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Two-Dimensional J-Resolved LASER and Semi-LASER Spectroscopy of Human Brain

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Abstract

Purpose—Two-dimensional (2D) J-resolved localized and semi-localized by adiabatic selective refocusing (LASER and semi-LASER) spectroscopy, named “J-resolved LASER” and “J-resolved semi-LASER”, were introduced to suppress chemical shift artifacts, additional J-refocused artifactual peaks from spatially dependent J-coupling evolution, and sensitivity to radiofrequency (RF) field inhomogeneity.

Methods—Three pairs of adiabatic pulses were employed for voxel localization in J-resolved LASER and two pairs in J-resolved semi-LASER. The first half of t_1 period was inserted between the last pair of adiabatic pulses, which was proposed in this work to obtain 2D adiabatic J-resolved spectra of human brain for the first time. Phantom and human experiments were performed to demonstrate their feasibility and advantages over conventional J-resolved spectroscopy (JPRESS).

Results—Compared to JPRESS, J-resolved LASER or J-resolved semi-LASER exhibited significant suppression of chemical shift artifacts and additional J-refocused peaks from spatially dependent J-coupling evolution, and demonstrated insensitivity to the change of RF frequency offset over large bandwidth.

Conclusion—Experiments on phantoms and human brains verified the feasibility and strengths of 2D adiabatic J-resolved spectroscopy at 3T. This technique is expected to advance the application of in vivo 2D MR spectroscopy at 3T and higher field strengths for more reliable and accurate quantification of metabolites.

Keywords

Localization by adiabatic selective refocusing (LASER); J-resolved magnetic resonance spectroscopy; J-refocused peak; J-resolved peak; chemical shift displacement error (CSDE)

INTRODUCTION

Using a higher magnetic field strength for human magnetic resonance spectroscopy (MRS) increases signal-to-noise ratio (SNR), which allows for shorter acquisition time or smaller

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detection volumes (1,2). However, the increased chemical shift dispersion sets higher demand on the bandwidth (BW) of radiofrequency (RF) pulses that are used in the localization for MRS, because chemical shift displacement error (CSDE) is proportional to the amplitude of static field (B_0) and reversely proportional to the BW of slice-selective RF pulses (1,3–5). Because two slice-selective 180° refocusing pulses are used, the chemical shift artifact is especially severe in the point-resolved spectroscopy (PRESS) (6). The limited BWs not only cause CSDEs but also lead to spatially dependent evolution of J-coupling, which, as emphasized in a recent paper by Edden and Barker (7), results in additional J-refocused peaks in conventional two-dimensional (2D) J-resolved spectroscopy (JPRESS) (7–9). For a pair of coupled spins with a large chemical shift difference, one spin may not undergo the 180° refocusing pulses due to the finite BW of the RF pulses in the voxel selected for its J-coupled partner. Therefore J-coupling will be refocused instead of evolving during the echo time (TE), which leads to additional so-called J-refocused peaks and reduces the intensities of the intended J-resolved peaks and thus impairs spectral quantification.

RF field (B_1) inhomogeneity is another issue at high magnetic field strengths because conventional RF pulses cannot provide uniform flip angles of the magnetization in the presence of nonuniform B_1 . Deviations from the intended flip angles not only lead to signal attenuation and additional unwanted signals, thus compromising the reliability, but also increase the sidelobes of the slice profile, leading to unwanted non-zero flip angles outside the region of interest (10). Accurate volume selection using slice-selective RF pulses is a prerequisite for ^1H MRS of the brain to prevent contamination of large lipid signal from scalp or water signal from poorly shimmed regions outside the selected volume (11).

The above issues can be solved or mitigated using adiabatic RF pulses (2,3,12–21). Adiabatic pulses offer large BWs and produce a uniform flip angle despite variation in B_1 , provided that the B_1 field strength is above a certain threshold. However, in contrast to conventional RF pulses which can rotate magnetization around an axis in the rotating frame, single adiabatic pulse cannot generate plane rotation (5,18). If a pair of adiabatic refocusing pulses are used, the second adiabatic refocusing pulse can compensate or cancel the phase dispersion generated by the first adiabatic refocusing pulse. Therefore, a pair adiabatic refocusing pulses is usually applied to define a slice. A single-shot spin-echo-based sequence called LASER, which stands for localization by adiabatic selective refocusing, was proposed for MRS (18). LASER uses a non-slice-selective excitation pulse followed by three pairs of adiabatic full-passage (AFP) pulses for signal refocusing as well as the selection of three orthogonal slices in space.

