Water as an Internal Reference for Spectroscopic Imaging: Variability Due to Partial Volume Estimates

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The unsuppressed 'internal' water signal was introduced as a concentration reference for single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS) of the brain over a decade ago (1). However, to our knowledge, a detailed description of how this method could be applied to spectroscopic imaging (SI) or an examination of its potential sources of error has yet to be reported. Here we examine the variability of this method due to the use of different tissue segmentation routines to classify white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) in order to account for partial volume effects.

Theory

In numerous single-voxel ^{1}H-MRS studies on regions of brain without CSF, metabolite concentrations have been estimated from the ratio of the metabolite (S_M) and parenchymal water signals ($S_{H2O\_GM/WM}$) scaled by the relaxation attenuation factors appropriate to each signal, R_M and $R_{H2O\_GM/WM}$, respectively, the number of protons giving rise to each signal, #H$_M$ and 2, respectively, and the concentration of pure water [H2O] (55.5M):

$$[M] = \frac{S_M \times R_{H2O\_GM/WM}}{S_{H2O\_GM/WM} \times R_M} \times \frac{2}{\#H_M} \times [H_2O] \qquad [1]$$

where $R_M = \exp[-TE/T2_M](1-\exp[-TR/T1_M])$ and $R_{H2O\_GM/WM} = \exp[-TE/T2_{H2O\_GM/WM}](1-\exp[-TR/T1_{H2O\_GM/WM}])$ (2). The relaxation times in the latter factor are either the GM, the WM, or the averaged GM and WM water proton T1 and T2 times, depending on whether the voxel is considered mostly GM, mostly WM, or a mixture of both. Hence, Eq. [1] ignores that the observed water signal from a voxel may arise from a combination of the GM, WM, and CSF water fractions, each weighted by different relaxation times. This situation is likely to obtain in SI studies on the brain, where the region of interest generally covers a broad and heterogeneous region of parenchyma and CSF. The following expression for calculating [M] from SI voxels takes into account the possible presence of CSF in the spectroscopic voxel as well as tissue differences in water relaxation rates:

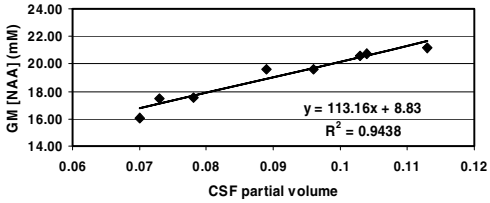
$$[M] = \frac{S_M \times (f_{GM} \times R_{H2O\_GM} + f_{WM} \times R_{H2O\_WM} + f_{CSF} \times R_{H2O\_CSF})}{S_{H2O}(1 - f_{CSF}) \times R_M} \times \frac{2}{\#H_M} \times [H_2O] \qquad [2]$$

where S_{H2O} is the observed water signal, f_{GM}, f_{WM}, and f_{CSF} are the volume fractions of water in GM, WM, and CSF, respectively, determined by image segmentation and the various tissue water densities, and R_{H2O_GM}, R_{H2O_WM}, and R_{H2O_CSF}, are the appropriate relaxation factors associated with each water pool. One can apply a statistical regression method (3) to [M] versus fractional GM in the parenchyma, extrapolating the regression line to GM=1 to estimate the concentration in pure GM and to GM=0 to estimate the value in pure WM.

Methods

Fourteen healthy adult subjects (6 male and 8 female) were scanned after written informed consent. T1-weighted images were obtained with a 3D fast low angle shot (FLASH) sequence (TR/TE=20/5.86ms, flip angle=25°, field of view (FOV)=200x200mm, resolution=192x192, 1.5 mm thick slice, total scan time=14min 22s) and T2-weighted images were obtained with a turbo spin echo (TSE) sequence (TR/TE=9700/50ms, turbo factor=5, FOV=200x200mm, resolution=192x192, 1.5mm thick slice, total scan time=6min 10s). SI was performed in a oblique transverse slice immediately above the lateral ventricles using a phase-encoded version of PRESS with or without water presaturation (TR/TE=1500/135ms, FOV=200x200mm, slice thickness=15mm, circular k-space sampling (radius=24), total scan time=9min42s). After zero-filling to 32x32 points in k-space, applying a Hamming filter, and 2D spatial Fourier transformation, the SI data were analyzed using LCModel (4). The results of the different segmentation approaches are compared with respect to the combined N-acetylaspartate and N-acetylaspartylglutamate concentration ([NAc]) in GM or WM, derived from regression analyses of the data ([NAc] as a function of fractional parenchymal GM). Either T1-, T2-, or a combination of T1- and T2-weighted image data sets were submitted to 3 commonly used image segmentation routines: 1) a K-means algorithm implemented by the IMGCON software (www.fmrib.ox.ac.uk), 2) a mixture model cluster analysis algorithm implemented by the Statistical Parametric Mapping (SPM2) software (www.fil.ion.ucl.ac.uk/spm), and 3) FSL's FAST segmentation routine (www.fmrib.ox.ac.uk/fsl/fast), based on a hidden Markov random field model and an associated expectation-maximization algorithm. Before segmentation by K-means or FSL, the brain was extracted using FSL's BET tool. All images were corrected for bias field inhomogeneities. Only the FAST and IMGCON (K-means) routines had the capability of performing multispectral (T1+T2) segmentation. To fully account for the partial volumes of each tissue fraction in each SI voxel, the segmentation maps from the image slices spanning the SI slab were smoothed to the same effective resolution as the SI data by convolving the maps with the point spread function of the SI data.

Results and Discussion



While the pooled-data estimates of [NAc] in WM ranged by less than ±3%, from 13.8 mM to 14.6 mM, the estimates of GM [NAc] ranged by ±14%, from 15.5 mM to 20.5 mM. The greater variability of the latter estimates can be largely attributed to variability in the partial volume estimates of CSF in regions of GM, i.e., along the interhemispheric midline and various sulci. This is illustrated in Fig. 1 for a sample data set, where the estimate of GM [NAc] is shown to correlate strongly (r^2=0.94) with the total CFS fraction determined by the applied segmentation method. Generally, partial volume estimates based on T1 image segmentation alone led to higher estimates of [NAc] in GM (20.08±0.61 mM) than those based on T2 image segmentation alone (17.07±1.64 mM) or those based on multispectral T1 and T2 image segmentation (18.06±1.28 mM). Comparisons of the segmentation methods across individual data sets in terms of the coefficient of variation (CV, mean/standard deviation) of the GM and WM [NAc] estimates revealed that the variability in WM [NAc] estimates was similar across methods (CV 0.087-0.105), consistent with little CSF being present in white matter regions. The variability in GM [NAc] was greatest for K-means methods (CV=0.145-0.181) and the SPM2 T2 method (CV=0.168), much lower for the SPM2 T1 (CV=0.093) and FAST methods (CV=0.069-0.112), and lowest for the estimates based on the FAST multispectral (T1+T2) method (CV 0.069).

A gold standard for brain image segmentation has yet to be established and, as we have shown here, even relatively sophisticated methods can yield different results that, in turn, lead to different estimates of the relative amounts of brain metabolites in GM and WM. While the current results were obtained using internal water as a concentration reference, accurate partial volume measurements are critical to all SI studies reporting regional metabolite levels in terms of "absolute" concentrations. Hence, these results suggest that at least one source of variability in the wide range of GM and WM metabolite levels reported by MR spectroscopists is the use of different segmentation methods to estimate partial volume effects.

References

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