Susceptibility Contrast in Deep Brain Gray Matter Areas in Multiple Sclerosis Studied With 7T MRI

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INTRODUCTION: Hypointensity of deep brain gray matter (GM) structures in T_2-weighted images (T2WI) of multiple sclerosis (MS) patients has been reported and suggested to represent increased iron deposition [1]. However, these findings are difficult to generalize because the contrast in T2WI depends on a number of MR parameters including TE, TR, and others. Here, we studied deep gray matter in MS patients quantitatively using magnetic susceptibility contrast including R_2^*, phase, and susceptibility maps, derived from high resolution 7 T data, that are highly sensitive to subtle brain iron deposition [2, 3]. In addition, we compared the correlation of each of these parameters with the putative iron concentration in the brains of healthy subjects.

METHODS: Nineteen clinically defined MS patients (F/M = 10/9, age = 45 $\pm$ 10 y/o, EDSS score = 0-6.0) and nine age-matched healthy volunteers (F/M = 5/4, age = 43.7 $\pm$ 10.4) participated in this study. A 2D multi-echo gradient-echo acquisition was performed with the following parameters: TE = 15.5/ 30.0/ 44.5 ms, TR = 2 s, resolution = 0.31×0.31 mm², slice thickness/gap = 0.8/0.2 mm, flip angle= 75°, bandwidth= $\pm$31.25 kHz. Up to 3 slabs, with 30 axial slices per slab, were acquired to cover the whole brain. A SENSE acceleration rate of 2 was used to shorten the scan time. Quantitative R_2^* maps were derived from mono-exponential fitting. To remove phase wraps, the complex data were first smoothed by a Gaussian filter (FWHM = 30 voxels) to determine the macroscopic background phase. Continuous phase maps were then generated by subtraction of the background phase from the original data. Susceptibility maps were derived from the first echo (TE = 15.5 ms) phase data using a threshold-based k-space division method [3, 4] with an optimized threshold value ($\alpha = 0.01$). Six regions of interest (ROIs) including substantia nigra (SN), red nucleus (RN), globus pallidus (GP), putamen (PU), caudate nucleus (CN) and thalamus (TH) were manually drawn on the magnitude images. Each ROI was drawn on multiple successive images to almost entirely cover each structure. R_2^*, phase and susceptibility values were averaged in each ROI, respectively, and then averaged across all the subjects in the group. Results in the patient group and control group were compared by two-way ANOVA and corrected for multiple comparisons. The iron concentration in each ROI, obtained from published data [5], was correlated with the R_2^*, phase, and susceptibility values in the control group.

RESULTS: Two representative axial slices of the MR images containing SN and RN areas from one MS patient (M, 40 yrs, EDSS = 1.5, MS yrs = 5) and one control volunteer (M, 42 yrs) are shown in **Fig. 1**. The SN and RN are

Fig. 1: *A representative axial slice containing SN and RN from one MS patient (top row) and an age- and sex- matched healthy volunteer (bottom row).*

Fig. 2: *The top row shows the correlation of R_2^*, phase and susceptibility with iron concentration in iron-rich deep brain areas in the control group. The bottom row shows a comparison between patients and controls in different regions: "*" indicates a significant difference (p < 0.05). The error bars are standard errors.*

readily identifiable in the magnitude and R_2^* maps as dark and bright regions, respectively. They are also visible in the phase maps, with phase effects extending well into the periphery. These iron-rich structures are also clearly visible in the susceptibility maps. As a validation [2], the putative iron concentrations in those six brain structures, obtained from the literature [5], were correlated with the MR ROI values as shown in the top row of **Fig. 2**. Only the data from controls were used for the correlation since the putative iron concentration data was obtained from healthy subjects only [5]. R_2^* was linearly correlated with iron content (r = 0.99). The phase and susceptibility also showed a linear increase with iron content, albeit with lower r-values (r = 0.84, 0.79, respectively). Notably, intra-region variance was smaller for susceptibility than phase. A comparison between MS patients and controls is shown in the bottom row of **Fig. 2**, indicating that most measures did not differ between patients and controls. An exception is the susceptibility in CN, which was significantly higher in patients (p < 0.05).

DISCUSSION: In control subjects, R_2^* showed a stronger correlation with putative iron content than phase and susceptibility. The weaker correlation observed in the phase and susceptibility data may indicate that other sources in the tissue, besides iron, contribute, or that the contrasts have different sensitivities to artifacts and noise. In most regions, no significant differences were observed between patients and controls, which may suggest that the overall average iron deposition in the deep brain GM in patients does not differ much from that in controls, relative to the variation among subjects. This result does not exclude the possibility of intra-regional variations in iron content that may differ between MS patients and controls, as was found previously [6]. A fine segmentation within each structure may be necessary to verify this.

REFERENCES: [1] Bakshi R et al, Arch Neurol 59:62-8, 2002; [2] Yao B et al, *Neuroimage* 44:1259-66, 2009; [3] Shmueli K et al, MRM 62:1510-22, 2009; [4] Wharton S et al, MRM 63:1292-304, 2010; [5] Craelius W et al, *Arch Pathol Lab Med* 106:397-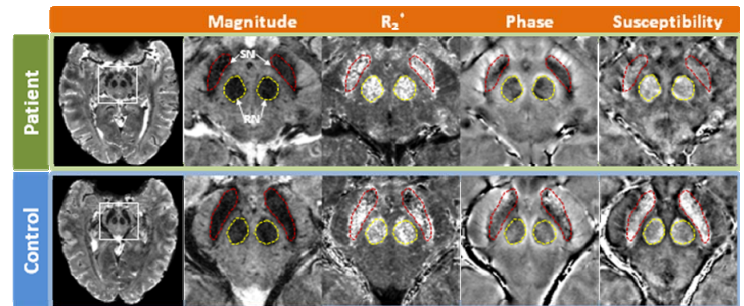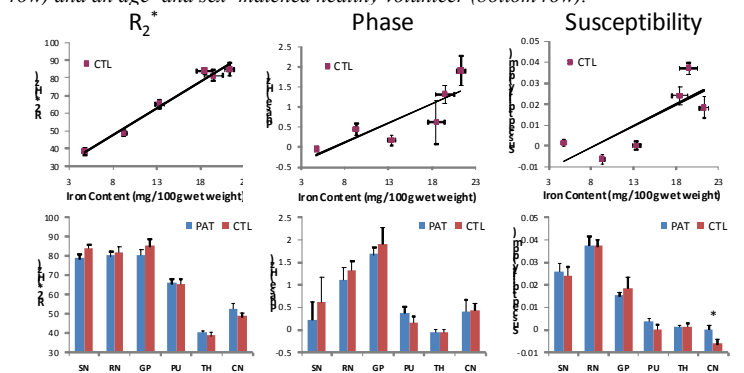9, 1982; [6] Haacke, EM et al, Int Angiol 29:149-57, 2010