^{1}H MRS in mild cognitive impairment: what are we measuring, and how good are we at it?

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Introduction: Diagnosis of mild cognitive impairment amnestic type (MCI-A), a risk state for developing dementia of the Alzheimer type, is only possible after symptoms of memory impairment are present, and relies on lengthy clinical evaluations, following the criteria defined by Petersen and the Mayo Alzheimer Disease Center [1]. Means to improve diagnosis capability and reduce diagnosis time are actively sought for, in an attempt to reduce disease burden on the society. The increases in myo-inositol (mI) and its ratio to N-acetyl aspartate (NAA), evidenced early in the disease process by short ^{1}H MRS exams, offer a promising avenue towards achieving this goal. Owing, in part, to the limited *in vivo* mI measurement repeatability, it was never clear, however, whether such ^{1}H MRS measurements represent independent measures of disease, further aiding diagnosis, or whether they are correlated to standard neuropsychological (NP) test results. The current report first validates the better capability of a previously suggested [2], alternative pulse sequence (Carr-Purcell PRESS or CPRESS) to separate MCI patients from elderly normal controls (NC's) based on the mI concentration and mI/NAA concentration ratio. It then ranks the performance of individual NP/MRS measures and computes discriminant functions that best separate the two cohorts of subjects. Last, it investigates the correlations between ^{1}H MRS measures and the NP test results.

Methods: Twenty MCI subjects and twenty age-matched NC's were included in the study. Comprehensive NP examinations probing language, verbal memory, visual memory, visuoconstruction, executive skills and visual motor integration were performed in all subjects, resulting in a total of 28 normalized NP classifiers per subject. All subjects were also scanned on a GE, 3T scanner. Spectra from one voxel (2cm x2cm x4cm), situated in the posterior cingulate gyrus (PCG)--a region well known for its involvement in MCI [3]--were acquired using a TE=35ms PRESS pulse sequence and a CPRESS sequence and quantified using LCModel (Figure 1). Statistical data analysis, aimed at identifying best approach for discriminating NC's from MCI subjects and understanding the correlation between various NP and MRS disease measures, was performed using SPSS 19.

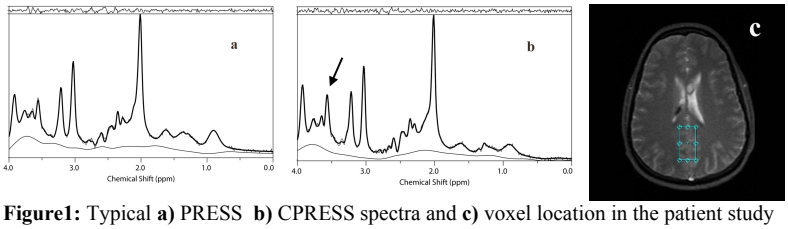

Figure1: Typical **a)** PRESS **b)** CPRESS spectra and **c)** voxel location in the patient study

