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Non-uniformly weighted sampling for faster localized two-dimensional correlated spectroscopy of the brain in vivo

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ABSTRACT

Two-dimensional localized correlated spectroscopy (2D L-COSY) offers greater spectral dispersion than conventional one-dimensional (1D) MRS techniques, yet long acquisition times and limited post-processing support have slowed its clinical adoption. Improving acquisition efficiency and developing versatile post-processing techniques can bolster the clinical viability of 2D MRS. The purpose of this study was to implement a non-uniformly weighted sampling (NUWS) scheme for faster acquisition of 2D-MRS. A NUWS 2D L-COSY sequence was developed for 7T whole-body MRI. A phantom containing metabolites commonly observed in the brain at physiological concentrations was scanned ten times with both the NUWS scheme of 12:48 duration and a 17:04 constant eight-average sequence using a 32-channel head coil. 2D L-COSY spectra were also acquired from the occipital lobe of four healthy volunteers using both the proposed NUWS and the conventional uniformly-averaged L-COSY sequence. The NUWS 2D L-COSY sequence facilitated 25% shorter acquisition time while maintaining comparable SNR in humans (+0.3%) and phantom studies (+6.0%) compared to uniform averaging. NUWS schemes successfully demonstrated improved efficiency of L-COSY, by facilitating a reduction in scan time without affecting signal quality.

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1. Introduction

Two-dimensional (2D) magnetic resonance spectroscopy (MRS) methods [1,2], such as localized correlated spectroscopy (L-COSY), have demonstrated the ability to uniquely resolve more metabolites than conventional 1D MRS [3–5]. The additional spectral dimension of 2D L-COSY increases spectral resolution and facilitates improved differentiation between metabolites which otherwise appear co-resonant with conventional 1D approaches [4–6]. However, clinical adoption of 2D L-COSY techniques has thus far been hindered by the unique challenges presented by 2D acquisition and reconstruction. Among these are long scan time needed for acquiring multiple Δt_1 increments, and spectral artifacts generated when 2D spectra are reconstructed using 1D-specific post-processing techniques. Addressing these challenges could spur clinical adoption of L-COSY and other similar techniques.

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2D L-COSY indirectly monitors t_1 evolution by incorporating incrementing time delays (Δt_1) between the refocusing and coherence-transfer pulses [3]. J-coupled spin systems experiencing coherence transfer during Δt_1 evolution exhibit different resonances during the readout phase. These resonances manifest as “cross-peaks” in the 2D spectrum with different frequencies during the t_1 evolution and t_2 readout periods ($F_1 \neq F_2$). Systems not exhibiting coherence transfer have identical frequencies during the t_1 evolution and t_2 readout periods and appear as “diagonal peaks” where $F_1 = F_2$. Cross-peaks can facilitate differentiation of metabolites with similar resonances by taking advantage of separation along the second spectral dimension. This added sampling results in longer scan time, as increasing spectral resolution along the F_1 dimension requires multiple Δt_1 increments. Typical in vivo 2D L-COSY studies on clinical MRI systems include 64 or more Δt_1 increments, resulting in scan times in the order of 20–40 min, particularly when coupled with multiple averages [3,4,7,8].

Using uniform averaging, SNR improves as a function of the square root of the number of excitations (N_{EX}), yet acquisition time (T_{Acq}) increases linearly with N_{EX} .

$$SNR \propto \sqrt{N_{EX}} \quad (1)$$

$$T_{Acq} \propto N_{EX} \quad (2)$$

Because J-coupling is independent of B_0 field strength, the distribution of signal is predictable along the t_1 dimension [9–11]. Non-uniformly weighted-sampling (NUWS) takes advantage of this predictability by matching the sampling frequency of Δt_1 increments to areas of greater signal density, rather than uniformly distributing averages across each increment [11–14]. By matching signal averaging to the empirically measured signal amplitudes, as shown in Fig. 1, NUWS can improve the acquisition efficiency of 2D MRS techniques. This can result in an SNR greater than what would be expected for a given total number of excitations. The relationship between SNR from a NUWS sequence compared to a uniformly-sampled sequence was described by Waudby et al. [14] as:

$$\frac{SNR_{NUWS}}{SNR_{Uniform}} = \frac{\sqrt{w^2}}{\bar{w}} \quad (3)$$

where w is the weighting and defined as:

