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Echo-time independent signal modulations for strongly coupled systems in triple echo localization schemes: An extension of S-PRESS editing

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ABSTRACT

The double spin-echo point resolved spectroscopy sequence (PRESS) is a widely used method and standard in clinical MR spectroscopy. Existence of important *J*-modulations at constant echo times, depending on the temporal delays between the rf-pulses, have been demonstrated recently for strongly coupled spin systems and were exploited for difference editing, removing singlets from the spectrum (strong-coupling PRESS, S-PRESS). A drawback of this method for *in vivo* applications is that large signal modulations needed for difference editing occur only at relatively long echo times. In this work we demonstrate that, by simply adding a third refocusing pulse (3S-PRESS), difference editing becomes possible at substantially shorter echo times while, as applied to citrate, more favorable lineshapes can be obtained. For the example of an AB system an analytical description of the MR signal, obtained with this triple refocusing sequence (3S-PRESS), is provided.

1. Introduction

The double spin-echo point resolved spectroscopy (PRESS) sequence [1] is, along with the stimulated echo acquisition mode (STEAM) [2], widely used in clinical MR spectroscopy. PRESS consists of a 90° excitation pulse followed by two 180° refocusing pulses (90° – [TE_1/2] – 180° – [TE_1/2] – [TE_2/2] – 180° – [TE_2/2] – Acquisition). The slice selective refocusing pulses generate the double spin echo and complete the volume localization, after slice selective excitation. Previous works have investigated signal dependencies of coupled spin systems on the PRESS interpulse delays (TE_1, TE_2) at constant echo times TE ($TE = TE_1 + TE_2$) [3] and signature variations observed on weakly coupled systems were explained by imperfections of the 180° refocusing pulses and the volume selection process [4]. For strongly coupled systems, the interpulse delays (TE_1, TE_2) present the dominating influence on the spectral shape. From a quantum mechanical point of view, this effect can be ascribed to the non-secular, off-diagonal terms of the Hamiltonian of the strongly coupled system. These off-diagonal terms are in fact responsible for a coherence transfer occurring throughout the evolution periods, in the absence of any RF pulse. As a consequence, assuming ideal rf-pulses, weakly coupled spin systems (and uncoupled spins in any case) do not display these modulations, since the non-secular terms in the Hamiltonian are negligible (or null, respectively). Manipulation of total echo times and interpulse delays in the PRESS sequence allows for optimization of the spectral signature of strongly coupled systems to favor their detection, as readily demonstrated in the framework of prostate spectroscopy for citrate measurements [5–9].

Another recent approach is to exploit the strong coupling signal dependence at fixed echo times for spectral editing. In the strong-coupling PRESS or S-PRESS method, two spectra acquired at the same echo time but using different interpulse delays are subtracted. By optimizing the sequence timings, the citrate signal alternates in sign between acquisitions and therefore accumulates while singlet signals are nulled in the difference spectrum [5,10]. A drawback of the method is that the large signal modulations needed for such editing occur at relatively long echo times such as 280 ms for citrate at 3 T [5].

In this work we consider overcoming this limitation by modifying S-PRESS with a third refocusing pulse (90° – **[TE_0/2] – 180° – [TE_0/2]** – [TE_1/2] – 180° – [TE_1/2] – [TE_2/2] – 180° – [TE_2/2] – Acquisition). The additional degree of freedom provides a means for manipulating the spin evolution to generate large signal modulations at shorter total echo times. Herein the signal behavior under 3S-PRESS excitation was investigated for an AB

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system (citrate), chosen as the simplest model of a strongly coupled spin system with clinical relevance, with the goal of assessing benefits of 3S-PRESS over the previously proposed S-PRESS editing method.

