

## In vivo quantification of excitatory and inhibitory neurotransmitters in amyotrophic lateral sclerosis

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**Background:** Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a disabling, rapidly progressing, and terminal neurodegenerative disorder. The hallmark of ALS is the combined degeneration of motor neurons in the brain and spinal cord. Cerebral degeneration is most severe in the precentral gyrus and is variably present to a lesser extent outside this region. Excitotoxicity is an important pathogenic process leading to neurodegeneration<sup>1</sup> with neural damage potentially related to altered excitatory (glutamatergic) or inhibitory (GABAergic) neurotransmitter metabolism. The objective of this study was to quantify glutamate and GABA in the motor cortex in patients with ALS using proton magnetic resonance spectroscopy (MRS).

**Methods:** Twenty-four patients with ALS and 15 healthy controls were studied. Subjects were not eligible if they had a history of head injury or psychiatric disease, or if they were on medications that had known GABAergic or glutamatergic effects. Clinical measures of upper motor neuron dysfunction included slowed finger and foot tapping speed, and spasticity quantified by the Modified Ashworth Scale.

Single voxel MRS was performed at 3 T using a quadrature birdcage coil for RF transmission and reception (Figure 1). A double-quantum filter technique was used for detection of the GABA signal.<sup>2</sup> This method detects the coupled GABA resonance at 3.01 ppm (Figure 2) with complete elimination of the uncoupled resonance of creatine at 3.03 ppm and with minimal contamination of macromolecules (<10% with respect to the edited GABA signal). Spectrally-selective sequences were used to separate the resonances of glutamate and glutamine between 2.35 and 2.45 ppm (Figure 2).<sup>3</sup> Ascertainment of GM, WM and CSF contributions within the voxel was determined using a 1-dimensional projection of the water signal following a STEAM sequence. Double-inversion recovery was used to discriminate between the water signals from the three fractions based on the differences in their T<sub>1</sub> and T<sub>2</sub> relaxation times. Metabolites were normalized using the water signal as an internal reference and using accepted T<sub>1</sub> and T<sub>2</sub> metabolite relaxation times reported in the literature to produce tissue concentrations in mmol/L.

**Results:** Motor cortex glutamate was reduced 13% ( $9.17 \pm 1.54$  vs  $10.58 \pm 1.02$ ,  $p=0.001$ ). GABA concentration was not different ( $0.77 \pm 0.27$  vs  $0.74 \pm 0.27$ ,  $p=0.73$ ). Increased GABA concentration in ALS correlated with lower finger tapping rates ( $r=-0.54$ ,  $p=.012$ ) and increased spasticity ( $R=0.32$ ,  $p=0.063$ ). A trend was also observed for increased glutamate and decreased finger tapping rates ( $r=-0.36$ ,  $p=0.088$ ) in ALS.

**Discussion / Conclusion:** Glutamate levels are decreased in the motor cortex in patients with ALS. This reduction may be secondary to neuronal loss. GABA levels were unchanged. GABA and glutamate correlated with clinical indices supporting their relevance to pathogenesis and as potential biomarkers of disease.

**References:** 1 Rothstein J, Ann Neurol 2009;65:S3-9. 2 Choi et al, MRM 2005;54(2):272-279. 3 Choi et al, MRM 2006;55(5):997-1005.

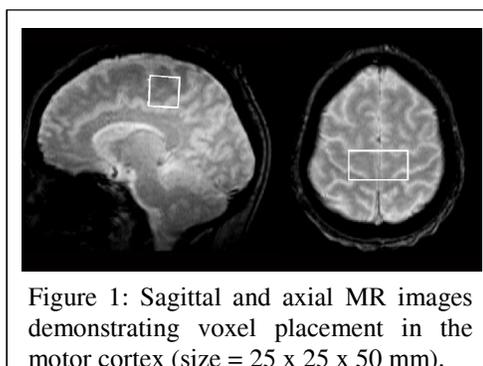


Figure 1: Sagittal and axial MR images demonstrating voxel placement in the motor cortex (size = 25 x 25 x 50 mm).

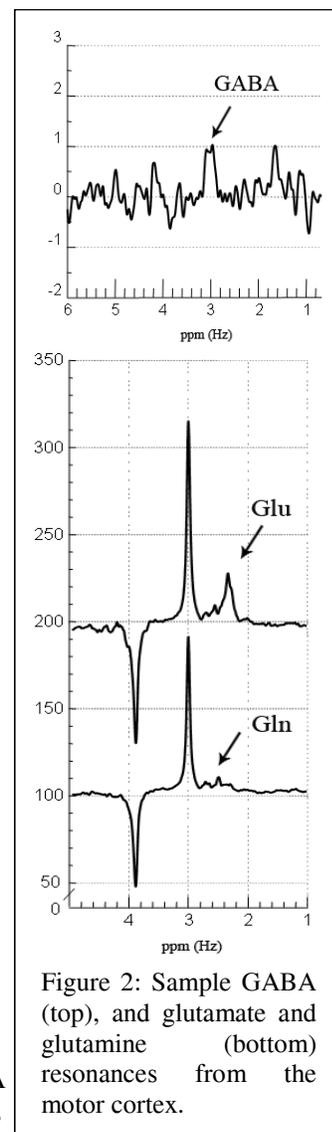


Figure 2: Sample GABA (top), and glutamate and glutamine (bottom) resonances from the motor cortex.