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Spectral editing of weakly coupled spins using variable flip angles in PRESS constant echo time difference spectroscopy: Application to GABA

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ABSTRACT

A general in vivo magnetic resonance spectroscopy editing technique is presented to detect weakly coupled spin systems through subtraction, while preserving singlets through addition, and is applied to the specific brain metabolite γ-aminobutyric acid (GABA) at 4.7 T. The new method uses double spin echo localization (PRESS) and is based on a constant echo time difference spectroscopy approach employing subtraction of two asymmetric echo timings, which is normally only applicable to strongly coupled spin systems. By utilizing flip angle reduction of one of the two refocusing pulses in the PRESS sequence, we demonstrate that this difference method may be extended to weakly coupled systems, thereby providing a very simple yet effective editing process. The difference method is first illustrated analytically using a simple two spin weakly coupled spin system. The technique was then demonstrated for the 3.01 ppm resonance of GABA, which is obscured by the strong singlet peak of creatine in vivo. Full numerical simulations, as well as phantom and in vivo experiments were performed. The difference method used two asymmetric PRESS timings with a constant total echo time of 131 ms and a reduced 120° final pulse, providing 25% GABA yield upon subtraction compared to two short echo standard PRESS experiments. Phantom and in vivo results from human brain demonstrate efficacy of this method in agreement with numerical simulations.

1. Introduction

At standard clinical field strengths, localized in vivo proton magnetic resonance spectroscopy (MRS) [1,2] has a relatively narrow bandwidth spectrum of visible metabolites with significantly overlapping spectral peaks, which can create difficulty in quantification. In contrast to in vitro NMR spectroscopy, multi-dimensional experiments are often too time-consuming for in vivo use, requiring other spectral editing methods, particularly for coupled spin systems that produce multiplets often overlapped by strong singlet resonances. One important metabolite of interest is γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, that has been investigated using many types of spectrally edited MRS. GABA is a six-spin system, that may be considered a weakly coupled system ($A_2M_2X_2$) at 4.7 T and higher magnetic fields, with *J*-couplings ~7 Hz and resonant frequencies occurring at chemical shifts of 3.01, 1.89 and 2.28 ppm [3]. Detection via proton MRS is inhibited due to spectral overlap with other metabolites. The main contaminants of the GABA signal are comprised from six different sources: N-acetylaspartate (NAA, two spin groups – A_3 and ABX), glutamate and glutamine (Glu and Gln, both AMNPQ groups), creatine (Cr, two singlets – A_2 and A_3), glutathione (GSH, three spin groups – A_2, AMNPQ and ABX), and macromolecular contributions. Specifically, the X_2 peak of GABA at 2.28 ppm is obscured by the MN and PQ resonances of Glu and Gln, while the GABA A_2 resonance at 3.01 ppm is overshadowed by the strong singlet peak of Cr with additional contribution from the AB spins of GSH. Fat and other macromolecule contamination primarily affects the M_2 multiplet at 1.89 ppm with secondary contamination due to the NAA A_3 peak at 2.01 ppm in poorly shimmed samples. A typical target for spectral editing of GABA is the A_2 group, which only has one strong overlapping resonance. The first measure of GABA in the human brain by proton MRS was performed by Rothman [4] utilizing an alternating spectrally selective refocusing pulse to alter the *J*-coupling evolution of the A_2 GABA multiplet. This method has been applied to a wide range of GABA studies [5]. Several other spectral editing techniques have been proposed including multiple quantum filtering, two dimensional spectroscopy and alternate methods [6–13]. All of these techniques provide a means to quantify GABA, however, multiple quantum filtering or use of spectrally selective pulses do not provide a full spectrum of all metabolites and all of these methods can be difficult to implement for standard clinical systems due to complex sequence design.

