Relaxometry-Based Spectroscopic Differentiation of Gray and White Matter in the Human Brain: On the Stability of Tissue Water as an Internal Reference

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Introduction: Recently, we introduced a rapid relaxometry technique for *in vivo* localized spectroscopy that incorporated a variable TR into a T_2 experiment with multiple relaxation curves (1, 2). This data acquisition paradigm not only allowed measurement of T_1 and T_2 but also provided separation of CSF and tissue water for spectroscopic compartmental analysis in the human brain. In this work, we specifically examine the stability of the variable repetition time T_2 technique by employing it to examine age-related differences in brain tissue.

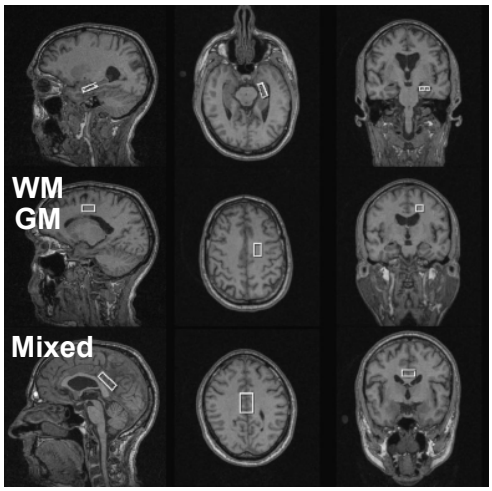

Figure 1. Representative brain regions where water relaxation curves were sampled: **(top)** hippocampal gray matter (GM), **(middle)** centrum semiovale white matter (WM), and **(bottom)** mixed tissue from the posterior cingulated (mixed).

Methods: Participants were 12 healthy young adults (26.1±3.2 yrs), 14 healthy middle-aged adults (48.9±2.7 yrs), and 11 healthy elderly adults (63.9±2.7 yrs). Relaxometery data (TDs: 1.6 and 3.2 s, TE range: 10-1500 ms, 24 points per curve, 2500 Hz SW) were acquired from hippocampal gray matter (mean size: 0.89 cm^3±9.8%), centrum semiovale white matter (mean size: 2.04 cm^3±6.4%), and posterior cingulate mixed tissue (mean size: 5.65 cm^3±5.2%) (see Fig 1). Voxels in pure WM and pure GM were carefully sized and positioned to minimize contamination from surrounding tissue. The water signal was phase corrected and then fit with AMARES. Relaxation curves were fit with mono-, bi-, and tri-exponential models to determine the best fit. As CSF metrics are proven to be unreliable, we confined our statistical analysis to the following metrics: S_{0_tis}/S_{0_total} (i.e., f_{tis}), T_{1_tis}, T_{2_tis}, and S_{0_total}/volume. The data was analyzed in two-parts: first, the effects of age group, tissue type, and spectroscopic metrics (f_{tis}, T_{1_tis}, and T_{2_tis}) were examined in a three-way ANOVA; second, the S_{0_total}/volume was compared in a three-way ANOVA with age group, gender, and tissue type as factors. The use of S_{0_total}/volume rather than S_{0_total} removes signal variations caused by differences in volume sizes and allows for direct comparison of different brain regions and tissue types.

Results and Discussion: For the mono- and bi-exponential models, the S_{0_total} per unit volume coefficient of variation (CV) was less than 5% (range 2-5%) for both intra- and inter-age differences for each tissue type. The results of the tri-exponential fit varied greatly between tissue types. In the gray matter, the results were not significantly different than the bi-exponential, as frequently only two exponentials were reported. In white matter, the CVs for inter- and intra-age average S_{0_total} per unit volume were less than 4%. In the mixed tissue, the tri-exponential fit resulted in the worst precision of all model fits for S_{0_total} per unit volume - double compared to other fits. Although our analysis of pure gray and pure white matter suggests that mixed tissue, such as from the posterior cingulate, should be represented by a minimum of three exponentials, the relaxation curves were relatively insensitive to such an analysis. Thus, all relaxation curves were best served by a bi-exponential model. For gray matter and mixed tissue, the long component was assumed to be due to contribution from CSF. For pure white matter, the two components were assumed to represent different water compartments in the tissue. All T_1 values and T_2 values were within normal ranges.

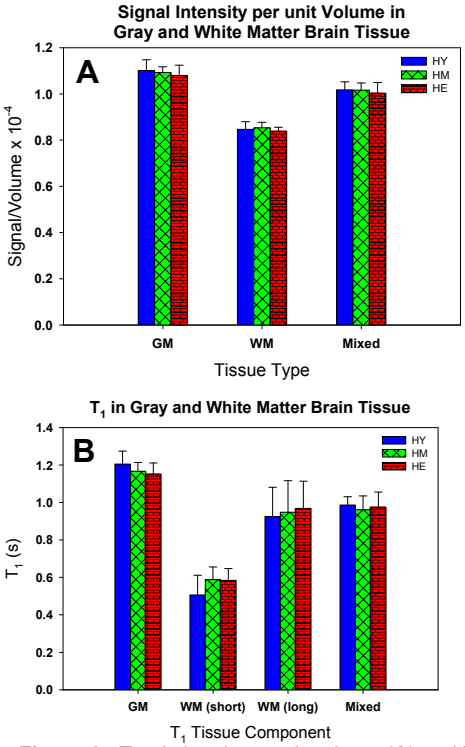

Figure 2. Total signal per unit volume (**A**) and T_1 values (**B**) for the three brain regions for three adult age groups: healthy young (HY), healthy middle aged (HM), and healthy elderly (HE).

Differences in S_{0_total} per unit volume were significant only for tissue types (p<0.001, F=142.5), but not for age groups (Fig 2A). In imaging terms, this simply indicates that the three brain regions in which the VOI was placed are visibly distinguishable in proton density images, regardless of age. In the ANOVA comparisons, when all the relaxometry metrics are considered (T_{2_tis}, T_{1_tis}, and f_{tis}), the tissues from the three brain regions are significantly different within each age group, but not across age groups – except for the hippocampus. T_{1_tis}, T_{2_tis}, and f_{tis} are significantly different across age groups in the hippocampus (p=0.01, F=2.553). Again, in imaging terms, this indicates that gray, white, and mixed matter tissue is distinguishable in T_2 and T_1 maps (and thus weighted images), but only the gray matter tissue of the hippocampus would show some visible effects of aging (Fig 2B – T_1 data only).

Comparison of the signal intensity across groups is difficult without correcting for variations caused by coil coupling. Nonetheless, Jost et al showed intra-subject variations to be only 5% without correction, and ~2.2% with corrections (3). With our intra-age signal per unit volume CVs less than 5% for results from the bi-exponential fits for all three tissue types, our results are slightly better than the CVs reported by Jost et al for their water signal uncorrected for differences in coil coupling. The similarity in the range for the CVs shows that the rapid relaxometry technique is stable for quantifying the water signal. Correcting for coil coupling could reduce CVs to less than 2%; however, even without such corrections, the use of water as a reference signal for spectroscopic quantitation should add no more than a 5% variation to the measurement of the metabolite concentrations when properly employed.

Conclusion: In this work we specifically examined the stability of the spectroscopic rapid relaxometry technique for quantifying the water signal in the human brain. Results show the method to be sensitive to age-related differences. However, with the current number of sampled points, multi-exponential tissue relaxation is not detectible. Thus the issue water signal is consistently under-reported in spectroscopy.

References: (1) Knight-Scott et al, JMR 2005; 173:169-174. (2) Knight-Scott, Proceed ISMRM 2007; 15:202. (3) Jost et al, JMRI 2005; 21:66–71.