

Ultra-High Field MRS in Healthy Aging and Early Cognitive Impairment

M. C. Stephenson¹, M. I. Schubert², M. Abaie², A. Napolitano², R. G. Jones³, P. G. Morris¹, and D. P. Auer²

¹SPMMRC, School of Physics and Astronomy, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom, ²Academic Radiology, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom, ³School of Community Healthy Sciences, University of Nottingham, Nottingham, Nottinghamshire

Background:

Metabolic profiles in the posterior cingulate (PCC) have been found to be perturbed in many mental disorders¹ and neurodegenerative diseases^{2,3}. In order to characterise changes in metabolite levels due to disease it is important to establish 'normal levels' and changes associated with healthy aging. The aim of this study was to investigate whether there are age-related changes in the PCC metabolic profile in healthy subjects, and to establish whether they differ in MCI and AD patients.

Methods:

Subjects: Thirteen healthy subjects (HV) (age range 19-72), one subject with mild cognitive impairment (MCI) (aged 77), and one Alzheimer's patient (AD) (aged 72) took part in the study. All subjects underwent medical interview and cognitive testing using the revised Addenbrooke's Cognitive Examination (ACE-R) to ensure no subjects with cognitive impairments were included in the healthy group and to correlate with metabolic profile.

MR Measurements: All MR measurements were acquired on a Philips Achieva 7T system. Subjects underwent a scanning session including MPRAGE anatomical images, for voxel localisation and segmentation, followed by a water-suppressed ¹H spectral acquisition from the PCC (STEAM TE/TM/TR=74/78/3000ms, VOI=25x25x30mm³, BW=3000Hz, No. samples = 2048). Six spectra were collected, each with 32 averages, and were phase-corrected and averaged together before spectral analysis in LCModel using water referencing. A non water-suppressed spectrum, (6 averages) was acquired to allow absolute quantification of metabolite levels. Total spectral acquisition time was ~11mins. An example acquired spectrum is shown in figure 1. Metabolite concentrations were estimated in arbitrary absolute units from LCModel, and concentrations of N-acetyl aspartate (NAA), myo-Inositol (mI), phosphocreatine (PCr), creatine (Cr), choline (Cho), glutamate (Glu), glutamine (Gln), γ -aminobutyric acid (GABA), aspartate (Asp), guanidino-acetate (Gua) and scyllo-Inositol (sI) were measured both, as given from LCModel (uncorrected), and following corrections to account for the %tissue within the voxel (corrected). Corrected values were calculated by co-registering the voxel position with the segmented MPRAGE images. Due to RF field inhomogeneities at 7T, segmentation of the MPRAGE images were carried out manually, using an image intensity threshold based technique, observing the region of the voxel. Concentrations of lactate (Lac) are given as uncorrected due to the occurrence of lactate in CSF. All correlations were assessed using Pearson's correlation coefficient. Significance was considered if p<0.05.

Results and Discussion:

Atrophy: Measurement of tissue percentages, obtained from within the voxel region, indicate the expected, but not significant, decrease with age ($<0.1\pm0.05\%$ per year, p=0.1, figure 2). The tissue % measured for the AD subject falls slightly outside the 95% confidence bounds, implying possible atrophy in the PCC due to disease, and the MCI subject also showed markedly elevated water content. Since the AD and MCI subjects were slightly older than the HV subjects there is a possibility that atrophy is non-linear, but the level of change measured is in agreement with previous studies⁴ where PCC atrophy has been shown in AD subjects compared with healthy age matched controls, as well as in MCI. Similarly, PCC atrophy was highly correlated with ACE-R cognitive scores (p<0.02) across the subjects.

Metabolic changes with healthy aging: Uncorrected levels of all measured metabolites, lactate excepted, tended to decrease with age. This is likely to be linked with the measured atrophy. Uncorrected lactate levels tended to increase with age, although this did not reach significance. Corrected levels of NAA, Glu and Asp were found to be significantly correlated with age in the HV group (p<0.05, p<0.001, p<0.04 respectively), showing significant decreases with increasing age. The measurement of age related decreases in NAA, Glu and Asp levels, independent of atrophy bias, may imply selective loss of neurons with age (NAA is thought of as a neuronal marker, and glutamate is found to be at much higher concentrations in neurons). However, segmentation of the MPRAGE images shows no correlation between WM or GM loss and age, although WM/GM segmentation was difficult due to poor tissue contrast and significant RF inhomogeneities. An alternative suggestion is that the age-associated metabolic changes reflect functional impairment rather than neuronal cell loss. A possible limitation of this study is that changes in relaxation rates of the metabolites may have affected the results due to the chosen medium long echo times. MRI measurements⁶ have indicated that T₂ values may increase with age, particularly in the WM, which would lead to the changes observed although more work must be done to fully separate the contributing factors.

Metabolic changes in AD and MCI: Tissue corrected levels of NAA, mI, Cr, Cho, Glu, Gln, GABA, Asp, Gua and sI were within the range of normal values (based on 95% confidence intervals) in healthy subjects. However, the level of PCr was significantly (68%) lower than 'predicted' levels in the MCI subject (based on extrapolation of trend with age from healthy subjects) and were 82% lower than predicted in the AD subject. PCr is known to play a vital role in energy metabolism in tissues and these results seem to agree with previous studies⁵ describing dysfunction in creatine kinase activity in AD. These preliminary results also cast doubt on the results of many previous studies whose findings relied on quantifying changes in metabolite levels relative to creatine, and assumed creatine to be constant. Utilizing increased spectral resolution, available at 7T, has allowed accurate separation of the Cr and PCr components, usually measured as PCr+Cr, and has shown marked changes in PCr levels with MCI and AD, whilst levels of Cr remained unchanged.

Conclusions:

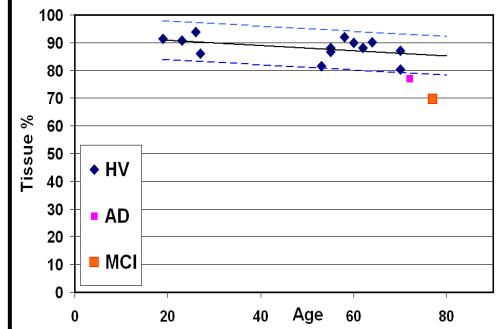


Figure 2: Correlation between %tissue measured in the PCC and age, in healthy volunteers (HV), the AD subject and the MCI subject. Blue dashed lines show 95% confidence bounds for HV.

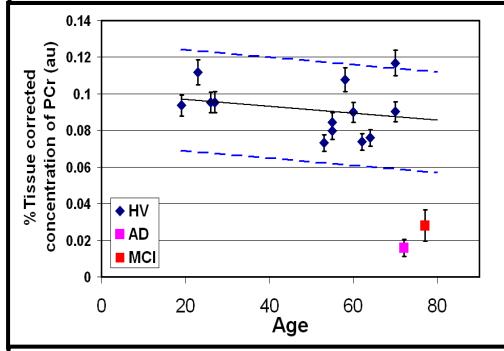


Figure 3: Plot indicating selective loss of PCr in subjects with AD and MCI

NAA, Glu and Asp were found to be significantly decreased with age in healthy subjects. This could be due to neuronal loss, since NAA is thought to be a marker of neuronal density, however it is possible this could also relate to loss of neuronal function, rather than cell loss. Interestingly, atrophy corrected metabolite levels reveal an intriguing preliminary finding of reduced PCr in subjects with mild cognitive impairment/early AD potentially supporting a crucial role for CK in dementia.

References: 1. Kizu, O. et al, *Neuroradiology* (2004), pp277 2. Godbolt, A. K. *Am.J. Neurology*, (2006) pp718. 3. Shimizu, E. et al, *J. Psychiatric Research*, (2007), pp49 4. Shiino, A. *NeuroImage* (2006), 33(1) pp17-26. 5. Gallant, M. *J. Biol. Chem.* (2006), 281(1) pp5. 6. Cox, E. et al. Abstract Submitted to ISMRM (2010).

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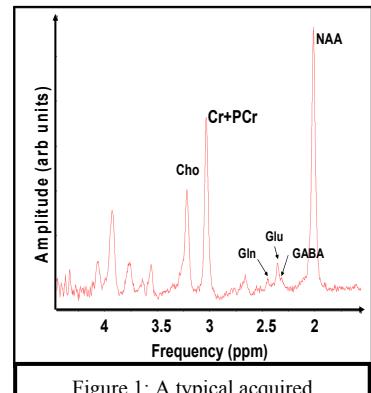


Figure 1: A typical acquired