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Activation volume vs BOLD signal change as measures of fMRI activation – its impact on GABA – fMRI activation correlation

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Abstract

Purpose—To explore the relative robustness of functional MRI (fMRI) activation volume and blood oxygen level-dependent (BOLD) signal change as fMRI metric, and to study the effect of relative robustness on the correlation between fMRI activation and cortical gamma amino butyric acid (GABA) in healthy controls and patients with multiple sclerosis (MS).

Methods—fMRI data were acquired from healthy controls and patients with MS, with the subjects performing self paced bilateral finger tapping in block design. GABA spectroscopy was performed with voxel placed on the area of maximum activation during fMRI. Activation volume and BOLD signal changes at primary motor cortex (M1), as well as GABA concentration were calculated for each patient.

Results—Activation volume correlated with BOLD signal change in healthy controls, but no such correlation was observed in patients with MS. This difference was likely the result of higher intersubject noise variance in the patient population. GABA concentration correlated with M1 activation volume in patients but not in controls, and did not correlate with any fMRI metric in patients or controls.

Conclusion—Our data suggest that activation volume is a more robust measure than BOLD signal change in a group with high intersubject noise variance as in patients with MS. Additionally, this study demonstrated difference in correlation behavior between GABA concentration and the 2 fMRI metrics in patients with MS, suggesting that GABA - activation volume correlation is more appropriate measure in the patient group.

Keywords

fMRI; GABA; BOLD signal; activation volume

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1. Introduction

Functional MRI (fMRI) is an MRI procedure used to detect brain activity. fMRI is primarily based on the coupling of neuronal activation and cerebral blood flow. During neural activity, local blood flow and the use of glucose increase at a rate that is higher than the oxygen consumption rate. This results in increased oxyhemoglobin concentration localized to the active area and a measurable change in the local diamagnetic oxyhemoglobin to paramagnetic deoxyhemoglobin ratio. This occurrence, known as the blood oxygen level-dependent (BOLD) effect, results in altered MRI signal with neural activity when using an MRI acquisition with proper contrast [1,2]. Both the amplitude of BOLD signal change [3–5] and the activation volume (total number of pixels over a defined statistical significance) as measured by the total number of activated voxels within a region of interest (ROI) [6–8] have been used by investigators to quantify fMRI activation. In order to do a comparison of findings from different studies using these two different metrics, it is important to study how they are related to each other. In order to test the overall robustness of the 2 metrics, we investigated the relationship between these two metrics not only in healthy controls but also in a population of patients with multiple sclerosis (MS).

Any difference in behavior of activation volume and BOLD signal change will be manifested in fMRI activation correlation with any other independent measurement. Given the recent research interest in understanding the role of Gamma aminobutyric acid (GABA), a major important inhibitory neurotransmitter in the central nervous system, in cortical plasticity as measured by fMRI activity [9–13], it is imperative to study GABA-fMRI activation correlation using both metrics. A choice between activation volume and BOLD signal change as an fMRI metric in general, and as a metric to be used in GABA-fMRI activation correlation, depends on the robustness of the metric. For example, the metric must be robust enough to be used in datasets with varying intersubject signal and noise fluctuations. In this study, we investigated the robustness of the 2 metrics and tested GABA-fMRI correlation with the 2 metrics.

Modulation of cerebral GABA levels has been linked to several neurological and neuropsychiatric disorders [14,15]. Understanding of network connectivity and activity in terms of local neurotransmitter modulation highlights the synaptic activity involved during different tasks. Interplay of excitatory glutamatergic neurons and inhibitory GABA-ergic interneurons is believed to regulate neuronal firing rates [16,17], thus contributing to BOLD fMRI signal [16,18]. Recently, investigators have begun to assess the role of GABA in cortical plasticity and have sought to study the correlation between fMRI activation and in vivo cerebral GABA concentration, as measured by MR spectroscopy (MRS) [9–13]. Although most of these studies have used BOLD signal change as the metric of fMRI activation [19–21], activation volume has also been used to quantify fMRI activation [13]. Activation volume as an fMRI metric is increasingly being adopted in studies with patient groups presenting with cortical plasticity, such as patients with multiple sclerosis (MS) [13,22,23].