$$w = hN_{EX} \quad (4)$$

where h is the height of the windowing function and N_{EX} is the number of excitations associated with a measurement. As noted by Waudby et al., Jensen's Inequality shows that:

$$\overline{w^2} \geq \bar{w}^2 \quad (5)$$

And therefore

$$SNR_{NUWS} \geq SNR_{Uniform} \quad (6)$$

Spectral acquisition schemes like an NUWS L-COSY sequence produce data structures whose complexity is often not accounted for by conventional 1D-specific post-processing strategies. Reconstructing 2D spectra with an uneven distribution of averages, or combining spectra from multiple receiving channels without accounting for this complexity can introduce artifacts to the resulting data. A dramatic example is the introduction of artificial “parallel diagonals” in 2D spectra resulting from the zero-phasing of each Δt_1 increment during conventional coil combination [15]. Zero-phasing of 2D data introduces artificial phase offsets to each Δt_1 increment, resulting in multiple parallel resonances distributed along the F_1 dimension. Developing a versatile offline processing tool enables additional flexibility in handling these complexities and anticipates future developments that may cause further deviation from conventional post-processing. This includes coil

combination schemes that preserve the phase along the t_1 dimension and signal averaging that accommodates uneven distribution of averages. Implementing a robust post-processing platform can therefore facilitate the development of these new advanced acquisition strategies both by enabling offline processing and improving data presentation. This platform could eliminate the need for data reconstruction to be tied to the proprietary software, instead providing a transparent and versatile tool to reconstruct spectroscopic data offline. Such a program could also improve the presentation of spectroscopic data, by taking advantage of the native plotting functions, or alternatively handle 2D-specific processing from raw data and then hand off partially processed spectra to specialized third-party software like Felix NMR (San Diego, CA). Effective presentation of spectroscopic data would allow clinicians to more quickly access the clinical findings contained therein, which could lead to more widespread adoption.

The primary goal of this study was to improve the acquisition efficiency of 2D L-COSY by weighting averages to take advantage of the distribution of signal along the indirect (t_1) dimension.

2. Materials and methods

2.1. Sequence development

NUWS 2D L-COSY sequences were developed for phantom and in vivo applications at 7T. The design of each NUWS sequence was optimized empirically by monitoring the distribution of signal along the t_1 dimension in uniformly-weighted 2D L-COSY datasets. L-COSY spectra were initially acquired from a phantom using the following parameters: TE/TR = 20 ms/2000 ms, 2048 t_2 points, 64 Δt_1 increments with 16 averages per increment, 34-min scan time. Increment durations were 0.4 ms with corresponding bandwidths of $F_2/F_1 = 4000$ Hz/2500 Hz. The voxel size was $2.0 \times 2.0 \times 2.0$ cm³ (8.0 ml) for all studies acquired using the brain phantom. Scans were acquired using a 32-channel “transmit/receive” head coil on a Siemens 7T whole-body scanner. All phantom scans were performed using a home-built white matter phantom containing sixteen brain metabolites commonly found in the brain [5,6] at physiological concentrations and with pH = 7.0.

Sequence optimization was performed by analyzing metabolic signal profiles while sequentially emphasizing the averaging of each Δt_1 increment. Emphasis of individual Δt_1 increments was accomplished as follows: a large dataset consisting of 64 Δt_1 increments with 16 averages per increment was initially obtained. 64 different iterations of the dataset were generated where 16 averages were maintained for a single Δt_1 increment and all but a single average was truncated for the remaining increments. The signal was normalized by comparing the signal intensity of a given metabolite peak for an emphasized increment to the signal of the dataset with a single average per increment.

