Differential effects of age on tissue water-referenced proton metabolites in basal ganglia, pons, and cerebellum using an MRS sequence optimized for glutamate detection

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Introduction

The non-invasive in vivo detection of the neurotransmitter glutamate (Glu) using Magnetic Resonance Spectroscopy (MRS) at a field strength of 3T has been challenging because of spectral overlap with signals from other metabolites (e.g., glutamine (Gln)) and a complicated multiplet structure due to strong J-coupling. Constant Time PRESS (CT-PRESS)[1] was introduced to detect J-coupled resonances with high signal-to-noise ratio by using effective homonuclear decoupling. We used CT-PRESS optimized for the detection of Glu[2] in healthy human subjects that also permitted comparison of the proton metabolite profile of three brain regions commonly affected in normal aging and neuropsychiatric conditions, such as alcohol dependence: the basal ganglia, cerebellum and pons.

Methods

Volunteers were 12 young (25.5±4.3 years) and 12 elderly (77.6±4.9 years), right-handed, non-smoking healthy men and women, recruited from the local community. The two groups did not differ significantly in education (young=16.25±2.2, old=17.08±2.0 years) or estimated general intelligence (young=113.67±5.7, old=118.17±5.9). MRS was performed on a GE 3T MR scanner. Single voxels were manually positioned in the basal ganglia (10.6cc), cerebellum (9.8cc) and pons (5.9cc). Left and right hemisphere acquisitions were randomized across subjects. The acquisition time was ~9min per voxel (average echo time (TE)=139ms, 129 chemical shift (CS) encoding steps, $\Delta t_1/2$ = 0.8 ms, repetition time=2s, 2 averages). An acquisition without water suppression was carried out (17 CS encoding steps, $\Delta t_1/2$ = 6.4 ms, 2 averages) to measure tissue water content which was used to normalize the metabolite signal intensities. Data acquired without water suppression were apodized in t_2 with a 5Hz Gaussian line broadening and zero-filled up to 4K points. After performing a fast Fourier transform (FFT) along t_2, water spectra were evaluated by peak integration. The amount of cerebral spinal fluid and tissue water was estimated by fitting the data to a bi-exponential model. Apodization of the water-suppressed data comprised multiplication with sine-bell functions in both time dimensions and zero-filling up to 4Kx1K data points. After performing a 2D FFT, effectively decoupled 1D CT-PRESS spectra were obtained by integrating the signal along f_2 within a ±13Hz interval around the spectral diagonal. Metabolite signals in the 1D spectra were determined by peak integration with an interval of ±6Hz.

Results

The quality of the spectra allowed evaluation of signals from N-acetyl-aspartate (NAA, 2.02ppm), choline containing compounds (Cho, 3.24ppm), total creatine (tCr, 3.03ppm and 3.93ppm), myo-Inositol (mI, 3.58ppm), Glu (2.36ppm), and Glu+Gln (Glx, 3.78ppm). Data from 2 basal ganglia, 1 pontine, and 5 cerebellar voxels were excluded due to poor spectral quality. A 2-group (young vs. elderly), repeated measures (3 regions and 6 metabolites) analysis of variance (ANOVA) revealed two significant interactions: group-by-region ($F(1,2)=3.772$, $P_{GG}=0.0355$) and group-by-region-by-metabolite ($F(1,10)=4.578$, $P_{GG}=0.0025$). Irrespective of age, metabolite values were generally higher in the pons and cerebellum than basal ganglia; NAA was highest in the pons, and tCr was highest in the cerebellum. The 3-way interaction indicated a significant influence of age: tCr levels were lower in the basal ganglia (P=0.0132) but higher in the cerebellum (P=0.005) and pons (P=0.05) of the elderly than the young. Glu was lower in the basal ganglia (P=0.0004), while Cho was higher in the pons (P=0.0169) of the elderly.

Because of the significant regional and age effects on tCr, the pattern of group differences using tCr as a referent differed from that based on water referenced values. As with the water-referenced data, ANOVA yielded a group-by-region-by-metabolite interaction ($F(1,8)=3.340$, $P_{GG}=0.0201$), but in the case of the ratios, NAA appeared to decline with age in the cerebellum (P=0.0382) and pons (P=0.0364) as did mI (P=0.0003) and Cho (P=0.001) in the cerebellum, whereas Cho in the basal ganglia was higher in the elderly than young (P=0.0136).

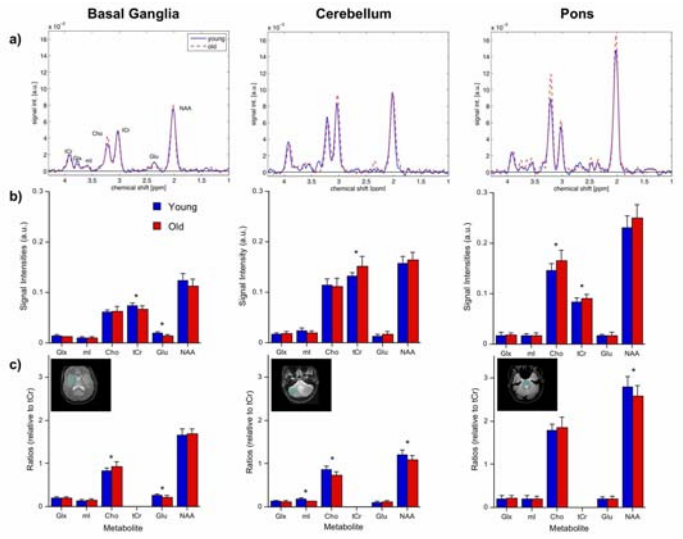

Figure 1: a) Sample spectra from a young (23 years, BLUE) and elderly man (75 years, RED). b) Average signal intensity of metabolites relative to tissue water. c) Average signal intensity of metabolites in ratios relative to tCr. *P<0.05, basal ganglia n=22, cerebellum n=19, pons n=23.

Discussion and Conclusion

The profile of proton metabolite spectral intensities varied with age and brain region. When expressed relative to water, tCr was lower in the basal ganglia and higher in the cerebellum and pons in the elderly compared with the young group. Cr levels are consistently reported as higher in the cerebellum than other regions, including the basal ganglia and pons[3-6]. Although NAA varied regionally, it showed no age effect when referenced to tissue water. Thus, only when referenced to tCr does NAA appear to decline with age. Studies focusing on cortical regions and using absolute metabolite quantitation are consistent with our observation of lack of healthy age-related differences in NAA across the three regions examined [7-9]. Similarly and comporting with our age-related increases in Cho in basal ganglia, studies reporting absolute concentrations note higher Cho in cortical gray matter with older age [7,10], whereas ratios suggests lower Cho with age in the basal ganglia. Perhaps because our MRS acquisition protocol was optimized for detection of Glu, its concentration was robust to quantification referent; specifically, Glu showed an age-related decline in the basal ganglia and is consistent with another report, which used the LC model for quantification[11].

In conclusion, given that tCr can vary with age and brain region, the interpretation of data with tCr as an internal reference should be guarded. Further, regional variation in metabolite concentrations likely reflects normal differences in constituents of the underlying tissue that need to be taken into account when assessing the effects of disease on focal brain tissue and chemistry.

Acknowledgements

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