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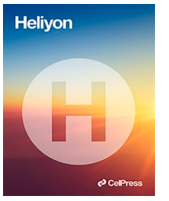

GABA, glutamate and excitatory-inhibitory ratios measured using short-TE STEAM MRS at 7-Tesla: Effects of macromolecule basis sets and baseline parameters

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ABSTRACT

Rationale and objectives: Macromolecules (MMs) affect the precision and accuracy of neurochemical quantification in magnetic resonance spectroscopy. A measured MM basis is increasingly used in LCModel analysis combined with a spline baseline, whose stiffness is controlled by a parameter named DKNTMN. The effects of measured MM basis and DKNTMN were investigated.
Materials and methods: Twenty-six healthy subjects were prospectively enrolled and scanned twice using a short echo-time Stimulated Echo Acquisition Mode (STEAM) at 7-T. Using LCModel, analyses were conducted using the simulated MM basis (MMsim) with DKNTMN 0.15 and an MM basis measured inhouse (MMmeas) with DKNTMN of 0.15, 0.30, 0.60 and 1.00. Cramér-Rao lower bound (CRLB) and the concentrations of gamma-aminobutyric acid (GABA), glutamate and excitatory-inhibitory ratio (EIR), in addition to MMs were statistically analyzed. Measurement stability was evaluated using coefficient of variation (CV).
Results: CRLBs of GABA were significantly lower when using MMsim than MMmeas; those of glutamate were 2–3. GABA concentrations were significantly higher in the analysis using MMsim than MMmeas where concentrations were significantly higher with DKNTMN of 0.15 or 0.30 than 0.60 or 1.00. Difference in glutamate concentration was not significant. EIRs showed the same difference as in GABA depending on the DKNTMN values. CVs between test-retest scans were relatively stable for glutamate but became larger as DKNTMN increased for GABA and EIR.
Conclusion: Neurochemical quantification depends on the parameters of the basis sets used for fitting. Analysis using MMmeas with DKNTMN of 0.30 conformed best to previous studies and is recommended.

1. Introduction

Gamma-aminobutyric acid (GABA) and glutamate (Glu) are representative inhibitory and excitatory neurotransmitters,

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respectively. The excitatory-inhibitory ratio (EIR) is widely used to investigate brain pathophysiology [1–3]. Proton magnetic resonance spectroscopy (MRS) at 7-T (7T) is advantageous over lower magnetic fields because the signal-to-noise ratio (SNR) increases and higher spectral resolution contributes to the detection of neurochemicals in low concentrations [4,5]. At 3-T (3T), spectral editing, such as MEcher-GArwood (MEGA)-point resolved spectroscopy (PRESS) [6], is frequently used; however, unedited measurements using short echo-time (TE) sequences have also been conducted.

Many short-TE MRS are used to measure GABA and other neurochemicals without spectral editing at 7T [7,8], such as semi-adiabatic localization by adiabatic selective refocusing (sLASER) [5,9], stimulated echo acquisition mode (STEAM) [1,4,10,11] and spin echo full intensity acquired localized (SPECIAL) [12,13] sequences with improved precision at 7T compared with 3T indicated by a reduced Cramér-Rao lower bound (CRLB), which represents the noise level [14]. However, the broad underlying signal of macromolecules (MMs) affects the precision and accuracy of quantitation, and their effects are more pronounced in short-TE MRS acquisitions, because the T2 relaxation time of MMs is very short.

MMs are simulated (MMsim) in the default LCModel analysis. MMsim consists of MMs at 0.9, 1.2, 1.4, 1.7, and 2.0 ppm, where MM at the 2.0 ppm peak consists of MMs at 1.95, 2.08, 2.25, and 3.00 ppm. However, many recent studies have found more MM peaks, and the use of measured MMs (MMmeas) is increasing [15–17]. In addition, many other factors, such as artifacts, substances that are not present in the basis set, inaccuracies in the simulated basis set, and incomplete water suppression, affect quantitation [17]. The LCModel analysis uses a polynomial spline baseline to fit and remove spectrum perturbations caused by these factors. Its stiffness is controlled by a parameter called DKNTMN, which sets up the spacing between the spline knots. The default value is 0.15, but it allows high flexibility and may result in overfitting and an inadequate estimation of neurochemical concentration [16]. Studies on the effect of different DKNTMN values combined with measured MMs, especially for a short-TE MRS, are still limited. When influence of measured macromolecules and spline baseline (DKNTMN 0.15–1.00) in LCModel analysis was investigated for semi-LASER at 9.4T, differences of above 15% in the neurochemical levels were observed for several metabolites [18], and investigation for the adequate analysis parameters that gives comparable neurochemical levels with other studies is required for the short-TE STEAM scans. This study investigated the effects of the macromolecular basis sets and DKNTMN parameters on the analysis of GABA, Glu and EIR measured using a short-TE STEAM sequence at 7T to find results consistent with those of prior studies using concentration relative to that of total creatine (tCr).

