Measuring Glutamate in the Human Brain by MRS: Reproducibility using Time Domain fitting at 3 Tesla.

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INTRODUCTION

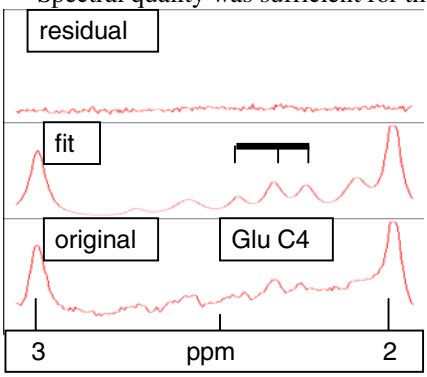
Glutamate is quantitatively the most important neurotransmitter in the brain and implicated in a wide range of physiological and pathological processes. Despite being the most abundant organic molecule in the brain, its detection and quantification by MRS is not easy, particularly at low field (1.5 T), where separation of glutamate and glutamine resonances is virtually impossible. At higher field the glutamate spin system becomes simpler, with the possibility to identify glutamate and glutamine independently. Here we report results from a study carried out at 3 T using time domain fitting to quantify glutamate in a group of normal volunteers.

METHODS

5 healthy volunteers underwent PRESS-localized MRS (TR/TE/Nex 2000/32/128, 2x2x2 cm) in a 3 Tesla Philips *Achieva* scanner. 3 voxel locations predominantly in grey matter were chosen: in the right and left motor cortices, plus a posterior voxel in occipital cortex. Acquisition of the 3 spectra was repeated at 30 min intervals on 3 - 5 occasions. Spectra were quantified using the AMARES[1] routine in jMRUI[2]. Prior knowledge for 15 spectral peaks was generated from phantom studies and spectral simulations of mixtures of metabolites under the same acquisition parameters as the study in vivo. An initial fit of the major singlet resonances was used to fix the phase correction and intrinsic linewidths, which were then used as prior knowledge for a full fit to 15 resonances, including the amino acid signals between 2 and 3 ppm (glutamate, glutamine, aspartate and NAA aspartyl signals). Glutamate was measured from the fitted amplitude of two of the C4 'triplet' resonances at 2.30 and 2.34 ppm which do not overlap the glutamine C4 signals. The absolute amplitudes and ratios to NAA and water (collected in a separate acquisition from the same voxel location) were recorded, and the coefficient of variation (cv = 100*s.d./mean) calculated for each voxel in an individual's spectra, and then averaged across individuals. Inter-subject variability was assessed by calculating the cv across individuals.

RESULTS

Spectral quality was sufficient for the glutamate C4 resonances to be identified and quantified in vivo.



Coefficient of Variation Table (%) averaged within subjects						
Peak	**Left motor cortex**		**Right motor cortex**		**Occipital cortex**	
	mean	**range**	**mean**	**range**	**mean**	**range**
G1	**9**	**9 – 14**	**13**	**5 – 22**	**10**	**4 – 16**
G2	**10**	**3 – 17**	**20**	**9 – 30**	**21**	**6 – 39**
NAA	**7**	**4 – 11**	**8**	**1 – 17**	**10**	**3 – 21**

The average cv for the glutamate resonances varied from 9-13% for the peak at 2.30 ppm (G1) and from 10-20% for that at 2.34 ppm (G2) across the three brain areas. The cv of the sum of G1+G2 varied from 9-13%. For comparison, the cv for NAA varied from 7-11% for the three brain regions. Unsurprisngly, the inter-subject variability was greater than that within subjects. The cv's of the absolute amplitudes of the G1 and G1+G2 signals varied between 19-35%, though of course this variability includes differences due to the scanner over different imaging sessions. Internally calculated ratios to water or NAA showed reduced cv's, in the range of 10-30%, with occipital cortex showing the highest degree of variability.

DISCUSSION AND CONCLUSION

Despite the much lower signal-to-noise of the glutamate signal compared to NAA, within subject reproducibility was only a little worse for the glutamate signals. This suggests that a within-subject, single session experiment designed to measure changes in glutamate, would be expected to detect as significant changes of less than 10% for a 12 subject study. Group comparisons would need much larger glutamate changes, of the order of 25% or more, for significant effects to be detected in a similar sized study.

REFERENCES

1. Mierisova S, et al**.** *NMR Biomed* 1998, **11:**32-39.
2. Naressi A, et al**.** *Magma* 2001, **12:**141-152.