Previous research has demonstrated a direct correlation between sensorimotor cortex GABA concentration and primary motor cortex (M1) activation volume in response to simple motor tasks in patients with MS and the lack of such correlation in healthy controls [13]. On the other hand, an inverse correlation between visual/anterior cingulate cortex GABA concentration and BOLD signal change in the respective cortex in response to task-activated fMRI has also been reported [19,20]. To put these findings from different studies using 2 different metrics into the same perspective, it must be determined whether cortical GABA concentration correlates with BOLD signal change (as it does with activation volume) in patients with MS and whether this metric correlates with activation volume/BOLD signal change in healthy controls. We therefore sought to determine how the correlation between GABA concentration and BOLD signal change compares with the correlation between GABA concentration and fMRI activation volume in healthy controls and in patients with MS. We also sought to compare the relative robustness of the 2 metrics as measures of fMRI activation.

2. Methods

Nineteen healthy controls and 29 patients with MS (relapsing-remitting type) were scanned with an Institutional Review Board-approved protocol using a whole-body 3 Tesla Siemens Tim Trio scanner (Erlangen, Germany). A circularly polarized transmit-receive head coil was used in the study. All participants in the study provided informed consent.

MR data acquisition has been described in detail by Bhattacharyya et al [13] and consisted of the following scans in sequential order:

- A localizer scan to obtain scout images;
- A gradient-recalled echo (GRE) scan for field-mapping;
- A T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) scan to obtain anatomical images;
- A gradient echo echoplanar fMRI scan (TR = 2000 ms; TE = 30 ms; flip angle = 90°; number of transverse slices = 32; field of view = 256 × 256 mm²; matrix = 64 × 64; slice thickness = 4 mm without any interslice gap; number of repetitions = 160; scan time = 5 min 20 s), in which 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;
- A MEGA-point resolved spectroscopy (MEGA-PRESS) scan of 2 × 2 × 2 cm³ voxel at the right sensorimotor cortex (TE = 68 ms; TR = 2700 ms; frequency-selective 44-Hz bandwidth 180° pulses placed at 1.9 and 1.5 ppm to minimize macromolecule contribution; number of averages = 96; scan time = 8 min 39 s);
- A PRESS scan of the same 2 × 2 × 2 cm³ voxel with water suppression enhanced through T1 effects (WET) [24] (TE = 68 ms; TR = 2700 ms; number of averages = 48); and
- A PRESS scan of the same voxel without water suppression (TE = 68 ms; TR = 2700 ms; number of averages = 1).

The placement of the spectroscopy voxel was based on the area of maximum activation during the fMRI scan using Siemens real-time Neuro3D program. The MEGA-PRESS scan was run with interleaved water signal-based navigator [25] for all but the last 5 patient scans, which were run in weak water-suppression mode. Fluctuation of the interleaved or residual water (in weak water-suppression mode) signal amplitude was used to detect motion during spectroscopy scans, and data with more than 3% shot-to-shot fluctuation were discarded for motion [13,25,26]. The motion-identification method was changed from interleaved water to residual water in weak water-suppression mode to improve the signal and ease of acquisition without any loss in efficacy in motion detection. The basic MEGA-PRESS module used in the 2 methods was the same, and the measured GABA concentration was not influenced by the change in motion detection scheme. This was validated by scanning known concentration GABA phantoms.

Before the *in vivo* scans were performed, the same volume ROI of a phantom containing 10 mM GABA and 10 mM glycine was scanned with both MEGA-PRESS and PRESS sequences at the same TR (2700 ms) and TE (68 ms). This was done to determine the editing efficiency of the MEGA-PRESS sequence.

2.1 Data analysis

fMRI and MRS data analyses were performed as previously described [13]. fMRI data analysis consisted of the following steps: (i) The first 4 volumes from the time series were discarded to accommodate for T1 equilibration effects; (ii) the data were then spatially filtered in the Fourier domain using a radially symmetric, 64-point, 2-dimensional Hamming filter; (iii) retrospective motion correction was performed using Analysis of Functional Neuroimages (AFNI) [27] software; (iv) activation analysis was performed by least-squares fitting the time series for each pixel to a boxcar reference function plus a slope [28]; (v) the resulting Student t maps and MPRAGE image for each subject were transformed into the standard stereotaxic space defined by Talairach and Tournoux [29] using AFNI [27]; and (vi) an ROI mask defining the primary motor cortex (M1) was drawn using the Human Motor Area Template (HMAT) in Talairach space [30]. Next, 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. The number of activated voxels thus determined was used as the measure of activation volume. Percent BOLD signal changes within M1 for each subject were calculated using the same threshold used to calculate activation volume, and voxel-wise noise calculation was performed by dividing the t-score by the amplitude of the BOLD signal change. The maximum, median, and mean of percent BOLD signal change of all the voxels within M1 were calculated.