Results: Consistent with previous literature reports [4], increases in mI and mI/NAA (and constant NAA) were shown in MCI patients with both MRS acquisitions. The best CPRESS measure (mI/NAA) significantly outperformed the best PRESS measure (also mI/NAA). The single best measure for identifying MCI subjects was found to be the Hopkins Verbal Learning Test- Delayed Recall normalized T-score (HVLT-DRS)), followed by the Clinical Dementia Rating Sum of Boxes (CDR-SOB) and CDR scores. The areas under the ROC curves (AUC's) for these tests, for the best MRS measures and a number of other NP tests, including the Wexler Adult Intelligence Scale (3rd edition) (Block design scaled score (WAIB-SS)), the Wechsler Memory Scale Revised Visual Reproduction Immediate Recall Scaled Score (VRII SS), MMSE and the Trail Making Test (part A) Scaled Score (TMT SS) are presented in Table 1. Stepwise discriminant analysis indicated that the discriminant function best separating NC's from MCI patients was construed from HVLT-DRS, CDR-SOB and CPRESS mI/NAA, allowing 92.3% of the subjects to be correctly classified. Interestingly, if CPRESS mI/NAA was withheld as factors among the 2 MRS and 28 NP measures, the best discriminant function consisted of solely CDR-SOB and HVLT-DRS scores, allowing only 89.7% of the subjects to be correctly classified. The statistical correlations between MRS results, CDR-SOB and the NP measures with the strongest correlations to the MRS results are shown in Table 2. First, note that stronger correlations between the NP scores and CPRESS data exist than between NP scores and PRESS data, underlying the fact that CPRESS may provide more precise overall mI measurements. Analysis of the known brain regions involved in the NP tasks is consistent with the correlation seen in Table 2. For example, the intersection of brain anatomical regions involved in verbal memory tasks (probed here by HVLT tests) (hippocampus and PCG [5]), and in visuoconstruction tasks (probed here by WAISB tests) (bilateral occipital-parietal-posterior temporal visual association cortices, the PCG, and a number of other brain regions- not including the hippocampus [6]) is exactly the PCG, probed by our MRS exam. Remarkably, though, the correlation between the increased mI (and constant NAA) concentrations seen the MRS exam (thought to reflect mostly glial cell health [7])- and the decreased performance of MCI subjects in NP tests (reflective of neuronal health) indicate a deep interconnection between neuronal and glial functions in this brain region.

Test	AUC
HVLT DRS	0.96
CDR SOB	0.89
CDR	0.81
VRII SS	0.81
MMSE	0.78
WAISB SS	0.75
TMT SS	0.71
CPRESS mI/NAA	0.8
PRESS mI/NAA	0.67

Table 1: *Area under the ROC curve for various NP and MRS tests.*

		CPRESS mI/NAA	PRESS mI/NAA	HVLT DRS	TMT SS	WAISB SS	CDR SOB
CPRESS mI/NAA	Pearson Corr.	1	.865	-.448	-.509	-.538	.249
	Sig. (2-tailed)		.000	.004	.002	.000	.127
PRESS mI/NAA	Pearson Corr.	.865	1	-.292	-.450	-.394	.184
	Sig. (2-tailed)	.000		.071	.007	.013	.263
HVLT DRS	Pearson Corr.	-.448	-.292	1	.552	.309	-.503
	Sig. (2-tailed)	.004	.071		.001	.056	.001
TMT SS	Pearson Corr.	-.509	-.450	.552	1	.412	-.435
	Sig. (2-tailed)	.002	.007	.001		.014	.009
WAISB SS	Pearson Corr.	-.538	-.394	.309	.412	1	-.326
	Sig. (2-tailed)	.000	.013	.056	.014		.043
CDR SOB	Pearson Corr.	.249	.184	-.503	-.435	-.326	1
	Sig. (2-tailed)	.127	.263	.001	.009	.043	

Table 2: Pearson correlation coefficients and p values between various NP and MRS measures.

Discussion and Conclusions: A small study was presented, aimed at understanding the relationship between brain function, as illustrated by performance on NP tests, and ^{1}H MRS data acquired from the PCG of NC and MCI subjects. Our results indicate that the MRS data (and in particular the CPRESS mI/NAA ratio) is a strong correlate of verbal memory (HVLT), visuoconstruction performance (WAISB) and visual motor integration (TMT). CPRESS mI/NAA was also shown to contribute to the discriminant function separating NC's from MCI subjects ahead of a large number of NP tests (probing, e.g. language, visual memory, or visual-motor integration), improving the NC/MCI separation capability of NP tests alone. The simplicity of the MRS acquisition may render it an essential part of a reduced future arsenal to diagnose and monitor MCI.

References: **1.** Petersen et al, Arch Neurol 1999;56(3):303; **2.** Hancu, NMR Biomed 2009; 22: 426; **3.** Kantarci et al, Neurology 2000;55(2):210; **4.** Kantarci et al, J Int Neuropsych Soc 2002; 8:934; **5.** Heun et al, Dement Geriatr Cogn Disord. 2006;22(2):165; **6.** Machulda et al, J Int Neuropsychol Soc. 2009 15(3): 372; **7.** Govindaraju et al, NMR Biomed. 2000 May;13(3):129.