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Rapid high-resolution three-dimensional mapping of T_1 and age-dependent variations in the non-human primate brain using magnetization-prepared rapid gradient-echo (MPRAGE) sequence

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Abstract

The use of quantitative T_1 mapping in neuroscience and neurology has raised strong interest in the development of T_1 -mapping techniques that can measure T_1 in the whole brain, with high accuracy and precision and within short imaging and computation times. Here, we present a new inversion-recovery (IR) based T_1 -mapping method using a standard 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence. By varying only the inversion time (TI), but keeping other parameters constant, MPRAGE image signals become linear to $\exp(-TI/T_1)$, allowing for accurate T_1 estimation without flip angle correction. We also show that acquiring data at just 3 TIs , with the three different TI values optimized, gives maximum T_1 precision per unit time, allowing for new efficient approaches to measure and compute T_1 . We demonstrate the use of our method at 7 Tesla to obtain 3D T_1 maps of the whole brain in common marmosets at 0.60 mm resolution and within 11 minutes. T_1 maps from the same individuals were highly reproducible across different days. Across subjects, the peak of cerebral gray matter T_1 distribution was 1735 ± 52 ms, and the lower edge of cerebral white matter T_1 distribution was 1270 ± 43 ms. We found a significant decrease of T_1 in both gray and white matter of the marmoset brain with age over a span of 14 years, in agreement with previous human studies. This application illustrates that MPRAGE-based 3D T_1 mapping is rapid, accurate and precise, and can facilitate high-resolution anatomical studies in neuroscience and neurological diseases.

Keywords

aging; development; longitudinal relaxation; magnetic resonance imaging; relaxometry

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Introduction

Quantitative T_1 mapping, also known as T_1 relaxometry, is a magnetic resonance imaging (MRI) technique increasingly useful in neuroscience and neurology. T_1 maps of the normal human brain reveal regional heterogeneity in T_1 across cortical gray matter (Steen et al., 2000), from which cortical areas can be demarcated (Bock et al., 2009; Sigalovsky et al., 2006). Abnormalities in T_1 values of the brain may indicate demyelination in diseases such as multiple sclerosis (Srinivasan et al., 2003; Vrenken et al., 2006) and Canavan's disease (Haselgrove et al., 2000). T_1 values of the gray and white matter also change with age in healthy humans (Saito et al., 2009; Suzuki et al., 2006). These applications require T_1 mapping with high resolutions in all three spatial dimensions to resolve cortical areas and pathological regions, and require high accuracy and precision because the regional heterogeneity and the pathological and age-related differences in T_1 are often within just a few percent. New techniques that meet these demands within a reasonably short imaging time can expand the scientific and clinical uses of T_1 mapping.

A prevalent and time-efficient method of three-dimensional (3D) T_1 -mapping is the variable flip angle method, which acquires spoiled gradient-echo images at two different flip angles (Cheng and Wright, 2006; Deoni et al., 2003; Venkatesan et al., 1998). In this method, imaging time is shortened by using repetition times (TR) on the order of a few milliseconds (Deoni et al., 2003), but the short TR , small flip angles and field inhomogeneities can severely degrade the precision and accuracy of estimated T_1 (Wang et al., 2006). Another prevalent way of measuring T_1 is based on inversion recovery (IR). IR-based methods are often regarded as being precise because the inversion maximizes the dynamic range of longitudinal magnetization, and accurate because T_1 can be estimated independent of flip angles. On the other hand, IR-based methods typically require long TR to allow full recovery of the longitudinal magnetization, which often makes total imaging time impractical in the clinical setting. One approach to expedite imaging in IR-based methods is to use a short TR to drive the longitudinal magnetization to a steady state prior to each inversion pulse (Haselgrove et al., 2004; Kaldoudi and Williams, 1993; Steen et al., 1994), and another approach is to acquire multiple readouts after each inversion pulse (Deichmann et al., 1999; Gowland and Mansfield, 1993; Shah et al., 2001), such as in the Look-Locker (LL) acquisition (Deichmann, 2005; Henderson et al., 1999). These two approaches have been combined in a new method that does LL acquisition under steady-state, but still uses a long TR ($\approx 6T_1$) between inversion pulses (Shin et al., 2009).

