Reduced Glutamate in the Hippocampus in Mild Cognitive Impairment and Alzheimer Disease

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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). The hippocampus is directly involved in memory formation and is a structure affected early in AD. 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) is a condition that may occur prior to AD. The purpose of this study was to measure absolute metabolite levels changes in the hippocampus of Normal Elderly Controls (NEC) over one year, and compare those with MCI and AD subjects; in particular, the metabolites *N*-acetylaspartate (NAA), glutamate (Glu), myo-inositol (mI), creatine (Cr) and choline (Cho).

Method: MRS and neuropsychological data were gathered at baseline from 15 NEC 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 23 mild to moderate AD patients [age = 73.9 ± 6.9 years, MMSE = 22.1 ± 3.2] on a constant dose of donepezil or galantamine. A subset of subjects (10 controls, 6 MCI and 6 AD) were studied a second time, 1.02 ± 0.28 years after their baseline scan. A 4 Tesla Varian/Siemens MRI scanner was used to acquire short echo time [TE = 46ms, TR = 3.2s] LASER localized proton MRS 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]. Spectra were lineshape corrected (QUECC [3]) prior to quantification. Metabolite levels were measured using semi-automated software (fitMAN) that incorporated prior knowledge of 19 metabolite lineshapes [3]. Figure 2 shows an example spectrum with the fitted result superimposed. Absolute concentrations were calculated by referencing to the internal water signal and corrected for tissue partial volume (gray matter, white matter, and CSF) calculated from T_1-weighted images using Statistical Parametric Mapping software (SPM5) [4]. Metabolite levels were compared between groups (NEC, MCI and AD) using a 1-way ANOVA and within groups using a General Linear Model with Repeated Measures approach. Significance was set at 0.05.

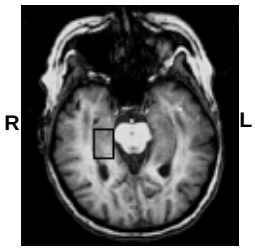

Figure 1: Transverse oblique slice with voxel on right hippocampus [T1-weighted 3D FLASH, FOV = 24 cm, slice thickness = 2.5 mm, TI/TR/TE = 500 / 9.5 / 5 ms]

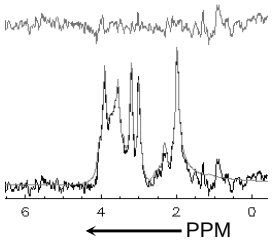

Figure 2: Post-processed spectrum shown with superimposed fit and residual signal (top)

Results and Discussion: A significant effect ($p < 0.05$) was found between groups for baseline NAA, Glu, Glu/mI and NAA/Cr measures. Absolute baseline measurements (mean ± SEM) are shown in Figure 3.There was a trend to lower NAA in MCI subjects compared to NEC ($p < 0.1$) and NAA was significantly lower in AD patients ($p < 0.05$). Glutamate was significantly lower ($p < 0.05$) in both MCI and AD subjects compared to NEC. Compared to NEC, there was a trend to lower Glu/mI in MCI subjects ($p < 0.1$) and AD subjects ($p < 0.01$). Glu/mI levels also tended to be lower in the AD group compared to MCI subjects ($p < 0.1$). Baseline MMSE scores showed a significant Pearson correlation with baseline NAA ($p < 0.01$, $r = 0.395$), Glu ($p < 0.01$, $r = 0.491$) as well as the change in Glu levels ($p < 0.05$, $r = 0.475$). A 1-way ANOVA on the change in metabolite levels or MMSE scores over 1-year showed no significant difference in the rate of change between groups. Within group, only mI and Cr were found to significantly increase ($p < 0.05$) in NEC over 1-year. The significant differences observed between groups at baseline were maintained for NAA and Glu at 1-year (Figure 4).

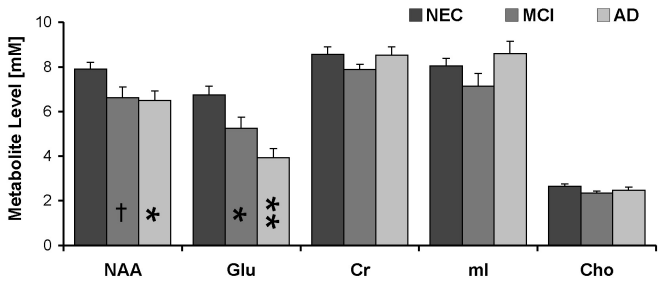

Figure 3: Cross-sectional metabolite results at baseline

† = $p < 0.1$ * = $p < 0.05$ ** = $p < 0.01$

Increased SNR at 4T improved metabolite quantification accuracy and permitted the use of a small hippocampal voxel. 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 AD subjects.

Conclusion: Glu was significantly reduced in both MCI and AD populations, and may be sensitive to early Alzheimer disease processes.

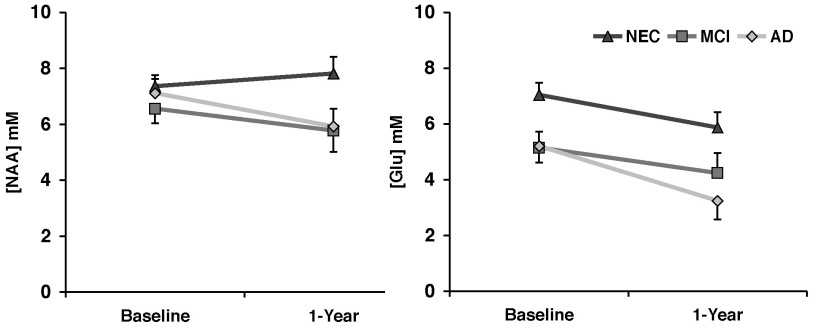

Figure 4: NAA and Glu levels over 1-year in a subset of subjects. Error bars are SEM.

References:

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