Estimation of Tissue Iron Contribution to ^1H_2O R_1 Values in Human Brain

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Introduction

The normal human adult brain tissue iron content ranges from 0.01 to 0.21 mg/g, corresponding to effective tissue water iron concentration ([Fe]) values of ~0.2 to 5.3 mM, and increases with age and in disease.[1,2] Brain iron is stored almost exclusively in ferritin-like proteins. The significance of tissue iron as an important brain ^1H_2O T_1 [$\equiv (R_1)^{-1}$] determinant has been argued based on *in vivo* relaxography correlated with *post-mortem* tissue sample iron content.[3] However, a confounding aspect arises because both tissue macromolecular mass fraction, f_M, and [Fe] strongly co-vary across the brain and with age, especially in the developing brain.[4] The variation in tissue ^1H_2O R_1 values at any given field strength ($\mathbf{B_0}$) can be empirically modeled using a multisite fast-exchange-limit equation: $R_1 = R_1' + r_{1M}f_M + r_{1Fe}[Fe]$; where R_1' is the value for pure saline (at 37°), and r_{1M}, and r_{1Fe} are the macromolecular site, and iron site relaxivities, respectively. In principle, each relaxivity could be further indexed for brain region or tissue subtype. The purpose of this study was to investigate the relative contributions of iron and macromolecular sites to human brain ^1H_2O R_1 values.

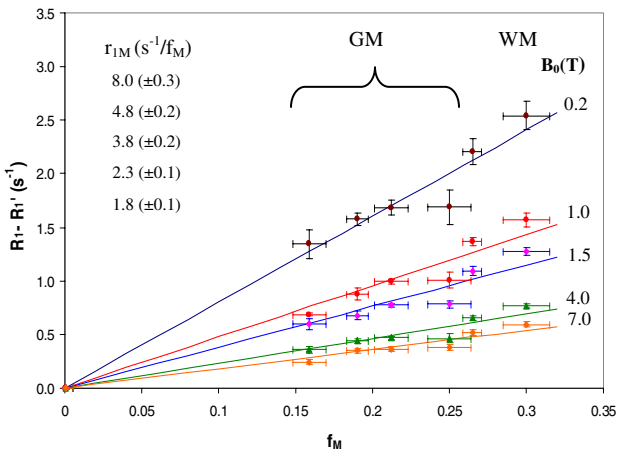
Methods

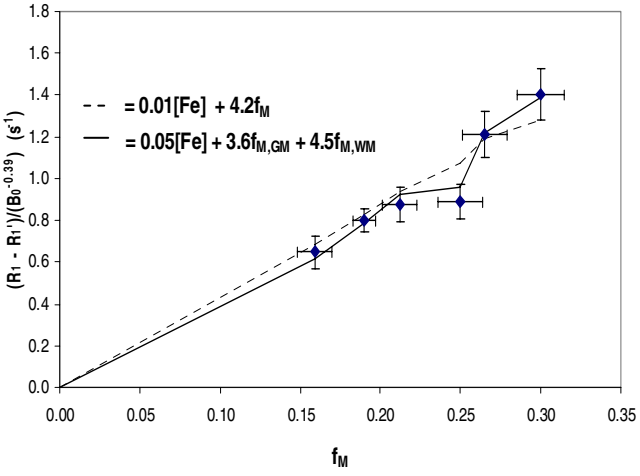
Three male volunteers with ages ranging 32-59 years were studied on multiple MRI instruments having different $\mathbf{B_0}$ values [0.2, 1.0, 1.5, 4.0, and 7.0T] within a time period of six months. All subjects provided informed consent before participating in this study. The axial slice chosen was a periventricular plane, oriented parallel to an imaginary line connecting the anterior and posterior commisures. For the relaxographic imaging of this slice, a modified Look-Locker technique was employed on each instrument. The inversion recovery (IR) was sampled at 32 times (τ) post adiabatic inversion using non-linearly spaced delays; 0.02 s $\leq \tau \leq$ 10 s. ROIs were manually selected from the following brain areas: a) frontal white matter (WM), b) putamen, c) caudate, d) thalamus, e) globus pallidus f) frontal cortex, g) ventricular cerebral spinal fluid (CSF). All values are reported as mean (± standard deviation), with the subject as the unit of analysis. Multivariate linear regression (SPSS) was used for parameter estimation.

Results and Discussion

For each tissue ROI the CSF ^1H_2O R_1 value [$R_{1CF} \approx R_1'$] was subtracted to obtain a catalyzed (excess) R_1 (i.e. $R_1 - R_{1,CSF}$) value. The brain tissue ^1H_2O excess R_1 values are plotted against the macromolecular mass fraction (f_M) in **Figure 1**. To first approximation, all of the excess R_1 variance can be attributed to tissue macromolecular content. The linear regressions, with each regression using r_{1M} as the only variable, are shown in Fig. 1. It is important to note that the ordinate (R_1, this work) and abscissa (f_M, ref. 4-6) measurements are completely independent. Although the fittings are quite reasonable ($r^2 > 0.9$), some systematic discrepancies are apparent across all $\mathbf{B_0}$ values. For example, the thalamus ^1H_2O R_1 values (at $f_M = 0.250$; [Fe] = 1.17 mM) each fall below the regression lines, while the globus pallidus (at $f_M = 0.265$; [Fe] = 5.30 mM) and frontal WM (at $f_M = 0.305$; [Fe] = 1.14 mM) R_1 values are each above the regression lines. This residual autocorrelation suggests that a single variable regression is insufficient, and that one or more additional parameters are required.

To more closely examine the fine structure evident in the Fig. 1 plots (particularly the discontinuity for the thalamus at $f_M = 0.25$), we average the excess R_1 values after removing their $\mathbf{B_0}$-dependence by dividing each excess R_1 datum by $(\mathbf{B_0})^{-0.39}$; essentially normalizing all data to a 1 T field strength. R_1 data thus transformed were then averaged for each tissue ROI. The results are plotted in **Figure 2**, where the error bars indicate the standard deviations. These results were modeled using literature f_M and [Fe] average values.[1,4-6] The fitting (dashed line, Fig 2) returned values of 4.22 (±0.17) s^{-1}/f_M and 0.014 (±0.014) s^{-1}/(mM Fe) for the macromolecular and iron relaxivities, respectively. Systematic deviations between the model and the data are still clearly evident, particularly for thalamus ($f_M = 0.25$) and WM data points. The final model used allowed gray matter (GM) and WM r_{1M} values to differ. The result for the three parameter regression (r_{1Fe}, $r_{1M,GM}$, $r_{1M,WM}$) is plotted as the Fig. 2 solid line. It clearly reproduces the fine structure expressed in the R_1 data. The major discontinuities in the Fig. 2 plots can be explained by [Fe] differences between GM structures. The discontinuity is most evident between the thalamus (a low [Fe] region) and the globus pallidus (a high [Fe] region). The parameters returned from the fitting are 3.64 (±0.17) s^{-1}/f_M for $r_{1M,GM}$, 4.53 (±0.17) s^{-1}/f_M for $r_{1M,WM}$, and 0.047 (±0.012) s^{-1}/(mM Fe) for r_{1Fe}, and all are significant brain ^1H_2O R_1 value predictors. Moreover, the r_{1Fe} value we obtain is in good agreement with that for *in vitro* ferritin reported by Goussin and colleagues.[7]





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