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Effects of Carrier Frequency Mismatch on Frequency-Selective Spectral Editing

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Abstract

Objectives—This study sought to investigate the effects of carrier frequency mismatch on spectral editing and its correction by frequency matching of basis functions.

Materials and methods—Full density matrix computations and Monte Carlo simulations based on magnetic resonance spectroscopy (MRS) data collected from five healthy volunteers at 7 T were used to analyze the effects of carrier frequency mismatch on spectral editing. Relative errors in metabolite quantification were calculated with and without frequency matching of basis functions. The algorithm for numerical computation of basis functions was also improved for higher computational efficiency.

Results—We found significant errors without frequency matching of basis functions when carrier frequency mismatch was generally considered negligible. By matching basis functions with the history of frequency deviation, the mean errors in glutamate, glutamine, γ -aminobutyric acid, and glutathione concentrations were reduced from 3.90%, 1.85%, 11.53%, and 3.43% to 0.18%, 0.34%, 0.40%, and 0.51%, respectively.

Conclusion—Matching basis functions to frequency deviation history was necessary even when frequency deviations during frequency-selective spectral editing were fairly small. Basis set frequency matching significantly improved accuracy in the quantification of glutamate, glutamine, γ -aminobutyric acid, and glutathione concentrations.

Keywords

glutamate; glutamine; GABA; glutathione; Spectral Editing

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Author contributions

An: study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript. Araneta: acquisition of data. Johnson: acquisition of data. Shen: study conception and design, analysis and interpretation of data, critical revision.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all participants.

INTRODUCTION

Magnetic resonance spectroscopy (MRS) is a valuable tool for studying chemical changes in the human body. Single voxel MRS generally uses summation of many averages to achieve the desired signal-to-noise ratio (SNR) for low concentration metabolites. However, the actual resonance frequency generally deviates from the carrier frequency over the relatively long course of an MRS scan, primarily due to subject motion and heating/cooling of various scanner components because of field gradients. Without correction, this carrier frequency mismatch and accompanying phase errors cause incoherent signal averaging, leading to reduced SNR, increased line broadening, and underestimation of metabolite concentrations.

For MRS experiments with frequency-selective spectral editing, the frequency-selective editing pulse has a fixed frequency with respect to the carrier frequency; in contrast, the actual resonance frequencies of metabolites deviate over time, resulting in different editing yields for different frequency excursions that, in turn, leads to quantification errors unique to spectral editing [1]. Recently, a retrospective frequency deviation correction method for spectral editing of γ -aminobutyric acid (GABA) was proposed by our laboratory [2]. It took into account the effect of carrier frequency mismatch when computing the basis functions for fitting the in vivo GABA MRS data acquired using an editing pulse with a top hat frequency profile. In that study, the history of frequency deviation during a long scan was determined by the frequency of the residual water signal in each individual spectrum. A basis array as a function of deviation of the metabolite chemical shifts was calculated. Then the basis set averaged over frequency deviation history was used to fit the in vivo data.

Most spectral editing techniques use very selective pulses for spectral editing to minimize contamination from co-edited signals. An unstated assumption has been that if frequency deviation is much smaller than the bandwidth of the editing pulse one should not expect significant effects of frequency deviation on metabolite quantification. This assumption has not been tested thoroughly because of the difficulty in generating a large number of basis sets spanning a sizable frequency range either due to lengthy procedure of the required phantom experiments or prohibitive computational cost of three-dimensional full density matrix simulations. Recently, we devised a high efficiency full density matrix simulation algorithm that reduces the three-dimensional point-by-point density matrix calculation to a one-dimensional problem and increased computational efficiency by orders of magnitude [3]. In this work, we evaluate the effects of small and large frequency deviations on spectral editing using editing pulses with high frequency selectivity. We also made a major improvement on the method proposed by van der Veen *et al.* to significantly increase the accuracy and efficiency of basis function computation. The effects of frequency matching of basis functions are quantified by performing Monte Carlo simulations to compare metabolite quantification results with and without using frequency matched basis functions. Surprisingly, we found significant differences in metabolite quantification results when carrier frequency mismatch was generally considered negligible. We also demonstrate that matching basis functions to frequency deviation history significantly improved accuracy in the quantification of Glu, Gln, GABA, and GSH concentrations when frequency deviations were large.

