# Whole-brain Proton MRSI Data Analysis using a Corticospinal Tract Atlas in Amyotrophic Lateral Sclerosis

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**INTRODUCTION:** Amyotrophic lateral sclerosis is a neurodegenerative disorder in which loss of motor neurons in the cerebral cortex, brain stem and spinal cord, and degeneration of the corticospinal cord (CST) are the pathological hallmarks. Quantification of brain metabolite changes using proton MRS methods in the motor cortex and CST of subjects with ALS in earlier studies were performed by defining regions-of-interest (ROI) manually at few select locations in these structures. Such an approach, specifically in CST, is bound to have subjectivity in drawing ROIs. In this study, a 3D brain white matter CST atlas was used to analyze whole-brain MRSI data for quantification of metabolites, N-acetyl aspartate (NAA), creatine (Cr) and choline (Cho) in the left- and right whole-CSTs of subjects with ALS and controls.

**METHODS:** MRI and MRSI data were obtained at 3T from 13 subjects with sporadic definite-ALS (mean age: 43 years,

age range: 34-50 years) and 47 age-range matched controls (mean age: 43 years). The MRSI data were obtained from the whole-brain using a volumetric EPSI sequence (TR/TE=1710/70 ms, 135 mm slab, $T_{acq}$= 26 min.; details in [1]). Data were processed using the MIDAS package [2, 3]. After 3D spatial smoothing, the processed MRSI data were interpolated to 64x64x32 mm$^3$ with the resultant voxel volume of ~1 mL. Then, this data was spatially registered with the MNI T1-MRI template at 2 mm isotropic resolution. For identifying CSTs, a single-subject brain white matter probabilistic atlas [4] in MNI space with both the left and right whole-CST defined in 3D volumes was chosen. This atlas was interpolated to match with the resolution of the template. Furthermore, two constraints were imposed on the original CST atlas,



**Figure:** T1-MRI template with the original (left) and modified (right) CST atlases overlaid on it.

labeled as oCST; that are, 1) to limit the spatial coverage of the CST atlas along the superior-inferior direction, few axial slices at both the ends of the CST atlas were excluded, and 2) to limit the selection of voxels with lower probability, only voxels with probability values >0.20 were included, and the resulting atlas was labeled as mCST (see in Figure). In each of the CST 3D-volumes, spectral quality was controlled by including only spectra from voxels with fitted linewidths ≤ 12 Hz and tissue volume ≥ 70% of the voxel volume. The NAA, Cr and Cho values (in institutional units) and Cho/NAA ratio were compared between the groups using the 2-tailed t-test, and a p-value of ≤0.05 was considered significant.
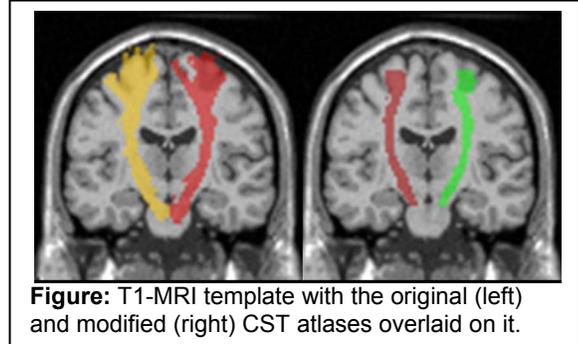
**RESULTS AND CONCLUSIONS:** In the table, the mean metabolite values for NAA, Cr and Cho, and Cho/NAA ratio in both the left and right whole-CST volumes in the control and ALS groups are listed. The observations from the table, in the ALS group as compared the control group, are: 1) significantly decreased NAA in the left and right CSTs, with % of

decrease ranging from 6.3% in the right to 10.9% in the left, 2) significant difference in Cr for the right, 3) significantly increased Cho in both the sides, and highly significantly increased Cho/NAA in both the sides (see the p-values). The results indicate that motor neuronal degeneration (NAA↓) and its consequent membrane breakdown and increased membrane synthesis (Cho↑) have occurred. The use of mCST, as compared to oCST, resulted in further decreased p-values

**Table:** Metabolite values and ratio in the left and right CSTs for the ALS and control groups. Mean ± SD and p-values (*p≤0.05, **≤0.01, ***p<0.0001) are provided. oCST and mCST indicate original and modified CST atlases, respectively. L= left, R= right.

| Metabolite | Group | oCST_L | oCST_R | mCST_L | mCST_R |
|---|---|---|---|---|---|
| NAA | ALS | 2359±210** | 2472±228* | 2433±236** | 2512±267** |
| | Control | 2600±234 | 2645±211 | 2730±244 | 2739±225 |
| Cr | ALS | 1681±103 | 1722±112* | 1704±120 | 1726±106* |
| | Control | 1607±159 | 1633±143 | 1633±157 | 1634±140 |
| Cho | ALS | 506±41** | 500±59** | 543±46** | 547±63** |
| | Control | 441±64 | 442±61 | 475±67 | 478±68 |
| Cho-NAA | ALS | 0.22±0.03*** | 0.21±0.02*** | 0.23±0.03*** | 0.22±0.03*** |
| | Control | 0.17±0.02 | 0.17±0.02 | 0.17±0.02 | 0.18±0.02 |

for NAA and Cho, indicating increased sensitivity of detecting metabolite differences. It is well known that metabolite levels in the CST of ALS patients are altered; however, all previous studies have used a subjective ROI-based approach to evaluate parts of the CST and not the whole CST. The CST atlas based metabolite evaluation shown in this study provides a convenient method for unbiased evaluation of metabolite levels in the whole-CST, and it can be segmented further to evaluate metabolite changes in each of the segments. This study shows the advantage of acquiring whole-brain MRSI data and the flexibility it provides for analysis using appropriate anatomical substructural brain atlases.

**REFERENCES:** [1] Govind V et al. *J Neurotrauma* 27:483-496 (2010); [2] Maudsley AA et al. *NMR Biomed* 19:492-503 (2006); [3] Maudsley AA et al Magn. Reson. Med. 61:548-559 (2009); [4] Oishi K et al *NeuroImage* 46:486-499 (2009).