# LONGITUDINAL 4T MAGNETIC RESONANCE SPECTROSCOPY OF THE HIPPOCAMPUS IN ALZHEIMER DISEASE PATIENTS ON GALANTAMINE

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**Background**: Alzheimer Disease (AD) is the most common form of dementia and is a progressive, degenerative disease of the brain resulting in cognitive and memory impairments [1]. One of the current methods of diagnosing and tracking AD is the Mini-Mental Status Exam (MMSE), which involves neuropsychological assessments of cognitive performance. Metabolite level changes within the hippocampus have been demonstrated in AD [2], and it has been postulated that these levels can be used to detect the early onset of AD and monitor treatment response. Galantamine (Gal), a cholinesterase inhibitor, is in clinical use for its ability to inhibit the breakdown of acetylcholine, an important neurotransmitter associated with memory [3]. The purpose of this study was to determine if the differences in three particular metabolites, glutamate (Glu), *N*-acetyl aspartate (NAA), and creatine (Cr), are significant between baseline and 4-month repeat measurements within the hippocampus of AD patients taking Gal, and if these differences correlate with MMSE scores.

**Method**: Proton magnetic resonance spectroscopy ($^1$H MRS) was used to measure the Glu, NAA, and Cr levels within the right hippocampus, outlined in Figure 1, of ten AD patients before (baseline) and 4 months after (4-month repeat) beginning an 8 to 16 mg daily dose of Gal. A 4 Tesla Varian/Siemens MRI scanner was used to acquire short echo time (TE = 46ms, TR = 3.2ms) LASER localized proton magnetic resonance spectra. Full, macromolecule, and water spectra were acquired from a 3.5 ± 0.6 ml voxel positioned mostly within the right hippocampus (rectangle in Figure 1). The spectra were line shape corrected (QUECC[4]), and the macromolecule spectrum subtracted from the full spectrum [5] prior to quantification. The resultant spectrum was fitted in the time domain (fitMAN software) incorporating 19 metabolite basis functions. The amounts of Glu, NAA, and Cr were determined from the area of their corresponding spectral peaks, shown in Figure 2, and then the ratios of Glu/NAA and Glu/Cr were calculated. The absolute metabolite concentrations were calculated by referencing to the internal water signal and correcting for tissue partial volumes. Statistical Parametric Mapping was used to calculate the partial volumes of gray matter, white matter, and cerebral spinal fluid within the measurement voxel [6] from $T_1$-weighted images (Figure 1). Paired two-tailed t-tests were used to compare baseline and 4-month absolute Glu, NAA, and Cr concentrations, the ratios of Glu/NAA and Glu/Cr, and MMSE scores.

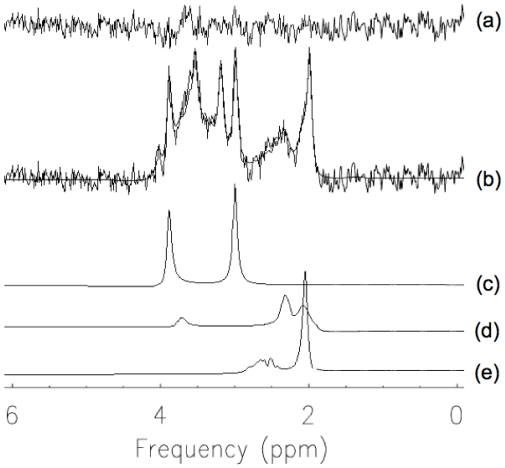


Figure 2: Post-processed pure metabolite spectrum with superimposed fit (b), residual (a), and basis curves for Cr (c), Glu (d), and NAA (e)

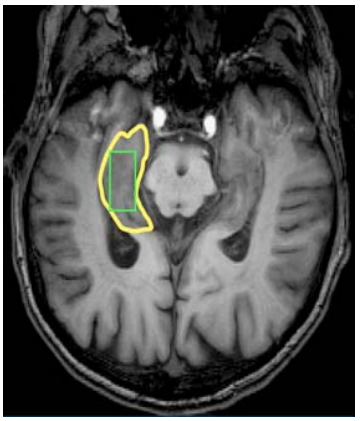

Figure 1: Transverse oblique slice with the hippocampus outlined and a rectangular measurement voxel ($T_1$-weighted #D FLASH, FOV = 24cm, slice thickness = 2.5 mm, TI/TR/TE = 500/9.5/5 ms)

**Results and Discussion**: A significant increase was found in the Glu/NAA ratio ($p < 0.05$) between baseline and 4-month repeat measurements in the ten AD patients, as shown in Figure 3. However, there were no significant changes in the ratio of Glu/Cr or the absolute Glu, NAA, or Cr concentrations over 4 months. Furthermore, the average MMSE baseline score was 25.6 and did not significantly change at 4 months. Glu is a major excitatory neurotransmitter, which is known to be involved in AD pathogenesis [7] and decreases in progressive AD. NAA is known as a marker of neuronal viability, and a reduction of NAA in the hippocampus of patients with AD has been reported [2]. Cr remains fairly constant with progressive AD, so its concentration is typically used as a relative control value [8]. Although the average MMSE scores did not change in this study, it has been reported that Gal improves cognitive functions in AD patients by increasing the activity of the cholinergic system [9], and could explain the increase in Glu/NAA.

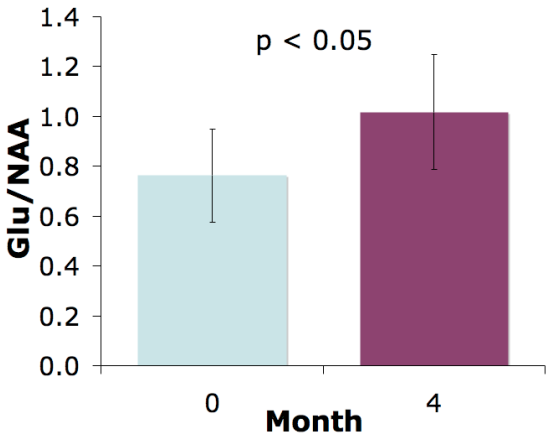


Figure 3: Baseline and 4-month repeat Glu/NAA ratios

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