2. Results

Data from all the participants were used for the analysis. The mean (standard deviation; SD) of CRLB ranged from 9.23 (1.14) to 15.81 (4.41) for GABA among the different analyses. The values analyzed using MMsim were significantly lower than those using

Table 1
Measurement results of GABA, Glu and EIR.

	MM basis	DKNTMN	CRLB		Concentration normalized by tCr		
			1st scan*[1]	2nd scan*[1]	1st scan*[1]	2nd scan*[1]	CV (%)
GABA	MMsim	0.15	9.23 (1.14)	9.69 (1.69)	0.23 (0.02)	0.23 (0.02)	4.70
	MMmeas	0.15	11.62 (1.47)	11.88 (2.20)	0.17 (0.03)	0.18 (0.03)	9.64
		0.30	11.73 (1.46)	12.00 (2.76)	0.17 (0.02)	0.18 (0.04)	12.71
		0.60	14.12 (2.21)	15.38 (4.52)	0.13 (0.02)	0.13 (0.04)	14.69
		1.00	14.62 (3.02)	15.81 (4.41)	0.12 (0.03)	0.13 (0.04)	12.56
	Ref. [9]				0.18[#]		
	Ref. [19]				0.19[#]		22.2
			1st scan	**2nd scan**	**1st scan*[2]**	**2nd scan*[2]**	**CV (%)**
Glu	MMsim	0.15	2.00 (0.00)	2.23 (0.43)	1.28 (0.07)	1.29 (0.07)	2.10
	MMmeas	0.15	2.00 (0.00)	2.08 (0.27)	1.27 (0.08)	1.28 (0.08)	2.10
		0.30	2.00 (0.00)	2.04 (0.20)	1.27 (0.07)	1.30 (0.07)	2.51
		0.60	2.00 (0.00)	2.08 (0.27)	1.17 (0.07)	1.18 (0.08)	2.81
		1.00	2.00 (0.00)	2.08 (0.27)	1.15 (0.08)	1.15 (0.07)	2.57
	Ref. [19]				1.23[$]		3.1
					1st scan*[1]	**2nd scan*[1]**	**CV (%)**
EIR	MMsim	0.15	n.a.		5.52 (0.38)	5.55 (0.49)	3.55
	MMmeas	0.15			7.40 (0.90)	7.23 (1.23)	8.16
		0.30			7.64 (0.78)	7.44 (1.64)	11.00
		0.60			9.22 (1.14)	9.49 (2.66)	13.08
		1.00			9.51 (1.49)	9.80 (2.51)	11.14
	Ref. [19]				6.38[#]		

The values in CRLB and concentration columns are mean (SD). Concentrations of GABA and Glu were normalized with that of total creatine (tCr). CRLB Cramér-Rao lower bound, CV coefficient of variation, EIR excitatory-inhibitory ratio, GABA γ-aminobutyric acid, Glu glutamate, MM macromolecule. *[1]Differenecs were statistically significant ($P < 0.001$) for all combinations except for those between MMmeas with DKNTMN = 0.15 and 0.30, and between MMmeas with DKNTMN = 0.60 and 1.00. *[2]Differeces were statistically significant ($P < 0.001$) for all combinations except for those among MMsim and MMmeas with DKNTMN = 0.15 and 0.30. [#]After subtraction of presumed MM signal and correction for T2 signal decay. [$]After correction for T2 signal decay.

MMmeas with any DKNTMN value in both the test and retest scans. Among the MMmeas, analyses using DKNTMN 0.15 or 0.30 showed significantly lower CRLB than that of 0.60 or 1.00. The CRLB values of Glu were mostly 2 but were 3 in a few cases in the 2nd scans. No significant difference in CRLB values was found in the first scan session, but the difference was significant in the 2nd scans when MMsim was used. See Table 1 for details including the results presented below and Fig. 2 for a representative case.