The Student t-scores were derived from the following equation:

$$t = \frac{c}{\sigma} \quad (1),$$

where c is the amplitude of the boxcar reference function, and σ is the error in c as determined from a linear 3-parameter least-squares fitting procedure [31]. Voxel-wise noise calculation was performed by dividing the signal amplitude (c) by the Student t-score.

Next, intersubject signal amplitude (S_c) and noise variation (S_σ) were calculated separately for controls and patients using the following equations:

$$S_c = \sqrt{\frac{\sum (c - \bar{c})^2}{n - 1}} \quad (2)$$

$$S_\sigma = \sqrt{\frac{\sum (\sigma - \bar{\sigma})^2}{n - \sigma}} \quad (3),$$

where n is the number of subjects (controls or patients).

An F-test was performed to compare the intersubject variations in signal and noise between the control and patient populations.

MRS data analysis was performed using jMRUI software [32,33] and consisted of the following steps: (i) Phase correction and frequency alignment was performed on a shot-by-shot basis; (ii) ON- and OFF-resonance spectra were generated by summing spectra obtained with 1.9 ppm and 1.5 ppm frequency-selective pulses respectively during the MEGA-PRESS scan; (iii) the GABA-edited spectrum was obtained by subtracting the OFF spectrum from the ON spectrum; (iv) the edited spectrum was apodized by a 5-Hz Gaussian filter; and (v) the resulting spectrum was zero filled.

Next, GABA concentration ([GABA]) was measured using water as an internal reference. The gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) contributions to each voxel composition (f_{GM_vol} , f_{WM_vol} , and f_{CSF_vol} , respectively) were determined with the FAST segmentation algorithm [34] of the FSL software library [35], with the anatomical MPRAGE used as the base image and a mask applied at the voxel location. The percentages of GM, WM, and CSF were used to perform quantification of GABA.

[GABA] was calculated in 2 steps:

- i. The [GABA]/[Cr] ratio was obtained in the first step from the MEGA-PRESS scan, using the following equation:

$$\frac{[GABA]}{[Cr]} = \frac{G^*}{I_{Cr} \times EE}, \quad (4)$$

where G^* is the area under the 3.01 ppm GABA peak from the edited (difference) spectrum, I_{Cr} is the area under the 3.04 ppm methyl peak of creatine

(Cr) in the OFF-resonance spectrum, and EE is the editing efficiency, obtained in a fashion similar to that used by Terpstra et al [36] by comparing the unmodulated GABA signal relative to glycine from a PRESS scan with the edited GABA signal with respect to glycine from the same voxel of the same GABA-glycine phantom. The difference between *in vivo* T2 of the Cr methyl and of the C⁴H GABA resonance was assumed to be identical. Also, because the T1 of GABA resonance is comparable to that of other metabolites [37], the T1 difference between GABA and Cr was neglected.

- ii. Next, the creatine level ([Cr]) was calculated from the PRESS scans (with and without water suppression) using the following equation from Gasparovic et al [38]:

$$[\text{Cr}] = \frac{I_{\text{Cr}} \times (f_{\text{GM}} \times R_{\text{H}_2\text{O_GM}} + f_{\text{WM}} \times R_{\text{H}_2\text{O_WM}} + f_{\text{CSF}} \times R_{\text{H}_2\text{O_CSF}})}{S_{\text{H}_2\text{O_obs}} (1 - f_{\text{CSF}}) \times R_{\text{Cr}}} \times \frac{2}{\#H_{\text{Cr}}} \times [\text{H}_2\text{O}], \quad (5)$$

