

# Three-Dimensional J-Resolved H-1 Magnetic Resonance Spectroscopic Imaging of Volunteers and Patients With Brain Tumors at 3T

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**A method that combines two-dimensional (2D) J-resolved spectroscopy with three spatial dimension magnetic resonance spectroscopic imaging (MRSI) is introduced to measure J-coupled metabolites of glutamate (Glu), glutamine (Gln), myo-Inositol (ml), and lactate (Lac) in the brain and to simultaneously obtain  $T_2$  values of choline (Cho), creatine (Cr), and N-acetyl aspartate (NAA). Relatively few points in the  $t_1$  dimension (six echo times) and a flyback echo-planar trajectory were incorporated in the acquisition to speed up the total acquisition time so that it was within a clinically feasible range (23 min). Data obtained using GAMMA software simulations and from phantoms have shown that the  $^4\text{CH}_2$  resonances of Glu can be separated from Gln at 2.35 ppm in TE-averaged spectra. Results from phantoms, six normal volunteers, and four patients demonstrated good signal-to-noise ratio (SNR). The J cross-peaks from the methyl group of Lac were visualized in the 2D spectra from the phantom and the glioma patient, and could be quantified from the spectra at  $J = \pm 4.17$  Hz. This technique also enables the evaluation of the changes in metabolite  $T_2$ . Compared with the values in normal white matter, the  $T_2$  values of Cho and Cr were statistically significantly increased in regions of glioma. Magn Reson Med 58:886–892, 2007. © 2007 Wiley-Liss, Inc.**

**Key words:** 2D J-resolved spectroscopy; 3D proton magnetic resonance spectroscopic imaging; brain tumors; 3T; glutamate; lactate

Proton magnetic resonance spectroscopy (MRS) has been widely used to allow assessment of glioma metabolism. Spectra acquired with long echo time ( $\sim 144$  ms) provide metabolites, such as Choline containing compounds (Cho), creatine (Cr), N-acetyl aspartate (NAA), lactate (Lac), and lipid (Lip), can help in distinguishing between normal brain and brain tumors, and different brain tumor types. In

vivo brain tumors show an increase of Cho due to increased membrane synthesis in neoplasm and a decrease of the neuronal marker NAA. Lac is a marker of anaerobic metabolism, and its  $\text{CH}_3$  component (1.3 ppm) often overlaps with  $\text{CH}_2$  groups in long alkyl chains of Lip arising from necrosis or subcutaneous Lip. Spectral editing using J-difference methods have been applied to separate Lac from Lip for the quantification of Lac, which can be used to assess the malignancy of tumors (1,2). However, there is often a loss in signal-to-noise ratio (SNR) during subtraction, and the methods are sensitive to phase and frequency variations between two acquisitions.

At short echo times ( $< 40$  ms), glutamate (Glu), glutamine (Gln), and myo-Inositol (ml) also appear in the spectrum, but peak overlap and complex coupling patterns make it difficult to isolate individual components, even at higher field strength. Two-dimensional J-resolved spectroscopy, a technique that has been performed on high-resolution NMR spectrometers for decades, more recently has been applied for in vivo MRS studies on clinical MR scanners (3,4). This technique enables the separation of J-coupling information from chemical shift by encoding J-coupling in the  $t_1$  dimension of a 2D spectrum using different echo times. The addition of the second frequency dimension also allows the separation of Lac from Lip (3). For in vivo studies, the number of echo times used for J-resolved MRS is typically 32 or 64 with  $F_1$  spectral resolution of  $\sim 3$  Hz based upon the coupling constant of Lac ( $\sim 7$  Hz) (5).

Recent studies have used this acquisition scheme in conjunction with averaging across the different echo times in the  $t_1$  domain to offer unobstructed detection of Glu at 3T, which has been termed TE-averaged point-resolved spectral selection (PRESS) (6). Since data are acquired at multiple echo times, it also enables measurement of  $T_2$  relaxation times of uncoupled resonances, which are important for accurate metabolite quantification (7). In prior studies, this method has been implemented as both a single-voxel acquisition with  $8\text{-cm}^3$  spatial resolution (6) and a 2D J-resolved magnetic resonance spectroscopic imaging (MRSI) pulse sequence (8) with one spatial dimension being acquired using phase encoding and the other using a flyback echo-planar trajectory (9) at 3T. The latter was acquired with  $1.8\text{ cm}^3$  nominal spatial resolution. The TE-averaged PRESS has provided more accurate quantification of Glu and offers the possibility of simultaneously measuring  $T_2$  but has only been applied to brain tumors in single-voxel acquisition mode (7). The extreme heterogeneity of gliomas means that multivoxel spectroscopic imaging with higher spatial resolution is required to provide

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more detailed information within the tumoral and peritumoral regions.