Recently, adiabatic pulses were employed in one-dimensional (1D) localized MRS, spectral editing, total correlation spectroscopy, and localized chemical shift correlated spectroscopy (L-COSY), etc (1,4,22–24). In this work, a LASER version of 2D J-resolved spectroscopy, named J-resolved LASER, was proposed to address the issues of JPRESS such as CSDE, spatially dependent J-evolution, and sensitivity to B_1 inhomogeneity. However, due to three pairs of AFP pulses employed in the J-resolved LASER sequence, the resultant long TE increases the apparent transverse relaxation T_2 effect, and the RF power deposition increases as well. Therefore, another scheme of volume selection, called semi-LASER (sLASER), was

proposed for J-resolved spectroscopy too. In the J-resolved sLASER sequence, a nonadiabatic, optimized slice-selective 90° excitation pulse is used instead of the combination of the non-slice-selective excitation 90° pulse and the first pair of AFP pulses, considering that a slice-selective 90° pulse produces a smaller CSDE than a slice-selective 180° pulse. In this way, only two pairs of AFP pulses are needed. The TE and the specific absorption rate (SAR) are therefore significantly reduced. Crusher gradients and phase cycling were exploited to suppress unwanted free induction decays (FIDs), stimulated echoes, and spin-echo signals. The RF power remains within the SAR limits and the CSDE is much smaller than that in conventional JPRESS. Experiments on phantoms and human brains were performed to demonstrate the feasibility and strengths of the new sequences.

METHODS

Phantoms, Subjects and Instrumental Setup

All experiments were performed on a Philips Achieva 3T whole body scanner (Philips Medical Systems, Best Netherlands), operating at a proton resonance frequency $f_0 = 127.74$ MHz. The body coil was used for transmission and a SENSE-Head-8 coil for reception. The clinically available maximum RF peak power is $13.5 \mu\text{T}$.

A phantom containing 50 mM N-acetyl-aspartate (NAA) in the buffer (pH 7.2) was made in house to examine the additional J-refocused peaks. The GE MRS Braino phantom (General Electric Medical Systems, Milwaukee, WI) was used to verify and compare the J-resolved LASER and J-resolved sLASER sequences with the JPRESS sequence. It contained the following brain metabolites and chemicals: (1) 12.5 mM NAA, (2) 10 mM creatine hydrate (Cr), (3) 3 mM choline chloride (Cho), (4) 7.5 mM *myo*-inositol (mI), (5) 12.5 mM glutamate (Glu), (6) 5 mM lactate (Lac), (7) 0.1% sodium azide, (8) 50 mM potassium phosphate monobasic (KH_2PO_4), (9) 56 mM sodium hydroxide (NaOH) and (10) 1 mL/L Gd-DPTA (Magnevist) (25,26).

Two healthy volunteers were recruited in this study. Written informed consent was obtained from the subjects and the study was approved by the local IRB.

Pulse Sequences

The diagrams of J-resolved LASER and J-resolved sLASER sequences are shown in Fig.1. The J-resolved LASER sequence (Fig. 1a) consists of a non-slice-selective 90° excitation pulse and three pairs of slice-selective 180° refocusing AFP pulses. A pair of crusher gradients is positioned symmetrically around each AFP pulse to suppress unwanted FIDs. To build the second dimension, the first half of the incremental period t_1 was inserted between the last pair of AFP pulses in the 2D J-resolved LASER sequence. To rephase the inhomogeneous evolution of γ_1 (the interval between the excitation RF pulse and the beginning of the first AFP spoiler gradient), another γ_1 was also placed between the last pair of 180° AFP pulses to form an echo. A minimum number of eight averages were acquired for every incremental t_1 . In addition to the crusher gradients, 8-step phase cycling was applied for suppressing unwanted FIDs.

Figure 1b depicts the J-resolved sLASER sequence. A slice-selective 90° excitation pulse, instead of the combination of the non-slice-selective 90° excitation pulse and a pair of AFP pulses in the J-resolved LASER sequence, was used for both slice selection and excitation, so the TE can be shorter while the CSDE caused by a regular slice-selective 90° pulse is much less than a 180° one.

The clinically available maximum B_1 of the quadrature transmit body coil of the Philips Achieva 3T MRI system is 13.5 μ T. With this B_1 value, the duration of an AFP pulse is 5.3 ms and its BW is 4748 Hz, whereas a conventional nonadiabatic RF pulse can only have a BW of about 2000 Hz for a 90° pulse and 1200 Hz for a 180° pulse. The water signal was suppressed by the VAPOR (variable pulse power and optimized relaxation delays) scheme except for the slice profile experiments. Along with each pair of AFP pulses, there were spoiler gradients with an amplitude of 10 mT/m and a duration of 0.31 ms (0.155 ms ramp-up/down times without top) around the first AFP pulse and with 8 mT/m and 0.31 ms (0.155 ms ramp-up/down times without top) around the second AFP pulse for phantoms experiments. In the in vivo experiments, the duration of spoiler gradients was adjusted to 1.81 ms with two ramps of 0.155 ms and a top of 1.5 ms.

