Quantitative Relaxographic Assessment of Age Related Changes in Non-Human Primate Brain

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Introduction: In vivo ^1H_2O T_1 measurements have been used extensively for characterizing age-related changes in normal human brain tissue.[1-7] A common finding in the first several years of life is a marked decline in cerebral T_1,[1,3-7] due primarily to an increase in macromolecular content in the developing brain.[8] Beyond the adolescent phase the change is more subtle, where brain tissue T_1 steadily decreases to a minimum near the fourth decade, followed by an increase in the later years.[1,4,7] Regression analysis of T_1 as a function of age revealed an empirical relationship for T_1(age) data in normal human brain.[1,4] Use of this characteristic model to fit T_1(age) in individuals with sickle cell disease revealed abnormal differences with respect to normal controls, suggesting that T_1(age) simulations may be useful for detecting diffuse pathology in genetic diseases.[6,7] Investigation of age-related trends in nonhuman primate T_1 data[9] could elucidate a fundamental understanding of primate brain development, and help establish relevant nonhuman primate models. Here we report findings from an age-related T_1 study of Japanese macaques (*Macaca fuscata*).

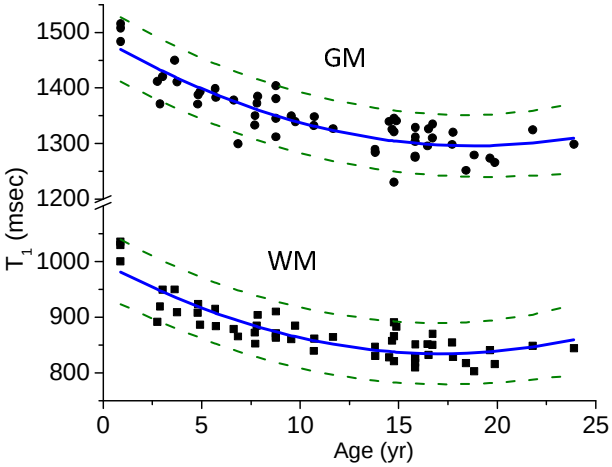
Methods: All animal care and experimental procedures were and approved by the institutional animal care and use committee. Fifty-three Japanese macaques (JMs) (21 Males, 31 Females, 1 Hermaphrodite, age range 0.9-23.9 yr) were selected from a free-ranging colony maintained by our institution. Animals were initially sedated with Telazol, intubated and maintained on 1% isoflurane in 100% O_2 during the MRI study. The animals were continuously monitored by pulse oximetry, respiration, and end tidal CO_2. All MR data were collected on a 3T MRI instrument (Siemens TRIO) using a quadrature transmit/receive extremity RF coil. Full volume parametric ^1H_2O T_1 (msec) maps were produced (per animal) from voxel wise fittings of turboFLASH acquisitions (3D TFL: TR/TE = 2500/3.49 msec; FA = 8º) collected with different inversion times (TI = 200, 900, 2000 msec; and without an inversion pulse). T_1 maps were produced by numerically evaluating the Bloch equations for the variable TI data set accounting for all RF pulses and delays with the constraint that each voxel exhibited a monoexponential IR recovery. The JM T_1 maps were then masked (performed manually for each animal) to select the entire brain, and white matter (WM) and gray matter (GM) T_1 values were obtained from fitting the two prominent peaks in the full volume T_1 histograms to a Gaussian function, and normalized fractional WM, GM, and CSF values were determined from ratios of the peak integrals to the entire histogram integral. All statistical analyses were performed using SPSS 15.0 (Chicago IL). MANCOVA was used to examine the group values for the effects of sex, using age as a covariate: P values were corrected for multiple comparisons. A common quadratic T_1(age) expression was used to fit the JM T_1 data: $T_1(age) = \beta_0 + \beta_1 \times age + \beta_2 \times age^2$.[1,4]

