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T1 and T2 Metabolite Relaxation Times in Normal Brain at 3T and 7T

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Abstract

This study was designed to measure T1 and T2 relaxation times of the singlets in normal brain at 7T. Our results demonstrated that the T_1 relaxation values of total creatine (tCr)-CH_3 and N-acetyl aspartate (NAA) in the parietal white matter significantly increased at 7T compared to 3T, while the T_1 of Choline-containing compounds (Cho) was similar between field strengths. T_2 values of all metabolites investigated were significantly shorter at 7T. To compare signal-to-noise ratio (SNR) values between different field strengths, data were corrected for the effects of T_1 and T_2 relaxation. The average SNR ratio between 7T and 3T was 1.6. The increase in peak height SNR was less than linear with respect to B_0, primarily due to the differences in linewidth. The average linewidth of tCr-CH_3 in TE-averaged spectra was 18.62 Hz while it was 8.38 Hz in the single echo time using spectral-spatial RF pulses at 7T. The Cramer-Rao lower bounds (CRLBs) of metabolites were much lower at 7T compared to 3T. These data are important for the optimization of acquisition parameters for future spectroscopy studies in clinical applications at 7T.

Keywords: Magnetic resonance spectroscopy; Signal-to-noise ratio; Metabolite T1 and T2 relaxation time; Linewidth; 7T

Introduction

Proton magnetic resonance spectroscopy (MRS) is a powerful noninvasive tool that has been widely used for the assessment of brain metabolites and the investigation of normal and abnormal metabolism in brain tissue. With the availability of improved hardware and acquisition techniques, in vivo single-voxel 1H-MRS and multi-voxel magnetic resonance spectroscopic imaging (MRSI) can offer new possibilities at high field strengths, such as 7T. Increased signal-to-noise ratio (SNR) and spectral resolution in short echo time single-voxel spectra at 7T compared to 1.5T, 3T and 4T have been demonstrated previously [1-3]. This increase in SNR can be used to shorten the total acquisition time and/or increase the spatial resolution. The heightened spectral resolution could provide improved detection of metabolites with lower concentrations and/or complex J-coupling patterns, such as myo-inositol (mI) and glutamate (Glu). At 3T, TE-averaged point-resolved spectral selection (PRESS) offers unobstructed detection of Glu at an effectively long echo time by averaging across the different echoes [4]. Compared with each individual echo spectra, the TE-averaged spectrum has a flat baseline, but preserved metabolites such as Glu, by cancelling the sidebands of multiplets thus providing more accurate quantification. Although TE-averaged PRESS has been widely used in clinical studies [5-8], its benefits have not been evaluated at ultra-high field strengths.

Despite the potential benefits of using a 7T whole body scanner, several factors can complicate the quantification of the resulting data and the number of applications in patients is still limited. These include artifacts from unsuppressed water, the differential effects of volume selection on metabolites of interest and poor magnetic field homogeneity. The question arises as to what extent these effects would compromise the anticipated increase in SNR in the data. New RF pulses have been developed specifically for high field to improve water suppression [9], reduce chemical shift artifact, and minimize peak power [1,10-12]. Optimized high-order shimming [13,14] and improved performance of the gradient system are also imperative for spectral acquisitions at ultra high field.

In deciding the data acquisition parameter at new field strength, it is important to select values that will accentuate the benefits from increased field strength while maintaining the advantages for regular use in the clinic. Because of the constraints of acquisition time and relatively long echo times of typical MRS techniques, spectral signals are usually not allowed to fully relax between excitations. This means that T_1 and T_2 values are required to obtain absolute metabolite concentrations and may have significant effects on SNR. T_2 values also play an important role on spectral resolution since the linewidth of a peak is inversely proportional to its T_2^*. The field-dependent trends of T_1 and T_2 relaxation times of metabolites have been demonstrated in a rat brain study [15] and summarized literature values based on studies from humans and theoretical calculations in grey matter and cerebellum regions were presented previously [1,16,17]. Further, a distinct correlation was reported between T_2 and relative white matter/gray matter composition for N-acetyl aspartate (NAA) and total creatine (tCr) CH_3 [18], but no studies have shown regional differences in T_1. In clinical applications, usually there is only time to acquire data with a single echo time, thus selecting the optimal scan parameters that facilitate reliable metabolite quantification for characterizing the spatial extent of disease is critical.