CSDE and J-Refocused Artifactual Peaks

The CSDE in the plane defined by an RF pulse can be expressed as:

$$\text{CSDE} = \frac{\Delta f}{\text{BW}} = \frac{\Delta \delta \cdot f_0}{\text{BW}}, \quad [1]$$

where f is the frequency difference of two resonances in hertz (Hz), δ is the chemical shift difference in ppm, BW is the bandwidth in Hz of the slice-selective RF pulse for the plane, and f_0 is the carrier frequency of the scanner in MHz. The chemical shift displacement artifact can be described as the percent voxel overlap between the resonances at two

chemical shifts according to Eq. [1]: $(1 - \frac{\Delta \delta \cdot f_0}{\text{BW}_x})(1 - \frac{\Delta \delta \cdot f_0}{\text{BW}_y})(1 - \frac{\Delta \delta \cdot f_0}{\text{BW}_z})$, assuming the voxel is defined by the intersection of planes x , y and z (1). For example, two resonances with a chemical shift difference of 3.5 ppm, only have a percent voxel overlap of 32% using the JPRESS sequence with a routine slice-selective 90° excitation pulse (BW ~ 2000 Hz) and two routine slice-selective 180° refocusing pulses (BW ~ 1200 Hz) on a 3T MRI scanner. In contrast, the percent voxel overlap can be increased to 74% using the J-resolved LASER sequence and 64% using the J-resolved sLASER sequence.

Now we investigate the effects of J-couplings on signal formation of conventional JPRESS ignoring relaxation, diffusion, etc. We consider a homonuclear J-coupled AX spin-1/2 system with a coupling constant J . In a part of the plane excited by a slice-selective 180° pulse for spin X, spin A does not experience the pulse due to the chemical shift displacement between the spins A and X (9). We can decompose the voxel into 2 distinct subvoxels: in subvoxel 1, spin A experiences the second 180° pulse, and in subvoxel 2, spin A does not experience the second 180° pulse (7,9). Assume M_X is the equilibrium magnetization per unit volume of spin X and Ω_m is the frequency offset of spin m ($m = A$ or X) in the rotating

frame, the signal arising from the subvoxels 1 and 2 at $t = t_2$ can be expressed as S_1 and S_2 , respectively, as follows:

$$S_1 = M_X V_1 e^{-i(\pm\pi J)(t_1+t_2)} e^{-i\Omega_X t_2}; S_2 = M_X V_2 e^{-i(\Omega_X \pm \pi J)t_2}, \quad [2]$$

where V_1 and V_2 are the volumes of subvoxels 1 and 2, respectively. As a result, the expected J-resolved peaks appear at $(F_1, F_2) = (-J/2, \Omega/2\pi + J/2)$ and $(J/2, \Omega/2\pi - J/2)$, and the additional J-refocused peaks at $(F_1, F_2) = (0, \Omega/2\pi \pm J/2)$. Therefore, there is no J-split for the J-refocused peaks along F_1 dimension. If spin X is also coupled with spins $i = 1, 2, 3 \dots n$, besides with spin A, the additional J-refocused peaks will appear at the middle of the intended J-resolved peaks caused by J-coupling of spins A and X along F_1 axis but with the same corresponding F_2 coordinate values:

$$S_1 = M_X V_1 e^{-i\pi(\pm J \pm J_1 \pm J_2 \dots \pm J_n)(t_1+t_2)} e^{-i\Omega_X t_2}; S_2 = M_X V_2 e^{-i\pi(\pm J_1 \pm J_2 \dots \pm J_n)(t_1+t_2) - i\pi(\pm J)t_2} e^{-i\Omega_X t_2}, \quad [3]$$

where J_i is the coupling constant between spins X and i , and the chemical shift displacement between spins X and i is ignored. Given $V = V_1 + V_2$, V_1 and V_2 can be written as:

$$V_1 = (1 - \frac{\Delta\delta_{AX} \cdot f_0}{BW_{\text{refocus}}})V; V_2 = \frac{\Delta\delta_{AX} \cdot f_0}{BW_{\text{refocus}}}V, \quad [4]$$

where δ_{AX} is the chemical shift difference in ppm of the spins A and X, BW_{refocus} is the bandwidth in Hz of the slice-selective refocusing pulse. Therefore, the intensity of the

intended J-resolved peaks will be weakened by a factor of $1 - \frac{\Delta\delta_{AX} \cdot f_0}{BW_{\text{refocus}}}$ (7,9). It can be concluded that a limited BW not only leads to additional J-refocused peaks but also reduces the intensities of the intended J-resolved peaks.