Results and Discussion: Summarized in **Table 1** are the mean T_1 and fractional tissue values obtained from full volume T_1 histograms. The mean WM and GM T_1 values in JM brain tissue are consistent with human T_1 values at 3T.[10] On the other hand, the mean WM and GM volume fractions, respectively, are significantly less and greater than tissue volume fractions in humans.[11,12] Group comparisons (adjusted for age) did not reveal any statistically significant sex-related differences in either T_1 or volume fractions. **Figure 1** displays the full volume T_1 histogram profiles of a young (~2.7 yr) and old (~21.8 yr) JM. There is a clear difference in the WM and GM peak positions, where the peak T_1 values are increased in the young macaque. In addition, the Fractional WM and GM are substantially different between the two animals. Linear regression of fractional WM and GM (not shown) vs. age revealed a slight, yet significant trend of increasing WM ($r = 0.15$, $p = 0.000003$) and decreasing GM ($r = -0.09$, $p = 0.009$), and CSF remained constant in this age range of JMs. The age-related changes in human brain T_1 are analogous to those observed in the Macaque T_1 values. **Figure 2** displays the T_1(age) fittings (and 95% C.I. plots) for mean histogram tissue values (regression coefficients are shown in **Table 1**). Interestingly, the model fits the JM T_1 data in both WM ($R^2 = 0.774$) and GM ($R^2 = 0.768$) quite well, where the structure in the curves is analogous to human data. Because analogous results were obtained in a nonhuman primate, it is possible that the variation in T_1 due to age is primarily caused by similar physiological processes between JM and humans. Analysis of the minimum T_1 value in the simulated curves indicates local minima of about 17 yr in WM, and 19 yr in GM, and this may be related to the discrepancy in the chronological and/or physiological age between humans and macaques.

Table 1. Mean (± SE) JM T_1 (msec) and tissue volume fractions (%), and regression coefficients obtained from T_1(age) simulations.

Histogram Values	WM	GM	CSF
Fraction (%):	29.7 (±0.3)	58.9 (±0.3)	11.3 (±0.2)
T_1 (msec):	865.6 (±9.6)	1333.7 (±11.7)	
Regression Model	**β_0**	**β_1**	**β_2**
WM:	998.1 (±11.3)	-19.0 (±2.2)	0.55 (±0.10)
GM:	1486.8 (±13.7)	-20.3 (±2.7)	0.54 (±0.12)

Note: standard error (± SE)



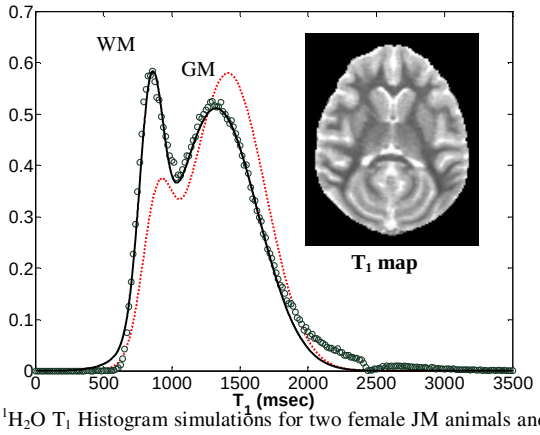


Figure 1. ^1H_2O T_1 Histogram simulations for two female JM animals and a T_1 map from one of the slices used in the histogram analysis (grayscale: 0-2000 msec). The black solid line represents the profile of a 21.8 yr old macaque, and red dotted line is the brain tissue profile of a 2.76 yr old animal. The T_1 histogram data is shown for the older macaque. The two curves clearly depict age-related differences in WM/GM T_1 peak values, and the relative WM/GM volume fractions between the two JMs. The relatively sharp peak near 950 msec is the WM peak, and the broad peak near 1350 msec is the GM peak; consisting primarily of cortical gray matter.

Figure 2. Scatter plot displaying the WM and GM (peak) histogram T_1 values vs. the age of the Japanese macaques. The simulated curves represent the curve fitting results obtained from least-squares regression of the T_1 (age) expression (see Methods section). The coefficients of the quadratic model are listed in Table 1. The olive green dotted lines represent the 95% confidence intervals.

Grant Support: OHSU/Vertex, SRA-05-07-1, Oregon Opportunity

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