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Incorporating homonuclear polarization transfer into PRESS for proton spectral editing: Illustration with lactate and glutathione

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Abstract

A proton spectral editing pulse sequence for the detection of metabolites with spin systems that involve weak coupling is presented. The sequence is based on homonuclear polarization transfer incorporated into the standard PRESS (Point RESolved Spectroscopy) sequence, which is a volume-selective double spin echo method, to enable spatial localization. All peaks in the region of interest are initially suppressed whether they are peaks from the target metabolite or from contaminating background. The target signal is then restored by polarization transfer from a proton that has a resonance outside the suppressed region and to which the target spins are weakly coupled. This is achieved by the application of a 90° hard pulse with phase orthogonal to that of the PRESS excitation pulse at the location of the first echo in PRESS and by optimizing the two PRESS timings, TE_1 and TE_2, for most efficient yield. Background signal not coupled to any protons outside the initially saturated region remains suppressed. The advantage of this sequence compared to multiple quantum filters is that signal from singlet peaks outside the suppressed area are preserved and can thus be used as a reference. The efficacy of the sequence was verified experimentally on phantom solutions of lactate and glutathione at 3.0 T. For the AX_3 spin system of lactate, the sequence timings were optimized by product operator calculations whereas for the ABX spin system of the cysteinyl group of glutathione numerical calculations were performed for sequence timing optimization.

Keywords: Spectral editing; PRESS; Polarization transfer; Lactate; Glutathione

1. Introduction

Multiple quantum (MQ) filters [1] and *J*-difference editing [2] are two common techniques employed in *in-vivo* proton spectral editing to reveal metabolites hidden or contaminated by large resonances from water, lipids, or uncoupled spins in brain. The method of *J*-difference editing relies on the subtraction of alternate scans and is thus susceptible to artifacts arising from motion and hardware instabilities. The MQ filter approach, when combined with a single-shot localization sequence, is less susceptible to such artifacts. The PRESS sequence [3] is often the localization method of choice because of its ability to perform three dimensional localization in a single scan and because MQ filtering pulses and gradients can be easily integrated into the body of the sequence [4]. PRESS-based double quantum (DQ) filters have been proposed for the detection of a number of target metabolites in *in-vivo* magnetic resonance spectroscopy (MRS) because of their ability to suppress signal from uncoupled spins [4–11]. On the other hand, the suppression of all singlet resonances in a spectrum is a disadvantage because the peaks from uncoupled spins such as from *N*-acetyl aspartate (NAA) at 2.01 ppm, creatine (Cr) at 3.02 ppm, or choline (Cho) at 3.2 ppm can act as an internal phase, frequency, and concentration reference. Methods of obtaining singlet data have been suggested whereby a separate free induction

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decay (FID) is acquired in the same scan after acquiring the MQ filtered signal [12,13]. However, this involves implementing additional radiofrequency (RF) and gradient pulses following the MQ filter acquisition period to render the signal from uncoupled spins observable. Furthermore, correction factors are required to take into account the additional T_2 decay experienced by the singlet signal in the method of Ref. [13] or the amount of singlet longitudinal magnetization available for excitation after the MQ filter part of the sequence in the method of Ref. [12]. Star-Lack and Spielman designed a zero quantum filter to enable the measurement of signal from lactate and singlets in the same acquisition [14] while simultaneously suppressing the contaminating lipid signal. This was achieved by means of carefully tailored frequency selective MQ filtering RF pulses and appropriate filter gradients both of which perform together to pass through zero quantum CH_3 Lac signal while creating a stimulated echo for Cr and Cho [14].

In this work we describe an alternative PRESS-based sequence that allows the simultaneous detection of desired singlets and coupled spins while suppressing overlapping background signal. The method does not involve frequency selective pulses or MQ filter gradients but is based on the concept of homonuclear polarization transfer and simply requires the implementation of an additional pulse to the basic PRESS sequence. Homonuclear polarization transfer has been employed previously in sequences designed for *in-vivo* applications. In particular, the two dimensional technique COSY [15], correlation spectroscopy, based on coherence transfer has been incorporated into modified versions of PRESS to permit spatial localization [16–18]. Homonuclear polarization transfer has also been exploited in one dimensional spectroscopy. The HOPE sequence is a subtraction technique that was designed for lactate editing and it achieves homonuclear polarization transfer by an altered PRESS sequence that consists only of 90° RF pulses [19]. Another one dimensional sequence involving polarization transfer is the elegant approach of Ref. [20] for the simultaneous detection of γ-amino butyric acid (GABA) and NAA. The method is based on presaturation, homonuclear polarization transfer, and the concept of subjecting certain spins (GABA at 3.01 and 1.9 ppm, and NAA at 2.01 ppm) to three refocusing pulses (two of which are slice selective). We present here a method similar to that of Ref. [20]; namely, a spatially-localized homonuclear version of the heteronuclear refocused INEPT sequence [21]. The efficacy of INEPT like homonuclear polarization transfer for observing Lac at 1.3 ppm while suppressing the overlapping lipid signal in a single scan has been previously shown [22], following which the method was combined with a stimulated echo volume-selective spectroscopy (VOSY) sequence to incorporate spatial localization [23]. The objective of this work is to demonstrate how the technique of Ref. [22] can be incorporated into the more commonly used PRESS sequence. The proposed sequence involves the application of a 90° pulse with phase orthogonal to that of the excitation pulse at the location of the first echo in PRESS and can easily be implemented on a clinical scanner. Initially, all signal in the region of interest (target signal and background signal to be eliminated) is saturated; the desired resonances are then retrieved via homonuclear polarization transfer from spins to which the target spins are weakly *J*-coupled while any background signal from protons not coupled to spins outside the suppressed region remains unobservable. We first verify the efficacy of the sequence in phantoms on the AX_3 spin system of Lac, after which we show that the applicability of the sequence is not limited to weakly coupled AX, AX_2, or AX_3 spin systems but can also be applied to spin systems in which the target spins are not magnetically equivalent so long as they are weakly coupled to a common spin (or spins) outside the initially suppressed spectral region. This is illustrated in phantoms with the ABX spin system of the cysteinyl group of glutathione (GSH). The AB resonance (2.92–2.97 ppm) of the cysteinyl group of GSH has been found to be the most suitable for detection of GSH by ^{1}H MRS [24]. In this paper, the feasibility of employing the proposed sequence for the simultaneous detection of GSH and suppression of the intense overlapping Cr resonance (3.02 ppm) is demonstrated. Both glutathione (GSH) and lactate (Lac) have been previously targeted for detection by MQ filters [10,11,14,24,25] and they are both of relevance in the study of tumours and their response to therapy [26,27] among other pathologies.

