Lower glutathione (GSH) concentration in the posterior cingulate cortex of healthy human elders measured at 7 T

Malgorzata Marjanska[1] and Melissa Terpstra[1]

[1]*Center for Magnetic Resonance Research and Department of Radiology, University of Minnesota, Minneapolis, MN, United States*

Target Audience: aging and dementia researchers, geriatricians, and MR spectroscopists

Purpose: Oxidative stress occurs at an early stage of age related cognitive decline[1]. Ascorbate (Asc, vitamin C) and glutathione (GSH) are key contributors to the antioxidant network. Although lower ^{1}H MRS GSH signal has been measured in the occipital cortex (OCC) of an elder cohort[2] that finding could have been confounded by differing transverse relaxation (T_2)[3]. The purpose of this work was to utilize short echo time (T_E) ^{1}H MRS to overcome confounding by age associated difference in T_2 to quantify GSH concentration ($[GSH]_{brain}$) in the aging brain. Innovation in focusing multiple transmitters to optimize power is utilized to scan a brain region that is more pertinent to the pathology of Alzheimer's disease (AD), i.e., the posterior cingulate cortex (PCC). Finally, we utilize a uniquely high field to facilitate Asc quantification. Our hypotheses were that GSH signal differences in the OCC would be less pronounced than when measured at long T_E and that age associated GSH differences would be more pronounced in the PCC than the OCC.

Methods: Normal volunteers, 7 young (age 18-22, 2 subjects scanned 3 times) and 5 elderly (age 70+, 2 subjects scanned 3 times), were studied using a 7-T, 90-cm horizontal bore magnet equipped with a Siemens console and body gradients. A home-built 16-element transmit-receive transmission line head array[4] was used and transmit phase of each channel was optimized via individual 1 kW CPC amplifiers[5].

In vivo ^{1}H NMR spectra were acquired from two voxels positioned in the OCC (volume of interest, VOI = 8 cm^3) and the PCC (VOI = 8 cm^3) using a STEAM sequence with VAPOR water suppression and outer volume suppression[6] (T_R = 5 s, T_E = 8 ms, NS = 64 for OCC, 128 for PCC). First- and second-order shims were adjusted using FASTMAP[7]. Metabolite concentrations were quantified using LCModel[8] with a simulated basis set (18 metabolites and experimental macromolecule spectra) and 8 mM total creatine as internal reference.

Results: Figure 1 shows the quality of the data obtained in this study and VOI placement. In the OCC, $[Asc]_{brain}$ and $[GSH]_{brain}$ were the same for young and elderly cohorts (Table 1). In the PCC, $[Asc]_{brain}$ was the same and $[GSH]_{brain}$ was significantly lower for elderly than young subjects (Table 1). Figure 2 shows $[GSH]_{brain}$ in the PCC for all subjects and all scans.

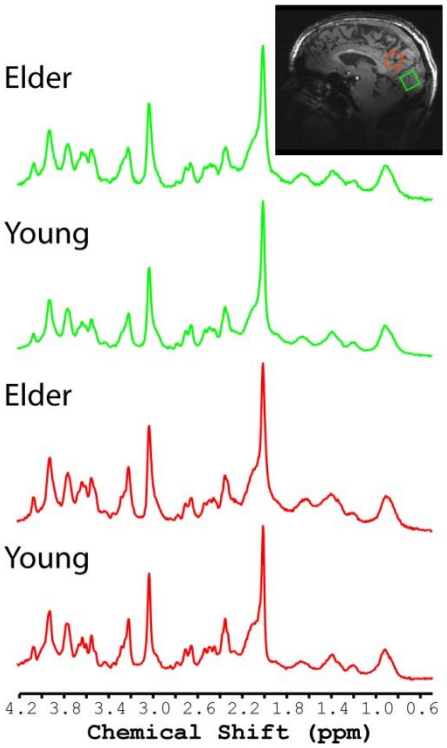

Figure 1. Representative spectra from one young and one elderly subject measured from OCC (green) and PCC (red).

Discussion: Constancy in $[Asc]_{brain}$ is consistent with expected homeostatic mechanisms[9]. A decrease in $[GSH]_{brain}$ with increasing age is consistent with data from animal models, although past studies were not localized to the OCC or PCC[10]. The lower GSH signal that was previously detected in OCC of elder subjects could have arisen from the T_2 shortening which was subsequently characterized.

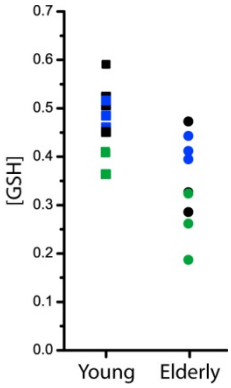

Figure 2. $[GSH]_{brain}$ in PCC of young and elderly subjects. The two retest subjects are designated in blue and green.

Conclusion: That [GSH] is lower in the PCC of elder subjects is an important advancement of knowledge, especially in absence of such a difference in the OCC because the PCC is highly impacted by AD while the OCC is not[11]. The constancy of [GSH] in the OCC could be utilized as an internal reference, leading toward discovery of a biomarker.

Table 1. Mean ± SD $[Asc]_{brain}$ and $[GSH]_{brain}$ in the two brain VOIs.

VOI	Metabolite	Young	Elderly	*p*
OCC	Asc	1.23 ± 0.15	1.38 ± 0.22	0.12
	GSH	0.48 ± 0.10	0.45 ± 0.15	0.56
PCC	Asc	1.13 ± 0.24	1.28 ± 0.20	0.15
	GSH	0.48 ± 0.06	0.35 ± 0.09	**0.003**

References: 1. MF Beal *et al.* Ann Neurol 2005, **2.** U Emir *et al.* NMR Biomed 2011, **3.** M Marjanska *et al.* PLoS One 2013, **4.** G Adriany *et al.* MRM 2008, **5.** GJ Metzger *et al.* MRM 2008, **6.** I Tkac *et al.* MRM 2001, **7.** R Gruetter, I Tkac MRM 2000, **8.** SW Provencher MRM 1993, **9.** FE Harrison, JM May Biol Med 2009, **10.** E Head *et al.* J Neurochem 2002, **11.** K Kantarci *et al.* Brit J Radiol 2007.

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