Signal Normalization for MR Spectroscopic Imaging Using Brain Tissue Water: Variability and Pathologic Detectability

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Introduction

Several methods for calibration of brain MR spectroscopic imaging (MRSI) data have been proposed. Referencing to brain tissue water signal has been recommended as this method accounts for RF inhomogeneities and coil loading, which present difficulties when using external reference methods. In this study two methods for deriving the brain tissue water signal are compared for signal normalization: 1) An interleaved MRSI-resolution water reference (WR) co-acquired with MRSI data [1], and 2) a high-resolution, quantitative water content (M0) mapping [2].

Materials and Methods: Studies were performed for 21 healthy subjects (age 26-59 years) and 8 subjects with mild traumatic brain injury (TBI) (age 20-34 years, Glasgow Coma Score 15) at 3.0 T (Trio/TIM; Siemens). The MRI protocol consisted of a T1-weighted MPRAGE sequence, TR/TE/TI/flip = 2150/4.38/1100 ms/8º, and two turbo FLASH sequences, TR/TE/flip = 8.4/3.7 ms/(3º and 15º) for high-resolution mapping of water-content and T1 [2], all acquired with 1 mm isotropic resolution. The volumetric MRSI used echo-planar readout with 50×50×18 *k*-space points, 500 spectral samples, sweep width 1250 Hz, CHESS water suppression, lipid inversion nulling with TI = 198 ms, and spin-echo acquisition with TR/TE = 1710/70 ms. It also included an interleaved water reference SI obtained using a gradient-echo acquisition, 20° excitation, and TE = 6.3 ms. The MRSI data were processed using the fully automated MIDAS software package [3], which included signal normalization to institutional units and spatial transformation to a brain atlas. Mean values of NAA, Creatine, and Choline for grey- and white-matter in each atlas-defined brain region (right and left frontal, temporal, parietal, occipital) were calculated following signal normalization based on either 1) the water reference MRSI signal (WR), or 2) the MRI-derived water signal calculated for each MRSI voxel (M0). The first method assumes constant water content over each of grey- and white-matter throughout the brain. The difference between the two normalization methods on each subject was tested using a correlation coefficient and paired *t*-test. The significance of their pathologic detection power in tissue-specific quantities in TBI group versus the age-adjusted healthy subjects was tested using an unpaired *t*-test.

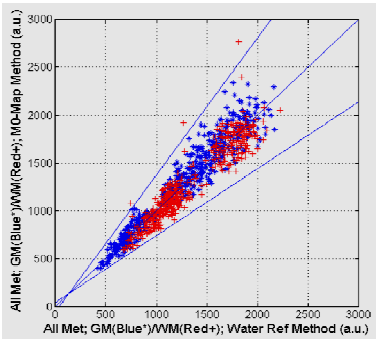

Fig 1: Mean values from both normalization methods (M0 vs. WR) for all metabolites, brain regions, and tissues (GM: blue, WM: red+) of all healthy subjects.*

Results: Figure 1 shows the mean metabolite values from the water-SI normalization versus the water-mapping normalization method for all metabolites, brain regions, and tissues of all healthy subjects after scaling (to ensure slope =1). The correlation coefficient (R=0.952) indicates strong agreement between the two normalization methods in healthy subjects (also; p-values > 0.1 for each metabolite and brain region). Examination of the individual metabolite mean values indicates smaller variation for the interleaved water reference method (Figure 2).

Analysis of differences between the TBI and control subject group is presented in Table 1. These results show while both normalization methods detected altered metabolites, in agreement with the clinical findings, the water-mapping normalization method provided higher sensitivity for differentiating the two groups. This result is consistent with improved metabolite quantitation in the presence of altered brain tissue water and T1 with the direct water measurement protocol.

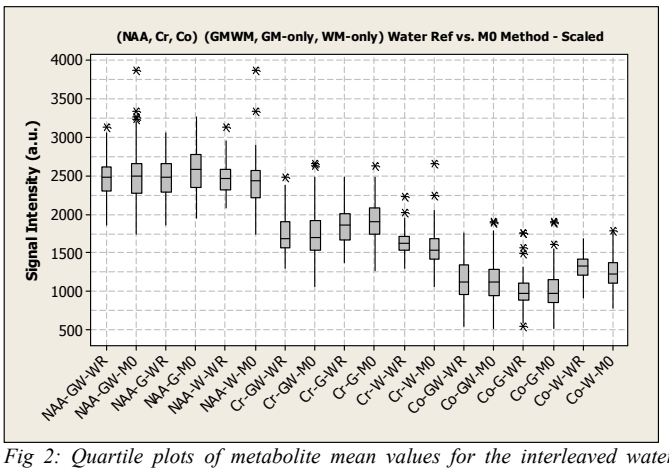

Fig 2: Quartile plots of metabolite mean values for the interleaved water reference (WR) and high resolution water mapping (M0) normalization methods for GM and WM of 21 healthy subjects. (represents outlier).*

Table 1: Statistical significances (: p-value <0.05, **: p-value <0.01, blank: not significant) for pathologic detectability of the interleaved water reference (WR) and water-content (M0) mapping methods in age-adjusted TBI patients vs healthy subjects.*

Brain lobe / Tissue / Metabolites	Frontal L	Frontal R	Temporal L	Temporal R	Parietal L	Parietal R	Occipital L	Occipital R
Gray matter								
NAA (WR)		*		*	**	*		
NAA (M0)	**	**	*	**	**	**		
Cre (WR)							*	*
Cre (M0)	*	*			*	**		
Cho (WR)								
Cho (M0)					*			
White matter								
NAA (WR)								
NAA (M0)		*				*		*
Cre (WR)		*	*		**			
Cre (M0)								
Cho (WR)								
Cho (M0)								

Discussion: Mapping of tissue water using an interleaved water MRSI provides a convenient reference for normalization of brain metabolites, although is subject to errors in the presence of pathology. The use of a separate water density measurement based on high spatial resolution water content mapping [2,4] addresses this potential source of error [5], which was demonstrated using the analysis of the brain injured subject group. Although this requires an additional MRI acquisition, the time required has been minimized by using a rapid dual-angle turbo FLASH protocol.

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References: [1] Maudsley AA *et al*, MRM 2009; 61:548–559. [2] Sabati M *et al*, ISMRM 2010; 18:2317. [3] Maudsley AA *et al*, NMR Biomed 2006;19:492–503. [4] Neeb H *et al*, Neuroimage 2008;42: 1094–1109. [5] Gasparovic C *et al*, MRM 2009: 62:583–590.