In vivo GABA measurement in MS sensorimotor cortex -- a marker for disease progression?

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Introduction

Several lines of data suggest that there are both inflammatory and neurodegenerative components to ongoing disease progression in multiple sclerosis (MS). Recent histopathological data have demonstrated that GABA levels are markedly reduced in MS patients in comparison to healthy controls. We have performed GABA measurement of sensorimotor cortex for both healthy controls and MS patients. We found a drop in the cortical GABA level in MS patients. In addition, we observed an inverse correlation between manual task performance and GABA level in MS patients.

Methods

MR scans were performed using a 3 Tesla Siemens whole body Tim-Trio scanner (Erlangen, Germany) with a CP head coil. Sixteen healthy subjects and fifteen patients were scanned with a MEGA-PRESS sequence (1) having water signal-based interleaved navigator (2). A 20 x 20 x 20 mm³ voxel at the motor cortex was selected prior to the spectroscopy scan from the area of maximum activation (Siemens Neuro3D program) following an IMRI scan in which each subject performed self-paced bilateral finger tapping in a block interleaved 32 second ON and 32 second OFF pattern. The frequency of the editing pulse was alternated in an interleaved fashion between 1.9 and 1.5 ppm to minimize macromolecule contamination. A water unsuppressed scan was acquired in a shot by shot basis, and the first four measurements were ignored in order to ensure steady state magnetization. Six controls¹ and nine patients² data were unacceptable because of motion as indicated primarily by the fluctuation of the navigator water signal (2). Three of the remaining patients were also scanned, as part of a different study, with fiber optic glove (Fifth Dimension Technologies, Inc., Irvine, CA) while performing finger tapping at a pace of 2Hz. The finger tapping data were recorded and analyzed for tapping rate and accuracy. Spectroscopy data were analyzed using jMRUI package. Phase corrections of the individual subspectra were performed using the residual water phase information. The individual subspectra were corrected for any frequency shift as well. The individual subspectra were added separately for 1.9 and 1.5 ppm editing pulse scans. The data were apodized with a 5 Hz Gaussian filter, zero filled, and baseline corrected. The gray matter, white matter and CSF contribution to the voxel composition was performed by using FAST segmentation algorithm of FSL software using a 3D MPRAGE as the base image. The GABA concentration was determined using the following equation:

\[
\text{GABA} = \frac{I_{\text{GABA}} \times 55}{I_{\text{W}} \times EE \times \text{meas}}
\]

where \( I_{\text{GABA}} \) is the area under the GABA peak in the edited spectrum, \( I_{\text{W}} \) is the area under the water peak in the water unsuppressed single acquisition spectrum EE is the editing efficiency, meas is the number of measurements, tcf is the correction factor for water concentration due to voxel composition, and the concentration of pure water is 55 M. The metabolite nulling scan data were used for macromolecule correction. The total volume of MS lesions with the voxel was measured. Normal appearing white matter MR visibility was taken to be 2.2% higher than normal white matter, and white matter lesion water content was assumed to be 6.3% higher than contralateral white matter in patients(3).

Results and Discussion

A representative single subject GABA edited spectrum is shown in Fig. 2. Upon careful consideration ten control subjects¹ data were acceptable. After correcting for the voxel composition, the motor cortex GABA concentration in controls was determined to be 1.37(49) mM, which is in reasonable agreement with the concentration reported from a different study. On the other hand, no GABA was detected in five out of seven patients, and the GABA level in the other two dataset was 1.80(89) mM. The tapping rates for patients with no GABA were -26.6 and -151.6, and the errors were 10 and 19 respectively. On the other hand the same metrics for the patient with motor cortex GABA were 144.4 and 0. For a group of 15 controls, also from a separate study, the rate and error were -10.9(14.0) and 5(8) respectively. A negative rate means that the person tapped slower than the prescribed rate of 2 Hz, while positive rate means tapping was faster than the prescribed rate. Even though this data is very preliminary, the fact that the patients with no measurable motor cortex GABA performed much worse (i.e. higher error rate) and tapped more slowly than the patient with a high level of GABA suggests that reduced cortical GABA concentration reflects disease burden. GABA measurement was taken from the contralateral cortex of the hand involved in tapping. Since the spectroscopy voxels were selected based upon IMRI activation during finger tapping, this constitutes a direct measure of cortical GABA level as a function of the corresponding cortical function. GABA concentration at the sensorimotor cortex in controls was determined to be 1.37(49) mM; five out of seven MS patients did not have any measurable cortical GABA, indicating a drop in the level in MS. Preliminary data suggest that the cortical GABA level in the contralateral hand region in MS patients is inversely correlated with the performance of a manual task.

Conclusion

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