# Precision and repeatability of in vivo GABA and glutamate quantification

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**Introduction:** As the primary excitatory and inhibitory neurotransmitters in the human brain, glutamate (Glu) and gamma-amino-butyric acid (GABA) are important for a variety of neurological and psychiatric disorders. GABA is also becoming the focus of increasing interest in functional neuroimaging, as resting in vivo GABA levels from MRS have been linked to changes in perfusion, peak gamma oscillation frequency, and blood oxygen level dependent (BOLD) fMRI signal during visual stimulation,[1,2] as well as the negative BOLD response in the default mode network.[3] However, robust spectroscopic quantitation of glutamate and GABA with MRS remains challenging due to the spectral overlap of these metabolites with each other and with glutamine (Gln). The reliable estimation of GABA is also hampered by the presence of a macromolecular resonance at 3 ppm, which can account for up to half the visible GABA peak.[4] The primary aim of this study was to estimate the within-session reproducibility of GABA and Glu concentrations derived using three different analysis methods, with a view to identifying the optimal analysis methodology for in vivo quantification of GABA and glutamate with MEGA-PRESS. A secondary aim was to investigate the reliability of GABA concentrations derived after subtraction of a metabolite nulled spectrum, in order to account for the macromolecular contributions to the GABA+ (GABA+MM) peak at 3 ppm.

**Methods:** The subject group consisted of thirteen healthy volunteers (5 female, mean age 29 years) with no history of neurological or psychiatric illness. MR imaging and spectroscopy studies were performed with a 3T GE HD.xt TwinSpeed MRI scanner (GE Medical Systems, Milwaukee, WI, USA), using an 8-channel receive-only head coil. Four consecutive resting single-voxel MEGA-edited[5] $^1$H MR PRESS spectra were acquired from a 2.5x3x4 cm$^3$ voxel of interest in the dorso-lateral prefrontal cortex (DLPFC) with TE/TR = 68/1800 ms and 320 averages (160 pairs). Additional metabolite nulled spectra were acquired from eight participants, using the same MEGA-PRESS acquisition with a pre-inversion pulse applied at TI=580 ms, (selected for optimal metabolite nulling on the basis of a series of pilot spectra acquired from one subject with different TI's and TE/TR = 68/1800 ms). Water-scaled metabolite concentrations were derived using LCModel[6] (with a simulated basis set[7]), the Amares algorithm in jMRUI[8,9] and with locally written peak fitting software in Matlab[1]. The intra-session reproducibility was quantified as the coefficient of variation of the GABA and Glx (Glu+Gln) concentrations derived for each analysis method. For the 8 participants with metabolite nulled spectra, the LCModel analysis was performed twice: firstly, with the raw MEGA-PRESS spectrum, and secondly with the MEGA-PRESS spectrum after prior subtraction of the corresponding metabolite nulled spectrum.

**Results:** The average GABA concentrations and CRLB reported by LCModel for the macromolecular-corrected and uncorrected spectra are given table 1, and the within-session reproducibility values for the GABA and Glx concentrations derived with LCModel, jMRUI, and matlab are given in table 2. The intra-session reproducibility was significantly higher for LCModel relative to the matlab peak-fitting method ($p<0.05$, paired t-test) and showed a trend towards improved reproducibility relative to jMRUI ($p=0.08$).

**Discussion:** The reproducibility of GABA concentrations derived with jMRUI and the matlab peak fitting method were comparable to that reported previously,[10] although LCModel provided the best intra-session reproducibility for both GABA and Glx. The CRLB values for the LCModel fit were higher for the metabolite nulled spectra than those derived from the raw, un-corrected MEGA-PRESS data and the sensitivity to GABA was lower (75% vs 100%). However, the accuracy of GABA quantification may be higher for the MM-corrected spectra despite the increase in uncertainty of the LCModel fit, as the uncorrected LCModel GABA values appear to overestimate the GABA concentrations, as described previously.[7] Further validation will be necessary to establish the accuracy of the GABA concentrations derived with and without metabolite nulling.

**Table 1**

| | raw | Metabolite nulled |
|---|---|---|
| avg. GABA (mean ±SD) | 2.0 ± 0.76 | 1.8 ± 0.98 |
| Average CRLB | 20% | 44% |
| sensitivity | 100% | 75% |

**Table 2**

| | Glx (%CV) | GABA (%CV) |
|---|---|---|
| LCModel | 6% | 7% |
| jMRUI | 18% | 9% |
| matlab | 9% | 12% |

**References:** [1]Muthukumaraswamy et al. *PNAS*, 106: 8357-61, [2]Donahue et al. *Neuroimage* 53:392-8, [3]Northoff et al. *Nat Neuroscience* 10:1515-17, [4]Kegeles et al. *Proc ISMRM* 2007:1391, [5]Edden & Barker *MRM* 58:1276-1282, [6]Provencher SW. *MRM* 30:672-679, [7]Dydak U et al. *Environ Health Perspect*. 2010 doi: 10.1289/ehp.1002192 [8]VanHamme et al. *JMR* 129:35-43 , [9]Naressi et al. *Comput Biol Med* 31:269-286, [10]Bogner et al. *Eur J Radiol* 73:526.531.