The purpose of this study was to estimate T_1 and T_2 relaxation times of the singlets of Choline-containing compounds (Cho), tCr-CH_3, and NAA in the parietal white matter of human brain at both 3T and 7T. Because two dimensional (2D) J-resolved spectroscopy was employed for T_2 estimation, it also allowed improved detection of Glu in the TE-

averaged spectra. The data were used to compare SNR, linewidth and quantification errors between 3T and 7T.

Materials and Methods

Subject

Twenty-four volunteers (thirteen males and eleven females, median age = 29 years) were recruited in the study. All subjects gave written and informed consent. The volume of interest (VOI), with a voxel size of 8 cm3, was localized in the parietal white matter. The number of subjects investigated for T_1 and T_2 relaxation times in the study were shown as follows: 8 volunteers for T_1 at 3T, 10 volunteers for T_2 at 3T, 12 volunteers for T_2 at 7T, and 7 volunteers for T_1 at 7T. Eight of these volunteers were scanned for both T_1 and T_2 at 3T, 2 volunteers for both T_1 and T_2 at 7T, and 3 volunteers were scanned for all the acquisitions.

MRS methods

All empirical studies were performed using an 8-channel receive-only, phased-array coil on a 3T GE Signa Excite scanner (GE Healthcare Technologies, Waukesha, WI) with body coil transmit, or a commercially available 8-channel array and a volume transmit head coil (NOVA Medical, Wilmington, MA) on a 7T GE scanner. The MR exam included the acquisition of anatomical images and spectral data.

Anatomical imaging consisted of T_1-weighted sagittal scout images (TR/TE = 70/2 ms at 3T and TR/TE = 5/1 ms at 7T), T_1-weighted spoiled gradient echo (SPGR) images (TR/TE = 26/3 ms) at 3T, and T_2*-weighted gradient recalled echo (GRE) (TR/TE = 250/11 ms) at 7T.

2D J-resolved point resolved spectral selection (PRESS) spectra were utilized to measure T_2 relaxation of metabolites at both 3T and 7T. The t1 was incremented by 2.5 ms from 35 ms to 192.5 ms for a total of 64 steps at 3T [5], while at 7T, 48 spectra were acquired at 5 ms increments starting at TE of 35 ms. With a TR of 2 s and a number of excitations (NEX) of 2, the total acquisition time was ~ 5 minutes at 3T and ~ 4 minutes at 7T. Overpress factors of 1.2 at 3T [19] and 1.4 at 7T were utilized to reduce chemical shift artifact, and very selective suppression (VSS) pulses [20] of 40 mm width were played out around the prescribed volume for outer volume suppression at both field strengths. The manufacturer's linear autoshim procedure was applied at 3T, and an in-house, higher-order shimming routine [14] was performed at 7T.

For T_1 studies at 3T, the TE-averaged PRESS data was obtained with 16 steps and an increment time of 10 ms at TR = 1 s with NEX=4, TR = 2 s with NEX = 4, and TR = 8 s with NEX = 2, respectively [5]. At 7T, custom-designed spectral-spatial RF (SSRF) pulses [21] with improved B1 insensitivity and greatly reduced chemical shift artifact were used with a TE of 90 ms, NEX = 64, and at TR = 1 s, 2 s, 4 s and 10 s.

All the spectral data were acquired with 2048 spectral points, and 4000/5000 Hz spectral width. To obtain estimates of coil sensitivities for the combination of the 8-channel data, unsuppressed water spectra were acquired at an echo time of 35 ms for each of the two PRESS acquisitions at 3T, and proton density-weighted GRE images were acquired using the manufacturer-provided parallel imaging calibration sequence (TR/TE=100/1 ms) at 7T.