2. Materials and methods

The 3S-PRESS editing concept is similar to S-PRESS published earlier [5], relying on the variation of interpulse delays at constant total echo time. Knowing the exact behavior of a strongly coupled metabolite of interest, it is possible to identify total echo times ($TE_{total} = TE_0 + TE_1 + TE_2$) for which a variation of the interpulse delays (TE_0, TE_1 and TE_2) results in modulation of the metabolite's spectral shape. Combinations of TE_0, TE_1 and TE_2 can be found for which the lineshape is either positive (up) or inverted (down). Subtraction of these two spectra, with the strongly coupled metabolite's signature in opposite phase, results in nulled signals from uncoupled spins in the spectrum as their shape and intensity depend exclusively on TE_{total}. The concept of 3S-PRESS was investigated for citrate, as a simple example for a strongly coupled two spin (AB) system with clinical interest. At 3 T, citrate presents strong coupling since the chemical shift difference ($\Delta = 0.146$ ppm corresponding to about 18 Hz on our system) is close to the *J*-coupling constant of 16 Hz. Optimization of sequence parameters was performed using quantum mechanical simulations, based on the density matrix formalism, using ideal rotation operators for the rf pulse simulation. Angular momentum and rotation operators were represented by matrices with complex elements in the spin-product basis; the operators were obtained by taking the Kronecker products of the corresponding single spin operators. In addition to the numerical simulations, an analytical solution based on the density matrix formalism [6,11] was derived for further comparison with experimental data and is provided in the Appendix.

Our approach was to initially consider fixed first echo times ($TE_0 = 0$, 2, 10, 20, 30 or 40 ms) and generate 2D-plots of signal intensity (defined as the integrated real part of the citrate lineshape) to examine the signal dependence on echo times TE_1 and TE_2. Note that in the limit of $TE_0 = 0$ ms, the 3S-PRESS scheme corresponds to S-PRESS. From the plots, a value for TE_0 was chosen which resulted in large signal intensity modulations with respect to variations in TE_1 and TE_2 while keeping the total echo time ($TE_0 + TE_1 + TE_2$) short.

Spectra from a citrate containing solution were acquired on a 3 T whole body scanner (Siemens, Erlangen, Germany), using a volume coil (TEM coil, MR instruments, Minneapolis, USA) for signal excitation and reception. The phantom contained 90 mM citrate, 61 mM potassium chloride, 18 mM calcium chloride, 14.7 mM magnesium chloride, 8.5 mM zinc chloride dissolved in a phosphate buffered saline (PBS) solution, adjusted to pH = 7, thereby resembling the composition of human prostatic fluid [12]. An additional 50 mM creatine was added to provide a singlet methyl signal for amplitude and phase reference. Coupling constant and chemical shift of citrate were determined to be $J = 16.02$ Hz and $\Delta = 0.144$ ppm, similar to values measured in the prostate *in vivo* [13]. Localized acquisitions ($2 \times 2 \times 2$ cm^3 volume) were performed using a standard PRESS implementation (Siemens, Erlangen, Germany) (1000 Hz bandwidth, 2048 points, 64 averages, TR = 3 s), to which a third refocusing pulse had been added. Post-processing consisted of slight exponential apodization (1 Hz), two times zero-filling, Fourier transformation and 0th order phase correction using the creatine signal as reference. To reduce relaxation effects for comparison with simulated spectra, creatine was scaled to the same amplitude in all acquisitions. Exponential broadening was applied to the simulated spectra to match linewidths observed in the experiments.

3. Results

For a fixed total echo time ($TE_{total} = TE_0 + TE_1 + TE_2$), different choices of the interpulse delays (TE_0, TE_1 and TE_2) lead to different signal intensities as measured by the integrated real part of the citrate signal. Fig. 1, upper panel, shows the citrate signal intensity for a fixed total echo time of 246 ms and $TE_0 = 40$ ms (solid line). More precisely, if TE_{total} and TE_0 are fixed, as for this figure (upper part), only one free parameter, chosen to be TE_1, remains and TE_2 is determined by $TE_2 = TE_{total} - TE_0 - TE_1$. The citrate signal intensity then oscillates with TE_1 between a positively (up) and a negatively (down) refocused lineshape. The degree of refocusing achieved, i.e. the amplitude of these TE_1 dependent oscillations, strongly depends on the choice of the fixed parameters TE_{total} and TE_0 (vide infra). Several choices of the total echo time for fixed TE_0 can be summarized in a two-dimensional plot as shown in Fig. 1, lower

