

High Resolution Magnetic Susceptibility mapping in patients with Clinically Isolated Syndrome

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Introduction: Multiple sclerosis (MS) involves inflammation and demyelination of axons in the central nervous system. Previous studies have focussed on monitoring blood brain barrier breakdown, multifocal inflammation, demyelination, oligodendrocyte loss, axonal loss, gliosis and remyelination, but none has proved to be a predictor of clinical outcome [1]. Oligodendrocytes and myelin are rich in iron [1,2] and neurodegeneration in MS might be expected to cause an accumulation of iron in deep grey matter (dGM) structures which have extensive expression of the transferrin receptor and the ferrous iron transporter [3]. The change in magnetic susceptibility due to iron accumulation causes local field shifts which can be detected on phase images particularly at ultra-high field (7T), and these are likely to be more directly related to iron concentration than T2 which also depends on the distribution of iron. Unfortunately, susceptibility perturbation can cause frequency shifts which project beyond the boundary of the perturber in phase images [4], but phase images can be inverted to produce maps of the distribution of magnetic susceptibility which are likely to be sensitive markers of change. The aim of this study is to measure the susceptibility of dGM structures in patients with Clinically Isolated Syndrome (CIS), an early manifestation of MS.

Methods: Thirteen patients with CIS were recruited from Nottingham University Hospital, along with 10 age-matched healthy controls; both groups were consented according to local ethics approval. Scanning was performed on a 7T Philips Achieva system, equipped with a 16-channel receive coil and head only volume transmit coil. A T2* weighted 3D gradient echo acquisition was used, covering the brain in 4 stacks. (192x164x100mm FOV per stack, 0.5mm isotropic resolution, TE = 20ms, TR = 150ms, flip angle 14°, SENSE factor 2, EPI factor 3, imaging time 8.5mins.). For each subject, 4 stacks of magnitude and phase images were merged and a binary mask of the brain was produced in FSL [5]. Prelude was used to unwrap the resulting phase images within the mask (Fig 1A). A high-pass filter was used to remove unwanted, non-local fields and the data were scaled by $\gamma B_0 TE$ to yield field maps in ppm. Susceptibility maps (Fig 1B) were created by division

of the field map in k-space by the dipole convolution kernel shown in Eq.[1], where β is the angle between \mathbf{k} and \mathbf{k}_z . The ‘division by zero’ problem occurring on a conical surface in k-space at $\beta = 54.7^\circ$ was overcome by using a simple threshold-based method [6]. The following ROIs ; Caudate Nucleus (CN), Putamen (PT), Globus Pallidus (GP), Internal capsule (IC), Pulvinar part of the thalamus (PV), and the remaining part of the Thalamus (TH) (Fig. 1C) were defined on five slices that were completely within all 6 regions for all subjects and the susceptibility values were averaged. Since susceptibility can only be measured relative to other tissues using the approach described here, the difference in susceptibility of each structure relative to the IC was then calculated and plotted for each group of subjects.

Results: Fig.1D plots the susceptibility in each ROI relative to the susceptibility of the IC for both subject groups. Using a one way ANOVA test with multiple comparison correction, there was a significant difference ($p<0.0001$) between the five regions of interest for the control subjects; CN-GP ($p<0.001$),CN-TH($p<0.01$),PT-GP($p<0.01$),PT-TH($p<0.001$),GP-PV($p<0.001$),GP-TH($p<0.001$),and PV-TH($p<0.01$).Furthermore, there was a significant difference between controls and patients for the CN and GP ($p<0.05$ Mann-Whitney and t-test, respectively).

The phase data showed different trends between ROIs and no significant difference between controls and patients in any of the regions.
Discussion: High resolution susceptibility mapping shows that the susceptibility in the CN and GP was significantly higher ($p<0.05$) in CIS patients than in healthy subjects, suggesting increased iron deposition in these two regions. Similar results have previously been reported from analysis of simple phase data [7]. In contrast, our study showed no significant differences in phase. This disagreement could be explained by the isotropic nature of the voxels used in our study revealing the non-local behaviour of susceptibility induced phase shifts that data sets acquired with high in-plane resolution but large slice thickness will tend to average out [8]. In a group of subjects with a wider range of disease durations, the increase in local field shift (related to susceptibility) was found to be related to disease duration in the CN and PT, but not in the GP [7]. Therefore it is likely that the reason that no change was observed in the PT in our study is that the CIS subjects studied were at an early stage in the course of their disease. Our findings suggest that susceptibility change in the CN and GP might provide an early marker for disease progression. Future work will involve scanning different groups of MS patients to see how such a biomarker varies with disease progression.

References:[1] Haacke et al. J Magn Reson Imaging,2009,**23**, 537-544 [2] Rohit Bakshi et al. Arch Neurol, 2002. **59**: p. 62-68.[3] Y.Ge et al. AJNR,2007. **28**, 1639-1644 [4] Schaefer et al, Neuroimage,2009, **48**, 126-137.[5] <http://www.fmrib.ox.ac.uk/fsl/> .[6] Wharton et al. ISMRM 2009, 463.[7] Hammond et al., Annals of Neurology.2008 **64**. p.707-713 [8] Andreas Deistung et al. MRM, 2008,**60**, 1155-1168.

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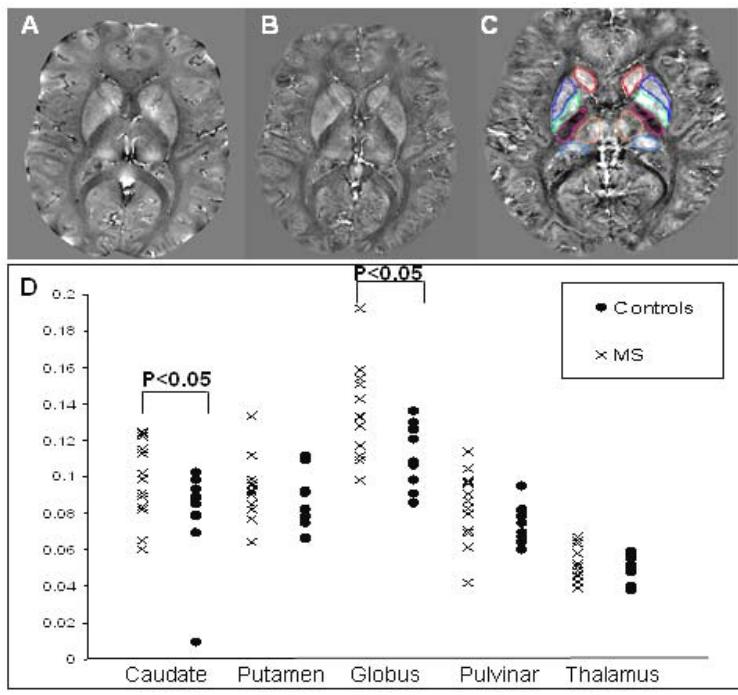


Figure: 1 (A) unwrapped filtered phase map (B) susceptibility map (C) Location of ROIs on susceptibility map (D) Statistical analysis of difference of magnetic susceptibility relative to the internal capsule for all subjects.

$$C(\mathbf{k}) = \frac{1}{3} - \cos^2 \beta \quad \text{Eq.}[1]$$