Dependence of $R_1$ on tissue microstructure: A group study of 100 subjects

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**Target Audience:** Those interested in quantitative MRI and the dependence of these parameters on tissue microstructure.

**Purpose:** Quantitative MRI aims to produce measurements, independent of scanner and acquisition protocol, with high diagnostic value. These measures require validation for use as markers of tissue microarchitecture and integrity by relating them to clinical quantities, such as myelin and iron content, which are usually only accessible via histological analysis. Myelin, iron content (most notably non-heme iron) and water fraction contribute to the overall longitudinal relaxation rate ($R_1 = 1/T_1$) values measured in vivo. The relative contribution of these components can be expected to vary spatially due to differences in local tissue microstructure. Here we explore the validity of using quantitative transverse relaxation rate ($R_2^*$) and magnetisation transfer (MT) maps as surrogate markers for iron and macromolecular fraction respectively in a model of $R_1$.

**Methods:** Three multi-echo 3D fast low angle shot (FLASH) datasets with 1mm$^3$ resolution were acquired with predominantly T1, PD or MT weighting$^{1,2}$ on a 3T whole body system (TIM Trio, Siemens Healthcare) on 100 subjects aged from 18 to 74 years. Calibration data were also acquired to correct $B_1$ inhomogeneities$^3$. The total scan time per subject was <25mins. Quantitative maps of MT, $R_2^*$ and $R_1$ were calculated using bespoke MATLAB tools (The Mathworks, USA) and the MT maps were segmented into grey and white matter using SPM8 (Wellcome Trust Centre for Neuroimaging, London). In the absence of any contrast agents, variation in tissue $R_1$ can be modelled empirically$^4$ as: $R_1 = R_1' + r_{1M}f_M + r_{1Fe}[Fe]$. $R_1'$ is the relaxation rate of free water under physiological conditions, $r_{1M}$ and $r_{1Fe}$ are the relaxivities at macromolecular and iron sites respectively, $f_M$ is the macromolecular fraction and $[Fe]$ is the iron concentration. Using MT and $R_2^*$ maps as voxel-specific surrogate markers$^{5,6}$ for the macromolecular and iron relaxivity terms respectively, the model can be fully expressed in terms of MR measures as: $R_1 = \beta_0 + \beta_1 MT + \beta_2 R_2^* + \epsilon$ where $\epsilon$ are the residuals of the fit and the set of $\beta$ parameters are global constants. This general linear model was solved using all voxels with a grey or white matter probability >20% to determine the $\beta$ parameters and the residuals.

**Results:** The linear model fits well with a mean Pearson coefficient of 0.89±0.05 across the 100 subjects and parameters: $\beta_0=0.2628\pm0.0102s^{-1}$, $\beta_1=0.4009\pm0.0144s^{-1}$ and $\beta_2=0.0018\pm0.0008$ (mean±SE, $\beta_1$ is dimensionless). Partial correlation analysis, controlling for scanner positioning, found significant positive correlation between $\beta_0$ and age ($p<0.05$) along with negative correlation between $\beta_2$ and both $\beta_0$ and $\beta_1$ ($p<0.01$). The residuals are generally close to the acquisition noise level, but the distribution of residuals suggests that the model fits are biased by 2%, -2% and -6% in the cortex, white matter (WM) and basal ganglia respectively (see figure).

**Discussion:** A single set of $\beta$ parameters suffices to model $R_1$ in both grey and white matter. There is remarkable stability in the free water and MT coefficients across this broad population suggesting that most microstructural differences are captured by the maps. The higher variation in $\beta_2$ may be due to noise in the $R_2^*$ map, calculated from data with a maximum TE of 19.70ms. Alternatively, it may reflect underlying biological variability or be due to non-linearities not captured by the model.

**Conclusion:** Tissue microstructure is altered in pathological conditions. Markers for these changes are of high clinical importance. Biophysical models using quantitative MR parameters, such as the one validated in a large cohort here, are a step towards accessing these important biological markers in vivo.

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