Reduced functional connectivity in normal aging in non-human primates

A. Coimbra[1], D. Feng[2], M. Holahan[1], J. Cook[1], D. Williams[1], and R. Baumgartner[2]
[1]Imaging, Merck & Co, Inc, West Point, PA, United States, [2]Biometrics, Merck & Co, Inc, Rahway, NJ, United States

INTRODUCTION:

Non-human primates are believed to provide models of human neurodegenerative diseases and other age-related neurological disorders. Characterizing the natural history of brain function in this animal model is crucial for differentiating normal physiological function from disease. In this work we explored the correlation between age and functional connectivity in lightly anesthetized Rhesus monkeys. Functional connectivity was expressed as goodness-of-fit (GOF) scores in the Posterior-cingulate cortex (PCC) a component region in the Default Mode Network (DMN, Greicius et al 2004). In humans, functional connectivity (GOF) in the DMN decreases with age (Damoiseaux et al, 2008). Animals from a wide age range were studied.

METHODS:

All animal procedures were reviewed and approved by Merck's IACUC. Two groups of animals were studied, "young adult", with ages ranging from 5 to 12 years (mean 7.8 yrs) and "geriatric" with age ranges 25 to 31 years (mean 27.7 yrs). Resting state functional MRI data were acquired in a Siemens Trio 3T system equipped with 12 channel head receive coil (BOLD GRE EPI, TR/TE=3000/28 ms, FA=90^{o}, matrix size=64x64, FOV=128x128mm, 30 axial slices, slice thickness=2mm, gap=0.5mm). Monkeys were initially anesthetized with 2% isoflurane and maintained at 1.2% during image data acquisition. Functional connectivity score, GOF, was derived from an independent component analysis (ICA) approach that measures degree of functional connectivity and spatial specificity of connectivity within a given network (Greicius et al 2004, Coimbra et al 2010). For this study we focused on the PCC, a component of the DMN. Animals were categorized as "young adult" (age<15 years, N=13) and "geriatric" (age>15 years, N=27). Two-sample t-test was used to test cross-sectional GOF difference between the two age groups. One additional animal was scanned (age 13 years) that was treated with MPTP, a neurotoxin that induces permanent symptoms of Parkinson's disease (PD).

RESULTS and CONCLUSION:

There was a significant difference in GOF between age groups (two-sample t-test p<0.03) that followed a similar trend as reported for humans (Damoiseaux et al 2008). On average, GOF was lower in geriatric monkeys than in young adult (p<0.03). Figure 1a shows an example independent component from ICA analysis where spatial configuration overlaps with the PCC ROI. Figure 1b shows box plots of GOF for each age group. Individual GOFs are depicted by the green dots. Interestingly, the PD animal, depicted by the red star, shows the lowest GOF score among young animals.

Overall, these results are in agreement with previously published results in humans; similarities exist between the characteristics of low frequency fluctuations of BOLD signal in awake humans and lightly anesthetized Rhesus monkeys. Particularly, these results indicate that the functional connectivity GOF score follows the same trend of decrease with age in both species suggesting the possible use of Rhesus macaques and GOF functional connectivity in translational investigations of age-related neurological disorders

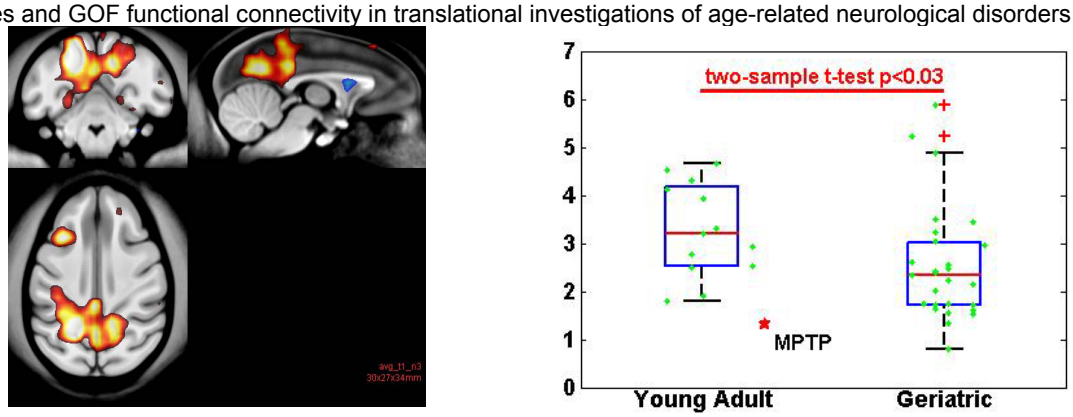

Figure 1: Example of ICA analysis result and GOF distribution within age groups. Figure 1a shows an example independent component from ICA analysis in which spatial configuration overlaps with the PCC ROI. Figure 1b shows boxplots of GOF for each age group and two-sample t-test p<0.03. Individual GOFs are depicted by the green dots. Interestingly the Parkinson's Disease animal, depicted by the red star, shows the lowest GOF score among young adult animals.

References: Greicius et al PNAS 2004, 101(13):4637; Coimbra et al ISMRM proceedings 2010; Damoiseaux et al Cerebral Cortex 2008, 18:1856.