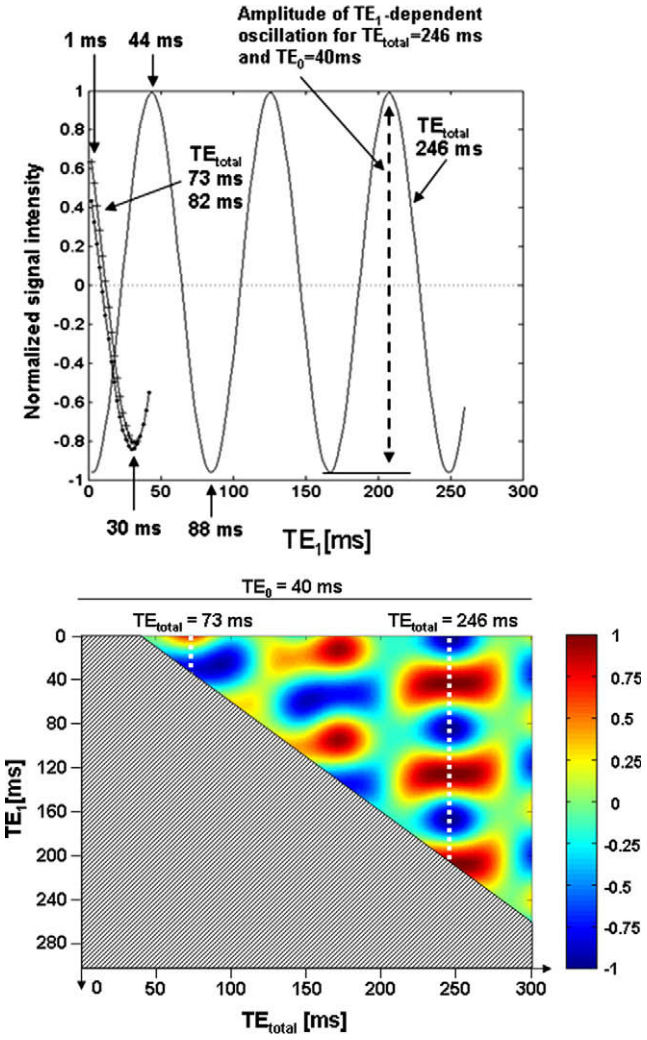

Fig. 1. *Upper panel:* Citrate signal intensity oscillations (intensity of the fully refocused multiplet normalized to 1) as a function of TE_1 while TE_{total} and TE_0 (40 ms) remain fixed. TE_2 is determined by $TE_2 = TE_{total} - TE_0 - TE_1$. The citrate signal oscillates between a positively (up) and a negatively (down) refocused lineshape, as indicated for $TE_{total} = 246$ ms, 73 ms or 82 ms. The oscillation amplitude strongly depends on the choice of TE_{total} and TE_0 (see Fig. 2). *Lower panel:* Simulated citrate signal intensity (3rd dimension) as a function of the total echo time (TE_{total}, *x*-axis) and TE_1 (*y*-axis) using 3S-PRESS. TE_0 was fixed to 40 ms and impossible combinations of TE_{total} and TE_1 were excluded from the plot. Vertical cuts as indicated for $TE_{total} = 246$ ms (compare to upper panel) and $TE_{total} = 73$ represent the TE_1 dependent oscillations at fixed TE_{total} which are used for editing.

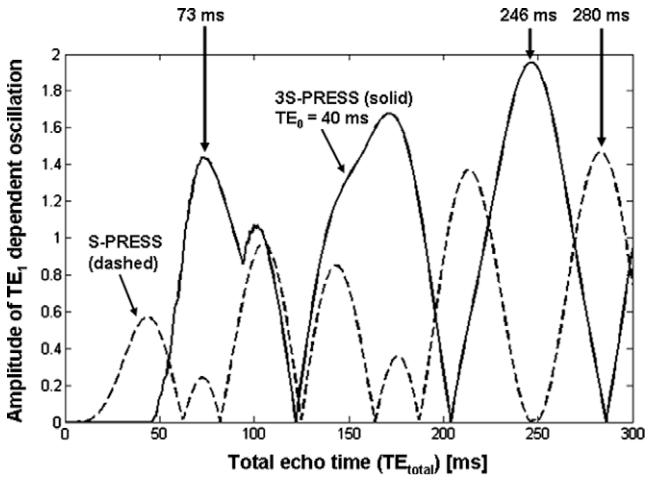

Fig. 2. Amplitudes of citrate signal TE_1-oscillations for different total echo times (TE_{total}) using S-PRESS or 3S-PRESS. With S-PRESS at TE_{total} = 280 ms (dashed line), the signal intensity varies ±0.75 units (normalized to the fully refocused citrate multiplet). For 3S-PRESS with TE_0 fixed to 40 ms, the same signal intensity variation is achieved for TE_{total} of only 73 ms (solid line). Note that this figure also displays the (relative) signal intensity of the difference spectra as a function of TE_{total}, neglecting relaxation.