MATERIALS AND METHODS

Pulse Sequence and Density Matrix Simulation

A previously proposed spectral editing MRS pulse sequence was used in this study [4]. To simultaneously measure glutamate (Glu), glutamine (Gln), GABA, and glutathione (GSH) at 7 T, the spectral editing sequence used a three-step editing approach in which the editing radiofrequency (RF) pulse was set to OFF, ON at 1.89 ppm, and to ON at 2.12 ppm. A simplified version of the spectral editing sequence (Fig. 1a) was used in the density matrix simulation to improve computation speed without affecting the accuracy of the computed basis functions. The editing pulse was a truncated Gaussian pulse with a duration of 10 ms and its frequency profile is plotted in Fig. 1b. A new post-processing method was used to simultaneously fit the three sets of spectra. In the simulated pulse sequence, the excitation pulse was an ideal 90° pulse without gradient. It should be noted that use of an ideal excitation pulse causes no significant errors in the simulated basis functions because the excitation pulse does not significantly contribute to nonuniform spatial distribution of J-coupling evolution. In contrast to the actual pulse sequence used on the scanner, the crusher gradients for the two refocusing pulses [5] and the editing pulse in the simulation were applied in three orthogonal directions. This arrangement of the gradients allowed the calculation of the propagator operators for the two refocusing pulses and for the editing pulse to be fully decoupled; thus the calculation only involved looping through one-dimensional spatial positions instead of two- or three-dimensional spatial points [6,3]. With this method, differences in crusher gradient arrangement result in no detectable differences in the computed basis functions, as long as the transverse magnetizations are sufficiently spoiled by the crusher gradients.

The density matrix simulation programs were developed in-house using the GAMMA NMR simulation C++ library [7]. Chemical shifts and coupling constants were obtained from the literature for GABA [8], GSH [9], and the rest of the metabolites [10]. We used 200, 2000, and 200 spatial points in the x, y, and z directions, respectively, to digitize the spectroscopy voxel. The reason to use 2000 data points in the direction of the crusher gradients for the editing pulse was that no gradient was applied when the editing pulse was turned on thus it was very efficient to compute 2000 spatial points in that direction, which makes the phases of the simulated basis spectra very accurate in the presence of Bloch-Siegert shift [11]. Based on the one-dimensional projection method [3], the spin density operator before the start of the first crusher gradient flanking the editing pulse was computed by summing the 200 density matrices in the x direction. To account for frequency deviation during the editing experiment, the rest of the spin density operator evolution was computed for 31 frequency deviation values ranging from -15 Hz to 15 Hz at 1 Hz intervals. For each frequency deviation value, the frequency of the editing pulse was shifted by the negative value of the frequency deviation; the spin density operator was computed using two one-dimensional summations of the digitized density matrices, first in the y direction with 2000 density matrices and then in the z direction with 200 density matrices. Free induction decay (FID) signals were then computed for each of the 31 frequency shift values. Each basis function contained three FIDs corresponding to the three different settings of the editing RF pulse. The simulation program was highly efficient. Specifically, it took about 7.6 minutes on a

laptop computer to compute 31 sets of basis functions, with each set corresponding to one frequency shift value, for a five-spin system such as Glu and Gln. Basis functions of acetate, N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), GABA, Glu, Gln, GSH, aspartate, total creatine (tCr), total choline (tCho), myo-inositol (mIns), taurine, scyllo-inositol, and glycine were simulated for fitting in vivo spectra in the range of 1.8 – 3.7 ppm. Other metabolites that do not have significant resonances within this target range were omitted. The Bloch-Siegert phase shift in both the acquired MRS data and the simulated basis functions was removed by multiplying the spectra with the complex-conjugate of the numerically computed phasor functions.