The goal of this study was to develop a new acquisition scheme that can provide data within a clinically feasible acquisition time and to develop postprocessing methods for interpretation of 2D J-resolved PRESS MRSI data with three spatial dimensions. This includes the development of strategies for improving the quantification of metabolites from these spectra using prior information concerning the J-coupling of metabolites such as Glu, mI, and Lac, as well as correcting for relaxation times of metabolites whenever possible.

## MATERIALS AND METHODS

### Simulated Data

PRESS spectra of Glu and Gln with TE values starting at 35 ms in six steps of 40 ms were simulated using GAMMA software (10) using prior knowledge of peak locations and J-coupling constants (5). The spectra were created with 1024 dwell points and a sweep width of 2000 Hz. A 4-Hz Lorentzian apodization in the  $t_2$  dimension, zero filling to 2048 points, and Fourier transform were applied and the resultant data were averaged in the  $t_1$  dimension.

### MR Data

All the empirical studies were performed using a transmit body coil and eight-channel phased array coil for signal reception with a 3T GE Signa scanner (GE Healthcare, Waukesha, WI, USA). The MR scans included the acquisition of both anatomic and spectroscopic imaging data.

Anatomical MR images comprised  $T_1$ -weighted sagittal scout images (TR/TE = 70 ms/2 ms at 3T), axial fluid attenuated inversion recovery (FLAIR) (TR/TE/TI = 10,002 ms/127 ms/2200 ms) and  $T_1$ -weighted spoiled gradient echo (SPGR) image (TR/TE = 26 ms/3 ms). In addition, proton density-weighted gradient echo images were acquired using the manufacturer-provided parallel imaging calibration sequence to obtain the estimates of coil sensitivities (TR/TE = 150 ms/2 ms) for the combination of the spectral data from each of the eight channels.

The J-resolved spectra were localized in three spatial dimensions using PRESS volume selection. To show the reliability of the relative position of metabolites, a single-voxel 2D J-resolved acquisition was performed in the metabolite phantoms with 2000 Hz sweep width and 1024 dwell point, resulting in spectral resolution in the  $F_2$  dimension of  $\sim 1.95$  Hz. The increment delay ( $t_1/2$ ) of the J-resolved acquisition was added before and after the final refocusing RF pulse in the PRESS sequence to encode  $t_1$ . The initial echo time was 35 ms. Six increments in the  $t_1$  dimension were acquired over a 25-Hz spectral bandwidth to yield an  $F_1$  resolution of 4.17 Hz per point.

The 3D J-resolved MRSI data were acquired utilizing a flyback echo-planar gradient trajectory (9), which allowed the encoding of one spatial dimension and the spectral dimension during a single readout, to speed up the acquisition time. The flyback echo-planar gradient was designed to provide a spatial resolution of 1 cm and was applied in the right/left direction for an FOV of 16 cm (16 spatial points). The spectral data were collected with 712 dwell

points and 988 Hz sweep width, which provides  $\sim 1.39$  Hz spectral resolution per point in the  $F_2$  dimension. The 3D spectral array size was  $16 \times 12 \times 8$  (right-left [RL]  $\times$  anterior-posterior [AP]  $\times$  superior-inferior [SI]) and the nominal spatial resolution was 1 cm<sup>3</sup>. With a TR of 1.2 s and a number of excitations (NEX) of 2, the total acquisition time for 3D J-resolved MRSI was 23 min.

### Study Population

An in vitro basis set from phantoms containing individual metabolites (50 mM Cho, 50 mM Cr, 50 mM NAA, 100 mM Glu, 100 mM Gln, 200 mM mI, and 200 mM Lac) was prepared by performing single-voxel 2D J-resolved acquisition on each phantom. To test the hypothesis that the 2D spectral cross-peaks of Lac can be separated from the overlapping Lips, the Lac phantom was covered with a thick piece of bacon and data was acquired using single-voxel 2D J-resolved acquisition.

A standard GE MRS phantom (12.5 mM NAA, 10 mM Cr, 3 mM Cho, 12.5 mM Glu, 7.5 mM mI, and 5 mM Lac), six healthy volunteers, and four patients with different kinds of primary brain tumors were included in the study. Patient diagnoses were: one undefined glioma (patient A) and three glioblastoma multiforme (GBM) patients (patients B, C, and D). To test the reproducibility of such data, we scanned the head phantom and two of the volunteers twice while positioning the excited volumes in similar regions.

## POSTPROCESSING AND ANALYSIS

Postprocessing was performed on a Linux Cluster in our laboratory (13 Sun Fire V60x Intel Xeon servers [2  $\times$  2.8 GHz, 1-GB memory], 4 Sun Fire V20z AMD Opteron servers [2  $\times$  2.4 GHz, 4-GB memory]) running Sun's N1 Grid Engine (Sun Microsystems, Santa Clara, CA, USA). Spectral arrays from the eight-channel coil were processed in parallel on separate central processing units (CPUs) and the signals were combined using in-house developed software that weighted the data by their coil sensitivities (11,12). Relative metabolite ratios were quantified using the LCModel package (13) for voxels within the PRESS box ( $8 \times 8 \times 4$ ) on a single SunBlade 1000 Workstation (Sun Microsystems).

The single voxel data were processed with phase and frequency corrections using the internal water signal, apodized with a 4-Hz Lorentzian function, zero-filled to 2048 points, and fast Fourier transformed (FFTed) in the  $t_2$  dimension. A second FFT was applied in the  $t_1$  dimension and a 45° rotation of the 2D spectra was performed to separate chemical shift and J-coupling information.

The 3D J-resolved MRSI data that were acquired using flyback readout trajectory were reordered to correspond to a rectilinear grid with resampling and phase corrections (9), followed by processing with first-point phasing and apodization in the  $t_2$  domain. The eight-channel data were then combined in the  $t_2$  domain. To estimate relative metabolite levels, the combined data were averaged in the  $t_1$  domain and then quantified using the LCModel package. Spectra were fitted between 4.0 ppm and 1.0 ppm. Metabolite ratios included in the analysis were those with rela-

tive Cramér-Rao lower bounds (CRLB) lower than 5% for Cho, Cr, and NAA, 20% for mI and Glu, and 25% for Glx (Glu+Gln). The peak heights of Cho, Cr, NAA, and Glu were computed automatically using in-house software for each voxel within the excited region from the TE-averaged data (14). The SNR of individual metabolites were estimated by dividing the heights of the peaks by the standard deviation (SD) of the noise from the peak-free region at the right end of the spectrum.

Six different echo-time spectra of the 3D J-resolved MRSI were each processed prior to averaging in the  $t_1$  dimension to estimate the  $T_2$  of each metabolite. The peak heights of Cho at 3.22 ppm, Cr-CH<sub>3</sub> at 3.02 ppm, and NAA at 2.02 ppm were estimated from each echo-time spectra (14), and then fitted to a single exponential function to calculate  $T_2$  metabolic relaxation times using the SAGE™ software package (General Electric, Milwaukee, WI, USA). The 2D spectra with three spatial dimensions were generated by applying a second FFT and 45° rotation in the  $t_1$  dimension. Only the  $T_2$  values with variances of the fit residue smaller than 10% were included in the analysis.

The coefficient of variance (CV) for reproducibility was calculated using the formula,  $CV = \sqrt{\sum_{i=1}^m SD_i^2 / m} / \bar{X} \times 100\%$ , where the SD<sub>*i*</sub> are the standard deviations of normalized peak heights in the voxel between two measurements,  $\bar{X}$  is the mean of the total voxels, and  $m$  is the number of the voxels. In addition, the CVs for the  $T_2$  values of metabolites in the phantoms were calculated using the SD divided by the mean.

The 3D J-resolved MRSI data were referenced to the 3D SPGR image by assuming that there was no movement between the image and spectra acquisition. The FLAIR image was aligned to the corresponding 3D SPGR image. Segmentation of the 3D SPGR brain images were performed automatically using a hidden Markov random field model with an expectation-maximization algorithm (15). The segmented white matter mask was then used to identify voxels that had at least 85% normal appearing white matter or 85% gray matter. The tumor lesions were restricted to the voxels within the  $T_2$  hyperintensities defined by  $T_2$ -weighted images. To avoid errors in identification of normal voxels, the edges of the PRESS box and ventricles were excluded from the analysis. Voxels that satisfied the above criteria were used for comparative analyses in the volunteer and patient data. Nonparametric Wilcoxon rank sum tests were used to assess the differences for the metabolic relaxation times, with a  $P$ -value of 0.05 considered to be significant.

## RESULTS

The oscillating coupling patterns for <sup>2</sup>CH and <sup>4</sup>CH<sub>2</sub> protons of Glu and Gln appear as pseudotriplets in the simulation, which makes it possible to leave only the center signal after averaging spectra with different echo times. The TE-averaged spectra of GAMMA simulations and single voxel phantom studies for pure Glu and Gln are shown in Fig. 1. The <sup>4</sup>CH<sub>2</sub> Glu resonance is clearly resolved from the <sup>4</sup>CH<sub>2</sub> Gln resonance both in simulations and in phantom studies with a chemical shift difference of 0.1 ppm.

Figure 2 shows the 2D J-resolved spectra recorded from the Lac phantoms with two localizations, one in the center

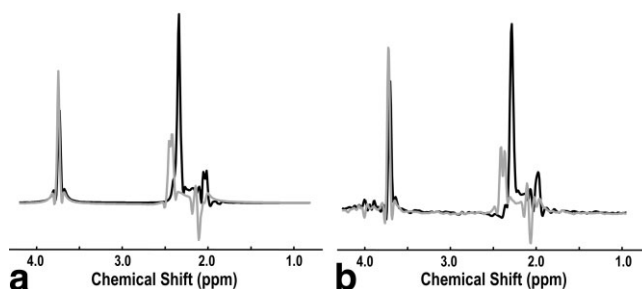


FIG. 1. Simulated (a) and phantom (b) TE-averaged PRESS spectra of Glu (black) and Gln (gray). The <sup>4</sup>CH<sub>2</sub> Glu resonance is clearly resolved from the <sup>4</sup>CH<sub>2</sub> Gln resonance in both simulations and phantom studies with a chemical shift difference of 0.1 ppm.

of the Lac phantom (voxel A) and the other contaminated with a part of bacon (voxel B). The J cross-peaks caused by the methyl group of Lac in the 2D spectrum were separated from the overlapping Lip peaks, which were compared with the 1D spectra extracted from  $J = 0.0$  Hz (TE-averaged spectrum). For comparison with resonances without J couplings, the TE-averaged spectrum of the NAA phantom was coplotted with the Lac spectrum. As expected, the doublet resonances of Lac were cancelled in the TE-averaged spectra, but successfully displayed in the 2D spectrum.

The estimates of reproducibility were obtained using a voxel-by-voxel comparison of the peak heights of different metabolites. The values of CVs were 4% for Cho, 5% for Cr, 6% for NAA, and 9% for Glu in the phantom, compared with 15%, 16%, 12%, and 35% in vivo, respectively. The CVs were relatively higher in vivo, especially for Glu.

Figure 3 illustrates the result of 3D J-resolved MRSI data acquired from the phantom. The TE-averaged spectra offered an unobstructed single Glu peak and a doublet of mI. The cross-peaks of Lac in the 2D spectrum in the region between  $F_2 = 1.5$  ppm and  $F_2 = 1.0$  ppm were distinctly visualized within the three spatial dimensions despite the fact that there were only six echo times recorded. The  $T_2$  values of Cho, Cr, and NAA in the phantom were  $194 \pm 14$  ms,  $296 \pm 26$  ms and  $550 \pm 72$  ms (mean  $\pm$  SD). With CVs of 7% for Cho, 9% for Cr, and 13% for NAA, the  $T_2$  values of metabolites were markedly uniform in the spectral array and could be used to reflect the regional  $T_2$  difference in vivo.

In vivo TE-averaged MRSI data were obtained with good SNR over the entire spectral array. The SNR values of Cho, Cr, NAA, and Glu in volunteers were  $17.0 \pm 4.9$ ,  $15.8 \pm 4.5$ ,  $33.4 \pm 11.5$ , and  $4.3 \pm 2.0$ , respectively. An example of white matter and gray matter voxels from the volunteer acquired with 3D J-resolved MRSI is given in Fig. 4. Compared with each individual echo spectra, the TE-averaged spectra had flat baselines but maintained the metabolites that had relatively shorter  $T_2$  values and thus provided more accurate quantification. The Glu/Cr levels were obviously higher in the gray matter voxel than those in white matter from the metabolic maps shown in Fig. 4. The ratios of mean metabolite levels in gray matter relative to white matter from six volunteers without corrections of relax-



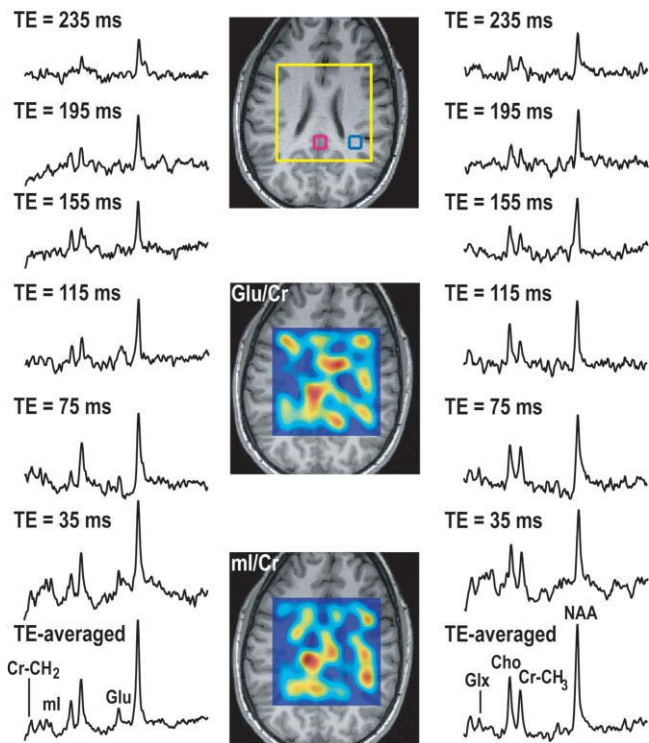


FIG. 4. 3D J-resolved MRSI acquired from a volunteer. The TE-averaged spectra from two voxels, gray matter and white matter, were plotted along each individual echo spectra. The metabolic maps were quantified using LCModel without corrections of relaxation time and plotted with the range between 0 and 2.20 for Glu/Cr and between 0 and 1.90 for ml/Cr.

in the lesions were statistically significantly longer than those in normal white matter ( $P < 0.005$ ), while  $T_2$  values of NAA were shorter, although without statistical significance.

## DISCUSSION

A J-resolved MRSI sequence with localization in three spatial dimensions was implemented within a clinically feasible scan time at 3T (23 min). Postprocessing methods were applied for interpretation and quantification of metabolites from these spectra for normal volunteer and patients with brain tumor. This technique allows simultaneous quantification of Glu independent of Gln, visualization and quantification of Lac methyl protons in 2D spectra, as well as evaluation of changes of metabolite  $T_2$  relaxation time, on a voxel-by-voxel ( $1\text{-cm}^3$  resolution) basis in a large 3D volume, typically  $\sim 256\text{ cm}^3$ .

J-resolved spectroscopy is one of the simplest 2D sequences, which allows separation of metabolites based on both chemical shift and J-modulation. A major drawback of this acquisition is its relatively long acquisition time due to numerous  $t_1$  increments required for wide bandwidth in the  $F_1$  dimension to avoid aliasing and fine spectral resolution for the separation of J-coupling resonances. Previously developed measurements based upon TE-averaged PRESS, offered effective separation of the Glu signal from NAA and Gln at 3T by canceling the side bands of

triplets or quintuplets (6), as well as suppressing the doublet, such as from the methyl group of Lac. To implement this technique in three spatial dimensions within a feasible total scan time, relatively few points in  $t_1$  are required. The  $t_1$  values used in this study were modified both to optimize for detection of Glu in the TE-averaged spectra and to visualize Lac in the 2D spectrum, in addition to using the fewest number of  $t_1$  points that allowed coverage in three spatial dimensions. Even spacing of 40 ms of echo time offers the possibility to visualize the Lac in the 2D spectrum, while more echo time points can provide more accurate  $T_2$  fitting. If only the TE-averaged spectra are of interest, the last echo time spectra can be omitted. The bandwidth in the  $F_1$  domain was small ( $\sim 25$  Hz) but large enough for the separation of methyl groups of Lac that have a spectral resolution of  $\sim 4.17$  Hz.

