GABA correlates differently with fMRI activation volume and BOLD signal in noisy datasets

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Target Audience: MR physicists, MR spectroscopists, fMRI analysts.

Purpose: There is a recent interest to correlate concentration of gamma amino butyric acid (GABA), an important inhibitory neurotransmitter, with functional MRI (fMRI) activation. As a metric of fMRI activation, different investigators have used (i) total number activated pixels (activation volume) within a region of interest (ROI) in healthy controls[1], or (ii) amplitude of blood oxygen level dependent (BOLD) signal change in patients with multiple sclerosis (MS)[2]. Recently, it was reported that activation volume, as determined by the number of activated pixels, is a more stable measure of fMRI activation than BOLD signal amplitude in noisy datasets, which is more pertinent in some patient groups, e.g. in MS[3]. Here we report GABA concentration, [GABA], correlation with the two fMRI metrics in MS to demonstrate the applicability of activation volume as a more stable metric in MS. We also report data to illustrate that activation volume is a more robust measure than BOLD signal change.

Methods: MR scans were performed using a 3 Tesla Siemens whole body Tim-Trio scanner (Erlangen, Germany). Data without motion corruption was obtained from 12 patients with MS and 11 healthy controls. The gradient-echo echo-planar fMRI scan parameters were: TR = 2000 ms; TE = 30 ms; flip angle = 90°; number of transverse sections = 32; and slice thickness = 4 mm without any interslice gap. Subjects performed self-paced bilateral finger tapping (index finger simultaneously in opposition to the thumb on each hand) in blocks of interleaved 32-second ON and 32-second OFF patterns. MR spectroscopy scan consisted of MEGA-PRESS scan with 2×2× 2 cm^3 voxels, TE=68 ms, TR=2700 ms, frequency selective 180^0 pulses placed at 1.9 and 1.5 ppm to minimize macromolecule contribution. The voxels were placed around the area of maximum activation in right sensorimotor cortex following bilateral finger tapping. Data analysis was done as in Bhattacharyya et al.[2]. fMRI data analysis consisted of (i) discarding the 1st 4 volumes from time series, (ii) spatial filtering using a 64-point, radially symmetric, 2-dimensional Hamming filter in the Fourier domain, (iii) retrospective motion correction using Analysis of Functional NeuroImages software (AFNI)[4], (iv) analysis for activation by least-squares fitting the time series for each pixel to a boxcar reference function plus a slope[5], (v) transforming Student *t* maps and MPRAGE for each subject into the standard stereotaxic space defined by Talairach and Tournoux[6] using AFNI[4], (vi) drawing ROI mask defining primary motor cortex (M1) using the Human Motor Area Template (HMAT) in Talairach space.[7] The number of activated voxels (Student $t > 3.5$, 1-sided, uncorrected $P < 3 \times 10^{-4}$) within the HMAT ROI mask corresponding to the right M1 was determined. Percent BOLD signal changes within M1 for all subjects were calculated using the same threshold as in activation volume calculation, and the noise at each voxel within M1 was calculated by dividing t-score by the amplitude of BOLD signal change. Inter-subject variation of signal amplitude and noise were determined in both controls and patients. The spectroscopy data analysis was done using jMRUI software (http://www.mrui.uab.es/mrui/) involved (i) shot by shot phase correction and frequency alignment, (ii) generating ON and OFF MEGA-PRESS spectra by summing the corresponding transients, (iii) subtracting the OFF spectrum from ON spectrum to generate edited spectrum, (iv) apodizing by a 5 Hz Gaussian filter and (v) zero filling. [GABA] was calculated using internal water reference scan as by Bhattacharyya et al.[2]

Results and Discussion: Plots of right sensorimotor [GABA] and activation volume as well as maximum %signal change right M1 in patients are shown in Fig. 1(a) and 1(b) respectively. While [GABA] is correlated with activation volume (as previously shown by Bhattacharyya et al[2]), [GABA] is not correlated with %signal change. The maximum, mean and median of %signal change in controls significantly correlated with the activation volume, while those metrics did not correlate in the patient population as shown in the Table. The inter-subject variation of signal amplitude was found to be similar in controls and patients, while the inter-subject variation in noise was higher in patients (p=0.08). This difference in noise characteristic very likely results in absence of proportionality between activation volume and BOLD signal in patients. A finer point to be made is that, even when reporting BOLD signal and not activation volume, a threshold has to be chosen to define the voxels over which to average the BOLD signal. As stated above, we observe the signal amplitude measurement to be noisy in MS patients. In this case, activation volume is a more stable measure, since it based solely on Student t, which is essentially BOLD signal change normalized to the signal standard deviation. Since activation volume is more stable measure for MS patients, it is reasonable that [GABA] correlation with activation volume may not behave the same way as with %signal change.

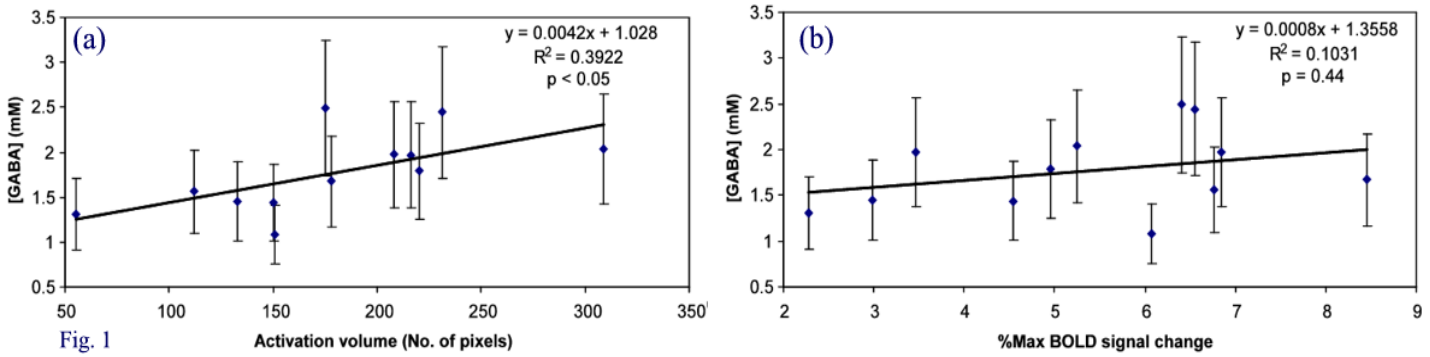

Fig. 1

* *Significant*	%Signal (Max)	%Signal (Mean)	%Signal (Median)
Controls (*n* = 11)	r = 0.7723 *p* < 0.005*	r = 0.6920 *p* < 0.02*	r = 0.6093 *p* < 0.05*
Patients (*n* = 12)	r=0.3242 *p* = 0.30	r=0.2523 *p* = 0.43	r=0.1600 *p* = 0.62

Conclusion: Our observation suggests that while sensorimotor GABA level correlates with fMRI activation volume in MS, it does not correlate with %signal change. This is in accord with the observation that activation volume, as determined by the number of activated pixels, is a more stable measure of fMRI activation than BOLD signal amplitude in noisy datasets, which is more applicable in some patient groups, e.g. in patients with MS. It is advisable to use activation volume as fMRI metric while correlating with spectroscopic measures in patient population.

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