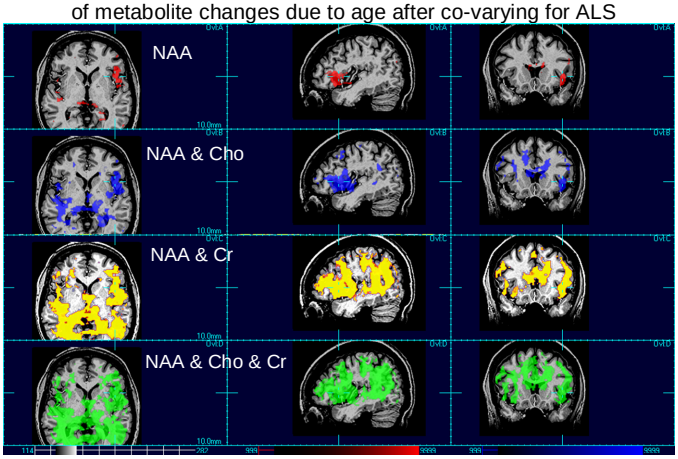
Multivariate Statistical Mapping of Spectroscopic Imaging Data

K. Young[1], P. Weber[1], V. Govindaraju[2], K. Sharma[2], A. Darkazanl[2], C. Studholme[1], L. Hall[3], A. A. Maudsley[2], and N. Schuff[1]
[1]University of California and VA Medical Center, San Francisco, CA, United States, [2]University of Miami, [3]University of South Florida

Background:
For many spectroscopic imaging (SI) studies of the brain it is important to measure the distribution of metabolites in a regionally unbiased way - that is without restrictions to a-priori defined regions of interest (ROI). Since SI provides measures of multiple metabolites simultaneously at each voxel, there is furthermore great interest in utilizing the multidimensional nature of SI for gains in statistical power. Voxelwise multivariate statistical mapping is expected to solve both issues but it has not been employed for SI before. In this study, which is part of the MIDAS project [(1)], we aimed 1) to develop and validate multivariate statistical mapping for SI and 2) to demonstrate that multivariate statistical mapping can be more powerful than univariate tests in identifying patterns of altered brain metabolites. Specifically, we compared multivariate to univariate tests in identifying regional patterns of metabolite alterations due to amyotrophic lateral sclerosis (ALS), a devastating brain disease of motor functions, and those due to aging.

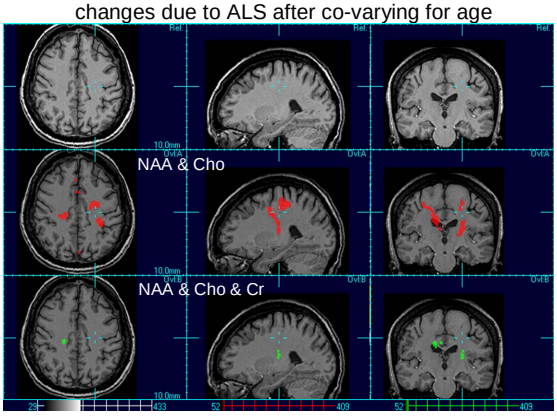
Figure 1: Uni- and multivariate statistical maps of metabolite changes due to age after co-varying for ALS



Methods:
A statistics toolbox that utilizes the statistical libraries of R[(2)] was developed and integrated into MIDAS. Among other applications it provides voxel based multivariate analysis of covariance (MANCOVA). The false discovery rate (FDR) was used for statistical interference in voxel-by-voxel comparisons[(3,4)]. To determine the gains in power provided by multivariate statistical mapping, multivariate statistical mapping was tested on SI data from 12 male patients diagnosed with definite ALS [age range 36 -56] and 12 male controls [age range 21 – 56] acquired at 3Tesla relative to univariate tests. Simulations in which local metabolite intensities were manipulated in half of the data sets and compared to the other half without manipulations were also performed to validate the methods. The spatial resolution of SI was about 0.6 cc (0.31 cc nominal). 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- and T2-weighted MRIs. The level of statistical significance was fixed at FDR = 0.05 for all tests.

Results:
Figure 1 depicts patterns of age-related brain metabolite changes in the group of ALS patients and controls combined after accounting for disease, using univariate tests (first row for NAA) and multivariate tests (NAA & Cho, NAA & Cr, NAA & Cho & Cr in rows 2 to 4, respectively). The results indicate that each multivariate test had greater power to detect age-related metabolite changes when compared to the univariate test. Note that, whereas a univariate test of NAA (row 1) and multivariate tests of NAA and Cho combined (row 2) imply that age-related metabolite changes primarily occur in the frontal lobe while sparing temporal and parietal regions, multivariate tests including Cr (rows 3 and 4) imply that the superior temporal and parietal lobes are also affected. Figure 2 shows multivariate test results of metabolite alterations in ALS after accounting for the age-related changes. Whereas univariate tests yielded no significant effects of ALS for any of the metabolites, multivariate tests revealed significant metabolite alterations in motor and pre-motor areas, extending along motor fibers. Moreover, multivariate tests of simultaneous NAA and Cho changes yielded on average larger clusters (in red) than multivariate tests including Cr (in green), implying that Cr changes in some regions more in concordance with NAA and Cho than in others.

Figure 2: Multivariate statistical maps of metabolite changes due to ALS after co-varying for age



Conclusion:
The results demonstrate that multivariate statistical mapping is a powerful approach for the analysis of SI data and in particular they imply that multivariate tests should be used whenever simultaneous changes of metabolites are expected.

Acknowledgement: This work is supported by NIH BRP grant, R01EB0822, and the Stanley Glaser Foundation.

References: (1) A.A. Maudsley, et al., Comprehensive processing, display and analysis for in vivo MR spectroscopic imaging, *NMR Biomed*, 19: 492-503 (2006).; (2) The R foundation for Statistical Computing, http://www.r-project.org/; (3) Benjamini Y, et al. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society 1995;57(1):289–300. (4) Genovese CR, et al:Thresholding of Statistical Maps in Functional Neuroimaging Using False Discovery Rate. Neuroimage 2002;(15):870–878.