2.2. Simulation methods for cross peak comparison

In order to determine the effects of NUWS on L-COSY cross peaks, four metabolites with prominent cross peaks were simulated using GAMMA simulation [16] with the same acquisition parameters as the phantom and in vivo measurements. The four metabolites included were: lactate (Lac), aspartate (Asp), GABA, and glutathione (GSH), and these were simulated using known chemical shift and coupling constants [17]. These metabolites were then imported into MATLAB and processed using the following steps: (1) metabolites were line broadened by 9 Hz to mimic the in vivo situation, (2) metabolites were transformed into the (F_2, t_1) domain and were duplicated nine times, yielding a ($F_2, t_1, 9$) matrix, 3) Noise was introduced to the ($F_2, t_1, 9$) matrix for each

Fig. 1. Non-uniform weighting-sampling (NUWS) profiles for the human brain (blue) and phantom studies (red). 384 excitations were acquired over 64 t_1 increments, an average of six per increment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

metabolite using a noise power similar to phantom acquisitions. The third dimension in this three-dimensional matrix acted as the averaging dimension for the simulated acquisition. The metabolites were then sampled using a uniform sampling scheme, the NUWS scheme used for the phantom measurements (NUWS 1), and the NUWS scheme used for the *in vivo* measurements (NUWS 2). For the uniform sampling scheme, the first six averages were used for every t_1 point, resulting in time equivalent acquisitions for the three sampling methods.

The prominent cross peaks of the four metabolites were analyzed both qualitatively and quantitatively. For quantitative comparisons, peak integration of the cross peak regions for each metabolite were used to determine overall signal improvement. The peak integrals of NUWS 1 and NUWS 2 were taken as a ratio with respect to the uniformly sampled cross peak integral, which was used to demonstrate SNR improvement. In addition, the cross peak regions were scaled to have the same maximum value, and a root mean square error (RMSE) was computed:

$$RMSE = \sqrt{\sum_{p=1}^p \left(I_{u,p} - \frac{\max(I_u)}{\max(I_{NUWS})} I_{NUWS,p} \right)^2} \quad (7)$$

Above, p is the number of points in each cross peak, $I_{u,p}$ is the intensity of point p of the uniformly sampled acquisition, $I_{NUWS,p}$ is the intensity of point p of the NUWS measurement, $\max(I_u)$ is the maximum of the uniformly sampled cross peak, and $\max(I_{NUWS})$ is the maximum of the NUWS cross peak. By normalizing the maximum peak values, this scaled RMSE is capable of demonstrating the differences in line shape between the uniformly sampled L-COSY and the NUWS L-COSY.

The NUWS scheme was developed proportional to the measured signal intensity for each increment and weighted to have 384 excitations – the equivalent of a six-average L-COSY study (12:48 min of scan time with 64 Δt_1 increments). Fig. 1 shows these empirically-optimized NUWS profiles selected for human brain studies (blue) and phantom studies (red), respectively. Empirical determination of signal amplitudes was performed separately for phantom and *in vivo* studies, using the oversampled studies consisting of 16 averages per increment. A sine-bell shaped NUWS profile was selected as the optimal scheme for phantom studies, but this profile was skewed toward the earlier increments to accommodate the shorter T_2^* relaxation times for human brain studies. Fig. 1 shows the number of averages for each Δt_1 increment for both *in vivo* and *in vitro* NUWS acquisition schemes.

The NUWS schemes were optimized by quantifying the effect of sequentially emphasizing the signal averaging for each t_1 increment on each quantified metabolite. By applying this optimization to only a single metabolite, the sequence could be made more versatile for applications in which only a specific metabolite is of interest. To demonstrate the viability of this strategy, an NUWS scheme was developed to maximize the yield of glutathione (GSH), a biomarker for oxidative stress relevant in several neurological pathologies [18–21]. The GSH-optimized sequence also featured 384 excitations over 64 t_1 increments, resulting in the same 12:48 min duration as the general NUWS sequence.

2.3. Data acquisition

Following sequence development, the NUWS L-COSY sequences were acquired in a comparative study along with a uniformly-weighted L-COSY sequence. Four healthy volunteers (ages 30–45 years) were scanned with both sequences. One volunteer was further scanned a total of five times to determine the intra-subject variability of the NUWS sequence. Phantom studies were performed by scanning the brain phantom ten times with both