Matching Basis Functions to Frequency Deviation History

To find the frequency deviations in the individual spectra, the tCr and tCho peaks in each individual spectrum were fitted by two Voigt curves. The relative chemical shift between the two Voigt curves was fixed and set to be the chemical shift difference between tCr (3.028 ppm) and tCho (3.210 ppm). Based on the fitting results, the frequency deviation of the spectrum was determined and then corrected by shifting the spectrum. Meanwhile, the zero-order phase of each individual spectrum was also determined in the fitting process and removed from the spectrum. Finally, the frequency and phase aligned individual spectra were separately averaged into three spectra corresponding to the three different settings of the editing pulse: editing OFF, editing ON at 1.89 ppm, and editing ON at 2.12 ppm. A histogram of the frequency deviations, which was a distribution of the frequency deviations at 1 Hz intervals, was generated for each of the three editing pulse settings. The basis spectra used in the subsequent fitting process were computed as the average of the basis spectra corresponding to 31 frequency deviation values, where the experimentally measured histogram was used as the weighting function.

Monte Carlo Simulations Based on In Vivo Data

In vivo MRS data were acquired at 7 T from a $2 \times 2 \times 2$ mL voxel placed in the pregenual anterior cingulate cortex (pgACC) of five subjects. Data were analyzed using Monte Carlo simulations to evaluate the effects of frequency matching of the basis functions. The MRS scan time for each voxel was 4 minutes, 23 seconds. Each dataset comprised a total of 72 interleaved FIDs with 24 FIDs for each of the three editing steps. The three averaged in vivo spectra which correspond to the three different settings of the editing pulse were fitted to obtain the concentrations, linewidths, and lineshape of the metabolites, as well as the noise level and a cubic spline baseline with 17 control points between 1.8 – 3.7 ppm for each spectrum. Based on these values and the frequency deviation history, 72 individual FIDs were simulated by summing the properly scaled, line-broadened, and frequency-shifted basis functions and then adding random noise to the sum. The simulated FIDs did not contain baseline signals. The 72 simulated individual FIDs were Fourier transformed into the frequency domain and Bloch-Siegert shift correction was applied. The individual spectra were then aligned and separately summed into three spectra corresponding to the three different settings of the editing pulse. The three spectra were fitted simultaneously using two different sets of basis functions: basis functions with and without frequency matching. This process of simulation followed by fitting the data was repeated 100 times using the two different sets of basis functions. Each iteration used a different realization of random noise

whose level was set to be the same as that of the in vivo data. Results obtained via the two different basis sets were compared with the input values of metabolite concentrations to compute relative errors.

RESULTS

Figure 2 displays the frequency deviation history as well as the reconstructed spectra and corresponding fits from one subject who had relatively large frequency deviations (mean: 3.5 Hz, SD: 3.7 Hz, maximum: 12.3 Hz). The in vivo spectra matched very well with the fits generated by the frequency matched basis spectra, and the residual signals were very small. The basis spectra of Glu, Gln, and GABA with and without frequency matching are compared in Figure 3. The subject's frequency deviation history was used to compute the frequency matched basis spectra. Significant differences were observed between the basis spectra with and without frequency matching. Monte Carlo simulated spectra and the corresponding fits based on the in vivo data (Fig. 2) are displayed in Figure 4 (Figure 4A used the basis functions without frequency matching and Figure 4B used the basis functions with frequency matching). The displayed spectra and corresponding fits were averaged over 100 repetitions. Significant artifacts were observed in the fit residual signals without frequency matching (Fig. 4A) but no visible artifacts were observed in the fit residual signals with frequency matching (Fig. 4B). The corresponding metabolite concentration values obtained by fitting the simulated spectra using the basis functions with and without frequency matching are given in Table 1. Using the set of basis functions without frequency matching, the relative errors in the quantified Glu, Gln, GABA, and GSH concentrations were 4.79%, 2.23%, 18.2%, and 4.50%, respectively. These values were significantly lower when using the frequency matched basis functions; the relative errors in the quantified Glu, Gln, GABA, and GSH concentrations were 0.23%, 0.50%, 0.31%, and 1.42%, respectively.