The mean (SD) of GABA concentration normalized by tCr ranged from 0.12 (0.03) to 0.23 (0.02). The concentration was significantly higher when MMsim was used compared to the others. Using MMmeas, GABA/tCr were significantly higher in the analyses with DKNTMN values of 0.15 or 0.30 than those of 0.60 or 1.00 in both the test and retest scans. The Glu/tCr values were 1.15 (0.07) −1.30 (0.07), with similar tendencies to GABA/tCr, but significant differences were observed with DKNTMN of 0.60 or 1.00 compared to the other three analysis conditions. EIRs were shown to be significantly different between DKNTMN of 0.15 or 0.30 and DKNTMN of 0.60 or 1.00, similar to the normalized concentration pattern of GABA.

The measurement stability between the test-retest scans indicated by the mean CVs ranged from 4.70% to 14.69% for GABA/tCr, 2.10%–2.81% for Glu/tCr, and 3.55%–13.08% for EIR. The CVs of GABA were significantly lower when analyzed with MMsim than with MMmeas, but no significant difference was found among the four DKNTMN conditions where MMmeas was used. This was the same for the CVs of the EIR. No significant difference in CVs was observed for Glu.

In the fitting results of MMmeas, the mean (SD) values of the CRLB were reasonably low, ranging from 2.50 (0.13) to 3.19 (0.08). The concentration values (in an arbitrary unit) ranging from 5.54 (0.12) to 4.87 (0.12) with significant ($P < 0.001$) trends to decrease with the increase of DKNTMN for both 1st and 2nd scans. No significant trend was observed for the CVs (See Table 2).

3. Discussion

This study investigated the effects of a measured MM basis and DKNTMN parameter compared with the default LCModel analysis (MMsim basis and DKNTMN = 0.15) for short-TE STEAM spectra. The measured concentrations of GABA were largely decreased by applying MMmeas and increasing DKNTMN values, although those of Glu were relatively stable. The concentration of GABA was much smaller than that of Glu, and the difference in the concentration estimated by different DKNTMN values was observed more in GABA. The spline spacing parameter, DKNTMN in LCModel controls the fitting flexibility for the baseline, which consists of smoothly varying components and spurious signals arising through imperfections during data acquisition [20]. The flexibility of baseline fitting may result in the over- or under-estimation of neurochemicals [18].

When PubMed search for "DKNTMN" in all fields, only one paper was found [21], but, when "MR spectroscopy spline baseline" was searched, 18 articles were found as of June 2, 2023. Among them, 10 studies explicitly described the DKNTMN that is the minimum spacing of the knots in ppm or equivalent values. Many of the studies investigated and compared different DKNTMN values, but they were equal to or below 1.00 [18,22–28], and two papers compared those of 0.15 and 5.00 [16,29]. No substantial change was observed in the stiffness of the spline baseline for DKNTMN values higher than 1 [18], and we investigated in the range of 0.15 to 1.00.

The CRLB of GABA was significantly lower using MMsim than using MMmeas, even when the same DKNTMN of 0.15 was used. CRLB is the estimated standard deviation expressed as a percentage of the estimated concentration. In default MMsim, one of the peaks was simulated at 2.25 ppm, which is close to that of GABA at 2.3 ppm. However, the peak height of MMsim is relatively flexible compared to the MMmeas, and this difference is considered to be one of the reasons for the lower CRLB of GABA using MMsim than MMmeas. The CRLB values of Glu ranged from 2 to 3, and the effects of the MM basis set and DKNTMN values were small.

The measured GABA/tCr was significantly higher using MMsim than MMmeas, and some effects of residual MMs were considered. GABA/tCr gradually decreased with increasing DKNTMN values, but what was the best DKNTMN parameter? It is difficult to answer this question because there is no absolute reference standard for GABA (/tCr) *in vivo*. A previous investigation of GABA/tCr values provided some insight. Hong et al. [9] measured GABA using a simultaneous interleaved acquisition of sLASER and MEGA-sLASER at the PCC to minimize the differential effect of extraneous factors at 7T. They conducted an LCModel analysis using the default setup for sLASER and fitting of one singlet peak model of GABA + at 3 ppm for the MEGA-sLASER spectrum edited at 1.9 and 7.5 ppm. The GABA/tCr and GABA+/tCr values were 0.26 and 0.27, respectively, after T2 decay correction for TE from 80 ms (MEGA-sLASER) to 38 ms (sLASER). These measured results are almost the same, and they are similar to our results using the default LCModel analysis with MMsim.

