Value of high field dependent transverse relaxation increase for increasing iron specificity in human brain

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Introduction: Increased iron deposition in subcortical gray matter has been suggested as a surrogate marker of neurodegenerative disorders, including Parkinson disease, Alzheimer disease and multiple sclerosis [1]. The transverse relaxation rate (R_2) is correlated with iron concentration and the effects of iron on R_2 increase linearly with field strength [2]. However, iron measurements from R_2 are confounded by water content/macromolecular fraction. Multiple field strength measurement can overcome this limitation and has been applied using dual spin echo sequences at 0.5 T, 1.5 T [3] or using FSE at 1.5, 3.0 T [4]. This Field Dependent R_2 Increase (FDRI) method [3,4], can also be applied using higher field strengths that have even greater iron sensitivity; however, to overcome inherent high field RF inhomogeneity, methods such as twice refocusing adiabatic pulses [2] or stimulated echo compensation [5] are required. A further high field limitation is increased SAR that can preclude multislice acquisition when using adiabatic pulses. The purpose of the study is to investigate FDRI using a multi-echo spin echo sequence as a means to increase iron specificity in subcortical gray matter using 4.7 T combined with 1.5 T.

Methods: Following informed consent from nine healthy subjects (34±10 years, age range 25-58 years, 6 male, 3 female), two dimensional multi-echo spin echo images, capturing multiple sub-cortical gray matter and white matter structures, were obtained in both single and multi-slice mode using a 4.7 T and 1.5 T MRI system. R_2 maps were acquired using stimulated echo compensation [5] with 2800 ms TR, 10 ms echo spacing, 32 echo train length, 4 mm slice thickness, 8 mm slice gap, and 256 x 145 imaging matrix, keeping the parameters consistent for both field strengths for single slice images. For multi-slice images with greater than 2 slices at 4.7 T, reduction in the number of echoes and an extended TR of 4000 ms were required to stay within SAR limits. Images were fit on a pixel-by-pixel basis using stimulated echo compensation. Average R_2 values were measured in frontal white matter, cortical gray mater, globus pallidus, caudate nucleus and putamen. Regressions of R_2 and FDRI versus non-heme iron were calculated using ages and the equations given in [6].

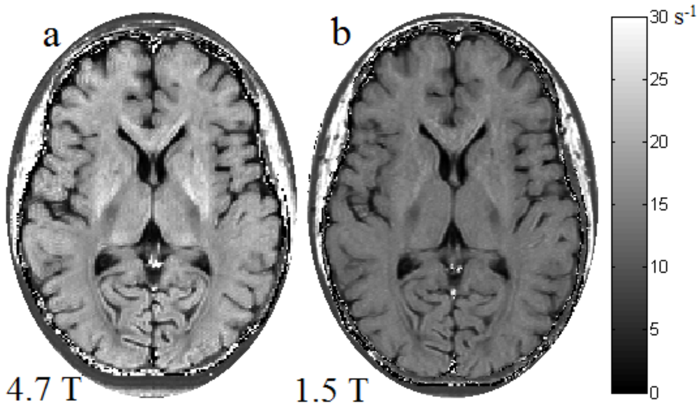

Figure 1: In vivo R_2 maps at a) 4.7 T and b) 1.5 T. Single slice acquisition with 32 echoes and 10 ms echo spacing.

Results: Figure 1 compares R_2 maps from one volunteer obtained at 1.5 T and 4.7 T. Increased R_2 values are observed at 4.7 T. The R_2 values from five brain regions at both field strengths and the differences (FDRI) are plotted against regional non-heme iron [Fe] in Fig. 2. Regression analysis of FDRI versus non-heme iron provides the highest correlation ($R^2 = 0.83$). Higher FDRI values indicate greater presence of iron. The results are consistent with previous studies [2]. However, transverse relaxation rates at 4.7 T alone also show a strong correlation ($R^2 = 0.80$), but the 1.5 T correlation is much weaker ($R^2 = 0.36$). Table 1 contains the average R_2 values at 1.5 T and 4.7 T for single and multi-slice. Consistent relaxation rates are observed for multislice acquisition at both field strengths indicating minimal effect of incidental magnetization transfer on the R_2 values. Multislice FDRI ($R^2 = 0.84$ for 8 slices, not shown) also shows strong correlation with iron and similar results to single slice FDRI.