Measurement of Slice Profile

The GE MRS Braino phantom was also used to measure the slice profiles of the 180° refocusing pulses used in the three J-resolved spectroscopy sequences. During data collection, a read-out gradient of 0.04 mT/m was applied along the same direction of the slice-selective gradient for the tested refocusing pulses. The experimental parameters were as follows: repetition time (TR) = 2000 ms, TE = 50 ms, number of signal averages (NSA) = 16, slice thickness = 30 mm, 1024 points acquired, duration of echo sampling = 512 ms, spectral width = 2000 Hz, and the RF offset frequency was set to water resonance frequency. The profile width at half height can be calculated using the following formula: Profile width = $\gamma \times \text{Slice thickness} \times \text{Amplitude of read-out gradient}$ (4). For a 30-mm slice thickness, an ideal profile is a rectangular with a width of 51.12 Hz.

Experiments on GE MRS Braino Phantom and NAA Phantom

The sequence parameters for the experiments on the GE MRS Braino phantom were as follows: voxel size = $30 \times 30 \times 30 \text{ mm}^3$, NSA = 8, TR = 2000 ms, minimum TE = 27, 30, and 39 ms for the JPRESS, J-resolved sLASER, and J-resolved LASER sequences, respectively, 32 TE steps with an incremental size TE (or t_1) = 10 ms. 1024×32 points were acquired

with spectral widths of 2000×100 Hz in the $F_2 \times F_1$ dimensions, total scan time = 8 mins and 32 s.

The NAA phantom experiments were used to assess the efficiency of suppressing additional J-refocused peaks by the proposed J-resolved LASER and sLASER sequences, compared with that of JPRESS. In the JPRESS sequence, a lower BW of 180° refocusing pulse (about 843 Hz) instead of the default 180° refocusing pulse “gtst1203” (BW = 1263 Hz) was employed to make J-refocused peaks clearly visible on the 2D JPRESS spectrum. The other parameters are the same as those used in the GE MRS Braino phantom experiments.

In Vivo Experiments on Human Brains

A $30 \times 30 \times 30$ mm³ voxel was placed aligned with the parieto-occipital junction of healthy volunteers. The durations of all spoiler gradients were 1.81 ms and the minimum TEs were 42 ms and 57 ms for the J-resolved sLASER and J-resolved LASER sequences, respectively. The other parameters were the same as those used on the GE MRS Braino phantom.

Spectral Data Processing and Analysis

The 2D MRS data were processed using the Felix software (Accelrys Inc. San Diego, CA, USA). The datasets were zero-filled from 1024 to 2048 points in the direct dimension (F_2) and from 32 to 128 points in F_1 . Solvent suppression with a sinebell window function of 32 Hz was applied. A skewed sinebell-squared window function with the skew parameter of 1, a size of 2048 points, and the phase of 90° was applied to F_2 . A skewed sinebell-squared window function with the skew parameter of 1, a size of 128 points and the phase of 90° was applied to F_1 . The combination of phase = 90° and skew parameter = 1 along both F_1 and F_2 has the advantage to present the 2D spectra with small linewidths and well resolved peaks especially along F_2 direction. A custom-made Matlab program was used for visualization and quantification of peak volumes.

RESULTS

Figure 2 shows the chemical shift displacements in three directions: anterior-posterior (AP), right-left (RL) and foot-head (FH) between the two voxels volume-selected for the chemical shift of 2 ppm (red solid box, for example a NAA peak) and 5.5 ppm (green dashed box, for example a lipid peak), using the JPRESS, J-resolved sLASER, and J-resolved LASER sequences on the GE MRS Braino phantom. The CSDEs were significantly suppressed using J-resolved LASER and sLASER sequences compared with JPRESS sequence. In JPRESS (Fig. 2a), the CSDE of the non-adiabatic slice-selective 90° pulse in AP direction is smaller than those of the non-adiabatic slice-selective 180° pulses in RL and FH directions. In J-resolved sLASER (Fig. 2b), the CSDE of the non-adiabatic slice-selective 90° pulse in AP is the same as that in JPRESS (Fig. 2a) because the same slice-selective 90° excitation pulses were used. However, the CSDEs in the other two directions: RL and FH were significantly suppressed by using two pairs of AFP pulses. In J-resolved LASER (Fig. 2c), the CSDEs in all three directions are significantly suppressed by using three pairs of AFP pulses.

