Image-Based Analysis of Metabolic Alterations with ALS

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INTRODUCTION:

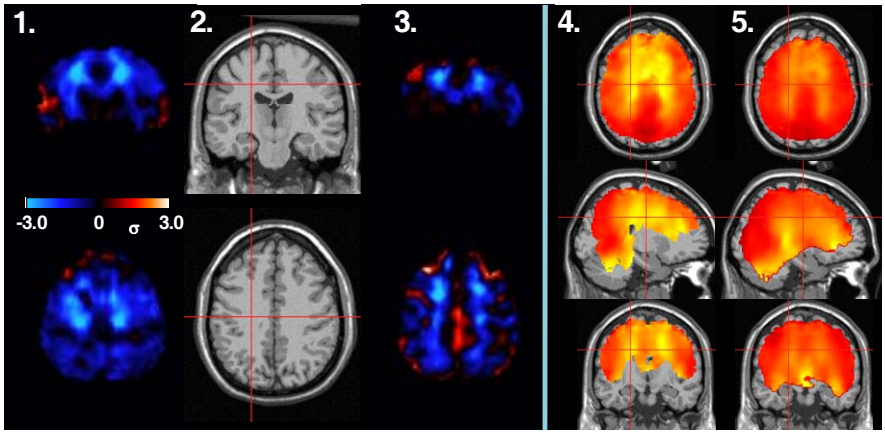
Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that is characterized by motor neuron degeneration. Diagnosis is based on clinical assessments; however, previous ^{1}H MRS studies have indicated the potential for using altered metabolite distributions as imaging biomarkers of disease. These previous studies have used single-voxel or 2D spectroscopic imaging (MRSI) measurements and in this report these observations are extended using high-spatial resolution volumetric MRSI and image-based comparisons of metabolite distributions against those of normal subjects.

METHODS:

MRI and MRSI data was obtained in 22 subjects diagnosed with sporadic definite ALS. Additional data was obtained from 18 control subjects matching the ALS subject age range of 40 to 59 y.o. Proton MRS data was obtained using a volumetric EPSI sequence at 3 T, with TE=70 ms, final voxel volume of 0.6 ml, and selection of a 14 cm slab covering the cerebrum. Reconstruction of the metabolite images using the MIDAS package[1] included spatial and signal intensity normalization of the metabolite images along with formation of images of the grey-matter, white-matter, and CSF content of each SI voxel, obtained by segmentation of coregistered T1-weighted MRI.

Analysis of all individual-subject data included formation of a difference, or z-score, image for each of the NAA, Creatine, and Choline images, as well as for the ratio images of Cho/NAA, Cho/Cr, and NAA/Cr. This analysis method indicates the difference between the metabolite value calculated from the known tissue content at each voxel, and the experimentally-measured image value, expressed as a function of the number of standard deviations of the data for the corresponding image region from the normal subject group. Additional processing included exclusion of voxels with fitted metabolite results of linewidth greater than 11 Hz. Additional analyses included formation of the average metabolite, and metabolite ratio, image from a subset of the ALS group, and tissue regression of metabolite values carried out for each brain region.

RESULTS AND CONCLUSIONS:



(1)-(3) Coronal and axial sections for individual Z-score NAA images and reference MRI; and average Cho/NAA for ALS (4) and normal subject groups (5).

Of the 22 studies, 7 were not analyzed due to inadequate data quality. An example z-score image for NAA is shown in column 1 of the Figure, which is for a subject with limb onset ALS (age 60, est. duration 45 mo., ALFRS 30). The image color scale is set such that the light-blue region corresponds to NAA loss equivalent to 3 standard deviations of the distribution in the normal subject group. This example shows a significant bilateral loss of NAA in the corticospinal tracts, in the region indicated in the reference MRI (Col. 2). Of the other datasets analyzed, 6 showed less-well defined decreases of NAA and increased Cho/NAA, and 7 did not show significant variation from the normal distributions. Variations in the localization of changes were observed, as for example shown in Col. 3 (age 43, ALSFRS 45), indicating a wider extent of NAA loss, although not reaching statistical significance. This was verified by generating an image from the mean values from the subset of 7 ALS subject data that each indicated some change in metabolite distributions. The Cho/NAA image for this result is shown in Col. 4 and can be compared to the result from the normal subject group shown in Col. 5. Here, increased Cho/NAA is evident over much of the frontal white matter region.

In conclusion, the image-based analysis of volumetric MRSI data shows great potential for analysis of metabolite changes in individual subjects, as well as detection of smaller variations across subject groups. Future developments will extend the analysis methods to integrate over larger, anatomically-defined, tissue regions, which should increase sensitivity for detection of changes in single-subject data.

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REFERENCES: 1) A.A. Maudsley, et al., *NMR Biomed*, 19: 492-503 (2006).