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A recently introduced spectral editing method, based on constant echo time (TE) difference spectroscopy using the double spin echo in PRESS [14], relies on signal variation between two asymmetric PRESS timings that maintain the same total TE. This method uses a standard PRESS technique, with changes only to the two inter-echo timings, which leads to signal variation for strongly coupled systems. This approach uses no spectrally selective pulses as used in the more common *J*-refocusing difference spectroscopy [4], and thus maintains spectral information in the addition spectrum from all singlets and non-varying coupled spin systems which are removed in the difference spectrum. However, the method does not apply to weakly coupled systems because changes to inter-echo asymmetry do not alter the evolution of weakly coupled systems when the refocusing pulses are 180°. Here, we propose a modification of the constant TE difference spectroscopy technique by inclusion of variable flip angles for the refocusing pulses. By changing the flip angle of one of the 180° pulses, we demonstrate that it is possible to introduce enough variation in asymmetric PRESS yield to allow application of this method to weakly coupled systems, particularly the A_2 GABA multiplet. The mechanism of this signal variation is the allowance for various degrees of homonuclear polarization transfer through antiphase coherence by application of a final refocusing pulse less than 180° at different times, but maintaining the same total TE. The effects of homonuclear polarization transfer on weakly coupled systems for PRESS have been well described in previous work applied to both the AX and lactate AX_3 spin systems [15,16].

Previous work has also used flip angle variations in a standard PRESS sequence for difference spectroscopy in weakly coupled systems. Specifically, Jung [17] applied PRESS difference editing to lactate by using identical sequence timing but varying both the second and third refocusing pulses (180° in the first experiment, 90° in the second). The resulting subtraction required prior multiplication by a factor of four to account for reduced signal in the 90° experiment. A second difference method applied to lactate [18] made use of only 90° pulses to maximize polarization transfer, with slight echo time variation between experiments. While both methods offer insight into the application of reduced flip angles in PRESS for difference spectroscopy, the substantial deviation from 180° refocusing limits the singlet signals in the resulting spectral additions, and reduces the value of these methods. Our method relies on PRESS asymmetry with only one flip angle variation to maximize the signal of singlets and achieve weakly coupled spin editing. We describe our method theoretically using numerical simulation, as well as in phantom and in vivo human brain experiments to detect the A_2 resonance of GABA while minimizing the contribution of the overlapping Cr peak.

2. Methods

The considered method is subtraction of two PRESS acquisitions using identical total TE but with varying asymmetry, and with a final refocusing pulse of α. We begin by considering a two spin weakly coupled system with simple analytical results, proceeding to full numerical simulation for the more complex GABA spin system, followed by experimental verification.

2.1. Analytical approximations

The theory behind the new difference technique can be illustrated analytically by considering the response of the simplest two spin AX system with coupling constant J_{AX}, resonant frequencies ω_A and ω_X, and using perfect RF pulses. For PRESS excitation, results for this simple spin system have been detailed by Jung [19] using variable refocusing pulses and timings. For the case of 180° refocusing pulses, the resulting normalized signal, *S*, at the start of the acquisition is:

$$S \propto \cos(\pi J_{AX}\mathrm{TE1} + \pi J_{AX}\mathrm{TE2}) = \cos(\pi J_{AX}\mathrm{TE}), \tag{1}$$

where TE1 and TE2 are the first and second echo times in the PRESS sequence, respectively, and TE1 + TE2 = TE. The addition of a variable final refocusing pulse flip angle α introduces greater complexity in the solution:

$$S \propto \frac{1}{4}\sin^2\alpha\left(1+\cos\left(\frac{1}{2}\Delta TE2\right)\right)(\cos(\pi J_{AX}TE1) - \cos(\pi J_{AX}TE)) + \frac{1}{2}(1-\cos\alpha)\cos(\pi J_{AX}TE), \tag{2}$$

where Δ is the chemical shift difference ($\Delta = \omega_A - \omega_X$). In the case where α is equal to 180°, Eq. (2) reduces to the standard PRESS relation, as in Eq. (1). Eq. (2) can be used to investigate any weakly coupled two spin system, or to gain insight into more complex systems. In the case of GABA, the signal computed from Eq. (2) for the AM coupling will be compared to the more accurate, though less intuitive, full numerical simulation incorporating the entire spin structure and slice selective pulses.

