Quantification of Short-TE Metabolite Signals in Human Brain at 3T using QUEST Algorithm and a Simulated Basis Set

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***Abstract*—** In vivo short-echo time (TE) proton magnetic resonance spectroscopy (^{1}H-MRS) is a useful method for quantification of human brain metabolites. To evaluate the performance of QUEST (quantitation based on quantum estimation) method, a Monte Carlo study was done using the weighted sum signal. 8 of 10 metabolites had low Cramer-Rao Lower Bounds (CRLB), but Asp and GABA showed relatively high CRLBs because these two peaks have low-concentration, complex multiplets that severely overlap with other. In in vivo study, QUEST reliably quantified NAA, Cho, Cr (CRLB < 5%) and somewhat reliably quantified Glu, Glx, and Ins (CRLB = 10-20%) in the basal ganglia of healthy subjects at 3T. However, GABA, Asp, Gln, GSH and Tau could not be reliably quantified (CRLB > 30%) at 3T MRI scanner. Therefore, QUEST method is feasible for in vivo quantification of short-TE metabolite signals.

Keywords— MR Spectroscopy, Brain metabolite, Quantification, QUEST, Simulated Basis Set.

I. INTRODUCTION

In vivo localized proton single-voxel MR spectroscopy (^{1}H-MRS) is a non-invasive technique that provides information on brain metabolism and physiology, which may be used in diagnosing diseases and monitoring the therapeutic response. Recently, the implementation of short-echo time (TE) MR spectroscopy at 3T has shown that glutamate (Glu), γ-amino butyric acid (GABA), and glutamine (Gln) in the basal ganglia of the brain can be reliably measured with standard single-voxel ^{1}H-MRS, without resorting to editing schemes. However, despite the greatly improved spectral quality due to the reduction of *J*-coupling effects and reduced T_2 decay for the metabolites, short-TE spectra introduce specific problems in quantification due to strongly overlapping metabolite resonances and the presence of macromolecules and lipids.

For ^{1}H-MRS spectra quantification, the most frequently used programs are LCModel (linear combination of model spectra of metabolite solutions in vitro) [1] and QUEST (quantitation based on quantum estimation) [2] working in the frequency and time domain, respectively. These methods use advanced prior knowledge based on a metabolite basis set computed either by quantum mechanics (like in QUEST) or measured in vitro (like in LCModel).

In this study, we used QUEST method and a simulated basis set for in vivo quantification at 3T MRI scanner. To test the performance of QUEST, a Monte Carlo study was done using a simulated ^{1}H-MRS signal and Cramer-Rao Lower Bounds (CRLB) were calculated. We also investigated how many and which metabolites can be reliably quantified in human basal ganglia. In addition, T1 and T2 relaxation times were calculated.

Accurate measurement of proton T1 and T2 relaxation times of brain metabolites in vivo is required for reliable and reproducible determination of absolute metabolite concentration in brain tissue. In this work T1 and T2 values for several metabolites in all subjects were examined by a localized PRESS [3, 4] sequence experiment, respectively. The averaged T1 and T2 values for each metabolite were used for correction. The concentration of in vivo metabolites in the basal ganglia was calculated, and was expressed as a concentration in units of mM.

II. METHODOLOGY

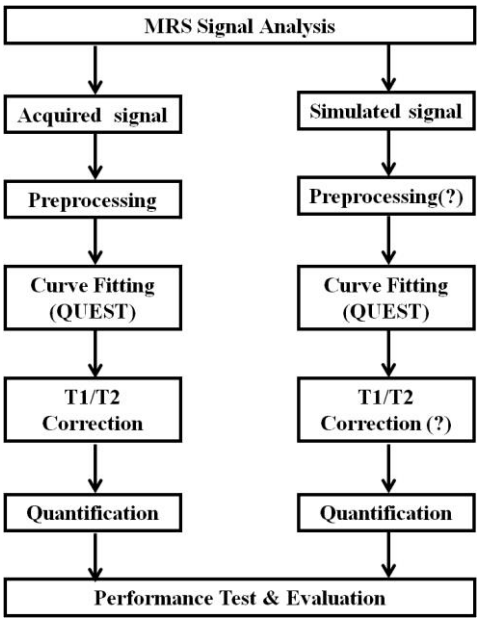

Fig. 1 Flowchart of the MRS data analysis

A. MRI System

10 healthy human subjects were examined with the same MRI/MRS protocol, which consisted of high-resolution imaging and proton single-voxel MR spectroscopy. The studies were performed on a 3.0T (Achieva 3.0 TX; Philips Medical System, the Netherlands) with the standard MRS acquisition software provided by manufacturer. A body coil was used for transmission and a dedicated 32-channel receiver-only array head coil was used for both MR imaging and MR spectroscopy.

