Understanding Cognitive Disorder Not Otherwise Specified: Evidence for Neurochemical Subtypes of Mild Cognitive Impairment

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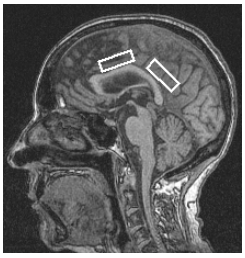
Introduction

Cognitive Disorder Not Otherwise Specified (Cognitive Disorder, NOS) is a diagnostic category used for individuals who do not fulfill specific criteria for dementia, yet exhibit deficits in one or more cognitive domains (memory, executive functioning, psychomotor speed etc). The inherent heterogeneity of this category severely limits its utility in the search for the biological components of neurodegenerative disorders. Efforts to improve the specificity of Cognitive Disorder, NOS have lead to the development of research criteria defining the unique clinical category of Amnestic Mild Cognitive Impairment (MCI)[1]. This diagnosis is based on a specific pattern of cognitive test results rather than biological characteristics that link it to a known disease process or distinguish it from other forms of age-associated cognitive decline. The identification of distinct cognitive/behavioral clusters prior to the onset of frank dementia could be invaluable in the development of interventional pharmacologics if supported by evidence of unique underlying biochemical phenomena. In this pilot study, we employed ^{1}H MRS to identify and compare the neurochemical profiles of two potential subtypes of Cognitive Disorder, NOS: amnestic and non-amnestic mild cognitive impairment.

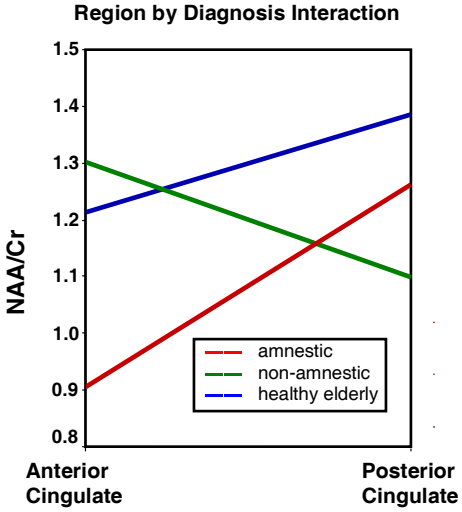
Method

Participants were 7 patients fulfilling Petersen's criteria for amnestic MCI[1] (3 women, 4 men; mean age: 72 ± 6 yrs), 8 patients classified as non-amnestic MCI (3 women, 5 men; mean age: 73 ± 5 yrs), and 8 healthy elderly volunteers (5 women, 3 men; mean age: 66 ± 8 yrs). ^{1}H MRS data were collected on a 1.5 T MRI system (STEAM: TE/TM/TR = 10/10/5000 ms, 112 excitations, 2500 Hz spectral width, volume ~ 6 cm^3) from the anterior and the posterior cingulate gyrus. Each study included a progressive TR T_2 experiment for compartmental analysis and a water reference for phase correction[2]. The regions of interest were selected based on i) evidence from Kantarci et al that ^{1}H MR spectral changes in the posterior cingulate are associated with memory dysfunction[3]; and ii) results from Grachev et al that correlate anterior cingulate MRS data with cognitive tests of executive functioning in healthy adults[4]. QUEST was used to quantify and separate the metabolite resonances from the macromolecule background[5]. Metabolite ratios were calculated from absolute concentrations measured in millimoles per kilogram of tissue water[6].



Results and Discussion

A univariate analysis of covariance using diagnosis (amnestic or non-amnestic MCI, or healthy elderly) and brain region (anterior or posterior cingulate) as predictors and using age as a covariate, revealed a significant diagnosis by brain region interaction for the N-acetyl-aspartate to creatine ratio (NAA/Cr: $F(2, 23) = 9.43$, $p < .01$). The NAA/Cr ratios were lower in the anterior than the posterior cingulate for both the healthy elderly participants and the amnestic MCI patients (see interaction graph). In comparison, NAA/Cr was higher in the anterior than the posterior cingulate in the non-amnestic MCI group. While amnestic MCI has been linked to an increased risk of the development of Alzheimer's disease, these findings suggest the possibility of a distinctly different neurodegenerative process for non-amnestic MCI. As previously reported by Dunham et al[7], differences in the NAA/Cr ratio were driven primarily by regional differences in the Cr concentration. The significance of this increase has yet to be determined, but may be related to putative neuroprotective effects of Cr in response to brain insult[8].



Conclusion

In this study, ^{1}H MRS revealed different regional neurochemical patterns for amnestic, non-amnestic and healthy elderly adults, suggesting great promise in the specification of potential neurochemical endophenotypes of mild cognitive impairment.

References: (1) Petersen RC et al. Arch Neurol 1999; 56:303-8. (2) Knight-Scott J et al. J Magn Reson 2005; 173:169-74. (3) Kantarci K et al Neurology 2000; 55:210-217. (4) Grachev ID et al. Molecular Psychiatry 2001; 6:529-539. (5) Ratiney H et al. MAGMA 2004; 16: 284-96. (6) Knight-Scott J et al. Magn Reson Imag 2003; 21: 787-97. (7) Dunham SA et al Proc ISMRM 14th 2005; p 249. (8) Balestrino M et al. Amino Acids 2002; 23:221-229.