2.2. Numerical simulations

For an arbitrary weakly coupled system (including GABA at 4.7 T), signal variations in TE space can be calculated for the PRESS sequence. Previous numerical simulation work with lactate has examined the PRESS timing dependency in detail [16]. Our method is based on an in-house, numerical spin simulation program [20]; other programs are also available [21]. The program segments the sequence into individual Hamiltonians characterized as a delay, radiofrequency (RF) pulse or gradient, calculates the density matrix after each segment, and produces a final half echo (free induction decay). RF pulses (based on standard experimental pulses, 256 points, 5 lobes, 2500 Hz selective bandwidth for a 2 ms pulse length) were modeled along with corresponding slice selection gradients to simulate points in space. In the case of soft pulses, they were divided into many sections with each section encompassing a small time interval with a complementary Hamiltonian. The small time interval for each pulse section allows the continued use of time-independent Hamiltonians.

The program was run for a range of TE1 and TE2 values (10–200 ms each, 5 ms increments), producing a total of 1600 half echoes. This procedure was repeated for each flip angle adjustment of a refocusing pulse according to a PRESS scheme of 90°–180°-α, where α was varied from 90° to 180° in increments of 5°, resulting in a total of $19 \times 1600 = 30400$ half echoes. For each spectrum produced, peak area and height calculations were performed, resulting in area maps illustrating signal modulation in TE space. The maps were used to determine the largest signal difference along a constant TE line, and therefore, the optimal value for the flip angle, α. Two time points from the optimal α map were chosen to simulate constant TE difference spectroscopy. To investigate the efficacy of the GABA subtraction experiment, the process was also repeated for Cr. The simulated spectra were broadened using a 3 Hz exponential filter, and GABA and Cr were combined using a parietal gray matter physiological concentration ratio of 5:1 [22].

2.3. Phantom and in vivo experiments

Both the analytical and simulation results were used to find the best constant TE line in TE space as well as the optimal final refocusing flip angle α, and timings for the pair of experiments. An optimized flip angle of 120° with total echo time of 131 ms was

used with subtraction of (TE1, TE2) = (21, 110) ms from (TE1, TE2) = (120, 11) ms.

Two cylindrical, pH-balanced phantoms were constructed containing (1) 100 mM GABA and (2) 100 mM Cr and 10 mM GABA. The first phantom was used to demonstrate the GABA lineshape obtained at the particular asymmetries, while the second phantom was used to determine Cr suppression using double the in vivo Cr:GABA ratio (10:1) [22]. In each case, the phantom was placed at isocentre and the same voxel position was used for all experiments. Localization was produced by the PRESS sequence with WET (Water suppression Enhanced through T1 effects) water suppression [23], using four Gaussian shaped pulses of 20 ms length, each selecting a 50 Hz range centered on the water resonance, followed by crusher gradients. The two sets of asymmetric PRESS timings used were interleaved into one sequence, with alternating half echoes acquired to minimize frequency drift and sequence specific abnormalities that may occur when subsequently acquiring two complete averaged half echoes at different asymmetries. Prior to alternating between echo times, the echoes were grouped into 8 average bins to allow for CYCLOPS (CYCLically Ordered Phase Sequence, [24,25]) phase cycling. Other sequence parameters included a $15 \times 15 \times 15$ mm voxel size, 512 averages per echo time, pulse lengths of 3 ms (1660 Hz bandwidth) and a repetition time (TR) of 1500 ms, resulting in a total acquisition time of 25 min, 36 s. Each spectrum was phase corrected using Cr as the reference, or in the absence of Cr, the GABA resonance at 3.01 ppm. The spectra were also frequency corrected to increase the subtraction accuracy by aligning the Cr resonance for each spectrum. The correction was performed for both sets of TE1 and TE2 before subtraction.

In vivo experiments were performed on healthy volunteers giving informed consent using the optimized timings identical to the phantom experiments. The acquisition parameters were similar to the phantom case except the voxel size was increased to $30 \times 30 \times 30$ mm with only 256 averages used (32 bins of 8 averages) leading to a 12 min 48 s total experiment time. The processing methods were the same as the phantom experiments.

All experiments were performed using a 4.7 T Varian INOVA (Palo Alto, CA) whole body MRI system, equipped with a 4 kW RF amplifier, a maximum gradient strength of 35 mT/m and maximum slew rate of 117 T/m∗s. A quadrature, 16-element birdcage head coil (27 cm diameter) was used for transmission and reception.

