

## Iron accumulation is a rare feature in multiple sclerosis lesions

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**Target Audience:** Clinicians, radiologist, MR researchers, basic scientists

**Purpose:** One of the main radiological signs of multiple sclerosis (MS) is the appearance of focal lesions due to inflammation and blood brain barrier breakdown. Focal lesions on MR frequency images have shown variability of contrast observed for different lesion types<sup>1</sup>. These frequency shifts in lesions have been attributed to iron accumulation<sup>2,3</sup>. However, it was also shown that microstructural changes cause strong frequency shifts, without changes in the magnetic susceptibility<sup>1,4-6</sup>. Moreover, histopathology studies report no iron content or iron content only in the rim of a few MS lesions<sup>7,8</sup>. If lesions contain iron, non-local effects that extend beyond the actual MS lesion should be visible. Focal, nearly spherical lesions should create a dipolar modification of MR frequency, similar to microbleeds, where the paramagnetic hemosiderin is responsible for the dipolar pattern. If, on the other hand, frequency shifts are caused by microstructural changes without changes in magnetic susceptibility, no such dipole features will be observed, indicating a lack of iron in MS lesions. Here, we investigated focal MS lesions for the presence and absence of these non-local effects in frequency maps.

**Methods:** 20 patients with relapsing-remitting MS were scanned serially once a month over 6 months. 17 out of 20 completed all serial scans (age range 28 -57yrs, mean = 39.5 yrs, Extended Disability Status Scale (EDSS) range 1-6, median EDSS=2.5, disease duration 1-27 yrs, mean =9.4 yrs). Gradient echo frequency shift images were acquired in axial orientation (FOV=240 x 166 x64mm<sup>3</sup>, reconstructed voxel size=0.43 x 0.43 x 1mm<sup>3</sup>, TR/TE=40/20ms) along with conventional imaging sequences (Fluid Attenuated Inversion Recovery (FLAIR), T1 Gd-contrast enhanced). All MR images were registered to the first time point in the frequency image space. Enhancing lesions and spherical T2-hyperintensities were identified using T1-Gd enhanced and FLAIR scans at all time points. Each lesion was visually inspected for dipole characteristics. Lesions were classified as dipolar if they showed a ring of reduced frequency in the equatorial plane and areas of increased frequency above and below the lesion.

Frequency maps were investigated in all three planes as shown in Fig. 1. The corresponding magnitude images were used for confirmation of spatial extent of lesions. Venograms were used to determine whether field distortions were due to deoxyhemoglobin in veins.

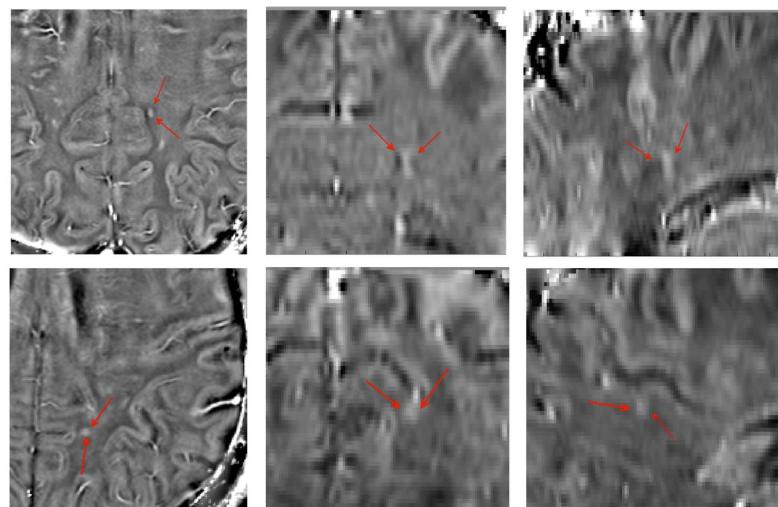
**Results:** In 9/17 subjects, 37 focal enhancing lesions were detected. Only 1/37 enhancing lesions and 4/90 of the non-enhancing lesions showed dipole characteristics as described above. Fig. 1 shows two non-enhancing lesions in all three planes, one (upper row) with a characteristic dipole and one without (bottom row).

**Discussion:** Dipole shaped distortions of the magnetic field indicative of iron accumulation are a rare phenomenon in MS lesions, as only 4% of all lesions in our cohort exhibited this feature. We did not observe a prevalence of recently enhancing lesions or non-enhancing lesions to show dipole characteristics (3% vs. 4%). This finding agrees with histopathological studies of post-mortem brains samples, where iron in MS lesions was found to be rather an exception than a standard feature. Also, our findings are in agreement with theoretical suggestions that the frequency contrast might be due to microstructural changes rather than changes of magnetic susceptibility<sup>4,5</sup>.

**Conclusions:** Iron accumulation in MS lesions is a rare feature and appears only in 4% of MS lesions.

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**References:** [1] Wiggemann et al., Neurology 81, 2013 [2] Haacke et al., J Magn Res Med 29, 2009 [3] Chen et al., Proc. Intl. Soc. Mag. Reson. Med 21, 2013, p.692 [4] He et al., PNAS 2009 [5] Yablonskiy et al. PNAS 2012 [6] Chen et al., ESMRMB 2013 [7] Pitt et al., Arch Neurol 67, 2010 [8] Bagnato et al., Brain 134, 2011



**Figure 1:** Upper row: An example of a non-enhancing lesion, which showed dipole characteristics. Bottom row: A non-enhancing lesion without dipole features. The same lesions are shown on MR frequency shift images (left to right): axially, coronally, sagitally.