

## Regional Brain T2-Relaxation Changes with Age in Healthy Adult Subjects

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### Introduction:

Noninvasive assessment of adult human brain changes resulting from neurologic, neuropsychologic, and neurocognitive deficits against normal aging remains difficult. Myelin and neurons undergo slow degradation with age, and those normative changes, as well as neurodegenerative processes inducing myelin and neuronal loss, increase free tissue water content. The pathological and treatment-related tissue changes can be assessed accurately after controlling for age-related brain changes, which mandates determination of normative changes in gray and white matter over wide-spread brain areas. Magnetic resonance T2-relaxometry provides a quantitative surrogate marker of brain tissue changes in both health and disease by assessing free tissue water content, which differs with different developmental patterns during normal development in pediatric over normal adult aging, and increases with disease processes. T2-relaxation values increase with increased free water content, in the absence of diamagnetic and paramagnetic substances, including hemosiderin deposition. T2-relaxometry has been used successfully to evaluate age-related tissue changes in pediatric and adult subjects, and to detect tissue abnormalities in multiple brain-related medical conditions. Thus, T2-relaxometry procedures can determine normative T2-relaxation values in adult subjects that could provide a means to evaluate integrity of gray and white matter sites during normal aging or during pathologic conditions. In this study, our aim was to assess adult age-related T2-relaxation changes in multiple brain sites, and to determine any gender-related differences in T2-relaxation values in those brain areas.

### Materials and Methods:

Sixty adult (age,  $47.4 \pm 9.0$  years; age range, 31–66 years; body-mass-index,  $24.7 \pm 3.8 \text{ kg/m}^2$ ; 38 male) subjects were studied. All subjects were healthy, without any known neurologic or other medical condition, and were recruited through advertisements at UCLA and in the Los Angeles area.

Brain studies were performed using a 3.0-Tesla MRI scanner (Magnetom Tim-Trio; Siemens), with a receive-only 8-channel phased-array head-coil. We collected high-resolution T1-weighted images using a MPRAGE pulse sequence (TR = 2200 ms; TE = 2.2 ms; inversion time = 900 ms; flip angle = 9°; matrix size = 256×256; FOV = 230×230 mm; slice thickness = 1.0 mm). Proton-density (PD) and T2-weighted images were acquired using a dual-echo TSE pulse sequence (TR = 10,000 ms; TE1, 2 = 17, 134 ms; flip angle = 130°; matrix size = 256×256; FOV = 230×230 mm; slice thickness = 4.0 mm; turbo factor = 5). Data were analyzed with SPM8, MRIcroN, and MATLAB-based custom software. Using PD and T2-weighted images, voxel-by-voxel T2 relaxation values were calculated (1, 2), and whole-brain T2 maps were constructed. Whole-brain T2 maps and T2-weighted images were normalized to Montreal Neurological Institute common space; normalized T2-weighted images were averaged to create background images. Using background images, we created a set of rectangular regions of interest (ROIs) from rostral, thalamic, hypothalamic, pontine, and cerebellar areas. Brain sites within the rostral brain included the bilateral anterior, mid, and posterior cingulate and insular cortices, caudate nuclei, putamen, globus pallidus, frontal white and gray matter, amygdala, ventral, mid, and dorsal hippocampus and temporal white matter, midline occipital gray matter, and occipital white matter. Other sites included the anterior, mid, and posterior regions of the corpus callosum. The thalamic ROIs included the bilateral anterior, mid, and posterior portions, and hypothalamic ROIs included the left and right hypothalamus. The cerebellar and pontine ROIs included the ventral, mid, and caudal pons, cerebellar deep nuclei, bilateral caudal and rostral cerebellar cortices, and bilateral inferior, mid, and superior cerebellar peduncles. These ROI masks and normalized T2-relaxation maps were used to determine mean T2-relaxation values of different brain areas. Pearson's correlation procedures were used to evaluate T2-relaxation changes of different brain areas with age. We used independent-samples t-tests to evaluate male and female T2-relaxation value differences of those sites.

### Results:

Rostral brain sites showed positive and negative correlations between T2-relaxation values of those areas and age. Bilateral regions, including the frontal white matter (left,  $r = 0.37$ ,  $p = 0.004$ ; right,  $r = 0.31$ ,  $p = 0.017$ ) and posterior insula (left,  $r = 0.42$ ,  $p = 0.001$ ; right,  $r = 0.28$ ,  $p = 0.034$ ) showed positive correlations with age, while the putamen showed negative correlations (left,  $r = -0.33$ ,  $p = 0.011$ ; right,  $r = -0.32$ ,  $p = 0.014$ ). Unilateral sites, including the left ventral temporal white matter ( $r = 0.26$ ,  $p = 0.045$ ), mid-insula ( $r = 0.35$ ,  $p = 0.007$ ), mid temporal white matter ( $r = 0.41$ ,  $p = 0.001$ ), posterior cingulate ( $r = 0.29$ ,  $p = 0.024$ ), dorsal hippocampus ( $r = 0.32$ ,  $p = 0.014$ ), and right dorsal temporal white matter ( $r = 0.37$ ,  $p = 0.004$ ) also showed positive correlations with age, as did the posterior corpus callosum ( $r = 0.30$ ,  $p = 0.019$ ). Thalamic regions that showed significant positive correlations between T2-relaxation values and age, included the right anterior ( $r = 0.30$ ,  $p = 0.021$ ), mid ( $r = 0.37$ ,  $p = 0.004$ ), posterior ( $r = 0.38$ ,  $p = 0.003$ ) thalamus, and left mid thalamus ( $r = 0.35$ ,  $p = 0.006$ ). The right hypothalamus showed a significant positive correlation ( $r = 0.27$ ,  $r = 0.039$ ); however, no correlations emerged on the left side. The ventral pons showed a significant T2-relaxation and age negative correlation ( $r = -0.28$ ,  $p < 0.029$ ). Age ( $p = 0.16$ ) and body-mass-index ( $p = 0.39$ ) did not differ between male and female subjects. Multiple brain areas in rostral, thalamic, and cerebellar sites, including the right frontal gray matter, left globus pallidus and putamen, right dorsal temporal white matter, and bilateral occipital white matter regions, showed significant differences in T2-relaxation values between male and female subjects.

### Discussion:

Multiple brain regions showed positive correlations between T2-relaxation values and age, suggesting that free water content increases with normal aging in those sites. Selected brain areas, including the putamen and ventral pons, showed negative correlations between T2-relaxation values and age, possibly reflective of hemosiderin deposition in those areas with increasing maturity. Several brain sites in frontal, temporal, occipital, basal ganglia, and cerebellar regions showed significant differences between males and females. The findings provide baseline T2-relaxation values of those sites against which disease-related tissue changes can be evaluated, and suggest the need for partitioning normal age- and gender-related changes during any such evaluation.

### References:

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