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Multi-dimensional microstructural imaging offers novel in vivo insights into brain pathology: an application to multiple sclerosis

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Synopsis

Magnetic resonance imaging is today the most versatile imaging method for characterization of multiple sclerosis (MS) in vivo, but clinical examinations lack sensitivity to capture changes in the tissue microstructure. Using a multi-dimensional microstructural imaging approach, we demonstrate how it is possible to obtain more specific and broader microstructural insights about the underlying pathology of MS. For this we use a comprehensive battery of conventional and novel diffusion weighted imaging and quantitative MRI sequences each capable of explaining different and complementary microstructural properties. This allows us to explore the underlying pathology of MS, which is normally only accessible with histology.

Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by inflammatory processes leading to demyelination and neurodegeneration. Both demyelination and axonal degeneration occur in diffuse lesions throughout the central nervous system, but microstructural changes are also present in the normal appearing white matter (NAWM)[1–3]. Magnetic resonance imaging (MRI) is today the most versatile imaging method for characterization of MS in vivo, where structural imaging is used to detect the dynamic of MS lesions and to extract clinical measures such as the lesion number and volume[4]. Yet, the lesion pattern is weakly associated with clinical disability scores and poorly predicts disease progression[5]. Newer MRI technologies such as diffusion tensor imaging (DTI) improve the sensitivity but still lack in specificity to the underlying microstructural pathological alterations in MS. Using a multi-dimensional microstructural imaging approach, we demonstrate how it is possible to obtain more specific and broader microstructural insights about the underlying pathology of MS. For this we use a comprehensive battery of novel diffusion weighted imaging (DWI) and quantitative MRI (qMRI) sequences each capable of explaining different and complementary microstructural properties. This allows us to explore the underlying pathology of MS, which is normally only accessible with histology.

Methods

The comprehensive protocol of MR sequences includes (figure 1):

- Microscopic fractional anisotropy (μFA) mapping using magic angle spinning of the q-vector (qMAS)[6]. μFA is sensitive to cell shape or microscopic anisotropy[7–9].
- Apparent exchange rate (AXR) mapping[10] using filter exchange imaging (FEXI)[11]. AXR is sensitive to cell-membrane permeability.
- Intra-cellular volume fraction (ICVF - mostly sensitive to axon density), orientation dispersion (OD - reflecting the architectural axonal organization), and isotropic signal fraction (ISOSF) mapping using multi-shell DWI and the NODDI model[12].
- Fractional anisotropy (FA) mapping using DTI[13].
- Magnetization transfer (MT) and proton density (PD) mapping using qMRI[14]. MT is sensitive to myelin content and PD is sensitive to mobile moities.
- Conventional structural scans (T1w, T2w, and FLAIR) were used for manual delineation of MS lesions and segmentation of white matter (WM).

While the conventional approaches allow for detecting the underlying pathology, the novel diffusion weighting and quantitative approaches might provide increased sensitivity to different microstructural features. A combination of the large array of approaches used in this study then allows for a nuanced view into the diseased tissue microstructure.

Thirty MS patients and 17 healthy controls (HC) were included. In the MS group, FLAIR hyperintense lesions were manually delineated. WM was segmented using FreeSurfer. In MS, lesions were masked from the WM ROIs. ROIs were then eroded by 2 voxels to reduce partial volume effects. All parameter maps were co-registered to the structural T1w-image and average parameters were extracted in HC WM (HC-WM), MS NAWM (MS-NAWM), and MS lesions (MS-L). Group-differences were evaluated using 2-sample T-tests.

Results and Discussion

Figure 2 plots the group average (standard deviation) as well as significance levels in the group comparisons.

MS-NAWM was associated with lower μFA and ICVF compared to HC-WM, while the other parameters were not significantly different between groups. This is consistent with histology showing that diffuse axonal damage (i.e decreased axonal density) is the dominant pathology occurring in MS-NAWM[1,15]. In MS-NAWM, primary demyelination is sparse, but myelin damage is a consequence of axonal damage[1]. This is also reflected in our multi-dimensional data, which shows no reduction in the myelin-sensitive parameter (MT) and no changes in permeability (AXR). However, a larger spread in MT was found in MS-NAWM compared with HC-WM.

In MS-lesions all parameters were significantly different from HC-WM and MS-NAWM.

Myelination: As expected, myelination (MT) was decreased in lesions. Increased AXR suggests increased cell permeability due to demyelinated axons or/and increasing number of glial cells in lesions[1]. Decrease in FA indicates a more isotropic compartment, but the μFA of 0.6 suggests that a fraction of demyelinated axons remain present in the lesions.

Axonal density: ICVF is clearly reduced compared with NAWM suggesting significant neurodegeneration. Less axonal dispersion (OD) was found in lesions, which could be due to less crossing fibers due to neurodegeneration or systematic degeneration of a specific axonal size population[16]. In general, it is expected that free water is increased in MS-lesions, which is supported by higher ISOSF and PD as well as lower FA.

Conclusion

Conventional scans, used in clinical examinations of MS, are sensitive to brain tissue changes, but less specific to features of tissue microstructure. The combination of qMRI and DWI gives a complementary view of brain pathology, currently only offered by post-mortem examinations. By using multi-dimensional imaging, and tracking changes over time, potentially allow for better diagnosis and treatment of patients.

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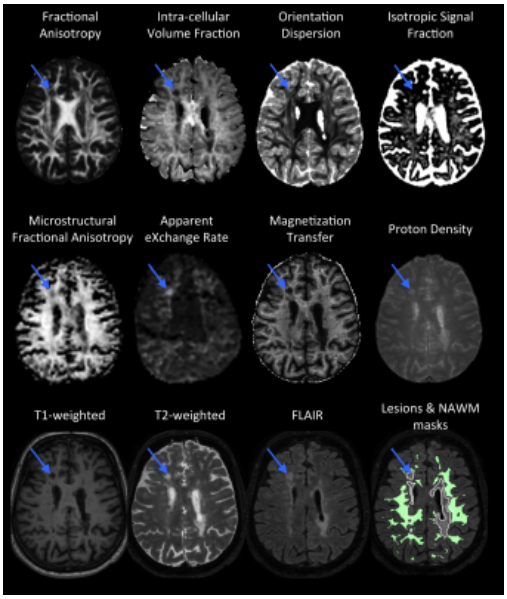
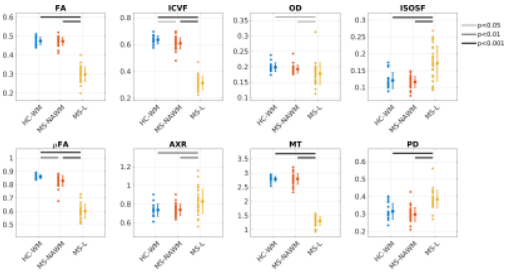
Figures



This figure shows the different parameter maps (row 1 & 2) and conventional structural scans (row 3) for a single MS subject. Blue arrow points at a single lesion in the left frontal lobe, showing contrast from normal appearing white matter (NAWM).



Within-group average and standard deviation for all parameters used. Individual subject values are plotted as colored dots. Significant between-group differences are indicated by solid black lines (line-width indicate significance level). Group differences between MS-NAWM and HC-WM were found for ICVF and μFA, all other maps were comparable between MS-NAWM and HC-WM. However, all parameters were different between MS lesions and MS-NAWM and HC-WM, reflecting strong demyelination and neuronal degeneration happening in the lesions.

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