B. MRS Data Acquisition

After the localizer scan, T_1-weighted sagittal, T2-weighted axial and coronal images were used for placing the volume of interest (VOI) in the subjects before MRS (Fig. 2). The voxel size was 2 × 3 × 2 cm^3 in basal ganglia region. For localization, spectra were obtained with a point-resolved spin-echo sequence (PRESS) [3, 4]. Shimming was performed automatically on the water resonance for optimization of the homogeneities in each VOI, and typically water peak linewidths of 4-8 Hz (full width at half-maximum; FWHM) were achieved on the subjects. After shimming procedure spectra were acquired with water suppression by applying three preceding chemical-shift-selective saturation (CHESS) pulses [5, 6], and the bandwidth of each CHESS pulse was 50 Hz. The following acquisition parameters were used: TR = 2500 ms, TE = 30 ms, 96 acquisitions, spectral width = 2000 Hz, and 1024 data points. A fully relaxed, unsuppressed spectrum (8 averages) was also acquired to measure the amplitude of the water peak in the localized volume as the internal reference.

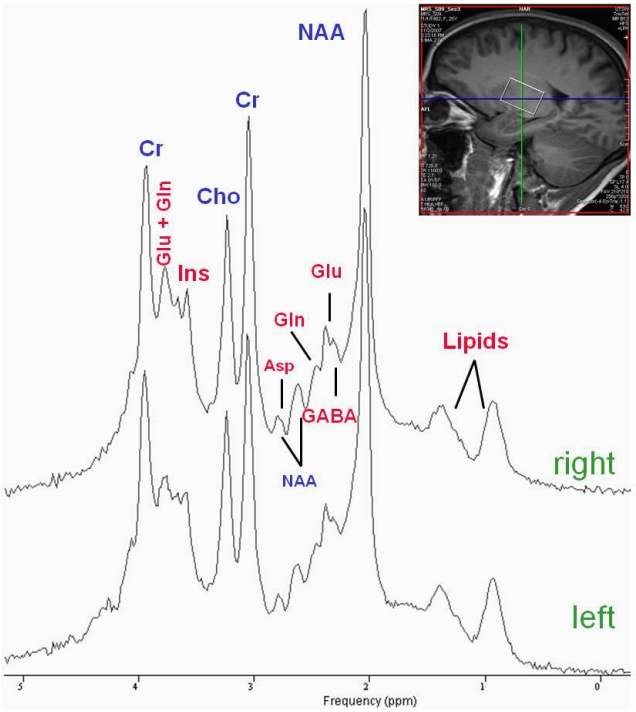

Fig. 2 Example of a short-TE MRS spectrum obtained from the basal ganglia region of human brain at 3T

C. Data Analysis: Preprocessing and Fitting

The jMRUI software package [7] provides a graphical user interface to perform time-domain analysis of in vivo MRS data. For the unsuppressed spectra, no line broadening was applied before Fourier transformation. Automatic phase corrections without baseline correction were applied and maximum peak of the water signal was assigned to 4.7 ppm. Peak integration was performed on processed spectra. In order to measure the in vivo brain metabolite peaks from the water-suppressed spectra, we performed a preprocessing that consisted of zero-filling of 2048 points, Gaussian apodization of 5Hz, Fourier transformation, and phase correction of the transformed spectrum. Removal of residual water components of the in vivo signal was performed in a preprocessing step using the Hankel-Lanczos singular value decomposition (HLSVD).