where f_{GM} , f_{WM} , and f_{CSF} are fractions of GM, WM, and CSF, respectively, in the voxel; $R_{\text{H}_2\text{O_GM}}$, $R_{\text{H}_2\text{O_WM}}$, and $R_{\text{H}_2\text{O_CSF}}$ are the relaxation attenuation factors for water in GM, WM, and CSF, respectively; $S_{\text{H}_2\text{O_obs}}$ is the area under the water peak in PRESS without water suppression; R_{Cr} is the relaxation attenuation for creatine methyl resonance; $\#H_{\text{Cr}}$ ($= 3$) is the number of protons in Cr methyl; and $[\text{H}_2\text{O}]$ ($= 55 \text{ M}$) is the concentration of pure water. f_{GM} , f_{WM} , and f_{CSF} were calculated as described previously [13] using the volume fractions of GM, WM, and CSF in the voxel ($f_{\text{GM_vol}}$, $f_{\text{WM_vol}}$, and $f_{\text{CSF_vol}}$, respectively). The number of lesions in the voxels for the patient population was counted using the MPRAGE images, and the difference in water content between normal-appearing WM and lesions was accounted for by implementing correction factors as described previously [13]. It should be noted that the number of WM lesions in the voxels was very small ($\sim 0.2\%$) and did not significantly affect the quantification of GABA.

[GABA] was then calculated by taking the product of (4) and (5).

3. Results

Datasets for 8 controls and 13 patients were discarded because of unacceptable subject motion [25,39]. Datasets for 2 of these controls discarded for spectroscopy analysis had no motion during fMRI scans and hence were included in the fMRI analysis. Datasets for 1 control and 4 patients had either too low or inconclusive GABA signal (the spectra either had GABA peak at the baseline level and could not be fitted with AMARES [40] with $<30\%$ standard deviation, or had other comparable peaks present in the edited spectra, very likely because of poor editing). In addition, 1 control had extremely high BOLD activation signal that was identified as a significant outlier ($P < 0.05$) using Grubbs' outlier test, and so the

data were excluded. Spectroscopy data from the remaining 9 healthy controls (8 female; age = 39.3 ± 14.1 y) and 12 patients with MS (9 female; age = 47.8 ± 8.4 y), and fMRI data from 11 healthy controls (9 female; age = 39.3 ± 13.6 y) and 12 patients with MS (same group as in spectroscopy) were included in this study.

Echoplanar imaging scans can cause gradient-induced heating, followed by cooling during the subsequent scans. Cooling during GABA editing after echoplanar imaging can cause frequency drift, which in turn can result in reduced editing efficiency or inefficient macromolecule minimization [41]. However, the maximum frequency drift during MEGA-PRESS acquisitions following echoplanar scans was 0.02 ± 0.01 ppm (2.5 ± 1.3 Hz) in both groups (healthy controls and patients with MS), and thus was not large enough to affect GABA editing significantly.

An example of an fMRI activation (percent BOLD signal change and activation volume) map is shown in Fig. 1. Fig. 1(a) displays (few relevant slices of 1 mm thickness and no gap) the M1 ROI as determined by HMAT. fMRI activation within the right M1 ROI is shown in Fig. 1(b) and a zoomed version of right M1 activation is shown in Fig. 1(c). A representative sample GABA spectrum is shown in Fig. 2. Glutamate (Glu) and glutamine (Gln) are also seen in the spectrum as a result of co-editing. The total number of all voxels was used to determine the activation volume, while percent BOLD signal change was obtained from the same voxels.

The overall signal and noise of BOLD signal were not significantly different between controls and patients. The difference in intersubject variation of BOLD signal amplitude between controls and patients was not statistically significant ($F = 1.37$; $P = .31$). However, the intersubject variation in noise was higher in patients than in controls ($F = 2.50$; $P = .08$).

A significant correlation between BOLD signal change and activation volume within the right M1 was seen in controls but not in patients (Fig. 3). The maximum, mean, and median percent BOLD signal changes were also significantly correlated with activation volume in controls but not in patients (Table 1).

Right sensorimotor [GABA] demonstrated significant correlation to M1 activation volume in patients with MS (Fig. 4a) as previously reported [13], but [GABA] in patients was not correlated with BOLD signal change (Fig. 4b). On the other hand, [GABA] in controls was not correlated with activation volume (as reported previously [13]) or with BOLD signal change (Fig. 5).

The significance of the correlation values reported here do not account for multiple comparisons. After corrections were made for multiple comparisons, the correlation between [GABA] and M1 activation volume in patients with MS still remained significant at the $P < 0.05$ level.