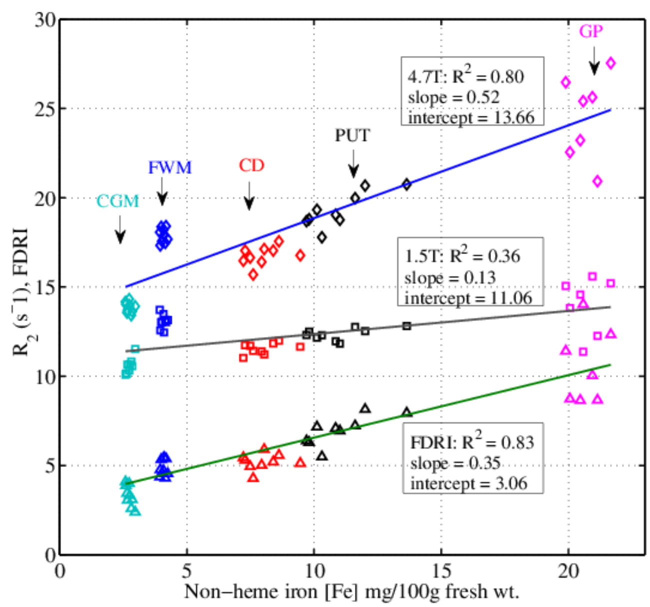

Figure 2: Relationship between non-heme iron concentration, relaxation rates and FDRI for five brain regions as determined with linear regression analysis. All R_2 values obtained with stimulated echo compensation in single slice mode. Cortical grey matter (CGM), frontal white matter (FGM), globus pallidus (GP), caudate nucleus (CD) and putamen (PUT).

Discussion: Transverse relaxation rates correlate strongly with non-heme iron using FDRI, but also using high field (4.7 T) alone (Fig. 2). Although iron induced relaxation rates increase with main magnetic field, single field R_2 measurements cannot provide iron specificity in all tissues due to the water content/macromolecular fraction confound. FDRI measurements eliminate this confound by subtracting R_2 values from higher field to that of lower field, relying on the fact that iron sensitivity increases linearly with field strength, while macromolecular R_2 effects are less affected by field increases. In Fig. 2 it is observed that R_2 values for frontal white matter (FWM) lie above the regression line at both field strengths due to the presence of higher macromolecular fraction (i.e., lower water content) than the subcortical gray matter territories. Using FDRI, the FWM values reflect the true iron content. Considering only the iron-rich subcortical grey matter territories, the single high field R_2 measurement appears sufficient in healthy subjects. However, in cases of pathology, selective increases in water content - through for example neurodegeneration - could make FDRI more valuable. We have also demonstrated multislice acquisitions and found very similar correlations to single slice mode between R_2, FDRI and non-heme iron. For this single component R_2 fitting, the incidental magnetization transfer reduced the signal but did not affect R_2. In white matter, exchange between multicomponent water pools was maximized by the delay between off-resonant excitation and on-resonant acquisition.

Conclusion: Increasing iron specificity with traverse relaxometry can be achieved using single or multislice FDRI at 4.7 T and 1.5 T. FDRI largely corrects for variable water and macromolecular content, but comes at a price of needing two field strengths. Similar correlations to FDRI were found using only a single high field (4.7 T) measurement in healthy controls due to both consistent macromolecular content and the increasing sensitivity to iron with increasing field strength.

References: [1] Schenck JF, Zimmerman EA, NMR Biomed 17(7) 2004. [2] Mitsumori et al. MRM 68(3) 2012. [3] Bartzokis G et al. MRM 29(4) 1993. [4] Sullivan EV et al. Brain Imag. Behav. 3(2) 2009. [5] Lebel RM, Wilman AH, MRM 64(4) 2010. [6] Hallgren B, Sourander P. J Neurochem, 3(1) 1958.

Table 1: R_2 values at 1.5 T and 4.7 T for different number of slices and echoes

# of slices	Frontal white matter		Cortical gray matter		Caudate nucleus		Putamen		Globus Pallidus	
	4.7 T	1.5 T	4.7 T	1.5 T	4.7 T	1.5 T	4.7 T	1.5 T	4.7 T	1.5 T
1	17.7±0.4	13.0±0.4	13.9±0.3	10.7±0.5	16.7±0.6	11.5±0.3	19.2±0.5	12.5±0.5	25.5±2.2	14.1±1.5
2	18.0±0.7	13.2±0.6	14.0±0.6	10.8±0.5	17.1±0.6	11.7±0.3	19.2±0.3	12.6±0.3	28.2±3.9	14.3±1.7
4	18.2±0.7	13.2±0.5	14.2±0.4	10.5±0.6	17.3±0.8	11.4±0.4	19.3±0.5	12.6±0.3	27.6±2.7	14.6±1.9
8	18.3±0.5	13.2±0.5	14.1±0.5	10.7±0.5	17.6±0.9	11.6±0.2	19.4±0.8	12.6±0.4	28.4±4.3	14.6±1.7