2. Theory

The modified PRESS sequence which we term PT-PRESS (Polarization Transfer PRESS) is displayed in Fig. 1. To understand the mechanism of the sequence, consider simple AX, AX_2, and AX_3 weakly coupled, proton spin systems. Prior to the PRESS excitation pulse, the signal from the target spins, X, and any overlapping peaks are saturated while the A spins are left unperturbed. Using product operator calculations, the evolution of spin A under the effect of the RF pulses (assumed to be ideal) and the scalar coupling interactions taking place during the time delays in the sequence can be calculated. To simplify calculations, the chemical shift evolution and its refocusing by the 180° pulses is ignored. The evolutionary terms are derived using standard transformations under RF pulse and scalar coupling Hamiltonians [15]. For an AX spin system, if we start with longitudinal A magnetization, the outcome of the sequence includes in-phase observable X magnetization given by $-X_Y \sin(\pi J_{AX}\mathrm{TE}_1)\sin(\pi J_{AX}\mathrm{TE}_2)$, the yield of which is a maximum (100%) when $\pi J_{AX}\mathrm{TE}_1 = \pi J_{AX}\mathrm{TE}_2 = \frac{\pi}{2}$, implying $\mathrm{TE}_1 = \mathrm{TE}_2 = \frac{1}{2J_{AX}}$. Essentially, the delay TE_1 is set to maximize the antiphase coherence state $A_X X_Z$ which is then transformed into antiphase X magnetization, $A_Z X_X$, by the 90°_y pulse. The delay TE_2 is set such that the antiphase X coherence state evolves into maximum in-phase X magnetization. Thus the signal from spin X can be retrieved, after being initially suppressed, from the magnetization of the A spin

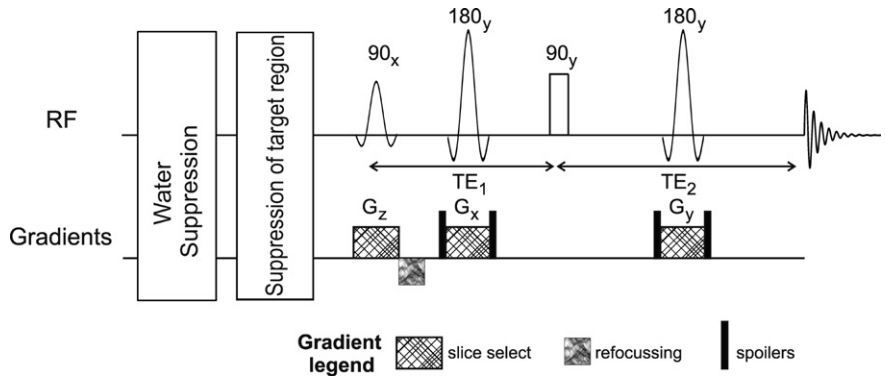

Fig. 1. Schematic diagram illustrating the modified PRESS sequence where essentially a 90° pulse with phase orthogonal to that of the PRESS excitation pulse is applied at the location of the first echo. The delays TE_1 and TE_2 are optimized for most efficient signal yield.

to which it is weakly coupled. Any background signal from protons not coupled to spins outside the initially saturated region remains suppressed. In addition, because the phase of the additional pulse is the same as that of the uncoupled spins outside the target region, the signal from those uncoupled spins remain unaffected by the pulse. Thus all singlet peaks outside the initially suppressed region are retained.

Similar product operator calculations can be carried out for AX_2 and AX_3 spin systems. For AX_2 spin systems, it can be found that the final in-phase X signal is given by $-(X_{1Y}+X_{2Y})\sin(\pi J_{AX}\mathrm{TE}_1)\ \cos(\pi J_{AX}\mathrm{TE}_1)\ \sin(\pi J_{AX}\mathrm{TE}_2)$. The maximum yield of X spins from this sequence is 50% and is achieved when $\mathrm{TE}_1=\frac{1}{4J_{AX}}$ and $\mathrm{TE}_2=\frac{1}{2J_{AX}}$. For AX_3 spin systems, the in-phase X signal at the onset of acquisition is given by $-(X_{1Y}+X_{2Y}+X_{3Y})\sin(\pi J_{AX}\mathrm{TE}_1)\cos^2(\pi J_{AX}\mathrm{TE}_1)\sin(\pi J_{AX}\mathrm{TE}_2)$ from which it can be deduced that the maximum obtainable in-phase X signal is ≈38.5% when $\mathrm{TE}_1\approx\frac{0.2}{J_{AX}}$ and $\mathrm{TE}_2=\frac{1}{2J_{AX}}$.

For spin systems that also involve strongly coupled spins, such as the ABX spin system of the cysteinyl group of GSH, product operator calculations increase in complexity [28] and a numerical approach for optimizing the sequence timings is more convenient.

3. Methods

3.1. Numerical

To optimize the timings of the sequence shown in Fig. 1 for the detection of GSH at 3.0 T a MATLAB program specifically addressing the ABX spin system of GSH was implemented to perform density matrix calculations of the spin system in response to the sequence. Chemical shift, scalar coupling, and RF field interactions were taken into account. Ideal refocusing pulses were assumed and relaxation was ignored. The number of sampling points and spectral width used to simulate the acquisition period were the same as the experimental values. The chemical shift (δ) and scalar coupling constants (J) were obtained from Ref. [29] and are as follows: $\delta_A=2.9264$ ppm, $\delta_B=2.9747$ ppm, $\delta_X=4.5608$ ppm, $J_{AX}=7.09$ Hz, $J_{BX}=4.71$ Hz, and $J_{AB}=-14.06$ Hz. In order to simulate the saturation of the AB spins prior to PRESS excitation, the initial density matrix was set equal to the longitudinal magnetization of the X spin only, I_{Z_X}, instead of equal to the sum $I_{Z_A}+I_{Z_B}+I_{Z_X}$. To estimate the amount of GSH signal contamination from the GABA triplet at 3.01 ppm a separate program was implemented to carry out the same calculations for the weakly coupled $A_2M_2X_2$ spin system of GABA. The following constants were used [29]: $\delta_{A1,2}=3.0128$ ppm, $\delta_{M1,2}=1.889$ ppm, $\delta_{X1,2}=2.284$ ppm, $J_{A1M1}=5.372$ Hz, $J_{A1M2}=7.127$ Hz, $J_{A2M1}=10.578$ Hz, $J_{A2M2}=6.982$ Hz, $J_{M1X1}=7.755$ Hz, $J_{M1X2}=7.432$ Hz, $J_{M2X1}=6.173$ Hz, and $J_{M2X2}=7.933$ Hz. The initial density matrix was set equal to the longitudinal magnetization of the M and X spins to simulate the saturation of the A spins in PT-PRESS.

3.2. Experimental

Experiments were conducted with a 3 T Philips Intera scanner and a transmit/receive birdcage head coil. A 50 Hz bandwidth hyperbolic secant inversion pulse was employed for water suppression with an inversion recovery delay of approximately 1100 ms. A small bandwidth was selected for the water suppression pulse to avoid exciting the A resonance of the AX_3 spin system of Lac and the X spin of the ABX spin system of GSH which resonate at approximately 4.1 and 4.56 ppm, respectively. It was experimentally verified that the inversion pulse had negligible effect on spins resonating at frequencies that deviated by more than 28 Hz from the frequency at which it was applied. In our GSH phantoms, the resonance frequency of the X spin of the GSH cysteinyl group was 31 Hz below that of water. To ensure that it was not affected by the water suppression pulse, the pulse's frequency was set to a value 5 Hz higher than that of the water resonance, safely excluding the X spin of GSH from the pulse's bandwidth. Suppression of the target region was carried out by a CHESS suppression sequence [30] consisting of three 90° sinc-Gaussian pulses of duration 10.7 ms and bandwidth

