Quantitative Susceptibility Mapping (QSM) indicates disturbed brain iron homeostasis in Neuromyelitis Optica

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PURPOSE: Neuromyelitis optica (NMO) is a severe, inflammatory demyelinating disease that typically affects optic nerve and spinal cord in a monophasic or recurrent manner [1]. Patients with NMO usually appear normal on conventional MRI or show lesions in areas of high aquaporin expression, being most commonly placed around the ventricles, the hypothalamus, the central canal of the spinal cord and the optic nerve [2]. In a recent study, Chen et al. [4] investigated deep grey matter (DGM) iron in patients with NMO using high-pass filtered phase imaging, a relatively indirect technique to assess tissue magnetic susceptibility [5]. Using this technique the authors did not find significant differences (p<0.05) between patients and normal controls. The purpose of the current study was to investigate brain iron and myelin in NMO patients using two quantitative imaging techniques, R_2* mapping and the relatively new Quantitative Susceptibility Mapping (QSM) [3],[5]. Our hypothesis was that QSM has a higher sensitivity toward detecting subtle susceptibility changes than high pass filtered phase imaging.

METHODS: 12 clinically confirmed NMO patients (6 female and 6 male; age 35.4y±14.2y) and 12 age- and sex-matched healthy controls (HC; 7 female and 5 male; age 33.9±11.3y) underwent MRI at 3 Tesla. We acquired triple-echo gradient-echo data with the following parameters: TR 38ms; TE_1=4.71ms, TE_2=15ms, TE_3=30ms, FOV 180x240 mm, 96 slices, voxel size 0.8x0.8x1.2mm^3. Raw multi-channel GRE images were combined, resulting phase images were unwrapped [6], and magnetic field maps were calculated from the temporal phase evolution [7]. Background fields were corrected using SHARP [8] (radii: 0.8 to 8 mm, TSVD threshold: 0.05) and corrected phase images were converted to susceptibility maps using HEIDI [5]. We calculated R_2* maps from the combined magnitude images using the power method and a compensation for macroscopic field gradients. Two experienced radiologists independently performed a blinded ROI-based group comparison analysis bilaterally in the following regions: thalamus (Tha), caudate nucleus (CN), globus palladius, putamen, red nucleus (RN), optic radiation (OR), splenium of corpus callosum (SCC), pons, frontal lobe WM and cerebellum. The regions are illustrated in **Figure 1**. We carried out the analysis with two different reference regions in the present study: whole brain (WB) and left thalamus (LT). Whole brain was chosen as it was previously used in other studies. Left thalamus was supposed to be less affected by global demyelination, spatially slowly varying inhomogeneities and artifacts, due to its spatial limitation and location deep in the brain. Normality of the data and differences between patients and controls were tested by Kolmogorov-Smirnov and t-test, respectively. A value of p<0.05 was considered as statistically significant.

RESULTS: When measured relative to LT, more diamagnetic (lower) susceptibility was found in patients in left putamen (p=0.038), left/right RN (p=0.001/p=0.018), right CN (p=0.033), and in right pons (p=0.025) (**Figure 2**). Referenced to WB, magnetic susceptibilities were decreased only in the right RN (p<0.01), and values in the SCC (p=0.038) as well as in the left Tha (p=0.020) were increased. R_2* was significantly decreased (p=0.050) in the left OR and a trend toward decreased R_2* was observed in the right OR (p=0.061).

DISCUSSION: The increased magnetic susceptibility in SCC and left Tha relative to WB is indicative for demyelination, in line with other studies reporting WM damage in these regions [3]. Decreased magnetic susceptibility in the iron-rich basal ganglia nuclei (using Tha as a reference), on the other hand, can be explained as lower brain iron concentrations (or chemical redistribution of iron into less magnetic forms) in the regions or higher susceptibility (demyelination, iron increase) in the reference region. While demyelination is a reasonable explanation, it is unlikely that the observed high susceptibility differences (**Figure 2**) in other regions are induced by demylination in the Tha. The sensitivity of WB susceptibility to local susceptibility changes, global demyelination, and spatially slowly varying artifacts is still poorly understood and it is likely that inter-subject variations of the numerically calculated average WB value renders the subtle disease-related tissue changes insignificant.

CONCLUSIONS: Our study demonstrates that, first, QSM is more sensitive than R_2* with respect to detecting tissue changes in NMO and, second, that the requirement of choosing a reference region represents a serious limitation for the interpretation of the maps. Being the first report of a disturbed iron homeostasis in NMO patients, further research is required to confirm the use of QSM as a new imaging biomarker in NMO.

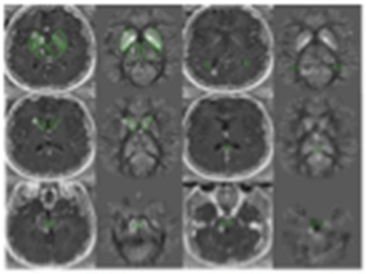

Figure 1: Representative ROIs (green) laid over six slices (columns) of the R_2* relaxation rate constant maps (first and third column;) and susceptibility maps (second and fourth column;).

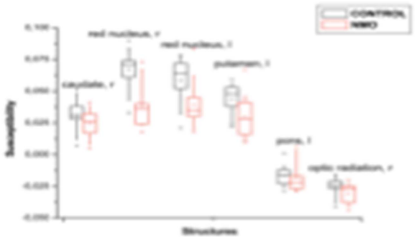

Figure 2. Box-plot of the magnetic susceptibilities in regions where differences were significant (p<0.05). Values given in ppm relative to the left Tha.

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