Glutamate reduction in ALS patients observed with MR spectroscopy at 7T

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Introduction: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder affecting upper motor neurons in the brain and lower motor neurons in the spinal cord. The pathogenesis of ALS is not yet elucidated, however, there is abundant evidence for excitotoxic effects of glutamate on motor neurons. This concept is supported by the evidence that riluzole, known to interfere with glutamate metabolism, is neuroprotective in ALS. The development of ultra-high field MRS allows for acquisition of single voxel spectra of the human brain at high SNR and with high chemical shift dispersion, enabling the spectral separation between Glutamate (Glu) and Glutamine (Gln) [1]. In vivo detection of Glutamate in human brain tissue is of great interest for research into ALS as it might be a marker of disease and provide more insights into the mechanisms involved in neurodegeneration.

Data Acquisition: For this prospective study 11 patients with ALS (8 males; average age 54.9 yr, range 34 - 69) and 11 healthy control subjects (8 males; average age 53.8 yr, range 35 - 65) were included. All subjects were scanned on a 7T whole body MR scanner (Philips Medical Systems, Cleveland, USA). A quadrature birdcage transmit head coil (Nova Medical Inc., Burlington, MA, USA) was used in combination with a 16 channel or 32 channel receive coil (Nova Medical Inc., Burlington, MA, USA) for transmission and reception of the signal respectively.

A single voxel sized $10 \times 20 \times 30$ mm^3 (RL, FH, AP) was located to cover the white matter of the left motor tract. A single voxel (STEAM) measurement at short echo time (TE = 6.8 ms TR = 2.5 s, 64 averages with 16 step phase cycling, no outer volume suppression (OVS), 2048 samples, bandwidth 4 kHz) was acquired. Water suppression was performed using variable-pulse power and optimized relaxation delays (VAPOR). An inversion recovery measurement was performed to estimate the macromolecular baseline (same acquisition parameters, added inversion pulse, TI = 720 ms). An additional acquisition without water suppression (two averages) was performed to estimate the phase and amplitude of the MR signal for a coil sensitivity weighted reconstruction of the data from the receive channels and to apply an eddy current correction. B_0 field homogenization was performed with FASTMAP using shim terms up to the second order [2].

Data Processing: Metabolite quantification for the STEAM spectra was performed with an LC-model based fitting, see figure 1. 9 metabolite model spectra for Creatine (Cr), γ-aminobutric acid GABA, Glutamate (Glu), Glutamine (Gln), glutathione (GSH), myo-Inositol (mI), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), and phosphocholine (PC) were generated using NMRSim (v5.2b Bruker Biospin, Billerica, MA) with chemical shifts and coupling constants taken from literature [3]. An average macromolecular (MM) spectrum was included as an additional model spectrum for the fitting procedure. The distributions of fitted concentration of measurements over the patients and controls is reported. Normalization was performed by scaling the Cr concentration to a reference value of 8 mM. Metabolite concentrations were compared between patients and healthy controls by T-test statistics.

Results: Of the 22 included subjects data quality of 14 subjects (8 patients and 6 controls) was deemed of sufficient quality to continue processing. The comparison between healthy controls and patients shows significant decreases in glutamate levels (P = 0.012) and NAAG levels (P = 0.016) between the groups. Levels in Gln, NAA, mI and PC show no clear differences, see figure 2.

Discussion: This study demonstrates a significantly reduced Glu and NAAG concentration in brain tissue of patients with ALS compared with healthy control subjects, using ultra-high field MRS. Our findings are supported by post-mortem measurements of amino acid contents in brain tissue of patients with ALS compared to control subjects [4,5]. These measurements have shown reduced glutamate in most brain regions and in the cervical cord of ALS patients, while glutamine contents were normal. Interestingly, CSF measurements have revealed elevated glutamate concentrations in patients with ALS suggesting there is some underlying disturbance in glutamate metabolism or transport in ALS [6].

The failure to properly regulate glutamate may result in raised extracellular levels of glutamate and reduced tissue levels. There are two MRS studies, both performed on lower field-strength, reporting increased glutamate/glutamine concentrations in ALS [7,8]. It is important to note that higher field-strength is well known to increase the SNR in MRS which allows for more reliable detection of metabolites in the lower concentration ranges such as glutamate, glutamine and NAAG. Future studies in a larger cohort of patients, however, will need to confirm our findings.

Our ultra high-field MRS results, demonstrating significant changes in a small number of subjects, are promising for glutamate and N-acetylaspartylglutamate concentrations as potential markers for disease in ALS.

References: [1]: Tkáç, MRM 2001;46:451, [2]: Gruetter MRM 1993 29:804, [3]: Govindaraju, NMR biomed 2000;13:129, [4]: Perry, Neurology 1987;37:1845, [5]: Tsai, Brain Res 1990;556:151, [6]: Perry, Ann Neurol 1990;28:12, [7]: Pioro, Neurology 1999;53:71, [8]: Han, JMRI, 2010;31(2):305
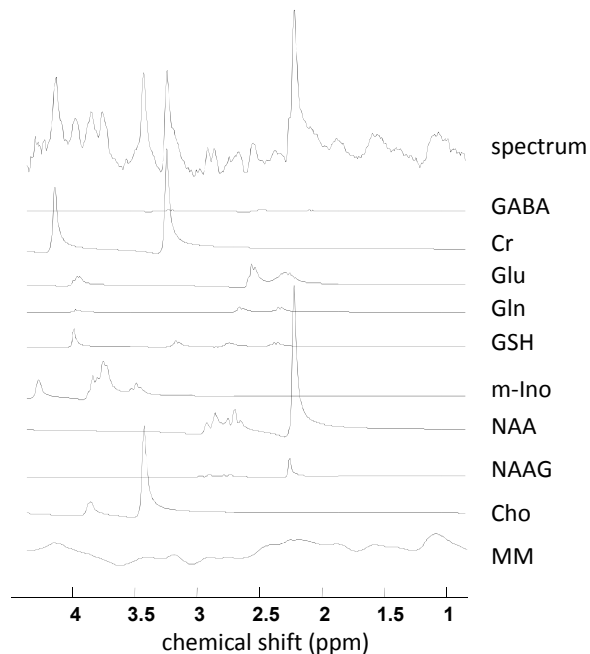
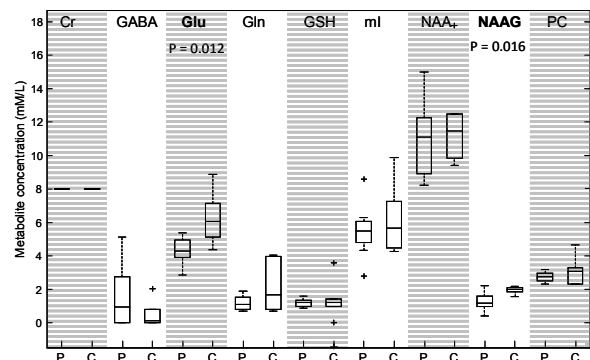Figure 1: Example spectrum and fitting of selected metabolites and macromolecules (MM).

Figure 2: Boxplots of inter-quartile ranges and medians of fitted concentrations, normalized to the Creatine level (set to 8mM/L). Of the selected metabolites only Glu and NAAG show significant differences.