Reliability of in vivo glutamate detection with MRS at 3T

R. L. O'Gorman[1,2], J. Noble[3], J. M. Stone[4], D. J. Lythgoe[5], M. A. McLean[6], F. A. Chowdhury[7], P. K. McGuire[4], M. P. Richardson[7], and G. J. Barker[5]
[1]Neuroradiology, King's College Hospital, London, United Kingdom, [2]MR-Zentrum, University Children's Hospital, Zurich, Switzerland, [3]Medical Engineering and Physics, King's College Hospital, London, United Kingdom, [4]Psychological Medicine and Psychiatry, Institute of Psychiatry, London, United Kingdom, [5]Centre for Neuroimaging Sciences, Institute of Psychiatry, London, United Kingdom, [6]Institute of Neurology, London, United Kingdom, [7]Epilepsy Research Group, Institute of Psychiatry, London, United Kingdom

Introduction: Glutamate is the primary excitatory neurotransmitter in the brain, and altered brain glutamatergic transmission has been implicated in a number of neuropsychiatric disorders including epilepsy[1] and schizophrenia[2]. A method for quantitatively and noninvasively measuring cerebral levels of glutamate (Glu) and glutamine (Gln) would therefore be of considerable interest and importance for a variety of clinical and research applications.

Magnetic Resonance Spectroscopy (MRS) presents a promising method for in vivo glutamate measurement, but robust spectroscopic quantitation of Glu is challenging due to the spectral overlap of Glu with Gln and GABA. A number of novel acquisition techniques have been reported to improve Glu detection with MRS[3-5], but most suffer from limited availability due to the requirement for specialist pulse sequences or high field (>3T) scanners[3,5-7]. An alternative approach would be to apply a standard point resolved spectroscopy (PRESS) sequence at an "optimal" echo time of 80–90 ms, at which point the spectral overlap of Glu with Gln is reduced due to the suppression of the outermost multiplet peaks.[3,8-10] This approach has been reported to improve the reliability of glutamate detection relative to spectral editing methods,[8] and has the added advantage of being widely available at 3T. The 80 ms spectra also exhibit reduced macromolecular signal relative to short echo time (TE) spectra, resulting in a flatter baseline. However, it is not known to what extent the increase in reliability arising from a flatter baseline may be offset by a decrease in reliability arising from a decrease in signal to noise ratio (SNR) with a longer echo time. In addition, the reliability of Glu concentrations is likely to depend on the quantification methodology as well as the acquisition protocol. The purpose of this study was to examine the precision of Glu measurements derived from both a short-TE (30 ms) PRESS ^{1}H-MRS acquisition protocol and a protocol utilising an echo time optimised for Glu/Gln separation, quantified using both frequency domain and time domain analysis methods.

Methods: Single voxel ^{1}H MR spectra were acquired from a 20x20x20 mm^3 volume of interest positioned in the anterior cingulate cortex using two PRESS acquisitions with echo time (TE) 30 and 80 ms and repetition time 3 s. Spectra were acquired from 8 subjects (3 male, age 22-48) with a 3T GE HDx MRI scanner (GE Healthcare, Waukesha, WI, USA) using an 8-channel receive-only head coil. Eight phantom spectra were also acquired for each echo time from a standard spectroscopy test object containing known concentrations of the major brain metabolites, (NAA: 12.5 mM, Cr: 10 mM, Cho: 3 mM, Glu: 12.5 mM). The scanning protocol in vivo also included a 3D IR-SPGR volume, which was segmented into grey matter, white matter and CSF using statistical parametric mapping (SPM2, Wellcome Dept of Cognitive Neurology) in order to correct the spectroscopy results for partial volume CSF contamination. Water-scaled metabolite concentrations were derived from the frequency domain MRS data using LCModel version 6.1-4F[11] and in the time domain using the Amares algorithm[12] in jMRUI[13]. The water concentration used for water scaling was corrected for the amount of CSF in the voxel, and the TE80 concentrations were corrected for T_2 effects using literature T_2 values and phantom measurements. The test-retest reliability (quantified as the coefficient of variation, %CV) of the glutamate, N-Acetyl Aspartate (NAA), choline (Cho), and creatine (Cr) concentrations was derived for each echo time and analysis method, both in vivo and in vitro.

