Quantitative assessment of iron in multiple sclerosis lesions

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1. Introduction
Iron is essential for normal neuronal metabolism including processes of myelination and mitochondrial energy generation, but excessive iron deposition may exert toxic effects [1]. Increased iron accumulation in deep gray matter has been described in multiple sclerosis (MS) and is believed to be indicative of neurodegeneration. Evidence for this comes from the observation of reduced basal ganglia signal intensities in T2 weighted images and also from quantitative relaxometry [2,3]. However, less information exists on the extent of iron deposits in MS lesions as well as in normal appearing white matter and their relationship to clinical findings. Improved lesion visibility on susceptibility weighted imaging (SWI) was ascribed to increased iron levels in MS lesions [4]. Recently, R2* relaxometry has been proved as sensitive means to quantitatively assess brain iron concentrations also within white matter structures [5]. Therefore, the purpose of this study was to quantitatively assess iron accumulation within MS lesions using R2* relaxometry and relate this to normal white matter and clinical parameters.

2. Subjects and Methods
MS patients and healthy controls underwent structural MRI of the brain at 3T (TimTrio, Siemens Healthcare, Erlangen, Germany). The cohort consisted of 116 patients (mean age 36.7±9.9 years, mean disease duration 7.7±7.9 years, median EDSS 2.0 (range 0.0-7.5); 34 clinically isolated syndrome (CIS), 71 relapsing-remitting MS (RRMS) and 11 secondary progressive MS (SPMS)), and 26 controls (mean age 30.3±7.1 years).
R2* mapping was done with a spoiled gradient echo sequence (TR/TE/FA = 68ms/4.92ms/20°, resolution = 1x1x4mm³) with 12 equally spaced echoes (echo spacing = 4.92ms). R2* was calculated from the multiecho data using a monoexponential fit and a truncation model [6]. A FLAIR sequence (resolution = 1x1x3mm³) served for identification and delineation of MS lesions and a high resolution MPRAGE (resolution = 1x1x1mm³) was used to calculate normalized brain volumes. T2 lesion load masks were affinely transformed to the R2* maps and eroded by one pixel to prevent partial volume effects at lesion rims. Four periventricular regions with a high probability for MS lesion occurrence were used to obtain average R2* rates of normal white matter in the controls. Averaged intraleisonal R2* rates were compared to normal white matter R2* rates and then were related to clinical and demographical data (including age, age at disease onset, disease duration, disease course, normalized brain volume, EDSS and the annualized relapse rate).

3. Results
Intraleisonal R2* rates were significantly decreased in MS patients compared to white matter R2* rates of controls (mean R2* in MS lesions = 14.3±3.0 s⁻¹, in controls = 20.1±1.3 s⁻¹, p<0.005). Exemplary FLAIR and R2* maps are shown in Figure 1. There was no statistically significant difference between intraleisonal R2* rates among MS patients with different disease phenotypes (Figure 2). In the entire MS cohort, intraleisonal R2* rates showed a negative correlation with T2 lesion load (r=-0.3; p<0.005) and a weak positive correlation with brain atrophy (r=0.2; p=0.05). There were no significant correlations between intraleisonal R2* rates and age, age at disease onset, EDSS, and in RRMS with the annualized relapse rate.

4. Discussion and Conclusion
Our results do not support expectations of increased iron accumulation in MS lesions, but rather indicate lower levels compared to normal white matter. Observed associations suggest an inverse relation of intraleisonal iron levels with the severity and extent of tissue damage, i.e. the more destroyed the brain parenchyma, the lower amounts of iron remain, which is in line with histopathological studies [7].

References: