^{1}H MR Spectroscopy of the Cingulate Gyrus Reveals Evidence for Unique Neurometabolic Profiles for Amnestic and Non-Amnestic Mild Cognitive Impairment

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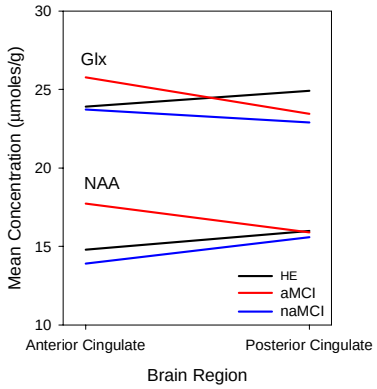
Introduction: Amnestic Mild Cognitive Impairment (aMCI) is widely believed to be a prodromal stage of Alzheimer's disease (AD) and thus a potential intervention point for treatment and testing of pharmacotherapeutic agents for AD (1). In recent years, it has been suggested that the Petersen's criteria for MCI(2), and its memory requirement, is too narrowly focused and may not account for non-demented, but cognitively compromised individuals without a memory complaint, i.e. non-amnestic MCI (naMCI) (3). Although the conversion rate to AD is lower in naMCI than in aMCI, the population of naMCI is substantially larger than that of aMCI, such that the total number of convertors to AD may be the same for both groups (4). Based on neuropsychological tests alone, neither clinical diagnosis of aMCI or naMCI is very stable over time, nor are their clinical outcomes assured. This lack of specificity indicates that these diagnoses identify risk rather than a true neuropathology. Classification of these potential prodromal states of dementia might be improved by biomarkers. In this work, we employ ^{1}H magnetic resonance spectroscopy, ^{1}H-MRS, to compare and establish the metabolic profiles of amnestic and non-amnestic MCI in the cingulate gyrus

Methods: Participants were 10 patients fulfilling Petersen's criteria for aMCI (70.6±5.9 yrs), 9 patients classified as naMCI (73.7±5.2 yrs), and 8 healthy elderly (HE, 66.3±7.6 yrs). Ages were not statistically different for the three groups. In addition to the cognitive tests for neuropsychological classification, each participant underwent a spectroscopy examination (1.5 T Siemens Magnetom Sonata MRI system) that included a STEAM experiment (VOI~6cm^3, TE/TM/TR = 10/10/5000 ms, 112 excitations, 2500Hz spectral width, and 819.2 ms acquisition window), a water reference for phase correction, and a progressive TR T_2 acquisition for compartmental analysis and absolute quantitation. In each participant, ^{1}H-MRS data were collected along the midline of the posterior cingulate gyrus and left of the midline in the anterior cingulate gyrus. QUEST was used to quantify the metabolite resonances (7). Absolute concentrations are reported in micromoles per gram of tissue water. Differences in absolute concentrations and differences in metabolite ratios were analyzed using a three-way ANOVA with Holm-Sidak planned comparisons. The three factors in the analysis were: diagnoses (HE, aMCI, naMCI), brain region (anterior, posterior), and metabolites (creatine (Cr), choline (Cho), myo-inositol (mI), N-acetyl-aspartate (NAA), and glutamate+glutamine (Glx)) or metabolite ratios Cho/Cr, mI/Cr, NAA/Cr, Glx/Cr, and NAA/mI.

Results and Discussion: Using absolute concentrations, significant global effects for metabolites ($p<0.001$) and diagnosis ($p = 0.034$) were detected. In planned comparisons, absolute concentrations of Glx and NAA, as well as the mI/Cr ratio, yielded complete stratification of the three groups, thus providing evidence for distinct neuropathological sub-types of MCI.



Amnestic MCI: Interestingly, in the posterior cingulate of the aMCI patients, decreased NAA/Cr, NAA/mI, and Glx/Cr, and increased mI/Cr relative to the HE group, is in agreement with previous literature (5,6). However, the analysis in absolute concentrations reveals a much more complex picture of aMCI. For instance, at short TEs NAA/Cr is reportedly only mildly lower in aMCI than in HE in the posterior cingulate, with many groups showing no significant effect. Our data shows that while NAA may be slightly lower, Cr levels are severely elevated and thus reduced NAA/Cr is driven by increased Cr. A similar analysis holds for reduced NAA/mI, the reduction in the ratio is driven primarily by increased mI. In comparison, in the anterior cingulate, in addition to elevation of Cr and mI, Glx and NAA are also elevated, relative to HE (see figure to right above). Thus, the anterior cingulate provides an additional critical distinction between HE and aMCI.

Non-Amnestic MCI: Compared to aMCI, it has only been in recent years that non-amnestic MCI has become a clinical and research focus. To our knowledge, this study represents the first ^{1}H MRS analysis of naMCI in the cingulate gyrus. The differences between naMCI patients and HE are more subtle than the differences between aMCI patients and HE. Overall, naMCI patients exhibit slightly lower metabolites levels in both the anterior and posterior cingulate, with the greatest difference occurring for posterior Glx, compared to HE. Metabolite ratios in naMCI exhibit a similar trend in changes between the anterior and posterior regions as HE.

Conclusion: Differences in regional metabolic patterns can provide an important distinction between mild cognitive impairment and normal aging changes. Furhermore, these regional differences support the hypothesis that non-amnestic and amnestic MCI represent not only different clinical diagnoses, but different neuropathologies.

References: (1) Kelley BJ and Petersen RC Neuro Clin 2007; 25:577-609. (2) Petersen RC et al. Arch Neurol 1999; 56:303-8. (3) Bozoki A et al. Arch Neurol 2001; 58:411-16. (4)-416. (4) Fisher P et a. Neurology 2007; 68:288-91. (5) Kantarci et al. Neurology 2000; 55:210-7. (6) Kantarci K et al. AJNR 2003; 24:843-849.