panel. The figure displays the simulated signal intensity (3rd dimension) as a function of the total echo time (x-axis) and TE_1 (y-axis). Impossible combinations of TE_{total} and TE_1 (such as $TE_{total} < TE_0 + TE_1 + TE_2$, with $TE_0 = 40$ ms and $TE_2 \geqslant 0$) have been excluded from the plot. Next to a vertical cut through the diagram at constant TE_{total} of 246 ms further oscillations at TE_{total} = 73 ms are indicated. While at constant TE_{total} of 246 ms, maximal citrate signal intensity oscillations are achieved, fairly strong oscillations can still be obtained for a short TE_{total} of 73 ms (solid line with "+" symbols in upper panel).

Dependence of these oscillations on the fixed parameter TE_0 are described in the following. First consider a fixed TE_0 = 0 ms in which the 3S-PRESS sequence is equivalent to the S-PRESS editing scheme [5]. The amplitude of the TE_1 dependent oscillations as indicated in Fig. 1 (upper panel), can be traced as a function of the only remaining free parameter TE_{total}. Fig. 2 shows this amplitude for varied TE_{total} (x-axis) and for fixed TE_0 (TE_0 = 0 ms, dashed line). The intensity of the fully refocused citrate multiplet is normalized to 1, therefore an oscillation between a completely up (1) and down (−1) refocused lineshape corresponds to an amplitude of 2. For S-PRESS (dashed line) maximum oscillation occurs at a total echo-time near 280 ms. Note that the signal intensity of the fully refocused multiplet cannot be achieved at echo-times up to 300 ms using S-PRESS. As TE_0 is increased from 0 ms, the amplitudes of the TE_1 dependent oscillations increase (data not shown), and a maximum occurs for TE_0 = 40 ms, illustrated by the solid line in Fig. 2. Oscillations are maximal at TE_{total} = 246 ms, where now almost complete refocusing of J-coupling can be realized. Compared to S-PRESS, the signal intensity is increased by about 30% (neglecting relaxation). Furthermore, at a total echo-time near 74 ms, oscillation amplitudes can be obtained that, in the S-PRESS scheme, were only possible at a considerably longer TE_{total} of 280 ms.

Editing with 3S-PRESS and S-PRESS requires acquisition of a spectrum with positive and negative signal intensity for subtraction. Therefore Fig. 2 displays the relative signal intensity of this difference spectrum as a function of TE_{total}. Based on the simula-