D. Data Analysis: Spectrum Curve Fitting

QUEST method [2], a quantitation tool for MRS data was employed to analyze the spectra obtained from the left and right basal ganglia at 3.0T (Fig. 3). QUEST, which is part of the jMRUI package, processes data in the time domain, and uses a prior knowledge based on metabolite basis set. In this study, 10 metabolite signals used in QUEST algorithm were quantum-mechanically simulated in NMR-SCOPE [8]: aspartate (Asp), choline (Cho), creatine (Cr), Glu, Gln, GABA, myo-inositol (Ins), N-acetylaspartate (NAA), glutathione (GSH), and taurine (Tau). The spine Hamiltonian parameters (number of spins, chemical shifts, J-couplings) were obtained from Govindaraju et al. [9]. Each simulated metabolite spectrum was analyzed by linear prediction singular value decomposition (LPSVD) [10], and one reference peak from the fitted metabolite spectrum was selected (usually the most prominent peak in the in vivo spectrum). These peaks included: 2.02 (NAA), 2.28 (GABA), 2.35 (Glu), 2.45 (Gln), 2.73 (Asp) 3.00 (Cr), 3.22 (Cho), 3.42 (Tau), and 3.56 ppm (Ins). Then, the prior knowledge was incorporated in the QUEST fitting routines to reduce the number of model parameters and thus to enhance the robustness and speed of the fit. QUEST offers only Lorentzian or Gaussian lineshapes for a given peak as the prior knowledge. In this study, a Lorentzian lineshape model was chosen for quantifying the in vivo brain metabolite peaks. The Cramer-Rao lower bound was used as a measure of fitting accuracy [11]. Uncertainty in the estimated metabolite concentration was the standard deviation (SD) of the metabolite signal amplitude as estimated using the CRLB. In the water unsuppressed spectra, water peak was fit at 4.7 ppm.

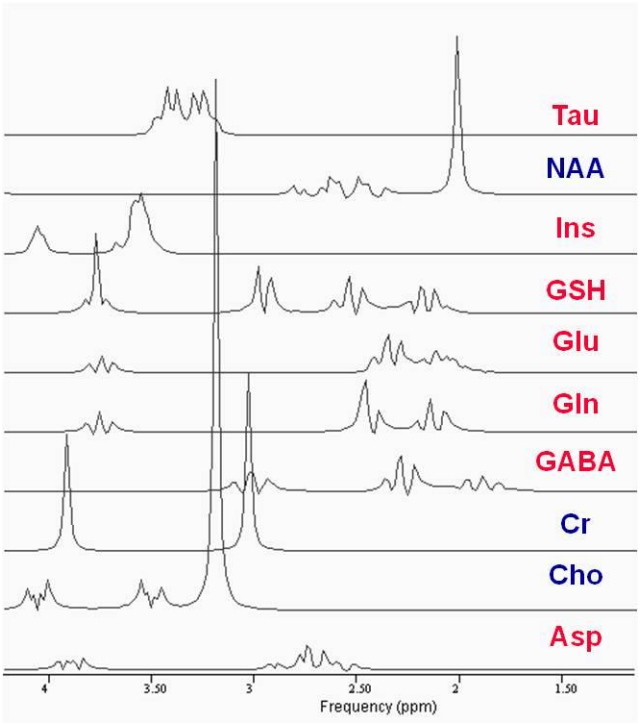

Fig. 3 Simulated metabolite signals by NMR-SCOPE

E. In Vivo Absolute Quantification

Absolute quantification of in vivo brain metabolite signals was acquired using the water peak as an internal reference. All acquisitions were recorded at maximum receiver gain, making corrections for different receiver settings unnecessary. Hence, the absolute metabolite concentration was calculated by the following equation [1]:

$$[C_i] = \frac{N_{H_2O}}{N_i} \times \frac{S_i}{S_{H_2O}} \times \frac{\left(f_{T_1} \bullet f_{T_2}\right)_{H_2O}}{\left(f_{T_1} \bullet f_{T_2}\right)_i} \times C_{H_2O} \quad [1]$$

where C_i is the concentration of the metabolite (mM), S_i is the amplitude of the metabolite and S_{H2O} is the signal amplitude of unsuppressed water in the localized spectrum. The terms N_i and N_{H2O} represent the number of ^{1}H nuclei contributing to the resonance of metabolites i (i = NAA, Cr, Cho, etc.) and water. The parameters f_{T1} and f_{T2} are the correction factors for T_1 and T_2 relaxation times, respectively:

$$f_{T_1} = 1 - \exp(-TR/T_1) \quad [2],$$

$$f_{T_2} = \exp(-TE/T_2) \quad [3]$$

For the estimation of T_1 and T_2 relaxation times, we measured the values of T_1 for several metabolites (e.g., NAA, Cr, and Cho) in all patients by performing a localized PRESS experiment at a fixed TE value (60 ms) and using five values of TR (800 – 4500 ms). We also measured the value of T_2 using five TE values (60 – 400 ms) at a fixed TR value (2500 ms). The values of T_1 and T_2 were obtained by fitting the data to a mono-exponential model as a function of TR and TE, respectively. Other metabolite signals were corrected for T_1 and T_2 effects according to the average of values reported in the literature [12-15]. For Glu, T_1 = 1220 ms and T_2 = 199 ms; and for Ins, T_1 = 1101 ms. For Gln and Ins at 3T, we assumed T_2 values similar to Glu for relaxation correction. For water signal, T_1 relaxation times was 1100 ms [14]; T_2 relaxation times was 80 ms [16]. We assume that the molar proton concentration of water (C_{H2O}) in the basal ganglia is ≈ 45 M. After the T_1 and T_2 corrections were made, the concentration of in vivo brain metabolites was calculated with Eq. [1], and was expressed as a concentration in units of mM.

III. PERFORMNCE TEST AND RESULTS

A. Monte Carlo Study

In the Monte Carlo study, each signal was weighted according to the published in vivo concentration values for normal adult brain (Fig. 4), and the weighted sum signal was used to test the performance of QUEST method (Fig. 5). Fig. 6 shows the quantification results of Monte Carlo study. All the metabolites were clearly identified using a metabolite basis set, and the estimated mean values were very close to the true values. The CRLBs for QUEST spectral fits were less than 5% for the most of the metabolites: NAA, Cho, Cr, Glu, Gln, GSH, Ins, and Tau. Metabolites such as Asp and GABA showed relatively high CRLBs (> 10%).