In the present work, we present a new IR-based T_1 -mapping method that allows the acquisition of high-resolution, three-dimensional T_1 maps. In our method, total imaging time is made short by employing the well-established magnetization-prepared rapid gradient-echo (MPRAGE) sequence (Mugler and Brookeman, 1990) to acquire multiple readouts per inversion pulse after driving the longitudinal magnetization to a steady-state with a relatively short TR ($\approx 2-3T_1$). MPRAGE is available on many commercial MRI scanners and has been widely used to obtain T_1 -weighted images (Bock et al., 2009; Deichmann et al., 2000; Mugler and Brookeman, 1991). However, it is rarely used for quantitative T_1 mapping, partly because the signal has a complex dependence on T_1 (Wright et al., 2008). Our approach avoids this problem by acquiring separate sets of MPRAGE images with different TIs and establishing a simple mathematical relationship amongst them. Imaging time is also shortened by acquiring data at just three different TIs , instead of the conventional approach of acquiring at more than three TIs . We demonstrate the implementation of this MPRAGE-based T_1 -mapping method at 7T and use it to study the age-dependent T_1 variations in gray and white matter in a small non-human primate, the common marmoset (*Callithrix jacchus*).

Theory

Three-parameter modeling of MPRAGE signal

The standard MPRAGE sequence comprises repeated cycles of the following events in succession: an inversion pulse with flip angle α near 180° , followed by an inversion delay TI , after which data is acquired with a train of n excitation pulses in a fast low-angle shot (FLASH) sequence (Deichmann et al., 2000; Mugler and Brookeman, 1990, 1991). Each excitation pulse has a small flip angle θ and is followed by the readout of one k-space line. The next cycle starts with a new inversion pulse at a time delay TD after the last excitation pulse of the previous cycle (see the Figure in Supplement 1). Hence, the repetition time between two successive inversion pulses is $TR = TI + (n - 1)TRE + TD$, where TRE is the time between two successive excitations in the FLASH sequence. Within each cycle, the longitudinal magnetization M_i immediately before the i -th excitation pulse is related to the magnetization M_{i-1} as in (Wright et al., 2008):

$$M_i = [1 - \exp(-TRE/T_1)] M_0 + \rho M_{i-1} \quad [1]$$

where

$$\rho = \exp(-TRE/T_1) \cos \theta. \quad [2]$$

At steady-state, the M_1 immediately before the first excitation of the next cycle is related to the M_n before the last excitation of the previous cycle:

$$M_1 = [1 - (1 - \cos \alpha) \exp(-TI/T_1)] M_0 - \cos \alpha \exp[-(TI+TD)/T_1] (M_0 - M_n \cos \theta) \quad [3]$$

From these equations, the M_i before each excitation pulse can be derived (see Supplement 1), as a linear function of $\exp(-TI/T_1)$:

$$M_i = A_i - \rho^{i-1} B \exp(-TI/T_1) \quad [4]$$

where

$$A_i = \chi \left(\sum_{j=0}^{i-2} \rho^j \right) M_0 + \rho^{i-1} \frac{1 + \cos \alpha \exp[-(TI+TD)/T_1] \left[\sum_{j=0}^{n-2} \rho^j \right] \chi \cos \theta - 1}{1 - (\cos \theta)^n \cos \alpha \exp(-TR/T_1)} M_0, \\ B = \frac{(1 - \cos \alpha)}{1 - (\cos \theta)^n \cos \alpha \exp(-TR/T_1)} M_0 \quad [5]$$

To measure T_1 , the MPRAGE is acquired at different TI values, but the sum $TI+TD$, which equals to $TR - (n - 1)TRE$, is kept constant by keeping all other MPRAGE parameters, including TR , n and TRE , constant across the MPRAGE runs. Under this constraint, both the A_i and the $\rho^{i-1} B$ in Eq. [4] become independent of TI , because A_i is a function of not TI alone, but $TI+TD$. Consequently, the longitudinal magnetization M_i is a linear function of $\exp(-TI/T_1)$.

