Determining the Contribution of Iron to Quantitative MRI of the Alzheimer's Brain

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Introduction

This study, which is a continuation of former MagLab-funded research (J. Dobson *et al.*) based at AMRIS [1], investigates the relationship between brain iron in Alzheimer's disease (AD), and the MRI parameters R_2 and R_2*. The goal is to assess the potential of altered iron status in AD as a diagnostic biomarker. Iron is an essential element in the brain, and managed by a sophisticated system of iron transport and storage proteins to avoid the toxicity that may result from excess free iron. However, evidence of iron dysregulation is present in many forms of neurodegeneration, and can result in region-specific accumulations of iron, or altered forms of storage and deposition, in regions vulnerable to degeneration. It would be advantageous to be able to detect changing iron status with clinical MRI, and optimization of scans for sensitivity to brain iron is an active area of research. High-resolution analysis of tissue, to test the relationship between MRI parameters and actual iron distribution, is an important step in validating clinical observations, and exploring biomarker potential. Donated brain tissue is used here to quantify R_2 and R_2* in regions of interest (ROI) from both AD and control cases. These are then sectioned, and ROI subjected to detailed iron analysis with synchrotron X-ray fluorescence (XRF) mapping.

Experimental

Tissue blocks were imaged in a 10 mm TXI radiofrequency probe using a 600 MHz Bruker Avance NMR spectrometer at AMRIS. Sample temperature was 3°C during measurement. Data were collected throughout the ROI in each tissue sample, with in-plane resolution 60 µm x 60 µm, slice thickness 80 µm, and FOV of 8 mm. A multiple slice multiple echo (MSME) routine was used to obtain R_2, and a multiple gradient echo (MGE) sequence to obtain R_2*. Image segmentation (**Figure 1a**), and R_2 and R_2* computation, was performed with Paravision v4.0 (Bruker) and Image J. Subsequent sectioning of the blocks at 30 µm thickness, in the same plane as the virtual MRI slices, permitted iron maps from within single MRI slices to be obtained and compared with calculated R_2 and R_2* maps.

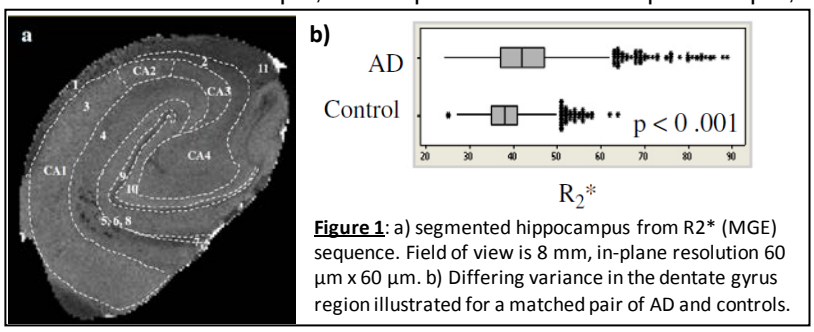

Figure 1: a) segmented hippocampus from R2* (MGE) sequence. Field of view is 8 mm, in-plane resolution 60 µm x 60 µm. b) Differing variance in the dentate gyrus region illustrated for a matched pair of AD and controls.

Results and Discussion

A set of AD and control hippocampus (HP), substantia nigra (SN) and pons cases were imaged at MR microscopy resolution, using a newly developed protocol that enables work with fragile unfixed tissues that have previously been frozen. Analysis of R_2* and R_2 was performed. Consistent results were obtained for the unfixed samples in each study group. The absolute R_2* differences in HP between AD and control were found to be almost negligible, but the variance in the distribution of R_2 and R_2* values (in distinct regions of hippocampus large enough to be segmented in clinical scans) is significantly different between AD and controls at $p<0.001$ (**Figure 1b**). Across the fields of the hippocampus, a positive correlation between iron and R_2*, and iron and R_2, was shown; this is consistent with observations at clinical field strength, and is useful confirmation that the relationship can be observed at 14 T in unfixed tissue samples, subsequent to their having been stored frozen. In summary, iron and MRI analysis of multiple brain regions in AD and age-matched controls has been completed, with HP, SN, and pons analyzed at AMRIS under MagLab Project 01243. The HP results have been published [2], and the pons and SN results have been accepted for presentation at the international ADPD meeting in March 2013.

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References

[1] J.F. Collingwood *et al.*, Alzheimer's and Dementia, **4**, 4(2), T365 (2008).

[2] Antharam V., *et al*., Neuroimage, **59**,1249 -1260 (2012).