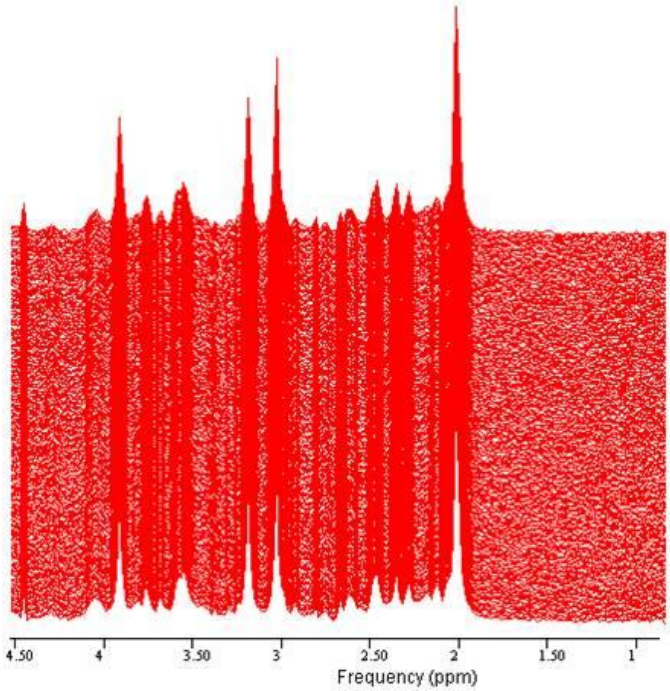

Fig. 4 Each set of 256 signals of each Monte Carlo study

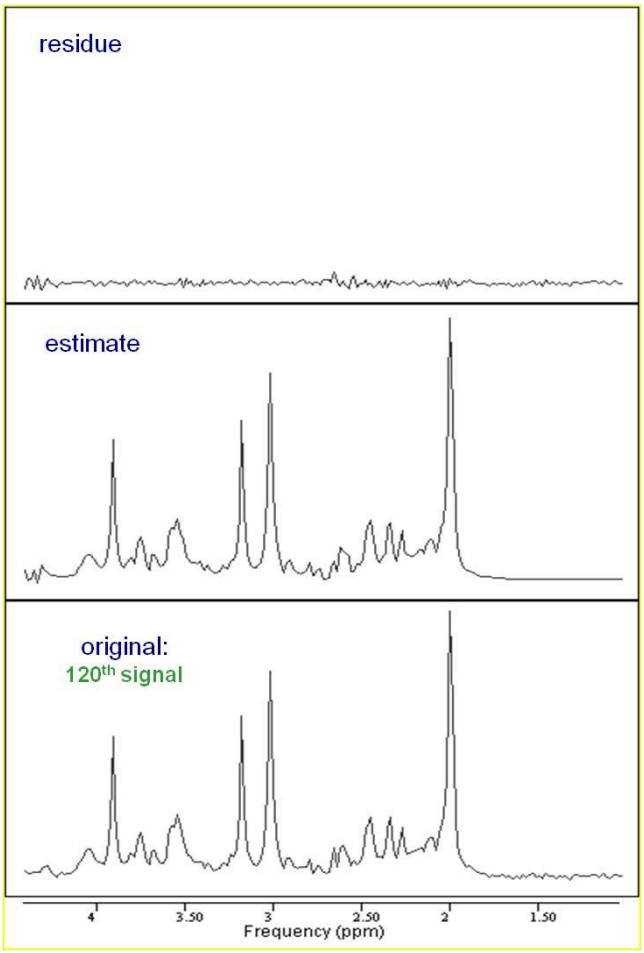

Fig. 5 Example of the QUEST using a simulated basis set

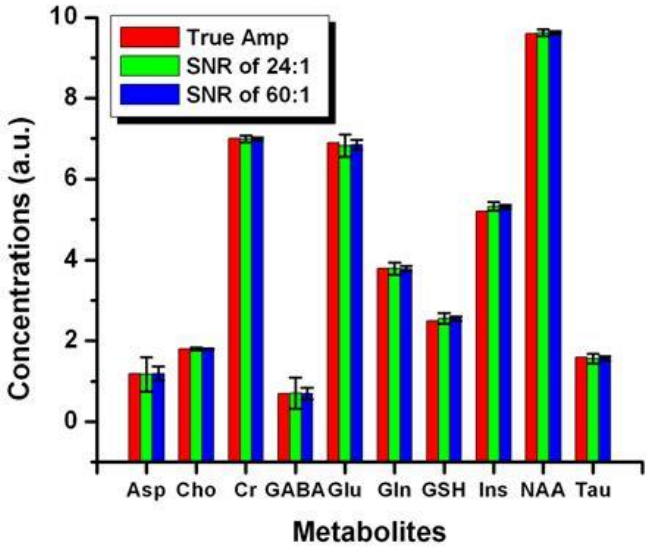

Fig. 6 Quantification results of Monte Carlo studies

B. T1 and T2 values

The spectroscopic voxel (8 ml) centered on the volume of interested region in basal ganglia (e.g., putamen, globus palidus) was carefully positioned using T1- and T2-weighted images in three orthogonal planes (Fig. 2). To calculate the absolute metabolite concentration, the present study measured the relaxation values in all subjects. Spectra were obtained at TEs of 60, 90, 135, 195, and 270ms using a fixed TR of 2.5 s. The averaged T2 relaxation times (mean ± SD) were NAA = 269 ± 61 ms, Cho = 269 ± 61 ms and Cr = 97 ± 10 ms from the ten subjects by fitting the data to a mono-exponential model (the value of r^2 > 0.99), respectively. Spectra were obtained using values of TR of 0.8, 1, 1.5, 2.5, and 4 s, respectively, at the same value of TE (60 ms). The averaged T1 relaxation times for NAA, Cho, and Cr were 1513 ± 156 ms, 1513 ± 156 ms, and 746 ± 118 ms, respectively. The T1 and T2 values of metabolites in this work are reasonably consistent with a brain tissue literature values [12-16].

C. In Vivo Quantification of Brain Metabolites

Fig. 7 shows the spectral fitting of an in vivo measurement on the healthy human basal ganglia. The subtract-QUEST method involves the metabolite basis set in the estimation of the background. In vivo absolute quantification results of QUEST using the simulated metabolite basis set are shown in Fig. 8. The measured metabolite concentrations gave estimated mean values very close to the reported values for human brain in the literature [4]. In Fig. 9, QUEST reliably quantified NAA, Cho, Cr (CRLB < 5%) and somewhat reliably quantified Glu, Glx, and Ins (CRLB = 10 ~ 20%) in the basal ganglia of healthy subject at 3T. however, GABA, Asp, Gln, GSH, and Tau could not be reliably quantified (CRLB > 30%). There were no statistically significant differences in metabolic concentrations between left and right sides.