4. Discussion

In this study, we found that although activation volume correlated with BOLD signal change in healthy controls, no such correlation was observed in the patient population. Our results

suggest that activation volume is a more robust measure than BOLD signal change in patients with MS.

The higher intersubject noise variation among patients very likely resulted in the absence of correlation between BOLD signal change and activation volume in patients, whereas the 2 metrics were correlated in healthy controls. It should be emphasized that in analysis of the BOLD signal, a threshold must be chosen over which to average the BOLD signal so that the effect of noise variation is minimized. On the other hand, activation volume is based solely on Student t, which is the BOLD signal change normalized to the standard deviation (ie, noise) of the measured signal, thus making activation volume a more robust measure with respect to noise variation. For this reason, we recommend activation volume as the preferred measure of fMRI activation in both healthy controls and patients. This is more relevant in groups with higher intersubject noise fluctuation (eg, in patients with MS); BOLD signal change might be an acceptable metric otherwise. We speculate that the higher intersubject noise fluctuation in patients is caused by the wider range of physiologic noise in the patient group.

Differences between right and left hemispheric somatosensory cortex activation volumes in response to bilateral finger tapping with no difference in BOLD signal change have been reported previously in healthy controls [42]. This observation, while not in line with our observation of correlation between the 2 metrics in healthy controls, still suggests that there is a difference in behavior between activation volume and signal change measures.

Given the recent interest in GABA MRS research, our study focused on the correlation behavior between GABA level and BOLD signal change/fMRI activation volume. However, our finding about the robustness of activation volume is applicable in general to fMRI research with patient groups. Although BOLD signal change is a commonly used metric of fMRI, activation volume is used in patient groups exhibiting cortical plasticity, as in MS [13,22,23].

Some possible confounders in the study include (i) GM volume dependences of [GABA] [26,43] and (ii) T1 and T2 relaxation differences between healthy subjects and patients with MS. However, the difference in BOLD signal change and fMRI activation volume correlation between the 2 groups (Fig. 1) would not be affected by either of these confounders. We speculate that this difference is reflected in the observed difference in correlation of [GABA] with BOLD signal change/activation volume in patients. In addition, there were no differences in tissue composition in the voxels between healthy controls (GM: 38(7)%, WM: 50(12)%, CSF: 12(8)%) and patients (GM: 35(8)%, WM: 49(11)%, CSF: 17(5)%), ensuring that voxel tissue composition did not result in systematic differences in GABA between the 2 groups.

The high (~50%) data rejection in the study was caused by strict adherence to motion criteria during scans. fMRI data rejection was based on assessment of motion using mean peak-to-peak displacement [44] as well as visual inspection. Visual inspection was based on motion artifact that included rings of activation around the outside of the brain, activation in the ventricles, and rapid pattern changes from slice to slice. For GABA editing, >3% signal

amplitude fluctuation of interleaved/residual water (in weak-suppression mode) was used as a criterion to discard data for motion corruption. Although this criterion is rather strict, we believe that this is necessary for GABA editing with J-difference editing methods, as without this method, it is possible to obtain spectra containing apparent high-quality “false positive” GABA resonance peaks in highly motion corrupted data [25]. A small voxel size of $2 \times 2 \times 2 \text{ cm}^3$ for GABA editing was used in this study to localize the voxel mostly in the functionally relevant M1 region. The choice of small voxel size could have contributed to a lower signal-to-noise ratio of GABA signals, thus resulting in GABA peaks at the baseline level in the spectra for 5 subjects.

Although an inverse correlation between [GABA] and BOLD signal amplitude corresponding to different functional activities in healthy controls has been reported in some studies [9,11,19,20,45], the measured GABA in these studies was affected by co-edited macromolecules. More recent studies with larger sample sizes [46] or with macromolecule-minimized GABA acquisition [13,47] showed a lack of such correlation in controls, in agreement with our observation.

It should be pointed out that the purpose of this study was to determine a robust measure of fMRI activation that can be applied in groups with significant intersubject noise variation. Having a group of patients with MS provides us with such a subject group. We are not demonstrating any dependence of fMRI activation metrics or GABA on MS pathology, which would be beyond the scope of this investigation. In addition, the recent spike in interest in correlating GABA and fMRI activation prompted this study to identify a metric of fMRI activation that would be appropriate to be used in such correlation. Correlation of fMRI activation with measures other than GABA needs to be dealt with in a similar fashion.