200 Hz. Each pulse was followed by a dephasing gradient of duration 10 ms and strength 10 mT/m; the directions of the three gradients were orthogonal to each other. The offset frequencies of the CHESS pulses were set at 1.3 ppm and 2.95 ppm, for Lac and GSH editing, respectively. The slice selective PRESS sinc refocussing pulses (bandwidth ≈930 Hz, length ≈10.3 ms) were designed to minimize the spatial extent of the tip-angle transition region. The PRESS pulses were applied in conjunction with gradients such that a $2 \times 2 \times 2$ cm^3 voxel was selected. Spoiler gradients of length 2.45 ms and strength 10 mT/m were applied prior to and after the refocussing pulses in three orthogonal directions. The additional 90° pulse that performed the polarization transfer was a 300 μs rectangular pulse. The offset frequency of this pulse was set at 2.7 and 3.8 ppm, for Lac and GSH editing, respectively. For optimal polarization transfer it is important that the phase of the hard pulse be orthogonal to that of the PRESS excitation pulse. Spatial localization alters the relative phases of the two pulses [6,24,31]; therefore, the phase of the pulse was varied in increments of 10° until the Cr signal (or desired singlet resonance) reached a maximum. At this point orthogonality between the phase of the additional 90° pulse and that of the PRESS excitation pulse had been achieved. It was verified that changing the phase of the editing pulse by 90° from the optimum phase resulted in a zero passage for the singlet peak intensity. To minimize signal contributions from outside the voxel of interest as a result of the polarization transfer pulse, it was found that for the *in-vitro* experiments presented here it was sufficient to alternate the phase of the PRESS excitation pulse and that of the receiver between $\pm x$. However, to make the sequence more suitable for an *in-vivo* setting, a four step phase cycling scheme was implemented where the phase of the PRESS excitation pulse and that of the receiver rotated through $\{x, y, -x, -y\}$ while the editing pulse cycled through $\{y, -x, y, -x\}$. In addition, the sequence was preceded by an outer volume suppression module which involved the excitation and dephasing of signal from six 30 mm slabs surrounding the voxel along the $\pm x$, $\pm y$, and $\pm z$ directions.

The efficacy of the sequence was verified on four different 6 cm diameter spherical phantoms of pH ≈7. The first phantom contained 10 mM Cr and 30 mM Lac; the second sphere was 70% filled with a solution of 10 mM Cr, 50 mM Lac. The remaining upper portion of the sphere contained canola oil. The third phantom consisted of 10 mM sodium acetate and 50 mM GSH, while the fourth one had the same constituents as the third with the addition of 15 mM Cr. To examine the integrity of spatial localization, a double compartment phantom consisting of two concentric spheres was used. The inner 6 cm diameter sphere was filled with approximately 10 mM Cr and 2.7 mM Cho, while the outer volume enclosed by a 9 cm diameter sphere was filled with 20 mM sodium acetate. All chemicals were purchased from Sigma–Aldrich Canada. Spectra were acquired in 32 averages, preceded by four dummy scans, with a repetition time of 3 s; 2048 complex data points were sampled at a frequency of 2500 Hz. For the detection of Lac by PT-PRESS, $TE_1 \approx \frac{0.2}{J_{AX}} = 28.8$ ms ($J_{AX} = 6.93$ Hz) and $TE_2 = \frac{1}{2J_{AX}} = 72$ ms as discussed in Section 2 for an AX_3 spin system. For the ABX cysteinyl group of GSH, the optimum timings were numerically calculated to be $TE_1 \approx 40$ ms and $TE_2 \approx 30$ ms (see Section 4).

All signal ratios quoted in this work were measured by relative areas.

4. Results

4.1. Lactate editing

Fig. 2(a–b) displays spectra acquired from the phantom containing 10 mM Cr and 30 mM Lac. The top spectrum was obtained with a standard PRESS sequence where $\{TE_1, TE_2\} = \{72$ ms, 72 ms$\}$ to give a negative Lac doublet. Fig. 2(b) shows the spectrum acquired with PT-PRESS with timings optimized for Lac editing via polarization transfer and with CHESS suppression of the 1.3 ppm region. The Lac signal is effectively retrieved with minimal effect on the Cr singlet peaks (≈90% of the Cr signal is retained). Assuming ideal RF pulses, product operator calculations predict that the area of the Lac doublet will be at its maximum but inverted when the total echo time is 144 ms ($\frac{1}{J_{AX}}$) and that the area of the edited doublet in Fig. 2(b) will be about 38.5% of the inverted doublet area (see Section 2); however, the ratio of the areas is approximately 66%. This is most likely due to the fact that the response of Lac to PRESS deviates from behavior predicted by product operator calculations as a result of spatial interference effects as termed by Ref. [32]. The signal yield of Lac in response to PRESS and therefore to any PRESS-based sequence such as PT-PRESS can suffer as a result of the spatially selective RF pulses and the large chemical shift difference between the two weakly coupled resonances of Lac (≈360 Hz at 3 T) which give rise to a relative shift in the location of the voxels of the A and the X spin [32,33]. Increasing the bandwidth of the RF pulses can reduce these spatial offsets. This is illustrated by spectra (Fig. 2(c–d)) acquired from the same phantom with a PRESS sequence consisting of 750 μs rectangular pulses and no spatial localization gradients. Signal was acquired from the entire 6 cm diameter spherical phantom and the increase in the ratio of Lac to Cr signal in both the PRESS and PT-PRESS spectra is evident. Furthermore, the area of the Lac peak acquired with PT-PRESS is approximately 34% of that acquired with PRESS which agrees closely with the predicted value obtained by product operator calculations (38.5%).

Fig. 3 demonstrates the efficacy of the sequence in suppressing unwanted overlapping signal from lipids (canola oil). All spectra were acquired with PRESS timings $\{TE_1, TE_2\} = \{28.8$ ms, 72 ms$\}$ from a phantom containing 10 mM Cr, 50 mM Lac, and a layer of canola oil.

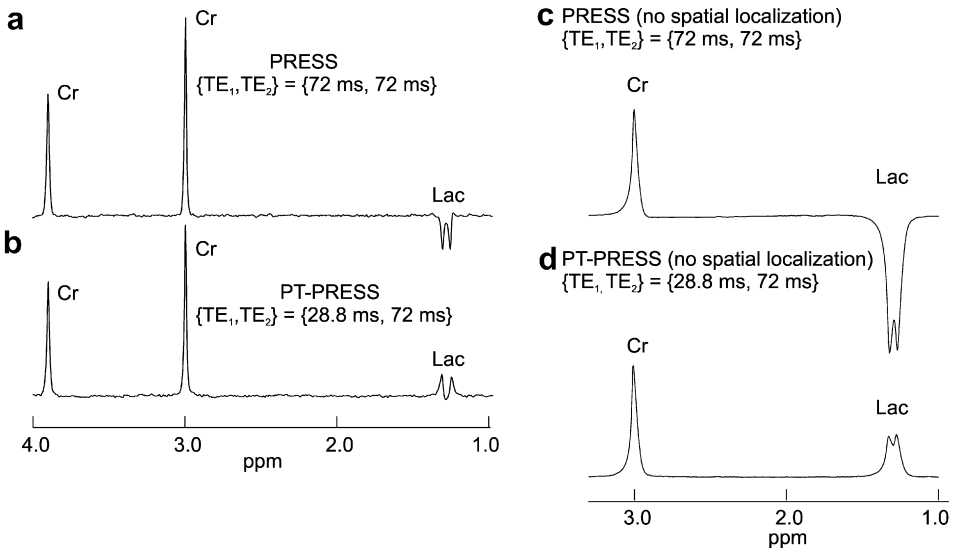

Fig. 2. Spectra (a–b) are from a $2 \times 2 \times 2$ cm^3 voxel of a 10 mM Cr/30 mM Lac phantom acquired with (a) PRESS, $\{TE_1, TE_2\} = \{72$ ms, 72 ms$\}$, and (b) PT-PRESS, $\{TE_1, TE_2\} = \{28.8$ ms, 72 ms$\}$, including CHESS suppression of the 0.5–2 ppm spectral region. Lactate signal at 1.3 ppm is recovered via polarization transfer from the Lac A spin at 4.1 ppm. Spectra (c–d) are from the whole 10 mM Cr/30 mM Lac phantom acquired with (c) PRESS $\{TE_1, TE_2\} = \{72$ ms, 72 ms$\}$ and (d) PT-PRESS. In both (c) and (d) the slice selective pulses were replaced with 750 μs rectangular pulses and the spatial localization gradients were removed.

