Estimation of myo-Inositol and macromolecule contents in Normal-appearing white and gray matter in MS using 3D-HMRSI at 3T

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Introduction

The *myo*-Inositol (mI) band at ~3.6 ppm was investigated at 3T using 3D H^1 MRSI, at echo time (TE) of 40ms in 168 patients with multiple sclerosis (MS) and 27 healthy volunteers. The quantification of this frequency region is challenging because of severe background contamination coming from broad macromolecules and surrounding metabolite peaks [1] (the complex Glutamate-Glutamine, taurine, glycine, alanine, glucose). In this present study, we accounted for this background while estimating mI concentration using the quantitation algorithm QUEST [2]. Macromolecule contents in normal-appearing white matter (NAWM) are estimated to evaluate disease-related changes compared to healthy volunteers.

Methods

The cohort of patients included 125 relapsing-remitting (RRMS), 28 clinically isolated syndrome (CIS), 12 secondary progressive (SPMS), 5 primary progressive (PPMS).27 healthy volunteers were used as controls. Both groups did not differ significantly in age (patients 42.7± 9.7 years; controls 39.2 ± 9.5 years). The 3D MRSI data were acquired using an 8-channel phased array coil in reception and a body coil in transmission on 3T GE Excite scanner (GE Healthcare Technologies, Waukesha, WI). The spatial localization of the PRESS box was in the supratentorial brain, covering 3 to 4 slices centered around the corpus callosum. TR was set at 1 s and the total acquisition time was around 15 minutes. High-Resolution SPoiled Gradient-Recalled echo T1 weighted images and Fast Spin Echo T2 weighted images were acquired for image guided slices positioning. T1 weighted images were also used to automatically segment white matter (WM), gray matter (GM), cerebro-spinal fluid (CSF) using the FMRIB's Automated Segmentation Tool (FAST), and the FSE was used to manually segment out T2 lesions.

8 channel data were combined, phase and frequency corrected by programs developed in our laboratory. Before the quantitation, the water and lipids peaks were removed using a filter based on HLSVD (Hankel Lanczos Singular Value Decomposition). Indeed, for some scans the lipids contamination from the bottom skull was not properly suppressed by the outer volume suppression bands.

The signals were quantified with the development version of QUEST of the jMRUI package, which semi-parametrically untangles, in the time domain, the nondescript background signal from the metabolite of interest signal(N-Acetyl compounds , creatine, , choline compounds, the Glutamate-Glutamine complex, *myo*-Inositol, mI). The basis set used was acquired *in vitro*.

For each voxel in the selection box, the percentage of GM and WM was computed from the segmented T1-weighted image. A linear regression in the percentage of GM–percentage of WM space was performed for each exam, assuming a null metabolite concentration in cerebro spinal fluid (CSF), to determine (NA)WM versus (NA)GM mI concentration. For patients, the voxels containing the manually segmented lesions were removed from the analysis. All the voxels presenting 2 Cramer Rao Lower Bounds greater than 20 % of the estimated concentration were rejected from the linear regression. In average, a total of 66 voxels were used for the linear regression for patients and 80 voxels for healthy volunteers. Quantitation for both patient and control data sets was T1 corrected using a T1 of 1s for WM and GM based on T1's previously estimated from another study performed by our group [2], assuming that there is no significant difference neither between patients and controls nor between WM and GM. For each exam a mean estimated background signal from voxels containing at least 80% of WM can be computed from the output of the QUEST quantitation method.

Results

Figure 1 shows the linear regression results in the percentage of WM-percentage of GM space for one patient. This 2 parameters fitting enable us to use a large number of voxels which can contain a small percentage of CSF. Figure 2 shows a mI interpolated map from an MS patient. In the bottom left of this slice one can appreciate an elevated mI concentration corresponding to visible MS lesion. NAWM mI was higher in the patient cohort than in the controls (mean 2.74 mM, standard deviation SD=0.57 versus mean 2.35 SD=0.38, $p<0.001$). Normal-appearing gray matter (NAGM) mI was also higher in patients than in the controls (mean 4.34 mM, SD= 0.97 versus 3.35 mM, SD=0.54, $p<0.001$). We found that mI concentration in the GM weakly correlates with age but not with Expanded Disability Status Scale score and not significantly enough with disease duration (see Table). Figure 3 shows a comparison of an averaged background signal from a patient scan versus the one from a healthy volunteer.

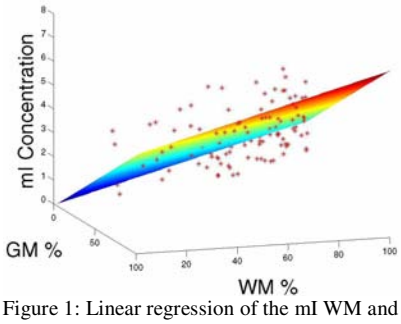

Figure 1: Linear regression of the mI WM and mI GM concentration.

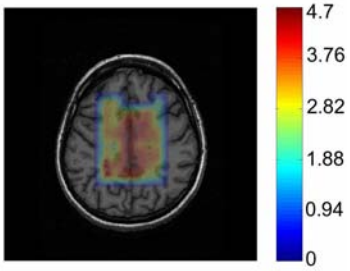

Figure 2: mI interpolated map.

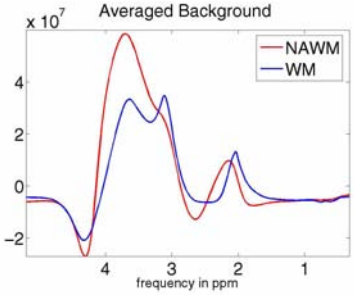

Figure 3: Averaged background spectrum from a patient scan (red) compared to the one from a healthy volunteer (in blue).

Discussion

mI concentration levels were statistically higher in both NAWM and NAGM in MS patients compared to healthy volunteers, with a greater increase in the NAGM than in the NAWM The absolute value we found for mI is slightly lower than what is usually report in the literature. This difference can be explained by the combined effect of 1) a difference in the mI versus background signal proportions 2) the GM versus WM discrimination, 3) the T1 weighted variation effect. However, the clinical impact of this increase of mI in MS did not relate to disability as measured by the EDSS. Some of the increase in the gray matter is partially related to age. The methods will be used to better evaluate the significance of macromolecules in MS.

Table: Spearman Correlation Coefficient r for EDSS, Disease Duration Age versus NAWM mI concentration, NAGM mI concentration and the corresponding *p* value.

	mI WM		mI GM	
	r	*p*	*R*	*p*
EDSS	0.09	0.25	0.1	0.15
Disease Duration	0.014	0.86	0.17	0.028
Age	0.08	0.029	0.20	0.01

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References [1] Kim et al, MRM 53:760-769, 2005 [2] Ratiney et al, MAGMA, 16(6):284-96, 2004 [3] Srinivasan et al, Brain, 128:1016-1025,2005