Brain Iron Levels Across the Japanese Macaque Lifespan

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Introduction: Iron (Fe) is an essential element for almost all living organisms. In mammals, Fe is crucial for oxygen transport, electron transport reactions associated with oxidative metabolism, DNA replication and repair, and many other biochemical functions (1-3). In the human brain non-heme iron content varies regionally, with the highest concentration in the globus pallidus (21 mg Fe/100 g tissue; 5.2 mM Fe), and relatively low concentration in the cortical gray matter (3 mg Fe/100 g tissue; 0.7 mM Fe) (4). Iron concentration in the human brain parenchyma increases non-linearly with age (4). Ferritin is the primary iron storage protein in the brain, and can accommodate up to 4500 iron (Fe^{3+}) atoms (5). Since free iron can catalyze oxidative tissue injury, elaborate iron handling and storage mechanisms exist to mitigate such effects. Increased brain iron has been implicated in many neurodegenerative disease states including Alzheimer's disease, Parkinson's disease, multiple sclerosis and others (1-3). For some conditions, such as NBIA, a rare autosomal recessive neurodegenerative disease (1,2), massively increased brain iron deposition is thought to be a primary disease pathology. The purpose of this study was to investigate high-field MRI relaxometry for non-invasive brain iron measurement across the Japanese macaque lifespan and compare to similar measurements in healthy humans.

Methods: The ONPRC Japanese macaque (JM) colony is housed year-round in an outdoor corral with a current total population of ~300. This study included 88 JM (48 female; 39 males, 1 hermaphrodite; age range 1-38 y) and 43 healthy human control subjects (24 females, 19 males; aged 22-61 y) scanned under IACUC and IRB approved protocols. All MRI data were acquired on a whole-body Siemens 3 Tesla (T) MRI instrument (Erlangen, Germany) using a using a 15 cm quadrature radiofrequency (RF) coil for the JM and a 24 cm 12-channel receive only RF coil for human brain. Animals were initially sedated with Telazol, intubated and maintained on 1% isolfurane in 100% O_2 and were continuously monitored by pulse oximetry, respiration, and end tidal CO_2 levels during the study. After shim adjustment and spatial localizers the following sequences were acquired for all JMs: 1) an axial 2D T_2-weighted TSE sequence (TR: 9000 ms; TE: 92 ms; ETL 9, FOV 180 mm x 160 mm, matrix: 320x240, ST 1.0 mm), and 2) an axial 2D PD TSE sequence (TR: 9000 ms, TE: 13 ms, ETL 9, FOV 180 mm x 160 mm matrix: 320x240, ST 1.0 mm). Sequences acquired for human data included an axial 2D T_2-weighted TSE sequence (TR: 12000 ms; TE: 90 ms; ETL 9, FOV 192 mm x 256mm, matrix: 240x320, ST 2.0 mm), and 2) an axial 2D PD TSE sequence (TR: 12000 ms, TE: 13 ms, ETL 9, FOV 192 mm x 256mm, matrix: 240x320, ST 2.0 mm). T_2 and the corresponding R_2 maps were calculated at each voxel using a mono-exponential decay function. Bilateral regions of interest (ROI) were placed in the caudate, putamen and pallidum using the base PD image as a reference. Brain iron content estimates were calculated using published regression equations from postmortem data based on age and subcortical region (4,6). The effects of age on R_2 were modeled with exponential functions based on the work of Hallgren and Sourander (4).

Results and Discussion: R_2 values significantly correlated with calculated estimates of brain iron content (Fe_{est}; mg/100g) in both JM (R_2=0.46*Fe_{est}+ 9.0; R^2=0.72, p<0.0001) and humans (R_2=0.44*Fe_{est}+ 8.0; R^2=0.83, p<0.0001). The models of R_2 changes with age demonstrate that in the JM, R_2 values increase rapidly during the first two decades of life and then begin to plateau at high levels. The time rate constants of the increasing R_2 values in the JM are very similar to the patterns of R_2 increase and iron accumulation seen in humans. However, the maximum R_2 values seen in the JM are much greater than the values seen in humans. This is especially apparent in the pallidum where R_2 values in the JM almost double those seen in humans. These findings suggest that JM continue to accumulate brain iron throughout much of their adulthood and attain brain iron concentrations that are much greater than the concentrations seen in human brains.

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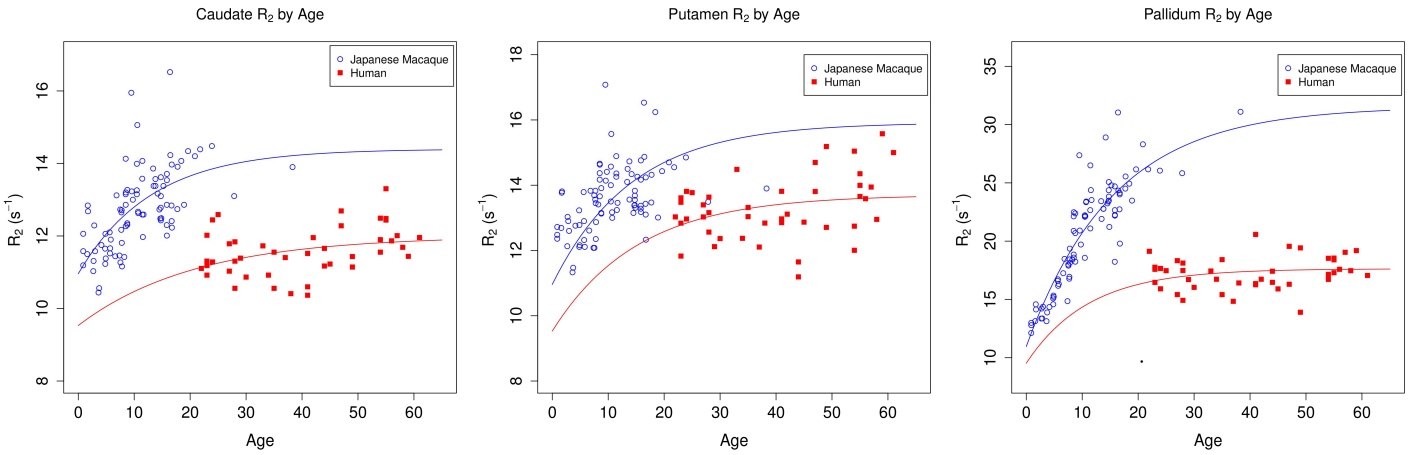

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