The slice profiles of the refocusing pulse of ‘gtst1203’ used in JPRESS and the AFP pulses used in J-resolved sLASER and J-resolved LASER sequences are shown in Fig. 3. It is

obvious that a single AFP pulse alone cannot be used for slice selection because the signal only exists in a very narrow bandwidth. As shown in Fig. 3, a pair of AFP pulses has higher intensity, a flatter top, steeper edges, and almost completely suppressed sidelobes compared with the refocusing pulse 'gtst1203'. Therefore, the pair of AFP pulses provides improved slice profile than "gtst1203". The 1D experiments on the GE MRS Braino phantom shows that the signals of LASER and sLASER are larger than the signal of PRESS at their respective shortest TEs (figure not shown for simplicity), although the TEs used in the LASER and sLASER sequences are 13 and 3 ms longer than the TE used in the PRESS sequence, respectively. The feasibilities of 2D J-resolved LASER and sLASER sequences were first verified by the experiments on the GE MRS Braino phantom. As shown in Fig. 4, J-resolved LASER and sLASER sequences produced very similar 2D J-resolved spectra with the JPRESS spectrum. The metabolites with coupled spin systems, i.e., Glu, NAA, mI, and Lac (marked in the figure), yielded expected J-resolved peaks arranged at a 45° angle to $F_1 = 0$ axis in the 2D spectra. Because J-multiplet resonances spread into the second dimension, these J-resolved peaks are easier to be resolved in 2D J-resolved spectra than in 1D spectra. Besides the similarity, differences between the J-resolved LASER and sLASER and conventional JPRESS spectra are shown in detail below, which demonstrate the strengths of J-resolved LASER and sLASER over conventional JPRESS. Fig. 4d–f are the zoomed views of the Lac doublet at 1.32 ppm in the white boxes of the left column (Fig. 4a–c). The additional J-refocused artifactual peaks (marked by the yellow solid arrows) are prominent in JPRESS (Fig. 4d), considerably reduced in J-resolved sLASER (Fig. 4e), and further reduced to a minimal level in J-resolved LASER (Fig. 4f). In contrast, the intended J-resolved peaks, as marked by the white dotted arrows, were the strongest in J-resolved LASER and the weakest in JPRESS. This was verified by the quantified peak volumes in Table 1.

Similar with the Lac spectra in Fig. 4, the spectra of NAA phantom in Fig. 5 also shows additional J-refocused artifactual peaks (marked by the red solid arrows) within the double-of-doublets at 2.4 ppm in JPRESS. In contrast, these artifactual peaks are barely seen in J-resolved LASER and sLASER spectra. As a result, the intended J-resolved peaks of the double-of-doublets at 2.4 ppm (marked by the white dotted arrows) were attenuated the most in JPRESS and the least in the J-resolved LASER. The finding on the J-resolved peaks is verified in Table 2, which presents the quantified volumes of intended J-resolved peaks of the two double-of-doublets at 2.4 ppm and 2.6 ppm. In addition, eight additional peaks (marked by the white dashed boxes) appear in the middle of the two double-of-doublets at 2.4 and 2.6 ppm in all three J-resolved spectra. The additional peaks resulted from strong J-coupling between the two spins at 2.4 and 2.6 ppm (27–29). The strong-coupling artifacts of NAA are also clearly seen in the three J-resolved spectra of Fig. 4. A symmetry-based suppression method using two spin-echoes of equal duration was reported to suppress these strong-coupling artifacts (30).

Figure 6 demonstrates how the signals were attenuated with the change of center frequency of RF pulses. Fig. 6a–d are the PRESS spectra and Fig. 6e–h the LASER spectra. The RF frequency offset was set to 2 ppm in Fig. 6a and 6e, 4 ppm in Fig. 6b and 6f, 6 ppm in Fig. 6c and 6g, and 8 ppm in Fig. 6d and 6h. The resonance intensities in PRESS were

significantly attenuated as the RF frequency offset was moved away from the frequencies of those resonance lines. However, the resonance intensities in J-resolved LASER were not attenuated when the RF frequency shifted within the pulse BW.

Figure 7 shows 1D spectra acquired from a voxel encompassing the parieto-occipital junction of a healthy volunteer using three J-resolved spectroscopy sequences at their respective minimum TEs. Compared with JPRESS (Fig. 7a), the lipid/macromolecular (MM) peaks at 0.9–1.6 ppm is reduced in J-resolved sLASER (Fig. 7b) and further reduced in J-resolved LASER (Fig. 7c).