Fig. 3(a) shows the large oil resonances that overwhelm the Lac signal in the 0.5–1.5 ppm area, while Fig. 3(b) displays the result of applying CHESS suppression to that spectral region. Applying the polarization transfer pulse effectively restores signal from Lac while the peaks from oil remain suppressed and the Cr singlet is unaffected; see Fig. 3(c).

4.2. Glutathione editing

The magnitude of the cysteinyl AB mutiplet of GSH to the PT-PRESS sequence was calculated as a function of the two PRESS echo times as shown in Fig. 4(a). The maximum generated signal was found to occur when $\{TE_1, TE_2\} = \{40$ ms, 30 ms$\}$. Fig. 4(b) displays a few calculated PT-PRESS spectra along with their experimental verification on the phantom containing 50 mM GSH and 10 mM sodium acetate. In general, the two sets of spectra closely agree. The lower amplitudes of the experimental spectra acquired at the longer echo times is most likely due to T_2 relaxation which was ignored in the calculations. In addition, any deviations between theory and experiment could be due to the fact that ideal RF pulses were assumed in the calculations. It could also be that the scalar coupling and chemical shift constants used in the simulations (obtained from Ref. [29]) were slightly different than the actual values of the GSH solution. Fig. 5 displays a short TE PRESS spectrum, $\{TE_1, TE_2\} = \{15$ ms, 15 ms$\}$, along with a PT-PRESS spectrum acquired with the optimized timings. In Fig. 5(b), it is clear that the Cr peak around 3 ppm is effectively suppressed by the CHESS suppression module while signal from the AB spins of the cysteine group of GSH is retrieved via polarization transfer from the X protons to which the AB spins are weakly coupled with a signal yield of ≈46.5% relative to the GSH signal in Fig. 5(a). Approximately 93% of the signal from the CH_3 singlet of sodium acetate is preserved.

4.3. Spatial localization

To demonstrate that the addition of the 90° pulse did not affect spatial localization in our experiments, tests were conducted on the double compartment phantom shown in Fig. 6(a). PRESS spectra acquired from the inner and outer compartments are displayed in Figs. 6(c) and (e), respectively. Switching on the $90°_y$ pulse at the first echo time had hardly any affect on the spectra as demonstrated in Figs. 6(d) and (f). The singlet peaks were approximately identical to those acquired with PRESS (≈2% less in intensity) and there was no visible evidence of any outer volume signal contaminating the spectra.

4.4. Phase of editing pulse

To quantify signal loss as a result of incorrectly setting the phase of the polarization transfer pulse in PT-PRESS, the signal intensities of GSH and acetate were calculated as a function of the phase difference between the PRESS excitation pulse and the polarization transfer pulse. Fig. 7 shows the results along with experimental confirmation. Theoretically, both GSH and acetate respond in the same manner. The signal is of course a maximum when the phase difference is 90°. An error of ±10° in the phase results in a signal loss of only ≈2%. If the phase is offset by ±20° the signal loss increases to about 6%.

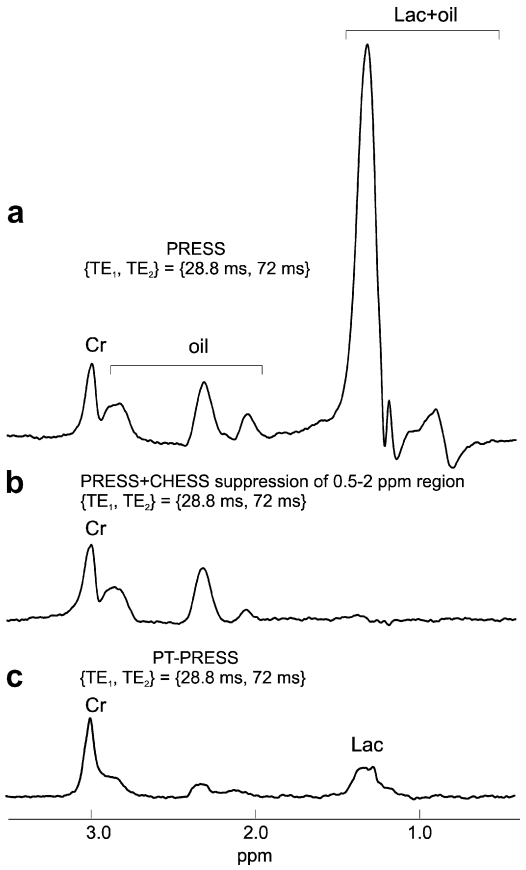

Fig. 3. Spectra acquired from a $2 \times 2 \times 2$ cm^3 voxel of a 10 mM Cr/50 mM Lac/canola oil phantom. All spectra were acquired with timings $\{TE_1, TE_2\} = \{28.8 \text{ ms}, 72 \text{ ms}\}$. Spectra show the response of the phantom to (a) basic PRESS, (b) basic PRESS in addition to CHESS suppression of Lac and oil in the 0.5–2 ppm region, and (c) PT-PRESS where switching on the editing polarization transfer pulse enabled the recovery of Lac signal at around 1.3 ppm while leaving the oil signal in that area suppressed. Spectra were line broadened to approximately 7 Hz to simulate *in-vivo* conditions.

5. Discussion and conclusion

This paper presented a proton spectral editing pulse sequence (PT-PRESS) that can be employed as an alternative to MQ filters for the detection of metabolites with spin systems that involve weak coupling. The sequence is based on the concept of homonuclear polarization transfer and is essentially a homonuclear version of the heteronuclear INEPT sequence [21] incorporated into the standard PRESS sequence to achieve spatial localization. The idea is to initially suppress all peaks in the region of interest whether they are peaks from the target metabolite or from contaminating background. The target signal is then restored by polarization transfer from a proton that has a resonance outside the suppressed region and to which the target spins are weakly coupled. This is accomplished by the application of a 90° hard pulse with phase orthogonal to that of the PRESS excitation pulse at the location of the first echo in PRESS and by optimizing the two PRESS timings, TE_1 and TE_2, for most efficient target signal yield. The advantage of this sequence compared to conventional MQ filters is that signal from singlet peaks outside the suppressed area are preserved and can thus be used as a concentration, phase, and frequency reference. Theoretically, it should be able to retain 100% of the reference singlet signal. In this work the CHESS sequence [30] was used to saturate the target spectral region; however, alternative suppression techniques such as SWAMP [34] would serve the same purpose. The efficacy of PT-PRESS for editing was verified on phantom solutions of Lac and GSH. The PT-PRESS sequence was capable of suppressing lipid signal that co-resonates with the 1.3 ppm peak of Lac while retaining about 90% of the Cr signal and 66% of the Lac signal that could be obtained with a PRESS sequence of timings $\{TE_1, TE_2\} = \{72 \text{ ms}, 72 \text{ ms}\}$ where the Lac doublet is inverted. However, as previously mentioned the response of Lac to PRESS and therefore also to PT-PRESS suffers as a result of spatial interference effects that become more pronounced at higher field strengths [32,33] as the bandwidths of the RF pulses become more comparable to that of the chemical shift difference of the weakly coupled A and X spins. Despite the fact that this Lac signal loss has been reported, PRESS with $TE = 144$ ms is still often employed for Lac detection because its inverted peaks helps in distinguishing it from lipids [33,35]. PT-PRESS offers a potentially better alternative because it allows lipid suppression and gives a comparable amount of Lac signal at a shorter total echo time (≈102 ms) thereby reducing losses due to T_2 relaxation. In the case of GSH, the yield of the AB multiplet of the cysteine moiety by PT-PRESS was comparable to that achieved with DQ filters [11]. The PT-PRESS sequence with timings optimized for the GSH ABX spin system provided ≈46.5% of the GSH signal acquired with a short TE PRESS sequence, $\{TE_1, TE_2\} = \{15 \text{ ms}, 15 \text{ ms}\}$ while suppressing the neighbouring Cr resonance and retaining ≈93% of the signal from the CH_3 group of sodium acetate at 2 ppm, which is where the peak from *N*-acetyl aspartate (NAA) would be *in-vivo*. In all cases, the target peak and the singlet peak had, as desired, the same phase and thus required the same zero order phase correction. It was found that switching on the CHESS suppression pulses to saturate the target spectral region affected the singlet peaks. Both the Cr and acetate signals dropped in amplitude by about 7% after the CHESS module was applied. This explains most of the signal loss of Cr in the lactate edited spectrum compared to PRESS (≈90% of Cr was observed). The remainder of the lost signal is most likely due to a deviation from the optimum phase of the polarization transfer pulse (see Fig. 7). Frequency offset effects were found to be negligible due to the very short duration of the polarization transfer pulse. For the singlet signal to be useful as a concentration reference and for accurate quantitation, the effect of the CHESS pulses on the singlet signal intensity should be taken into account when evaluating spectra acquired with PT-PRESS. Furthermore, it should be realized that errors in setting the phase of the editing pulse may translate into

