In vivo Evaluation of Iron Content with Quantitative Magnetic Resonance Imaging

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Introduction: Alzheimer's Disease is a progressive neurodegenerative disorder with neuropathological hallmarks of amyloid (Aβ) plaques, neurofibrillary tangles (NFT's), and a progressive loss of neurons (brain atrophy) (1). Aβ plaques and NFT's are known to be major sites for catalytic redox activity when combined with high concentrations of iron, which contribute to oxidative stress in the AD brain. Oxidative stress eventually causes characteristic nuclear changes of neuronal apoptosis and the activation of apoptotic cell kinases leading to cell death and atrophy (2). Iron distribution in tissue is a natural contrast agent for magnetic resonance imaging (MRI) and provides a unique mechanism for *in vivo* quantitative iron mapping (3). Transverse relaxation rates R_2* (=1/T_2*) and R_2 (= 1/T_2) are sensitive MRI parameters for evaluation of tissue iron concentration. Determining the quantitative relationship between iron concentration and R_2* relaxation is important in establishing interactions between brain iron distributions and AD.

Methods:

Magnetic Resonance Imaging Procedure:

The animal MRI studies were undertaken with a 3.0 T Medspec S300 MR imaging-spectrometer using a home-built gradient insert (9.5 cm aperture and 100 G/cm). The R_2* and R_2 measurements of the brain were performed using a 25 mm trans/receive volume coil; the R_2 measurements are done with a multi spin-echo sequence while the R_2* uses the mGESEPI (multi Gradient-Echo Slice Excitation Profile) technique which allows for reliable T_2* measurements without magnetic susceptibility artifacts (4). Body temperature of the anesthetized mice (C57BL/6) were maintained at 37ºC while it was placed prone into the RF coil.

Phantom Model of Iron Load in Brain tissue:

We have created a phantom model that simulates the T_1 and T_2 the brain's white and gray matter tissues by altering agar and gadolinium concentrations. The R_2* of the model has been calibrated for both 22 ºC and 37 ºC so that both *in vivo* and *ex vivo* iron measurements can be simulated. An iron solution is titrated and thoroughly mixed such that the resulting final [Fe^{+3}] ranges from 0 to 240 μg/g wet weight; encompassing iron concentrations that are found in human and animal brains.

Results:

Figure 1 – Near-Right: Bar graph representing T_2* dependence on iron load in the Gray Matter phantoms ([Fe^{+3}] ranges from 0 to 240 μg/g wet weight). The graph shows a gradual decrease in T_2* relaxation that is monotonic with iron concentration. All values are significantly different from one another demonstrating that the mGESEPI T_2* measurement is sensitive to the varied concentration of iron in the system. Far-Right: T_2* parameter map of the iron loaded 37 ºC Gray Matter phantom. Higher iron concentrations result in lower signal intensities and, thus, are darker on the T_2* map.

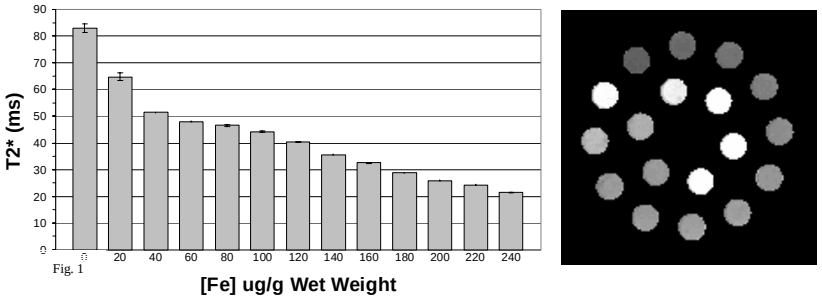

Fig. 1

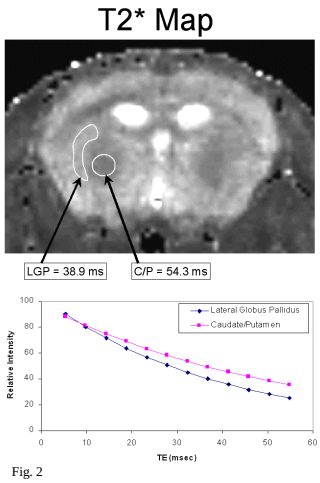

Fig. 2

Figure 2 – Left-Top is a representative T_2* parameter map of a mouse with the corresponding relaxation plot for two regions of interest beneath. The T_2* relaxation has proven to be more sensitive to iron than standard T_2 sequences. The lateral globus pallidus is known to have a high iron content while the caudate/putamen is known to have a lower iron content. This is clearly differentiated by the two relaxation plots (Left-Bottom).

Figure 3 – Near Right: *In vivo* mean iron concentrations of six regions of interest (ROI) from six mice. The R_2* values were converted into iron concentrations using the phantom calibration curves. The LGP, RN, and CC are known to be of higher iron content than the C/P, MC and SC (5). All three of the higher iron regions had significantly larger R_2* values and than the lower iron regions (*, $p<0.001$). The LGP R_2* was significantly higher than all other structures (**, $p<0.005$). Far-Right: is a T_2* map and Perl's/DAB stained section of the same slice selection. High iron regions are darker on the T_2* map and darker red/orange on the Perl's stained tissue. The iron staining shows that there is a good correlation between T_2* maps and the histochemically iron stained sections.

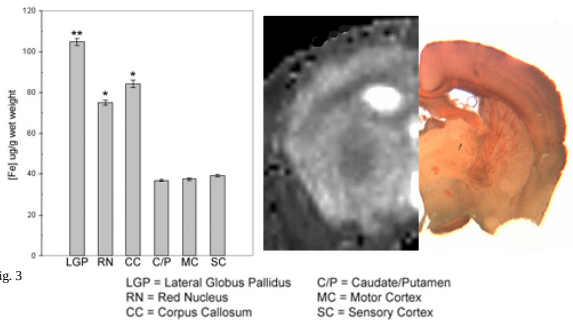

Fig. 3

Discussion: In this study, we establish the quantitative relationship between iron concentration and R_2* with a novel phantom model. This work aims to accurately and quantitatively measure the *in vivo* iron content of brain tissue through the usage of our calibration curve comparing iron concentration to R_2* relaxation time. The data demonstrates that the mGESEPI T_2* technique is reliable and sensitive for discrimination of iron rich regions. The phantom data demonstrate that there is a nearly linear correlation between the iron concentration and T_2* values with the phantom system. We also show that there is a good correlation between T_2* maps and the histochemically iron stained sections. These results illustrate that our method allows for quantitative iron measurement without macroscopic susceptibility artifacts. The subsequent studies will focus on the development of an *in vivo* calibration curve comparing R_2* to iron measurements in the mouse brain to facilitate quantification of iron in the human brain.

References:

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