This linear relationship is also maintained in the MPRAGE image signal. The signal S in a voxel of the reconstructed image is related to the longitudinal magnetizations M_i :

$$s = \sum_i Fw(i) M_i \sin \theta \exp(-TE/T_2^*) = \xi \left(\sum_i Fw(i) A_i \right) - B \xi \left(\sum_i Fw(i) \rho^{i-1} \right) \exp(-TI/T_1) \quad [6]$$

where $\xi = \sin \theta \exp(-TE/T_2^*)$ and $Fw(i)$ is the Fourier weight of each k-space line in the voxel, which is determined solely by the phase-encoding scheme used by MPRAGE. Eq. [6] indicates that the image signals are described by the three-parameter model

$$S = p_1 - p_2 \exp(-TI/T_1) \quad [7]$$

where $p_1 = \xi \left(\sum_i Fw(i) A_i \right)$ and $p_2 = \xi \left(\sum_i Fw(i) \rho^{i-1} \right)$. Since p_1 and p_2 remain unaltered across the MPRAGE runs that differ in only TI , S is a linear function of $\exp(-TI/T_1)$.

MPRAGE images are subject to blurring along the centric phase-encoding direction, which can be ameliorated by applying a high-pass spatial filter to the k-space data (Deichmann et al., 2000), such that each $Fw(i)$ is multiplied by a unique weight w_i . In Supplement 1, we show that with this spatial filtering technique, the parameter p_2 remains unaltered across runs, and the three-parameter model remains valid, as long as the same filter is applied to all MPRAGE images. This allows the use of spatial filtering in our MPRAGE-based T_1 -mapping method.^[1]

TI optimization by simulation^[2]

Based on the three-parameter model described by Eq. [7], T_1 and the two other parameters p_1 and p_2 can be estimated by using a least-squares fitting algorithm, such as the Levenburg-Marquardt or the Powell method, to fit the data acquired at multiple TI values (Crawley and Henkelman, 1988; Gowland and Mansfield, 1993; Ogg and Kingsley, 2004; Ordidge et al., 1990). In doing so, it is important to find the number of sampled TIs and their values that maximize the signal-to-noise ratio (SNR) of the estimated T_1 . Such TI optimization can be made by a simulation algorithm that assumes Gaussian and temporally random measurement noises. As described in (Ogg and Kingsley, 2004), the simulation begins with computing the dimensionless noise function $f(N, TI_j/T_1)$, which is a function of the number N of sampled TIs and their values TI_j (where $j = 1, 2, \dots, N$). This function is equivalent to $Q(t, T)$ in (Zhang et al., 1998) and to the square of the factor b in (Crawley and Henkelman, 1988).

The simulated signal-to-noise ratio (SNR) of the estimated T_1 is the parameter p_2 in Eq. [7] divided by the square root of the noise function $f(N, TI_j/T_1)$. Maximizing the SNR is equivalent to searching the TI values that minimize the noise function, since p_2 is not an explicit function of TI_j .^[3] Previous works often relied on a pre-determined sampling paradigm, such as linear, quadratic or geometric sampling. Here, however, we allow each TI_j value to vary independently between $0.1T_1$ and $10T_1$, and the noise function $f(N, TI_j/T_1)$ is computed for a N -dimensional matrix of sampled TI values. The minimum element in the N -dimensional matrix of $f(N, TI_j/T_1)$ and its corresponding set of TI values are then identified.

Practically, however, it is more meaningful to maximize the precision per unit imaging time. This can be defined as the T_1 SNR multiplied by the square root of N_{repeat} , the number of repeats per unit time (Crawley and Henkelman, 1988; Ogg and Kingsley, 2004). If the MPRAGE is run at N different TIs , the imaging time for one T_1 measurement is $N \cdot TR$, and $N_{repeat} = 1/(N \cdot TR)$ repeats can be made in unit imaging time. Thus, the T_1 SNR per unit time is:

$$\Gamma = \frac{B\xi\left(\sum_i Fw(i)\rho^{i-1}\right)}{\sqrt{N \cdot TR \cdot f(N, TI_j/T_1)}} \quad [8]$$

Note that B is a function of TR (see Eq. [5]). Because $B/\sqrt{TR}$ decreases monotonically with TR at any θ and α , TR shall be set at minimum in order to maximize Γ . Since TR needs to be the same in all MPRAGE runs for T_1 mapping, its minimum is limited by the maximum TI value: $\min(TR) = TI_{\max} + nTRE$. Taking this into account, optimization of $TI_{\max}$ needs to be performed by maximizing Γ in Eq. [8], whereas the optimal number and values of other TIs can be determined directly from minimizing the noise function $f(N, TI_j/T_1)$.

