Structural and Water Diffusion MRI Profiling of Ageing in Rhesus Monkeys

A. Coimbra[1], D. Welsh[1], M. Holahan[1], R. Hargreaves[1], D. Williams[1]
[1]Imaging Research, Merck Research Laboratories, West Point, PA, United States

Introduction

Neurodegenerative diseases, by definition, are characterized by neuronal dysfunction typically associated with cell death and/or axonal demyelination, and are more prominent in the elderly. Such neuronal losses yield macro-structural morphological changes such as atrophy, observable *in-vivo*, through structural MRI scans. More subtle ultra-structural changes may be probed by Diffusion Tensor MRI (DT-MRI). DT-MRI measures rates (apparent diffusion coefficient, ADC), and preferential direction (fractional anisotropy, FA) of water diffusion; in living tissues, it provides insight into changes in microenvironment (in the scale of tens of micrometer) due, e.g., to increased free space following neuronal death and increased water permeability subsequent to demyelination. Our objective is to characterize the normal morphological and DT-MRI changes as related to ageing in Rhesus monkeys. Such profiles could provide a physiological MRI template that may serve as the basis to track neurodegenerative pathology in this animal model.

Subjects and Methods

MRI scans were performed on elderly (N=18, 23-29 y) and young (N=6, 3-10 y) rhesus monkeys. Monkeys were intubated under ketamine anesthesia, and maintained with 1.5% isofluorane and mechanical ventilation during scanning. All animal handling procedures were approved by the Institutional Animal Care and Use Committee at Merck Research Laboratories. Scans were performed on a 3T Siemens/Trio and using Siemens eight-channel array head coil. A total of four structural scans were performed: 1) 3D MPRAGE (TR/TE/NA/FA 1.47s/4.38ms/4/12°), 128x128x64 mm^3 FOV, 256x256x80 matrix; 2) and 3) 2D TSE (10/19-117/4/160), 96x128x64 mm^3 FOV, 192x256x80 matrix and 4) 2D True IR (10/11/4/120) with an inversion time of 500 ms, 96x128x64 mm^3 FOV, 192x256x80 matrix. A 2D spin echo EPI sequence was used for the DT-MRI (8.1/85/10/90), sensitizing gradients were applied in 6 direction at b values 0 and 1000 s/mm^2 with an inversion pulse (TI=2250ms) applied to minimize any diffusion signal coming from cerebro-spinal fluid. All processing was scripted in MATLAB (MathWorks Inc., http://www.mathworks.com/), with calls to external functions from the FMRIB Software Library (FSL, University of Oxford, http://www.fmrib.ox.ac.uk/fsl) and SPM2 package (University College London, http://www.fil.ion.ucl.ac.uk/spm/). FSL was used to extract the brain and, from the four different contrasts (pulse sequences), segment the brain into four tissue categories: gray matter (GM), white matter (WM), cerebro-spinal fluid (CSF) and others. Mutual information algorithms from SPM2 were used to co-register all images to a template brain image previously aligned in the AC-PC plane. The SPM Diffusion toolbox was also used to calculate the diffusion tensors. In-house routines estimated ADC and FA. The ADC and FA maps were masked to extract the brain. Density histogram analysis of both maps was used to characterize water diffusion of the brain region. Among other parameters we extracted density peak, location of the peak and location where area under the curve (AUC) reached 25, 50 and 75% of total AUC.

Results

Structural scans showed that with ageing, GM volume decreases and ventricular (CSF) space increases. The present cross-sectional data pool, showed an average atrophy rate of 0.75%/yr in GM volume and an increase in CSF volume at 2.9%/yr. GM/CSF ratio showed a marked (best) correlation with age (Pearson r=-0.83, see figure 1) with annualized rate of change yielding 1.9%/yr. Diffusion scans showed that ADC values for the elderly brain had a wider distribution compared to the young brain (figure 2). Thus, peak density normalized to whole brain was smaller in elderly (0.0999/0.0138, mean/sd) as compared to young (0.1204/0.0141); ADC@25% of total AUC was smaller in elderly (0.689/0.021 $x10^{-3}$ mm^2/s) than young (0.708/0.016), and inversely ADC@75% was larger in the elderly (0.943/0.080) than young (0.863/0.042). Additionally, the location of the peak shifted with ageing (young=0.723/0.020, elderly=0.702/0.020). Finally, a trend towards overall decrease of FA in the elderly brain was observed whereby the peak location shifted to smaller values with age (young=0.145/0.012, elderly=0.135/0.016).

Conclusion

Our structural data are consistent with previously published data [1] in that brain volume decreases with age. We are currently extending our morphological analyses to sub-structures of the brain. To our knowledge, no previous DT-MRI data has been published in the rhesus monkey. However, our results are similar to those published in humans [2]. Structural and DT-MRI scans are being repeated at 4 month intervals for tracking longitudinal changes and to control for inter-subject variability.

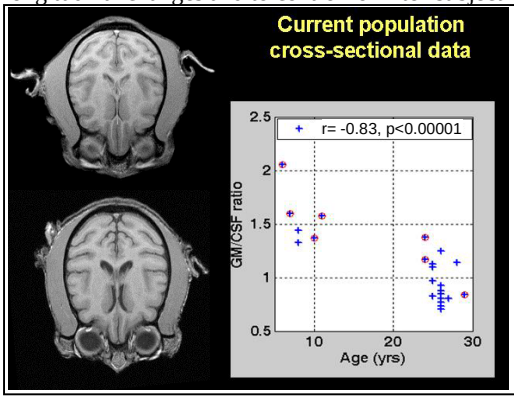

Figure 1: Typical anatomical scans of a young (3 year-old, top-left) male and an elderly (27 year-old, bottom-left) female rhesus monkey. Note the increased ventricular space (dark regions) in the older monkey's brain and the visible change ratios between gray matter and CSF. This change in ratio with age is systematical as depicted in the scatter plot (right).

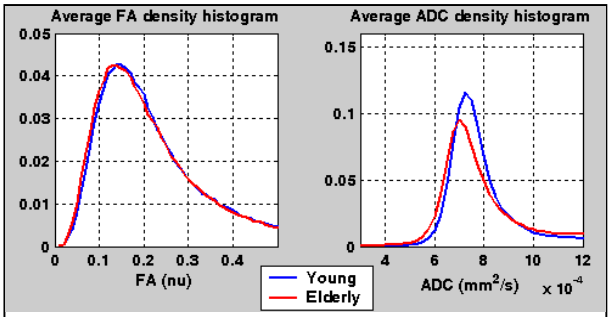

Figure 2: Average density histograms for FA, left, and ADC, right. Albeit subtle, a significant shift in the FA histogram peak was observed. ADC histograms showed more marked changes (see text).

References

[1] Anderssen et al, (1999) *Brain Research* 829:90–98; [2] Nusbaun et al (2001) *Am J Neuroradiol* 22:136–142