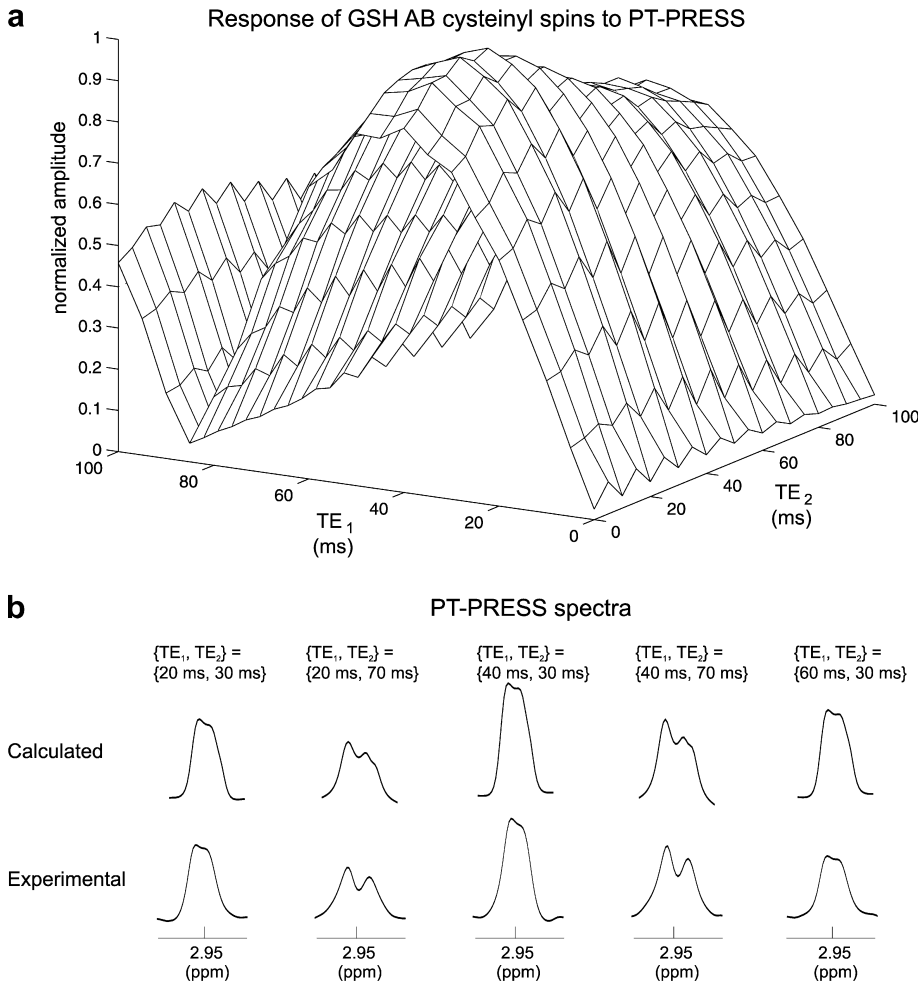

Fig. 4. A calculated mesh plot of the magnitude of the *AB* multiplet of the cysteinyl group of GSH as a function of the two timings $\{TE_1, TE_2\}$ in PT-PRESS at 3.0 T is shown in (a). The maximum amplitude occurs at about $\{TE_1, TE_2\} = \{40\text{ ms}, 30\text{ ms}\}$. The spectral response of the *AB* spins of the cysteine moiety of GSH to PT-PRESS as a function of different echo time combinations is displayed in (b) where both theoretical and experimental results are compared.

errors in quantitation on the order of a few percent if the signal of both the target spins and the singlet resonance do not change by the same amount in response to a change in the phase of the editing pulse.

The simultaneous editing of a target metabolite and the retention of an uncoupled resonance to provide a reference signal has been achieved previously by other techniques [12–14,20,36]. Two of these sequences were designed for Lac editing and the simultaneous detection of Cr (and Cho) [14,36]. The selective zero quantum filter described in Ref. [14] allowed the acquisition of 37% of the Cr signal and 41% of the Lac signal obtained with a PRESS sequence with TE = 144 ms at 1.5 T. While we can comment that our technique, PT-PRESS, permits at least 90% of the Cr signal to be retained, we cannot make a direct comparison between the Lac signal yield of PT-PRESS and that of Ref. [14] because at 3 T the spatial interference effects are worse. To make a fair comparison, the performance of the selective zero quantum filter would have to be evaluated at 3 T. A similar statement can be made when comparing PT-PRESS with the sequence of Lei and Peeling [36], which was implemented at 7 T and at 9.4 T, and involved a double quantum (DQ) coherence transfer sequence for Lac editing and additional pulses to create a stimulated echo for Cr (and Cho). The stimulated echo recovered ≈45% of the signal from uncoupled spins. The other three referenced methods were designed for the observation of the *A* spins of GABA (≈3 ppm) and uncoupled spins. GABA can be represented as an $A_2M_2X_2$ spin system where the *A* spins are weakly coupled to the *M* spins that have a chemical shift of ≈1.9 ppm [29]. Two of the methods were similar in that a DQ filter was employed for GABA editing and that two separate FIDs were collected [12,13]. In Ref. [13], a truncated DQ filtered FID was acquired following which an RF pulse and a gradient pulse were applied to refocus signal from uncoupled spins; because the acquisition of the two signals was not simultaneous, signal from the uncoupled spins underwent further signal loss due to T_2 relaxation. In the technique of Ref. [12], the DQ filtered FID was acquired and was immediately followed by a

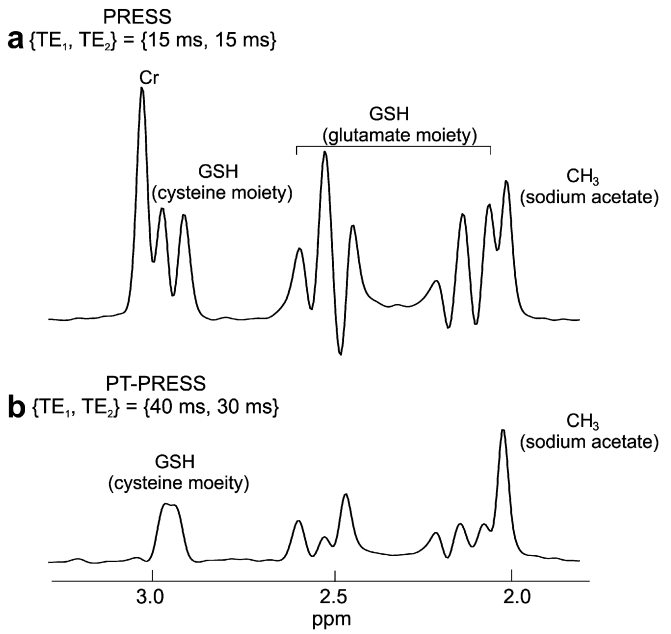

Fig. 5. Spectra acquired from a $2 \times 2 \times 2$ cm^3 voxel of a 15 mM Cr/50 mM GSH/10 mM sodium acetate phantom. Spectra show the response of the phantom to (a) basic PRESS with short echo times $\{TE_1, TE_2\} = \{15$ ms, 15 ms$\}$, and (b) PT-PRESS with timings $\{TE_1, TE_2\} = \{40$ ms, 30 ms$\}$ optimized for GSH detection; switching on the editing polarization transfer pulse enabled the recovery of GSH signal at around 2.95 ppm while leaving the Cr signal in that area suppressed. Spectra were line broadened to approximately 7 Hz to simulate *in-vivo* conditions.

