Contamination-free measurement of GABA in the human brain by optimized PRESS at 7.0 T in vivo

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INTRODUCTION: GABA, a major inhibitory neurotransmitter, is associated with several neuropsychiatric disorders. Precise measurement of this low-concentration metabolite is of high significance. A vast majority of prior studies focused on detection of the H4 resonance at 3.0 ppm by means of difference editing utilizing its J coupling to the H3 resonance at 1.9 ppm [1-3]. This method is susceptible to potential cancellation errors of the creatine (Cr) CH_3 singlet and to macromolecule (MM) contaminations arising from potential coedting of the species with coupled resonances at 3.0 and 1.7 ppm [4]. Coediting of the GABA moiety of homocarnosine (HC) may be inevitable [5,6] because HC has coupled resonances at 2.96 (H4), 1.9 (H3) and 2.36 (H2) ppm [6,7]. As an alternative, targeting the GABA H2 resonance at 2.28 ppm [8] may permit GABA estimation with minimal interference of HC. Here we report measurement of GABA by PRESS whose echo time was optimized for detection of the GABA H2 resonance at 7T. GABA estimation by PRESS and difference editing is discussed.

METHODS: PRESS and difference editing were used for measuring GABA in the human brain at 7T. For PRESS, the first and second echo times were optimized, with numerical simulations, as (TE_1, TE_2) = (31, 61) ms, which allowed separation of the GABA H2 multiplet (2.28 ppm) from the glutamate (Glu) H4 multiplet (2.35 ppm). For difference editing, a MEGA sequence [9] was used to edit the GABA H4 resonance (3.0 ppm) *via* its J coupling to the H3 resonance. Twelve millisecond Gaussian 180° pulses (bandwidth = 96 Hz = 0.32 ppm at half amplitude) were applied with carrier at 1.9 or 1.5 ppm in alternate scans to cancel the coedited MM signal [10], as indicated in **Fig. 1**. The MEGA echo time was 70 ms. *In-vivo* scans were conducted on a Philips whole-body 7T scanner, using a birdcage head transmit RF coil with a 16-channel phased-array receive coil. 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). Data were obtained from the medial occipital cortex in 5 healthy volunteers (voxel size 3×3×3 cm^3) (3 male and 2 female). Scan parameters included TR = 2.5 s, NEX = 256, SW = 5 kHz, and 4096 sampling points. The carrier of the slice-selective RF pulses was set to 2.7 ppm for both PRESS and MEGA. Data were analyzed with LCModel, using 3D-volume localized calculated basis spectra. Published chemical shifts and J coupling constants [6,7] were used in the simulation. LCModel spectral fitting was performed between 0.5 - 4.1 ppm. The GABA concentration was estimated with reference to Cr at 8 mM. LCModel GABA estimates in PRESS and MEGA-difference spectra were normalized to the PRESS and MEGA-edit-off Cr estimates, respectively.

RESULTS AND DISCUSSION: At PRESS TE = 92 ms, line narrowing occurred to the H4 multiplets of GABA, Glu, glutamine, glutathione between 2.2 - 2.6 ppm, thereby leading to complete separation between the signals, as illustrated in **Fig. 1** (top trace) [11]. LCModel fitting reproduced the *in vivo* data well, resulting in residuals without substantial chemical-shift dependence. In all MEGA edited spectra, a signal was detectable at ~3.0 ppm, with SNR ≅ 3. The H2 resonances of Glu, Gln, and GSH were coedited, giving a composite signal with amplitude 1.5 - 2 times greater than the 3.0 ppm signal in the difference spectra. In the PRESS spectrum of **Fig. 2**, the small GABA H2 signal is clearly discernible at 2.28 ppm, with negligible overlap with the Glu and HC multiplets. This was the case in all spectra from 5 subjects. The PRESS GABA signal at 2.28 ppm was 1.5 - 2 times as large as the MEGA-edited signal at 3.0 ppm, primarily due to the higher GABA yield in PRESS compared to MEGA (2.4 times). The *in-vivo* PRESS to MEGA-edited signal ratio was somewhat smaller than the computer-simulated PRESS GABA H2 to MEGA H4 signal ratio (2.0 *vs*. 2.5). In LCModel fitting of MEGA edited spectra, GABA and HC signals were not properly differentiable; namely, zero HC was returned in 4 cases (as shown in **Fig. 2**) and non-zero HC in one case (subject 5 in **Fig. 3**). GABA estimates by MEGA were greater than PRESS GABA estimates in all cases, the mean values of GABA concentrations by MEGA and PRESS being 1.15±0.16 and 0.80±0.06 mM (mean±SD, n=5; p = 0.004), respectively (**Fig. 3**). This result indicates that, in MEGA, GABA may be overestimated due to contaminations from HC and possibly MM although the editing 180° pulse was applied to minimize the effects on 1.7 ppm [5]. CRLBs were ~2 fold larger in PRESS than in MEGA. Given its ability of measuring GABA with minimal contaminations and with small variations in multiple subjects, the optimized PRESS may provide an effective tool for detecting potential alterations in GABA levels in patient populations. Lastly, short-TE (32 ms) PRESS data were acquired in 2 subjects for comparison; GABA was not properly measurable (< 0.1 mM; CRLB > 150%) (data not shown).

