Correlation between cerebral glutathione, dietary intake and cognitive function in aging and Alzheimer's disease

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TARGET AUDIENCE: Clinicians and scientists who are interested in brain health in aging and Alzheimer's disease.

INTRODUCTION: Increasing evidence suggests the important role of cerebral antioxidant defenses in aging and neurodegeneration. Glutathione (GSH) is a critical antioxidant that provides neuroprotection against oxidative stress [1]. We hypothezed that lower GSH concentrations might a) indicate increased susceptibility to oxidative damage leading to functional and cognitive decline in aging and Alzheimer's disease (AD) and b) be related to life style choices such as diet. The objective of this study was to measure the association between cerebral GSH concentration and cognitive function, as well as the possible influence of dietary intake on the brain GSH levels in young and older adults and AD patients using advanced ^{1}H multiple-quantum filtered chemical shift imaging (MQ CSI) of GSH [2].

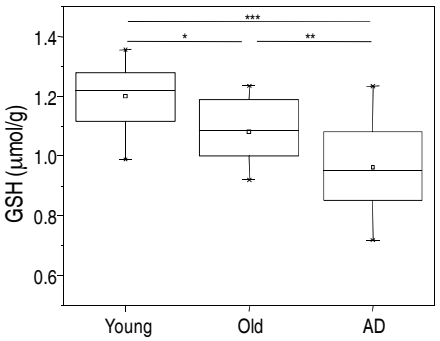

Fig. 1. *In vivo* measurements of brain GSH of AD subjects (AD: n=13, CDR=1-2) and age/sex-matched nondemented controls (Old: n=13, CDR=0) and healthy young subjects (Young: n = 13) using the GSH CSI technique. (*: $p < 0.01$; **: $p = 0.02$; ***: $p < 0.001$)

METHODS: Thirty nine subjects participated in the study: 13 young adults (mean age ± SD = 26 ± 6 yrs), 13 healthy older adults (73±5 yrs, Clinical Dementia Rating (CDR) = 0) and 13 AD patients (73±5 yrs, CDR = 1-2). All MR scans were performed on a Siemens Skyra 3 T MR system. The doubly selective MQ CSI of GSH uses a double-band frequency selective 180° pulse during the MQ preparation period for spectral selection of GSH signals at 4.56 and 2.95 ppm [2]. The MQ CSI parameters were TE/TR = 115/1500 ms, 8 × 8 phase encoding steps, FOV = 20 cm × 20 cm, matrix = 8 x 8, and slice thickness = 3 cm, and nominal voxel size = 2.5 × 2.5 × 3 cm^3 without zero-filling. An axial CSI slice was positioned to cover the area above the corpus callosum across the frontal to parietal regions [2,3]. GSH concentration was determined from the regions of interest ("mainly frontal", "mainly parietal", and "fronto-parietal") using the simultaneously measured creatine (Cr) signal as an internal concentration reference [4]. Each subject's dietary intake was recorded using the Dietary History Questionnaire II to characterize subject's usual eating habits. The neuropsychological testing battery includes memory, language, working memory, executive function, verbal fluency, and visuospatial ability.

RESULTS AND DISCUSSION: The mean GSH concentration in the aging brain was 10% lower ($p < 0.01$) than in the young controls. GSH concentrations in AD patients were 11% lower compared with their age/sex-matched controls ($p < 0.02$) (Fig. 1). Among the neuropsychological tests conducted, 11 out of 16 tests showed a correlation ($p < 0.05$) with GSH. For example, Digit Span Backward (DSB) scores were correlated ($p < 0.0001$) with GSH levels in the parietal region in AD patients and age/sex-matched non-demented controls (Fig. 2). In contrast, DSB did not show significant correlation with GSH in the frontal region, indicating the region specific oxidative damage. Our finding is consistent with cognitive impairment and the presence of systemic oxidative stress in AD [5]. Preliminary analysis showed AD patients have lower percent total calories from protein, dietary beta-carotene and vitamin K. Vitamin A was marginally lower in the AD group. No difference was found in phytochemicals and amino acids. Analysis of cerebral GSH and nutrient intake showed that GSH concentrations were positively correlated with dairy servings ($r = 0.31$, $p = 0.04$), which is consistent with our recent findings in older adults [6]. Supplemental vitamin C intake showed a marginal positive relationship with cerebral GSH concentrations ($r = 0.28$, $p = 0.06$).

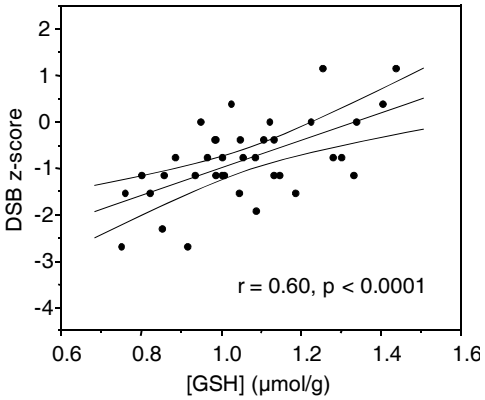

Fig. 2 Correlation between GSH and attention/executive function in aging and AD. Raw scores of Digit Span Backward (DSB) test were converted to z-scores using means ± SD.

REFERENCES: 1. Behl. *Biol Chem*. **383**:521 (2002). 2. Choi & Lee. *NMR Biomed* **26**:28 (2012). 3. Choi et al. *Multi Scler* **17**:289 (2011). 4. Choi et al. *MRM* **51**:1115 (2004). 5. Schrag et al. *Neurobiol Dis*. **59**:100 (2013). 6. Choi et al. *Am J Clin Nutr* (in press). This work is partly supported by American Health Assistance Foundation and the Hoglund Family Foundation.