Measurement of glycine in gray and white matter in the human brain by 1H-MRS at 7.0 T in vivo

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INTRODUCTION: Abnormal levels of glycine (Gly) are implicated in neuropsychiatric disorders [1,2]. Recent studies indicate that Gly may be a biomarker of tumor malignancy [3-5]. The Gly concentrations in the normal brain tissue *in vivo* were reported as 0.5 - 1 mM, as measured in recent ^{1}H-MRS studies [5-7]. These studies all focused on gray matter dominant brain regions. When a regional distribution of Gly levels exists, evaluation of the abnormal concentrations in disease conditions may require comparison of Gly estimates from matched brain regions. Here we report the first noninvasive measurement of Gly concentrations in gray and white matter (GM and WM) in the human brain, achieved by optimized ^{1}H-MRS at 7T.

METHODS: Experiments were carried out on a whole-body 7T scanner (Philips Medical Systems), using a birdcage head transmit RF coil with a 16-channel phased-array receive coil. Single-voxel localized proton MRS spectra were obtained from the anterior and posterior brain regions in 10 healthy volunteers (2 voxels per each subject; size 22 - 27 mL) (6 male and 4 female; age 29±4). MRS data were acquired with a Gly-optimized PRESS sequence (TE = 150 ms) [8]. Spatial localization RF pulses included an 8.8 ms 90° RF pulse (BW = 4.7 kHz) and an 11.9 ms 180° RF pulses (BW = 1.4 kHz). First and second-order shimming for the selected volume was carried out using FASTMAP. Data acquisition parameters included TR 2.5 s, sweep width 5 kHz, 4096 sampling points, and 128 signal averages. Spectra were acquired in multiple blocks, each with 4 averages. A four-pulse variable-flip-angle scheme was used for water suppression. The carrier of the volume selective RF pulses was set to the Gly resonance (3.55 ppm). The multi-block data were processed individually for correcting for frequency drifts and residual eddy current artifacts. Data were analyzed with LCModel software, using model spectra of 21 metabolites as basis set, calculated with density matrix simulations that included the volume selective RF and gradient pulses. The spectral fitting range was set to 0.5 - 4.1 ppm. The compositions of GM, WM, and CSF within the voxel were estimated from the T_1-weighted images using Statistical Parametric Mapping software (SPM5). The Gly concentration within each voxel was estimated using the GM+WM water signal as reference. The water concentration in GM+WM was estimated using published water concentrations in GM and WM [9]. To obtain Gly levels in GM and WM, the Gly estimates from the 20 voxels of 10 subjects were fitted to a linear function of fractional GM content.

RESULTS AND DISCUSSION: The Gly singlet resonance at 3.55 ppm is overlapped with the multiplets of myo-inositol (mIns), choline (Cho), and threonine (Thr). At PRESS (TE_1, TE_2) = (100, 50) ms at 7T, the overlapping multiplets are reduced substantially. A computer simulation indicated that, for a concentration ratio of [mI]:[Cho]:[Thr]:[Gly] = 5:1:1:1, the composite signal at 3.5 - 3.7 ppm is dominated by Gly and mIns signals at 3.55 and 3.62 ppm, respectively. At this condition, the Gly singlet is completely differentiated from the mIns multiplet (**Fig. 1**). The sum spectrum in **Fig. 1**, created from an approximate physiological concentration ratio, predicts an *in vivo* spectral pattern from the human brain. *In-vivo* spectra from four brain regions of healthy volunteers in **Fig. 2** all showed a gly-mIns composite signal pattern at 3.5 - 3.7 ppm predicted by the simulation. Following the normalization of the spectra with respect to brain water signals, the signal intensities were different between brain regions. The Gly signals were larger in spectra from medial frontal and occipital regions (where GM is dominant) than in spectra from WM-dominant regions, indicating that Gly concentration may differ between GM and WM. **Figure 3** presents the estimated Gly concentration as a function of the fractional GM content for frontal and occipital brain in 10 subjects. A linear correlation of the estimated Gly concentration *vs*. fractional GM content was statistically significant ($p < 0.001$) with goodness of fit at $R^2 = 0.75$. The Gly concentrations in GM and WM were estimated from the intercepts of the linear regression line to the ordinate axes, assuming that the metabolite levels in CSF are negligible. The Gly concentrations in GM and WM were obtained as 0.99 and 0.04 mM (95% confidence intervals 0.84 - 1.13 and –0.10 - 0.19), respectively.

