GABA-fMRI activation volume correlation suggests GABA is a marker of cortical adaptation in multiple sclerosis

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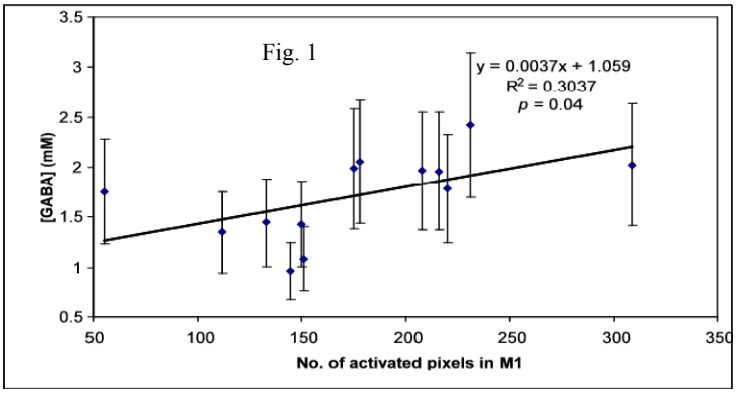
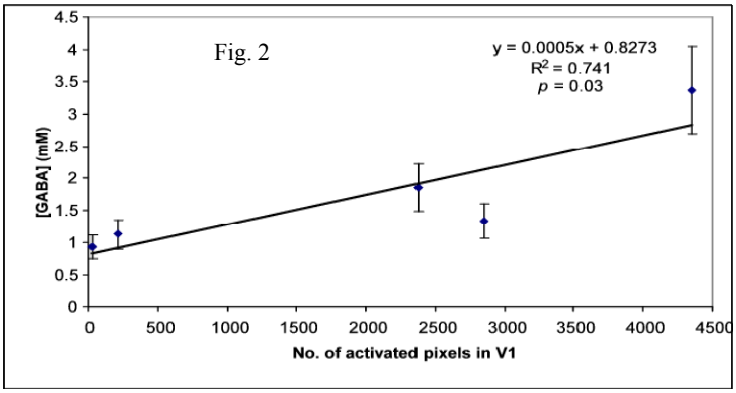
Introduction: An increase in the extent of functional cortical activation in MS patients versus controls during performance of specific tasks has been reported and interpreted as cortical reorganization/adaptation(1, 2). The mechanism of this reorganization mechanism is largely unknown. Also, impaired motor performance in MS has been reported to be associated with increased GABA level ([GABA]) in sensorimotor cortex, suggesting a role of GABA in MS disease process(3). On the basis of these observations, we examined the dependence of task specific fMRI activation on [GABA] levels in the functionally relevant cortices; we specifically addressed the sensorimotor and visual (occipital) cortices for this study. Our sensorimotor cortex (SMC) data as well as preliminary data from visual cortex (VC) suggest a direct correlation between fMRI activation volume and [GABA].

Methods: MR scans were performed using a 3 Tesla Siemens whole body Tim-Trio scanner (Erlangen, Germany). Nineteen healthy controls and 30 patients with MS participated in the sensorimotor cortex study. From these participants, datasets for 8 controls and 14 patients were discarded because of unacceptable subject motion(4, 5). GABA signal was below our measurement sensitivity or inconclusive in the SMC datasets for 1 control and 3 patients either due to measurement sensitivity limits or corrupted data. Data from the remaining 10 healthy controls and 13 MS patients were included in this study. Eight MS patients with optic neuritis were scanned in the VC study, of which dataset for 3 patients were discarded because of motion. GABA was measured with a MEGA-PRESS sequence(6) (TE=68 ms, TR=2700 ms, editing pulse frequency=1.90 ppm, 180^0 editing pulses were placed symmetrically about 1.70 ppm to minimize macromolecule contamination) implemented with motion identification(4, 5). MRUI software was used for spectroscopy data analysis(7), and absolute GABA level was measured after correcting for the gray matter (GM), white matter (WM) and CSF contribution, as well as for T1 and T2 relaxation as in Ref(8). In the SMC study the subjects performed self paced bilateral finger tapping (4.5 cycles, 32 s ON, 32 s OFF), and the number of activated pixels within the right primary motor cortex (M1) was determined (Student $t >$ 3.5, 1-sided, uncorrected $p < 3 \times 10^{-4}$) within the Human Motor Area Template region of interest mask corresponding to M1. A 2×2×2 cm^3 voxel at the right motor cortex was selected for the spectroscopy scan from the area of maximum activation (using Siemens Neuro3D program) following the fMRI scan. In the VC study, the subjects watched a circular black and white radial checkerboard, which was split into four quadrants each flashing at a rate of 7.5 Hz (4 cycles, total duration ~6 min 30 s). The activation map corresponding to each quadrant was computed. The (activation) value





from voxels in the whole brain (thresholded at p<0.0005) was added together to get the activation volume. Number of activated pixels in primary visual cortex (V1) was calculated within the same hemisphere from which the 3×3×3 cm^3 spectroscopy voxel was selected. Only the quadrants corresponding to the activation of the relevant hemisphere were included in the analysis.

Results and Discussion: We observed a significant correlation between M1 activation volume and sensorimotor [GABA] in the patients with MS (N=13, r=0.5511, $p < 0.05$) as shown in Fig. 1. No significant correlation was seen between M1 activation volume and [GABA] in the healthy controls (N=10, p=0.81). Significant correlation between V1 activation volume and occipital [GABA] was observed as well in the patients (N=5, r=0.8608, $p < 0.05$) as shown in Fig. 2. Our VC study has smaller number of subjects, but the preliminary finding shows correlation of fMRI activation and the relevant cortical [GABA] in two different functionally relevant areas, i.e. motor and visual. Increase in number of activated pixels indicates cortical adaptation that correlates with GABA in both motor and visual cortices.

Conclusion: Our observation of increased cortical [GABA] with increased activation in two different functional cortices in MS patients and the absence of such correlation in healthy controls suggests that GABA plays a role in the cortical reorganization/adaptation process.

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