On using optimized MRS acquisitions for improved mild cognitive impairment diagnosis

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Introduction

Mild cognitive impairment (MCI) is a risk state for developing dementia of the Alzheimer type. Current diagnosis, only possible after symptoms of memory impairment are present, is based on lengthy clinical evaluations, following the criteria defined by Petersen and the Mayo Alzheimer Disease Center [1]. One of the alternative methods proposed in the past for MCI diagnosis is proton magnetic resonance spectroscopy (^{1}H MRS). As normal subjects progress towards MCI, an elevation in myo-inositol (mI) appears in the spectra of MCI subjects. Further progression towards AD results in a decline in N-acetyl-aspartate levels. Accurate and repeatable mI measurements may offer a simple means of diagnosing, monitoring progression, or treatment response in MCI patients. Unfortunately, due to the complicated spectral pattern of mI, and in spite of its relatively high concentration in normal brain (~6mM), such repeatable measurements are difficult to obtain. Recently, a pulse sequence (Carr-Purcell PRESS or CPRESS) was identified through simulations [2] to produce more repeatable mI measurements than a standard, short TE PRESS sequence (typically used in a clinical setting for mI quantification [3]). At the same time, comparable performance is expected for CPRESS and TE=35ms PRESS for NAA measurements [4]. The current report further validates the prior simulation results *in vivo*, in a cohort of MCI patients and elderly normal controls (NC's), and discusses the impact that more repeatable mI concentration measurements may have in diagnosing MCI or monitoring disease evolution or treatment.

Methods

Five MCI subjects and five age-matched NC's were scanned on a GE, 3T scanner. Spectra from one voxel (2cmx2cmx4cm) were acquired using both a TE=35ms PRESS pulse sequence and a CPRESS sequence. The voxel was placed in the posterior cingulate gyrus of each subject, a region well known for its involvement in MCI [3]. The scans were repeated 3 times in a day, with the subject removed from the scanner between the scanning sessions. Intra-volunteer, inter-session coefficients of variation expressed as a percentage of the mean (%CV's) were computed for these scans. Seven more normal controls and seven more MCI patients were scanned using the same protocol. These additional subjects were scanned once with both sequences in a single scanning session.

Results

Table 1 displays the repeatability measures (% CV's and Cramer Rao Lower Bounds (CRLB's)) for mI concentration measurements for the 5 NC's and 5 MCI subjects scanned 3 times in a day. Note that both the CRLB's and the %CV's are smaller for CPRESS than for PRESS, confirming the improved mI measurement performance of CPRESS. Figure 1 displays the mI concentrations and the mI/NAA ratio for all 12 normal subjects (blue symbols) and 12 MCI patients (red symbols) scanned. While all 4 graphs show increases on the order of 18% in the mI concentration and mI/NAA ratios in MCI patients, confirming previous reports of no significant decrease in the NAA concentration in MCI, significant within-class (normal or MCI) decreases in variability are seen when moving from PRESS to CPRESS. The average within-class variability for mI measurements decreases from 24% (PRESS) to 17% (CPRESS), and from 18% (PRESS) to 12% (CPRESS) for mI/NAA. As a consequence, significantly higher separation power exists between the NC's and MCI subjects. While shifting from PRESS to CPRESS, p values for one-way ANOVA decrease from 0.11 to 0.028 when measuring mI levels, and from 0.029 to 0.002 when measuring mI/NAA levels. The areas under the ROC curves (displayed in Figure 2) using mI/NAA as a disease marker increases from 0.76 (PRESS) to 0.854 (CPRESS), confirming the better ability of CPRESS in separating normal controls from MCI patients.

	PRESS	CPRESS
CRLB (NC)	8.6	5.5
CRLB (MCI)	8.8	4.8
%CV's (NC)	7.8	5.6
%CV's (MCI)	10.2	6.8

Table 1: CRLB's and % CV's for mI concentration for NC's and MCI (CPRESS and PRESS data)

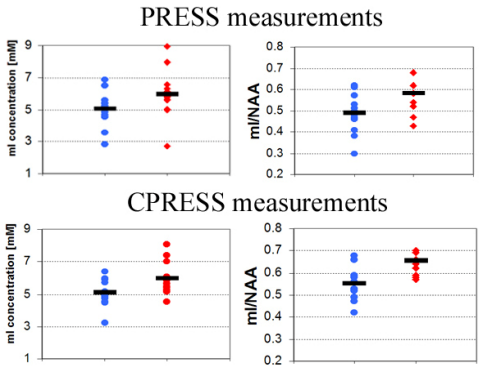

Figure 1: PRESS and CPRESS mI and mI/NAA measurements for NC's (blue) and MCI's (red)

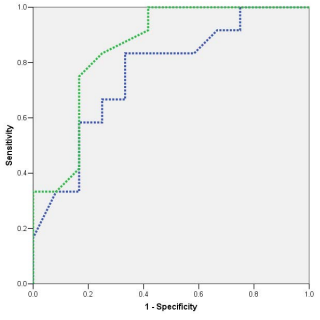

Figure 2: ROC curves for mI/NAA using CPRESS (green) and PRESS (blue)

Discussion and conclusions

A small scale *in vivo* study is presented, comparing the ability of two pulse sequences (CPRESS and TE=35ms PRESS) to separate normal controls from MCI subjects based on their mI and mI/NAA levels. It is demonstrated that the increased intra-volunteer repeatability of mI measurements using CPRESS translates into decreased intra-class variability, and improved separation between NC's and MCI subjects. Although overlap between the two classes of subjects still exists, the choice of a better pulse sequence can dramatically decrease the number of subjects enrolled in a clinical trial that would, e.g. monitor the effect of a treatment in MCI subjects. For example, assuming 10% change in the mI levels due to treatment, and 5% measurement variability for CPRESS (compared with 8% for PRESS), a decrease in the number of subjects to be enrolled in each of the treated and untreated groups from 18 to 8 would be obtained, should a short TE PRESS sequence be replaced with CPRESS.

References

1. Petersen et al, Arch Neurol 1999;56(3):303-308; **2.** Hancu, NMR Biomed 2009; 22: 426-435; **3.** Kantarci et al, Neurology 2000;55(2):210-217; **4.** Hancu, J Magn Res Imaging 2009; 30:1155-1162.

Support: NIH R211NS054303