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 sensorimotor cortex of MS patients could potentially lead to better understanding of the disease process. Multiple 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 addition 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 sensorimotor 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:
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 cm³ voxel 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 ratio of GM to WM GABA concentrations in the voxel. 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.

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 slope as in controls. [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:

<table>
<thead>
<tr>
<th>CC of [GABA] and MSFC scores</th>
<th>CC of [GABA] and 9-hpt scores</th>
<th>CC of [GABA] and 25 ft walk scores</th>
<th>CC of [GABA] and PASAT scores</th>
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<tbody>
<tr>
<td>Controls (N=10)</td>
<td></td>
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<tr>
<td>-0.2233</td>
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<td>Patients (N=9)</td>
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<td>-0.4697</td>
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*P-value < 0.005

![Fig. 1](image)

![Fig. 2](image)