The incorporation of the flyback echo-planar gradient readout scheme (9) was necessary to acquire the J-resolved MRSI data in human studies because it speeds up the data acquisition (23 min). The slight disadvantage of this method is the 12% to 22% loss in SNR per unit time for the flyback MRSI as compared with the conventional MRSI (9). In this case, the fast acquisition was critical to acquire the patient data and the SNR obtained from the in vivo data was adequate for quantification of the metabolites

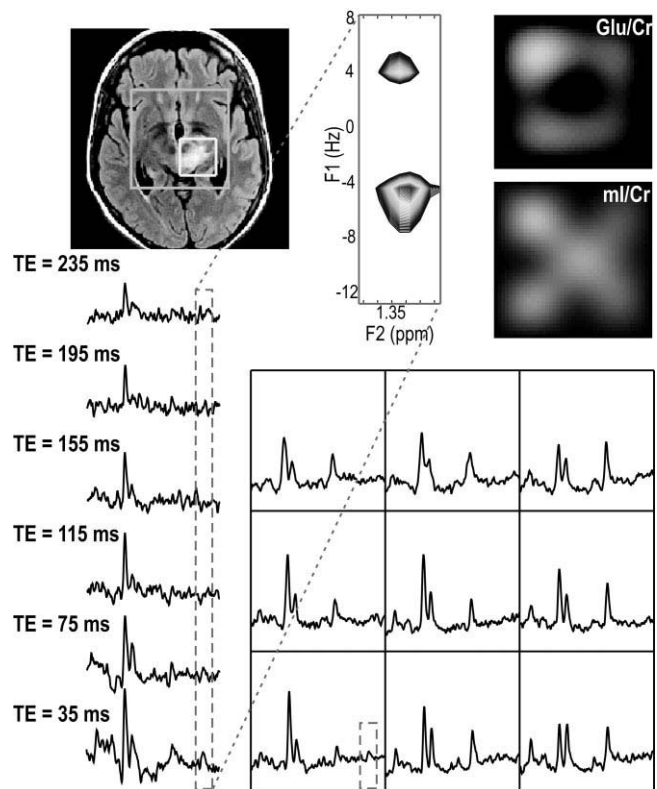


FIG. 5. 3D J-resolved MRSI acquired from a patient with glioma. The TE-averaged spectra corresponds to the location in the  $T_2$ -weighted image. The 2D spectrum with the expanded region centered at 1.35 ppm extracted from the labeled voxel, which was compared with six individual echo time spectra. The metabolic maps of Glu/Cr and ml/Cr are plotted with the same scale as in Fig. 4.

Table 1  
Relative Metabolite Levels Quantified by LCModel Without Corrections for Relaxation Time From Six Normal Volunteers and Four Patients With Primary Brain Tumors\*

	Cho/Cr	NAA/Cr	Glu/Cr	Glx/Cr	mI/Cr
WM	0.34 ± 0.08	2.17 ± 0.50	1.77 ± 0.68	2.33 ± 1.29	1.48 ± 0.53
GM	0.26 ± 0.06	1.62 ± 0.45	1.91 ± 0.75	2.69 ± 1.34	1.38 ± 0.46
Patient A	0.57 ± 0.16	1.14 ± 0.33	1.47 ± 0.57	2.12 ± 1.36	1.61 ± 0.66
Patient B-D	0.40 ± 0.10	1.21 ± 0.39	1.63 ± 0.68	2.97 ± 3.01	1.57 ± 0.60
Total $T_2$ lesions	0.45 ± 0.14	1.20 ± 0.38	1.58 ± 0.64	2.74 ± 2.67	1.58 ± 0.62

\*Numbers refer to mean ± SD.

WM = white matter, GM = gray matter.

targeted in our study. Since 16 spatial encodings are achieved in the flyback readout at 1-cm spatial resolution (16 cm FOV), aliasing from subcutaneous Lip into the region of interest can be eliminated along this direction (RL). One of the potential limitations of this technique is the need to trade off spectral bandwidth with spatial resolution and sampling efficiency. With the gradient system available on our clinical system, at spatial resolution of 1 cm<sup>3</sup>, the spectral bandwidth for the waveform designed for this study was 988 Hz, which was large enough to cover the metabolites of interest in the brain. Although the total acquisition time was shortened, there still could be some motion artifacts. The multiple echoes were chosen to be the inner loop while the phase-encoding steps were chosen to be the outer loop to minimize errors between echo times, but some spatial distortions may still exist and would be reflected as a smearing in the spatial domain.

