Evidence of elevated Glutamate and glial activity in Multiple Sclerosis using TE-Averaged Spectroscopy at 3T

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Introduction

Glutamate and glutamine are two important neurotransmitters in the central nervous system. Under pathological conditions excess glutamate in the synaptic space can trigger a toxic cascade leading to cell death [1]. Histopathological studies have linked axonal injury to the presence of glutamate-producing immune cells in the proximity of Multiple Sclerosis (MS) lesions [2] as well as a lack of glutamate clearance by oligodendrocytes in normal-appearing white matter [3]. Glutamate is mainly concentrated in neurons and Glutamine in astrocytes. Since myo-inositol (mI) is a putative marker of glial cells and NAA is a neuronal marker, the potential impact of glial/neuronal cell population differences can be minimized by normalizing glutamate by NAA and glutamine by mI. It will be valuable to have a non-invasive method to reliably assess the relationship between these metabolites. In conventional PRESS spectroscopic sequences there is significant overlap between NAA, Glutamate and Glutamine making it difficult to isolate individual contributions of these metabolites. We demonstrate the feasibility of unobstructed single resonance detection of glutamate using proton magnetic resonance spectroscopy at the clinically accessible 3T field strength. Levels of glutamate (Glu), glutamine (Gln), myo-inositol (mI) and NAA in MS lesions and normal appearing white matter (NAWM) are compared with normal control white matter.

Methods

Data were acquired on a 3T Signa scanner (Menlo Park, CA) using the standard quadrature head coil and PROBE/SVQ™ (automated PRESS). This sequence was modified (PRESS-2DJ) [4] to collect TE-averaged data in 64 increments of 2.5 ms starting at TE = 35 ms. TR was set at 2s for all studies. Spectra were derived from an 8cc voxel in a parietal white matter (WM) region, surrounding an acute gadolinium (Gad) enhancing lesion or non enhancing chronic hypointense T1 lesion. 16 MS patients and 10 controls (CTRL) were scanned (**Table 1**). This single voxel sequence was modified to acquire some preliminary in-vivo TE-averaged spectroscopy imaging (CSI) data over a two-dimensional (2D) region (~60 cc) with the following parameters: 4 TE increments of 30.0 ms, TR = 1.0s, matrix size = 8x8x1, voxel resolution of 6cc. The spectral data were quantified with the LCmodel algorithm [5]. LCmodel analyzes the in vivo spectrum as a linear combination of individual in-vitro metabolite spectra that constitute a basis set. The TE-averaged sequence was used to acquire this basis set which comprised of NAA, Glu, Gln, mI, Choline and Creatine. The LCmodel concentrations were corrected for T1 relaxation effects. Results are reported only if the error estimates in LCmodel were within 20% for glutamate, NAA and myo-inositol and within 40% for glutamine.

Table 1	N (M /F)	Age	Disease Duration	EDSS
CTRL	10 (4/6)	33.1 ± 9.1	--	--
MS	16 (7/9)	43.8 ± 12.5	8.9 ± 7.8	3.4 ± 2.4

Results

In a conventional 3T PRESS spectrum at TE 35, the N-acetyl group of NAA (2.02 ppm) is overlapped with glutamate, and glutamine signals making it difficult to isolate the glutamate resonance. In comparison, TE-averaged PRESS (**Figure 1)**, fully resolves the glutamate at 2.35 ppm ($Glu_{2.35}$) from overlap resulting in its unobstructed detection. The LCmodel quantification results of the PRESS 2DJ single voxel spectra are outlined in **Table 2**. The Glu and the Glu/NAA levels in Gad enhancing lesions are enhanced relative to chronic lesions. This difference cannot be explained by decrease in NAA alone. Glu levels in Gad lesions are significantly different (p = 0.01) from CTRL WM. Correction for partial volume effects and edema [6] are expected to enhance these differences. Significant differences were also seen in the mI (**Figure 2**) and glutamine (Gln) levels between CTRL WM and MS lesions. Reliable estimates for glutamine were obtained only for a subset of voxels and are indicated in the table (*). This could be associated with low biological concentrations of glutamine. Preliminary in-vivo TE-averaged CSI data acquired over a two-dimensional region (**Figure 3**) of interest are shown in **Figure 4**. While a component of the Glu resonance at 2.35 ppm was well resolved, there appears to be some chemical shift artifacts and insufficient water suppression in some voxels. The SNR of Glu at 2.35 ppm from the central voxel was 30.0.