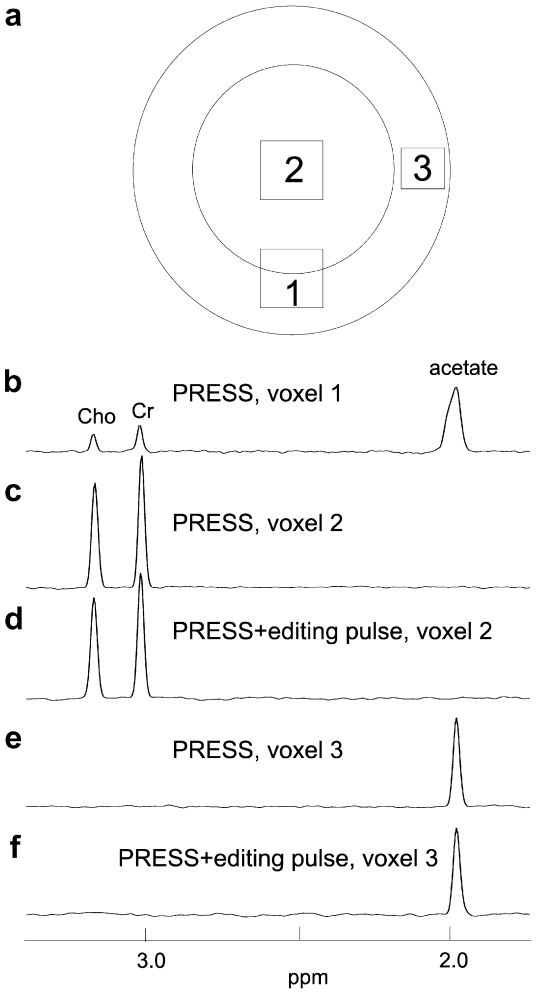

Fig. 6. A schematic diagram of the double compartment phantom is shown in (a). The inner compartment contained 10 mM Cr and 2.7 mM Cho while the outer compartment was filled with 20 mM sodium acetate. Spectra were acquired from the three labeled voxels with a PRESS sequence, $\{TE_1, TE_2\} = \{15$ ms, 15 ms$\}$. Voxels 1 and 2 were $2 \times 2 \times 2$ cm^3 and voxel 3 was $1.5 \times 1.5 \times 1.5$ cm^3 in volume. The spectrum shown in (b) was obtained from voxel 1 to illustrate the constituents of the phantom. A PRESS spectrum acquired from the inner compartment of the phantom is shown in (c). The same experiment was repeated but with the editing pulse switched on (with phase orthogonal to the PRESS excitation pulse); the resulting spectrum is displayed in (d). Spectra (e) and (f) were acquired from voxel 3, with the editing pulse turned off and on, respectively.

PRESS sequence for Cr signal acquisition. Maximum Cr longitudinal magnetization was not available prior to PRESS excitation because the Cr signal was affected by the DQ filer part of the sequence, resulting in a signal loss for Cr. To compare the performance of PT-PRESS to the mentioned GABA editing methods, the timings were numerically optimized for observation of the A spins of GABA ($\approx$3 ppm). Theoretically, it was found that the GABA signal was a maximum when the sequence timings were set to $\{TE_1, TE_2\} = \{20$ ms, 30 ms$\}$; the GABA yield was approximately 36% of the signal attainable by a 90° pulse-acquire experiment. This is higher than the maximum 25% signal yield achievable by a DQ filter [37]. Furthermore, PT-PRESS inherently allows the simultaneous detection of signal from uncoupled spins (ideally 100% of the signal) outside the initially suppressed spectral region. PT-PRESS is quite similar to the method presented by Ref. [20] for the simultaneous detection of the A_2 peaks of GABA and the singlet resonance of NAA. The technique of Ref. [20] provided a superior GABA yield than PT-PRESS at 3 T (PT-PRESS offers $\approx$30% less signal) because of the extra refocusing pulse applied to refocus the scalar coupling evolution between the M_2 and N_2 GABA spins, thereby reducing signal loss from the A_2 spins. The extra refocusing pulse was a doubly selective pulse designed to refocus the GABA protons at 3 and 1.9 ppm. To effectively use the signal from NAA as a concentration reference care had to be taken that the selective pulse completely refocused the NAA signal. In addition, like with PT-PRESS, the phase of the homonuclear polarization transfer pulse would have had to have undergone careful calibration (although not discussed in Ref. [20]). While the selective refocusing pulse is of value in GABA editing, it is redundant for cases such as Lac and GSH editing where the protons coupled to the target spins are not coupled to any other spins. PT-PRESS thus presents a more general sequence that can potentially be applied to any weakly coupled spin system provided the echo times are appropriately optimized.

A limitation of the presented sequence is that perfect editing of the target peak might not be achievable if the

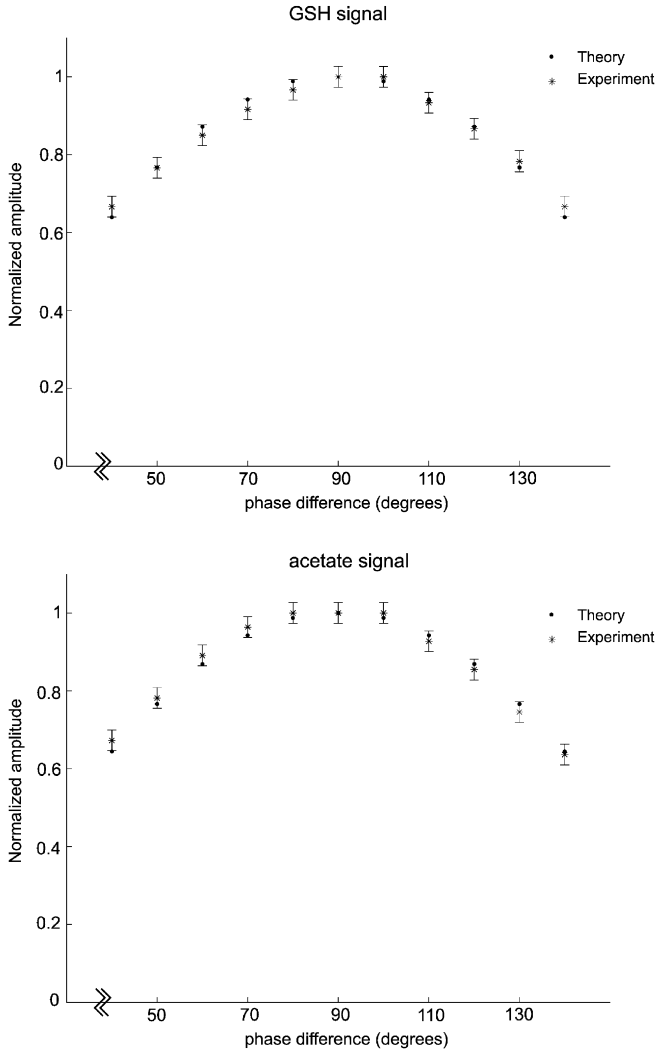

Fig. 7. The responses of the CH_3 group of acetate and the cysteinyl AB spins of GSH to a change in the phase difference between the PRESS excitation pulse and the polarization transfer editing pulse. The dots indicate the calculated response while the asterisks show experimental confirmation of the simulations. The error bars are half the peak-to-peak noise. Theoretically, both GSH and acetate respond identically. An error of $\pm 10°$ in setting the phase of the editing pulse only results in $\approx 2\%$ signal loss.