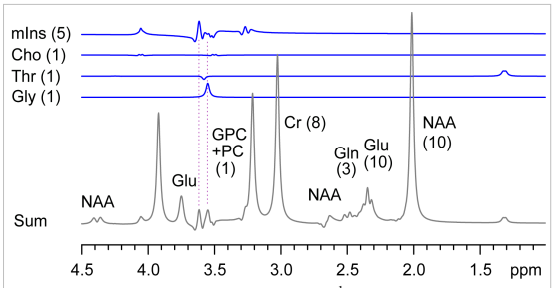

FIG 1. Numerically-calculated ^{1}H spectra illustrate differentiation between Gly and mIns by PRESS (TE = 150 ms) at 7T. Spectra are scaled according to the concentration ratios given in the brackets. Spectra are broadened to singlet linewidth of 9 Hz. Relaxation effects were not included in the simulations.

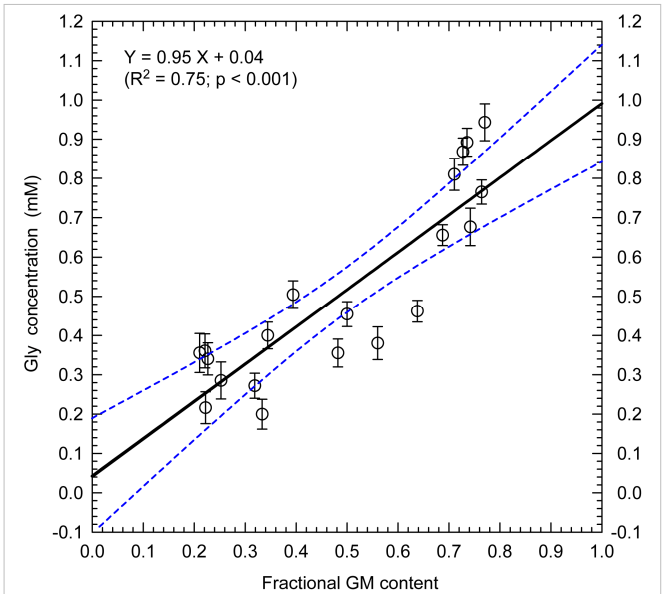

FIG 3. Linear regression of Gly concentration *vs*. fractional gray matter content. Error bars indicate standard deviation of the Gly estimates. The dashed lines (blue) indicate 95% confidence intervals of the linear fit.

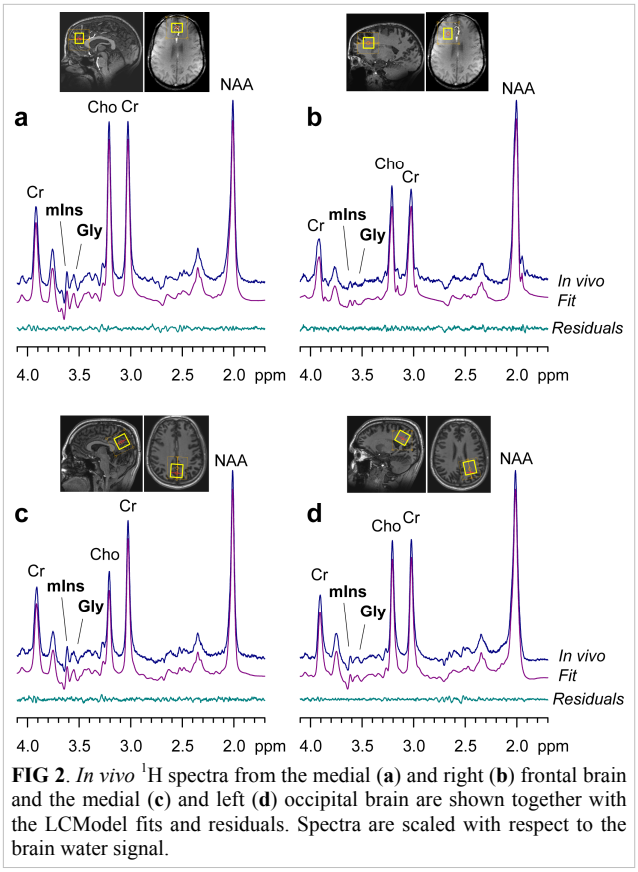

FIG 2. *In vivo* ^{1}H spectra from the medial (**a**) and right (**b**) frontal brain and the medial (**c**) and left (**d**) occipital brain are shown together with the LCModel fits and residuals. Spectra are scaled with respect to the brain water signal.

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