Proton Observed Phosphorus Editing (POPE) for in vivo detection of phospholipid metabolites

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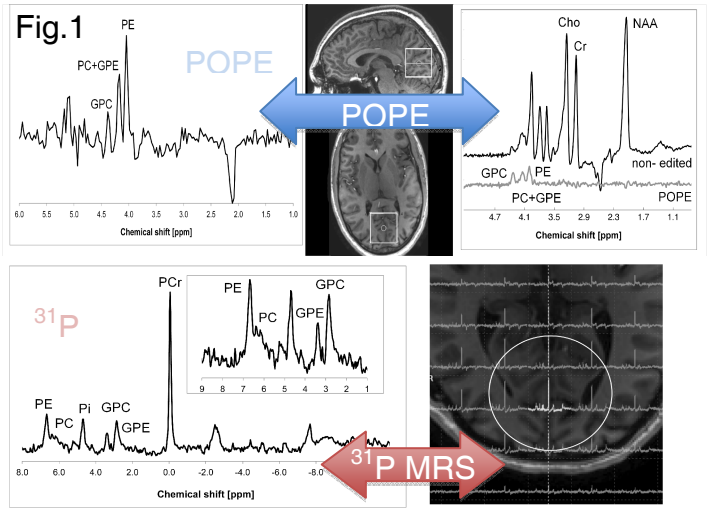
Introduction: Abnormal metabolism of phospholipids has been measured by ^{31}P magnetic resonance spectroscopy (MRS) in several brain pathologies [1,2]. However, the low sensitivity of ^{31}P MRS hinders its true translation to clinical use. While ^{1}H to ^{31}P polarization transfer [3,4] multi-echo acquisitions [5] and ultra-high field [6] have been shown to improve the signal-to-noise ratio (SNR) in ^{31}P MRS, detection via ^{1}H MRS has an intrinsically higher sensitivity (i.e. $(\gamma^{1}H/\gamma^{31}P)^{3}$). Unfortunately, in the ^{1}H MR spectrum the signals of phosphocholine (PC), phophoethanolamine (PE) glycerophosphocholine (GPC), and glycerophosphoethanolamine (GPE) are completely overlapped by signals from other metabolites and cannot be resolved *in vivo*. Using heteronuclear editing techniques we hypothesize that it is possible to separately detect PC, PE, GPE and GPC in the brain with ^{1}H MRS. Here we compare the SNR of PC, PE, GPC and GPE per square root time detected by proton observed phosphorus editing (POPE) and Ernst angle excitation ^{31}P MRS *in vivo* at 7 Tesla.

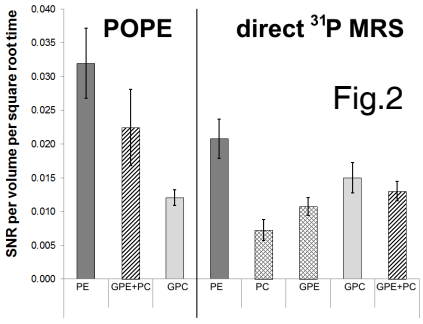
Methods: The POPE editing sequence consists of a selective inversion pulse on the ^{31}P channel applied in conjunction with a ^{1}H refocusing pulse. If the echo time is chosen as $1/J_{HP}$, coupled protons exhibit an 180° phase shift with respect to uncoupled protons. Subtraction of MR spectra with and without the applied inversion pulse on the ^{31}P channel results in the selective observation of protons attached to phosphorus nuclei. Inter-pulse delays of a semi-LASER localization sequence were optimized to achieve full absorptive signal of the ^{1}H spins of PC coupled to the ^{31}P nucleus at 4.2 ppm, (using a J-refocused echo-time of 160 ms ($1/J_{HP}$)).



