3T Magnetization Transfer Imaging Reveals Correlation with Cerebral Iron Concentration *in vivo*

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Introduction: Iron is one of the most important and abundant physiological metals, occurring endogenously in almost all organisms. Most brain iron is non-heme and is stored primarily in the form of ferritin. Physiologically, different gray matter structures of the brain are known to have varying iron content (1). Increased presence of non-heme iron in the brain is also known to be linked to a variety of devastating neurodegenerative disorders such as Alzheimer's (AD) and Parkinson's disease (PD) (2). Furthermore, iron labeling is also a popular approach for cell tracking and has been used to label reporter genes. Presently, detection of differences in iron content by MRI can be done using T2 and T2* imaging. Magnetization transfer (MT) imaging has also been reported to be sensitive to ferritin content in the heart (3). When performing whole-brain MTR imaging at 3T, we recently found gray matter heterogeneity between structures well known for their different iron content (4). We show here that these MTR differences correlate extremely well with the known non-heme iron concentration *in vivo* (9 age-varied healthy volunteers). Using ferritin-doped agarose phantom (of known iron content), we show that MTR *in vitro* also shows an even better distinctive correlation with iron concentration. These findings indicate the exciting possibility of using a similar approach for the clinical assessment of iron storages diseases.

Methods: Nine healthy adults (26-42 years of age) were scanned after written informed consent. Studies were performed on a 3T Philips Intera (Philips Medical Systems, Best, The Netherlands) with transmitting quadrature body coil and SENSE head coil for reception. MT-weighted images at offset frequency $\omega = 1.5$kHz, $S(\omega)$, were acquired using a 3D-spoiled gradient echo, TR/TE/α = 65ms/15ms/9°, with a 25 ms non-selective sinc-shaped MT pre-pulse (peak amplitude = 10.5μT) and multi-shot echo planar imaging. Other parameters: whole brain field of view = 204x204x90 mm (ap,rl,fh), acquired resolution: 1.4x1.4x1.5 mm, total scan time 1min56s. Three averages were performed to increase SNR. The MTR was calculated voxel by voxel: $MTR = 1-S(\omega)/S_o$ where S_o is the image in the absence of MT preparation. Six ROIs were manually selected: parietal cortex (Crtx), caudate nucleus (CN), putamen (Put), substantia nigra (SN), and globus pallidus (GP) (Fig. 1). These regions were selected because the landmark study from Hallgren and Sourander (1) quantified and reported the age-adjusted the non-heme iron concentration in these locations. MTR was plotted against iron concentration [Fe] which was also adjusted for age according to (1). To verify the *in vivo* results, phantoms with known [Fe] were investigated. Equine horse spleen ferritin (14.24 mg Fe/ml) was added to 4% agarose by serial dilution resulting in iron concentrations of 0, 2, 4, 8, 16, 32, 64 mg/100g agarose. MTR images were acquired as above with the exception of 30 slices at 0.5mm slice thickness. Quantitative comparisons were performed by linearly regressing MTR against age-adjusted [Fe] *in vivo* and against known [Fe] *in vitro*, and the correlation coefficient, *r*, reported as the measure of the strength of correlation.

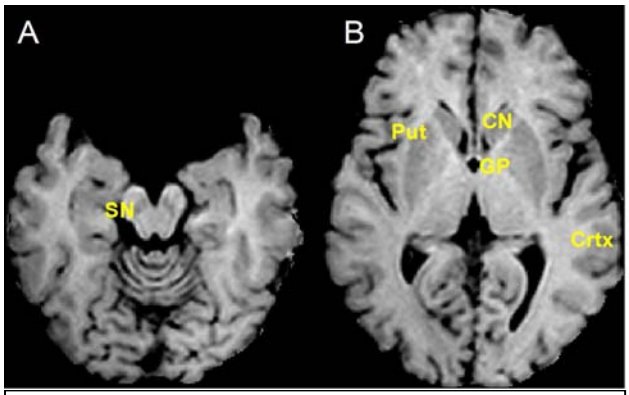

Figure 1: 3T MTR images at the level of (A) inferior colliculi and (B) lateral ventricles. Yellow text demarcates the gray matter structures chosen for comparison with [Fe]. All structures were appreciated in all volunteers.