Data processing

Post-processing was applied on a single SunBlade 1000 Workstation (Sun Microsystems, Santa Clara, CA). Eight-channel data were combined in the time-domain using the unsuppressed water signal [22] at 3T, and using in-house developed software which utilized the theory based on a sensitivity encoding (SENSE) reconstruction with a reduction factor (R) of 1.0 as described in a previous article [19] at 7T. The spectral data were apodized by a 4 Hz Lorentzian filter at both 3T and 7T, and then spectra were processed with a Fast Fourier Transform (FFT). The data were quantified using a previously published methodology [5, 23].

To calculate T_2 values, peak heights of Cho at 3.22 ppm, tCr-CH$_3$ at 3.02 ppm, and NAA at 2.02 ppm were extracted from the spectra after fitting to a mono-exponential function using the SAGE software packageTM (General Electric, Milwaukee). At 3T, the 56 spectra included in the fitting ranged from a TE of 55 ms to 192.5 ms in order to reduce the contamination of macromolecules and/or J-coupled multiplets. The T_2 at 7T of Cho and tCr-CH3 were estimated from the 55 ms TE out to the first spectrum with SNR smaller than 2 times the standard deviation of noise. This included a minimum of 22 spectra. The NAA intensities were fitted from 55 ms to 270 ms (44 spectra) at 7T. Only T_2 fits with variances of the fit residue smaller than 10% were included in the analysis.

For the T_1 studies at 3T, the data acquired with J-resolved PRESS were first averaged in the t1 dimension and then the signal intensities were quantified and normalized by the NEX before fitting. The T_1 values were calculated from partial T1 saturation using a two-parameter least-square fitting routine according to the equation

$$S/S_0 = 1 - 2\exp[-(TR - TE/2)/T_1] + \exp(-TR/T_1)$$

where S is the signal intensity acquired at three different TRs, S_0 is the fully relaxed signal intensity, and the effective TE is 110 ms at 3T and 90 ms at 7T.

To compare the SNR and linewidth of spectra between 3T and 7T, the TE-averaged spectra were generated using a subset of TEs ranging from 35 ms to 190 ms and a spacing of 5 ms for a total of 32 echoes at both field strengths. The peak parameters of the metabolites were computed automatically within the excited voxel using in-house software [23]. The SNR of individual metabolites were estimated by dividing the peak heights of Cho, tCr-CH$_3$ and NAA, by the standard deviation of the noise from the peak-free region at the right end of the spectrum [23]. The effects of T_2 differences between 3T and 7T were corrected by multiplying the estimated SNR ratios from the 7T data over the 3T data for Cho, tCr-CH$_3$ and NAA by the T_2 factor,

$$f_{T2} = \exp(-TE/T_{2(3T)})/\exp(-TE/T_{2(7T)}) \, ,$$

where the effective TE of the TE-averaged spectra is 112.5 ms, and T_1 correction factor is

$$f_{T1} = \frac{1 - 2\exp[-(TR - TE/2)/T_{1(3T)}] + \exp(-TR/T_{1(3T)})}{1 - 2\exp[-(TR - TE/2)/T_{1(7T)}] + \exp(-TR/T_{1(7T)})}$$

The TE-averaged spectra were quantified using the LCModel package [24]. Metabolite signals for the basis set, which included Cho, Cr, NAA, Glu, Gln, mI and Gly, were generated using GAMMA simulations [25] with prior knowledge of chemical shift and J-coupling [26]. Metabolites with relative Cramer-Rao lower bounds (CRLB) lower than 25% were included in the analysis. Due to the relatively small spectral band width of SSRF pulses (712 Hz), an in vitro basis set of individual metabolites was prepared for quantification of spectra acquired at TE/TR=90/2000 ms.

Statistics

Nonparametric Wilcox on rank sum tests were applied to evaluate differences in SNR, T_1, and T_2 relaxation times between 3T and 7T with a P value of 0.05 being considered significant.

Results

An example of the 2D J-resolved data from a volunteer acquired at 3T and 7T is shown in Figure 1. Note that the spectra are displayed with the same noise scale and plotted using the same spectral resolution in parts per million (ppm). Compared to the 3T data, the 7T spectra demonstrated higher SNR. Along with the increase of the echo time, the signal intensities of Cho, tCr-CH$_3$ and NAA decayed at a faster rate at 7T compared to the data set at 3T.