When editing was conducted at 1.5 and 1.9 ppm to delete undesirable MM contribution at 3.0 ppm that is J-coupled to MM at 1.7

Table 2
Measurement results of MMmeas.

DKNTMN	CRLB		Concentration (A.U.)		
	1st scan	2nd scan	1st scan*2	2nd scan*2	CV (%)
0.15	3.00*1 (0.10)	3.19*1 (0.08)	5.53 (0.09)	5.54 (0.12)	4.81 (0.77)
0.30	2.50*1 (0.13)	2.54*1 (0.10)	5.53 (0.12)	5.53 (0.12)	6.38 (0.99)
0.60	2.77 (0.10)	2.92 (0.08)	5.15 (0.11)	5.11 (0.11)	4.96 (0.81)
1.00	2.81 (0.08)	2.96 (0.04)	4.93 (0.11)	4.87 (0.12)	5.30 (0.76)

The values in CRLB and concentration columns are mean (SD). Concentration values are presented in arbitrary unit (A.U.). CRLB Cramér-Rao lower bound, CV coefficient of variation. *1Differences were statistically significant ($P = 0.016$) between DKNTMN = 0.15 and 0.30. *2Differences were statistically significant ($P < 0.001$) for all combinations except for that between DKNTMN = 0.15 and 0.30. There was a significant linear trend ($P < 0.001$) to decrease in MM concentration with the increase of DKNTMN in both 1st and 2nd scans.

ppm [30], GABA concentration was reduced to 53.5% at the anterior cingulate cortex [31]. When this reduction rate is applied, the abovementioned GABA+/tCr concentration at PCC will decrease from 0.26–0.27 [9] to 0.14 for GABA/tCr, but correction for T2 signal decay is also required because the sLASER used a TE of 38 ms, whereas our study used a very short TE of 5 ms. The T2 values of tCr and GABA measured at PCC using 7T were 121 and 63 ms, respectively [32]. The GABA/tCr of the former study increases from 0.14 to 0.18 after T2 decay correction. When van de Bank et al. [19] conducted a multi-center 7T-MRS study at PCC using sLASER (TE = 30 ms) and analyzed the spectra with LCModel including their measured MM basis, the mean ratio of GABA over tCr at PCC was 0.16, which increases to 0.19 after T2 decay correction to a TE of 5 ms. The GABA/tCr values of our study fitted with DKNTMN of 0.15 and 0.30 were 0.17–0.18, and these values are almost the same as those obtained in previous studies.

Glu/tCr tended to decrease with an increase in DKNTMN, but the changes were smaller compared to GABA/tCr in our study. The mean ratio of Glu to tCr at the PCC was 1.16 in the abovementioned multi-center study [19]. The T2 relaxation time of Glu is 93 ms at the occipital cortex at 7T [33], and this value is 1.23 for a TE of 5 ms. When Oeltzschner et al. measured 17 healthy aged participants at PCC using 7T STEAM (TE = 15 ms) with default LCM analysis, the mean Glu/tCr was 1.292 [34]. The nearest Glu/tCr value in our study (1st scan: 1.27) was obtained when analyzed with MMmeas using DKNTMN of 0.15 and 0.30. This Glu/tCr ratio was nearly equal to that when MMsim was used (1st scan: 1.28). Glu has a large peak at 2.35 ppm; there was no substantially overlapping MM peak; different DKNTMN values caused little over- or underestimation of Glu. The Glu/tCr were 1.18 and 1.15 when DKNTMN values of 0.60 and 1.00, respectively, were used, suggesting underestimation caused by these parameters.

The EIRs in our study were the lowest when the spectra were analyzed using MMsim, and they increased by using MMmeas with an increase in DKNTMN, except for DKNTMN of 1.00. EIRs are mainly affected by GABA concentration. The mean EIR measured at the PCC in the multi-center study was 7.23 [19], which increased to 8.2 after T2 signal decay correction. The nearest EIR in this study (7.64) was obtained in the LCModel analysis using DKNTMN 0.30 with MMmeas. From the viewpoint of consistency with the former multi-center study that used 7T at PCC, this combination is considered most appropriate, as were the results of GABA/tCr and Glu/tCr, although DKNTMN 0.15 might be acceptable.