To achieve optimal sensitivity for both ^{31}P and ^{1}H MRS in the brain, we used a thin quadrature ^{31}P surface coil (2 partly overlapping loops, 13 cm diameter) (MR Coils BV, Drunen, the Netherlands) with 8 ^{1}H traps, fitted tightly inside a 16 channel ^{1}H receiver head coil (Nova Medical, Inc, Burlington, MA, USA) interfaced to a 7 Tesla MR system (Phillips, Cleveland, USA). Five healthy volunteers participated in this study after having given informed consent. B_0 shimming was performed with 2nd order shim fields. Water suppression was performed using VAPOR with a suppression bandwidth of 180Hz. The adiabatic refocusing pulses had a B_1 of 12μT and bandwidth of 1128Hz. POPE was performed with a broadband inversion pulse on the ^{31}P channel. TR was 4.5s, NSA was 160, voxel size 64ml, total acquisition time was 12 min. ^{31}P MRS was performed using a pulse acquire experiment with an adiabatic BIR4 excitation pulse with a flip angle of 60^{0} and TR of 2180ms (Ernst angle for T1 of 3s). For the direct ^{31}P acquisition, a 3D Chemical Shift Imaging (CSI) dataset was acquired (FOV 160x160x160 mm^3, matrix size 8x8x8, 1NSA), with voxel volume of 54.3cc after k-space filtering and total acquisition time of 14 min.

Data analysis: One voxel from the CSI data set matching the POPE voxel location was extracted (Fig. 1). Both the POPE and the direct ^{31}P MRS data were apodized using a matched filter (broadening factor equal to $1/\pi T_2^*$ [7]). The T_2^* was determined by fitting the linewidth of creatine in the non-edited POPE spectrum, while the ^{31}P T_2^* was set to 2.5 times the ^{1}H T_2^* (i.e. $\gamma^{1}H/\gamma^{31}P$). The T_2^* filtered data were then used to determine the SNR of PC, PE, GPC and GPE in the spectral domain. The noise was calculated as the standard deviation of the signal from a resonance-free part of the spectrum. Peak heights were determined for PE, PC, GPE, and GPC individually. SNR per unit volume per square root time was calculated for each data set and corrected for the difference in acquisition volume (64 vs 54 ml).

Results and Discussion: The average SNR per square root time and per unit of volume of the POPE data was higher than in the direct ^{31}P MRS data (Fig. 2). The difference is largest for PE where an average gain of 34% was achieved when using POPE compared to direct ^{31}P MRS. POPE resulted in an average SNR loss of 45% for GPC. Direct comparison of PC and GPE was not possible as these signals overlap in the POPE MR spectrum. However, when comparing the (SNR_{PC+GPE}) in the POPE data to the $\sqrt{(SNR_{PC}^2 + SNR_{GPE}^2)}$ in the direct ^{31}P MR spectrum, an average gain of 38% was found for POPE. In phantom experiments a 2.8 fold increase in SNR of PC in the POPE method was achieved [8]. Reasons for the lower sensitivity gain of POPE in the *in vivo* setting, is the loss of signal intensity due to T2 relaxation during the relative long TE that is needed for ^{31}P J-coupling evolution. Furthermore, physiological B_0 and B_1 fluctuations can lead to signal loss as editing is sensitive to subtraction errors. In addition, the linewidth at 7T is often dominated by B_0 non-uniformities, compared to the line broadening caused by J-coupling. The contribution of these non-uniformities to the overall linewidth is obviously 2.5 times higher for ^{1}H than for ^{31}P, which would reduce the SNR up to a factor √2.5 in the *in vivo* proton-detected spectrum.



Conclusion: In the POPE sequence with semi-LASER localization, the optimum TE for ^{1}H can be matched to that of ^{31}P. While the *in vivo* linewidth at 7 Tesla is dominated by unresolved J-coupling and intrinsic tissue inhomogeneities, the gain with POPE compared to direct ^{31}P MRS was 30-40%. Using this sequence sensitivity enhanced detection of individual phospholipid metabolites in the brain is feasible with ^{1}H MRS using ^{31}P editing.

References: *[1] Negendank, NMR in Biomed 1992, 5, p303 [2] Jensen, Psychiatry research 2006,2 p127 [3] Klomp, NMR Biomed 2008;21p444 [4] Mancini MRM 2003,50 p578 [5] van der Kemp NMR Biomed 2013, 26 p1299 [6] Lagemaat MRM 2014, 26 [7] Otazo 2006, 56 p1200 [8] Klomp, ISMRM 2013, # 2008*