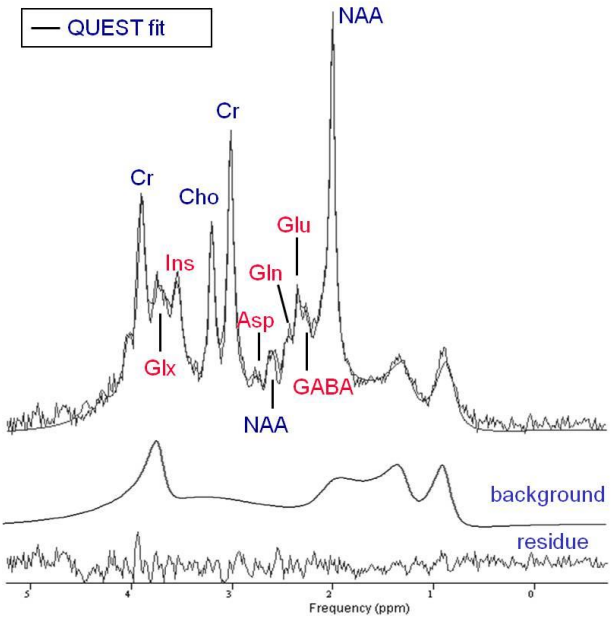

Fig. 7 In vivo QUEST quantitation result with estimation of the background at 3T

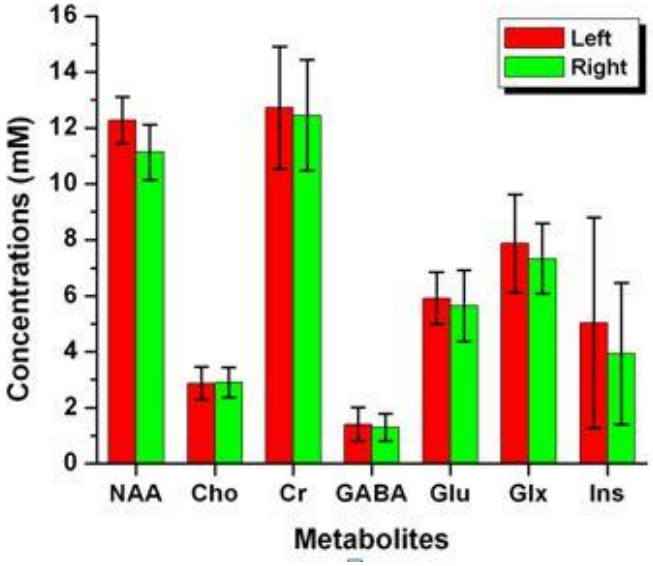

Fig. 8 Metabolite concentration estimates using a simulated basis set (left and right basal ganglia)

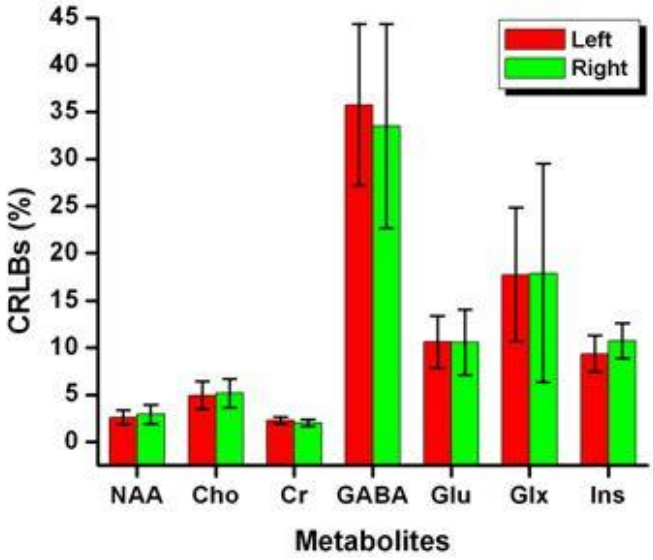

Fig. 9 CRLBs estimates of the metabolite signals

IV. CONCLUSION

In Monte Carlo studies, 8 of 10 metabolites had low CRLBs, but Asp and GABA showed relatively high CRLBs because these two peaks have low-concentration, complex multiplets that severely overlap with other, which make their quantification difficult. In in vivo study, QUEST reliably quantified 5 of 10 metabolites in the basal ganglia of healthy subjects at 3T. However, GABA, Asp, Gln, GSH and Tau could not be reliably quantified. So, to detect these small metabolites, one of solutions is to use spectral editing or a based on direct measurement of the metabolite-nulled background signal. QUEST method is feasible for in vivo quantification of short-TE metabolite signals, but the background estimation using QUEST depends on the chosen number of truncated data-points. Therefore, an automatic and robust way to select the number of truncated data-points is needed for background modeling.

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