Results and Discussion: The results indicate a striking correlation between 3T MTR and non-heme iron concentration *in vivo*. Fig. 1 shows MTR images at the level of the inferior colliculi (A) and lateral ventricles (B) demonstrating the location of the regions of interest chosen for quantitative comparison. Fig. 2 shows regional MTR as a function of age-adjusted non-heme iron concentration taken from data reported in (1). The red line represents the linear regression showing an outstanding relationship between the MTR data and [Fe] ($r = 0.90$; $p < 0.001$). Fig. 3 shows MTR results in the ferritin-doped agarose phantoms of known iron concentration. Excellent correlation between MTR and iron concentration was found ($r = 0.98$, $p < 0.001$).

Conclusion: *In vivo* MTR imaging of the brain at 3T revealed a very strong correlation with iron content. Examination of MTR in phantoms of known iron concentration confirmed this correlation. The fact that MTR can be used to detect small differences in iron content in the brain may have potential for many diseases that have shown a pathologic increase in intracerebral iron concentration, such as Alzheimer's, Parkinson's and many others. A further potential application is detection and tracking of iron-labeled cells, where *in vivo* quantification has been notoriously difficult.

References: 1) Hallgren B and Sourander P. J. Neurochemistry 1958. Vol 3: 41-51. 2) Schenk J and Zimmerman E. NMR Biomed. 2004;17:433-445. 3) Papanikolaou N, et al. Acta Radiologica (2000) Vol. 41(4): 348 4) Smith SA, et al. ISMRM 2005, #417, p.94.

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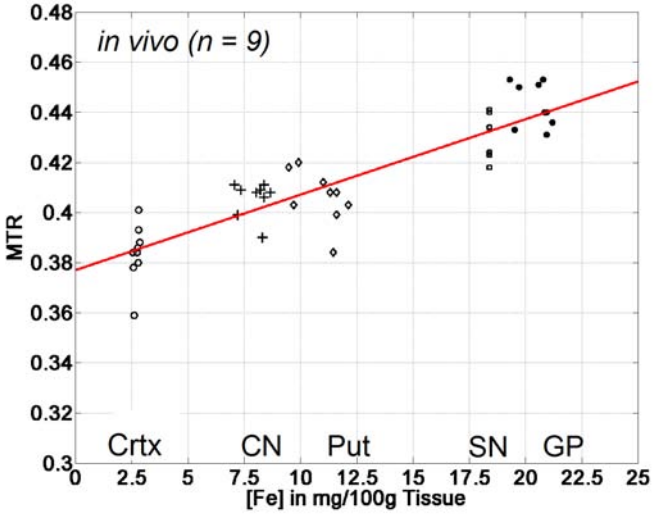

Figure 2: *In vivo* regional MTR values taken from 9 age-varied volunteers vs. reported age adjusted [Fe]. Red line indicates regression analysis ($r = 0.90$, $p < 0.001$).

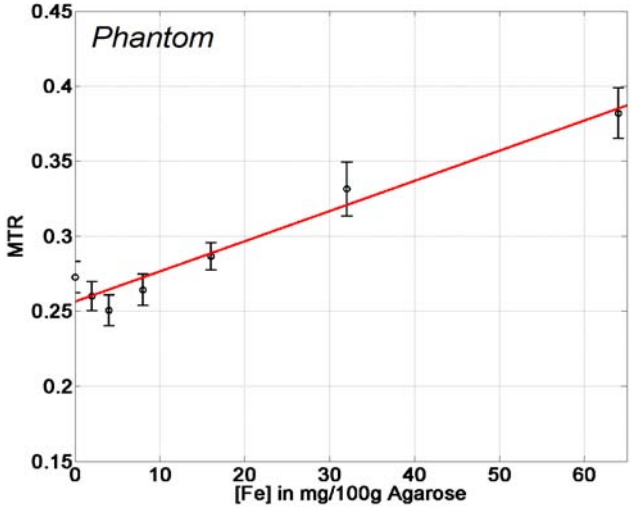

Figure 3: *In vitro* MTR values taken from ferritin-doped agarose (4%) vs. known iron concentration. Red line indicates regression analysis ($r = 0.98$, $p < 0.001$).