Rapid T_1 estimation from data at three TI values

The simulation reveals that the optimal number of sampled TIs is three (see Results). When data are acquired at just three TI values, T_1 can be estimated directly from the data without using nonlinear least-squares fitting algorithms. Specifically, using Eq. [7] to describe image signals $S_{TI_{\min}}$, $S_{TI_{\text{med}}}$ and $S_{TI_{\max}}$ acquired at any three TI values $TI_{\min}$, TI_{med} and $TI_{\max}$, respectively, such that $TI_{\min} < TI_{\text{med}} < TI_{\max}$, these signals are related by:

$$\frac{S_{TI_{\max}} - S_{TI_{\min}}}{S_{TI_{\max}} - S_{TI_{\text{med}}}} = \frac{\exp[(TI_{\max} - TI_{\min})/T_1] - 1}{\exp[(TI_{\max} - TI_{\text{med}})/T_1] - 1} \quad [9]$$

Eq. [9] represents a nonlinear transformation of the three image signals onto a T_1 value. Because the right side of Eq. [9] monotonically decreases with increasing T_1 for $TI_{\min} < T_1 < TI_{\max}$, a look-up table can be prepared by linearly sampling the right side of Eq. [9] and estimating the corresponding T_1 values. For each voxel, the left side of Eq. [9] is computed from the three data sets, and the value corresponds to an index in the look-up table, from which T_1 is found. With this method, T_1 is estimated very rapidly because the left side of Eq. [9] can be computed simultaneously for all the voxels of the 3D volume and converted to the T_1 map using the lookup table. The sampling spacing of the look-up table limits the precision of the T_1 estimation.

The phase information of images is necessary for T_1 estimation using Eq. [9], because inverted longitudinal magnetizations give rise to 180° shifts in phase. One approach used in previous IR-based T_1 -mapping works (Gowland and Leach, 1991; Kim et al., 1994) is to reconstruct all images as complex-numbers, and then normalize the phases of signals at TI_{med} and $TI_{\min}$ with respect to signals at the longest inversion time, $TI_{\max}$. This approach can be challenging for multi-channel data acquired using multiple elements of a phased-array coil, because different channels may have different phase shifts. Nonetheless, such phase shifts are generally fixed, so Eq. [9] remains valid for signals from each individual channel. A direct average of Eq. [9] across channels may be inappropriate, as channels with weak signals may introduce large errors to the average. Instead, we modify Eq. [9] to average across channels separately for the numerator and the denominator:

$$\frac{\sum_k \left(\left\| S_{TI_{\max}}^k \right\| - S_{TI_{\min}}^k \left\| S_{TI_{\max}}^k \right\| / S_{TI_{\max}}^k \right)}{\sum_k \left(\left\| S_{TI_{\max}}^k \right\| - S_{TI_{\text{med}}}^k \left\| S_{TI_{\max}}^k \right\| / S_{TI_{\max}}^k \right)} = \frac{\exp[(TI_{\max} - TI_{\min})/T_1] - 1}{\exp[(TI_{\max} - TI_{\text{med}})/T_1] - 1} \quad [10]$$

where $\|$ stands for the modulus, and $k = 1, 2, \dots$ is the identification number of each channel.

Methods

Phantom and animal MRI setup

Two phantoms were used to optimize and evaluate the MPRAGE-based T_1 -mapping method. The first phantom was a cylindrical tube (diam.: 27 mm) filled by water doped with sodium chloride (62 mM) and copper(II) sulfate (0.53 mM) (Model 1P T10768, Bruker Biospin, Ettlingen, Germany). The second consisted of the fixed brain of an adult female marmoset (age: 4 yr) that was euthanized and perfused with 4% paraformaldehyde (Bock et al., 2009).

Twenty common marmosets (*Callithrix jacchus*, age: 1.8-15.8 yr) were used to measure age-dependent T_1 variations. Each animal was placed in prone position with the head stabilized by ear bars and tooth bar, and maintained under anesthesia by mechanical ventilation of air mixed with 2% isoflurane through an endotracheal tube. Physiological parameters were maintained within normal ranges (end-tidal CO_2 : 24-30 mmHg; rectal temperature 37.5-39.0 °C). All marmosets recovered fully from anesthesia. Seven randomly chosen marmosets were measured in sessions separated by more than three weeks and less than four months. Protocols were approved by the Animal Care and Use Committee of the National Institutes of Health.