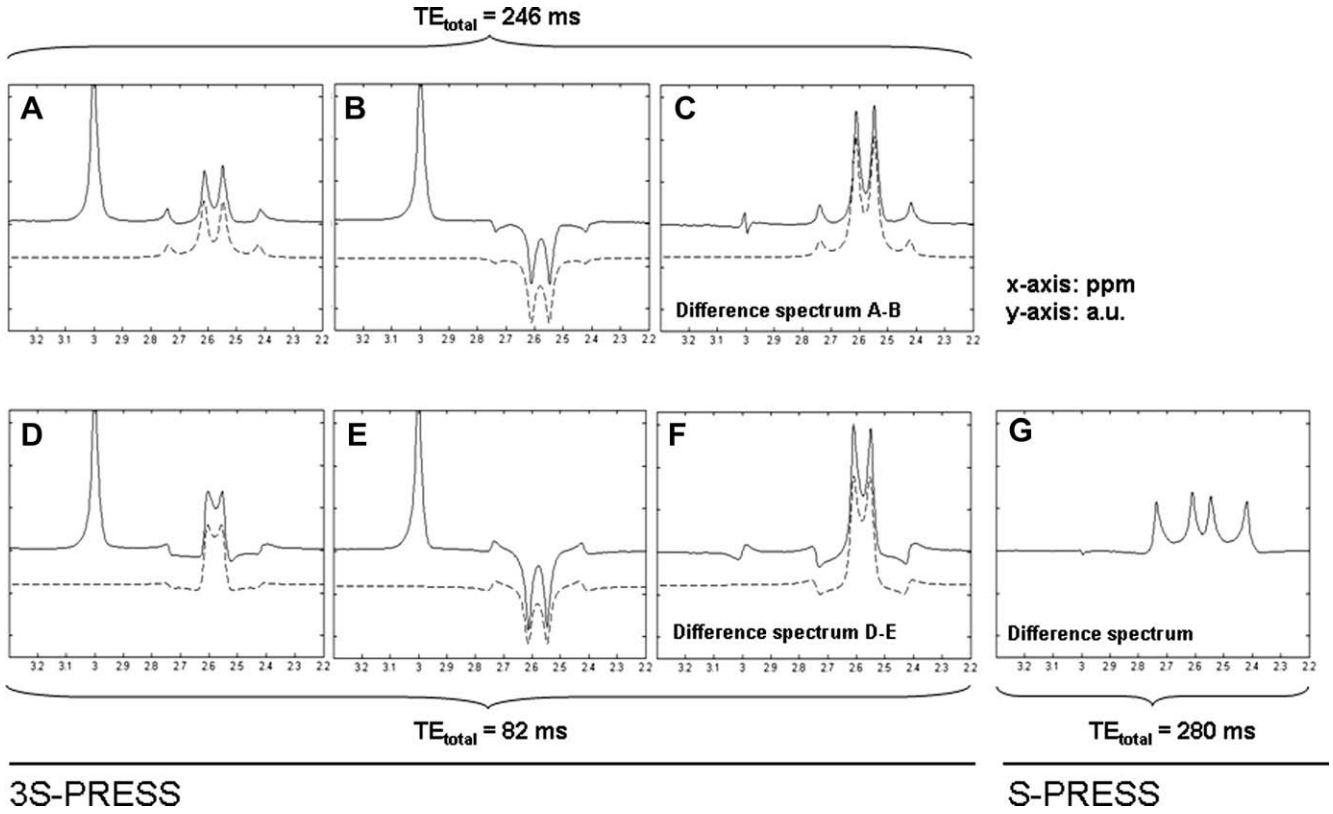

Fig. 3. Spectra acquired at 3 tesla from a phantom containing citrate and creatine using 3S-PRESS and a total echo time of 246 ms (A and B) or 82 ms (D and E) (solid lines) as well as difference spectra of the respective acquisitions (C and F). An S-PRESS difference spectrum using a TE_{total} = 280 ms is shown for comparison (G). Simulated spectra of the citrate lineshapes are indicated as dashed lines. While the creatine singlet is almost completely removed in all difference spectra (C, F and G), the citrate peak height is doubled using 3S-PRESS at a total echo time of 82 ms (F) as compared to S-PRESS at TE_{total} = 280 ms.

tions, experimental spectra with positive and negative intensities were acquired at a total echo time of 246 ms with, respectively, $TE_1 = 44$ ms, $TE_0 = 40$ ms, $TE_2 = 162$ ms (positive spectrum) and $TE_1 = 88$ ms, $TE_0 = 40$ ms, and $TE_2 = 118$ ms (negative spectrum), and are provided in Fig. 3. Experimental spectra were also acquired at a total echo time of 82 ms with, respectively, $TE_0 = 40$ ms, $TE_1 = 1$ ms, $TE_2 = 41$ ms (positive spectrum) and $TE_0 = 40$ ms, $TE_1 = 30$, $TE_2 = 12$ ms (negative spectrum). An echo time of $TE_1 = 1$ ms corresponds, in this context, to an rf pulse applied nearly on top of the spin echo formed by the preceding two pulses. As stated above, larger signal oscillations occur at the shorter total echo time of 73 ms though the necessary interpulse delays limited our experimental shortest total echo time to the longer TE_{total} of 82 ms with a similar oscillatory behavior as shown in Fig. 1 (upper panel, solid line with crossed symbols). As seen in Fig. 3 for the different interpulse delays but constant total echo time of 246 ms (Fig. 3A and B) or 82 ms (Fig. 3D and E), up–down modulation of the citrate multiplet is observed as predicted by the simulations while the uncoupled creatine signal around 3.0 ppm remains unchanged. The simulated lineshapes (dashed lines in all figures) closely follow the experimental lineshapes (solid line) for all total echo times and interpulse delays (with virtually no difference to the analytically calculated lineshapes, see Appendix). Subtraction of "up" minus "down" modulated spectrum for constant TE_{total} (spectrum 3A minus spectrum 3B for $TE_{total} = 246$ ms and 3D minus 3E for $TE_{total} = 82$ ms) shows the well formed citrate multiplets as predicted by simulations (dashed line, Fig. 3C and D). Following subtraction, creatine has almost disappeared. Compared to an S-PRESS difference spectrum at 280 ms (Fig. 3G), the integrated citrate lineshape acquired with 3S-PRESS at 246 ms (Fig. 3C) is increased by about 20%. With respect to peak heights, however (determining the SNR), the most intense citrate signal is obtained under 3S-PRESS excitation at 82 ms echo time, whereas peak amplitudes are lowest in the S-PRESS spectrum (Fig. 3G).