contaminating protons also exhibit scalar coupling with spins that lie outside the initially suppressed spectral region. Larger contamination is likely if the T_2 relaxation constant of the background spins is comparable to or higher than that of the target spins and if both, background and target spins, exhibit similar scalar coupling evolution. The latter would occur if the background and target protons belong to the same type of spin system and molecular group and if they have comparable scalar coupling constants (with spins that lie outside the pre-saturated spectral area). For the case of GSH editing, the AB cysteinyl peak could be contaminated by signal from the A spins of GABA that resonate at 3.01 ppm. It would not be desirable to include the M protons of GABA (1.91 ppm) among the initially saturated spins because this would result in the suppression of the useful NAA peak at 2.01 ppm. Therefore, some of the GABA signal at 3.01 ppm will be restored by the PT-PRESS editing pulse via polarization transfer from the M spins. The response of both GABA and GSH to a PT-PRESS sequence with timings optimized for GSH detection is shown in Fig. 8(a) assuming equal concentrations of both metabolites. Averaged values from the literature indicate that the ratio of the concentrations of GSH to GABA is approximately 1.67:1 in the human brain [38]. It was estimated theoretically assuming this ratio that the main GSH peak (2.9–3 ppm) would increase by about 20% as a result of overlapping GABA signal. One solution to this problem is to employ sequence timings that yield an acceptable amount of GSH but that minimize contamination from GABA. It was found numerically that if the timings of PT-PRESS were set to $\{TE_1, TE_2\} = \{60\text{ ms}, 30\text{ ms}\}$ then the yield of GABA dropped drastically by $\approx 97\%$ while that of GSH was only reduced by about 20% (compared to is maximum yield). This is illustrated in Fig. 8(b) assuming equal concentrations of GSH and GABA. If we take the ratio of the concentrations of GSH to GABA to be 1.67:1 then the main peak of GSH drops in amplitude by a negligible 0.4% as a result of residual GABA signal with the new timings. Therefore, PT-PRESS is a sequence which holds promise for the

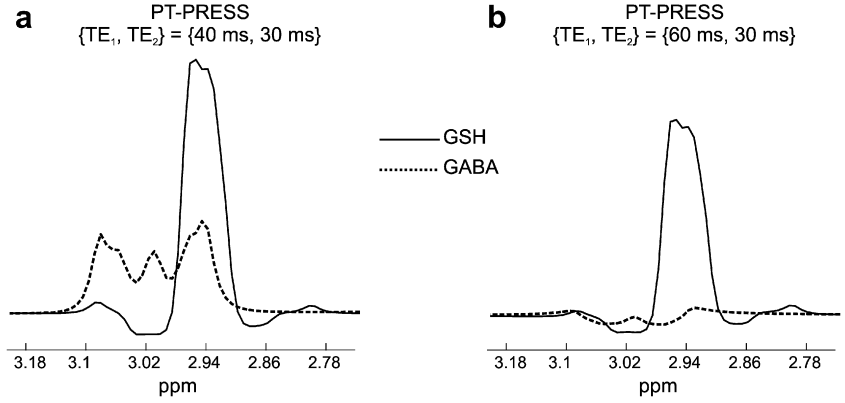

Fig. 8. Comparison of the calculated response of both GSH and GABA in the 3 ppm region to (a) PT-PRESS, $\{TE_1, TE_2\} = \{40\text{ ms}, 30\text{ ms}\}$, and (b) PT-PRESS, $\{TE_1, TE_2\} = \{60\text{ ms}, 30\text{ ms}\}$, assuming equal concentrations of both metabolites.

simultaneous detection of GSH and NAA from brain *in-vivo* with minimal contamination from background Cr and GABA. In the case of Lac detection, the overlapping lipids may also exhibit scalar coupling with spins outside the pre-saturated region, resulting in contamination of the Lac peaks. Lipids contain 30 or more protons [39] and therefore simulating their response is not an easy task. Reference [39] chose 1-pentene to represent a lipid hydrocarbon chain. The 1-pentene molecule can be represented as an $A_3B_2C_2DEF$ spin system where the A, B, C, D, E, and F spins have chemical shifts of 0.91, 1.41, 2.02, 5.8, 5.93, and 5.00 ppm, respectively [39]. If we consider this to be a model for true lipids then of concern are scalar coupling interactions which involve the A and B protons. They are J-coupled to each other; however, since their spectral region is pre-saturated, this should not be of consequence. Nevertheless, the B spins are also coupled to the C spins which can result in lipid signal contaminating the Lac resonance. A solution to this would be to increase the bandwidth of the saturation pulses beyond the 2 ppm region. Of course, the effect of this on Cr would have to be taken into account. Admittedly, in reality the lipids may have a number of resonances between 2 and 3 ppm (as seen in Fig. 3) which may be involved in scalar coupling with the lipid resonances that lie in the Lac region. An alternative solution to minimize lipid infiltration is to exploit the short T_2 of lipids [26] and increase the second time delay of PT-PRESS from $\frac{1}{2J_{AX}}$ (≈72 ms) to $\frac{3}{2J_{AX}}$ (≈216 ms) which according to product operator calculations would result in an inverted in-phase Lac doublet (although the effect of the slice selective pulses with this timing would have to be determined).

Future studies will be conducted to evaluate the performance of the sequence *in-vivo*. Modifications that may be implemented include having the option of making the editing pulse slice selective and improving the technique of optimizing its phase by developing a calibration scan that can be carried out on the water peak [24].

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References

[1] U. Piantini, O.W. Sorensen, R.R. Ernst, Multiple quantum filters for elucidating NMR coupling networks, J. Am. Chem. Soc. 104 (1982) 6800–6801.

[2] D.L. Rothman, K.L. Behar, H.P. Hetherington, R.G. Shulman, Homonuclear ^{1}H double-resonance difference spectroscopy of the rat brain *in vivo*, Proc. Natl. Acad. Sci. USA 81 (1984) 6330–6334.

[3] P.A. Bottomley, Selective volume method for performing localized NMR spectroscopy, U.S. Patent 4,480,228. 1984.

[4] L. Jouvensal, P.G. Carlier, G. Bloch, Practical implementation of single-voxel double-quantum editing on a whole-body NMR spectrometer: localized monitoring of lactate in the human leg during and after exercise, Magn. Reson. Med. 36 (1996) 487–490.

[5] F. Du, W.J. Chu, B. Yang, J.A. Den Hollander, T.C. Ng, In vivo GABA detection with improved selectivity and sensitivity by localized double quantum filter technique at 4.1 T, Magn. Reson. Med. 22 (2004) 103–108.

[6] J.R. Keltner, L.L. Wald, B.B. Frederick, P.F. Renshaw, In vivo detection of GABA in human brain using a localized double-quantum filter technique, Magn. Reson. Med. 37 (1997) 366–371.