3. Results

3.1. Analytical calculations

From inspection of Eq. (2) for the PRESS sequence, the first term is a maximum at $\alpha = 90°$ and zero when $\alpha = 180°$. The term oscillates depending on the chemical shift difference and the TE2 time. The choice of total TE $\sim 1/J$ with very short TE1 (TE $\sim$ TE2) maximizes the J dependence of this term. With a long TE1 and short TE2 (TE $\sim$ TE1), the cosine difference part of this term approaches zero. The second term is independent of the asymmetry and is maximal at $\alpha = 180°$. Based on Eq. (2), TE space intensity maps were produced for an average coupling constant of 7.3 Hz, and a chemical shift difference of $\Delta = 1420$ rad/s (226 Hz), approximating the AM coupling in GABA at 4.7 T. The effects of reduced flip angle on this weakly coupled system are shown in Fig. 1a and b with $\alpha = 180°$ and $\alpha = 120°$, respectively. At a value of $\alpha = 120°$, the maximum available signal is 75% before any subtraction experiment compared to $\alpha = 180°$. Reducing α to 120° also leads to rapid fluctuations in the TE2 direction caused by homonuclear polarization

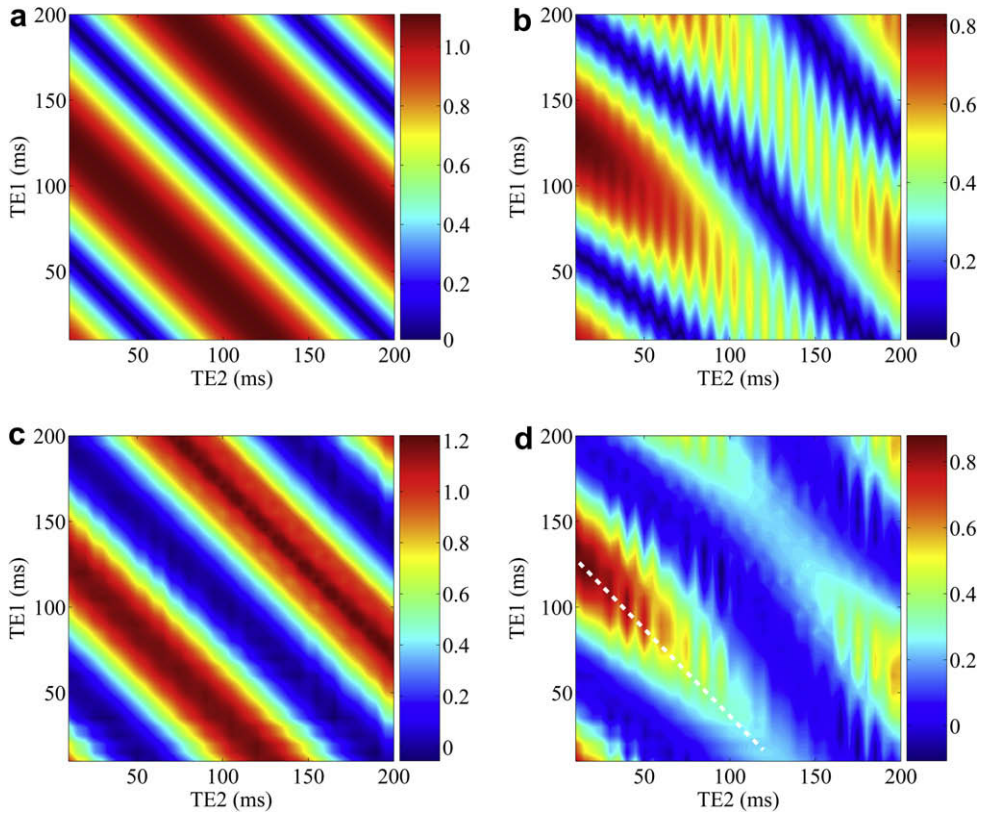

Fig. 1. TE space area maps calculated by Eq. (2) for the A spin of a weakly coupled AX system with parameters of $J = 7.3$ Hz and $\Delta = 1420$ rad/s and a final refocusing flip angle of (a) $\alpha = 180°$, and b) $\alpha = 120°$. The results for the A_2 spins of GABA using the full simulation are shown with (c) $\alpha = 180°$, and (d) $\alpha = 120°$. In each set (analytical and simulation), the yield is normalized to the short TE PRESS case (TE1 = TE2 = 10 ms).