All measurements were carried out on a 7T/30cm USR/AVIII MRI scanner (Bruker Biospin). For phantom measurements, a volume coil (Model 1P T8102, Bruker Biospin; inner diam.: 3.5 cm) was used for both RF transmission and reception. For marmoset measurements, a custom-built birdcage volume coil (inner diam.: 12 cm) was used for RF transmission, and a custom-built five-element receive-only phased-array RF coil was positioned on top of the marmoset head for RF reception.

MPRAGE sequence and measurements^[6]

Our 3D MPRAGE sequence comprised repeated cycles of an initial non-selective, adiabatic hyperbolic secant inversion pulse (nominal flip angle: 180°), followed by the acquisition of multiple readouts (k-space lines) with minimum TE and TRE , using the paradigm of centric phase encoding along one direction (Deichmann et al., 2000). Because Eq. [3] assumes steady-state, four dummy repetitions (with no actual data acquisition) were added to the beginning of each MPRAGE run. Gradient spoiling (2.5 G/cm, 0.31 ms) was applied after each readout. Acquisition of k-space was split into 1, 3 or 4 segments in the centric phase-encoding direction. In addition, a standard IR sequence was readily converted from the MPRAGE sequence, by setting the number of segments as the matrix size on the centric phase-encoding direction, so that only one k-space line was acquired after each inversion pulse.

All relevant MPRAGE parameters including TI values were listed in Tables 1 and 2.^[7] Measurements in the doped water phantom serve to validate the simulations of optimal TI values. For TI_{med} optimization, we measured T_1 from 27 MPRAGE runs that had the same TR (2150 ms) but different TI : 70 ms (as TI_{min}), 1494 ms (as TI_{max}), or one of 25 TI values in between (as TI_{med}). In addition, we acquired 27 standard IR runs with the same TI and TR . For TI_{max} optimization, we measured T_1 from 10 sets of MPRAGE runs, with each set comprising 3 runs that had the same TR and TI_{min} (70 ms), but different TI_{max} . In each set, TI_{med} was at the simulated optimal value that corresponded to each TI_{max} ,^[8] TR was 180 ms longer than TI_{max} , and because we were interested in the T_1 SNR per unit imaging time, the number of repeats of each run was adjusted according to TI_{max} such that the total imaging

time was roughly the same across all 10 sets (see Table 2). In the fixed brain phantom, T_1 maps were measured from MPRAGE runs with 1 and 4 segments, and from standard IR runs. The one-segment MPRAGE sequence for the fixed brain was also used for *in vivo* measurements, with adjustments made in only TI and TR (Table 1). For each marmoset, T_1 map was obtained *in vivo* from three MPRAGE runs without repeats (total imaging time: 10.3 min.).^[9]

Data analysis

T_1 maps were computed by Eq. [10] using complex-valued images, which were reconstructed from k-space data without combination of the different RF channels. The sampling spacing of the look-up table was set to 0.5 ms. For the doped water phantom, T_1 was also computed by nonlinear fitting (Levenberg-Marquardt) of data to the three-parameter model^[10] with the polarity of signal determined by its phase with respect to the phase at the longest TI (Gowland and Leach, 1991). Spatial SNR of T_1 was computed as the mean divided by the standard deviation across voxels within the uniform phantom.

For the fixed brain phantom, temporal SNR of T_1 was computed as the mean divided by the standard deviation across repeats of the MPRAGE runs. In addition, a T_1 map was computed from the standard IR runs using Eq. [10]. Compared to this T_1 map, the T_1 maps from MPRAGE runs showed blur, which was ameliorated by applying a high-pass spatial filter along the centric phase-encoding direction (dorsal-ventral). Specifically, we used the filter function in Eq. [19] of (Deichmann et al., 2000):

$$w_i = 1 / [a + (1 - a) \cdot b^{i-1}] \quad [11]$$

where a and b were values between 0 and 1. All k-space data acquired with the i -th excitation pulse were multiplied by the corresponding filter weight w_i . After the same filter was applied to all MPRAGE data, a T_1 map was computed from the reconstructed complex-valued MPRAGE images. Within the brain, the a and b values that minimized the average difference between this T_1 map and the T_1 map from standard IR were obtained using a least-square fitting algorithm.^[11]