Figure 8 shows the in vivo 2D J-resolved spectra acquired from the parieto-occipital junction of another healthy volunteer using three J-resolved spectroscopy sequences. Compared with the 2D spectra of the GE MRS Braino phantom in Fig. 4, the in vivo 2D J-resolved spectra of the human brain have obviously larger linewidths as well as more apparent “phase-twist” lineshape (7) especially in the singlet resonances of NAA, Cr, and Cho (marked by the green arrows). Except for the above differences, the spectra acquired from the human brain and the GE MRS phantom exhibit very similar 2D J-resolved spectra, which further verified the feasibility of the proposed J-resolved LASER and sLASER sequences for in vivo application. There are two obvious differences among the three J-resolved spectra of the human brain. The first one is on the lipid/MM peaks. Similar with Fig. 7, the lipid/MM peaks are clearly seen in both JPRESS and J-resolved sLASER spectra but barely shown in the J-resolved LASER spectrum. Furthermore, the lipid/MM peaks in the J-resolved sLASER spectrum (Fig. 8b) were not reduced distinctly compared with the JPRESS spectrum (Fig. 8a), because the slice close to the scalp was defined by a regular slice-selective 90° pulse in both sequences. In contrast, the extracranial lipid due to CSDE was significantly suppressed in J-resolved LASER using three pairs of AFP pulses for voxel localization. The second obvious difference is on the residual water peak, which is most prominent in JPRESS, reduced in J-resolved sLASER and smallest in J-resolved LASER. This observation is consistent with a recent report of adiabatic localized COSY spectra (4). Decrease in residual water and out-of-volume lipid/MM signals will benefit the spectral quantification, especially for those metabolites with resonances close to the strong “phase-twisted” water or lipid peaks.

Compared to the 2D J-resolved spectra of the GE MRS Braino phantom in Fig. 4, the metabolites in the human brain yielded very similar resonances in Fig. 8 (see marked metabolites) and even those additional peaks of NAA due to strong J-coupling in phantom spectra (Figs. 4 and 5) also clearly show in the in vivo spectra. However, the GE MRS Braino phantom only contained NAA, Cr, Cho, Glu, mI and Lac, while there are about 20 MRS-detectable metabolites in the human brain. Some metabolite resonances still overlap with each other in the in vivo spectra, such as Glu resonances with glutamine (Gln) resonances at 3.75 ppm, NAA with Gln at 2.45 ppm and aspartate (Asp) at 2.65 ppm. Quantification of 2D MRS spectra by peak volumes needs precise selection of peak areas free from any overlap (29,31). Quantification can be further improved by 2D fitting such as ProFit (32). However, correlation matrix analysis revealed that two metabolites could not be reliably retrieved by quantitation algorithms if all the resonances of one metabolite reside at the same locations in spectral space as those of the other metabolite (33–35). Because of the

above reason, J-resolved LASER and J-resolved sLASER possess obvious advantages over conventional JPRESS because suppression of CSDE and additional J-refocused artifactual peaks as well as reduction of residual water peak and lipid/MM signals can significantly reduce the chance of overlap and thus improve the spectral quantification of 2D MRS data.

DISCUSSION

In the present work, J-resolved LASER and sLASER sequences were proposed and tested in phantom and human experiments. The AFP pulses can produce uniform flip angle over a large BW. As shown in Fig. 6, the resonance intensities in the J-resolved LASER spectra were hardly affected by the change of RF frequency offset in a wide range. In contrast, the resonance intensities in the JPRESS spectra were severely attenuated when the offset frequency was moved away from the frequencies of the resonance lines.

As shown in Fig. 7, the CSDEs in the form of extracranial lipid signal were reduced evidently in J-resolved LASER and sLASER compared to JPRESS. In Fig. 8, the reduction of extracranial lipid signal is not obvious in J-resolved sLASER compared to JPRESS, because the regular slice-selective 90° pulse in the J-resolved sLASER sequence was set to define the slice close to the scalp.

