Fractional anisotropy as a tool for characterization of white matter fiber tract integrity in the aging rhesus monkey brain

A. Coimbra[1], M. A. Holahan[1], Y. Tymofyeyev[2], R. Hargreaves[1], J. J. Cook[1], D. S. Williams[1]

[1]Imaging Research, Merck Research Laboratories, West Point, PA, United States, [2]Biometrics Research, Merck Research Laboratories, West Point, PA, United States

Introduction:

Diffusion tensor imaging (DTI) and anisotropy indexes have been used to assess integrity of white matter fiber tracts in the human brain [1]. In the present studies we explored the possibility of using DTI as a longitudinal tool for probing fiber integrity in the rhesus monkey by evaluating reproducibility of fractional anisotropy (FA) measurement in the corpus callosum (CC) in a group of four young adult monkeys. Second, as part of a continuing effort to evaluate the potential of quantitative MRI to characterize aging in the primate brain, we made FA measurements in the CC of monkeys aged 3-30 years.

Methods:

Monkeys were intubated under ketamine sedation, and anesthesia maintained with 1.5% isofluorane and mechanical ventilation during scanning. All animal handling procedures were approved by the Institutional Animal Care and Use Committee. Scans were performed on a 3T Siemens/Trio using Siemens eight-channel array head coil. A T1 weighted scan was performed for structural imaging (3D MPRAGE, TR/TE/NA/FA 1.47s/4.38ms/4/12^{o}, 128x128x64 mm^3 FOV, 256x256x80 matrix). A 2D spin echo EPI sequence was used for the DT-MRI (8.1/85/10/90), sensitizing gradients were applied in 6 directions at b values 0 and 1000 s/mm^2 with an inversion pulse (TI=2250ms) applied to minimize any signal contamination from cerebro-spinal fluid. All processing was scripted in MATLAB (MathWorks Inc., http://www.mathworks.com/), with calls to external functions from the SPM2 package (University College London, http://www.fil.ion.ucl.ac.uk/spm/). Rigid body transformation was used to co-register all images to a brain image template where anterior and posterior commissures were made coplanar. The SPM Diffusion toolbox was also used to calculate the diffusion tensors. In-house routines estimated FA maps. Regions of interest including the CC were drawn on the FA maps in the mid-saggital plane. The reproducibility of FA measurements was determined in a group of four young adults each scanned three times over 4 months during which FA values were assumed to have remained constant. Coefficients of variation (CV = 100% x standard deviation / mean) were measured for each animal and analysis of variance and power analysis were performed to estimate population sample sizes necessary to detect group differences (e.g. between populations of demented and aged matched normal subjects). Cross-sectional evaluation of FA changes with age was performed.. Age realted effects were examined in 47 monkeys (20 males and 27 females) spanning a wide range of ages, from 3 to 30 years.

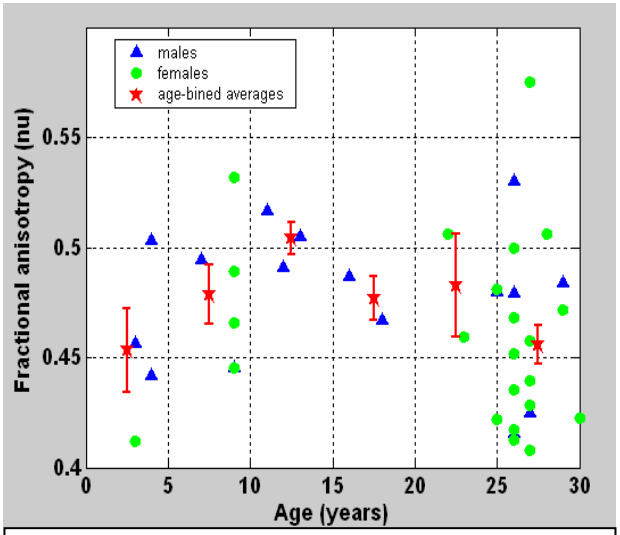
Results:

The reproducibility studies showed that the mean FA value in the CC was 0.5 (range .48 to .54) and CVs for the FA averaged 5.7% across subjects (range, 3.5 to 9.7%). Based on this variability, estimate of population sample size required to achieve 80% statistical power for a group difference of 10% (at $p<0.05$) is only 5-6 subjects per group. When FA is plotted against age, an inverted U shape can be observed in the profile (see figure). There is however substantial variation of FA in the oldest segment of this monkey population. There was no apparent gender related trend.

Conclusion:

FA measurements in rhesus monkeys using the above protocol are reproducible. The age-related inverted U FA profile in monkeys is similar to that reported previously in humans for FA [2] and another MRI myelin marker, R2 [3]. This profile was suggested to be due to gradual late myelination of the genu at younger ages peaking in early adulthood, and followed by gradual decrease due to myelin breakdown at older ages[3].

[1]Rose et al. 2000; [2]Hasan et al. 2004; [3]Bartzokis et al. 2004



Cross-sectional age profile of FA. Triangles=males, circles=females, stars=average for bins of 5 years w/ SEM error bars. Note the inverted U shape of distribution.