Spectrally-Selective Refocusing for Brain Glutamate and Glutamine Measures: Application to Human Prefrontal and Motor Cortices

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INTRODUCTION

Similarity between the glutamate (Gln) and glutamine (Gln) spin systems causes significant spectral overlap, making it difficult to measure the metabolites reliably using conventional spectroscopy at clinically accessible magnetic fields. One of the small differences between the systems is the chemical shift of their C4 protons. This is ~0.1 ppm, approximately 13 Hz at 3.0 T. We have exploited this spectral difference to discriminate the signals between the metabolites. Spectrally-selective 180° RF pulses with excitation bandwidth of ~12 Hz, implemented within PRESS, were used for measuring Glu and Gln in separate scans *in vivo*.

METHODS

Fig. 1 illustrates an overview of the filtering strategy. For an 86-ms long Gaussian 180° pulse (truncated at 20%) within PRESS, the height of the Glu and Gln C4 proton multiplets changes with the carrier of the Gaussian pulse, as shown in the figure. At carriers of 2.35 and 2.51 ppm, the difference in signals from Glu and Gln becomes maximal. Tuning of the spectrally selective refocusing pulse to these frequencies permits the discrimination of the Glu and Gln signals in separate scans. Two triple-band 180° RF pulses were designed for selective detection of Glu and Gln, Fig. 2. First, a Glu filter included an 81.9-ms long triple-band 180° pulse (T180). The pulse had a single Gaussian RF waveform (truncated at 20%) that incorporated successive RF phase variations [1], designed for refocusing at 2.35, 3.02, and 3.92 ppm. The refocusing at 2.35 ppm was for generation of the Glu C4 target multiplet at 2.35 ppm. The creatine (Cr) singlets at 3.02 and 3.92 ppm were acquired simultaneously for use as a reference in phase correction. Second, a Gln filter had a 90.5-ms long T180 which was designed for refocusing at 2.51, 3.02 and 3.92 ppm. The Cr signals were also acquired with this filter. The refocusing at 2.51 ppm generated a Gln target multiplet at 2.39 ppm. Given durations of RF pulses and spoiling gradients, the shortest possible TE was 128 and 136 ms for the Glu and Gln filters, respectively. The TE of the Glu filter was set at 128 ms, which gave the greatest target peak. The TE of the Gln filter was 158 ms, at which the combined contribution of NAA and GSH was minimal. Simulation indicated that, at these echo times, the peak height of the target multiplet is, ignoring T_2 effects, both 62% with respect to the 90°-acquired multiplet from an identical voxel. In addition, for a Glu-to-Gln concentration ratio of 3, contamination of each target multiplet was < 3%. For *in vivo* conditions, NAA and GSH caused an additional spectral overlap that was well predicted by the simulation and resolved with spectral fitting.

In vivo tests of the filtering sequences were conducted on ten healthy volunteers; prefrontal cortex (30×25×30 mm^3) of seven subjects and motor cortex (25×25×50 mm^3) of three subjects. Experiments were carried out at 3.0 T in an 80-cm bore magnet, interfaced to a SMIS console. A 28-cm diameter quadrature birdcage coil was used for RF transmission and reception. The density-matrix simulation of the filters was programmed with Matlab.

RESULTS AND DISCUSSION

Fig. 3 presents a pair of *in vivo* spectra from the human prefrontal cortex, together with the results of spectral fitting and the individual components. The metabolites considered in the fitting were Glu, Gln, Cr, NAA (Asp moiety), and GSH (Glu moiety). Spectra which were calculated using the published coupling schemes [2] and broadened according to the experimental linewidth of the Cr peak, were used as basis spectra for the least-square fitting. In all spectra from the Glu filter, the Glu target multiplet was uniquely observed at 2.35 ppm. A small hump at 2.58 ppm was attributed to NAA. The fitting of the Glu filtered spectrum gave concentrations, relative to Cr, of 1.36 for Glu, 0.48 for Gln, and 1.38 for NAA. The relative concentrations of Glu and NAA were used for fitting of the Gln filtered spectrum, resulting in 0.44 for Gln and 0.32 for GSH. For the *in vivo* spectra obtained from the composite gray/white matter tissues in the prefrontal and motor cortices, assuming identical T_1 and T_2 between Glu, Gln and Cr, the Glu and Gln concentrations relative to Cr were estimated as shown in Table 1.