For *in-vivo* T_1 mapping, the same high-pass spatial filter (Eq. [11]) derived for the fixed brain phantom was applied to all MPRAGE images (see Supplement 2 for results without the filter). T_1 maps obtained from the same marmoset on different days were co-registered by rigid-body affine transformation. The marmoset brain was manually segmented from the skull and head muscles, and its T_1 histogram was computed in bins spaced by 10 ms. To characterize the white matter's T_1 , a cerebrum region of interest (ROI) was defined as the portion of brain that was dorsal to the horizontal plane across the anterior and posterior commissures (AC and PC), and with anterior, posterior and dorsal boundaries at 4 mm anterior to AC, 4 mm posterior to PC, and 8 mm dorsal to AC-PC, respectively (see the insets of Fig. 4). T_1 histogram in this cerebral ROI showed one peak each for the gray and the white matter, and fitted well to the sum of two Gaussian functions. Characteristic T_1 values for the gray and the white matter were taken at the two Gaussian maxima of this fitted histogram. The linear relationships of these T_1 values with the marmoset age were characterized by the correlation coefficient (r) and the slope ($\Delta T_1 / \Delta \text{Age}$). Confidence interval of the slope was estimated by re-sampling the subject pool with replacement (nonparametric bootstrapping).^[12]

Results

TI optimization based on simulation

The noise function $f(N, TI_j/T_1)$ was computed as an N -dimensional matrix for all TI_j values ranging from $0.1T_1$ to $10T_1$ (see Theory). The computation was validated by replicating the results reported in Table 2 of (Zhang et al., 1998) for $N = 3, 4, 5$ and 6 . The TI values were sorted such that $TI_1 < TI_2 \dots TI_{N-1} < TI_N$. Then, with the minimum TI (TI_1) at zero, we identified for each maximum TI value (TI_N) the set of medium TI values ($TI_2 \dots TI_{N-1}$) that minimized $f(N, TI_j/T_1)$ and thereby maximized the T_1 SNR.

Fig. 1 shows the noise function as a function of TI_2 when using $N = 3$ TI values (Fig. 1A), and as a function of TI_2 and TI_3 when using $N = 4$ TI values (Fig. 1B), for TI_N at 2, 3 or 5 times T_1 . In Fig. 1B, the noise function was minimized by sampling at a single medium TI value (i.e. $TI_2 = TI_3$) (see the most dark-reddish spots). This value was equal to the TI_2 value that minimized the noise function with $N = 3$ (compare Fig. 1A and Fig. 1B). The minimum value of noise function was inversely proportional to $N-1$, namely was 1.5 times larger at $N = 3$ than at $N = 4$ (see the scales of f in Fig. 1). [13] Sampling at unequal medium TI values (i.e. $TI_2 \neq TI_3$) gave higher noise function values, though the value of TI_2 that minimized the noise function was fairly constant for different values of TI_3 , and vice-versa (see horizontal and vertical green-yellowish zones in Fig. 1B). [14] Similarly (data not shown), using $N = 6$, $f(N, TI_j/T_1)$ was minimized by six TI values that were simply two repetitions of the three TI values optimized with $N = 3$. [15] In summary, the simulation results show that in order to minimize the effects of noise on T_1 estimation, it is most optimal to sample the data at just three different TI values.

With this three- TI -sampling (i.e. $N = 3$) rule established, we studied the optimal values of the three inversion times ($TI_{\min} < TI_{\text{med}} < TI_{\max}$). $TI_{\min}$ was always most optimal at zero, the lowest possible value. The optimal TI_{med} was dependent on $TI_{\max}$. As reflected in Fig. 1A, when $TI_{\min}$ was zero, the TI_{med} (TI_2) that maximized SNR was 0.67, 0.81, 0.88, 0.92 and 0.95 times T_1 , at $TI_{\max} = 2T_1, 3T_1, 4T_1, 5T_1$ and $10T_1$, respectively. [16] The optimal TI_{med} also increased with $TI_{\min}$; for example, the curve in Fig. 2A shows that at $TI_{\min} = 0.20T_1$, optimal TI_{med} was $1.09T_1$ at $TI_{\max} = 4.38T_1$ (see Table 2 for more examples). The optimal $TI_{\max}$ was determined from maximizing the SNR per unit time, Γ , in Eq. [8] with MPRAGE-specific parameters. As an example, the curve in Fig. 2B shows the simulation result with $TI_{\min} = 0.20T_1$ and a TI_{med} optimized for each $TI_{\max}$, and with the parameters used to measure the dope-water phantom ($n = 18, nTRE = 0.2T_1, \theta = 9^\circ$ and $\alpha = 180^\circ$). Γ was maximal at $TI_{\max} = 4.20T_1$, and this optimal value of $TI_{\max}$ did not change by more than 20% when these MPRAGE-specific parameters changed within normal ranges (n : 10~60; $nTRE/T_1$: 0.1~0.3; θ : $6^\circ \sim 12^\circ$ and α : $150^\circ \sim 180^\circ$ tested).

