Optimization of GSH Measurement in Multiple Sclerosis

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Introduction: Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system that affects over 2.1 million people worldwide. In the United States, there are about 400,000 people suffering from MS and 200 more people diagnosed with MS each week. 85% of the people with MS are first diagnosed with relapsing-remitting MS (RRMS) and many of them progress into a secondary-progressive MS (SPMS) after an initial period of RRMS [1]. In the early stage of MS (RRMS), Magnetic resonance imaging (MRI) can track MS-related inflammatory processes by determining the number and size of gadolinium-enhanced lesions and T1/T2 lesions [2]. However, as the disease progress into SPMS, these markers of inflammation on MRI decline [2] and instead MRI can only provide progressive brain atrophy information [3]. Some studies have shown that oxidative stress may be a major contributor to neurodegeneration in SPMS while the inflammatory markers are absent at this stage [4]. Glutathione (GSH) is an important marker of oxidative stress since it plays a crucial role in protecting cells from oxidative damage by defending against radicals. Therefore, a non-invasive method to measure in vivo GSH in human is important. Magnetic resonance spectroscopy (MRS) fits this role perfectly. Previous studies have shown that multiple quantum filtering techniques chemical shift imaging (CSI) of MRS can detect and measure GSH levels in brain [2] at 3T. However, to our knowledge, no studies have used the more widely available single-voxel spectroscopy and analysis tool LCModel to measure GSH levels in MS patients and to determine optimal voxel placement for GSH measurement, which may improve disease characterization and monitoring.

Figure 1. Four different MRS voxel locations in brain shown in three plane T1w MRI: a. ACG, b. STWM, c. Tha, d. PUT.

Objective: The goal of this study is to prove the feasibility of GSH measurement in human using readily available methods: 3T MRI scanner, single voxel ^{1}H MRS and LCModel analysis as well as the optimal voxel placement for GSH measurement in MS patients and healthy control.

Methods: Six subjects (3 MS patients: 1 RRMS, 1 primary progressive (PPMS), and 1 SPMS, 3 age-matched healthy controls, age 34-48, all male) were recruited for this study. All subjects were consented under local IRB approval. This study was performed in a Simens 3T Verio scanner and using 32-channel head coil. Single Voxel MRS was acquired using conventional PRESS in four different brain regions shown in Figure 1: Anterior Cingulate Gyrus (ACG; 40x20x20 mm), Superior Temporal White Matter (STWM; 20x20x20 mm), Thalamus (Tha; 20x15x15 mm), and Putamen (PUT; 20x15x15 mm). All voxels were acquired using TE = 30 ms, TR = 1.5 s, bandwidth = 1 kHz, 512 complex data points, water saturation, and 64 averaged acquisitions. Unsuppressed water spectrum with the same parameters but without water suppression and 16 averages. Total scan time: 2.25 minutes per voxel. PRESS data was analyzed using LCmodel. GSH quantification will be undertaken and Cramér–Rao lower bound (CRLB) of GSH quantification will be calculated in order to compare reliability of measurement of each voxel location.

Figure 2. CRLB of four different MRS voxel locations: ACG, STWM, Tha and PUT

Results and discussion: The GSH measurements in the conventional PRESS voxels in ACG and STWM in all six subjects had a Cramér–Rao lower bound (CRLB) below 20% as shown in Figure 2. Three of six measurements in the Tha and Put had a CRLB below 20%. One subject had a CRLB that approximately double the mean CRLB in PUT. Among all four voxel locations, ACG had the lowest mean CRLB for GSH measurement, which was followed by STWM then Tha and Put with the highest mean CRLB. The mean FWHM and the mean SNR of each voxel demonstrated the same trends as shown in Table 1 with increasing linewidths and worsening SNR. The improvements in spectral fitting, linewidths and SNR in ACG and STWM suggest that they are the better voxel locations for GSH measurement compared to Tha and PUT. The GSH concentration in each voxel was also quantified using LCModel in this study; however, GSH concentration in healthy controls and MS patients didn't differ from each other significantly. This is likely due to the different stages of MS in the patients and the small number of subjects. However, with these high quality and reliable voxel locations and methods, we anticipate seeing GSH differences between these two groups with a greater number of subjects.

Voxel	Mean CRLB (GSH%SD)	Mean FWHM (Hz)	Mean SNR
ACG	10.83 ± 2.4	6.5±2.3	30.5±9.4
STWM	15.16 ± 4.3	6.8± 0.8	19.8±6
Tha	20.67± 6.3	9.9±2.1	7.5±1.9
PUT	27.4 ±19.1	10.9±3.2	9±4.2

Table 1. Mean CRLB, mean FWHM and mean SNR of four voxels locations

Conclusion: Among all four voxel locations, voxels in ACG and STWM provide the most reliable measurements of GSH in both MS patients and healthy controls. The feasibility of GSH measurement in MS patients and healthy controls using readily available methods-3T MRI scanner, single voxel 1H MRS and LCModel analysis is proven by this study.

Reference:

1) National Multiple Sclerosis Society, from http://www.nationalmssociety.org/about-multiple-sclerosis/index.aspx. 2) Choi IY et al. Mult Scler. 2011; 17 (3):289-96. 3) Bakshi R et al. Lancet. Neurol 2008; 7: 61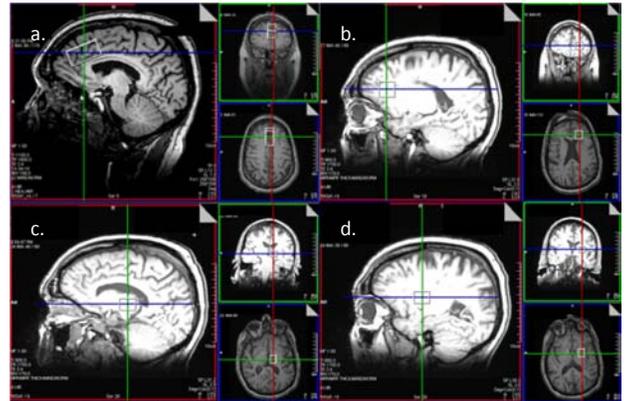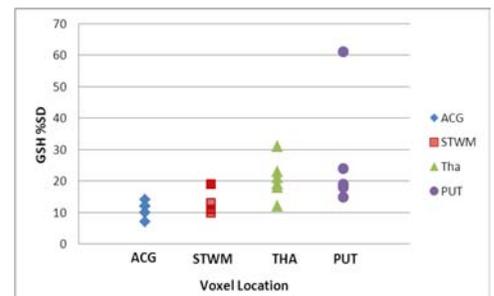5–625. 4) Gonsette RE. J Neurol Sci. 2008; 274:48–53.