the NUWS and uniformly-weighted L-COSY sequence. Common scan parameters were as follows: TE/TR = 20 ms/2000 ms, 2048 t_2 points, 64 Δt_1 increments of 0.4 ms duration, bandwidths of $F_2/F_1 = 4000$ Hz/2500 Hz. Total duration of the t_1 encoding was 25.2 ms while using 64 Δt_1 increments. The NUWS L-COSY sequence featured a variable 1–9 averages per Δt_1 increment and had a total duration of 12:48 min. The uniformly-weighted L-COSY sequence featured identical scan parameters except that a uniform eight averages were acquired per increment, resulting in a total scan time of 17:04 min. For comparison purposes, the post-processing program was used to generate a six-average-equivalent 2D L-COSY dataset by truncating the final two averages from each t_1 increment of the uniformly-weighted dataset. As with the NUWS spectra, these data also contained information from 384 total excitations, simulating an equivalent 12:48 min duration – though these were uniformly distributed over the 64 Δt_1 increments. A $2.5 \times 2.5 \times 2.5$ cm³ (15.6 ml) voxel was localized in the occipital lobe for human brain studies while a $2.0 \times 2.0 \times 2.0$ cm³ (8.0 ml) voxel was used in the phantom studies. Both of these voxel sizes are smaller than the respective voxels presented in an earlier reproducibility sequence with 2D L-COSY [5] study, reflecting improvements made in B_1 field homogeneity performance through the incorporation of Shinnar-LeRoux (SLR) pulses and improved shimming using the Siemens-provided FASTESTMAP algorithm. All studies were performed using the same 32-channel head coil and a 7T MRI/MRS scanner.

2.4. Coil combination & data processing

Processing 2D L-COSY data from phased-array coils result in the introduction of “parallel diagonal” artifacts in the 2D spectra when processed through conventional coil combination schemes meant for 1D MRS. These artifacts probably arise from zero-phasing of each Δt_1 increment performed in the phase matching step of coil combination. To test this hypothesis, data from the 32-channel head coil were processed in two ways: (1) conventional coil combination with zero-phasing of each Δt_1 increment and (2) phase-preserving coil combination where zero-order phasing was performed only on the first Δt_1 increment and these offsets were carried through each subsequent increment. Performing these custom coil combinations necessitated the development of an independent post-processing platform to operate directly on raw data from the scanner. Reconstructing 2D spectra from the raw data required: signal averaging, resolving oversampling, filtering, phase correction, eddy current compensation [22], Fourier transform and coil combination [15,23] and was performed in MATLAB (The Mathworks, Natick, MA). Fig. 2 contains a flow chart showing processing steps involved in this reconstruction algorithm.

Once processed, reconstructed 2D spectra were quantified using the peak integral volume method [5,6,10] and the known chemical shifts of the brain metabolites [17]. Signal quality was determined by comparing the SNR, which was computed by dividing the signal (S) to the standard deviation of the noise (σ_{Noise}) derived from a region of the 2D spectra where no signal was expected. For a given metabolite i , the SNR was defined as:

$$SNR_i = S_i / \sigma_{\text{Noise}} \quad (8)$$

where multiple cross-peaks from a single metabolite were quantified, the signal was measured as the sum of each cross-peak integral. Each metabolite resonance was quantified for both the NUWS and uniformly-weighted sequences, and then normalized to the SNR of the uniformly-weighted sequence. This normalization allowed SNR comparisons to be performed across an average of all metabolites rather than focus on a particular one.

Fig. 2. Flow chart showing the post-processing steps involved in reconstructing 2D L-COSY spectra from raw data.

3. Results

The simulation results demonstrated differences between the uniformly sampled and NUWS L-COSY acquisition methods. Fig. 3 shows the cross peaks for Lac, Asp, GABA, and GSH for all three acquisition methods. It is clear that differences are present in the peak shapes, especially for GSH and GABA. These differences are further highlighted in Fig. 4, where a single F_1 line is shown for the three sampling schemes. While they appear very similar, some areas in the cross peak have increased signal using NUWS 1 and 2. Quantitatively, this increased signal amounts to slight SNR enhancement for the two NUWS methods, as tabulated in Table 1. RMSE values show that NUWS 1 has more differences in peak shape than NUWS 2. However, when comparing the RMSE values to the total signals in the cross peak regions, these RMSEs correspond to only 2–3% differences.

Fig. 5 shows SNR from the 17:04 min duration uniformly-weighted and 12:48 min duration NUWS studies acquired from the human brain and from the phantom, normalized to the SNR of the uniformly-weighted study. The NUWS schemes produced SNR of 0.3% (human brain inter-subject and intra-subject) and 6.4% (phantom) higher than the 17:04 uniformly-weighted studies.

