, RRMS patients had GM density reduction in the R postcentral gyrus and L MFG. Compared to RRMS, SPMS patients had GM density reduction in the R MFG, caudate nuclei, bilaterally, L insula and L anterior cerebellar lobe. Compared to SPMS, PPMS had GM density reduction in bilateral orbital frontal cortex and WM reduction in the dorsal mesencephalon, while compared to PPMS, SPMS had GM density reduction in the L parietal cortex and L insula (Figure 1 and 2). No correlations were found between GM and WM changes and EDSS and LL.

Conclusions

In MS patients, brain tissue volume decrease follows different patterns of regional distribution according to the disease phenotype. In line with previous studies on GM atrophy [2, 6, 7], our study shows a preferential fronto-temporal cortical atrophy in MS patients. WM damage seems to be predominant in the early phases of the disease, while GM atrophy seems to be more evident in the progressive forms. The lack of correlations between regional GM and WM atrophy and EDSS might be due to the heavy weighing of this scale on locomotor function. The lack of correlations between regional GM and WM atrophy and TLV suggests that factors other than macroscopic WM lesions are determinants of brain atrophy in MS.

References

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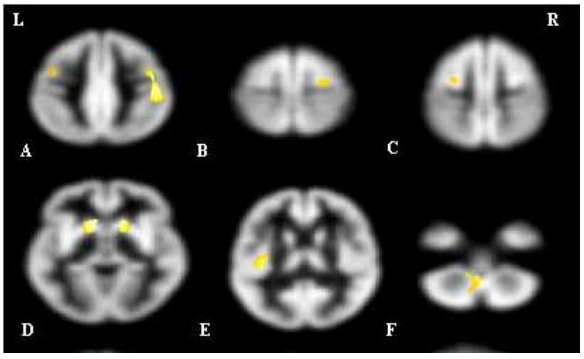

Figure 1

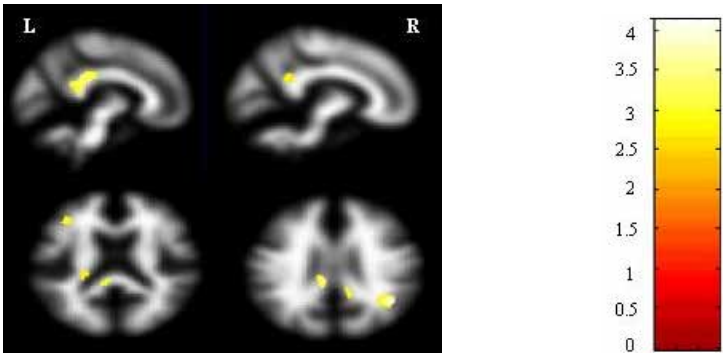

Figure 2

Figure1. VBM of GM. A, regions of significantly reduced cortical GM volume in RR as compared to CIS patients. B-F, regions of significantly reduced cortical GM volume in SPMS as compared to RRMS patients.

Figure 2. VBM of WM. Regions of significantly reduced WM volume in CIS patients as compared to controls.