Figure 2 shows spectra acquired at 4 different TRs and the T1 fitting for a volunteer at 7T. The T_1 and T_2 relaxation values for Cho, tCr-CH$_3$ and NAA at both 3T and 7T are given in Table 1. As expected, the T_1 values of metabolites were higher at 7T relative to those at 3T, while the T_2 values were shorter. Statistically significant differences were found for both the T_1 and T_2 relaxation values between 3T and 7T for Cho, tCr-CH$_3$ and NAA with P < 0.05 except for the T_1 value of Cho, which was relatively longer at 7T, but not statistically significant.

The estimated linewidths for Cho, tCr-CH$_3$ and NAA after correcting for filtering are given in Table 2. When expressed in terms of ppm, the estimated linewidths for Cho, tCr-CH3 and NAA in the TE-averaged spectra were 0.034 ± 0.010, 0.032 ± 0.009 and 0.041 ± 0.012 ppm, respectively, at 3T, and 0.058 ± 0.011, 0.063 ± 0.014 and 0.063 ± 0.010, respectively at 7T. Linewidths for spectra acquired at a single echo time using SSRF at 7T were 0.024 ± 0.010, 0.028 ± 0.010 and 0.039 ± 0.007 ppm for Cho, tCr-CH3 and NAA, respectively. The ratios of linewidths for the TE-averaged spectra (32 echoes) at 7T relative to 3T were 1.73, 1.97 and 1.52. However, the estimated linewidths of the
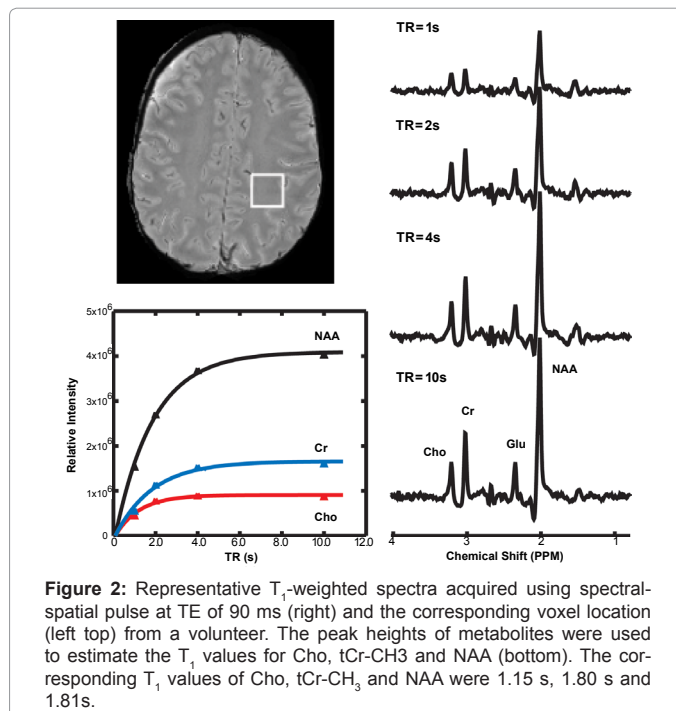

Figure 1: 2D J-resolved spectra acquired at 3T (left) and 7T (right). The spectra were displayed with the same ppm scale, and the vertical scales of all the spectra were normalized to the noise level of the different spectra. Note that the scale between individual echo spectra and the TE-averaged spectra were different, with the TE-averaged spectra scaled up for better visualization.

Figure 2: Representative T_1-weighted spectra acquired using spectral-spatial pulse at TE of 90 ms (right) and the corresponding voxel location (left top) from a volunteer. The peak heights of metabolites were used to estimate the T_1 values for Cho, tCr-CH3 and NAA (bottom). The corresponding T_1 values of Cho, tCr-CH$_3$ and NAA were 1.15 s, 1.80 s and 1.81s.