Frequency deviation history and reconstructed spectra and corresponding fits from a second subject who had small frequency deviations (mean: -1.8 Hz, SD: 0.4 Hz, maximum: |-2.7| Hz) during the MRS scan are displayed in Figure 5. Monte Carlo simulated spectra and corresponding fits based on the in vivo data (Fig. 5) are displayed in Figure 6 (Fig 6A used the basis functions without frequency matching and Fig 6B used the basis functions with frequency matching). Some small artifacts were observed in the fit residual signals in Fig. 6A but no visible artifacts were observed in the fit residual signals in Fig. 6B. The corresponding metabolite concentration values obtained by fitting the simulated spectra based on this set of in vivo data are given in Table 2. Using the set of basis functions without frequency matching, the relative errors in the quantified Glu, Gln, GABA, and GSH concentrations were 2.88%, 1.51%, 9.35%, and 3.06%, respectively. These values were significantly lower when using frequency matched basis functions; the relative errors in the quantified Glu, Gln, GABA, and GSH concentrations were reduced to 0.25%, 0.37%, 0.33%, and 0.94%, respectively.

The relative errors in the metabolite concentrations from all five subjects were given in Table 3. On average, the magnitude of frequency deviation during each scan was 2.4 ± 1.8 Hz, which is relatively small for clinical MRS scans. Using the set of basis functions without frequency matching, the mean relative errors in the quantified Glu, Gln, GABA, and GSH

concentrations were 3.90%, 1.85%, 11.53%, and 3.43%, respectively. Using the set of frequency matched basis functions, the mean relative errors in the quantified Glu, Gln, GABA, and GSH concentrations became significantly lower, which were 0.18%, 0.34%, 0.40%, and 0.51%, respectively. Taken together, the results suggest that frequency matching of the basis functions is still necessary even if the frequency deviations are fairly small.

Because the resonances of NAA, tCr, tCho, and mIns were much less affected by the editing pulse, the errors in their quantification were quite small without frequency matching of the basis functions. Nonetheless, a general trend of reduced quantification errors after frequency matching of basis functions was also observed in Table 3.

DISCUSSION

Errors originated from partially missing the editing target are associated with the use of spectrally selective RF pulse, which is a general feature of all spectral editing sequences except the few that do not use spectrally selective RF pulses at all (e.g., certain multiple quantum filtering sequences). For the five subjects, the magnitude of frequency deviation during each scan was 2.4 ± 1.8 Hz, which is only 2.2% of the 107 Hz bandwidth of the editing pulse. The significant quantification errors due to small magnitude frequency deviations suggest that correction of frequency deviation should be beneficial in spectral editing using spectrally selective RF pulse even when the frequency deviations during the MRS scans are generally considered negligible. Frequency matching of basis functions is an additional step specific for spectral editing. It can be applied after frequency and phase alignment of the in vivo data performed in either the time domain [12] or frequency domain [13]. In this work, frequency and phase alignment of the in vivo data as well as data fitting are performed in the frequency domain. These operations can also be performed in the time domain while using the frequency matched basis functions for improved accuracy in metabolite quantification.

Our Monte Carlo simulations demonstrated that frequency matching of basis functions significantly improved accuracy in the quantification of Glu, Gln, GABA, and GSH concentrations even if the frequency mismatches were only a few Hertz. After a prospective frequency correction technique [14–16] is used to intercept the worst damage of frequency drift over the course of an MRS scan, small amount of frequency deviation often still exists in the acquired MRS data. Therefore, frequency matching can also be applied to the prospectively corrected data to further reduce errors in the quantification of metabolite concentrations.