Compared to the reconstructed uniformly-weighted data-set with the equivalent number of excitations, the NUWS schemes resulted in 13% higher SNR between subjects, 14% higher SNR within the same subject who was scanned five times and 18% higher SNR in the phantom studies. Considering the shorter duration of 25.2 ms with 64 Δt_1 increments, higher SNR may be possible using longer t_1 evolution.

Fig. 6A and B show 2D spectra acquired from 17:04 min uniformly-weighted and 12:48 min NUWS L-COSY sequences, respectively. Despite the shorter scan duration, each of the metabolite resonances detected during the uniformly-weighted study were also detected by the 12:48 min NUWS scan. Each of these spectra were reconstructed and plotted in MATLAB using the developed post-processing program. Identified in both figures are also diagonal peak resonances due to choline (Cho), creatine (Cr) and N-acetylaspartate (NAA) as well as cross-peak resonances due to aspartate (Asp), glutamate (Glu), glutamine (Gln), glutathione (GSH), isoleucine (Ile), lysine (Lys), myo-Inositol (mI), NAA, phosphocholine (PC), glycerophosphocholine (GPC), phosphoethanolamine (PE) and the overlapping resonances of mI and Cho (mI + Cho). Despite comparable SNR, some additional ridging could be seen in each of the three human brain scans around the region

Fig. 3. The cross peaks for Lac, Asp, GABA, and GSH are shown for simulated acquisitions utilizing uniform sampling (left), non-uniformly weighted-sampling for phantom measurements (NUWS 1, middle), and non-uniformly weighted-sampling for in vivo measurements (NUWS 2, right). Minor differences arising from the three sampling schemes are apparent, but the overall line shapes remain similar for all three acquisition methods.

Fig. 4. A direct comparison (right) between the three sampling schemes is shown for the cross peaks of Lac, Asp, GABA, and GSH from the simulated measurement. The cross peaks for the four metabolites using uniform sampling are shown on the left, and the red line indicates the F_1 line used for the comparison. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
The quantitative SNR enhancement and scaled RMSE between the two non-uniformly weighted-sampling schemes (NUWS 1 and NUWS 2) and the uniformly sampled simulated acquisition are shown. Scaled RMSE is indicative of the total difference between the line shapes, whereas SNR enhancement indicates the increase in overall signal for the cross peaks.

Cross peak	NUWS 1		NUWS 2	
	SNR enhancement	RMSE	SNR enhancement	RMSE
Lac	1.03	2.21	1.02	1.84
Asp	1.04	1.45	1.02	1.05
GABA	1.04	2.48	1.01	1.57
GSH	1.14	1.32	1.05	1.18

Lac: Lactate, Asp: Aspartate, GABA: gamma-aminobutyric acid, GSH: glutathione.

of lipids at $F_1 = 1.2$ ppm. Volume integral measurements of this region showed that this lipid ridging was pronounced by a factor of 1.42 ± 0.224 in the NUWS spectra. The brain phantom did not contain any lipids and thus resulting spectra were not subject to this ridging.

To test whether the selective emphasis of t_1 increments through averaging would significantly affect metabolite ratios, the ratios of each quantified peak to the diagonal resonance of Cr at 3.0 ppm were compared between uniformly-weighted and NUWS spectra.

Table 2 shows the ratios (Cr_d) for five metabolites (the diagonal peaks {Cho_d, NAA_d} and cross peaks {GSH, Glu and Gln}) in both human brain and phantom studies. Across all quantified metabolites, the ratio with respect to creatine varied by 8.9% on average between the NUWS and uniformly-weighted sequences for human studies and 4.5% in phantom studies. These differences represent the variability as a percentage of the ratio and are in line with coefficients of variation (CVs) of 2D L-COSY studies observed by previous studies [4–6]. A two-tailed student's t -test performed on the

Fig. 5. Average SNR of 16 brain metabolites quantified from uniform eight-average (blue) and NUWS studies (red), along with average SNR from a simulated, six-average study (gray). Results are shown for multiple subjects (inter-subject), same subject scanned multiple times (intra-subject) and phantom studies and all values have been normalized to the uniform eight-average scan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

each quantified metabolite ratio showed no significant differences (using significance level of $p < 0.01$) between the uniformly-weighted and NUWS datasets.