Results: The precision of the in vitro and in vivo metabolite concentrations is given in table 1, and the average in vivo metabolite concentrations measured across the subject group are given in table 2. For the frequency-domain analysis, the test-retest reproducibility of the concentrations varied from about 5-10% in vivo and 2-7% in vitro, and there was no significant difference in the reliability of the metabolite concentrations between the two echo times ($p>0.05$, paired t-test). For the time-domain analysis, the reproducibility of the derived concentrations ranged from 2-20% in vivo and 3%-10% in vitro, although glutamate was not detected for all the short-TE scans.

Table 1: Average precision (% coefficient of variation) of the metabolite concentrations measured in vitro (left) and in vivo (right).

	LCModel: in vitro				**LCModel: in vivo**			
	Cr	Glu	NAA	Cho	Cr	Glu	NAA	Cho
TE30	2.0%	5.4%	3.2%	5.2%	5.8%	9.3%	5.9%	7.4%
TE80	2.4%	6.9%	6.6%	4.1%	5.5%	11%	6.5%	5.2%
	JMRUI: in vitro				**JMRUI: in vivo**			
TE30	8.5%	ND	3.9%	8.1%	15%	ND	7.9%	13%
TE80	3.3%	10%	6.1%	4.0%	6.4%	21%	1.8%	2.6%

Table 2: Mean (SD) metabolite concentrations derived with LCModel and jMRUI for each echo time in vivo

LCModel				
	NAA	Cr	Cho	Glu
TE30	11.9 (1.6)	9.80 (1.2)	2.76 (0.36)	13.1 (1.9)
TE80	12.4 (1.9)	13.0 (1.3)	3.43 (0.5)	11.1 (2.0)
JMRUI				
TE30	14.8 (2.4)	7.27 (1.3)	3.99 (1.2)	20.9 (15.5)
TE80	13.7 (1.9)	8.10 (1.2)	3.76 (0.7)	2.09 (0.61)

Discussion: The longer echo time optimised for Glu/Gln separation (80ms) may offer improved reproducibility and increased sensitivity for glutamate detection relative to a standard short echo time PRESS protocol when time-domain fitting methods are used for metabolite quantitation, but this protocol appears to offer little improvement in precision when frequency-domain methods like LCModel are used for analysis. The precision results demonstrate a trend towards improved reliability for glutamate detection with short echo time spectra and frequency domain analysis methods, although the TE80 spectra and time domain analysis methods offered better precision for some of the other major metabolites, (notably NAA and Choline).

Conclusion: Glutamate can be reliably detected using a standard PRESS acquisition at 3T, and the reliability of MRS data for glutamate as well as the other major brain metabolites can be improved through careful choice of PRESS acquisition protocol and analysis methodology.

References: [1]Helms et al. *JNNP* 2006; 77:489-494 [2]Stone et al. *J Psychopharmacol* 2007; 21:440-452. [3]Hu et al. *J Mag Reson* 2007; 185:204-213, [4]Thompson & Allen *MRM* 1998; 39:762-771, [5]Hurd et al. *MRM* 2004; 51:435-440, [6]Theberge et al. *Am J Psychiatry* 2002; 159:1944-1946, [7]Kassem and Bartha *MRM* 2003; 49:918-927, [8]Shubert *Neuroimage* 2004; 21:1762-1771, [9]Snyder et al. Proc ISMRM 2009:2394, [10]Jutras et al. Proc ISMRM 2009: 4283, [11]Provencher *MRM* 1993; 30:672-679, [12]Vanhamme et al. *J Magn Reson* 1997; 129:35-43, [13]Naressi et al. *Computers in Biology and Medicine* 2001; 31:269-286.