Whereas the most optimal TI values can be identified by simulations, it must be noted that deviations from these values are well tolerated without much loss in T_1 SNR. For example, the curve in Fig. 2A shows that Γ remained within 80% of its maximum value for a wide range of TI_{med} ($0.68\text{--}1.74T_1$). Similarly, the curve in Fig. 2B shows that Γ remained within 80% of its maximum value for $TI_{\max} > 2.37T_1$. Hence, a large range of T_1 values can be measured precisely with given TI_{med} and $TI_{\max}$. In other words, we only need very coarse *a priori* knowledge of the T_1 range of interest in order to choose the three optimal TI values for T_1 measurement.

Experimental validation of TI optimization

Fig. 2 also shows that the spatial SNR of T_1 measured by MPRAGE in the doped water phantom fitted well to the simulation. This phantom had $T_1 = 341 \pm 4$ ms (mean $\pm$ SD across voxels) [17] measured by the standard IR method via nonlinear fitting [18] to data at 25 TIs (not

shown), and all T_1 values were normalized by this T_1 value for the purpose of SNR simulation. In both measurements of spatial SNR as a function of TI_{med} (Fig. 2A) and of TI_{max} (Fig. 2B), total imaging time was made approximately constant (see Table 2) so that the measured spatial SNR was comparable to the simulated SNR per unit time, Γ . The good fits in both panels suggest that the random Gaussian noise assumption made in the simulations characterized well the noise profile of MPRAGE-based T_1 mapping in a uniform phantom.

We also confirmed that measuring the MPRAGE data at $N = 3$ TI values produced similar or higher T_1 SNR per unit time compared to measuring the data at $N = 4$ TI values (from which T_1 was computed by nonlinear fitting^[19]). For example, with the same total imaging time, the spatial T_1 SNR measured with a single medium TI (336 ms) and $N_{\text{repeat}} = 32$ was 16% higher than that measured with two unequal medium TIs (268 and 420 ms) and $N_{\text{repeat}} = 24$. Finally, we confirmed that for the MPRAGE data measured at $N = 3$ TI values, our rapid method (Eq. [10]) is equivalent to the nonlinear fitting method. That is, T_1 values calculated by both methods were – within the sampling spacing (0.5 ms) of the look-up table used – identical.^[20]

Comparison with standard IR methods

Fig. 3 compares the T_1 maps measured by MPRAGE to that measured by a standard IR sequence (see Methods) in the fixed marmoset brain. In this sample, about 95% of voxels in the brain had T_1 values in the range of 560-760 ms. As illustrated in Fig. 3A, the MPRAGE sequence introduced a noticeable blurring along the centric phase-encoding (vertical) direction, which increased with a decreasing number of k-space acquisition segments. Such blurring decreased the accuracy of the T_1 measurement due to a spatial mixing of compartments with different T_1 , for example near the boundary between gray and white matter. Fig. 3C quantified this inaccuracy in the T_1 maps measured by MPRAGE, using the standard IR measurement as reference. The error in T_1 within 560-760 ms remained within 2% when using the four-segment MPRAGE (dotted curve), and within 4% when using the one-segment MPRAGE sequence (dashed curve). The MPRAGE-measured T_1 values were higher than the corresponding values measured with standard IR for low- T_1 voxels (primarily white matter), and lower than with standard IR for high- T_1 voxels (primarily gray matter). This was mainly because blurring from gray matter voxels increased the T_1 in white matter voxels near the gray-white matter boundary, and vice versa.