	T_1 (s)			T_2 (ms)		
	Cho	tCr-CH$_3$	NAA	Cho	tCr-CH$_3$	NAA
3T	1.06 ± 0.11	1.38 ± 0.13	1.38 ± 0.13	170 ± 18[a]	151 ± 15	262 ± 37
7T	1.24 ± 0.21	1.78 ± 0.23	1.73 ± 0.22	131 ± 16	121 ± 12	170 ± 11
P	*0.072*	*0.021*	*0.004*	*<0.001*	*<0.001*	*<0.001*

[a]N=9. One data point was excluded because the variance of the fit residue was larger than 10%

Table 1: T_1 and T_2 relaxation values of Cho, tCr-CH3 and NAA at 3T and 7T (mean ± SD). A non-parametric Wilcoxon rank sum test was used for the statistical analysis.

	Cho	**tCr-CH$_3$**	**NAA**
3T TE-avg (32 echoes, N=10)	4.30 ± 1.26	4.06 ± 1.18	5.28 ± 1.54
7T TE-avg (32 echoes, N=12)	17.32 ± 3.35	18.62 ± 4.11	18.66 ± 2.98
7T single echo (SSRF, N=28)	7.06 ± 2.83	8.38 ± 3.08	11.66 ± 1.98

Table 2: Line widths of Cho, tCr-CH$_3$ and NAA at 3T and 7T (mean ± SD, Hz).

	Cho	tCr-CH$_3$	NAA
3T	59 ± 9	62 ± 9	134 ± 16
7T	66 ± 24	76 ± 29	167 ± 39
SNR 7T : 3T	**1.12**	**1.23**	**1.25**
T1 effects	1.06	1.14	1.12
T2 effects	1.21	1.17	1.26
7T : 3T	**1.44**	**1.64**	**1.76**

Table 3: SNR values of metabolites measured at 3T and 7T (mean±SD). The SNR ratios of Cho, tCr-CH3 and NAA between 7T and 3T from the TE-averaged spectra (32 echoes) were compared with the same data after the corrections by relaxation values.

spectra acquired with a single echo time using spectral-spatial pulses and TE of 90 ms at 7T were much narrower compared to the TE-averaged data at the same field strength and those at 3T in terms of PPM.

The SNRs of metabolites from the TE-averaged spectra are displayed in Table 3. Only an 11%-28% increase in SNR was observed at 7T relative to that at 3T. The effective TE of the TE-averaged spectra was 112.5 ms and the TR was 2 s. Since statistically significant differences
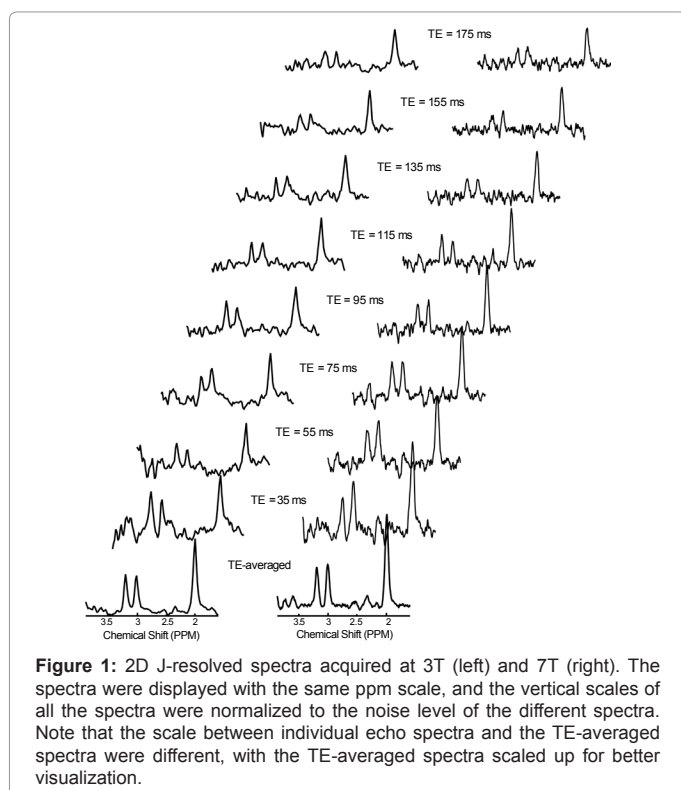
	7T (32 echoes, N=12)	3T (32 echoes, N=10)	3T (64 echoes, N=10)
Cho	2% ± 0.7%	4% ± 0.5%	4% ± 0.7%
tCr-CH₃	2% ± 0.5%	4% ± 0.5%	4% ± 0.5%
NAA	1% ± 0.5%	2% ± 0.5%	2% ± 0.0%
Glu	9% ± 3.6%	19% ± 5.0%	19% ± 3.4%
		(N=5)	(N=7)
Glx	9% ± 4.3%	20% ± 5.4%	17% ± 3.3%
		(N=6)	(N=7)
mI	10% ± 3.9%	16% ± 1.1%	18% ± 3.4%
	(N=11)	(N=5)	(N=5)
mIG	10% ± 3.7%	17% ± 2.6%	18% ± 3.1%
	(N=11)	(N=6)	(N=5)