Fig. 7 shows the cross peak due to GSH at $[F_2, F_1] = 4.5, 2.9$ ppm as seen in spectra from a uniformly-weighted sequence of 17:04 duration as well as NUWS and GSH-optimized sequences of 12:38 duration. The peak integral of GSH was higher in the GSH-optimized sequence at 5.29 than either the uniformly-weighted (5.12) or NUWS (4.93) studies.

Fig. 8 shows the 32-channel coil data processed through conventional zero-phasing coil combination and through the phase-preserving method in which only the first t_1 increment is zero-phased and the phase offsets are carried through the remaining increments. The parallel diagonal artifacts can be clearly seen in

the conventionally-combined data, but do not appear when the same data are processed with the phase-preserving method. These results clearly demonstrate the loss of phase information along the t_1 dimension to be the underlying cause of these parallel diagonal artifacts. This phase-preserving scheme was subsequently incorporated into the offline post-processing platform developed as part of this study.

The MATLAB-based program was used to perform scaling, averaging, zero-filling, linear prediction, line-broadening filters, phase correction, eddy current correction [22] and DC offset removal. After Fourier transform, spectra were quantified using the volume integral method based on the known chemical shifts of metabolites [17]. A description of the MATLAB-based program is presented in the [supplementary section](#).

4. Discussion

NUWS scheme was implemented to improve the acquisition efficiency of 2D L-COSY in both human and phantom studies at 7T. The resulting NUWS sequences produced SNR slightly higher (6.4% in phantom and 0.3% in human brain) than that of an eight-average sequence of longer duration. Though these gains in performance are within the test-retest reproducibility range of the sequence, they reflect a substantial performance gain over an equivalent-duration sequence. The SNR was 14–18% higher than what would be expected of a uniformly-weighted sequence of equivalent duration. These performance gains are in line with the ‘real world’ increase in SNR of 10–20% described by Waudby et al. [14]. The balanced sine-bell scheme that was implemented for brain phantom did not show comparable performance gains in human studies (data not shown), likely due to the faster T_2^* relaxation times in vivo during the t_1 evolution of 25.2 ms. The sine-bell profile was then skewed toward the earlier t_1 increments for human brain studies to accommodate these faster T_2^* relaxation times observed in tissues. This heavier weighting on the earlier t_1 increments had the tradeoff of somewhat increased lipid ridging. This may preclude NUWS for specific applications focusing on

Fig. 6. (A) 15.6 ml occipital lobe 2D L-COSY spectrum from a 17:04 min duration uniformly-averaged scan from the occipital lobe of a normal volunteer (age 32). Metabolite peaks assignments are based on (21). Sagittal and axial images showing voxel localization are shown in the lower left of each spectrum. (B) 15.6 ml occipital lobe 2D L-COSY spectrum from a 12:48 min NUWS scan from the same voxel location as Fig. 6A. The same metabolite peaks have been identified and labeled [21].

Table 2

Metabolite signal ratios of Cho_d/Cr, NAA_d/Cr, GSH/Cr, Glu/Cr and Gln/Cr in uniformly-averaged (Uniform) and NUWS sequences for human brain and phantom studies.

	Inter-subject (n = 4)		Intra-subject (n = 5)		Brain phantom (n = 10)	
	Uniform	NUWS	Uniform	NUWS	Uniform	NUWS
Cho_d/Cr	0.68 ± 0.05	0.69 ± 0.05	0.68 ± 0.04	0.73 ± 0.02	1.14 ± 0.03	1.16 ± 0.02
NAA_d/Cr	1.22 ± 0.12	1.24 ± 0.12	1.44 ± 0.10	1.41 ± 0.14	1.90 ± 0.04	1.90 ± 0.02
GSH/Cr	0.05 ± 0.02	0.05 ± 0.01	0.03 ± 0.004	0.04 ± 0.006	0.03 ± 0.005	0.03 ± 0.004
Gln/Cr	0.22 ± 0.01	0.22 ± 0.02	0.19 ± 0.02	0.19 ± 0.01	0.44 ± 0.07	0.42 ± 0.07
Glu/Cr	0.23 ± 0.02	0.25 ± 0.03	0.27 ± 0.03	0.33 ± 0.09	0.71 ± 0.07	0.68 ± 0.06

Cho_d and NAA_d are the diagonal peaks.

