

# Age-related changes in long and short echo time proton magnetic resonance spectroscopy of the brain

D. J. McIntyre<sup>1</sup>, R. A. Charlton<sup>2</sup>, H. S. Markus<sup>2</sup>, F. A. Howe<sup>1</sup>

<sup>1</sup>Basic Medical Sciences, St George's, University of London, London, United Kingdom, <sup>2</sup>Clinical Neurosciences, St George's, University of London, London, United Kingdom

## Introduction

Age related cognitive decline remains incompletely understood. Historically, this has been ascribed to neuronal loss and grey matter atrophy, but more recent evidence has questioned this and suggested an important role for age related changes in the white matter<sup>1,2</sup>. This study has applied 1H chemical shift imaging as a functional probe to study brain metabolic changes with age, and is the first study of the ageing brain to use CSI at both short and long echo times to investigate metabolite R<sub>2</sub> values as well as metabolite ratios. A major aim was to identify which parameters were most sensitive to changes with age.

## Methods

Ninety healthy adults between fifty and ninety years with no history of neurological or psychiatric disorders were recruited. Equal numbers of males and females were recruited to each decade. MR studies were carried out on a 1.5T GE Signa LX using a quadrature birdcage head coil. 1H 2D CSI data were acquired at both short and long echo times (TE=30 and 136ms, TR=2000), with matrix size 16x16, 22cm field of view, 15mm slice thickness, NEX=1, 1000Hz sweep width, 512 points. The same transmitter and receiver gains were used at long and short echo to allow calculation of metabolite R<sub>2</sub>. The standard water-suppressed GE PROBE-SI sequence was used with PRESS localisation. An ROI approximately 70mm square was prescribed over white matter in the centrum semiovale, immediately superior to the ventricles. MRS analysis was performed by an operator blinded to the ages of the participants. Data were processed in SAGE and automatically quantified by LCMoDel<sup>3,4,5</sup>. Metabolite values were corrected for chemical shift artefact by a program written in-house. Spectra were examined for evidence of lipid and lactate. Data from voxels containing only pure white matter were averaged to give a single data point from each subject. Correlations with age were calculated in SPSS 11.0 for: metabolite ratios for NAA/Cr, Cho/Cr and NAA/Cho at short and long TE; ml/Cr at short TE; and the R<sub>2</sub> for NAA, Cho and Cr from the LCMoDel values at long and short echo. Calculated R<sub>2</sub> values will be offset by the R<sub>2</sub> of the model solutions used to calibrate LCMoDel, but this small systematic error will not affect any relationship with age.

## Results & Discussion

After Bonferroni correction for multiplicity, the R<sub>2</sub> of NAA increased significantly with age, and NAA/Cr decreased significantly with age at both short and long echo. Interestingly, over this age range 50-90, the trend in R<sub>2</sub> is opposite to that previously reported over the range 15-78<sup>6</sup>. No other parameters correlated with age, although Cho/Cr showed a trend towards reduction with age at both echo times, which was not significant after multiplicity correction. The age-related change in R<sub>2</sub> of NAA is insufficient to account for the age-related decrease in NAA/Cr even at long echo, suggesting true changes in metabolite concentrations occur. The trends observed are consistent with increased creatine with age, as previously reported in single-voxel studies<sup>7</sup>; the weaker correlation of Cho/Cr and ml/Cr with age compared to NAA/Cr may be attributed to the higher signal to noise of the NAA resonance in brain spectra. Lactate was not detected in any spectra. Strong lipid resonances were observed in some subjects, and the incidence increased with age (p=0.012 for logistic regression against age). Lipid occurrence was uncorrelated with cholesterol, body mass index or white matter lesions; furthermore, the lipid resonances were invariably observed in the midline of the brain. We believe the resonances to result from lipid deposits in the falx cerebri, rather than the brain tissue itself; such deposits have previously been observed in ageing populations by MRI and CT<sup>8,9,10</sup>, but never by MRS.

	N	R	p-value (2-tailed)	Significance		N	R	p-value (2-tailed)	Significance
NAA R <sub>2</sub>	79	0.405	0.00021	S	Cr R <sub>2</sub>	79	0.216	0.056	NS
NAA/Cr 30ms	83	-0.323	0.0029	S	ml/Cr 30ms	83	-0.206	0.062	NS
NAA/Cr 136ms	80	-0.325	0.0033	S	Cho R <sub>2</sub>	79	0.176	0.12	NS
Cho/Cr 30ms	83	-0.283	0.0096	NS	NAA/Cho 30ms	83	0.073	0.51	NS
Cho/Cr 136ms	80	-0.283	0.011	NS	NAA/Cho 136ms	80	0.057	0.62	NS

**Table 1.** Correlations of MR parameters with age, sorted by p-values. After multiplicity correction, the NAA apparent R<sub>2</sub> shows an increase with age and the NAA/Cr ratios at both long and short echo times show decreases with age which are significant at the p=0.05 level; Cho/Cr shows a trend towards reduction with age at both echo times which falls short of significance.

## Conclusions

The strongest correlation with age is the R<sub>2</sub> relaxation rate of NAA, which increases with age over the range 50-90 years. There is no change in R<sub>2</sub> for the other metabolites, which unlike NAA are found in all cell types within the brain, suggesting a neuron-specific mechanism in ageing. The age-related changes in metabolite ratios are consistent with an increase in creatine with age, and appear to be dominated by changes in metabolite concentrations, rather than by changes in R<sub>2</sub>. Since short-echo spectroscopy gives higher signal to noise, is able to quantify more metabolites, and gives consistently lower p values for correlations between metabolite ratios and age, we propose that it should be preferred for future studies of ageing brain.

**Acknowledgements.** This work was sponsored by Research into Ageing programme grant 227 and Cancer Research UK [CRC], grant no. C12/A1209. We thank staff and volunteers from Church Lane Surgery, Church Lane, Merton Park, London, SW19

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