Selectivity Enhancement of Glutamine in Human Brain by Triple Refocusing at 3T: Application to Hippocampus

C. Choi[1], C. Tamminga[2], A. Stan[2], D. Douglas[1], P. Mihalakos[2], and S. Morris[2]

[1]Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States, [2]Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas, United States

INTRODUCTION

Similarity of the glutamine (Gln) and glutamate (Glu) spin systems gives rise to a significant spectral overlap, making it difficult to discriminate these metabolites in human brain using short-TE PRESS or STEAM at clinically accessible magnetic fields. Measurement of Glu is relatively straightforward due to the high concentration. However, because of its relatively low concentration and the close proximity of its resonances to those of NAA_{Asp} and Glu, detection of Gln remains as a challenge at 3T. A prior editing study that utilized narrow-band selective refocusing indicates the *in vivo* feasibility at 3T [1], but the output signals are sensitive to frequency drift due to the potential subject motion. A recent study reports *in vivo* application of TE/TM-optimized STEAM at 3T and 4T [2], but the partially-refocused stimulated echo results in reduced Gln and Glu signals. Here, we report a triple refocusing method for simultaneous detection of Glu and Gln, that is capable of fully-refocused signal return and immune to the frequency drift.

METHODS

Proton triple refocusing has been explored for differentiation of Gln and Glu at 3T (Philips Medical Systems, Cleveland, OH, USA). A non-space selective 180° RF pulse (T_p = 60 ms; BW = 270 Hz), tuned to 2.4 ppm, was applied between the slice-selective 180° radio-frequency (RF) pulses of PRESS, refocusing the resonances between 1.3 and 3.5 ppm. Spatial localization was obtained with a 6.6-ms 90° RF pulse (BW = 6.3 kHz) and two 8.9-ms 180° RF pulses (BW = 1.9 kHz). Subecho times were optimized for simultaneous detection of the Gln and Glu C4 proton resonances, with density matrix simulation incorporating slice-selective RF and gradient pulses. An echo time set, (TE_1, TE_2, TE_3) = (23, 74, 18) ms, was obtained based on the following criteria: 1) maximize the Gln peak amplitude, 2) minimize the overlap between Gln and NAA_{Asp}, and 3) minimize the overlap between Gln and Glu. For this third purpose, the Glu signal was suppressed. Published chemical shift and coupling constants [3] were used. *In vivo* tests of the filtering sequence were conducted on hippocampus (50×15×15 mm^3) of five healthy subjects. A quadrature birdcage head coil was used for RF transmission and reception. LC model software [4] was used for spectral analysis.

RESULTS AND DISCUSSION

Fig. 1 presents calculated spectra of Glu, Gln, NAA_{Asp}, GSH_{Glu}, GABA, $NAAG_{Asp}$ and Cr at a concentration ratio of 10:3:10:1:1:2:8, for 90°-acquisition and the triple refocusing. In the triple refocused spectra, the Gln C4 proton peak appears at 2.39 ppm and is therefore well separated from the NAA_{Asp} multiplet. The Glu C4 proton resonance peak is brought about at 2.29 ppm, with negligible overlap with the Gln peak. The amplitude ratios of the filtered Glu and Gln multiplets with respect to 90°-acquisition were 28% and 60%, respectively. A numerical calculation indicates that the amplitude of this filtered Gln peak is two-fold compared to that from the reported STEAM scheme [2], ignoring relaxation effects. It is predicted from the filtered sum spectra with and without Gln in Fig. 1 that Glu and Gln can be detected simultaneously without substantial interferences from the neighboring resonances *in vivo*.

Fig. 2 presents filtered *in vivo* brain spectra from five healthy subjects. A Gln peak is discernible consistently in all spectra. The LC model fit result of a triple refocused spectrum is shown in Fig. 3. For the five healthy subjects, the concentrations of Gln, Glu and NAA in hippocampus were estimated to be 2.8±0.7, 10.5±0.6 and 9.7±0.6 mM with reference to Cr at 8 mM, with fit standard deviations of 10±2%, 6±2% and 2±1% respectively.