The 2D spectra acquired on the GE MRS Braino phantom (Fig. 4) and the NAA phantom (Fig. 5) show additional J-refocused peaks in JPRESS spectrum while these additional artifactual peaks were significantly suppressed in J-resolved LASER and sLASER spectra. The additional J-refocused artifactual peaks double the number of peaks of weakly-coupled spin systems in the 2D J-resolved spectrum and make the spectrum more crowded and thus more difficult to resolve and quantify the metabolite signals. Furthermore, the intensities of the intended J-resolved peaks are attenuated by the factor of $(1 - f/BW)$ (7–9). It will further impair the quantification of JPRESS spectra if this factor is not considered or not considered correctly. The imperfect flip angle of last 180° RF pulse also leads to additional artifactual peaks which are known as “phantom” and “ghost” responses in heteronuclear J-spectra reported by Bodenhausen et al. (36). However, the “phantom” and “ghost” multiplets can be eliminated by phase cycling or gradients, but the J-refocused peaks have the same coherence transfer pathway as the J-resolved peaks and cannot be removed by phase cycling or gradients (7,36).

In Table 1, the J-refocused peaks were smaller in J-resolved LASER than J-resolved sLASER because the t_2 noise along F_2 axis was weaker in J-resolved LASER than that in the J-resolved sLASER. The t_2 noise level increases with the signal amplitudes in the spectrum (37). In the case of the GE MRS Braino phantom experiments, the level of the noise along F_2 axis was mainly controlled by the amplitude of dominant residual water signal. The residual water signal was strongest in the JPRESS spectrum and weakest in the J-resolved LASER spectrum, which therefore brought about the strongest t_2 noise in the JPRESS spectrum and the weakest t_2 noise in the J-resolved LASER spectrum (see Fig. 4d–f). This is also the reason that the total Lac peak volume (sum of the J-refocused peak volumes and J-resolved peak volumes) is larger in the JPRESS spectrum than those in the J-resolved sLASER and J-resolved LASER spectra as shown in Table 1.

Reducing spectral overlap is an efficient way to improve the quantification of 2D J-resolved spectra. We proposed combining the following two schemes: (1) using J-resolved LASER or J-resolved sLASER instead of JPRESS to suppress the additional J-refocused artifactual peaks, thus reducing the chance of spectral overlap and at the same time maintaining the intensities of intended J-resolved peaks, and (2) using so-called “maximum-echo sampling” (i.e., starting data acquisition immediately after the second spoiler gradient of the last AFP pulse) instead of commonly used half-echo sampling (38). In half-echo sampling, J-resolved spectroscopy suffers from long dispersive tails due to the 2D phase-twist lineshape (marked by green arrows in Fig. 8), which increases the chance of spectral overlap especially along the $F_1 = 0$ axis. Maximum-echo sampling will tilt the peak tails away from the $F_1 = 0$ axis so overlap can be mitigated especially from the prominent resonances of NAA, Cr, Cho, residual water, and lipids. What is more, due to a large sampling interval ($t_1 = 10$ ms), the maximum t_1 is 310 ms at the last t_1 step. Significant signal loss due to T_2 -weighting effects is a major drawback of 2D J-resolved spectroscopy with half-echo sampling. Therefore, using the maximum-echo sampling with the acquisition starting directly after the final crusher gradients and a much smaller sampling interval (for example $t_1 = 0.8$ ms), the T_2 -weighting effects can be minimized (31,38).

In summary, J-resolved LASER and J-resolved sLASER spectroscopy were proposed in the present work and verified with the phantom and human brain experiments. To the best of our knowledge, this is the first time to report 2D adiabatic J-resolved spectroscopy on the human brain. Compared with JPRESS, both versions of adiabatic J-resolved spectroscopy significantly suppressed the additional J-refocused artifactual peaks and reduced the CSDE. Between the two adiabatic J-resolved spectroscopy methods, J-resolved sLASER sequence has the advantages of shorter TE (or possibly higher SNR) and lower SAR, but the CSDE in J-resolved sLASER is larger than that in J-resolved LASER. Although SNR will be potentially lower in J-resolved sLASER and J-resolved LASER than JPRESS, the following advantages, the insensitivity to B_1 inhomogeneity, the ability to provide uniform flip angle over large BWs, and the suppression of chemical shift artifacts and additional J-refocused artifactual peaks, make J-resolved LASER and J-resolved sLASER spectroscopy promising in the in vivo application for more reliable and accurate quantification of metabolites.

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Fig. 1.

Diagrams of (a) J-resolved LASER and (b) J-resolved sLASER sequences. To build the second dimension, the first half of incremental period $t_1/2$ was inserted between the last pair of AFP pulses. RF-AM shows the amplitude modulation profiles of the AFP pulses, RF-FM the frequency modulation profiles. Δ_1 is the interval between the excitation RF pulse and the beginning of the first AFP spoiler gradient. Δ_2 is the interval between a pair of AFP spoiler gradients, including the AFP pulse.

