# Shortening of metabolite relaxation times of prefrontal cortex in mild cognitive impairment

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## Introduction

Reasonable estimates of relaxations times of brain metabolites are important for accurate quantification of MR spectra and because they are an insight into the cellular environment changes. Most studies concern calculation of the T2 at 1.5T but only very recently the T2 has been measured at 3T. The TE-Averaging PRESS (1) is a spectroscopic sequence which was initially proposed in order to solve the overlapping problems of Glutamate and Glutamine resonances. In our study we applied this technique in order to effectively measure the transverse relaxation time of the most prominent brain metabolites. The study was performed on subjects suffering from Mild Cognitive Impairment (MCI) and on matched controls in order to assess a possible marker for the early stages of Alzheimer Disease (AD).

## Material and Methods

Investigations were performed on a 3-T Siemens Allegra Head scanner. 16 water suppressed (16 averages each) and 16 unsuppressed water spectra (PRESS sequence) with TE ranging from 35 ms to 185 ms in 16 steps were acquired in two voxels of 30x20x10 $mm^3$ localized in the left and right prefrontal cortex of 5 MCI patients (age 61-68, MMSE 28-29) and 5 healthy volunteers. The spectroscopic acquisition parameters were: TR= 2s, 8 steps double EXOR phase cycle (only for unsuppressd spectra), 2048 complex points, 2 kHz bandwidth. The spectra were corrected by eddy currents with unsuppressed water spectra and phased by jMRUI software package. The amplitude of NAA (2.02 ppm), of tCr (3.03 ppm) and of Cho (3.21 ppm) peaks was computed by AMARES fit implemented in jMRUI. The transverse relaxation times of respective metabolites' resonances amplitudes were calculated with a mono-exponential model by using a two parameters least-squares fit. Before looking at differences between AD and controls, we checked whether there was any lateralization (4) of T2 values in the left and right side in AD patients. Insignificant differences ($p>0.2$) allowed us to include the data from both sides in the same independent-samples t-test analysis.

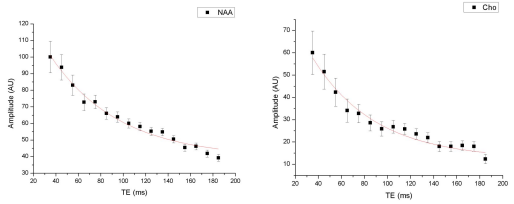


Fig.1: Examples of fitting for the 3 metabolites under investigation.

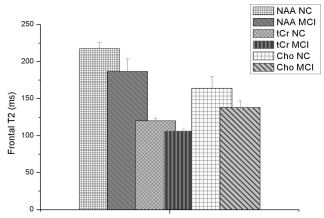


Fig.2: Comparison of the mean values in MCI and Normal Control (NC)

## Results

The NAA, Cho and Cr T2 in the right prefrontal cortex for healthy and MCI subjects are reported in Table1.

All metabolites we investigated showed a significant decrease of the metabolite T2 values in MCI patients: -13% for NAA ($p<0.035$), -9% for tCr ($p<0.01$) and -15% for Cho ($p<0.035$).

| Metabolite | HC (ms) | MCI (ms) |
|---|---|---|
| NAA | 214±9 | 186±15 |
| tCr | 117±5 | 106±5 |
| Cho | 162±13 | 137±9 |

Table 1

## Discussion and conclusion

To our knowledge, this is the first report of metabolite T2 variations in MCI. However, a spectroscopy study looking at spin-spin relaxation times of tissue water and cerebrospinal fluid showed a shortening in T2 of water in AD (5).

Firstly, T2 relaxation of brain water content has been shown to be multiexponential, probably reflecting 3 main compartments: a very slow component, related to cerebrospinal fluid; a slow component, related to intra and extracellular water, and a fast relaxing component, related to water trapped in the myelin bilayers (6). The two last components are related to the tissue itself, and the intra and extracellular component is known to weight comparatively more. Consequently, pathologic alterations in water T2 are probably mainly related to this latter contribution, even if the relative variations of the intra and extracellular fractions are not able to be discriminated. The extracellular fraction can in fact dominate the phenomenon, when local edema occurs.

On the other hand, T2 relaxation of the metabolites we studied may reflect the intracellular or even subcellular compartment, where those metabolites are found. In fact, NAA is supposed to be mainly mythocondrial (7). Consequently, our findings strongly suggest a specific variation in the intracellular or subcellular environment. Secondly, a decrease in metabolite relaxation times can be likely also related to the presence of elevated iron levels associated with many neurodegenerative disorders (8). Indeed, there is evidence of a positive correlation between R2 and iron levels (9-11). The reason can be double and arising from the presence of at least two forms of iron: one more diffusely distributed than the other. These two forms can affect the relaxation in two different ways: free iron will contribute to T2 through the dipole-dipole mechanism, while iron in even larger aggregate forms will likely have an enhanced effect on T2 by generating considerable and relatively static magnetic field inhomogeneities (12).

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