Impaired Motor Performance in MS is Associated with Increased GABA Level in Sensorimotor Cortex

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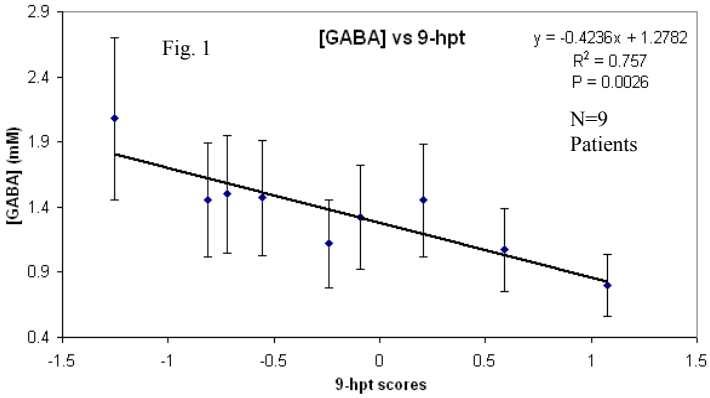
Introduction:

Sensorimotor cortex GABA level is reported to be affected in diseases associated with motor impairment (e.g. in focal dystonia (1). Since motor function is affected in multiple sclerosis (MS), *in vivo* measurement of GABA level in the sensormiotor cortex of MS patients could potentially lead to better understanding of the disease process. Mulitple sclerosis functional composite (MSFC) (2) is a clinical measure of MS and has three components: (i) timed 25 foot walk (measure of ambulation), (ii) 9 hole peg test (9-hpt)(measure of arm function), and (iii) paced auditory serial addidition test (PASAT) (measure of cognition). Since the 9-hpt component (3) of MSFC measures motor function in patients it may be expected to be correlated with the sensormotor GABA level. Using a variant of the MEGA-PRESS sequence (4) with proper motion assessment (5), we have measured *in vivo* GABA level in the sensorimotor cortex of healthy controls and MS patients. Our results show strong negative correlation between [GABA] and 9-hpt scores in MS patients.

Methods:

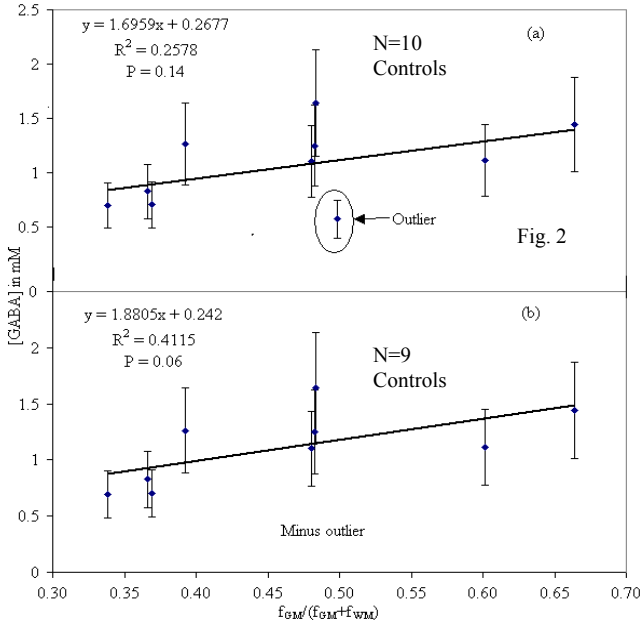
CC of [GABA] and MSFC scores	CC of [GABA] and 9-hpt scores	CC of [GABA] and 25 ft walk scores	[CC of [GABA] and PASAT scores
Controls (N = 10)			
-0.2233	0.1035	-0.1680	-0.3341
Patients (N= 9)			
-0.4697	-0.8652*	-0.3609	0.0503

*P-value < 0.005



MR scans were performed using a 3 Tesla Siemens whole body Tim-Trio scanner (Erlangen, Germany) with a CP head coil. Healthy controls and MS patients were scanned with a MEGA-PRESS sequence (4) having water signal-based interleaved navigator (5) to assess and discard portion of motion-corrupted data. A 2×2×2 cm^3voxel at the motor cortex was selected prior to the spectroscopy scan from the area of maximum activation (Siemens Neuro3D program) following an fMRI scan in which each subject performed bilateral finger tapping in a block interleaved 32 second ON and 32 second OFF pattern. The frequency of the editing pulse in MEGA-PRESS was alternated in an interleaved fashion between 1.9 and 1.5 ppm to minimize macromolecule contamination. A metabolite-nulling scan was also performed (TI = 650 ms) to account for any residual macromolecule contamination. Data were acquired in a shot by shot basis, and the first four measurements were ignored during analysis in order to ensure steady state magnetization. PRESS scans with and without water suppression were performed for absolute quantification following the editing scans. For absolute quantification, the gray matter, white matter and CSF contribution to the voxel composition was performed by using the FAST segmentation algorithm (6) of the FSL software library (7) with the anatomical 3D MPRAGE as the base image, and applying a mask at the voxel location. MRUI software was used for spectroscopy data analysis (8). [GABA]/[Cr] ratio was first obtained from the editing scans following the procedure in (9). Next [Cr] was obtained from the PRESS scans as in (10). The GABA concentration, [GABA] was next determined by taking the product of [GABA]/[Cr] and [Cr]. For patient data, appropriate correction was made for the number of lesion pixels in the voxel of interest. Correlation coefficients of [GABA] and MSFC (and its three components) were calculated. For the control population, a statistical regression analysis was performed as in Ref. (11) and the gray matter and white matter GABA concentrations were calculated by plotting [GABA] vs $f_{GM}/(f_{GM}+f_{WM})$, where fGM and fWM are gray matter (GM) and white matter (WM) water contribution in the voxel. The GM and WM GABA concentration were estimated by extrapolating the regression line to $f_{GM}/(f_{GM}+f_{WM}) = 1$ and 0 respectively. Since the cortical gray matter GABA concentration may vary within patients, a similar linear regression analysis was not performed on patients' data. As a first order approximation, the ratio of GM and WM GABA concentrations was assumed to be similar in MS patients and controls. Using a range of ratios, the correlation coefficients were recalculated using gray matter GABA levels in MS patients.

Results and Discussion:



As can be seen from the Table and Fig. 1, there is a very strong inverse correlation between [GABA] and 9-hpt component of MSFC in MS patients. Since higher 9-hpt corresponds to better performance, this indicates impairment of motor activity with increase in GABA concentration in the patient population. Linear regression analysis (Fig. 2) resulted in GM and WM [GABA] ratio of 8.83±3.25 in controls. GM [GABA] in patients were estimated using a range of ratio of 4 to 12 in patients; the GM [GABA] thus estimated showed similar high inverse correlation with 9-hpt scores. [GABA] did not have any significant correlation with the other components of MSFC in patients, and also were not correlated with any component of MSFC in controls. Interestingly, no significant difference in [GABA] was observed between controls and patients.

Conclusion:

Higher sensorimotor cortex [GABA] level was observed in motor cortex of MS patients with more motor impairment. The correlation between impairment and GABA was highly significant. This may indicate a compensatory mechanism in MS. No such effect was observed in healthy controls.

Acknowledgements:

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References:

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