In the simulated pulse sequence, the crusher gradients for the editing pulse were placed in a different direction, orthogonal to the gradients flanking the two refocusing pulses. This allowed the effects of the frequency selective editing pulse and its crusher gradients to be accurately computed via the highly efficient one-dimensional projection method, which was originally designed for the PRESS and STEAM sequences without any editing pulse. For this reason, an ideal excitation pulse without localization gradients was used in the simulations, such that the localization gradients for the editing pulse and the two refocusing pulses could be put into three orthogonal directions.

It is also important to note that computing the basis functions for frequency matching within a reasonable amount of time is challenging even using the highly accelerated one-dimensional technique [3] because many sets of basis functions—for example, 31 in the present study—corresponding to different frequency deviation values must be computed. In the prior study [2], computing 31 sets of basis functions for the 31 frequency deviation values would have taken 31 times as long because each set of basis functions were computed independently. The present method significantly improves computational efficiency because it computes the array of basis functions by keeping the chemical shift values of the metabolites unchanged while offsetting the editing pulse frequency by the negative value of the frequency deviation. This allows many parts of the simulations to remain the same despite the different frequency deviation values; thus, they only need to be computed once. As a result, the time required to compute 31 sets of basis functions in the present study was only 23% longer than that needed to compute a single set of basis functions, reducing the computation load by a factor of 25.

Ideally, a spectral editing experiment should have high selectivity to overcome spectral overlap but low sensitivity to frequency deviation due to subject motion and/or system instability. Unfortunately, these two desirable characteristics are in fundamental conflict, given that spectral selectivity is achieved by precise placement of the editing pulse in the frequency domain. Without frequency matching of the basis functions, flat-top editing pulses are often used to avoid significant changes in editing yield due to frequency deviation. However, flat-top editing pulses generally yield a large time-bandwidth product, which leads to a long duration and/or large bandwidth. An editing pulse with long duration makes the minimal TE longer and a large bandwidth makes an editing pulse less frequency selective, leading to undesired co-editing. As this study has demonstrated, higher spectral selectivity and less sensitivity to subject motion and system instability can be reconciled using post-acquisition frequency matching. The high effectiveness of frequency matching observed in this study opens the possibility of further increasing the spectral selectivity of the editing pulse in many spectral editing experiments to improve the purity of the edited signal while relying on post-acquisition frequency matching to eliminate editing errors due to frequency deviation.

In conclusion, full density matrix computations and Monte Carlo simulations based on in vivo spectral editing MRS data collected at 7 T were used to analyze the effects of carrier frequency mismatch on spectral editing. Relative errors in metabolite quantification were calculated with and without frequency matching of basis functions. The algorithm for numerical computation of basis functions was also improved for markedly higher computational efficiency. We found significant differences in metabolite quantification results with and without frequency matching of basis functions when carrier frequency mismatch was generally considered negligible. Matching basis functions to frequency deviation history can significantly improve accuracy of metabolite quantification in spectral editing experiments.

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Figure 1.

a Schematics of the simplified spectral editing pulse sequence used in full density matrix simulations. Repetition time (TR) = 3.5 s; echo time (TE) = 56 ms; TE₁ = 40 ms; T_d = 15.3 ms; editing radiofrequency (RF) pulse setting = OFF, ON at 1.89 ppm, and ON at 2.12 ppm.

b Frequency profile of the 180° editing pulse.

Figure 2.

Frequency deviation history and reconstructed spectra and corresponding fits from a $2 \times 2 \times 2$ cm³ voxel in the pregenual anterior cingulate cortex (pgACC) with relatively large frequency deviations (mean: 3.5 Hz, SD: 3.7 Hz, maximum: 12.3 Hz). Repetition time (TR) = 3.5 s; echo time (TE) = 56 ms; TE₁ = 40 ms; T_d = 15.3 ms; spectral width = 4000 Hz; number of data points = 1024; number of averages = 72; and total scan time = 4 mins, 23 s.

