Glutamate levels in normal appearing white and gray matter in Multiple Sclerosis using TE-Averaged MRSI at 3T

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Introduction

Histopathological [1] and animal models [2] in Multiple Sclerosis have provided compelling evidence of a glutamate mediated disease process in Multiple Sclerosis (MS). Using MR spectroscopic techniques we have demonstrated a methodology for an unobstructed measurement of glutamate at 2.35 ppm [3] that is well separated from NAA and glutamine at 3T. This single voxel technique was used to demonstrate elevated levels of glutamate in the normal appearing white matter (NAWM) and active gadolinium enhancing lesions in Multiple Sclerosis [4]. Recently we have extended the single voxel TE-Averaged PRESS technique for two dimensional (2D) spectroscopic imaging of glutamate [5] (TE-Averaged MRSI). Using normal volunteer data we have shown significantly higher levels of glutamate in the gray matter relative to white matter as anticipated, demonstrating the successful implementation of TE-Averaged PRESS for spectroscopic imaging of glutamate. In this study we use TE-Averaged MRSI to assess white and gray matter glutamate levels in a large MS patient cohort and compare this with controls.

Methods

In-vivo data were acquired on a 3T GE Signa scanner using an 8-channel phased array coil (Medical Advances). TE-Averaged MRSI data [5] were acquired on 15 controls and 99 MS patients (**Table 1**) from a 2D region above the corpus callosum. The acquisition parameters in the J resolved dimension were identical to previous single voxel implementation of the TE-Averaged scheme [4] i.e. 64 echo time steps starting at TE = 35 msec with an echo time increment of 2.5 msec. The spatial data were acquired with a nominal in-plane spatial resolution of 1.2x1.0 cm over a single slice of thickness of 1.5 cm in the supratentorial brain just above the corpus callosum. The excited region of interest was typically ~ 110 cc. With the number of excitations = 2 and TR = 1.0 s, the scan time for this TE-Averaged MRSI acquisition was ~ 21 minutes. All data was sent to a SUN Ultra 10 workstation for post-processing, using programs developed in our laboratory. LCmodel was used for quantification of Glutamate levels. The T1-weighted images were segmented into gray matter (GM), white matter (WM), and cerebro-spinal fluid (CSF) compartments which were re-grid to the spectroscopic resolution to yield the percent white and gray matter within each voxel. By modeling the metabolite concentrations as a linear function of WM content, "pure" GM and WM metabolite concentrations were extrapolated from the end points of the linear fit [6] for each subject. Spectroscopic voxels were included in the linear fit only if their concentration estimate were within 15% Cramer-Rao bounds for glutamate. Data were included only if the total number of voxels in the linear fit exceeded 15 with a good distribution of WM content. Statistics were assessed using two-tailed student t statistic with unequal variance.

Table 1	N (M /F)	Age	Disease Duration	EDSS
CTRL	1/14	36.8 ± 9.2	--	--
MS	26/73	42.1 ± 9.8	8.9 ± 7.8	1.8 ± 1.4

Results

A representative 2-dimensional TE-Averaged MRSI excitation region and glutamate map from an MS patient is shown in **Figure 1** and **Figure 2** respectively. The linear fit of the glutamate concentration to the percent white matter is shown using data from all controls (**Figure 3A**) and all MS patients (**Figure 3B**). Similar fits were obtained for each subject. The extrapolated values of such linear fits were used to generate the "pure" WM and GM values for each subject. Following such analysis, the glutamate levels in MS normal appearing white matter (NAWM) (8.2 ± 1.2) mM was significantly elevated ($p < 0.001$) relative to control WM (7.3 ± 0.8) mM (**Figure 4A**). The MS normal appearing gray matter (NAGM) glutamate levels (10.1 ± 2.1) mM were not significantly different from controls (10.3 ± 1.5) mM (**Figure 4B).** The metabolite concentrations were not corrected for T1 relaxation although collection of MRSI data for T1 correction is ongoing. Based on our previous results [4] in which T1 relaxation of glutamate in MS were not found to be significantly different from controls, we anticipate that such a T1 correction will not alter these results.