REFERENCES

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2. V. Govindaraju *et. al.*, NMR Biomed. **13**, 129 (2000).

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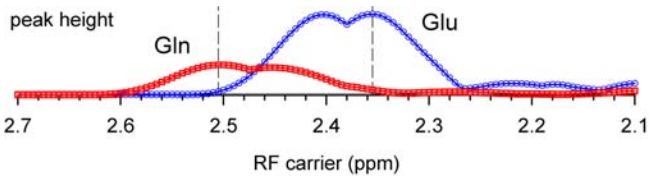

FIG. 1. An overview of the spectrally-selective refocusing method is illustrated, as an example, for an 86-ms long Gaussian 180° RF pulse within PRESS. Separation of Glu and Gln signals is achieved at carriers of 2.35 and 2.51 ppm, indicated by vertical dashed lines. A Glu-to-Gln concentration ratio of 3 is assumed.

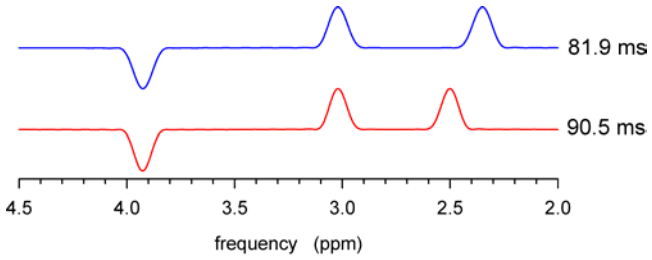

FIG. 2. Refocusing profiles of the triple-resonance selective 180° (T180) RF pulses. The durations were 81.9 and 90.5 ms for the Glu and Gln filters, respectively.

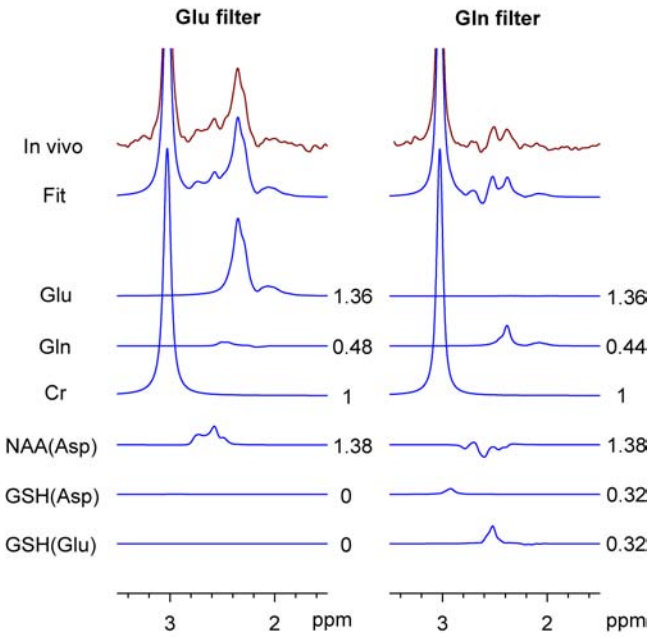

FIG 3. Spectral fitting for a pair of *in vivo* prefrontal spectra, obtained with the Glu (left) and Gln (right) filters. The resulting relative concentrations are shown for each components; Glu, Gln, Cr, NAA, and GSH. TR = 2.4 s. NT = 64 (Glu), 128 (Gln).

Table 1. Glu and Gln concentrations relative to Cr, measured by spectrally-selective refocusing, for the human prefrontal and motor cortices.

	[Glu]/[Cr] (mean±SD)	*[Gln]/[Cr] (mean±SD)*	*GM (%)*	*WM (%)*	*CSF (%)*
Prefrontal (n=7)	1.30±0.09	0.43±0.06	63±3	23±2	14±3
Motor (n=3)	1.16±0.08	0.34±0.11	40±4	43±2	17±2