transfer [16], leading to lack of full chemical shift refocusing. This causes oscillations dependent on the chemical shift difference, Δ, which are spaced every $(4\pi\Delta)$ s in this case. The constant TE line with greatest signal variation occurs at TE = $1/J$ (136 ms), and with a repeating pattern proportional to $1/J$. The signal along this $1/J$ line decreases steadily as the TE2 time is increased, which allows for increased polarization transfer that conflicts with the in-phase magnetization contribution and leads to decreased net multiplet area. This signal variation due to the decreased flip angle allows difference spectroscopy experiments to be performed using the same total TE, but different asymmetries. A possible choice for TE1 and TE2 based on Fig. 1b is near either axis along the TE = $1/J$ line to maximize the signal difference. The optimization of the flip angle for difference spectroscopy is a combination of reducing losses due to decreased flip angle and maximizing the signal variation in TE space by flip angle reduction. Eq. (2) predicts an optimized flip angle of 90° for the second refocusing pulse for maximal AM spin system yield in the difference experiment. The maximum theoretical yield for the GABA weakly coupled system difference spectroscopy experiment is 30% at $\alpha = 90°$. At $\alpha = 120°$, the maximum yield is 25%. In general, a flip angle closer to 180° is preferred since singlet resonances are also reduced as the flip angle deviates from 180°.

3.2. Numerical simulations

Fig. 1c and d illustrate TE space area maps for the A_2 multiplet of GABA using the complete simulation accounting for the full spin system and RF pulse shape, which produces roughly similar maps to the simple AM analytical approximation in (1a) and (b). The values are normalized to the PRESS short echo case when TE1 = TE2 = 10 ms, and relaxation effects are not considered. In (1c), $\alpha = 180°$ results in a symmetric pattern in TE space. The period between two similar points in the map is $1/J$ (J = 7.3 Hz) or 136 ms in either the TE1 or TE2 direction, similar to the analytical description. The optimal flip angle for signal variation along a line of constant TE was determined to be $\alpha = 120°$, to provide sufficient signal while maximizing the signal variation. The TE space map for GABA A_2 is shown in (1d) for this particular case.

The period along the vertical TE1 direction in (d) remains $1/J$ as in (a) due to complete refocusing, but is altered along the TE2 direction. The dotted white line shows a constant TE line with good asymmetry (TE = 131 ms). Two time points from this line were chosen to perform difference spectroscopy, specifically: (TE1, TE2) = (21, 110) ms and (120, 11) ms. Fig. 2 shows spectra from the simulation for GABA and Cr using these PRESS timings with a final refocusing pulse of 120°. The individual spectra in (2a) and (b) show the full Cr A_3 signal obscuring the relatively small GABA signal at 3 ppm. Note the large signal variation between GABA spectra in (a) and (b), producing a large remnant in the difference spectrum in (c), where the Cr signal is negligible. Analysis of the GABA A_2 areas result in a 25% GABA yield in the subtraction spectrum compared to the equivalence of two short echo PRESS (TE1 = TE2 = 10 ms) experiments.

3.3. Phantom and in vivo experiments

Fig. 3 illustrates phantom GABA spectra using the chosen timings. In a), (TE1, TE2) = (120, 11) ms, while in b) (TE1, TE2) = (21, 110) ms, with subtraction in c). The final refocusing pulse α is 120° at left and 180° at right. The spectra with 120° are in good agreement with the simulation in Fig. 2. Note also that the spectra with $\alpha = 180°$ at right provide additional signal amplitude for each spectra but poorer subtraction. From the GABA and Cr phantom, precise subtraction of both Cr singlets with approximately 100-fold singlet suppression was achieved in the difference spectrum.