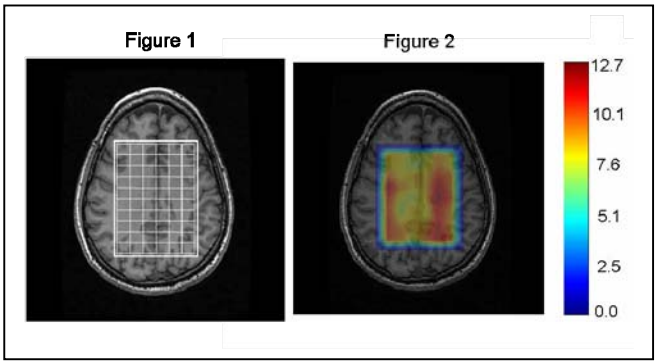
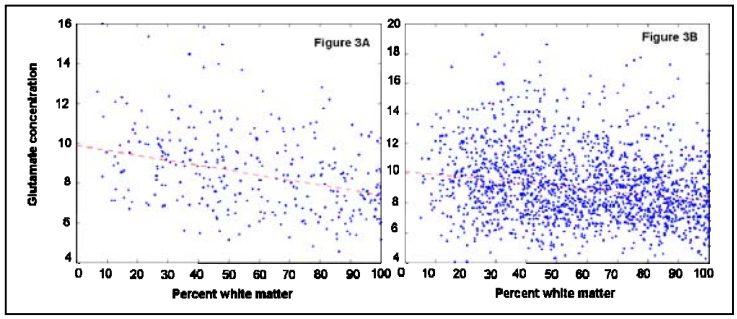
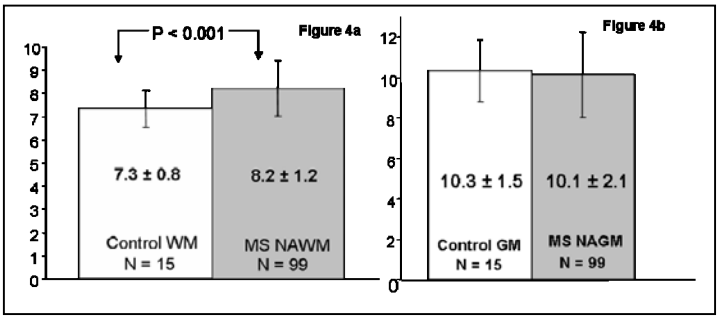


Figure 1: TE-Averaged MRSI excitation region. **Figure 2**: Glutamate map from an MS patient. The elevated glutamate in NAWM relative to NAGM is apparent. The low intensity at the edge of the PRESS box is an artifact of excitation. **Figure 3A**: Linear fit to glutamate concentrations (in mM) from all controls. **Figure 3B**: Linear fit to glutamate concentrations (in mM) from all MS patients. **Figure 4A**: Glutamate levels in control WM and MS NAWM. **Figure 4B**: Glutamate levels in control GM and MS NAGM.





Conclusions: The elevation of glutamate in the NAWM with TE-Averaged MRSI is consistent with our previous single voxel technique [4] thereby confirming our findings. In contrast to single voxel data, MRSI data allows an improved assessment of metabolite concentrations in white matter and gray matter. The clinical significance of elevation of glutamate in the white matter and not in gray matter is that inflammatory processes that could be the cause of elevated glutamate are more important in the NAWM than the NAGM where there is a relative paucity of such processes.

References [1] Werner, et.al. 2001, Ann. Neurol. 50, 169 [2] Pitt et. al. 2000, Nat Med. 6, 67 [3] Hurd et. al. MRM, 2004 51, 435 [4] Srinivasan, R et. al. , Brain, 2005, 128, 1016 [5] Srinivasan et.al., 2005, Neuroimage, in press, [6] Hetherington, H et. al. 1996, MRM 36, 21-29.

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