Editing pulse at 1.89 ppm **Editing pulse at 2.12 ppm** **Figure 3.**

Basis spectra of glutamate (Glu), glutamine (Gln), and gamma-aminobutyric acid (GABA) with and without frequency matching when the editing pulse was ON at 1.89 ppm and 2.12 ppm, respectively. The relatively large frequency deviations (Fig. 2) were used to compute the frequency matched basis spectra. Significant differences were observed between the basis functions with and without frequency matching as shown by the difference spectra.

Figure 4.

Monte Carlo analysis of in vivo data with relatively large frequency deviations (Fig. 2). The displayed spectra and corresponding fits were averaged over 100 repetitions such that small residual signals were distinguishable from noise. (A) Basis functions without frequency matching were used. There were significant artifacts in the fit residual. (B) Basis functions with frequency matching were used. There were no visible artifacts in the fit residual.

Figure 5. Frequency deviation history and reconstructed spectra and corresponding fits from a dataset with relatively small frequency deviations (mean: -1.8 Hz, SD: 0.4 Hz, maximum: $|-2.7|$ Hz).

Figure 6.

Monte Carlo analysis of in vivo data with relatively small frequency deviations (Fig. 5). The displayed spectra and corresponding fits were averaged over 100 repetitions. (A) Basis functions without frequency matching were used. There were significant artifacts in the fit residual. (B) Basis functions with frequency matching were used. There were no visible artifacts in the fit residual.

Table 1.

Metabolite concentration by Monte Carlo analysis of an in vivo dataset with relatively large frequency deviations. Two different sets of basis functions—with and without frequency matching—were used in the fitting.

	Input value	Without frequency matching	Relative error (%)	With frequency matching	Relative error (%)
Glu	1.281	1.342 ± 0.014	4.79	1.284 ± 0.013	0.23
Gln	0.319	0.327 ± 0.017	2.23	0.321 ± 0.018	0.50
GABA	0.102	0.084 ± 0.007	18.2	0.102 ± 0.007	0.31
GSH	0.273	0.261 ± 0.010	4.50	0.277 ± 0.010	1.42
NAA	1.273	1.271 ± 0.008	0.19	1.272 ± 0.008	0.08
tCr	1.000	1.000 ± 0.004	0.02	0.998 ± 0.004	0.16
tCho	0.277	0.276 ± 0.001	0.49	0.276 ± 0.001	0.16
mIns	0.701	0.695 ± 0.007	0.80	0.701 ± 0.007	0.00

Table 2.

Metabolite concentration by Monte Carlo analysis of an in vivo dataset with relatively small frequency deviations.

	Input value	Without frequency matching	Relative error (%)	With frequency matching	Relative error (%)
Glu	1.174	1.140 ± 0.012	2.88	1.177 ± 0.012	0.25
Gln	0.305	0.301 ± 0.014	1.51	0.307 ± 0.014	0.37
GABA	0.086	0.094 ± 0.006	9.35	0.086 ± 0.006	0.33
GSH	0.289	0.298 ± 0.008	3.06	0.292 ± 0.008	0.94
NAA	1.291	1.293 ± 0.006	0.12	1.290 ± 0.006	0.08
tCr	1.000	0.997 ± 0.003	0.28	0.999 ± 0.003	0.15
tCho	0.287	0.287 ± 0.001	0.08	0.287 ± 0.001	0.10
mIns	0.684	0.686 ± 0.005	0.29	0.684 ± 0.005	0.06

Table 3.

Relative errors (%) in metabolite quantification by Monte Carlo analysis of five subjects. On average, the magnitude of frequency deviation during each scan was 2.4 ± 1.8 Hz.

	Without frequency matching	With frequency matching
Glu	3.90 ± 2.24	0.18 ± 0.06
Gln	1.85 ± 1.19	0.34 ± 0.12
GABA	11.53 ± 4.61	0.40 ± 0.23
GSH	3.43 ± 1.18	0.51 ± 0.64
NAA	0.28 ± 0.26	0.09 ± 0.01
tCr	0.21 ± 0.22	0.08 ± 0.06
tCho	0.20 ± 0.18	0.11 ± 0.03
mIns	0.63 ± 0.45	0.09 ± 0.07