In conclusion, our results suggest that activation volume is a more stable measure than BOLD signal change in datasets with higher intersubject variation of fMRI noise (eg, in patients with MS). Although [GABA] correlated with activation volume in patients with MS, it is reasonable that it did not exhibit the same behavior in respect to BOLD signal change. This finding is significant in the interest of relating GABA to task-related BOLD signal change and resting-state low-frequency BOLD fluctuation. Based on these results, we also suggest using activation volume instead of BOLD signal change in patients with MS.

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Abbreviations

AFNI	Analysis of Functional Neuroimages
BOLD	blood oxygen level-dependent
CSF	cerebrospinal fluid

GABA	gamma amino butyric acid
GM	gray matter
GRE	gradient-recalled echo
HMAT	Human Motor Area Template
MEGA-PRESS	MEGA-point resolved spectroscopy
MPRAGE	magnetization-prepared rapid acquisition gradient echo
MRS	MR spectroscopy
MS	multiple sclerosis
ROI	region Of interest
WM	white matter

References

1. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A*. 1990; 87:9868–72. [PubMed: 2124706]
2. Ogawa S, Lee TM. Magnetic resonance imaging of blood vessels at high fields: in vivo and in vitro measurements and image simulation. *Magn Reson Med*. 1990; 16:9–18. [PubMed: 2255240]
3. Georgiou-Karistianis N, Stout JC, Dominguez DJ, Carron SP, Ando A, Churchyard A, et al. Functional magnetic resonance imaging of working memory in Huntington's disease: Cross-sectional data from the IMAGE-HD study. *Hum Brain Mapp*. 2014
4. Tie Y, Rigolo L, Norton IH, Huang RY, Wu W, Orringer D, et al. Defining language networks from resting-state fMRI for surgical planning-a feasibility study. *Hum Brain Mapp*. 2014
5. Ludemann L, Forschler A, Grieger W, Zimmer C. BOLD signal in the motor cortex shows a correlation with the blood volume of brain tumors. *J Magn Reson Imaging*. 2006; 23:435–43. [PubMed: 16506145]
6. Hou BL, Bradbury M, Peck KK, Petrovich NM, Gutin PH, Holodny AI. Effect of brain tumor neovascularity defined by rCBV on BOLD fMRI activation volume in the primary motor cortex. *Neuroimage*. 2006; 32:489–97. [PubMed: 16806983]
7. Krasnow B, Tamm L, Greicius MD, Yang TT, Glover GH, Reiss AL, et al. Comparison of fMRI activation at 3 and 1.5 T during perceptual, cognitive, and affective processing. *Neuroimage*. 2003; 18:813–26. [PubMed: 12725758]
8. Al-Asmi A, Benar CG, Gross DW, Khani YA, Andermann F, Pike B, et al. fMRI activation in continuous and spike-triggered EEG-fMRI studies of epileptic spikes. *Epilepsia*. 2003; 44:1328–39. [PubMed: 14510827]
9. Donahue MJ, Near J, Blicher JU, Jezzard P. Baseline GABA concentration and fMRI response. *Neuroimage*. 2010; 53:392–8. [PubMed: 20633664]
10. Stagg CJ. Magnetic Resonance Spectroscopy as a tool to study the role of GABA in motor-cortical plasticity. *Neuroimage*. 2014; 86:19–27. [PubMed: 23333699]
11. Stagg CJ, Bachtar V, Johansen-Berg H. The role of GABA in human motor learning. *Curr Biol*. 2011; 21:480–4. [PubMed: 21376596]
12. Floyer-Lea A, Wylezinska M, Kincses T, Matthews PM. Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning. *J Neurophysiol*. 2006; 95:1639–44. [PubMed: 16221751]
13. Bhattacharyya PK, Phillips MD, Stone LA, Bermel RA, Lowe MJ. Sensorimotor cortex gamma-aminobutyric acid concentration correlates with impaired performance in patients with MS. *AJNR Am J Neuroradiol*. 2013; 34:1733–9. [PubMed: 23493890]