4. Discussion and conclusion

The S-PRESS technique was introduced as a simple modification of the commonly used PRESS sequence allowing the editing of strongly coupled spin systems, mainly citrate. In the present work we show that by extending S-PRESS with a third refocusing pulse, the peak height of the edited citrate signal can be doubled while using a 3-fold shorter echo time (3S-PRESS at $TE_{total} = 82$ ms as compared to S-PRESS at $TE_{total} = 280$ ms). Note that, as creatine (used as reference) was scaled to the same amplitude in all spectra, this increase in peak height is solely due to a more favorable citrate lineshape, cumulating the signal intensity in the center doublet. Taking in addition transverse relaxation into account (T_2 near 170 ms as measured for prostate tissue [7]), a nearly 6-fold signal increase in citrate peak height can be expected.

Refocusing pulses (180° pulses) are commonly known to invert chemical shift- but not *J*-coupling evolution [14]. Furthermore, if supposed as an ideal 180° rotation, these pulses do not produce any coherence transfer between coupling partners and the spectral shape of a weakly coupled spin system will depend solely upon the evolution time between signal excitation and reception. On the other hand, strong coupling leads to coherence transfer throughout the evolution period. Without introducing coherence transfer, ideal 180° refocusing pulses do, by inverting signs on the product operators, alter paths which strong coupling transfer follows [5]. Thus while maintaining the overall echo time constant, positioning of the refocusing pulses allows shaping the spectral signature of strongly coupled spin systems, as demonstrated in the S-PRESS concept. The third refocusing pulse added in the 3S-PRESS sequence provides an additional degree of freedom for this adjustment. Influences of pulseshapes, finite pulse lengths and signal localization, as described previously [15], were of negligible influence in this context, as demonstrated by the very close coincidence between simulated and experimental spectra. Such influences may, however, limit the capacity to suppress signals from weakly coupled spin systems by difference spectroscopy [3], and can be avoided with appropriate choice of rf-pulses [4]. Theoretically, an extension of this editing approach to more than three refocusing pulses is possible, providing further degrees of freedom for shaping strong coupling pathways throughout the echo time evolution. In practice, however, the interpulse delays optimal for editing are increasingly difficult to realize due to durations of rf-pulses and gradients for spoiling and slice selection.

S-PRESS difference spectroscopy of citrate in the prostate has been demonstrated in former work and resonances of creatine, choline and lipids were successfully removed from the spectrum. Acquired at an echo time of 160 ms at 1.5 tesla [5], the spectrum displayed low signal to noise because of the relatively short T_2 of citrate within prostatic tissue. As two-dimensional spectroscopy method at 3 tesla with a total echo time of 282 ms, S-PRESS was found a useful alternative to *J*-PRESS when detecting citrate in the added dimension and measuring J and δ [13]. More recently, S-PRESS allowed the differentiation of brain glutamate from glutamine *in vivo* while measuring myo-Inositol in the same spectrum. Simulations suggest the possibility to measure further strongly coupled metabolites as Aspartate, NAA aspartate moiety, Taurine and *N*-acetylaspartylglutamate [16].

Adding a third refocusing pulse to S-PRESS increases the sensitivity of the sequence to pulse flip angles (i.e. rf power maladjustments) and careful pulse calibration has been necessary throughout this work to achieve the presented results. More elaborate phase cycling might be needed for an *in vivo* application to eliminate unwanted coherences and outer volume contamination [17]. However, the theoretical signal to noise gain of up to six achievable for citrate in the prostate at a shorter echo time with a more favorable line shape, compared to S-PRESS at an echo time of 280 ms at 3 T, more than offsets possible losses. 3S-PRESS therefore has an interesting potential to improve the practical use of citrate editing or 2D spectroscopy in prostate exams, allowing shorter measurement times and better signal detection. For other strongly coupled metabolites such as glutamate or myo-Inositol, a signal intensity gain compared to S-PRESS, as demonstrated for citrate might be possible and, even though this remains to be demonstrated, would offer further interesting perspectives for brain spectroscopy applications.