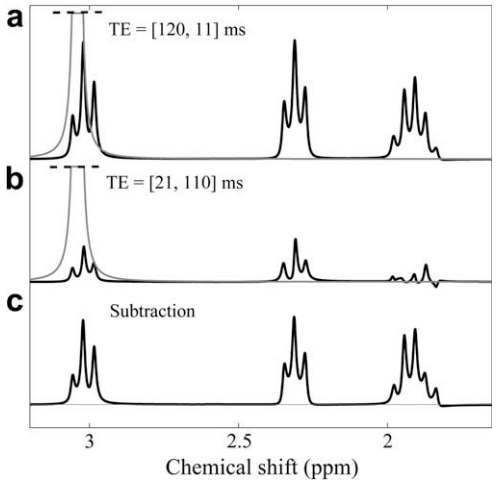

Fig. 2. Spectra from the subtraction simulations with $\alpha = 120°$ at timings of (a) TE1 = 120 ms, TE2 = 11 ms, and (b) TE1 = 21 ms, TE2 = 110 ms. The subtraction spectra are shown in (c). The Cr spectra are shown as the light grey lines, and have been truncated in (a) and (b). The spectra have been line broadened with a 3 Hz exponential filter to match phantom data.

An example of the in vivo spectra, along with the resulting subtraction are illustrated in Fig. 4. The optimized timings and flip angle were the same as the phantom experiment. The line shape of the subtraction spectrum in (4c) is similar to the simulation in the 3 ppm vicinity, indicating favorable detection of GABA at these particular timings. A maximum frequency shift of ~1 Hz was observed during the experiment, which was corrected by frequency aligning of the bins. In addition, to achieve even greater level of singlet alignment, the two in vivo spectra were also amplitude balanced using the N-acetylaspartate singlet.

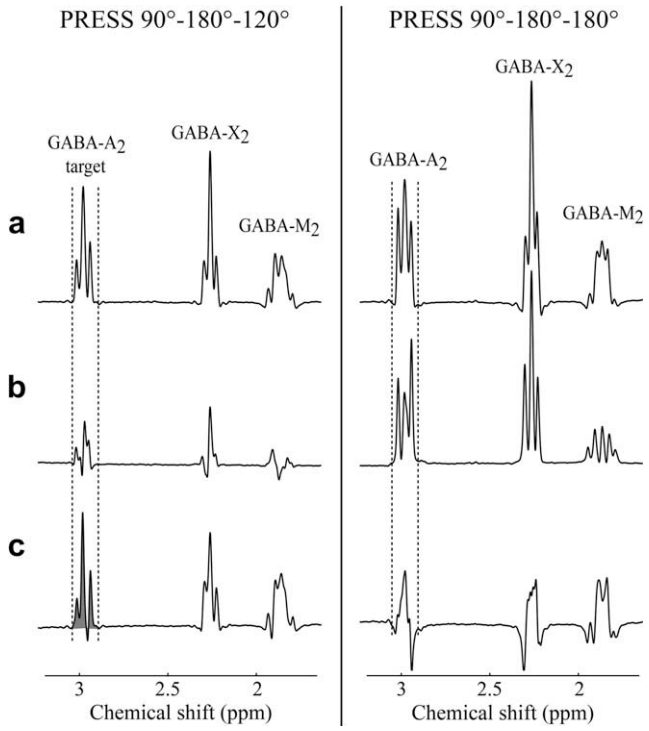

Fig. 3. Phantom experiments with GABA only at both timings used for the difference spectroscopy experiment: (a) TE1 = 120 ms, TE2 = 11 ms, and (b) TE1 = 21 ms, TE2 = 110 ms, with the resultant subtraction spectrum in (c). At left, a final refocusing pulse of 120° was used with comparison to 180° at right. Note both timing asymmetry and flip angle variation are necessary to produce high yield in the subtraction.