Compared to short-echo MRSI data, the TE-averaged spectra have less contamination from macromolecules and offer unobstructed Glu, which allows more accurate quantification. The simplification of spectra is at the cost of generating a large dataset, which complicates the postprocessing and may be time-consuming or require parallel processing. In this study, only the TE-averaged spectra ( $F_1 = 0$  Hz) were quantified using LCModel (13) instead of using 2D fitting, such as ProFit (16), which may further improve quantitative accuracy. The methyl group of Lac was visualized in the 2D spectra and could also be quantified from the spectra extracted from the 2D spectra at  $J = \pm 4.17$  Hz.

Estimates of reproducibility for Cho, Cr, and NAA demonstrated excellent results in phantoms: 4% for Cho, 5% for Cr, 6% for NAA, and 9% for Glu. These CV values were calculated based on a voxel-by-voxel basis using the peak

heights of metabolites. The estimates for Cho, Cr, and NAA in vivo were 15%, 16%, and 12%, respectively, slightly higher than those in the phantoms. Registration of the position of the PRESS localization volume between two scans (17) may help to improve these results. Although the TE-averaged spectra offered a single peak for Glu and less macromolecular contamination, it was possible that Glu was overestimated because of the inclusion of the short echo data in the TE-averaged spectra. The relatively large CV for Glu suggests that baseline fitting is still necessary for quantifying the TE-averaged spectra.

Ratios of relative metabolite levels without corrections of relaxation time were estimated in the regions of normal gray matter and white matter from volunteers and  $T_2$  hyperintense lesions from gliomas. As expected, the ratio of Glu/Cr was slightly higher in the gray matter, while mI/Cr was higher in the white matter due to the Cr being higher in gray matter. The ratios of mean metabolites for Glu and mI were higher in the gray matter, which is consistent with a previous study (8). Data from three GBM patients showed that Glx/Cr was increased in the  $T_2$  hyperintense lesions and Glu/Cr was reduced, which suggests an increase of Gln in these patients. These in vivo studies demonstrated good quality and are extremely promising.

The  $T_2$  relaxation times of Cho, Cr, and NAA were also estimated from these 3D data. The small variances obtained from the phantom suggested that the procedure used to estimate  $T_2$  values was reliable. The mean  $T_2$  values of metabolites were similar to prior studies (18), and the differences in  $T_2$  values between normal white matter and  $T_2$  hyperintensity lesions were consistent with previous work (7). This may offer a new index for characterizing tumors.

In conclusion, phantoms and in vivo experiments showed that the 2D J-resolved approach was successful in detecting unobstructed metabolite peaks corresponding to Cho, Cr, NAA, mI, Glu, and Lac from the simplified spectra along with the flat baseline, and simultaneously allowed estimation of  $T_2$  values of the singlets. The SNR of the 2D J-resolved 3D MRSI performed on the human clinical 3T scanner was able to provide excellent spatial and spectral resolution within the human brain. After establishing procedures for the acquisition, reconstruction, and quantification of 2D J-resolved PRESS MRSI with three spatial dimensions, this methodology can be incorporated into protocols being used to evaluate patients with glioma and may provide improved characterization of the tumors.

Table 2  
 $T_2$  Relaxation Times of Metabolites From Six Volunteers and Four Primary Brain Tumor Patients\*

	Cho	Cr	NAA
WM	205 ± 77 (192) $N = 217$	148 ± 35 (145) $N = 219$	314 ± 105 (299) $N = 298$
GM	265 ± 81 (248) $N = 12$	155 ± 41 (142) $N = 27$	221 ± 66 (216) $N = 39$
Total $T_2$ lesions	245 ± 94 (222) $N = 83$	174 ± 50 (166) $N = 46$	322 ± 160 (260) $N = 59$

\*Numbers refer to mean ± SD (median) in ms, and  $N$  represents the number of voxels involved in the group.

WM = white matter, GM = gray matter.

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