Reduced motor cortex GABA in amyotrophic lateral sclerosis

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Introduction

Although the cause of Amyotrophic lateral sclerosis (ALS) remains elusive, there is evidence that the glutamate system plays a role in the disease pathophysiology. There is also discussion that decreased inhibition through GABAergic pathways may contribute to neuronal damage in ALS. Our study aimed to investigate differences in GABA concentration in the motor cortex and the subcortical white matter between ALS patients and healthy controls (HC) using edited MR spectroscopy.

Methods

Ten ALS patients and nine age- and sex-matched HC were studied. Subjects were imaged on a Philips Achieva 3T system (Best, Netherlands) using an 8-channel phased array head coil for receive and body coil for transmit. PRESS and edited MEGA-PRESS spectra were acquired from two 3x2x3 cm^3 voxels in left motor cortex (centred on the 'hand knob') and left subcortical white matter located caudally to the motor cortex (as shown in Figure 1). PRESS spectra were acquired with TR/TE=2000/35 ms, using VAPOR water suppression. The MEGA-PRESS experiment was performed to edit GABA signals with frequency selective editing pulses (duration 14 ms) applied at 1.9 ppm (in ON scans) and 7.46 ppm (in OFF scans) in an interleaved fashion. MEGA-PRESS spectroscopy was analyzed using in-house post-processing software in Matlab with Gaussian curve fitting to the GABA and inverted N-acetylaspartate (NAA) peaks. Cerebral spinal fluid correction was performed. Two-tailed independent sample t-tests were used to determine differences in GABA levels between ALS and HC groups with a significance threshold set at p=0.05.

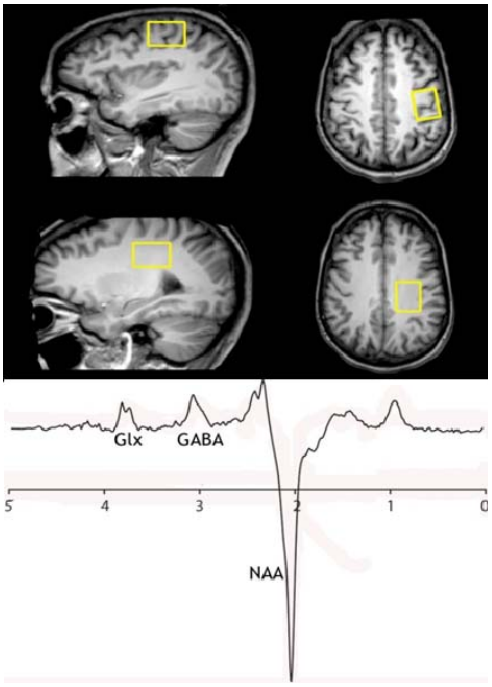

Figure 1: Location of motor cortex (above) and white matter (middle) voxels and a typical GABA-edited MRS spectrum (below)

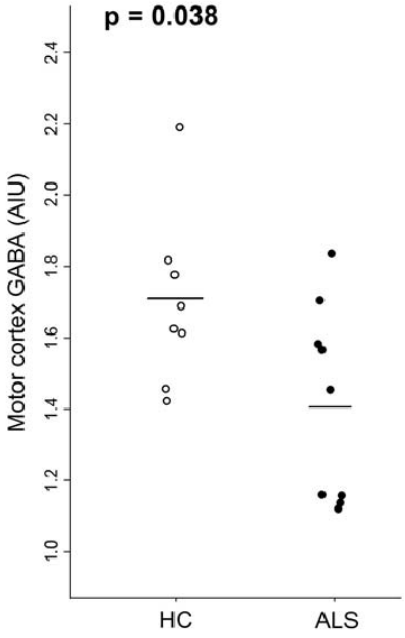

Figure 2: Motor cortex GABA concentration is significantly reduced in ALS subjects, compared to healthy controls.

Results

A typical edited GABA spectrum from the motor cortex region is shown in Figure 1. Good quality spectra with high signal-to-noise ration were acquired in all subjects. As shown in Figure 2, ALS subjects demonstrated significantly lower levels of GABA within the left motor cortex (1.42±0.27 AIU) compared to HC (1.70±0.24 AIU; p=0.038). There were no significant mean GABA level group differences in the left subcortical white matter between the ALS subjects (1.42±0.30 AIU) and the HC (1.53±0.34 AIU;p=0.45). There were no significant correlations between GABA levels and upper motor neuron disease scores.

Discussion

Our results suggest that lower levels of GABA are present in the motor cortex of ALS patients. These findings are concordant with prior PET studies which have demonstrated lower cortical $GABA_A$ receptor binding as well as transcranial magnetic stimulation studies which have demonstrated increased cortical excitability in the setting of ALS. It is therefore conceivable that GABAergic transmission alterations play a significant role in ALS pathophysiology. These findings need to be replicated in larger cohorts of patients to further elucidate the role of GABAergic dysfunction in ALS.