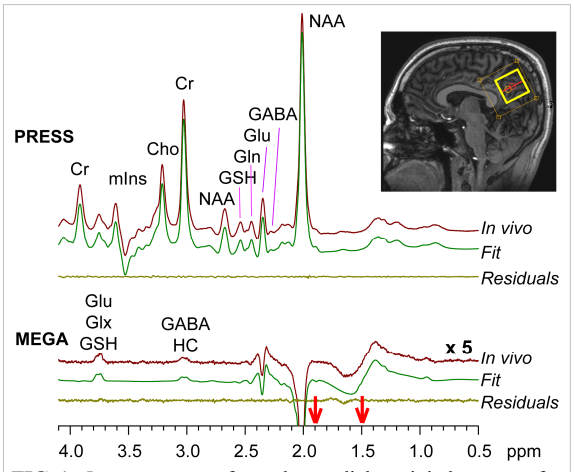

FIG 1. *In vivo* spectra from the medial occipital cortex of a healthy volunteer, obtained with PRESS (TE = 92 ms) and MEGA difference editing (TE = 70 ms) are shown together with LCModel fits and residuals. Two arrows indicate the carrier frequencies of the 180° pulses in alternate scans. MEGA edited spectra are 5-fold magnified. HC denotes homocarnosine.

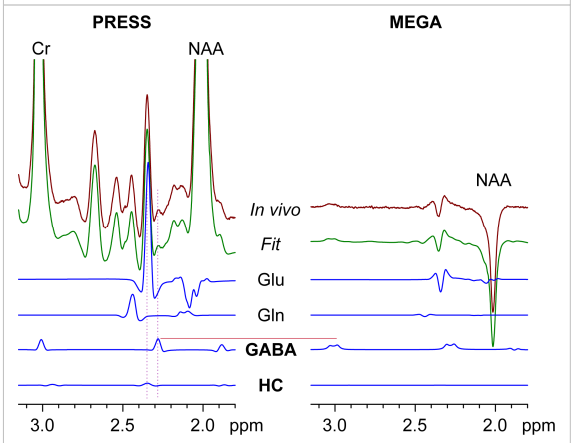

FIG 2. *In vivo* spectra in Fig. 1 are magnified and shown together with spectral components of Glu, Gln, GABA and HC (homocarnosine). Vertical dotted lines are drawn at 2.28 ppm (GABA) and 2.35 (HC) in the PRESS spectrum. A horizontal line (red) is drawn for comparison between the PRESS GABA H2 peak and the MEGA-edited 3.0-ppm signal.

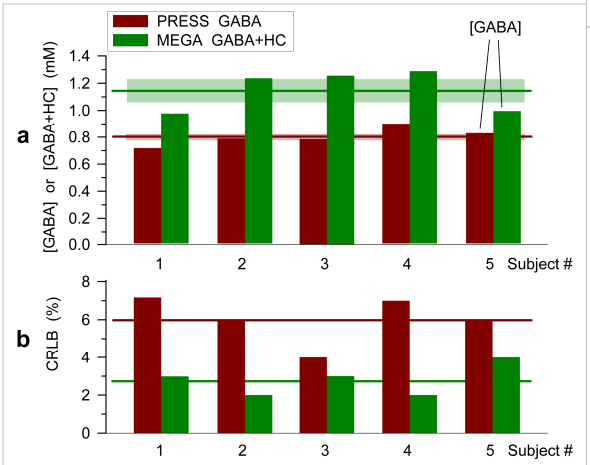

FIG 3. (**a**) GABA estimates by PRESS (brown) and GABA+HC estimates by MEGA editing (green) from 5 subjects. (**b**) Cramer-Rao lower bounds (CRLB) of GABA and GABA+HC. In (**a**), horizontal lines and horizontal bars indicate the mean values and standard deviation of the estimated concentrations. Figures 1 and 2 are the data from subject 1.

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