[7] H. Kim, J.M. Wild, P.S. Allen, Strategy for the spectral filtering of myo-inositiol and other strongly coupled spins, Magn. Reson. Med. 51 (2004) 263–272.

[8] H. Lei, J. Peeling, Simultaneous spectral editing for gamma-aminobutyric acid and taurine using double quantum coherence transfer, J. Magn. Reson. 143 (2000) 95–100.

[9] R.B. Thompson, P.S. Allen, A new multiple quantum filter design procedure for use on strongly coupled spin systems found in vivo: its application to glutamate, Magn. Reson. Med. 39 (1998) 762–771.

[10] A.H. Trabesinger, P. Boesiger, Improved selectivity of double quantum coherence filtering for the detection of glutathione in the humans brain in vivo, Magn. Reson. Med. 45 (2001) 708–710.

[11] T. Zhao, K. Heberlein, C. Jonas, D.P. Jones, X. Hu, New double quantum coherence filter for localized detection of glutathione in vivo, Magn. Reson. Med. 55 (2006) 676–680.

[12] I-Y Choi, S-P Lee, H. Merkle, J. Shen, Single-shot two-echo technique for simultaneous measurement of GABA and creatine in the human brain in vivo, Magn. Reson. Med. 51 (2004) 1115–1121.

[13] A.H. Wilman, M. Astridge, R.E. Snyder, P.S. Allen, Same-scan acquisition of both edited J-coupled multiplets and singlet resonances of uncoupled spins for proton MRS, J. Magn. Reson. B 109 (1995) 202–205.

[14] J.M. Star-Lack, D.M. Spielman, Zero-quantum filter offering single-shot lipid suppression and simultaneous detection of lactate, choline, and creatine resonances, Magn. Reson. Med. 46 (2001) 1233–1237.

[15] R.R. Ernst, G. Bodenhausen, A. Wokaun, Principles of Nuclear Magnetic Resonance in One and Two Dimensions, Clarendon Press, Oxford, 1987.

[16] L.N. Ryner, J.A. Sorenson, M.A. Thomas, 3D localized 2D NMR spectroscopy on an MRI scanner, J. Magn. Reson. B 107 (1995) 126–137.

[17] M.A. Thomas, K. Yue, N. Binesh, P. Davanzo, A. Kumar, B. Siegel, M. Frye, J. Curran, R. Lufkin, P. Martin, B. Guze, Localized two-dimensional shift correlated MR spectroscopy of human brain, Magn. Reson. Med. 46 (2001) 58–67.

[18] A. Ziegler, B. Gillet, J.C. Beloeil, J.P. Macher, M. Decorps, J.f. Nedelec, Localized 2D correlation spectroscopy in human brain at 3T, MAGMA 14 (2002) 45–49.

[19] M. Bunse, W-I Jung, F. Schick, G.J. Dietze, O. Lutz, HOPE, a new lactate editing method, J. Magn. Reson. B 109 (1995) 270–274.

[20] J. Shen, J. Yang, I-Y Choi, S.S. Li, Z. Chen, A new strategy for in vivo spectral editing. Application to GABA editing using selective homonuclear polarization transfer spectroscopy, J. Magn. Reson. 170 (2004) 290–298.

[21] G.A. Morris, Sensitivity enhancement in nitrogen-15 NMR: polarization transfer using the INEPT pulse sequence, J. Am. Chem. Soc. 102 (1980) 428–429.

[22] M. Von Kienlin, J.P. Albrand, B. Authier, P. Blondet, S. Lotito, M. Decorps, Spectral editing *in vivo* by homonuclear polarization transfer, J. Magn. Reson. 75 (1987) 371–377.

[23] A. Knuttel, R. Kimmich, Single-scan volume-selective spectral editing by homonuclear polarization transfer, Magn. Reson. Med. 9 (1989) 254–260.

[24] A.H. Trabesinger, O.M. Weber, C.O. Duc, P. Boesiger, Detection of glutathione in the human brain in vivo by means of double quantum coherence filtering, Magn. Reson. Med. 42 (1999) 283–289.
[25] M. Muruganandham, J.A. Koutcher, G. Pizzorno, Q. He, In vivo tumor lactate relaxation measurements by selective multiple-quantum-coherence (Sel-MQC) Transfer, Magn. Reson. Med. 52 (2004) 902–906.
[26] E. Adalsteinsson, D.M. Spielman, J.M. Pauly, D.J. Terris, G. Sommer, A. Macovski, Feasibility study of lactate imaging of head and neck tumors, NMR Biomed. 11 (1998) 360–369.
[27] P.E. Thelwall, A.Y. Yemin, T.L. Gillian, N.E. Simpson, M.S. Kasibhatla, Z.N. Rabbani, J.M. Macdonald, S.J. Blackband, M.P. Gamcsik, Noninvasive in vivo detection of glutathione metabolism in tumors, Cancer Res. 65 (2005) 10149–10153.
[28] L.E. Kay, R.E.D. McClung, A product operator description of AB and ABX spin systems, J. Magn. Reson. 77 (1988) 258–273.
[29] V. Govindaraju, K. Young, A.A. Maudsley, Proton NMR chemical shifts and coupling constants for brain metabolites, NMR Biomed. 13 (2000) 129–153.
[30] A. Haase, J. Frahm, W. Hanicke, D. Matthaei, ^{1}H NMR chemical shift selective (CHESS) imaging, Phys. Med. Biol. 30 (1985) 341–344.
[31] J. Keltner, L.L. Wald, P.J. Ledden, Y.C.I. Chen, R.T. Matthews, E.H. Kuestermann, J.R. Baker, B.R. Roden, B.G. Jenkins, A localized double-quantum filter for the in vivo detection of brain glucose, Magn. Reson. Med. 39 (1998) 651–656.
[32] D.A. Yablonskiy, J.J. Neil, M.E. raichle, J.J.H. Ackerman, Homonuclear J coupling effects in volume localized NMR spectroscopy: Pitfalls and solutions, Magn. Reson. Med. 39 (1998) 169–178.
[33] T. Lange, U. Dydak, T.P.L. Roberts, H.A. Rowley, M. Bjeljac, P. Boesiger, Pitfalls in lactate measurements at 3T, Am. J. Neuroradiol. 27 (2006) 895–901.
[34] R.A. de Graaf, K. Nicolay, Adiabatic water suppression using frequency selective excitation, Magn. Reson. Med. 40 (1998) 690–696.
[35] F. Yamasaki, J. Takaba, M. Ohtaki, N. Abe, Y. Kajiwara, T. Saito, H. Yoshioka, S. Hama, T. Akimitsu, K. Sugiyama, K. Arita, K. Kurisu, Detection and differentiation of lactate and lipids by single-voxel proton MR spectroscopy, Neurosurg. Rev. 28 (2005) 267–277.
[36] H. Lei, J. Peeling, Simultaneous lactate editing and observation of other metabolites using a stimulated-echo-enhanced double-quantum filter, J. Magn. Reson. 137 (1999) 215–220.
[37] A.H. Wilman, P.S. Allen, *In vivo* NMR detection strategies for gamma-aminobutyric acid, utilizing proton spectroscopy and coherence-pathway filtering with gradients, J. Magn. Reson. B 101 (1993) 165–171.
[38] R.A. De Graaf, D.L. Rothman, *In vivo* detection and quantification of scalar coupled ^{1}H NMR resonances, Concepts Magn. Reson. 13 (2001) 32–76.
[39] L.A. Stables, R.P. Kennan, A.W. Anderson, J.C. Gore, Density matrix simulations of the effects of J coupling in spin echo and fast spin echo imaging, J. Magn. Reson. 140 (1999) 305–314.