Enhanced Detection of Glutamate in the Human Brain Using Very Short Echo Times

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Introduction: Glutamate (Glu) excitoxicity is hypothesized to play a primary role in the etiology of many neurodegenerative diseases and psychiatric disorders, such as Alzheimer's disease (1), schizophrenia (2), and amyotrophic lateral sclerosis (3). Efforts to examine Glu clinically have been hampered by difficulty in separating the overlapping resonances of Glu and glutamine, especially on clinical strength MRI systems at 1.5-T and less so at 3-T. In this work, we specifically examine the capability of a VTE phase rotation STEAM (PR-STEAM) sequence (4) to detect glutamate in comparison to other sequences optimized for glutamate detection: PRESS (5), STEAM (6), and TE-Averaging (7).

Methods: All studies were performed under an IRB approved protocol. The data were collected on a clinical Magnetom TIM Trio 3-T MRI system (Siemens Medical Solutions, Inc., Erlangen, Germany) from 9 healthy participants (7 females/2 males, mean age: 32.8 ± 7.3 years, range: 19-45). Voxels were localized in the anterior cingulate gyrus: (Figure 1) TR=2000-ms, VOI~7.2-cm^3, NEX=256, 2.5-kHz bandwidth, and 2048 complex points. To acquire data from all four sequences in approximately 1 hour, TRs were fixed to 2000-ms. VTE PR-STEAM spectroscopy sequence parameters were: TM/TE = 10/6.5-ms, $\Delta\varphi_1 = 135°$, $\Delta\varphi_2 = 22.5°$, $\Delta\varphi_3 = 112.5°$, and $\Delta\varphi_{ADC} = 0°$. The TE-Averaging sequence parameters for the TE were: range = 30-180-ms in 10-ms steps with 16 averages per step. The TE for the PRESS sequence was 40-ms, and the STEAM parameters were TM/TE = 6/72-ms. All data were phased and apodized to improve the SNR using an in-house IDL program (ITT Visual Information Systems, Boulder, CO, USA). Basis sets were simulated using the GAVA (8) software package and imported into LCModel (9) for quantitation. To assess the precision for Glu identification, coefficient of variation (CV) values were calculated for each spectroscopic technique and compared.

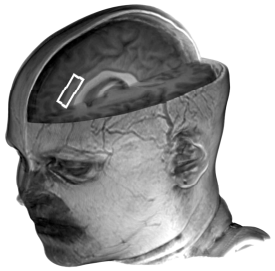

Figure 1. Representative T_1-weighted image showing the voxel placement (~7.2-cm^3) along the midline of the anterior cingulate gyrus.

Results: Figure 2 shows typical spectra and LCModel fits for each of the four spectroscopy sequences. The C-4 Glu resonances around 2.34-ppm are clearly visible as double peaks with VTE PR-STEAM and short TE PRESS, and as a single peak with TE-Averaging and 72-ms TE STEAM. Compared to the 6.5-ms PR-STEAM, Glu C-4 resonances in 40-ms TE PRESS spectrum are not as well isolated. Suppression of macromolecule and broad metabolite signals led to excellent isolation of a single C-4 Glu peak in both TE-Averaging and 72-ms TE STEAM spectra. For the detection of Glu, out of the four sequences examined here, VTE PR-STEAM appears to be the most precise with a CV of 7.1%, followed by TE-Averaging with a CV of 8.9%, PRESS with a CV of 11.9%, and lastly the 72-ms TE STEAM with a CV of 13.8%. Across the four sequences, the Glu ratios range from a low of 1.01 to a high of 1.23 (Table 1), with an average of 1.11 ± 0.09. These values are in excellent agreement with Mullins et al. Glu measurements in the anterior cingulate gyrus. While all four sequences are viable methods for detecting Glu, VTE PR-STEAM appears to be the best choice in terms of precision.

Table 1. Glu/Cr Ratio Results

Sequence	Ratio ± SD	CRLB ± SD
PR-STEAM	1.12 ± 0.08	5.3 ± 0.9
PRESS	1.09 ± 0.13	6.3 ± 0.7
STEAM	1.23 ± 0.17	7.4 ± 1.0
TE-Averaging	1.01 ± 0.09	6.2 ± 0.7

Discussion: In conclusion, Glu can be identified with great precision at VTEs even when localized in the frontal lobe. The results from this study show VTEs should be the preferred method for detecting Glu over short TE PRESS, mid-range TE STEAM, and TE-Averaging. Alternatively, techniques such as SPECIAL (10) that can double the SNR and still achieve VTEs may lead to further improvements in the detection of Glu.

References: 1) Hattori N et al. NeuroReport 2002;13:183-186. 2) Theberge J et al. Am J Psychiatry 2002;159:1944-1946. 3) Han J et al. J Magn Reson Imaging 2010;31:305-308. 4) Knight-Scott J et al. Magn Reson Imaging 2005;23:871-876. 5) Mullins PG et al. Magn Reson Med 2008;60:964-968. 6) Yang S et al. Magn Reson Med 2008;59:236-244. 7) Hurd R et al. Magn Reson Med 2004;51:435-440. 8) Soher et al. J Magn Reson 2007;185:291-299. 9) Provencher SW. NMR Biomed 2001;14:260-264. 10) Mlynarik V et al. Magn Reson Med 2006;56:965-970.

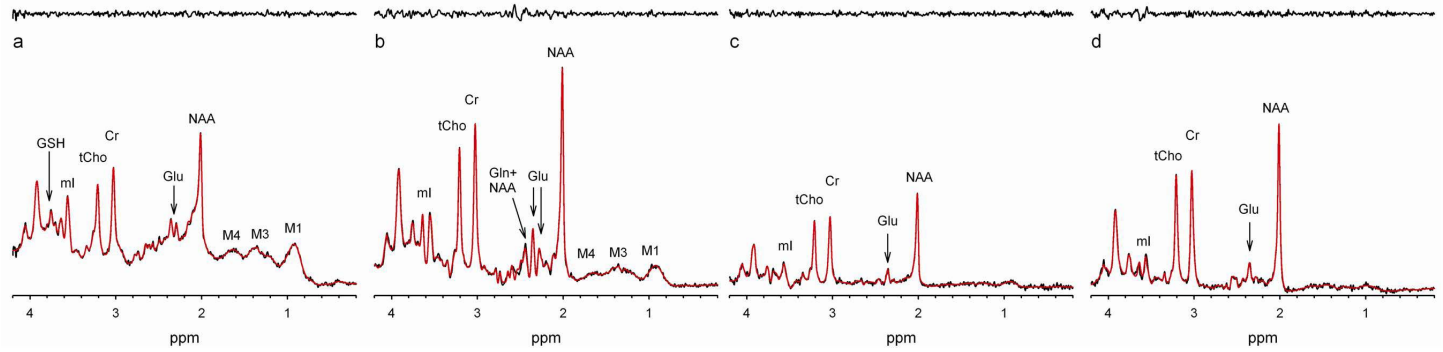

Figure 2. Typical spectra from (a) 6.5-ms TE PR-STEAM, (b) 40-ms TE PRESS, (c) 72-ms TE STEAM, and (d) TE-Averaging with the LCModel fit (—), residue (—), and original spectrum (—). The C-4 Glu resonance is observed as two peaks in (a) and (b) and as a single peak in (c) and (d). Examination of the residue reveals that all metabolites and macromolecules are accounted for in the fit.