INTRODUCTION: Previous $^1$H MRS/MRSI studies on Alzheimer’s disease (AD) showed reduced NAA in various regions of the brain, including the association cortices [1], presumably reflecting neuron loss. Interpretation of these findings was complicated by variations of voxel tissue composition, choice of regions of interest (voxel selection), or a combination of both, which could produce biased results. In order to investigate the extent to which NAA changes in AD are independent of structural and regional variations, our goals were:

(1) To overcome problems related to voxel tissue composition by determining NAA in “pure” gray matter (GM) and “pure” white matter (WM) of AD. This was accomplished by analyzing the regression of NAA against the voxel tissue composition, similar to previous reports [2,3].

(2) To overcome problems related to voxel selection by analyzing the NAA distribution in different brain regions. This was accomplished by histogram analysis of NAA distributions in frontal and parietal cortex.

(3) Finally, to test whether these NAA changes add power to discriminate AD from controls over that from quantitative MRI measures.

METHODS: Eleven AD patients (75.1 ± 6.4 years; MMSE 16.1 ± 8.7) were studied by MRI and $^1$H MRSI (1.5T Vision, Siemens Inc.) and compared with 11 normal elderly of comparable age. Multislice $^1$H MRSI (TR/TE=1800/135ms; 1.5ml effective voxel size) was applied to measure NAA in frontal and parietal lobes. Slice-selective inversion (TI=170ms) and k-space extrapolation [4] were used to reduce lipid contamination in the $^1$H metabolite spectra. Automated curve fitting was used to determine NAA [5]. The compositions of the MRSI voxels in terms of CSF, GM, WM, and WM/SH were estimated from coregistered segmented MRIs and used for atrophy correction of NAA and for regression analysis. The regression of NAA as a function of GM voxel content was used to estimate NAA in “pure” GM and “pure” WM. Between group differences of NAA distributions in frontal and parietal cortex were evaluated by comparing the group NAA means at various percentiles. Effect sizes of MRSI and MRI measures and their combinations were computed to test discrimination power. Between group differences were tested using Wilcoxon rank test.

RESULTS: The table shows that “pure” GM NAA levels of AD were reduced by 12.8% in the parietal cortex and by 10.9% in the frontal cortex when compared to controls. By contrast, “pure” WM NAA levels were not significantly different between the groups, in both parietal and frontal cortex. Furthermore, the regression slopes (data not shown) suggested that in AD, NAA is lower in GM than in WM, whereas in controls, NAA is higher in GM. The figure shows the histograms of the NAA distribution in parietal cortex of AD and controls (line plot for clarity). AD when compared to controls had 13.7% (p = 0.007) lower NAA at the 50th percentile and 16.8% (p=0.0005) at the lower 10th percentile of the distribution. A similar trend was observed for NAA in frontal cortex of AD. Finally, the effect size of MR segmentation measures alone (i.e. percent cortical GM loss = %cortGM) was 1.6. However, %cortGM combined with “pure” NAA yielded an effect size of 2.0, and %cortGM combined with lower 10th percentile NAA yielded an effect size of 2.5, indicating that both $^1$H MRSI measures provided additional information to MRI for the discrimination of AD from controls.

DISCUSSION: Using regression and histogram analysis of multiple voxel data, we found reduced NAA levels in the parietal and frontal cortex of AD, but not in WM, consistent with the known distribution of AD pathology. Furthermore, because these data were corrected for tissue atrophy and for variations of tissue composition, our results provide evidence that NAA reductions in AD occur independently from structural variations as measured by MRI. The finding of NAA differences between AD and controls in GM but not in WM emphasizes the importance of adjusting for voxel tissue composition when evaluating MRS data. The histogram analysis suggests that the NAA distribution in AD is skewed towards lower values, possibly reflecting NAA changes from tissue in different stages of neurodegeneration. Finally, the finding that the $^1$H MRSI measures combined with MRI measured increased the effect size over that of MRI alone indicates that $^1$H MRSI adds information to the discrimination of AD from HC.

In conclusion, our results suggest that NAA abnormalities measured by $^1$H MRSI may provide valuable information in addition to MRI for the diagnosis of AD.

REFERENCES: