Deep gray matter R2* in patients with multiple sclerosis, their healthy siblings and unrelated healthy controls

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Target Audience: Radiologists, neurologists, medical physicists and technologists.

Purpose:
Multiple sclerosis is an autoimmune disorder of the central nervous system characterized by two pathologic processes: episodic inflammation resulting in focal demyelination of nerve fibres and axonal loss (classic lesions observed using MRI) and progressive neurodegeneration. Iron was suggested to play a role in neurodegenerative diseases because it is a catalytic centre in the Fenton reaction, a chemical reaction which results in oxidative stress. Oxidative stress may play a role in neurodegenerative diseases, such as Parkinson or Huntington disease. In both these diseases increased iron levels were detected in various areas of the deep gray matter. In MS, numerous MRI studies using T2, T2*, mapping, T2* mapping or susceptibility contrast also suggest an increase in iron content in the deep gray matter of the brain. Moreover, a linear correlation between R2* and iron concentrations in the deep gray matter has been shown. However, it is not clear whether iron is a cause, a result or a mere epiphenomenon of MS. The etiology of MS is uncertain but it is clear that genetic factors play important roles in susceptibility and clinical course. It has been shown by twin, half-sibling, adoptee and stepsibling studies that the increase of MS among family members is indicative of genetic sharing rather than common shared family environment. In this study we performed R2* relaxometry in deep gray matter in people with definite MS, their healthy siblings and non-related healthy controls.

Methods:
Patients with clinically definite MS, their healthy siblings and non-related healthy controls were recruited. In total, 101 subjects were scanned. Data were acquired from January to December 2011 on a 3T Philips Achieva scanner using an 8-channel phased array head coil. In addition to conventional MRI (PD-, T2-, T1-weighted scans), DTI data were acquired with an EPI sequence at 2.2 x 2.2 x 2.2mm3 and 0.83 x 0.83 x 2.2mm3 reconstructed (TR = 7465ms, TE = 75ms, b = 1000, 16 directions). R2* data were acquired using a flow compensated gradient echo sequence with 5 echoes (TR = 28ms, first TE = 5ms, ΔTE = 5ms; flip angle = 17°; voxel size 0.9 x 1 x 1.6mm3 acquired and 0.8 x 0.8 x 0.8mm3 reconstructed; field of view = 230 x 165 x 110mm3). R2* maps were computed by voxel-wise fitting of a mono-exponential function using a correction for background field inhomogeneities, which were measured with unwrapped phase images of the first two echoes. In late October 2012, one group member not related to this study created a preliminary list of 13 subjects in each group. The Oxford Atlas template was transformed from MNI space into the SWI subject space via FA using FSL’s FNIRT and FLIRT tools. Blinded operators visually inspected registration and manually corrected ROIs based on venograms and registered FA maps. ROIs were eroded by one voxel to avoid partial volume effects. Average R2* values were computed for each structure. Statistical analysis was performed using ANOVA and Kruskal-Wallis to test significance between groups.

Results:
39/101 subjects are equally distributed for the three cohorts. The figure displays the average R2* values and standard error in four deep gray matter regions. A trend for an increase in R2* was observed for the MS cohort compared to controls in all four regions although there were no significant differences between these two cohorts. The siblings didn’t show any particular trend with MS or controls. The lowest p-value was found in the globus pallidus between MS and controls (p=0.09, p=0.76 for siblings and controls).

Discussion:
Higher R2* values are thought to be associated with higher iron concentrations. Although there were no significant differences in R2* between the cohorts, the observed trend of an increase in R2* for the MS group with respect to the control group agrees with other studies using R2*. The results obtained for 13 patients, 13 siblings and 13 controls so far fail to demonstrate an underlying genetic basis for these potential differences in R2* suggesting that increased iron concentration in the deep gray matter is secondary to the disease process rather than a trigger.

Conclusion:
We used R2* as a surrogate imaging marker for iron in the brain of patients with MS, their healthy siblings and healthy controls. The findings suggest that iron accumulation is a result rather than the cause of MS pathogenesis.

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