Evaluation of the effects of aging and gender differences on the concentrations of cerebral metabolites by general linear model analysis

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Introduction: Age-related changes and gender differences of the concentrations of cerebral metabolites, including N-acetyl group (NA), creatine + phosphocreatine (Cr), choline-containing compounds (Cho), *myo*-inositol (mI) and glutamate (Glu) determined by *in vivo* proton MRS are not always in good agreement between reports. One of the critical factors that cause these discrepancies is heterogeneity of tissue composition (gray matter, white matter, cerebrospinal fluid (CSF), etc) in regions of interests (ROIs). Simple and multiple linear regression models have been used to investigate these changes [1]. We will expand these models to general linear model analysis using the tissue composition as a covariate, and investigated the age-related changes and gender differences in the concentrations of these cerebral metabolites.

Material and Methods: Four 8-ml ROIs (the posterior gray matter (P-GM), the posterior white matter (P-WM), the anterior gray matter (A-GM), and the anterior white matter (A-WM)) were located on each of the 77 healthy subjects (range 22.1-76.3 years old, mean age 48.4 years old, 37 males and 40 females), and spectra were acquired with PRESS protocol (TR/TE = 6000/25ms, 64 accumulations)) by using a whole-body 3.0-Tesla system. Based on 3D T_1-weighted images, the cerebrum were segmented to gray matter, white matter, CSF and other tissues by SPM99 (Statistical Parametric Mapping, The Welcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm). Spectra were analyzed quantitatively by using LCModel software [2] with correction of the volume loss due to the contamination of CSF. We set a variable, gray matter ratio (GMR) as the fraction of the volume of the gray matter to the volume of total brain tissue (the sum of the gray matter and the white matter) in a ROI.

The presumed general linear model is

$$C_{mi} = \beta_0 + \beta_1 \text{ x } [\text{AGE}]_i + \beta_2 \text{ x } [\text{GMR}]_i + f(x) + \varepsilon_i \quad \text{for } i = 1, 2, \ldots, n \qquad (1)$$

, where C_m is the concentration of metabolite m, β_0 is a constant, β_1 and β_2 are coefficients for the variables. If a subject is a female, x equals 0, and if a subject is a male, x equals 1 and $f(1)$ is defined to be 0. n is the total number of spectra of each ROI, and ε is a random error. The model equations of each metabolite were statistically evaluated. In all analyses, $p < 0.05$ was considered significant.

Results: The concentration of NA, a neuronal marker, was significantly decreased in A-GM with aging. The concentrations of Glu were decreased in P-WM, A-GM and A-WM. The concentrations of mI, a glial marker, were increased in all four ROIs, and the concentrations of Cr were increased in posterior two ROIs (P-GM and P-WM). The concentrations of Cho were not changed significantly with aging. As regard to gender, the concentration of Cr in A-WM was higher in females than in males.

Conclusions: The results demonstrated that the concentrations of cerebral metabolites change in different spatial distributions with aging. The increase of mI is most widely observed, while the changes of NA, Glu and Cr are more specific to regions and/or brain tissues. The presented method minimizes the effect of the variation in ROI placement and enable us to evaluate spectrum from individual subject more precisely.

P-GM

		β	SE	p
mI	Intercept	0.52	1.72	ns
	Age	0.0166	0.0038	<0.0001
	GMR	5.09	1.96	<0.05
	$f(0)$	0.08	0.12	ns
Cr	Intercept	-0.38	2.16	ns
	Age	0.0110	0.0047	<0.05
	GMR	9.66	2.45	<0.0005
	$f(0)$	0.06	0.15	ns

P-WM

		β	SE	p
Glu	Intercept	4.93	0.60	<0.0001
	Age	-0.0144	0.0053	<0.01
	GMR	6.84	1.93	<0.001
	$f(0)$	0.08	0.18	ns
mI	Intercept	1.99	0.41	<0.0001
	Age	0.0159	0.0036	<0.0001
	GMR	3.81	1.33	<0.01
	$f(0)$	0.16	0.13	ns
Cr	Intercept	3.76	0.40	<0.0001
	Age	0.0086	0.0035	<0.05
	GMR	5.49	1.29	<0.0001
	$f(0)$	0.24	0.12	ns

A-GM

		β	SE	p
NA	Intercept	5.84	3.06	ns
	Age	-0.0211	0.0072	<0.005
	GMR	7.59	3.42	<0.05
	$f(0)$	0.22	0.26	ns
Glu	Intercept	2.76	3.86	ns
	Age	-0.0276	0.0090	<0.005
	GMR	11.91	4.30	<0.01
	$f(0)$	0.12	0.32	ns
mI	Intercept	2.20	2.18	ns
	Age	0.0142	0.0051	<0.01
	GMR	4.32	2.43	ns
	$f(0)$	0.12	0.18	ns
Cr	Intercept	1.29	2.33	ns
	Age	-0.0051	0.0054	ns
	GMR	9.34	2.59	<0.001
	$f(0)$	0.14	0.20	ns

A-WM

		β	SE	p
Glu	Intercept	5.09	0.42	<0.0001
	Age	-0.0160	0.0059	<0.01
	GMR	6.19	1.59	<0.0005
	$f(0)$	0.29	0.19	ns
mI	Intercept	2.57	0.31	<0.0001
	Age	0.0146	0.0043	<0.005
	GMR	3.48	1.17	<0.005
	$f(0)$	0.01	0.14	ns
Cr	Intercept	4.45	0.26	<0.0001
	Age	0.0051	0.0036	ns
	GMR	3.26	0.99	<0.005
	$f(0)$	0.41	0.12	<0.001

Table: The results of general linear model analysis. Only the values of the models which were proved to be significantly predictive are listed.

References: 1. Brooks JC, et al. Cereb Cortex 2001; 11: 598-605. 2. Provencher SW. Magn Reson Med 1993; 30:672-9