^{13}C MRS of the brain without decoupling

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Background: Energy regulation plays a critical role in multiple fundamental brain processes, and ^{13}C MRS, following the infusion of ^{13}C-labeled glucose and/or acetate, is the primary non-invasive tool available for the in-vivo measurement of the complex metabolic interplay between neurons and glia and glutamate (Glu)/glutamine (Glu) cycling[1]. However, low sensitivity is a fundamental problem, and while methods have been presented to measure these quantities, decoupling requirements limit human use to the dorsal cerebrum and magnetic fields $\leq 4T$[1]. The most SNR efficient approach is to exploit ^{13}C-^{1}H J coupling and the larger ^{1}H gyromagnetic ratio for both polarization and readout using a Proton-Observed Carbon-Edited (POCE) pulse sequence[2]. While magnetic fields $\geq$ 7T are required to distinguish the targeted metabolites in the crowded ^{1}H spectrum, SAR-intensive decoupling needed to simplify in vivo spectra has limited these studies to preclinical models. Here, we propose a new ^{1}H-[^{13}C] sequence that removes peak splitting for J-coupled spins without decoupling, potentially enabling TCA- and Glu/Gln-cycling rates to be measured throughout the human brain.

Methods: As shown in Fig. 1a, our approach makes use of quadrature detection ideas to selectively acquire the up-field and down-field peaks from a J-coupled doublet. A conventional POCE sequence is followed by a pulse module that provides a 90º phase shift in the J-coupling coherence plane, which simply consists of simultaneous 180º ^{1}H and ^{13}C RF pulses with TE = 1/(2J) (see Fig. 1b). In this multi-shot approach, sums and differences of spectra, acquired by toggling the 180º ^{13}C RF pulse on and off, generate spectra containing either all of the up-field or down-field doublet peaks. Removal of uncoupled nuclei (e.g. water) is provided by the four-acquisition sequence shown in Fig. 2a.

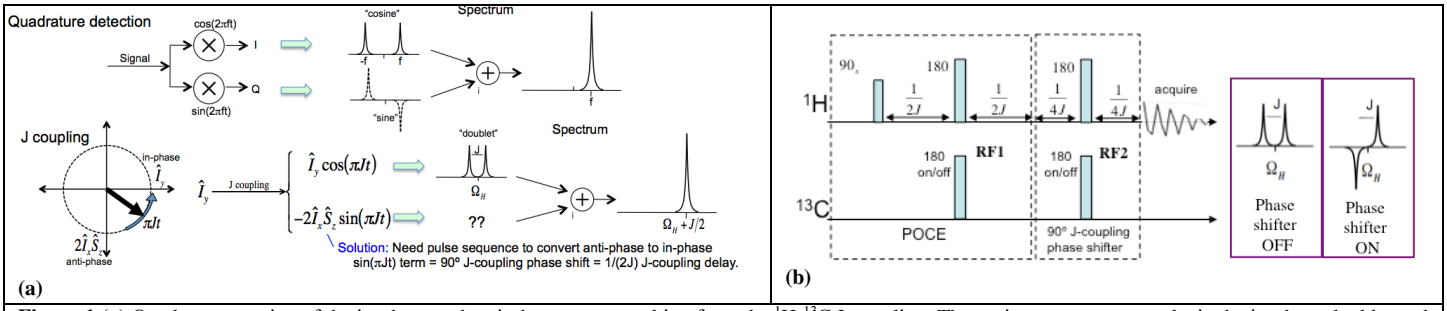

Figure 1 (a) Quadrature sensing of the in-phase and anti-phase terms resulting from the ^{1}H-^{13}C J-coupling: The cosine component results in the in-phase doublet and the 90^{0} phase shifted sine term gives anti-phase doublets. Effective decoupling is achieved by combining the two **(b)** Schematic of the POCE pulse sequence block followed by the J-coupling 90^{0} phase shifter. By toggling the 180^{0} pulses RF1 and RF2, we get combinations of in-phase and anti-phase doublets that can be appropriately combined during reconstruction, resulting in simplified spectrum.

Results: Performance of the PRoton Observed Carbon Edited Effectively Decoupled (PROCEED) sequence was tested on a 600 MHz Varian Inova spectrometer using a thermally polarized [U-^{13}C] Glutamate sample (0.5M in D_20, J=130 Hz). Spectra from the 4-cycle acquisition (see Fig 2a) are shown in Fig. 2b. Combining the data sets as (Acq1-Acq2)+i(Acq3-Acq4)=PROCEED^{+}, yields only the up-field doublet components, while the alternative reconstruction, (Acq1-Acq2)-i(Acq3-Acq4)=PROCEED^{-}, yields the down-field terms. By separately storing each acquisition, both the PROCEED^{+} and PROCEED^{-} spectra can be generated, and independent metabolite concentration estimates can then be combined for improved SNR.

	RF1	RF2	Coherences
Acq 1	OFF	OFF	$\hat{R}_y + \hat{I}_y$
Acq 2	180^0	OFF	$\hat{R}_y - \hat{I}_y$
Acq 3	OFF	180^0	$\hat{R}_y - 2\hat{I}_x\hat{S}_z$
Acq 4	180^0	180^0	$\hat{R}_y + 2\hat{I}_x\hat{S}_z$

Recon: Acq 1 – Acq 2 ± *i* (Acq 4 – Acq 3)

I = ^{1}H spins J coupled to ^{13}C, R = uncoupled ^{1}H spins

(a)

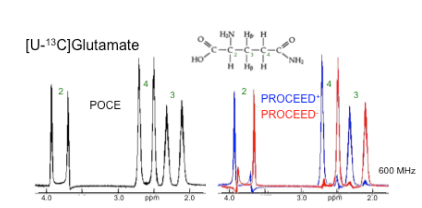

Figure 2 (a) Acquisition scheme in PROCEED and the resulting coherences from On/Off combinations of the RF1 and RF2 pulses of the POCE and Phase shifter blocks respectively.
(b) PROCEED+ = (Acq1-Acq2)+i(Acq3-Acq4) yields up-field and PROCEED- = (Acq1-Acq2)-i(Acq3-Acq4) yields down-field peaks. All ^{1}H chemical shifts are refocused and uncoupled spins suppressed.

Conclusion: The proposed improved POCE method, PROCEED, eliminates splitting due to short-range ^{13}C-^{1}H J-coupling. Although the overall SNR for the PROCEED method is √2 less than that achieved using a decoupled POCE acquisition, spectral simplification and reduced metabolite peak overlap is achieved without SAR-intensive decoupling. The elimination of decoupling makes in vivo ^{13}C MRS of neuroenergetics and neurotransmitter cycling potentially viable for studies throughout the human brain.

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References:

1. D. L. Rothman, H. M. De Feyter, R. A. Graaf, G. F. Mason, and K. L. Behar, "13C MRS studies of neuroenergetics and neurotransmitter cycling in humans," NMR Biomed., vol. 24, no. 8, pp. 943–957, Aug. 2011.
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