Table 4: The Cramer-Rao lower bound (CRLB) of metabolite concentrations using LCModel for the TE-averaged spectra at both 3T and 7T (mean ± SD).
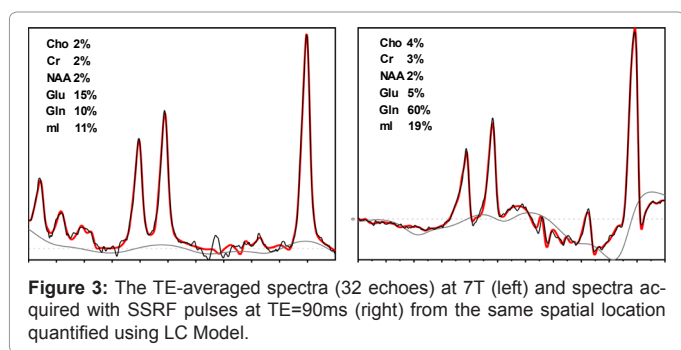

Figure 3: The TE-averaged spectra (32 echoes) at 7T (left) and spectra acquired with SSRF pulses at TE=90ms (right) from the same spatial location quantified using LC Model.

were found between relaxation values at 3T and 7T (Table 1), correcting for relaxation times is imperative for spectra acquired with a long TE and short TR. After correcting for the effects of T_1 and T_2 relaxation values, a 1.6-fold increase in SNR was achieved at 7T compared to 3T.

The CRLBs of metabolites from the TE-averaged spectra using LCModel were compared between both field strengths (Table 4). The CRLB of those metabolites were lower at 7T than at 3T and there was a higher percentage of detectable metabolites for Glu, Glx (Glu+Gln), mI and mIG (mI+Gly) with CRLB<25% at 7T. Compared with the TE-averaged spectra (64 echoes) at 3T, the CRLB of the TE-averaged spectra with only 32 echoes at 7T were still smaller, even though they were acquired in only half of the amount of time. An example, the TE-averaged spectra (32 echoes) and spectra acquired with SSRF pulses (TE=90 ms) at 7T from the same spatial location and quantified using LCModel, is shown in Figure 3. The CRLB for Cho, Cr, NAA and Glu of spectra acquired with SSRF pulses at TE/TR = 90/2000 ms was 4.6 ± 0.8%, 3.1 ± 0.4%, 2.1 ± 0.4% and 7.7 ± 1.7%, respectively.

Discussion

With the increasing number of 7T scanners and improvements in data acquisition techniques and hardware capabilities, transitioning from 3T to ultra high field strength has been widely discussed. Designing the appropriate acquisition parameters for obtaining MRS/MRSI data at 7T requires the measurement of T_1 and T_2 metabolite relaxation times in localized spectra from normal volunteers to maximize the benefits of increased field strength.

