Tracking The Individual Lesion Myelination Status In Multiple Sclerosis

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Introduction: Demyelination and remyelination, the depletion and reconditioning of axonal hull structures, takes places concomitantly in Multiple Sclerosis (MS) lesions. The balance or imbalance of destruction and repair may influence the degree of therapy response but cannot be visualized nor quantified *in vivo* so far. Myelin Imaging (MI) has shown great promise to reliably measure the relative myelin content in MS white matter (WM)[1]. New quantitative image analysis strategies are needed to obtain specific information on the myelination status of single lesions, the intra-patient and inter-patient variability, and, the time course of lesional compartment myelination. We used the whole-brain relaxation method *Multi-component Driven Equilibrium Single Pulse Observation of T1 and T2* (mcDESPOT) that allows the evalutation of myelination by means of measuring the myelin volume fraction (VFM)[2]. Its capability to retrieve isotropically resolved whole brain VFM maps enables to embrace the entire brain lesional compartment into the analysis. We hereby present a new approach to track single lesion myelination and volume over time

Methods: A 1.5T MR scanner (Siemens Sonata, Siemens AG, Erlangen Germany) and 8-channel head RF coil were used to derive multi-component T1 and T2 information from sets of *Fast Low Angle SHot* (FLASH) and true *fast imaging with steady state precession* (TrueFISP) data acquired over a range of flip angles at constant TR with FOV = 22cm, matrix = 128x128, slice thickness = 1.7mm; FLASH: TE/TR = 2.0/5.7ms, $\alpha = \{5,6,7,8,9,11,13,18\}°$; TrueFISP: TE/TR = 1.71/3.42ms and $\alpha = \{9,14,19,24,28,34,41,51,60\}°$. The total mcDESPOT imaging time was ~13min. VFM maps were derived using the established mcDESPOT processing method[2]. An additional 3D-fluid attenuated inversion recovery (FLAIR) sequence was obtained to segment WM lesions as single volumes of interest.

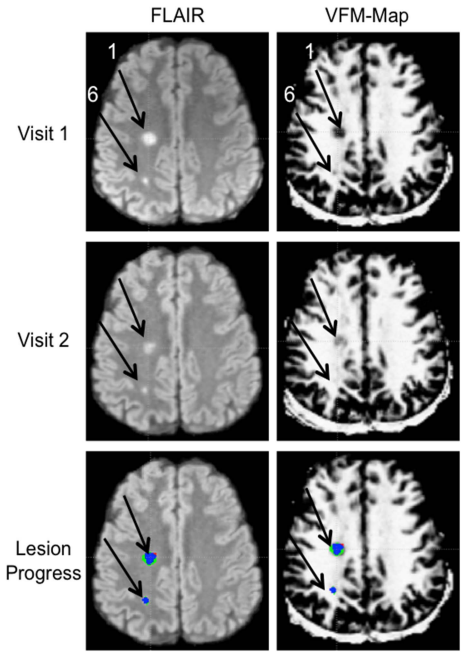

Fig.1 WM lesions and its color-coded change in volume.

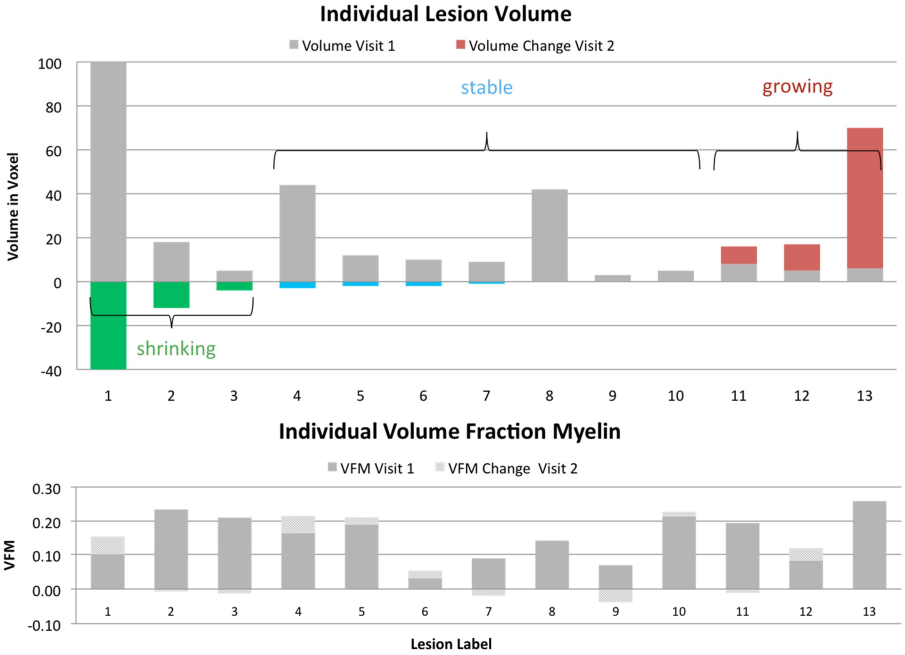

Fig.2 WM lesions of the same exemplary patient as of Fig.1; lesions were plotted separately to visualize the relationship of volume and myelination changes. Lesions sorted by volume change (*upper plot*).

MRI data of n = 15 MS patients was acquired at baseline and 6 months follow-up. Common data post processing involved brain extraction and co-registration[1]. A semi-automatic approach was used for lesion pre-segmentation of both time-points to generate binary masks of well-defined MS lesions in FLAIR data[1]. The lesion-labeling algorithm was designed in the MATLAB environment and additionally used the *Image Processing Toolbox*. MATLAB function *bwlabeln* was applied to tag MS lesions in the 3D mask. For every lesion of the follow-up 3D mask the algorithm determined an intersection in space with labeled lesions and those of the previous time-point to identify correspondence. Subsequently the algorithm distinguished new lesions without intersections with lesions of the first time-point. Finally vanished lesions were determined. Accordingly, every lesion obtained a global label for separate observation in a prospective time-series. Individual lesion parameters were determined to identify lesions as *growing, shrinking, or, stable* and VFM was read out. Lesions smaller than 3mm^3 (3 FLAIR voxels) were excluded from the analysis.

Results: The specific analysis of mcDESPOT derived whole-brain VFM maps allowed the assessment of individual WM lesion myelination status and volume. Growing, shrinking and stable lesion subsets were found in individual patients. Decreasing and increasing VFM was found in all subsets independently from volume change over time (mean VFM change 0.0083; range -0.0380 - 0.0548).

Discussion: We applied a new image analysis algorithm to a longitudinal follow-up myelin imaging in early MS. Preliminary data in early MS patients revealed an independent relationship of lesion volume development and the lesion myelination status. The hereby-presented approach of myelin imaging data processing is being applied to a greater cohort of early drug-naive and subsequently treated MS patients to scrutinize the extent of possible therapeutic response.

Conclusion: We earlier found average lesion tissue myelination being a risk factor for clinically definite MS development[4]. However, to date it remains unclear if initial MS immunohistological patterns including the disease-related lesional demyelination are heterogeneous and if they are preserved over the disease course or under treatment. Due to the generally restricted access to biopsy material, their selective nature within the biopsied individual and early disease states and the rare existence of repeated or even longitudinal samples, a non-invasive repeatable imaging technique will better allow characterizing tissue destruction. Given mcDESPOT to be an *in vivo* method capable to reflect the brain tissue myelin content, the specific course of myelin loss can be described.

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[3] Metz et al., Ann Neurol. 2014; 75(5):728-38 [4] Kitzler et al. Proc. Intl. Soc. Mag. Reson. Med. 2013; 21; 5710