Exploiting the Chemical Shift Displacement Effect in the Detection of Glutamate and Glutamine (Glx) with PRESS

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Introduction

The collective levels of glutamate (Glu) and glutamine (Gln), often referred to as Glx, are relevant in the study of tumours as well as neurodegenerative and psychiatric diseases. The Point RESolved Spectroscopy sequence, PRESS, with a short echo time, TE, is often employed for such studies, with the targeted Glx peaks being those of the C_4 protons (≈ 2.4 ppm). However, at short TEs the C_4 Glx proton signal suffers contamination from macromolecules, as well as from N-acetyl aspartate (NAA), and gamma aminobutyric acid (GABA) [1-2]. Using a longer TE reduces the macromolecular baseline, but the strong coupling interactions that the C_4 protons of Glu and of Gln exhibit cause their signal to rapidly decay with increasing echo time. The objective of this work is to demonstrate a method that can yield high Glx signal at long TEs. The technique is applicable to spins that are involved solely in weak coupling; therefore, it is suitable for detecting the C_2 proton resonances of Glx (≈ 3.78 ppm). The idea is to employ a PRESS sequence with refocusing pulses that have bandwidths smaller than the chemical shift difference between the C_2 and C_3 protons of Glx. This ensures that the C_2 Glx protons are refocused in the voxel of interest while the C_3 protons to which they are weakly coupled are not, allowing the J-coupling evolution of the C_2 Glx protons to be "refocused" no matter what the PRESS echo time is. While the theory behind this is not new [3], the concept, to our knowledge, has not been previously exploited in the *in-vivo* detection of Glx.

Methods

Two versions of the PRESS sequence were employed. In one version, the PRESS sinc refocusing pulses were of standard bandwidth (bandwidth ≈ 680 Hz, length ≈ 5.5 ms) and in the second version, the refocusing pulses were of the same shape but were 30.8 ms in length with a narrow bandwidth of 121 Hz which is much less than the chemical shift difference between the C_2 and the C_3 protons of Glu and of Gln (≈ 207 Hz at 3 T). The offset frequency of the pulses was set to approximately 3.74 ppm. A four step phase cycling scheme was employed where the phase of the excitation pulse and that of the receiver were cycled through {x, y, -x, -y}. Water suppression was carried out by a CHESS module, and the PRESS sequence was also preceded by outer volume suppression elements to minimize the amount of skull lipid signal appearing in the *in-vivo* spectra as a result of the chemical shift displacement effect. It was found empirically that the timings {TE_1, TE_2} = {100 ms, 70 ms} for the small-bandwidth PRESS sequence minimized Glx contamination from myo-inositol (mI). A 2x2x2 cm^3 voxel was selected in all experiments and a repetition time of 3 s was used.

Results

Figure 1(a) shows the calculated response of the C_2 proton of Glu to a short-TE PRESS sequence (TE = 30 ms), to a one-pulse acquire sequence, and to PRESS sequences where the refocusing pulses exclusively target the C_2 proton. It is clear that the response to the latter situation yields as much signal as a one-pulse acquire situation. The experimental outcome from experiments conducted on a 50 mM Glu phantom is displayed in Fig. 1(b). A comparison between the two spectra obtained with TE_1 = TE_2 = 80 ms indicates that replacing the 680 Hz bandwidth refocusing pulses by the 121 Hz bandwidth pulses results in signal that is about 1.5 times larger in height and three fold greater in area. Calculations and experiments yielded similar results for Gln. Figure 2(a) displays a short-TE PRESS spectrum acquired from a phantom consisiting of 50 mM Glu/ 23.9 mM Gln/ 31.1 mM mI where overlap of mI and Glx can be observed in the 3.7 ppm region. Applying the narrow-bandwidth PRESS sequence with optimized timings yields a triplet peak for Glx that does not suffer contamination from mI. The applicability of the sequence *in vivo* is demonstrated in Fig. 3. Figure 3(a) shows a short-TE PRESS spectrum acquired from the occipital lobe of a normal male. The Glx peak in the 3.75 ppm region is clearly contaminated by mI and the macromolecule baseline. The benefit of employing the small-bandwidth PRESS sequence with optimized timings is exhibited in Fig. 3(b); high Glx signal is maintained, signal from mI is minimized, and the relatively long TE ensures the decay of the macromolecule baseline. Although the creatine (Cr) peak at 3 ppm cannot serve as an internal reference because most of the signal contributing to it is from outside the desired voxel, the Cr resonance at 3.9 ppm can take over this role.

Conclusion

We have demonstrated in this work a PRESS sequence that can yield high signal, comparable to that which can be achieved by a one-pulse acquire sequence, from the C_2 protons of Glx at long echo times which is favourable for the decay of macromolecule signal.

References

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2. L. Hofmann, J. Slotboom, C. Boesch, R. Kreis *Magnetic Resonance in Medicine*, **46**, 855, 2001.
3. D.A. Yablonskiy, J.J. Neil, M.E. Raichle, J.J.H. Ackerman *Magnetic Resonance in Medicine*, **39**, 169, 1998.

Figures

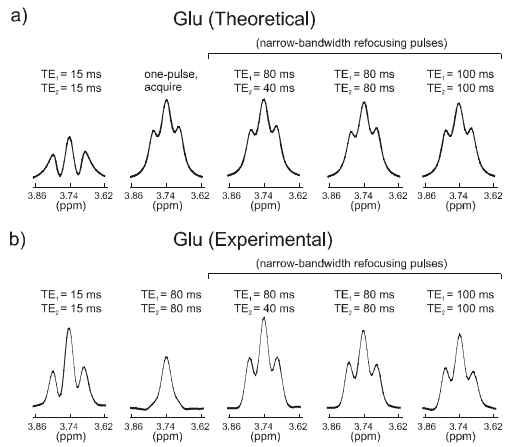

Figure 1: Calculated and experimental responses of Glu to PRESS with regular bandwidth pulses and narrow bandwidth pulses.

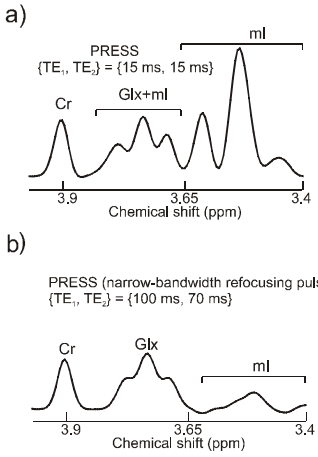

Figure 2: Spectra acquired from a phantom containing Glx and mI in physiological ratios found in gray matter. Spectra were acquired in 32 averages.

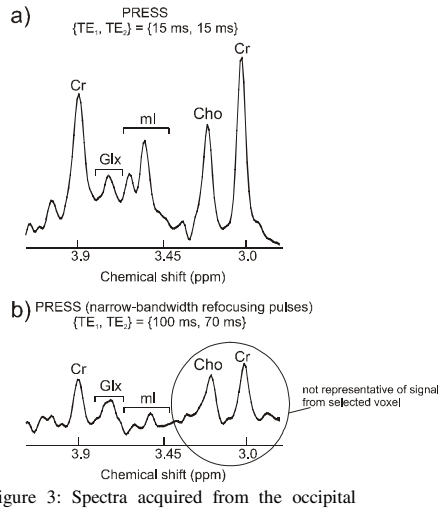

Figure 3: Spectra acquired from the occipital lobe of a normal male in 128 averages.