Our study compared T_1 and T_2 values in the parietal white matter. The T_1 and T_2 relaxation times of metabolites measured at 3T were similar to published values [18], and the trend of changes in T_1 and T_2 relaxation values upon the increase of field strength from 3T to 7T are close to those reported in the rat brain [15]. The T_1 values of tCr-CH₃ and NAA were anticipated to be significantly longer at 7T, while

the increase in T_1 for Cho was smaller and thus not significant when compared to values at 3T, consistent with results from the rat brain [15]. On the other hand, the T_2 values of all the metabolites were dramatically shortened at 7T relative to those at 3T. Due to lengthening T1 relaxation times and shortening T_2 relaxation times, metabolite resonances were more saturated at 7T compared to those at 3T. Previous research describing the opposing changes in T_2 for Cho and tCr relative to NAA suggests that ratios of Cho/NAA are higher in brain tumor than normal appearing brain at longer echo times [27]. This suggests that longer TR and shorter TE are beneficial for spectral acquisitions at 7T to utilize the SNR gained with increasing field strength and that a lower TE at 7T should be considered for clinical applications.

Another issue that we investigated was the anticipated increase in linewidths due to larger susceptibility artifacts at higher field. The linewidths in the TE-averaged spectra at 3T were close to those previously reported [19], however, the linewidths of the TE-averaged spectra were worse than those acquired with a single echo time using spectral-spatial pulses at 7T. The linewidths in the single echo time spectra at 7T were close to values published previously as well [1-3, 28]. This discrepancy could be attributed to small frequency offsets and/or phase variations when the signal intensities decay with the increasing of TE in the 2D J-resolved spectra. Although the spectral-spatial pulses offer much narrower spectral linewidth at 7T than the TE-averaged spectra at 3T, only longer TEs (≥ 90 ms) and small spectral bandwidth (712 Hz) are permitted for this RF pulse, which limits its application. In addition, the higher susceptibility at 7T required a larger overpress factor, which may cause in homogeneities from outside of the ROI to degrade the spectral quality and result in the broadening of peak linewidths.

The spectra data acquired with SSRF pulses at TE=90 ms also showed a good separation of Glu from Gln. The CRLB in these spectra were slightly smaller compared to the TE-averaged spectra, which maybe the results of T_2 effects from averaging decreasing the accuracy of quantification. This observation demonstrates the potential utility of this sequence for evaluating diseases such as Multiple Sclerosis, in which Glu is an important marker[29].

On average, SNRs were 1.2-fold higher for the TE-averaged spectra at 7T compared to 3T. Increased SNRs were, on average, suggesting that the effects of T_2 shortening reduce the elevated SNR due to increased field strength in the long TE spectrum. After corrections for differences in relaxation times, the mean SNR ratio was 1.6. Although this ratio was below the theoretical 2.33-fold increase, this was not surprising due to the large linewidth broadening in the TE-averaged spectra at 7T, as illustrated in Table 2. In previous studies, researchers have reported elevated SNR values with a single echo time spectra at 7T compared to 1.5T, 3T and 4T [1-3], which implies that improved shimming or phase/frequency correction before averaging in the analysis of TE-averaged spectra will be beneficial in future studies.

Although the linewidths of the TE-averaged spectra at 7T were much broader than at 3T, the comparison of CRLB in the TE-averaged spectra (32 echoes) between 3T and 7T clearly demonstrated increased precision of quantification at 7T, which is consistent with previous studies in a single short echo time spectra [1-3]. Despite a reduction in scan time by a factor of two at 7T, the precision of quantification was higher in the 7T TE-averaged spectra (32 echoes) compared to the TE-averaged spectra with 64 echoes. This can be attributed to a larger spectral dispersion at high field that has the potential to separate different metabolites at 7T compared to 3T. Our data showed that the

TE-averaged spectra, which were initially designed for detection of Glu at 3T, offer enhanced quantification at 7T.

In conclusion, this study showed the differences in T_1 and T_2 metabolite relaxation times in normal parietal white matter between 3T and 7T, and also evaluated the efficacy of TE-averaged spectra at 7T. These data are important for the optimization of acquisition parameters for future MRS/MRSI studies at 7T, which may further improve the sensitivity and specificity of this technique for future clinical applications.

Acknowledgements

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