In-vivo 3T ^{1}H magnetic resonance spectroscopy of the brain reveals elevated *scyllo*-inositol in patients with mild Alzheimer's disease

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Introduction: ^{1}H MRS studies of patients with probable Alzheimer's disease (AD) and mild cognitive impairment (MCI) have demonstrated metabolic abnormalities compared to healthy older adults in reduced *N*-acetylaspartate (NAA) and elevated *myo*-inositol (mI) in the posterior cortical and temporal regions[1]. *Scyllo*-inositol (sI), a product of mI metabolism, may similarly be of interest in AD and MCI, although to date we are aware of no studies examining the sI peak in AD. Elevated sI levels have been reported in the normal aging human brain [2], and abnormal sI is reported in patients with different neuropathologies, including mitochondrial enzyme deficiency [3], certain brain tumors [4], HIV [5], hepatic encephalopathy [6], and chronic alcoholism [7]. This study examined 3T ^{1}H MRS of sI in the posterior cingulate gyrus of patients with AD and MCI relative to healthy older controls, as the improved spectral quality of 3T allows for more reliable sI measurement than is possible at 1.5T.

Method: We performed ^{1}H MRS on a Philips Intera 3T MRS scanner in 12 patients with mild AD, 21 patients with MCI, and 20 healthy older adult controls. Participants with a history of diabetes, alcoholism, or liver disease were excluded. Spectra were acquired using PRESS sequences with 1024 samples, spectral bandwidth of 2000 Hz, and 128 acquisitions with TR/TE = 2000/32 in the posterior cingulate gyrus [1]. The cingulate VOI was placed in reference to T1 saggital and T2 coronal scans (see Figure 1). All spectra were measured by one spectroscopist. Following ^{1}H MRS data collection, a time domain fitting analysis that utilizes complete prior *in vitro* knowledge on all metabolites was performed to generate metabolite ratios [8]. This procedure derived metabolic ratios of NAA, mI, and sI in reference to Cr. Group differences in NAA/Cr, mI/Cr and sI/Cr were compared using One-way ANOVA with LSD post-hoc. sI/Cr ratios were correlated with other MRS ratios and with the Mini Mental Status Examination (MMSE)[9] as an index of dementia severity.

Results: The sI peak (see Figure 2) was identified at 3.342 parts per million (ppm), referenced to the NAA-acetyl signal set at 2.008 ppm. Representative spectra from an AD patient (Figure 2) and a normal control (Figure 3) are shown. The ANOVA comparing groups on sI/Cr was significant: $F(2, 48) = 3.351$, $p < 0.05$ (see Table). Post hoc comparisons revealed higher sI/Cr for AD patients compared to controls ($p < 0.05$). MCI patients exhibited a trend towards elevated sI/Cr compared to controls ($p = 0.061$) but were not different from AD patients. The ANOVAs for NAA/Cr and mI/Cr were not significant, although post-hoc analyses revealed that AD patients showed higher mI/Cr compared to controls ($p < 0.05$). sI/Cr and mI/Cr were not significantly correlated ($r = -0.100$, $p = 0.489$). Last, sI/Cr was negatively correlated with MMSE scores ($r = -0.319$, $p < 0.05$).

Conclusion: We report an elevation of sI/Cr in the posterior cingulate of mild AD patients compared to healthy older controls. As previously documented, there was also elevation of mI/Cr in the mild AD patients[1]. This is the first documented evidence that mild AD patients show elevations in both sI and mI relative to healthy controls. However, sI and mI were not correlated in our sample, suggesting that these metabolites might reflect different aspects of abnormal brain metabolism in AD. sI also showed a trend towards elevation in MCI and thus might serve as an early marker of AD in this patient group. Lastly, sI was negatively associated with overall cognitive severity, suggesting that sI ratios could be useful in tracking the progression of AD over time. Further research with sI in AD appears warranted.

References:

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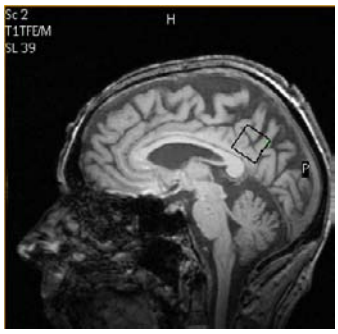

Figure 1

Table: MRS ratios across controls, MCI patients, and mild AD patients

	Controls (n = 20) X (SD)	*MCI Pts (n = 21) X (SD)*	*Mild AD Pts (n =12) X (SD)*	*P Value*
sI/Cr	0.0512 (0.0305)	0.0732 (0.0419)	0.0850 (0.0362)	0.043
mI/Cr	0.9260 (0.1332)	1.0227 (0.18927)	1.0742 (0.2957)	0.111
NAA/Cr	1.6228 (0.1548)	1.5402 (0.2963)	1.5119 (0.2390)	0.376

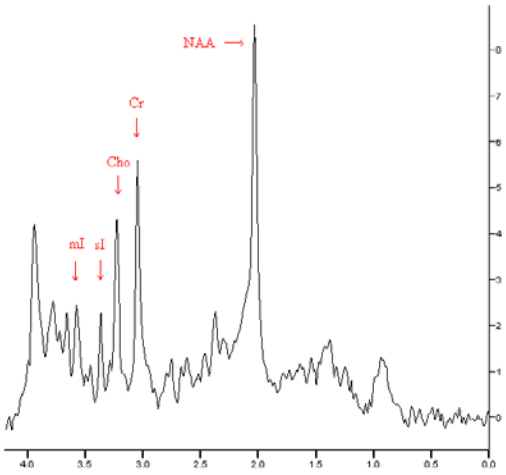

Figure 2

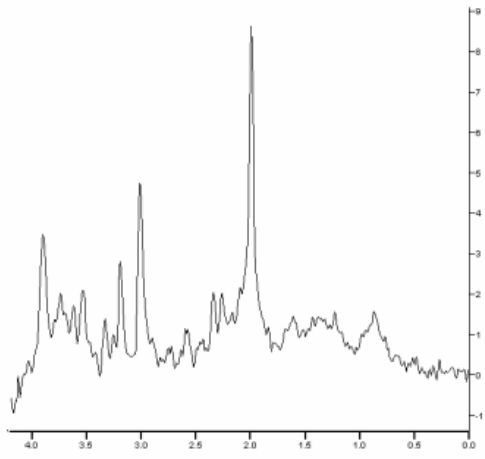

Figure 3