The measurement CVs of GABA and Glu concentrations were 22.2% and 3.1%, respectively, in a multi-center study using sLASER [19]. Those of a STEAM sequence at PCC using 7T were 10.7% and 3.2% when the MM signals were suppressed by a nonselective inversion pulse [35]. The CVs of GABA/tCr and Glu/tCr in this study were 4.70–14.69% and 2.10−2.81%, respectively. They increased almost synchronously with the increase in DKNTMN but remained within the range of previous studies. The measurement reliability of this study was comparable to that of previous studies.

A short-TE STEAM sequence was used in this study at 7T. Short-TE acquisition is advantageous, considering the relatively short T2 value of GABA at 7T. It is also advantageous for peaks with *J*-coupling, including GABA, because the signal modulation by *J*-coupling, which results in signal reduction, is reduced. Recently, the *J*-refocusing method has been proposed and long-TE sequences can reduce this effect; however, the signal is affected by T2-dependent signal decay [36]. The effect of T2 decay on the EIR can be minimized using the short-TE STEAM sequence.

This study has some limitations. First, measurements were conducted only at the PCC because no significant regional difference in the MM components was reported [13]. Second, the mean age of the participants were 26, and the highest age was 47 years old in this study. Altered macromolecular patterns have been reported in older participants, but the number of participants was relatively limited [15]. A recent investigation of 102 healthy participants (20–69 years old) found that the macromolecular MR spectrum did not change with healthy aging [37]. Based on these considerations, the results of this study is considered be applicable to healthy elderly participants. Third, comparison of concentration was conducted based on creatine ratios. This was because the absolute quantitation is affected by scanners, sequences, parameters and so on. Therefore, concentration of GABA and Glu were normalized as ratios using that of creatine.

In conclusion, LCModel analysis using MMmeas and DKNTMN value of 0.30 was found to yield the most concordant amount of GABA, Glu and EIR with comparable measurement CVs to the previous studies after correction for T2 signal decay. This proposed analysis condition will contribute to comparison with other studies and is recommended for the future analysis using the short-TE STEAM spectra.

4. Materials and Methods

4.1. Participants

Twenty-six healthy participants (15 males and 11 females, mean age 26 years, aged 20–47 years) with no known history of head trauma, neuropsychiatric disorders or substance abuse were recruited through local advertisement and enrolled in this study. Written informed consent was obtained from all participants with the approval of the Institutional Review Board (Y1143-1), in accordance with the provisions of the Declaration of Helsinki.

4.2. MR acquisition

Scans were conducted using a 7T whole-body scanner (MAGNETOM 7T, Siemens Healthineers, Erlangen, Germany) and a single-channel transmit volume and 32-channel receiver head coil (Nova Medical, MA, USA). Three-dimensional (3D) T1-weighted images were acquired using gradient echo (TR/TE, 4.5/2.05 ms; flip angle [FA], 16°) or magnetization-prepared rapid gradient-echo (TR/TE/TI, 2300/August 2, 1050 ms; FA, 6°) sequences in 0.8-mm isotropic spatial resolution. Proton MR spectra were acquired using a short-TE STEAM sequence (TR/TM/TE, 8000/45/5 ms; spectral width, 6 kHz; data points, 2048; Siemens prototype sequence) for 32

averaging (scan time, 4 min 48 s) with water suppression using variable pulse power and optimized relaxation delays technique and outer volume suppressions to improve the localization performance [11]. The water spectra were also acquired. A MRS voxel of 20 × 20 × 20 mm^3 was positioned at the posterior cingulate cortex (PCC) across the midsagittal plane on the T1-weighted images. Shimming was conducted using the Fast, Automatic Shim Technique using Echo-planar Signal readouT for Mapping Along Projections, (FASTESTMAP, Siemens prototype sequence). The radiofrequency (RF) pulse transmit power was calculated using a mid-sagittal B1map acquired by Saturation Prepared with 2 RApid Gradient Echoes (SA2RAGE, Siemens prototype sequence). The participants were examined twice with off-magnet intermissions for around 5 min to evaluate test-retest stability.