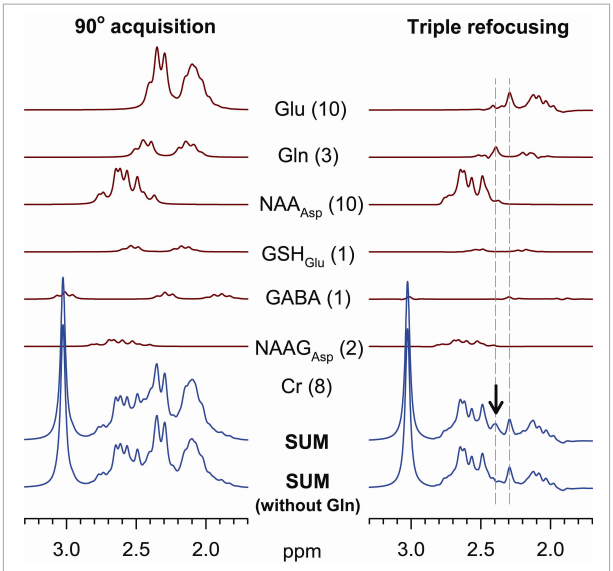

FIG. 1. Calculated spectra of Glu, Gln, NAA, GSH, GABA, NAAG and Cr, following 90°-acquisition and triple refocusing, are shown for a concentration ratio of 10:3:10:1:1:2:8. The sub-echo times of triple refocusing are (TE_1, TE_2, TE_3) = (23, 74, 18) ms. The presence and absence of Gln make a noticeable difference in triple refocused spectra (indicated by an arrow). Vertical lines are drawn at 2.39 and 2.29 ppm. Spectra are broadened to 0.04 ppm (5 Hz).

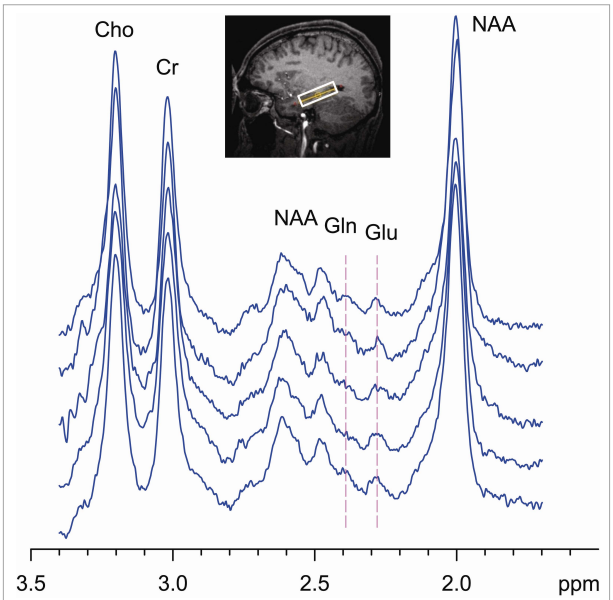

FIG. 2. *In vivo* human brain spectra from the hippocampus (50×15×15 mm^3) of healthy subjects, obtained with triple refocusing. TR = 2 s. TE = 115 ms. NEX = 512.

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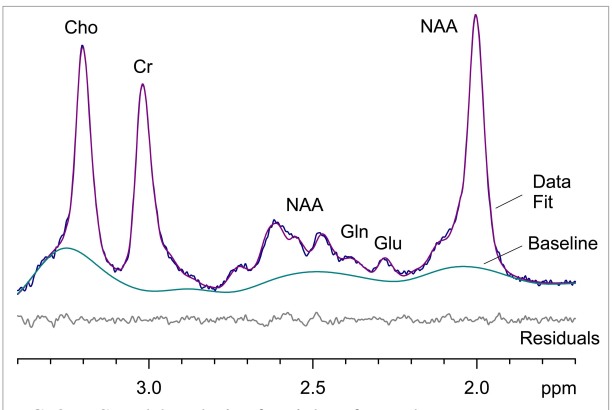

FIG. 3. LCModel analysis of a triple-refocused spectrum.