Water as an Internal Reference for Spectroscopic Imaging: Methodology, Application, and Comparison to Other Methods

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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 describe a method for using water as a concentration reference in SI and its application to a study on gray matter (GM) and white matter (WM) metabolite concentrations in healthy adult subjects.

Theory

In single-voxel ^{1}H-MRS studies on regions of brain without cerebrospinal fluid (CSF), metabolite concentrations have often 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. In some studies, to account for the presence of CSF in the voxel, $S_{H2O\_GM/WM}$ has been approximated by the term $S_{H2O}(1-f_{CSF})$, where S_{H2O} is the total water signal and f_{CSF} is the CSF fraction. However, even with this modification, Eq. [1] ignores that the GM, WM, and CSF water fractions that give rise to the observed water signal are each weighted by different relaxation times. This situation is likely to occur in SI studies on the brain, where the region of interest generally covers a broad and heterogeneous volume 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:

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

where f_{GM}, f_{WM}, and f_{CSF} are the fractions of water in GM, WM, and CSF, respectively, and R_{H2O_GM}, R_{H2O_WM}, and R_{H2O_CSF} are the appropriate relaxation factors associated with each water pool. The water fractions can be related to the tissue volume fractions determined by image segmentation by taking into account the relative water fraction in each segmentation fraction. Assuming that the relative densities of MR-visible water in GM, WM, CSF are 0.78, 0.65, and 0.97 (1), respectively,

$$f_{GM} = \frac{f_{GM\_s} \times 0.78}{f_{GM\_s} \times 0.78 + f_{WM\_s} \times 0.65 + f_{CSF\_s} \times 0.97}, \; f_{WM} = \frac{f_{WM\_s} \times 0.65}{f_{GM\_s} \times 0.78 + f_{WM\_s} \times 0.65 + f_{CSF\_s} \times 0.97}, \; f_{CSF} = \frac{f_{CSF\_s} \times 0.97}{f_{GM\_s} \times 0.78 + f_{WM\_s} \times 0.65 + f_{CSF\_s} \times 0.97} \qquad [3\text{-}5]$$

where the fractions f_{GM_s}, f_{WM_s}, and f_{CSF_s} are the fractional tissue volumes determined by image segmentation. To estimate metabolite concentration in pure GM or WM, one can apply a statistical regression method (3) to [M] and fractional GM, extrapolating the regression line to GM=1 to estimate the concentration in GM and to GM=0 to estimate the value in WM. We note that an approximation of the GM-WM water signal simply as $S_{H2O\_tot}(1-f_{CSF\_s})$ divided by a mean relaxation attenuation for parenchyma will overestimate this signal and thus underestimate the metabolite values, particularly at long TE (> 30ms) and short TR (<6s) and in voxels with significant CSF, owing to the much longer T1 and T2 of the CSF water magnetization and hence greater attenuation of its signal relative to the GM and WM signals.

Methods

Fourteen healthy adult subjects (6 male and 8 female) were scanned after written informed consent. T1-weighted images (e.g., Fig. 1B) 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 (e.g., Fig. 1A) 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 an 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) (example spectrum shown in Fig 1C). 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 T1- and T2-weighted image data sets were segmented by FSL's FAST segmentation routine (www.fmrib.ox.ac.uk/fsl/fast) using a multispectral approach (e.g., Fig. 1D). To fully account for each tissue fraction in the SI voxels, the segmentation maps from the image slices spanning the SI slice were smoothed to the same effective resolution as the SI data by convolving the maps with the point spread function of the SI data. The combined N-acetylaspartate and N-acetylaspartylglutamate (NAc), choline (Ch), and creatine (Cr) results from LCModel were then corrected using Eqs. [2]-[5]. The relaxation times used for the various relaxation attenuation factors were taken from published reports (GM water: T1=1.304, T2=0.093 (5); WM water: T1=0.660, T2=0.073 (5,6); CSF: T1=2.93, T2=0.23 (6); NAc: T1=1.28,T2=0.34 (7); Ch:T1=1.09,T2=0.35 (7); Cr:T1=1.09,T2=0.35 (7)). The results from all 14 subjects were pooled before regression analysis, as shown in Fig. 2 for the analysis of [NAc] data.

Results and Discussion

In spite of numerous reports on the GM-WM differences in brain metabolites measured by proton magnetic resonance spectroscopy, there is still no consensus on the magnitude and/or direction of these differences. Estimates of NAA or NAc in GM in just the last decade have ranged from about 20% less (8) to nearly 50% more (9) than NAA or NAc in WM. In the present work, the GM and WM concentrations of NAc, Cho, and Cr based on FAST multispectral segmentation and the pooled data were: GM [NAc]=17.2mM; WM [NAc]=14.4mM; GM [Ch]=3.3mM; WM [Ch]=2.6mM; GM [Cr]=13.9mM; WM [Cr]=7.1mM. The GM/WM [NAc] ratio of 1.20 is close to the middle of the range reported by others. Furthermore, if we assume that 15-30% of the NAc signal in WM derives from NAAG (10), the mean WM concentration of NAA in this study can be estimated to be 10.0-12.1 mM, which, along with the values for Ch and Cr reported here, are well within the range reported by others.

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Fig.1

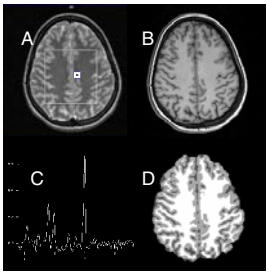

Fig.2