Fig. 7. Zoomed-in cross peak of GSH at $[F_2, F_1] = 4.5, 2.9$ ppm from scans using uniformly-averaged, NUWS and GSH-optimized sequences.

resonances found in the region of lipids at 1.3 ppm, including lactate, whose above-the-diagonal resonance appears at $F_1/F_2 = 4.1/1.3$ ppm. However, quantification of lactate can still be performed on the opposite cross-peak at $F_1/F_2 = 1.3/4.1$ ppm, making lipid ridging a minor drawback of the NUWS scheme.

The simulation experiments show mild improvement using the NUWS methods when compared to the uniformly sampled method. In particular, SNR enhancement is shown to be between 2 and 14% for these metabolites. Also, cross peak shapes are modified by 2–3%. Since specific in vivo T_2 values for Lac, Asp, GABA, and GSH are unknown, a more accurate simulation could not be performed. By incorporating shorter T_2 times into the simulation, the SNR of the cross peaks would be further enhanced and the line shapes may be increasingly altered. These distorted line shapes may not have as large of an impact on quantitation, however, due to the fact that line broadening is already severe for in vivo data, the fine structure of the cross peaks are usually undetectable in vivo, while SNR improvements are noticeable.

Because of the selective emphasis of particular t_1 increments, NUWS could produce a differential impact on the signal intensity of metabolic resonances relative to relaxation times and the distribution of noise. This would produce slight differences in metabolite ratios between NUWS and uniformly-weighted studies, though the studies would remain internally consistent. To understand the magnitude of this potential source for variability, the quantified metabolite ratios were compared between NUWS and uniformly-weighted studies. The difference in metabolite ratios with respect to creatine were found to be generally less than 10%, suggesting the metabolite ratios generated from a NUWS scan can be reliably compared with those from a uniformly-weighted study. It is possible that variations in SNR below the measurable precision of the sequence may have been introduced to the

sequence by the NUWS scheme. While it was expected that metabolite ratio discrepancies in scans of normal human anatomy would be slight, further testing with the sequence is needed in pathological conditions, like brain tumor, which can affect relaxation times.

While the post-processing program is capable of handling a variety of file formats, including outputting files readable in LC Model [24], the program is currently limited by relying on simple volume integrals for metabolite quantification. Future developments in the program will focus in incorporating a prior knowledge based fitting algorithm such as ProFit [25], to more reliably perform quantification and to better separate overlapping resonances. This initial study demonstrates the viability of NUWS in accelerating 2D MRS acquisition, but a larger study, particularly focused on the effects of variable relaxation times in pathology, is needed before such a technique can replace conventionally-acquired L-COSY.

NUWS can be made even more specific and versatile by accounting for differences in the t_1 evolution of different metabolites. Optimizing the distribution of averages could be used to selectively enhance not only overall signal quality but the quality of specific metabolite resonances. This could lead to further improvements to acquisition efficiency in applications where only a narrow range of metabolite resonances are of interest. Because the emphasis of particular metabolites would necessarily affect metabolite ratios, comparative studies, for example in longitudinal research, would require the consistent use of the same optimized averaging schemes. NUWS can also be used to optimize averaging inefficiencies at lower fields, although specific weighting schemes must be empirically optimized for different field strengths, as they were optimized for this study. Retaining signal strength while shortening scan sequences has greater potential than merely

Fig. 8. 2D L-COSY spectra from a 27.0 ml voxel localized in human brain processed through conventional zero-phasing coil combination (A, B) and phase preserving coil combination (C, D). Phase angles of each t_1 increment can be seen on the left (A, C) and the labeled spectra appear on the right (B, D). Parallel diagonal artifacts can clearly be seen in the zero-phased data.

reducing overall scan times by shortening TR or by other means. This technique is expandable, in that the time saved from weighting the averages in a 2D spectroscopy scan could in turn be used to improve signal strength while not extending scan times over that of the constant-average schemes. A shorter scan, like that generated by NUWS could be combined with an increased repetition time (TR), to improve SNR over and above that of the uniformly-weighted 2D MRS scans. The processing, plotting and quantification of the data generated by this technique, as well as the successful coil combination of the 2D spectra, demonstrate the utility of the offline post-processing facilitated by the newly-developed MATLAB-based program. In combination, these developments could make the clinical application of 2D MRS faster, easier and more versatile.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jmr.2017.02.012>.

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