Regional age-related changes in the monkey brain measured with proton magnetic resonance spectroscopy

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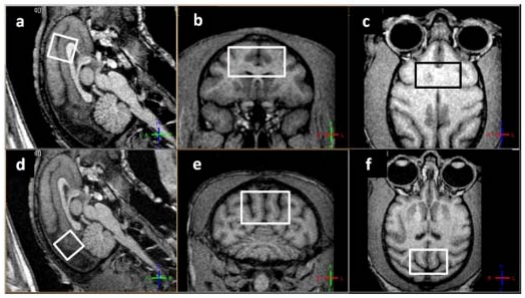
Introduction: Assessment of age-related changes in brain metabolites using ^{1}H-MRS has been so far almost exclusively used in humans, where the centrality of the interest is offset by large inter-individual differences across the subject population, resulting in a wide range of results even for similar brain areas[1]. The non-human primate model is a particularly attractive model for studying the neural correlates of normal aging because of the extended homology between the monkey and the human brains, the ability to closely control for the individual history of subjects in a monkey population, the lack of neurological diseases such as Alzheimer disease and other forms of dementia, and the access to post-mortem tissue and various in-vivo interventions that can be tested in the frame of age-related phenomena. In this study, a tightly controlled population of 20 rhesus monkeys was used, and ^{1}H-MRS together with tissue volumetric information from high resolution anatomical MRI images were employed to carefully assess regional concentrations of brain metabolites.

Figure 1: locations of the anterior and posterior VOIs



Methods: 20 rhesus monkeys (*Macaca Mulatta)*, ages 6-27 years, were used for this study. *MRI/MRS experiments*: 3T Philips whole body Intera MRI scanner (Philips Medical Systems, Best, The Netherlands). RF coil: 6-channel synergy head coil, RF transmission through the quadrature body coil. *T_1-weighted images*: 3D-T1TFE, TR/TE=8ms/3ms, inter-shot delay = 2800ms, magnetization preparation = inversion, NEX = 6, resolution = 0.6x0.6x0.6 mm3. *Single VOI MRS*: PRESS, TR/TE=3500ms/38ms, NEX = 256. VOI dimensions: 13mm A-P, 13mm dorsal-ventral and 25mm L-R = 4.2 cm^3. Figure 1 shows the two locations for the VOIs – anterior (upper row) and posterior (lower). Areas included in the anterior VOI are: anterior cingulate cortex, rostrum and genu of the corpus callosum, supplementary motor area and parts of Brodmann area 46. The posterior VOI included visual areas and posterior areas of the medial-parietal cortex. *Analysis*: tissue segmentation and tissue probability maps were obtained using a in-house C++ visualization software (see figure 2). The tissue fractions of gray matter, white matter and CSF within the co-registered VOI were calculated to correct for CSF fraction in the quantification process, as well as to allow for correlation of the MRS results with tissue type. MRS analysis was performed with LC Model (www.s-provencher.com) in combination with a home written MATLAB code for CSF correction.

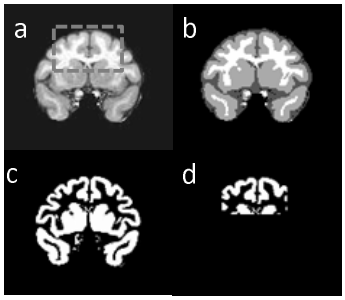


Figure 2: (a) T1W image; (b) Segmentation results; (c) GM probability map; (d) GM intersected with the frontal VOI.

Results and brief discussion: Table 1 shows age-related correlations of tissue fractions within the VOIs and globally. A significant global decrease in GM fraction (f_{GM}) is observed, coupled with a significant increase in f_{WM} and no significant change in f_{CSF}. In table 2, the MRS results indicate that this GM thinning is not associated in either VOI with decrease in NAA, raising the possibility that age related GM shrinkage is not explained by neuronal loss, a notion supported by electromicrography results[2]. The significant age-related increase in myo-inositol (MI) in the anterior VOI may indicate increase in astroglial volume. This finding is corroborated by immunohistochemistry results[3] where an age-related increase in astroglia was found in frontal and parietal white matter. Increases in creatine and phosphocreatine (tCr) in the frontal VOI were also significant, possibly related to an age-related decrease in creatine kinase activity[4]. NAA and Choline (Cho) did not vary significantly with age, but showed strong correlation with tissue fraction – NAA positively with GM and Cho positively with WM (and negatively with GM), as was found in some previous MRS studies in humans.

Table 1	*Mean (St. Dev.)* Correlation with age (Anterior VOI) N=20	*Mean (St. Dev.)* Correlation with age (Posterior VOI) N=19	*Mean (St. Dev.)* Correlation with age (whole brain) N=19
f_{GM}	0.49 (0.03)	0.56 (0.05)	***0.44 (0.03)***
	r=-0.38, p=0.10	r=-0.19, p=0.43	***r=-0.60, p=0.006(**)***
f_{WM}	0.42 (0.04)	0.28 (0.03)	***0.31 (0.02)***
	r=0.25, p=0.29	r=-0.01, p=0.96	***r=0.502, p=0.03(*)***
f_{CSF}	0.09 (0.02)	0.17 (0.05)	0.24 (0.04)
	r=0.08, p=0.75	r=0.15, p=0.53	r=0.16, p=0.51

Table 2	*Concentration (i.u.) Mean (St. Dev.)* Correlation with age (anterior VOI) N=20	*Concentration (i.u.) Mean (St. Dev.)* Correlation with age (posterior VOI) N=19	*Correlation with f_{GM} (both VOIs) N=39*	*Correlation with f_{WM} (both VOIs) N=39*
NAA	9.11 (1.29)	11.41 (1.24)		
	r=0.18, p=0.44	r=-0.38, p=0.11	***r=0.60, p<0.001***	***r=-0.71, p<0.001(**)***
Cho	1.62 (0.3)	1.06 (0.24)		
	r=-0.24, p=0.31	r=-0.36, p=0.13	***r=-0.62, p<0.001***	***r=0.66, p<0.001(**)***
MI	7.00 (1.35)	6.32 (1.22)		
	r=0.47, p=0.03(*)	r=0.13, p=0.59	r=-0.25, p=0.15	r=0.20, p=0.215
Cr	10.60 (1.02)	10.12 (0.94)		
	r=0.45, p=0.04(*)	r=0.02, p=0.95	r=-0.28, p=0.1	r=0.16, p=0.345

Conclusion: Significant age-related regional changes in metabolite concentrations have been observed in a tight population of rhesus monkeys that are in good correlation with histological and immunohistochemical observations. The exact nature of these changes and the overall mechanism responsible for regional physiological age-related decline of brain tissue are far from being clear, and so are their implications on behavior and cognitive ability. We argue, however, that a multimodal MRI/MRS approach, one that in the future will include additional modalities such as DTI and perfusion MRI will allow forming a more complete picture of regional age-related phenomena in the brain, in a model that has high significance for aging studies in humans.

References: 1. Haga, K. K., et al. (2007). Neurobiol Aging (online view). **2.** Peters, A., et al. (1998), Cereb Cortex 8(8): 671-84. **3.** Sloane, J. A., et al. (2000), Brain Res 862(1-2): 1-10. **4.** Smith, C. D., et al. (1997), Neurobiol Aging 18(6): 617-22.

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