Fig. 2. Chemical shift displacements between 2 ppm and 5.5 ppm in the three directions (AP, RL, and FH) generated by the pulse sequences of (a) JPRESS, (b) J-resolved sLASER, and (c) J-resolved LASER. The red line boxes are the voxels volume-selected for the chemical shift of 2 ppm (for example a NAA peak) and the green dash ones for 5.5 ppm (for example a lipid peak).

Fig. 3.
The slice profiles of the refocusing pulses of gtst1203 (black dash line), a single AFP pulse (blue dotted line) and a pair of AFP pulses (red solid line).

Fig. 4.

2D spectra from GE MRS Braino phantom: (a) JPRESS with TE starting at 27 ms, (b) J-resolved sLASER with TE starting at 30 ms; and (c) J-resolved LASER with TE starting at 39 ms. (d–f) are the zoomed views of the white boxes showed in (a–c) to illustrate the doublet of Lac at 1.33 ppm, respectively. The 2D J-resolved LASER and sLASER spectra show almost the same pattern as the JPRESS spectrum. However, compared with the JPRESS spectrum, the additional J-refocused peaks (marked by yellow solid arrows) are significantly suppressed and the intended J-resolved peaks (marked by white dashed arrows) are less attenuated in the J-resolved LASER and sLASER spectra. The additional J-refocused peaks are strongest in JPRESS and weakest in J-resolved LASER. In contrast, the intended J-resolved peaks are strongest in J-resolved LASER and weakest in JPRESS. Most of the J-multiplets such as NAA, ml, Lac, and Glu can be clearly separated in the 2D spectra.

Fig. 5.

2D spectra of NAA at 2.20–2.75 ppm: (a) JPRESS using low-BW pulses, (b) J-resolved sLASER, and (c) J-resolved LASER. The red solid arrows mark the additional J-refocused peaks and the white dotted arrows the intended J-resolved peaks. There are eight additional peaks due to strong coupling effects in all the three spectra, marked by the white dashed boxes.

Fig. 6.

Signal attenuation in the 1D spectra of the GE MRS Braino phantom with the change of center frequency of the RF pulses of JPRESS (a–d) and J-resolved LASER (e–h) at their respective minimum TEs. The RF frequency offset was set to 2 ppm in (a) and (e), 4 ppm in (b) and (f), 6 ppm in (c) and (g), and 8 ppm in (d) and (h). The resonance intensities in JPRESS are attenuated significantly when the RF frequency is moved away from the frequencies of those resonance lines, while the resonance intensities in J-resolved LASER are stable.

Fig. 7. 1D spectra acquired from a voxel encompassing the parieto-occipital junction of a healthy volunteer using (a) JPRESS, (b) J-resolved sLASER, and (c) J-resolved LASER sequences at their respective minimum TEs. The lipid/MM peaks at 0.9, 1.3 and 1.6 ppm are strongest in PRESS and smallest in LASER.

Fig. 8. 2D spectra acquired from a voxel encompassing the parieto-occipital junction of another healthy volunteer using (a) JPRESS, (b) J-resolved sLASER, and (c) J-resolved LASER. The lipid signal from the scalp is clearly seen in the JPRESS and J-resolved sLASER spectra but barely observed in the J-resolved LASER spectrum. Moreover, compared with JPRESS, the residual water signal is smaller in J-resolved sLASER and smallest in J-resolved LASER. The “phase-twist” lineshape is marked by the green arrows.

Table 1

Peak volumes of additional J-refocused artifactual peaks vs. intended J-resolved peaks of Lac at $F_2 = 1.32$ ppm in Fig. 4.

Experiments	J-refocused peak volume (i.u.)		J-resolved peak volume (i.u.)	
	$F_2 = 1.32$ ppm		$F_2 = 1.32$ ppm	
	left	right	left	right
JPRESS	462	432	728	706
J-resolved sLASER	313	253	877	781
J-resolved LASER	166	136	892	835

Peak volumes of two double-of-doublets (intended J-resolved peaks) of NAA at $F_2=2.6$ ppm and 2.4 ppm in Fig. 5 (normalized to NAA singlet peak volume at 2.0 ppm).

Table 2

Experiments	Peak volumes of double-of-doublets (from left to right in Fig. 5)							
	$F_2 = 2.6$ ppm				$F_2 = 2.4$ ppm			
JPRESS	0.039	0.041	0.089	0.088	0.061	0.079	0.042	0.035
J-resolved sLASER	0.055	0.070	0.091	0.082	0.084	0.080	0.082	0.048
J-resolved LASER	0.059	0.069	0.103	0.093	0.053	0.090	0.093	0.048