4T Magnetic Resonance Spectroscopy of the Hippocampus in Alzheimer Disease and Mild Cognitive Impairment

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Background: Alzheimer disease is characterized by progressive memory and cognitive decline. Conventional methods of diagnosing and tracking Alzheimer Disease (AD) primarily involve neuropsychological assessments of cognitive performance including the Mini-Mental Status Exam (MMSE). One structure affected early in the disease process is the hippocampus, which has a primary role in the formation of new memories. It is postulated that metabolite changes in this region may serve as a surrogate marker for disease progression [1] and may be more sensitive than clinical assessments and volumetric measures of atrophy. Mild Cognitive Impairment (MCI) may occur prior to Alzheimer disease. The purpose of this study was to characterize the metabolite differences in the hippocampus of normal elderly, those with MCI, and those with AD, and in particular the metabolites *N*-acetylaspartate (NAA), glutamate (Glu) and myo-inositol (MI).

Method: Data were gathered from 15 control subjects [mean ± SD, age = 78.3 ± 5.9 years, MMSE = 29.2 ± 0.9], 7 MCI patients [age = 69.6 ± 13.0 years, MMSE = 28.0 ± 1.3] and 18 mild to moderate AD patients [age = 73.9 ± 6.9 years, MMSE = 22.1 ± 3.2] taking donepezil or galantamine. A 4 Tesla Varian/Siemens MRI scanner was used to acquire short echo time [TE = 46ms, TR = 3.2s] LASER localized proton magnetic resonance spectra from a single voxel [3.8 ± 0.7 mL] positioned largely within the right hippocampus (Figure 1). Both full spectra and macromolecule spectra were acquired, and the macromolecule signal subtracted to obtain a pure metabolite spectrum [2]. Figure 2 shows an example spectrum that has been mathematically modeled. Spectra were also lineshape corrected (QUECC [3]) prior to quantification. Metabolite levels were calculated using semi-automated software (fitMAN) that incorporated prior knowledge of 19 metabolite lineshapes. Absolute concentration levels were calculated by referencing to the internal water signal and corrected for tissue partial volume (gray matter, white matter, and CSF) calculated using Statistical Parametric Mapping [4]. For the data analysis, Alzheimer subjects were divided into mild and moderate groupings based on MMSE scoring (mild = 21-24 and moderate ≤ 20). Control and MCI groups were then compared to mild, moderate and the combined mild + moderate AD cohort. For this cross sectional study, conventional unpaired two-tailed t-tests assuming equal variance were used for most comparisons. The non-parametric Mann-Whitney U-test was used when comparing groups of unequal size. Multivariate logistical regression analysis was used to generate a Receiver Operating Curve (ROC) incorporating several metabolite measurements.

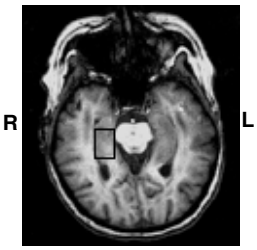

Figure 1: Transverse oblique slice with voxel on right hippocampus [T1-weighted 3D FLASH, FOV = 24 cm, slice thickness = 2.5 mm, TI/TR/TE = 500 / 9.5 / 5 ms]

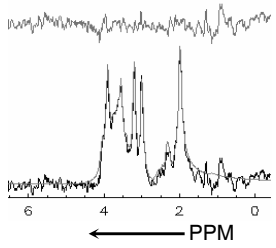

Figure 2: Post-processed spectrum shown with superimposed fit and residual signal (top)

Results and Discussion: A decreasing trend in Glu ($p<0.1$, Mann-Whitney U-test) was noted between MCI and control groups. A significant decrease was found in NAA levels ($p<0.05$, 2-tailed t-test) and Glu ($p<0.01$, 2-tailed t-test) between all AD subjects and controls. No significant changes were found in MI between any groups. No significant correlations were found between metabolite levels and MMSE scores. Figure 3 depicts absolute NAA and Glu levels for all patient populations.

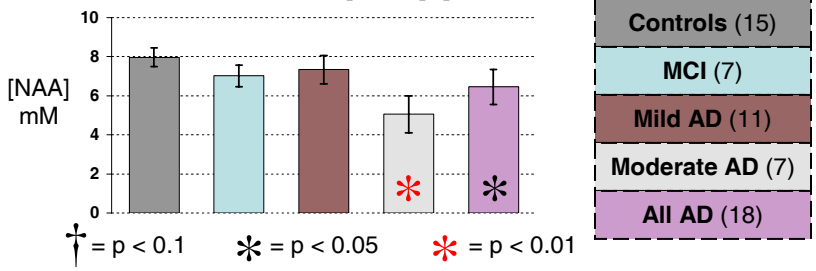

Figure 3: NAA and Glu levels in all study groups

The increased signal to noise ratio and spectral dispersion at 4T increased metabolite level quantification accuracy and precision and permitted the use of a small voxel largely within the hippocampus. Although the difference between MCI and controls did not reach significance with this small sample size, Glu did show sensitivity to early AD. The known role of glutamate as a major excitatory neurotransmitter potentially implicates it in the pathology of dementia. NAA is typically associated with neuronal density or viability, and was significantly reduced in moderate AD subjects only. The ideal biomarker must be able to differentiate controls from MCI from AD, however with the current cross-sectional analysis a useful ROC curve can only be drawn between controls and AD subjects (Fig. 4) Which shows good sensitivity (92%) when comparing all AD subjects to controls at a specificity of 80%. In the future, longitudinal patient data will be used to assess intra-individual metabolite alterations, as these may be more sensitive in discriminating different stages of disease progression.

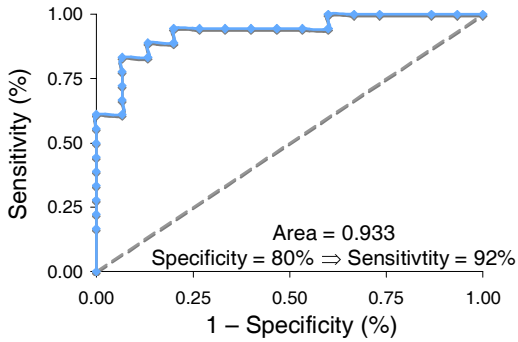

Figure 4: [NAA]+[Glu] multivariate ROC of AD vs. Controls

References:

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[2] Kassem et al. Magn Reson Med, 49(5):918-27 (2003)
[3] Bartha et al. Magn Reson Med 44(4):641-5 (2000)
[4] Schubert et al. Neuroimage 21(4):1762-71 (2004)