Maturational and Aging Effects on Human Brain Apparent Transverse Relaxation

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Abstract

The goal of this study was to address the need for comprehensive reference data regarding maturational and aging effects on regional transverse relaxation rates ($R_2$) of the brain in normal humans. Regional $R_2$s were measured in twenty-five brain structures from a sample of seventy-seven normal volunteers 9 to 85 years of age. The relationships between regional $R_2$ and age were determined using generalized additive models, without the constraint of a specified a priori model. Data analysis demonstrated that the brain tissue $R_2$-age correlations followed various time courses with both linear and non-linear characteristics depending on the particular brain structure. Most anatomical structures studied exhibited non-linear characteristics, including the amygdala, hippocampus, thalamus, globus pallidus, putamen, caudate nucleus, red nucleus, substantia nigra, orbitofrontal white matter and temporal white matter. Linear trends were detected in occipital white matter and in the genu of corpus callosum. These results indicate the complexity of age-related $R_2$ changes in the brain while providing normative reference data that can be utilized in clinical examinations and studies utilizing quantitative transverse relaxation.

Introduction

The transverse relaxation time ($T_2$) and transverse relaxation rate ($R_2$), where $R_2 = 1/T_2$, play a fundamental role in generation of MRI contrast in the human brain. Quantitative $T_2$ and $R_2$ values are important in the study of various brain disorders, including brain tumors, schizophrenia, multiple sclerosis, autism, and Alzheimer’s disease [1,2,3,4]. Previous studies on brain transverse relaxation have shown a general trend of $T_2$ decrease during maturation while, conversely, showing a $T_2$ increase during aging [5,6,7,8,9,10,11,12,13,14,15,16,17,18]. Despite these trends, the $T_2$-age correlation in the human brain is not yet well characterized, making interpretation of deviations from normative values uncertain.

Saito et al. studied 18 normal volunteers and 33 patients with either no or small brain lesions at 1.5 T and showed that $T_2$ for the brain falls into four distinct periods of life: 0–2 years old (maturation period), 2–20 years old (development period), 20–60 years old (adult/hood period) and ≥60 years old (senescence period) [8]. Most of the subjects in this study, however, had brain disorders, raising the concern that the reported $T_2$ values do not represent truly normal findings. A study at 1.5 T by Siemonsen et al. on 50 patients (12–91 years of age) with no significant brain lesions except white matter leukoaraiosis, found an increase in $T_2$ that linearly correlated with age in the thalamus and three white matter structures, but not in the caudate nucleus and lentiform nucleus [9]. Another study on 70 normal subjects aged 3 weeks to 31 years showed that $T_2$ decreased with increasing age; the rate of decrease was greater at a younger age and slower in the years after [10], indicating a nonlinear relationship with age. Kim et al. studied the corpus callosum in 33 normal pediatric subjects aged 3–15 years at 3 T and reported a significant $T_2$-age correlation in the splenium, but not in the genu [11]. After studying 33 normal subjects aged 19–59 years at 3 T, Hasan et al. did not find significant $T_2$-age correlation in the caudate nucleus [12]. The discordant findings of these previous studies demonstrate the need for establishing a more comprehensive $T_2$ mapping data set, based on a larger normal cohort with a greater age range and more brain structures.

The analytic approaches used in the previous studies of $T_2$-age correlations have been based on a priori models. Most of them have employed linear regression [9,11,12,13,18]. Hasan et al. reported using both linear and quadratic terms to estimate the aging effects on $T_2$ and the relation between $T_2$ and age in whole brain gray and white matter, caudate nucleus, and the anterior limb of internal capsule followed a quadratic, U-shaped curve [17]. Although plausible, little histopathological data is available to...
support these a priori models. Therefore, the current study was designed to address these limitations and elucidate the effects of development and aging on regional T2/R2 in the normal human brain without the bias of a priori models. In this study, we employed generalized additive models (GAM), a well-known nonparametric approach to regression that can accommodate any potential nonlinear relationship [19]. The goals of this study were: 1) to establish standardized, normative T2 maps of several age intervals as references for clinical trials and routine examinations, 2) to determine continuous developmental and aging characteristics in representative brain structures, and 3) to determine the regional T2 differences among these brain structures.

Methods

Seventy-seven volunteers without known neurologic or psychiatric disorders aged 9 to 85 years (41 males and 36 females) participated in the study (see Table 1). There was no significant difference between the age distributions in the two genders. To exclude abnormal cognitive disorders, the 39 subjects over the age of 50 (average education 14.9±1.6 years) received the Mini-Mental State Examination (MMSE) [20] and the Clinical Dementia Rating Scale (CDR) [21]. All 39 subjects had a CDR score of 0, meaning fully oriented; their average score on the MMSE was 29.1±1.0, which is in the normal range of 25 to 30. The study protocol was approved by the Penn State Hershey Institutional Review Board. All subjects or parents of subjects under 18 years old gave informed, written consent prior to participation.

The T2/R2 mapping was acquired on a 3 T scanner (Bruker MedSpec S300 with TEM head coil, Bruker BioSpin Corporation, Ettlingen, Germany) with maximal strength 3 gauss/cm using a 9-echo spin-echo sequence with TE from 11.8 to 106.2 ms (TR = 4000 ms, flip angle = 180°), Gaussian radio-frequency (RF) pulse, bandwidth = 80 kHz, 20 2.5-mm-thick axial slices with no gap between slices centered at hippocampus, FOV = 25×25 cm², acquisition matrix = 256×192, reconstruction matrix = 256×256, number of average = 1). A test-retest was performed on five same magnet. No significant difference was observed between R2s acquisition matrix = 256.

The T2 of the tissue for a given TR and, thus, was excluded from the T2/R2 estimation. The resultant spatial resolution of the R2 map was 1×1×2.5 mm³. Then the R2 maps were normalized to the Montreal Neurological Institute brain template [22] using SPM5 (Wellcome Trust Centre for Neuroimaging, University College London, UK) [23]. The normalized R2 maps had a spatial resolution of 1×1×2.5 mm³. These data are available on-line at http://www.pennstatehershey.org/web/nmrlab/resources1.

Regional R2s were obtained from manually drawn regions of interest (ROI) in twenty-five brain structures as shown in Figure 2. These structures were chosen because they are: 1) functionally important and well-studied; 2) clinically important as they involve in many neurological disorders such as Alzheimer’s disease and Parkinson’s disease; and 3) they are relatively homogeneous structurally and have clear boundaries with neighboring structures. Cortical gray matter was not studied because of significant partial volume effects from subcortical white matter and cerebrospinal fluid signal on the surface of the brain. In order to select regions of interest (ROIs) that were representative of given brain structures with minimal contaminations of surrounding tissues, the following rules were followed: 1) an ROI should be in the center of the structure where the R2 distribution is relatively homogeneous; 2) tissues surrounding an ROI in the two adjacent slices should be within the same structure; and 3) an ROI should be at least one voxel away from surrounding structures in the image plane. Eighteen gray matter and seven white matter structures with clear boundaries from surrounding structures were selected from the R2 maps, as illustrated in Figure 2. They are the amygdala, head of hippocampus, genu of corpus callosum, anterior and posterior nucleus of thalamus, head of caudate nucleus, globus pallidus, putamen, substantia nigra, red nucleus, orbitofrontal white matter, anterior temporal white matter, and occipital white matter. The size of ROIs varied from 21 voxels (e.g., red nucleus) to 107 voxels (e.g., the anterior nucleus of

Table 1. Age distribution of the study cohort.

| Age (year) | Number of Subjects |
|-----------|--------------------|
| 9–12      | 6                  |
| 13–19     | 8                  |
| 20–29     | 14                 |
| 30–39     | 6                  |
| 40–49     | 4                  |
| 50–59     | 16                 |
| 60–69     | 9                  |
| 70–79     | 6                  |
| >80       | 8                  |

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Figure 1. Example T2 relaxation regression plot of left putamen from a healthy 33-year-old man. The plus signs are the signal intensity; the solid line is the fitted curve for the T2/R2 estimation (R² = 0.999). doi:10.1371/journal.pone.0031907.g001
thalamus) in order to provide representative values for the given brain structures.

The relationship between $R_2$ and age was examined with generalized additive models [19]. These models allow the mean of the dependent variable ($R_2$) to depend on an additive predictor (age) through a nonlinear link function and are especially useful for visualizing the relationship between a dependent variable and one or more independent variables. The specific GAM employed extends simple linear regression by expanding the linear form of the expected value of the dependent variable:

$$E(R_2) = \alpha + \beta \times \text{age}.$$  \hspace{1cm} (2)

Thus, the model relating $R_2$ to age can be expressed as:

$$E(R_2) = \alpha + \beta \times \text{age} + \text{spline(age)},$$  \hspace{1cm} (3)

where $\alpha$ is the intercept, $\beta$ is the slope, and spline(age) is the partial smoothing spline term.

Plots of partial predictions spline(age), the estimated smoothing spline function, versus age along with a 95% confidence band were used to assess where nonlinearities occurred between $R_2$ and age. If the 95% confidence limits cover the zero axis of the independent variable, it indicates that the nonlinear component of age is not significant. The shape of the plot of partial spline predictions indicates the form of the functional relationship between $R_2$ and age. For example, a quadratic shape of the plot would indicate a quadratic relationship between $R_2$ and age. Additionally, plots of the prediction of $R_2$ overlaid with the observed data allow assessment of the goodness of fit. All models were fit using the GAM procedure in SAS (SAS Institute, Inc. Cary, NC, USA).

**Results**

Among the twenty-five ROIs in this study, twenty-four were symmetrically located on the two hemispheres (bilateral) while one in the midline of the brain. Among these twenty-four bilateral ROIs, no significant difference in $R_2$ between the two corresponding ROIs on each hemisphere (paired t-test, $p>0.14$) was

![Figure 2. ROIs shown on a normalized $R_2$ map from a healthy 33-year-old man.](https://example.com/figure2)
observed. Thus, the $R_2$ values from bilateral ROI pairs were averaged and used for subsequent analysis. The $R_2$ values in Figures 3, 4, 5, 6, 7 are from 13 discrete brain structures with twelve being bilateral and one along the midline. Significant correlations between $R_2$ and age were observed in all brain structures examined (see Table 2). As a general trend, the relationship between $R_2$ and age was nonlinear ($p<0.05$) in most of the structures. Moreover, all examined gray matter structures, except the caudate nucleus, exhibited strong, nonlinear age correlations, while most white matter structures showed negative linear age correlations. These relationships are illustrated in Figures 3, 4, 5, 6, 7 and, depending on the particular structures, comprise several different patterns. For example, the $R_2$ in the genu of corpus callosum and occipital white matter decreased linearly with age ($p<0.001$ for the linear component and $p>0.17$ for the nonlinear component) (see Figures 6 and 7). In these cases, the corresponding plots of the smoothing spline functions lie within the 95% confidence band containing the zero axis over the entire age range. For the remaining structures some portion of the 95% confidence band lies outside of the zero axis, indicating non-linear age correlations. The $R_2$ vs. age plots for most of the gray matter structures studied (e.g., the hippocampus, amygdala, globus pallidus, thalamus, red nucleus and substantia nigra) showed a quadratic pattern where $R_2$ increases during adolescence and young adulthood ($<30$ years), plateaus in middle age (30 to as early as 40 or as late as 60 years, depending on the structures), and finally, decreases in older age (Figures 3, 4, 5). In the putamen and caudate nucleus, the $R_2$-age correlation appears to follow a logarithmic pattern that continues to increase after adolescence, but at a slower rate (Figures 4 and 5). In contrast, most of the white matter structures studied (e.g., the genu of corpus callosum, bilateral orbitofrontal and occipital white matter) showed a significant descending trend between $R_2$ and age (Figures 6 and 7).

Table 3 shows the average $T_2$ values of thirteen brain structures in normal adults. A significant heterogeneity in the $T_2$ distribution in the brain was observed. The average $T_2$ of these structures in twenty-six 30–59 year-old healthy normal subjects varied from 60.58±2.21 ms (globus pallidus) to 100.34±1.29 ms (hippocampus). When the sample age range was extended to 20–85 years, the average $T_2$ varied from 61.31±2.42 ms (globus pallidus) to 101.60±2.25 ms (hippocampus). No significant gender difference in $T_2$ for the brain structures studied was shown (for the age range 30–59 years, two-sample t-test, $p>0.24$; for the age range 20–85 years, two-sample t-test, $p>0.07$).

**Discussion**

This study presents the maturational and aging effects on transverse relaxation in representative human brain structures at 3 T. The results provide needed normative data for clinical examinations and research studies utilizing transverse relaxation at this field strength. Compared to the 3 T data published previously, the transverse relaxation times acquired in this study are similar to the results reported by Wansapura et al. [15], but significantly shorter than those from other reports [7,13,17,18]. Most of the $T_2$ data previously published [13,17,18] were collected using the dual-echo method, which tends to estimate a longer than reality relaxation time. The $T_2$ data in Wansapura’s study were acquired with a multi-echo sequence, however, they were only acquired from a single slice, which are not sufficient to determine a quantitative baseline for general human brain studies [15]. The data from Gelman et al. [7] were obtained using a novel “Gradient-Echo Sampling of Free Induction Decay and Echo (GESFIDE)” pulse sequence designed to simultaneously measure both $T_2$ and $T_2^*$ [24]. Although innovative, the GESFIDE method leads to a systematically shortened $T_2$ compared to those measured with the conventional, multiple spin-echo sequence on clinical systems. In the GESFIDE sequence, a long inter-echo delay (90 ms) was used to acquire a spin-echo and a series of gradient echoes during the inter-echo delay with multiple strong readout gradients. The source of the difference in $T_2$ is likely from the enhanced $T_2$ sensitivity to the static magnetic inhomogeneity due to water diffusion by the applied gradients during the inter-echo delay by the GESFIDE method. Bartha et al. investigated the mechanism of $T_2$ relaxation in the human brain measured with multi-echo spin-echo method. Their study demonstrated that the loss of phase coherence of water magnetization due to local static magnetic field gradient could not be refocused by the 180° pulse if a significant water diffusion present during the inter-echo delay [25]. In fact, the $T_2$ relaxation rate depends on the square of inter-echo delay time between acquisitions of spin-echo images for $T_2$ measurement. The inter-echo delay for our measurement was 11.8 ms compared to delays as long as 98 ms in other studies. Thus, from a mechanistic point of view, apparent $T_2$/R2 values could vary significantly depending on the imaging sequence used and acquisition parameter settings. For the purpose of general clinical applications where measurement reproducibility and general availability are important, our apparent $T_2$ measurement from the brain was conducted with a commonly used multi-echo spin-echo sequence with minimum inter-echo delay.

An important implication related to the above issue is the underlying mechanism of $T_2$ change with age demonstrated by this study. $T_2$ relaxation depends on water molecule mobility and microscopic magnetic environment that, in turn, depends on histological and physiological factors in the tissues and can be altered by pathological changes. As discussed earlier, depending on the specific brain structures, imaging acquisition parameters, such as echo time and inter-echo delay, should also be considered for data interpretation. For example, $T_2$ relaxation measured using longer inter-echo delay is more sensitive to the local static magnetic field gradients associated with tissue conditions such as iron contents, particularly, in the iron-rich regions (e.g., substantia nigra). Conversely, shorter echo-delay would lead $R_2$ to be more dependent on tissue cellularity changes in the brain structures such as white matter where water molecule diffusions are more restricted. In our study, the shortest possible inter-echo delay (11.8 ms) was used.

With respect to specific brain structures and the range of age, our data exhibited varied $R_2$-age relationships. From 9 to 30 years of age, significant positive correlation between tissue $R_2$ and age was observed in all of the nine gray matter structures studied (i.e., amygdala, hippocampus, anterior and posterior nucleus of thalamus, globus pallidus, putamen, caudate nucleus, red nucleus, and substantia nigra). The $R_2$-age correlation after age 40, however, demonstrated more diverse characteristics. In the anterior nucleus of thalamus, $R_2$ increases with age and reaches its maximum at about age 40, and decreases steadily in the older age. It is interesting to note that $R_2$ reaches its maximum in the hippocampus at a much later age, at about age 60, indicating its more dynamic characteristic over the life span. In the iron-rich brain structures (globus pallidus, red nucleus, and substantia nigra), the downward trend in $R_2$ after age 40 is less apparent, and in some structures (putamen and caudate nucleus), there was even an upward trend. Thus, the characteristics of $R_2$-age correlations identified, particularly in iron-reach structures, are likely a result of two major contributing effects: 1) decreasing cellularity that decreases $R_2$, and 2) increasing iron content that increases $R_2$. A postmortem study showed that non-heme iron concentration in
Figure 3. Scatter plots and fitted curves of $R_2$-age correlations in amygdala, hippocampus and anterior thalamus. Graphs in the left column are partial predictions plots of estimated smoothing spline functions against age with a 95% confidence band for the whole curve; graphs in the right column plot the predicted values of $R_2$ against age (solid line) with the observed data overlaid (plus signs). Top, amygdala; middle, head of hippocampus; bottom, anterior thalamic nucleus.

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Figure 4. Scatter plots and fitted curves of $R_2$-age correlations in posterior thalamus, globus pallidus and putamen. Graphs in the left column are partial predictions plots of estimated smoothing spline functions against age with a 95% confidence band for the whole curve; graphs in the right column plot the predicted values of $R_2$ against age (solid line) with the observed data overlaid (plus signs). Top, posterior thalamic nucleus; middle, globus pallidus; bottom, putamen.

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Figure 5. Scatter plots and fitted curves of $R_2$-age correlations in caudate, red nucleus and substantia nigra. Graphs in the left column are partial predictions plots of estimated smoothing spline functions against age with a 95% confidence band for the whole curve; graphs in the right column plot the predicted values of $R_2$ against age (solid line) with the observed data overlaid (plus signs). Top, head of caudate nucleus; middle, red nucleus; bottom, substantia nigra.

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Figure 6. Scatter plots and fitted curves of $R_2$-age correlations in corpus callosum, orbitofrontal and temporal white matter. Graphs in the left column are partial predictions plots of estimated smoothing spline functions against age with a 95% confidence band for the whole curve; graphs in the right column plot the predicted values of $R_2$ against age (solid line) with the observed data overlaid (plus signs). Top, genu of corpus callosum; middle, orbitofrontal WM; bottom, anterior temporal WM. doi:10.1371/journal.pone.0031907.g006
The brain increases with age [26], which would lead to an increase in $R_2$ accordingly [27]. The increase in iron concentration with age in the putamen and caudate nucleus has reached a level that its contribution to $R_2$ becomes so significant even though our $R_2$ mapping method is relatively less sensitive to tissue iron contents because of the short inter-echo spacing. Thus, tissue iron likely plays an important role in the changes of transverse relaxation in the iron-rich brain structures during normal aging.

The relationships between $R_2$ and age showed quadratic dependence in most gray matter structures studied, which is consistent with the observation by Hasan et al. in a study of normal subjects aged 15–58 years [17]. In the white matter structures, $R_2$ appears to follow a general downward trend with less apparent quadratic age-correlation than those in gray matter. The change in $R_2$ in these brain structures could reflect the more dominant changes in tissue cellularity and/or myelination during maturational and aging processes. $T_2$ in white matter is known to consist of multiple components significantly influenced by the structure of myelin. They are generally classified into three components: 1) a fast relaxing component ($T_2 \sim 10–50$ ms) from the water located within the myelin sheath, 2) an intermediate component ($T_2 \sim 55–110$ ms) from intracellular and extracellular water in the tissue, and 3) a long component ($T_2 > 1$ s) from cerebrospinal fluid [28]. The fast component of $R_2$ from myelin water needs to be measured using special sequences with short echo-times (<10 ms) and very long echo-trains (>32 echoes).

| Structure            | $\beta$ (year$^{-1}$·sec$^{-1}$) | t-value | p-value   | Chi-square | p-value |
|----------------------|---------------------------------|---------|-----------|------------|---------|
| Amygdala             | 0.0047                          | 4.5     | <0.0001   | 65.56      | <0.0001 |
| Hippocampus          | 0.0017                          | 2.44    | 0.017     | 101.18     | <0.0001 |
| A_Thalamus           | −0.0078                         | −5.09   | <0.0001   | 80.05      | <0.0001 |
| P_Thalamus           | 0.0024                          | 1.00    | 0.32      | 54.13      | <0.0001 |
| Globus Pallidus      | 0.0054                          | 1.77    | 0.081     | 40.09      | <0.0001 |
| Putamen              | 0.0353                          | 11.19   | <0.0001   | 27.59      | <0.0001 |
| Caudate Nucleus      | 0.0205                          | 8.37    | <0.0001   | 8.66       | 0.013   |
| Red Nucleus          | 0.0034                          | 1.2     | 0.2344    | 54.85      | <0.0001 |
| Substantia Nigra     | 0.0131                          | 3.9     | 0.0002    | 41.09      | <0.0001 |
| G_Corpus Callosum    | −0.0160                         | −9.01   | <0.0001   | 3.60       | 0.17    |
| Orbitofrontal_WM     | −0.0138                         | −8.61   | <0.0001   | 19.58      | 0.0004  |
| A_Temporal_WM        | −0.0042                         | −2.39   | 0.0192    | 19.77      | <0.0001 |
| Occipital_WM         | −0.0152                         | −10.76  | <0.0001   | 2.51       | 0.29    |

Note: A, anterior; P, posterior; G, genu; WM, white matter.

Table 2. Linear and non-linear correlation between $R_2$ and age in the brain.

Figure 7. Scatter plot and fitted curve of $R_2$-age correlation in the occipital white matter. Graph on the left side is a partial prediction plot of estimated smoothing spline function against age with a 95% confidence band for the whole curve; graph on the right side plots the predicted values of $R_2$ against age (solid line) with the observed data overlaid (plus signs).

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Table 3. Brain T2 (ms, mean/standard deviation) in adults.

| Age Range | Amy | Hip | CN | GP | Pu | RN | SN | A_Tha | P_Tha | G_CC | Orbfr_WM | A_Tem_WM | Occ_WM |
|-----------|-----|-----|----|----|----|-----|-----|-------|-------|------|----------|----------|--------|
| 20–85 years | 81.73/3.36 | 72.00/3.10 | 77.79/3.12 | 77.07/3.11 | 79.66/2.74 | 90.36/3.35 | (n = 65) |
| 30–59 years | 81.06/2.22 | 71.69/3.35 | 66.31 | 63.07/3.51 | 60.01/2.47 | 60.01/2.47 | 59.00/2.47 | 60.01/2.47 | 60.01/2.47 | 60.01/2.47 | 60.01/2.47 | (n = 26) |

Note: A, anterior; P, posterior; Amy, amygdala; Hip, hippocampus; CN, caudate nucleus; GP, globus pallidus; Pu, putamen; RN, red nucleus; SN, substantia nigra; Tha, thalamus; G_CC, genu of corpus callosum; Orbfr, orbitofrontal; WM, white matter; Tem, temporal; Occ, occipital.

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