4.3. Spectrum analysis

Analysis was conducted using LCModel version 6.3-1L, which uses a priori knowledge of the spectral components to fit neurochemical resonances using the standard STEAM basis-set. Additionally, an in-house MM basis set was created using a method similar to that used in a previous study [13]. Briefly, 17 healthy young participants (9 males, aged 20–30 years) were scanned using the above-mentioned sequence and parameters with an inversion pulse (TI = 950 ms and 128 averaging; other parameters were the same as above) to suppress long T1 neurochemicals [12] and measure short T1 MM [38]. Residual neurochemical peaks were fitted using a pseudo-Voigt function and removed. The averaged MM spectrum and baseline were incorporated to create a MMmeas (Fig. 1). Spectrum analyses were conducted using MMmeas with DKNTMN values of 0.15 (default), 0.30, 0.60, and 1.00 [18], in addition to the default LCModel setup (MMsim + DKNTMN = 0.15). The spectral range of the analysis was 0.2–4.0 ppm. Eddy current correction and water scaling for quantification were performed using the water spectra. Concentrations of GABA and Glu were normalized to those of tCr.

4.4. Statistical analysis

The repeatability of concentration measurements was evaluated using intrasubject coefficients of variation (CVs) derived from the standard deviation (SD) of the two measurements divided by their mean. The means of the CRLBs, concentrations, and test-retest CVs were calculated. Differences were evaluated among different LCModel parameters using repeated measures ANOVA. A P value < 0.05 was considered significant after *post-hoc* test. Analyses were conducted using MedCalc version 20.112 (MedCalc Software Ltd, Ostend, Belgium).

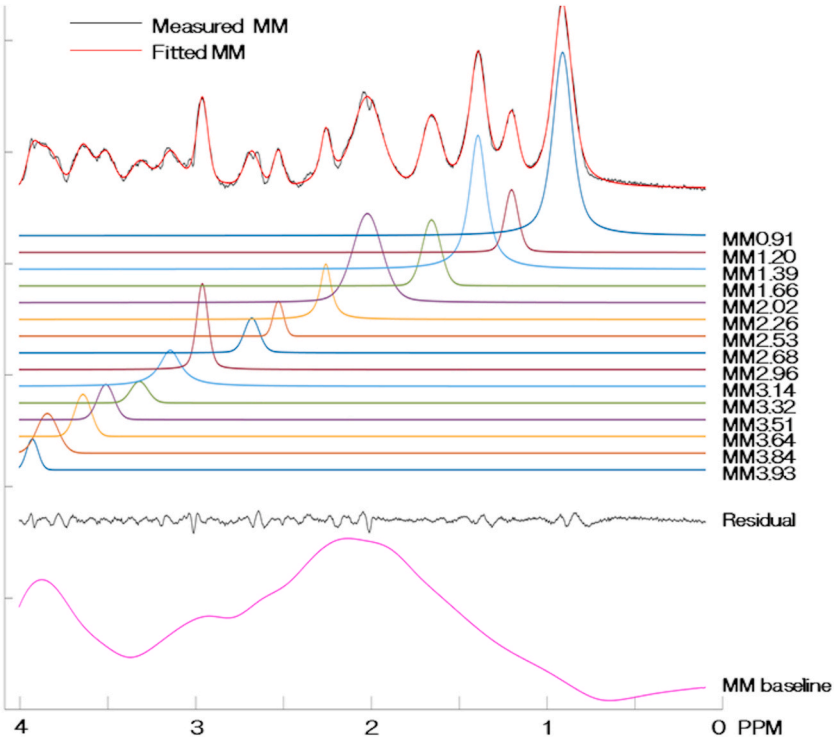

Fig. 1. The measured MM spectrum (black) and fitted MM basis (red) of 17 young normal participants used in this study. The 15 MM peaks fitted were centered at 0.91, 1.20, 1.39, 1.66, 2.02, 2.26, 2.53, 2.68, 2.96, 3.14, 3.32, 3.51, 3.64, 3.84 and 3.93. Residual and baseline are also presented. The vertical axis is an arbitrary unit. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