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Appendix A

The density matrix formalism [11] was used to derive the transverse magnetization of an AB system from a $90_x - \tau_1 - 180_y - \tau_2 - 180_y - \tau_3 - 180_y - t$ sequence resulting in an analytic solution consisting of 16 cosine terms, 8 terms for the "inner lines" resonating at frequencies of $\pm(d - b) \equiv \pm\beta$ and 8 terms for the "outer lines" resonating at frequencies of $\pm(d - c) \equiv \pm\Gamma$ where $d = J/4$, $b = -J/4 + \Omega/2$, $c = -J/4 - \Omega/2$, and $\Omega = (J^2 + \delta^2)^{1/2}$. The general solution is thus of the form

Table 1
The 8 inner and 8 outer line amplitudes (columns 1 and 2, respectively) and their phases (column 3) for the 16 cosine terms contributing to the AB signal at time t immediately following the third 180_y pulse in a $90_x - \tau_1 - 180_y - \tau_2 - 180_y - \tau_3 - 180_y - t$ sequence. Appropriate additions of $(d-b)\tau_d$ and $(d-c)\tau_d$ must be added to the phases in column 3 to account for the τ_d delay readout after the final 180_y pulse.

Amplitude (A_i)	Amplitude (B_i)	Phase (Ψ_i)
$8p^3q^3(p+q)^2$	$4p^2q^2(p^2-q^2)^2$	$\beta(\tau_1+\tau_2+\tau_3)$
$2pq(p+q)^2(p^2-q^2)^2$	$-4p^2q^2(p^2-q^2)^2$	$\beta(\tau_1+\tau_2)+\Gamma\tau_3$
$2pq(p+q)^2(p^2-q^2)^2$	$(p^2-q^2)^4$	$\beta(\tau_1+\tau_3)+\Gamma\tau_2$
$-2pq(p+q)^2(p^2-q^2)^2$	$4p^2q^2(p^2-q^2)^2$	$\beta\tau_1+\Gamma(\tau_2+\tau_3)$
$4p^2q^2(p^2-q^2)^2$	$2pq(p-q)^2(p^2-q^2)^2$	$\beta(\tau_2+\tau_3)+\Gamma\tau_1$
$(p^2-q^2)^4$	$-2pq(p-q)^2(p^2-q^2)^2$	$\beta\tau_2+\Gamma(\tau_1+\tau_3)$
$-4p^2q^2(p^2-q^2)^2$	$-2pq(p-q)^2(p^2-q^2)^2$	$\beta\tau_3+\Gamma(\tau_1+\tau_2)$
$4p^2q^2(p^2-q^2)^2$	$-8p^3q^3(p-q)^2$	$\Gamma(\tau_1+\tau_2+\tau_3)$

$$S(t) = \Sigma A_i \cos[(d-b)t + \Psi_i] + B_i \cos[(d-c)t + \Psi_i]$$

The amplitudes and phases of the 16 cosine terms are provided in Table 1 in which $p = \cos(\phi/2)$, $q = \sin(\phi/2)$ and $\tan\phi = J/\delta$. The solution provided in the table is completely general but also free of the "echo time" concept in that spectra from any combination of τ_1, τ_2 and τ_3 can be generated along with any variable pre-readout delay τ_d following the final 180_y pulse. In practice, only a subset of the timing delays possible in the table are employed such that full refocusing occurs after each 180_y pulse. Furthermore, classic spectroscopic readouts would begin at the center of the third echo to avoid frequency dependent phase modulations even for singlet resonances. Comparing the timing delays in the table with the sequence in which these restrictions are accounted for, namely, for a $90_x - TE_1/2 - 180_y - TE_1/2 - TE_2/2 - 180_y - TE_2/2 - TE_3/2 - 180_y - TE_3/2$ – acquisition sequence, leads to the following identities:

$$\tau_1 = TE_1/2$$
$$\tau_2 = TE_1/2 + TE_2/2$$
$$\tau_3 = TE_2/2 + TE_3/2$$
$$\tau_d = TE_3/2$$

which will serve to bridge the use of Table 1 for practical applicability including appropriate modification of the phase terms (column 3, Table 1) to account for the pre-readout delay τ_d following the final 180_y pulse (Table 1 caption). The spectra generated from the table were evaluated using an analytic Fourier transform of the individual cosine terms multiplied by a line broadening factor $\exp(-R_2 t)$, and assuming an infinite continuous readout from 0 to ∞. Results were found to be in very good agreement with the simulated spectra used for optimizations throughout this work (data not shown).

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