14. Chang L, Cloak CC, Ernst T. Magnetic resonance spectroscopy studies of GABA in neuropsychiatric disorders. *J Clin Psychiatry*. 2003; 64(Suppl 3):7–14.
15. Wong CG, Bottiglieri T, Snead OC 3rd. GABA, gamma-hydroxybutyric acid, and neurological disease. *Ann Neurol*. 2003; 54(Suppl 6):S3–12.
16. Buzsaki G, Kaila K, Raichle M. Inhibition and brain work. *Neuron*. 2007; 56:771–83. [PubMed: 18054855]
17. Fergus A, Lee KS. Regulation of cerebral microvessels by glutamatergic mechanisms. *Brain Res*. 1997; 754:35–45. [PubMed: 9134957]
18. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature*. 2001; 412:150–7. [PubMed: 11449264]
19. Muthukumaraswamy SD, Edden RA, Jones DK, Swettenham JB, Singh KD. Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. *Proc Natl Acad Sci U S A*. 2009; 106:8356–61. [PubMed: 19416820]
20. Northoff G, Walter M, Schulte RF, Beck J, Dydak U, Henning A, et al. GABA concentrations in the human anterior cingulate cortex predict negative BOLD responses in fMRI. *Nat Neurosci*. 2007; 10:1515–7. [PubMed: 17982452]
21. Walter M, Henning A, Grimm S, Schulte RF, Beck J, Dydak U, et al. The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression. *Arch Gen Psychiatry*. 2009; 66:478–86. [PubMed: 19414707]
22. Cifelli A, Matthews PM. Cerebral plasticity in multiple sclerosis: insights from fMRI. *Mult Scler*. 2002; 8:193–9. [PubMed: 12120689]
23. Rocca MA, Mezzapesa DM, Falini A, Ghezzi A, Martinelli V, Scotti G, et al. Evidence for axonal pathology and adaptive cortical reorganization in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis. *Neuroimage*. 2003; 18:847–55. [PubMed: 12725761]
24. Ogg RJ, Kingsley PB, Taylor JS. WET, a T1- and B1-insensitive water-suppression method for in vivo localized ¹H NMR spectroscopy. *J Magn Reson B*. 1994; 104:1–10. [PubMed: 8025810]
25. Bhattacharyya PK, Lowe MJ, Phillips MD. Spectral quality control in motion-corrupted single-voxel J-difference editing scans: an interleaved navigator approach. *Magn Reson Med*. 2007; 58:808–12. [PubMed: 17899594]
26. Bhattacharyya PK, Phillips MD, Stone LA, Lowe MJ. In vivo magnetic resonance spectroscopy measurement of gray-matter and white-matter gamma-aminobutyric acid concentration in sensorimotor cortex using a motion-controlled MEGA point-resolved spectroscopy sequence. *Magn Reson Imaging*. 2011; 29:374–9. [PubMed: 21232891]
27. Cox RW, Jesmanowicz A, Hyde JS. Real-time functional magnetic resonance imaging. *Magn Reson Med*. 1995; 33:230–6. [PubMed: 7707914]
28. Lowe MJ, Russell DP. Treatment of baseline drifts in fMRI time series analysis. *J Comput Assist Tomogr*. 1999; 23:463–73. [PubMed: 10348457]
29. Talairach, J., Tournoux, P. Co-Planar Stereotaxic Atlas of the Human Brain. New York: Thieme Medical; 1988. p. 122
30. Mayka MA, Corcos DM, Leurgans SE, Vaillancourt DE. Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage*. 2006; 31:1453–74. [PubMed: 16571375]
31. Press, W., Flannery, BP., Teukolsky, SA., Vetterling, WT. Numerical recipes: the art of scientific computing. Cambridge: Cambridge University Press; 1986.
32. <http://www.mrui.uab.es/mrui/>
33. Naressi A, Couturier C, Devos JM, Janssen M, Mangeat C, de Beer R, et al. Java-based graphical user interface for the MRUI quantitation package. *Magma*. 2001; 12:141–52. [PubMed: 11390270]
34. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. 2001; 20:45–57. [PubMed: 11293691]
35. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004; 23(Suppl 1):S208–19. [PubMed: 15501092]