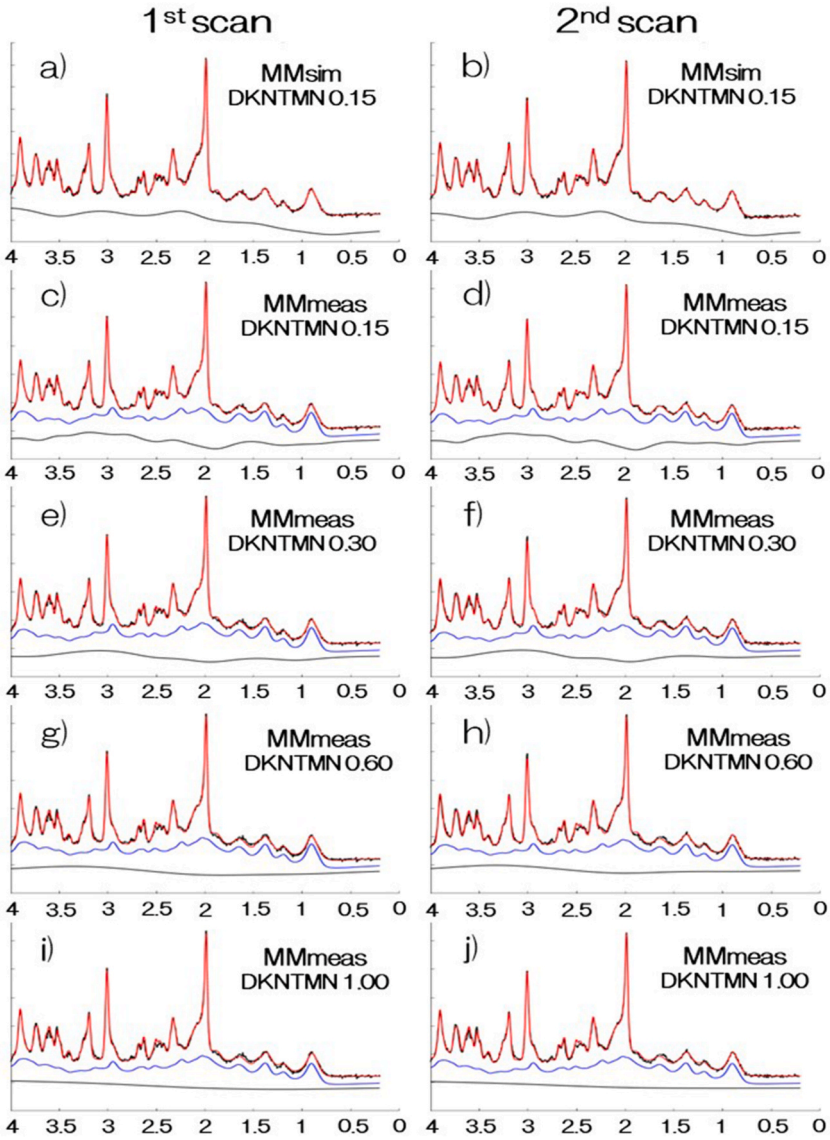

Fig. 2. The spectra and analyses of a 29-year-old female. The measured (black) and fitted (red) spectra, the MMmeas (blue) and the baseline (black) are presented. MMmeas and baseline are shifted to avoid overlap. The plots are very similar between the 1st and 2nd scans. Subpanels a and b are measured using MMsim and DKNTMN 0.15. Those of c and d, e and f, g and h, and i and j are measured using MMmeas and DKNTMN 0.15, 0.30, 0.60 and 1.00, respectively. Gradual stiffening of the baseline is observed by the increase of DKNTMN values. The horizontal axis is the chemical shift in parts per million (ppm), and the vertical axis is an arbitrary unit. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Author contribution statement

Tomohisa Okada: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Hideto Kuribayashi: Conceived and designed the experiments.

Yuta Urushibata: Ravi Teja Seethamraju: Sinyeob Ahn: Contributed reagents, materials, analysis tools or data.

Koji Fujimoto: Thai Akasaka: Performed the experiments; Analyzed and interpreted the data.

Tadashi Isa: Conceived and designed the experiments; Analyzed and interpreted the data.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tomohisa Okada, received research grants from the Japan Society for the Promotion of Science KAKENHI Grant (21H03806), the Japan Agency for Medical Research and Development (21dm0307003h0004), and Siemens Healthcare K.K., Japan (MRA-IPA3). Two coauthors, Hideto Kuribayashi and Yuta Urushibata are employees of Siemens Healthcare K.K. Other two coauthors, Ravi Teja Seethamraju and Sinyeob Ahn are employee of Siemens Healthcare, USA.

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