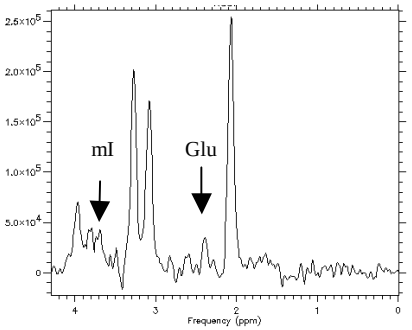
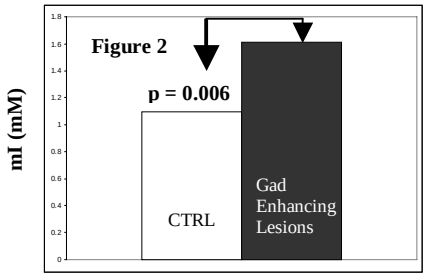
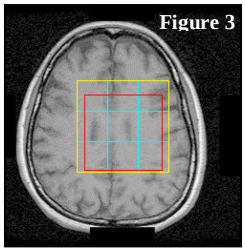


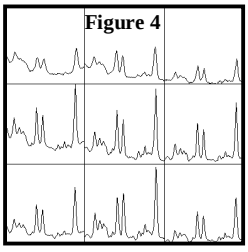
Figure 1: The TE-averaged PRESS 2DJ single voxel spectrum from a Gad enhancing lesion. The Glutamate peak at 2.35 ppm is well detected.

Table 2	Glu (mM) Mean ± std	NAA (mM) Mean ± std	Glu/NAA Mean ± std	mI (mM) Mean ± std	Gln (mM) Mean ± std	Gln/mI Mean ± std
CTRL WM [N=10]	3.26 ± 0.79	10.1 ± 1.16	0.33 ± 0.09	1.09 ± 0.23	0.99 ± 0.31 [N = 7]*	0.89 ± 0.34
NAWM [N=13]	3.37 ± 0.65	9.94 ± 2.1	0.34 ± 0.10	**1.47 ± 0.37**	1.08 ± 0.29 [N = 5]*	0.70 ± 0.26
Gad Enhancing Lesions [N=7]	**4.01 ± 0.77**	9.51 ± 1.83	**0.43 ± 0.12**	**1.67 ± 0.34**	**1.58 ± 0.40** [N=6]*	0.98 ± 0.32
Chronic Lesions [N=7]	3.23 ± 0.66	8.89 ± 1.37	0.36 ± 0.09	**1.49 ± 0.33**	1.45 ± 0.21 [N=2]*	1.06 ± 0.28

Table 2: Comparison of metabolite concentrations between normals and MS patients. **Figure 2:** Myo-inositol concentration in Gad enhancing lesions (black) compared with control white matter (white). **Figure 3:** Slice showing the 2D region of interest used to acquire TE-averaged CSI data (**Figure 4**).







Conclusions

These results support the link between acute MS lesions and altered glutamate metabolism. The importance of glial activity in MS brains, through myo-inositol and glutamine measurements, can also be investigated in vivo using TE-averaged sequence, which was found to be excessive in NAWM and MS lesions. TE-averaged CSI would require active effort for further optimization.

References

[1] Rothstein, 1996, Neurology;47:S19-S25, [2] Werner, 2001 Ann Neurol;50:169-180 [3] Pitt, 2003 Neurology; 61:1113-1120 [4] Hurd, 2003, MRM in press [5] Provencher, 1993 MRM;30:672-679 [6] Helms 2001, MRM 2001;46:256-263.

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