Bilateral sensorimotor GABA correlation is not driven by voxel segmentation

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Target audience: Researchers interested in the link between neuroanatomy and neurophysiology, specifically GABAergic inhibition. This work may be relevant to studies where interhemispheric connectivity or even plasticity (such as in stroke recovery) is of interest.

Purpose:

Edited MRS of GABA allows for the *in vivo* detection of GABA, the main inhibitory neurotransmitter in the human brain. Recent studies have shown functionally relevant links between MRS measured GABA levels, brain activity, behavior, and disease (for a review, see[1]). To date, no study has shown inter-regional correlations of GABA concentration. This is important because it suggests that GABA levels are functionally and regionally specific. However, no studies have examined individual differences in GABA concentration in homologous regions. While hemispheric asymmetries exist for some higher-order regions (e.g. areas involved in language such as Broca's area), the somatosensory and motor cortices have similar structure and function between the hemispheres, and inhibition between bilateral motor cortices is important for motor control[2-3]. In this study we set out to examine whether GABA concentration is correlated between spatially separate but functionally related brain regions: the left and right primary sensorimotor cortex (SIMI). The study was performed in two separate cohorts using different scanners.

Methods: Participant consent was obtained under local IRB approval: *Neuroimaging:* Edited MRS measurements of GABA were made in two sensorimotor volumes $(3cm)^3$ centered on the left and right hand knob (as seen in Figure 1A). In order to perform the bilateral measurements symmetrically, the water-fat shift direction associated with the left-right and head-foot slice selection were reversed for the left hemisphere (relative to the right). Cohort 1: Scanning for this cohort was carried out on a GE Signa HDx 3T MRI scanner (8-channel head coil for receive and the body coil for transmit) with two repeats per voxel. MEGA-PRESS sequence parameters: TE 68 ms; TR 1800 ms; 16 ms editing pulse applied at 1.9 and 7.46 ppm (ON and OFF experiments); 320 transients; 2k datapoints; 2 kHz spectral width. Cohort 2: T1-weighted MPRAGE images were acquired in each subject, prior to MRS. A similar MEGA-PRESS GABA measurement was applied, using a 3T Philips Ingenia MRI scanner (32-channel head coil; body coil for transmit) without repeat per voxel. Sequence parameters were: TE 68 ms; TR 2000 ms; 14 ms editing pulse applied alternately at 1.9 and 7.46 ppm (ON and OFF experiments); 320 transients; 2k datapoints; 2 kHz spectral width. *Analysis:* All data were analysed using Gannet[4] programmed in MATLAB (The Mathworks, Natick, MA). For Cohort 1, individual spectra were phase-corrected and frequency-aligned to 3.03 ppm, in a pair-wise fashion, on the basis of the Creatine (Cr) signal. Scans were rejected if the frequency of the Cr peak deviated more than 3 standard deviations from the mean. For Cohort 2, frequency and phase correction were performed using Spectral Registration. GABA concentration in 'institutional units' was quantified from the ratio of the integral of the edited GABA signal (determined by fitting to a Gaussian model) to the integral of the unsuppressed water signal from the same volume (determined by fitting to a Lorentzian-Gaussian model) and a constant multiplier used to account for differences in T1 and T2 relaxation times of water and GABA and the editing efficiency. For cohort 1, individual GABA concentrations in each hemisphere were taken as the mean between the two repeat scans. For Cohort 2, co-registration of MRS voxel position to the T1-weighted image and segmentation of the image, using FAST[5] allowed the tissue composition to be expressed as percentage gray matter (GM%), white matter (WM%) and cerebrospinal fluid (CSF%). Pearson correlation coefficients were used to determine interregional correlations. Jackknife analysis was performed for cohort 1 to determine the effect of outliers. To exclude the potential for the correlation to be driven by grey matter, these correlations were also included.

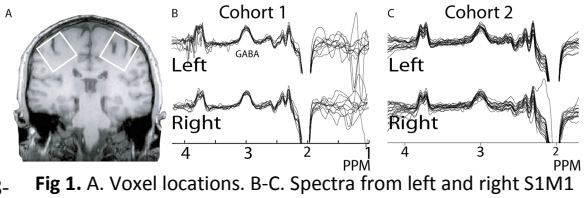

Fig 1. A. Voxel locations. B-C. Spectra from left and right S1M1

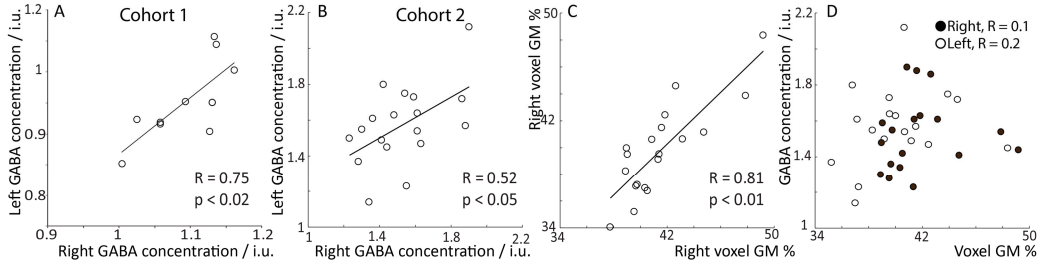

Fig 2. A-B. GABA correlates between hemispheres. C. Grey matter correlates between hemispheres. D. GABA is not correlated with % grey matter.

Results: Fig 1B shows spectra from Cohort 1 from both left and right sensorimotor cortex. Fig 1C shows this for Cohort 2. For Cohort 1, GABA concentration in left SIMI was significantly correlated with GABA concentration in right SIMI, as seen in Fig 2A ($r = 0.75$, $p < 0.02$). Jack-knife analysis produced a range of r values between 0.63 and 0.86, all of which were significant at $p < 0.05$. The mean fitting residuals between the two regions were similar (all fitting residuals < 15%, means left SIMI 5.3% ± 2.7; mean right SIMI 5.3% ± 1.3; $p > 0.9$), suggesting that the concentration difference was not due to differences in data quality between the two regions. For Cohort 2, GABA concentration in left SIMI was significantly correlated with GABA concentration in right SIMI, as seen in Fig 2B ($r = 0.52$, $p < 0.03$). The percentage of grey matter (GM%) in the two voxels was also highly correlated ($r = 0.81$, $p < 0.0001$, Fig 2C), however GM% was not correlated with GABA concentration in either the right or left side (Fig 2D), or across all data pooled ($R<0.23$ and $p > 0.37$ for all three tests).

Discussion: We showed a significant correlation in GABA concentration between the left and right S1M1, in two cohorts. Although voxel tissue composition is also highly correlated between sides, this does not explain significant variance in the GABA concentration or its bilateral correlation. This strongly supports the idea that individual differences in GABA reflect differences in tissue microstructure (e.g. density of GABAergic neurons) rather than bulk tissue properties. We show here that individual differences in GABA concentration, which have previously been described as functionally and regionally specific, are correlated between homologous sensorimotor regions. This correlation is not driven by bulk differences in voxel tissue composition. We believe that our results demonstrate that there are neurochemical 'signatures' of brain anatomy, potentially complementary to functional or structural measures.

References: 1. Puts et al, Prog. NMR Spectr. 2013; 2. Morishita et al., Physiol. Rep. 2014; 3. McGlone F et al. Behav Brain Res. 2002. 4. Edden et al. JMRI, 2013; 5. Zhang et al. IEEE Trans Med Imag. 2001.