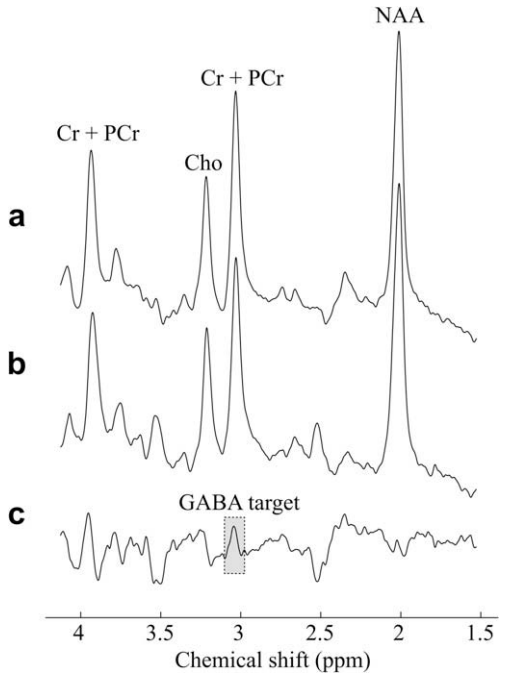

Fig. 4. In vivo spectra for the difference spectroscopy experiment with timings of (a) TE1 = 120 ms, TE2 = 11 ms and (b) TE1 = 21 ms, TE2 = 110 ms. The resultant subtraction is shown in (c), highlighting the targeted GABA signal. Other coupled spin systems also have subtraction residuals including myo-inositol (~3.5 ppm) and the aspartyl resonance of NAA (~2.5 ppm).

4. Discussion

The analytical results with a two spin AX system provided an intuitive understanding of the effects of reduced refocusing pulse flip angles in the PRESS sequence. Although the full simulation method incorporating the entire spin structure of GABA is needed to determine the exact response, the AX system also provides a rough approximation of the results for GABA, as demonstrated in Fig. 1. The full simulation and experimental results show that it may be possible to detect GABA at 3 ppm via constant TE difference spectroscopy at 4.7 T, by varying the flip angle of the second refocusing pulse and using signal asymmetries in TE space. This technique is simple to implement with a standard PRESS sequence, and is therefore available for clinical use. The same results are obtained if the first refocusing pulse is varied, although the asymmetries are flipped in TE space.

In our application to GABA, we chose the line at TE = 131 ms as shown in Fig. 1d with (TE1, TE2) = (120, 11) ms and (21, 110) ms to provide maximal signal difference. While these timings led to maximal yield in subtraction, the extreme variation in intra-echo times by using either end of this line may not be ideal under experimental conditions. For example, the Cr singlet in the phantom experiment was found to have a slightly smaller (~1%) reduced signal for the (TE1, TE2) = (120, 11) ms choice. This effect is partly due to T1 recovery differences between the two spectra when using short TR. Assuming an approximate T1 of 1400 ms for GABA at 4.7 T [26], a 3% reduction in signal is expected in the short TE2 case, if a TR of 1500 ms is used. This T1 effect can be minimized with longer TR times. Two additional effects not accounted for by the simulation may have subtle influence. First, while T2 decay is similar for both timings due to the same TE, the varied inter-echo spacing of the RF pulses may lead to different refocusing of slow diffusion effects. Second, poorly tuned systems could be affected by the different placement of spoiling gradients relative to the start of the half echo causing slightly different eddy current effects. All of these subtle effects can be minimized by choosing slightly more central timings along the TE line illustrated in Fig. 1d. For our in vivo experiment, we used the NAA singlet peak to balance signal levels before subtraction to achieve greater Cr suppression, and minimize these potential confounds. The in vivo result provides barely adequate SNR, which is a limitation of all GABA editing methods owing to its low concentration. More averaging or a larger volume could increase the SNR further, but at the cost of more time or poorer spatial localization. Other residual metabolites are also visible across the in vivo spectrum, but do not affect the GABA measurement. While this method can provide a quantitative result for GABA, it is perhaps best suited for measuring elevated GABA levels.

Other improvements to the pulse sequence are possible. More optimal refocusing pulses could further improve the yield similar to that shown by Schick [27]. In our case we used the standard sinc pulses supplied with the system, which led to suboptimal refocusing in portions of the voxel. Improvements could also be made by using more advanced phase cycling schemes; however, care would need to be taken to continue to minimize the number of acquisitions within each bin and consequently reducing the line broadening due to frequency drift. In this work we used CYCLOPS but methods such as EXORCYCLE [28] could be preferable to minimize imperfect pulses.

In conclusion, a new difference spectroscopy method for detection of weakly coupled spin systems has been demonstrated for editing the 3.0 ppm multiplet of GABA at 4.7 T. The method makes use of two asymmetric PRESS sequences with identical total echo time, and requires reduction of the final refocusing flip angle. The method is very simple to implement given a standard PRESS sequence, requires no spectrally selective pulses and maintains all singlet resonances through spectral addition.

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