Title:

Multiparameter MR quantification of microstructural tissue alterations in multiple sclerosis.

Lommers E.[1, 2], Reuter G.[1], Simon J.[3], Degueldre C.[1], Balteau E.[1], Phillips C.[1], Maquet P.[1, 2]

1. GIGA Institute, University of Liege, Belgium.

2. Clinical Neuroimmunology Unit, Neurology Department, CHU Liege, Belgium.

3. Psychology and Cognitive Neurosciences Research Unit, University of Liege, Belgium

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS). Focal demyelinating lesions, i.e. plaques, are the pathological hallmark of MS (1). However, histopathological studies have shown that diffuse and chronic inflammation occurs within the normal appearing brain tissues (NABT), escaping detection on conventional MRI (2). Focal and diffuse processes seem to be partly independent and combine in varying proportions to drive the clinical pattern of evolution, relapsing or progressive MS (3).

We aim at quantifying the difference in microstructure of NABT between MS patients and healthy controls (HC), using a multiparameter mapping (MPM) imaging protocol developed in the framework of an international collaborative effort (4). This protocol derives fully quantitative and reproducible (4) high-resolution maps of multiple parameters (MT, R2*, R1)

which values are directly influenced by myelin and iron contents (5) (6) (7).

Methods

36 MS patients, classified as relapsing-remitting MS (RRMS) or progressive MS (primary and secondary progressive – PMS), and 36 HC took part in this study. MPM protocol and additional FLAIR sequence were acquired on 3T MRI scanner in approximately 20 minutes (4). MT, R2* and R1 quantitative maps were estimated using the *hMRI* toolbox (http://hmri.info) (8) (Figure 1). Quantitative maps were segmented with the *USwithLesion* (https://github.com/CyclotronResearchCentre/USwithLesion*)* toolbox in different cerebral tissue classes: cortical grey matter (CGM), deep grey matter (DGM), normal appearing white matter (NAWM) and lesions (9). For each participant, the three quantitative MR parameters (MT, R2*, R1) were extracted from all voxels of the 3 tissue classes (CGM, DGM, NAWM), based on the 90% probability to belong to the tissue class. The brainstem and cerebellum were excluded. Summary measurements were computed as median values for each tissue class and MR parameter. Due to the influence of normal aging on brain microstructure, quantitative parameters were all corrected for age. Three two-way multivariate analyses of variance (MANOVA), one for each parameter (MT, R2* and R1), estimated the effects of group (HC, RRMS, PMS) and tissue class (CGM, DGM, NAWM), using age and scanner as independent variables of no interest. Tukey's post-hoc analyses were performed when necessary to explore significant principal effects. We consider an alpha level for statistical significance at 0.05.

Results

Two-way MANOVAs testing for group differences revealed that vector of means was different across groups for each parameter: MT [Wilks' Lambda = 0.50, F (6,128) = 8.92, $p < 0.001$, $R^2 = 0.50$], R1 [Wilks' Lambda = 0.67, F (6,128) = 4.77, $p = 0.0002$, $R^2 = 0.33$], R2* [Wilks' Lambda = 0.64, F (6,128) = 5.39, $p < 0.0001$, $R^2 = 0.36$]. More specifically, MT in CGM and NAWM was lower in patients than in HC, suggesting a diffuse demyelination in these tissue classes. Patient groups did not significantly differ from each other, although MT in CGM and NAWM tends to be lower in PMS group. In DGM, MT was lower in PMS patients than in HC. R2* and R1 from CGM and NAWM were lower in patients than in HC suggesting reduction of myelin and/or iron content. Patient groups did not significantly differ from each other. We did not observe any increase of R2* in DGM between HC and patients (Figure 2(a)). Group by scan interaction was significant for R2* [Wilks' Lambda = 0.80, F (6,128) = 3.06, $p < 0.007$, $R^2 = 0.20$], due to a simple interaction value in CGM and NAWM for R2*.

Conclusion

This cross-sectional study illustrates the interest of simultaneous quantitative estimation of multiple MR parameters in the assessment of NABT in MS. Because each parameter is differentially sensitive to myelin and iron, the MPM approach proves superior to semi-quantitative single-parameter relaxometry by positioning MS patients in a three-dimensional and multi-tissue space (Figure 2(b)). Future large-scale studies should evaluate the reproducibility and predictive values of these results.

References

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Figures

Figure 1: Multiparameter quantitative maps

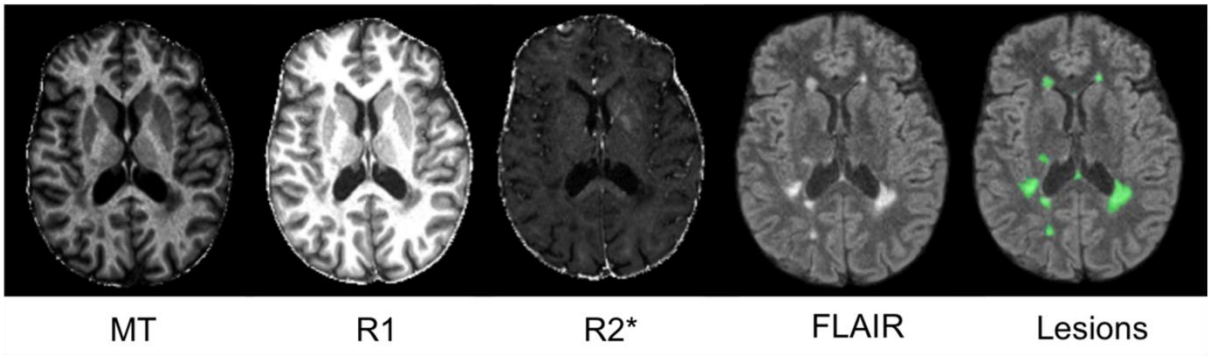

Figure 2: Violin plots and results of post-hoc analysis for each parameter in each tissue class (a)
Positioning MS patients and HC in the three-dimensional and multi-tissue space (b)