Quantification of Individual and Group Uncertainty of Gamma-aminobutyric Acid Concentration in Different Brain Regions Using Residual Bootstrap Analysis

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Purpose: Gamma-aminobutyric acid (GABA) is one of important inhibitory neurotransmitters, closely related to mental illness such as depression and schizophrenia. MEGA-PRESS, a spectral editing technique in MRS [1], is a non-invasive method for detecting GABA concentration *in vivo*. However, for individual measurements, due to the imperfect system performance, the variable voxel of interest (VOI) localization and natural variations between volunteers, conventional statistical method based on a group of large samples often fails to reach robust uncertainty estimation of the acquired data. Residual bootstrap is a model-based technique to resample fitting residual [2], which is useful for estimating the uncertainty of GABA detection from individual and group studies in different brain regions. In this study, data from volunteers was acquired using a robust prototype with MEGA-PRESS pulse sequence, and the residual bootstrap analysis was used to assess uncertainty in different regions, variability from repeated scans, and natural variation among different subjects.

Methods: Twelve healthy volunteers (7 females) with age ranging from 23 to 36 (females: mean age±SD = 25±4 yr.; males: mean age±SD= 27±5yr.) participated in the study, and each volunteer was scanned for at least two times with a time gap more than 1 week to test the individual measurement repeatability. The GABA concentration ($GABA_+$) in anterior cingulate cortex (ACC) and occipital cortex (OCC) of brain was detected using MEGA-PRESS pulse sequence without MM suppression. VOIs of spectroscopy were chosen as followed: (1) ACC with size of 20mm×30mm×40mm, and (2) OCC with size of 30mm×30mm×30mm. Fig.1 showed the VOI localizations in two regions. All MRS scans were conducted on a 3T MAGNETOM Verio (Siemens AG, Erlangen, Germany) equipped with 32-channel head coil. The spectra data were analyzed with Gannet package [3]. The $GABA_+$ signal of each measurement was fitted by five-parameter Gaussian model. Because of the unknown noise distribution, the fitting residual ε was calculated by $Y=Y_{fit}+\varepsilon$. The bootstrap samples were generated with random resampled residuals ε^*, which was represented by $Y^*=Y_{fit}+\varepsilon^*$. The bootstrap samples were refitted again and the area of new fitted Gaussian curve was calculated for $GABA_+$ quantification. After 1000 times resamples, the uncertainty of GABA measurement $\sigma(GABA_+)$ were estimated by bootstrap samples, and the estimated $GABA_+$ concentration $\overline{GABA_+}$ as the average from all bootstrap samples was calculated. Coefficient of Variation (CV) was also calculated as $CV=\sigma(GABA_+)/\overline{GABA_+}$. For Group study, the uncertainty of inter-subject described the reproducibility of GABA detection for two scans (J=2) in the same region among 12 (I=12) volunteers. The uncertainty of inter-subject was calculated with $\sigma(GABA_+)_{inter}=\sqrt{\frac{1}{I-1}\sum_{i=1}^{I}\left(\frac{1}{J}\sum_{j=1}^{J}GABA_{+ij}-\overline{GABA_+}\right)^2}$, where $GABA_{+ij}$ was measured from i th subject and j th scan, and $\overline{GABA_+}$ was the mean value of all subjects and scans in one region. For individual studies, the uncertainty intra-subject reflected the repeatability of two scans in two regions, which was calculated with $\sigma(GABA_+)_{intra}=\sqrt{\frac{1}{J-1}\sum_{i=1}^{I}\left(\frac{1}{J}\sum_{i=1}^{I}GABA_{+ij}-\overline{GABA_+}\right)^2}$.

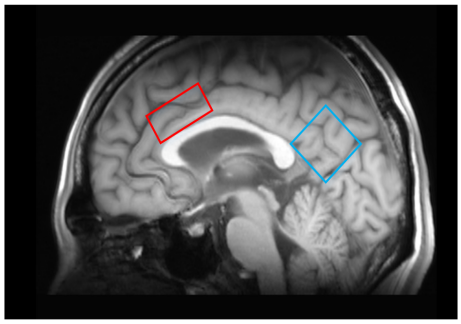

Fig.1 The VOI localizations in ACC (marked with red box) and OCC (marked with blue box)

Results and Discussion: Fig. 2 shows the $GABA_+$ of all volunteers with residual bootstrap analysis in OCC and ACC, and Tab. 1 is the statistical results of mean value, intra- and inter-subject uncertainty and CV in OCC and ACC. The uncertainty of each measurement in both OCC and ACC was robustly estimated by residual bootstrap analysis showed in Fig. 2. The mean value in OCC was higher than that in ACC, which represented higher $GABA_+$ concentration in VOI of OCC. The intra-subject uncertainty and CV of OCC was lower than ACC, which indicated a better repeatability. The inter-subject uncertainty and CV in OCC was much higher than in ACC, showed that the measurements in OCC had higher fluctuation than ACC. The CV of intra-subject was lower than of inter-subject, showed that $GABA_+$ had better repeatability in same subject, but had significant variation among subjects in these regions.

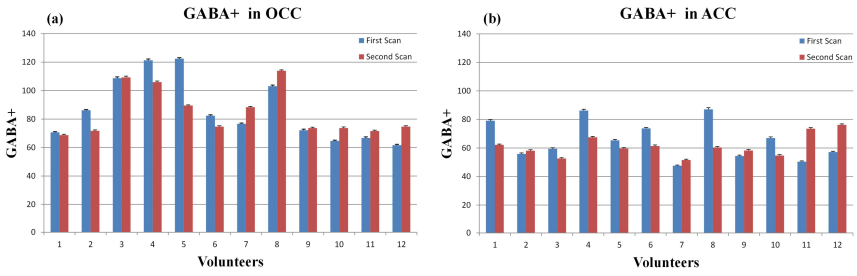

Fig.2 $GABA_+$ of all volunteers with residual bootstrap analysis in OCC (a) and ACC (b). Each volunteer had two scans

Conclusion: The Residual bootstrap analysis gave a robust uncertainty estimation of individual and group GABA detection in ACC and OCC. The results showed that, the $GABA_+$ in OCC had better repeatability for individual study, and in ACC had better reproducibility for group study. After residual bootstrap analysis, the robust intra-subject uncertainty estimation also showed better repeatability in same subject, and reflected the variation between different volunteers. The residual bootstrap method can also provide a robust data fitting optimization and uncertainty quantifications in metabolites detection of different brain regions.

Tab.1 Mean value, intra- and inter-subject uncertainty and CV in OCC and ACC

VOI	Intra-subject		Inter-subject		Mean
	Uncertainty	CV	Uncertainty	CV	
OCC	1.23	1.43%	18.16	21.24%	85.50
ACC	2.79	4.96%	8.06	12.73%	63.30

References: [1] Mescher M. et al, NMR Biomed. 1998, 11:266-272. [2] Chung S. et al, NeuroImage 33 (2006) 531–541 [3] Richard A.E. E. et al, JMRI. 2014, doi: 10.1002/jmri.24478