Evidence for elevated brain iron concentration in patients with

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INTRODUCTION: Alzheimer Disease (AD) is the most common cause of dementia in the elderly, and there is evidence that iron may be involved in the mechanisms that underlie some of the neurodegenerative processes associated with this type of dementia. Disruption of brain iron homeostasis is a crucial event in the early pathogenesis of AD, and it is likely that this disruption occurs at the molecular level decades earlier than the appearance of clinical symptoms. Magnetic field correlation (MFC) imaging is a novel quantitative technique developed in our laboratory and is based on the quantitative characterization of the local magnetic field experienced by water protons in biological tissues. Interestingly, the MFC is strongly dependent on the spatial distribution of the microscopic magnetic field inhomogeneities, such as those generated by ferritin iron localized in oligodendrocytes, and therefore is likely to be a more specific measure of iron content than R2 or R2*. The MFC can be measured using an asymmetric spin echo sequence. In this abstract, we have assessed brain iron concentrations as measured by MFC in patients with AD, subjects with Mild Cognitive Impairment (MCI) and age-matched controls (AMC) by using parametric MFC maps and histogram analysis.

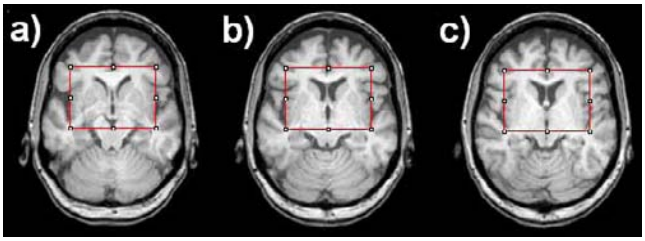
METHODS: Asymmetric spin echo images were acquired using a single-shot EPI sequence from 7 AD patients (mean age 71.4 years, mean GDS score 4.5), 6 MCI subjects (mean age 71.5 years, mean GDS score 3) and 14 age-matched controls (mean age 66 years) on a 3.0 T MRI scanner (Trio, Siemens Medical Solutions). Subjects were recruited through the Alzheimer's Disease Center at New York University School of Medicine. Diagnoses were based on NINCDS-ADRDA and DSM IV criteria. 20 slices (2 mm thick) were acquired using a 128 x128 matrix, FOV 256 mm, TR/TE = 2000/46ms with five refocusing pulse shifts (0.0, -4, -8, -12, and -16 ms). Data was processed using in house MATLAB (Mathworks, Natick, MA) scripts, and MFC maps were calculated by fitting the signal intensity as a function of the pulse shifts, to a Gaussian function [Eqn.1], on a pixel-by-pixel basis. The maps were thresholded at an MFC value of 1225 s^{-2} and a square region of interest was placed in the center of the brain on three consecutive slices in which the putamen and globus pallidus were clearly visible. The total number of voxels remaining in this region after thresholding were normalized to the area of the ROI and the histograms were subsequently computed from these maps.

$$\frac{S(t_s)}{S(0)} \approx \exp\left[-2t_s^2\gamma^2 K\left(\frac{TE}{2}\right)^3\right] \qquad \text{[Eqn. 1]}$$

where $S(t_s)$ = magnitude of the asymmetric SE, S(0) = magnitude when t_s=0, TE = echo time, γ = proton gyromagnetic ratio and K=MFC.

RESULTS: Figure 1 shows three consecutive slices from an AMC used in the generation of the histograms, and figure 2 depicts representative MFC maps obtained from a 69 year-old patient with AD with GDS 4 (a), a 62 year-old MCI subject with GDS 3 (b) a 63 year-old age-matched control (c). Although no significant difference was observed between AD patients and MCI subjects (p=0.222), a significant difference was observed between AD patients and AMCs (p=0.037). Figure 3 is a bar graph illustrating the fraction of voxels (mean ± SEM) with MFC values above 1225 s^{-2} generated for the three groups of subjects. This threshold level was chosen based on preliminary histogram analyses in our lab since a separation between the groups was evident at MFC values beyond 1225 s^{-2}. The histogram analysis has the advantage that the subjectivity intrinsic to the ROI analysis can be avoided, yielding results that are relatively insensitive to the investigator performing the analysis.

DISCUSSION: T2-weighted MRI has been used as a means of imaging regional cerebral iron levels [1] and studies have reported variations in brain iron levels between young adults, aged adults, and AD subjects [2]. The usefulness of T2 as a measure of iron content is limited, however, since changes in T2 values may be associated with different pathologic substrates other than iron (including edema, inflammation, demyelination and axonal loss) making the interpretation difficult. The feasibility of *in vivo* quantitative MFC imaging and its high correlation with putative iron concentrations has been previously reported in normal adults [3]. While these preliminary data are still being evaluated, the most striking feature in the three groups (as seen in figure 2) is the change in MFC values in the basal ganglia region, known for its high iron content. Our preliminary results suggest that MFC can be used a non-invasive method of quantitatively assessing iron-related alterations amongst AD patients, MCI subjects and AMCs.



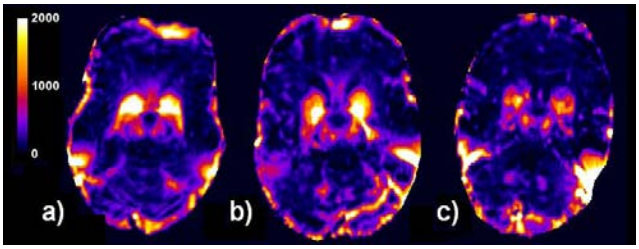


Figure 1 (top row). Three consecutive slices from an AMC used in the creation of the histograms.
Figure 2 (bottom row). MFC Maps of (a) AD patient (b) MCI subject and (c) AMC

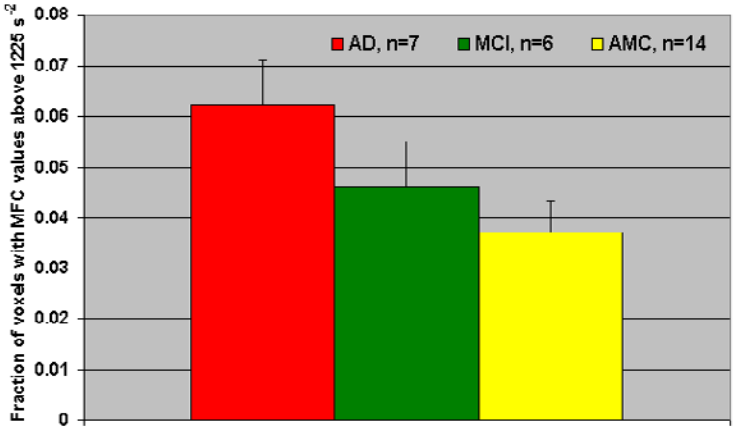


Figure 3. MFC Histogram for AD, MCI and AMC subjects

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