Glutamate-Glutamine detection using ^{1}H MRS in the human cervical spinal cord at 3T

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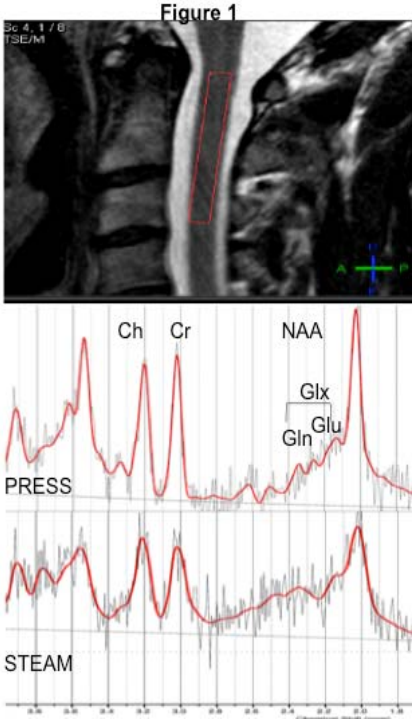
Introduction

The spinal cord is a particularly challenging region of interest for magnetic resonance spectroscopy (MRS) due to its small volume, B_0 inhomogeneities, and physiological motion [1]. However, recent spinal cord studies have shown that detection and quantification of metabolites dominating ^{1}H spectra such as NAA, Cr and Ch can be achieved [2,3]. Alterations in Glutamate (Glu) concentration, the major excitatory neurotransmitter, has been reported to play a role in a number of neurodegenerative diseases [4,5]. Its detection, at 2.35ppm though, has also been challenging in the brain, due to its multi-component, highly-coupled structure, and overlap with the glutamine peak (2.45ppm); however, despite the difficulties in its measure, Glu concentration changes in neurodegenerative diseases have been reported. In this study we demonstrate the feasibility of quantitative measurements of the Glutamate/Glutamine complex (Glx), in the cervical spinal cord of normal healthy controls using ^{1}H MRS at 3T, essential for a more complete overview of Glx in the CNS. Sequences readily available on clinical systems were compared for measuring Glu and Glx in the spinal cord, namely short echo time (TE) PRESS and STEAM. Simulations show shorter TEs minimize J-evolution of Glu and signal decay. Due to the multiplet nature of Glu and the small chemical shift range of ^{1}H MRS, detection is particularly susceptible to motion, hence subject's immobilization was also required. Results on 5 subjects show that it is possible to set-up a clinically feasible protocol for Glx detection in the cervical spinal cord, still providing information from other key metabolites.

Method

Written informed consent was obtained from all 5 healthy participants, age 32±2yrs (3M, 2F).. Three subjects underwent the spectroscopy protocol on 3 separate occasions for reproducibility measurements. All MR experiments were performed on a 3T Achieva system (Philips Medical Systems, Best), with a 16-channel neurovascular coil selecting ony the 4 neck elements for receiving MRS data to reduce noise from elements distant from the ROI. To reduce motion during scanning an MR compatible cervical collar was worn by all volunteers (Bodymedics Range, Talar Made Ltd, UK). 2.1mL voxels were placed within the spine from C1-C3 for each volunteer (Figure 1a). A survey and T1w sagittal-oblique and coronal-oblique scans, aligned with the main axis of the spinal cord, were used for voxel placement. Particular attention was required to avoid contamination of CSF in the prescribed voxels and PRESS/STEAM scans were cardiac triggered at 3RR using a Peripheral Pulse Unit (PPU) device, which resulted in a TR of ~3000ms. Triggered iterative shimming was found to provide the best linewidths (~20Hz). A comparison of PRESS (TE=30ms) and STEAM (TE=11ms and TM=17ms) with MOIST water suppression was performed, collecting 376 averages for a total scan time of 45 mins, including the localiser scans. Water scaled MRS data was quantified using LC model with basis sets simulated in GAMMA for PRESS and matlab for STEAM [6]. Cramer-Rao-Lower-Bounds (CRLB) values provided by LC model were used to asses the reliability of the fit, with poor fits indicated by CRLB values >20%.

Figure 1



Results

Short TE (30ms) PRESS enabled a more reliable detection of Glx and Glu than STEAM for all subjects ($p<0.05\%$), as reflected in the lower CRLB (Table 1). In fact, the CRLB for all subjects was ≤20. A mean Glx concentration of 5.7±1.1mmol/l was found in the cervical spinal cord in healthy controls using PRESS. Intersubject reproducibility was found to be even better then for NAA (Glx (CV)=20%, NAA(CV)=26%). Neither Glx nor Gln were fitted reliably using STEAM in any subjects despite the shorter TE (mean CRLB ~50%). The measurement of Glu itself did not pass the <20% CRLB threshold with either sequence. Therefore, intrasubject reproducibility of Glx using PRESS was tested in 3 subjects. Differences in Glx were found to be under 25% (averaging 13%) for these subjects, with the reproducibility of other metabolites in the range of 0.5-15%.

	PRESS TE 30 CRLB		**STEAM TE 11 CRLB**	
	Glu	Glu+Gln	Glu	Glu+Gln
Sub 1	30%	20%	48%	48%
Sub 2	30%	16%	59%	59%
Sub 3	25%	16%	na	33%
Sub 4	25%	15%	59%	59%
Sub5	21%	19%	89%	48%
Mean	26.2 ±1.6%	17.2± 0.8 %	63.8± 7.1%*	49.4± 4.4% *
CV	**6%**	**5%**	**11%**	**9%**

Discussion

This study has led to the successful detection of Glx in the spinal cord in vivo, which is clinically relevant in many neurodegenerative diseases such as multiple sclerosis, as well as in spinal cord injury. To the best of our knowledge, the detection and quantification of Glx in the cervical spinal cord using ^{1}H MRS has not been reported previously. PRESS localization with TE=30ms has been shown here to enable reliable measurements of Glx using a clinical scanner and within acceptable scan times. Despite lower achievable echo times STEAM failed due to lower SNR. An inherent reduction of 50% in signal is expected when going from PRESS to STEAM and averaging for almost 20 mins was unable to overcome this to provide acceptable fitted spectra for Glx. The spectral quality improvement when using a cervical collar to restrict motion, in addition to short TE PRESS, allows the elusive, strongly coupled Gln and Glu to be detected. Future development will include obtaining shorter scan times and more specific Glu editing techniques.

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