36. Terpstra M, Ugurbil K, Gruetter R. Direct in vivo measurement of human cerebral GABA concentration using MEGA-editing at 7 Tesla. *Magn Reson Med*. 2002; 47:1009–12. [PubMed: 11979581]
37. Mescher M, Merkle H, Kirsch J, Garwood M, Gruetter R. Simultaneous in vivo spectral editing and water suppression. *NMR Biomed*. 1998; 11:266–72. [PubMed: 9802468]
38. Gasparovic C, Song T, Devier D, Bockholt HJ, Caprihan A, Mullins PG, et al. Use of tissue water as a concentration reference for proton spectroscopic imaging. *Magn Reson Med*. 2006; 55:1219–26. [PubMed: 16688703]
39. Bhattacharyya, PK., Beall, EB., Lowe, MJ. Residual water for motion identification in J-difference editing. Kitzbühel, Tyrol, Austria: 2010 Feb 24–28.
40. Vanhamme L, van den Boogaart A, Van Huffel S. Improved method for accurate and efficient quantification of MRS data with use of prior knowledge. *J Magn Reson*. 1997; 129:35–43. [PubMed: 9405214]
41. Harris AD, Glaubitz B, Near J, John Evans C, Puts NA, Schmidt-Wilcke T, et al. Impact of frequency drift on gamma-aminobutyric acid-edited MR spectroscopy. *Magn Reson Med*. 2014; 72:941–8. [PubMed: 24407931]
42. Ludemann L, Forschler A, Wust P, Zimmer C. Quantification of fMRI BOLD signal and volume applied to the somatosensory cortex. *Z Med Phys*. 2007; 17:108–17. [PubMed: 17665733]
43. Choi IY, Lee SP, Merkle H, Shen J. In vivo detection of gray and white matter differences in GABA concentration in the human brain. *Neuroimage*. 2006; 33:85–93. [PubMed: 16884929]
44. Jiang AP, Kennedy DN, Baker JR, Weisskoff RM, Tootell RBH, Woods RP, et al. Motion detection and correction in functional MR imaging. *Human Brain Mapping*. 1995; 3:224–35.
45. Violante IR, Ribeiro MJ, Edden RA, Guimaraes P, Bernardino I, Rebola J, et al. GABA deficit in the visual cortex of patients with neurofibromatosis type 1: genotype-phenotype correlations and functional impact. *Brain*. 2013; 136:918–25. [PubMed: 23404336]
46. Harris AD, Puts NA, Anderson BA, Yantis S, Pekar JJ, Barker PB, et al. Multi-regional investigation of the relationship between functional MRI blood oxygenation level dependent (BOLD) activation and GABA concentration. *PLoS One*. 2015; 10:e0117531. [PubMed: 25699994]
47. Mikkelsen M, Evans CJ, Stone AJ, Warnert EAH, Singh KD. Endogeneous GABA Concentration and Haemodynamic Responses to Graded Visual Contrast. *Proc Intl Soc Mag Reson Med*. 2015; 23:0140.

Fig. 1.

Example of fMRI activation map showing percent BOLD signal change and activation volume within M1 ROI. M1 ROIs from HMAT displayed on 1-mm thick slices without any gap; right M1 in blue and left M1 in red (a); BOLD signal change within the M1 ROI (Student $t > 3.5$, 1-sided, uncorrected $P < 3 \times 10^{-4}$) (b); zoomed version of BOLD signal change (c).

Fig. 2.
Representative single subject edited spectrum. Co-edited glutamate (Glu) and glutamine (Gln) are also seen in the spectrum.

Fig. 3.
M1 activation volume correlates with percent BOLD signal change in healthy controls (a) but not in patients with MS (b).

Fig. 4.
M1 GABA level ([GABA]) correlates with activation volume (a) but not with percent BOLD signal change (b) in patients with MS.

Fig. 5.
M1 GABA level ([GABA]) does not correlate with percent BOLD signal change (a) or activation volume (b) in healthy controls.

Table 1

Correlation coefficients between percent BOLD signal change and fMRI activation volume in controls and patients with MS.

	Percent BOLD signal change (maximum)	Percent BOLD signal change (mean)	Percent BOLD signal change (median)
Controls (n = 11)	$r = 0.7723; P < .005^*$	$r = 0.6920; P < .01^*$	$r = 0.6093; P < .05^*$
Patients (n = 12)	$r = 0.3242; P = .30$	$r = 0.2523; P = .43$	$r = 0.1600; P = .62$

* Significant correlation.