Increased iron accumulation occurs in the earliest stages of demyelinating disease: an ultra-high field susceptibility mapping study in Clinically Isolated Syndrome

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Abstract
Objective: To determine, using ultra-high field magnetic resonance imaging (MRI), whether changes in iron content occur in the earliest phases of demyelinating disease, by quantifying the magnetic susceptibility of deep grey matter structures in patients with Clinically Isolated Syndrome (CIS) that is suggestive of multiple sclerosis (MS), as compared with age-matched healthy subjects.

Methods: We compared 19 CIS patients to 20 age-matched, healthy controls. Scanning of the study subjects was performed on a 7T Philips Achieva system, using a 3-dimensional, T2*-weighted gradient echo acquisition. Phase data were first high-pass filtered, using a dipole fitting method, and then inverted to produce magnetic susceptibility maps. Region of interest (ROI) analysis was used to estimate magnetic susceptibility values for deep grey matter structures (caudate nucleus, putamen, globus pallidus, the thalamus and its pulvinar).

Results: Significantly increased relative susceptibilities were found in the CIS group, compared with controls, for the caudate nucleus (p < 0.01), putamen (p < 0.01), globus pallidus (p < 0.01) and pulvinar (p < 0.05). We found no significant nor consistent trends in the relationship between susceptibility and age for either the study controls or CIS patients, in any ROI ($r^2 < 0.5; p > 0.05$). In CIS patients, the time elapsed since the clinical event and the Expanded Disability Status Scale (EDSS) scores were not correlated with iron levels in any ROI ($r^2 < 0.5; p > 0.05$); however, a moderate correlation ($r^2 = 0.3; p < 0.01$) was found between the T1 lesion load and the mean susceptibility of the caudate nucleus.

Conclusion: CIS patients showed an increased iron accumulation, as measured using susceptibility mapping of the deep grey matter, suggesting that iron changes did occur at the earlier stages of CIS disease.

Keywords
Deep grey matter, demyelinating disease, early MS, iron, magnetic resonance imaging, Clinically Isolated Syndrome, susceptibility mapping, ultra-high field, brain regions

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Introduction
There is growing evidence of iron accumulation in the deep grey matter of patients with multiple sclerosis (MS), from both in vivo magnetic resonance imaging (MRI) and histopathological studies,1 but it is not clear how early in the disease these changes occur. Our study addresses this question by taking advantage of the unique ability of ultra-high field (7T) MRI to detect iron deposition in the CNS, to assess iron concentration in the deep grey matter of patients.