The blurring was ameliorated by applying a high-pass spatial filter (Eq. [11]) to the MPRAGE k-space data. Fig. 3B shows the filter applied to the one-segment MPRAGE data that made the yielded T_1 map as nearly identical as possible to the T_1 map from standard IR. The filter parameters were $a = 0.216$ and $b = 0.952$. The filtering substantially improved the accuracy of T_1 map by reducing the error in T_1 from within 4% to within 1% when using the one-segment MPRAGE (solid curve, Fig. 3C).^[21] In addition, the precision of T_1 map gauged by temporal SNR was roughly uniform across the brain (Fig. 3D), and for the one-segment data decreased from 75 before to 30 after the high-pass spatial filtering was applied. This decrease in precision was an expected result of the elevated noise level due to spatial filtering (Deichmann et al., 2000). With the spatial filter calibrated by the fixed brain phantom, we now use the one-segment MPRAGE protocol for whole-brain T_1 mapping, and for measuring the age-dependent T_1 variations.^[22]

In-vivo T_1 mapping of the marmoset brain

Volumetric T_1 maps were measured for 20 marmosets at 0.60 mm isotropic resolution. The histograms of T_1 from brain voxels were similar in shape across individuals, and showed distinct peaks corresponding to the gray matter (Fig. 4A). However, the peaks corresponding

to white matter were not salient, unlike typical whole-brain T_1 histograms in humans, which show a distinct and stronger peak for white matter than for gray matter (Srinivasan et al., 2003; Suzuki et al., 2006). This is mainly due to the lower white-to-gray matter volume ratio in the non-human primate species. To better characterize the T_1 distribution in white matter of the marmoset, we analyzed the T_1 histogram within the cerebrum ROI (see Methods), which contained a major portion of the cerebral white matter. This histogram, like the histogram of human brain, fitted well to the sum of two Gaussian functions (Fig. 4B), allowing for the cerebral white matter T_1 to be characterized by the peak of the left Gaussian function, which was 1270 ± 43 ms (mean $\pm$ SD across subjects). Meanwhile, cerebral gray matter T_1 was characterized by the peak of histogram, which was at 1735 ± 52 ms. These values agree with our previous measurements of gray matter T_1 in the marmoset obtained with an IR-EPI sequence (Bock et al., 2009).

T_1 maps and histograms were highly reproducible across different measurements in the same subject (Fig. 5A&C). The percentile T_1 difference in brain voxels between a pair of sessions in the same subject typically had a Gaussian distribution (not shown), with a standard deviation of $4.1 \pm 0.5\%$ (mean $\pm$ SD, across 10 pairs). This represented a temporal SNR of about 25, which was remarkably close to that in the phantom measurement.^[23] The differences in T_1 values at the histogram peaks were also small between sessions in the same subject: 19 ± 16 ms for the cerebral white matter T_1 and 28 ± 19 ms for the gray matter T_1 (see gray symbols in Fig. 6). These values were smaller than the standard deviations of white and gray matter T_1 across subjects (43 and 52 ms, respectively), indicating larger variances across subjects than across sessions in the same subject. As an illustration of this inter-subject variability, Fig. 5B shows the T_1 histograms that were shifted from each other in two subjects, aged 7.4 and 10.8 years. Fig. 5D shows that the differences between T_1 maps in the two subjects were largely global, i.e., higher T_1 values in one subject versus another were found in both gray and white matter.

Age-related T_1 variations

Fig. 6 shows that part of the inter-subject variations in T_1 can be attributed to T_1 decreases with increasing marmoset age. The mean T_1 in the whole brain (including ventricles filled with cerebrospinal fluid) decreased significantly with age (Fig. 6A, rate = -0.28% /year, 90% confidence interval: $-0.37 \sim -0.19\%$ /year). This age-dependent T_1 decrease also occurred for both gray matter and white matter in the cerebrum ROI. Cerebral gray matter T_1 decreased with age (Fig. 6B, rate = -0.39% /year, 98% confidence interval: $-0.59 \sim -0.20\%$ /year) faster than cerebral white matter T_1 did (Fig. 6C, rate = -0.23% /year, 90% confidence interval: $-0.44 \sim -0.03\%$ /year). In other words, the cerebral gray matter T_1 decreased faster than 0.20% per year ($P < 0.01$), and no increase of white matter T_1 with age was observed ($P < 0.05$).

Discussion

In the present work, we developed a new method based on a standard MPRAGE sequence to measure T_1 with high spatial resolution and high degrees of accuracy and precision within reasonably short imaging time. By varying only the inversion time TI , but keeping all other sequence parameters constant, the signal in acquired MPRAGE images becomes linear to $\exp(-TI/T_1)$, allowing T_1 maps to be estimated from data acquired at multiple TI s. Using both simulations and phantom measurements, we showed that acquiring data at just three different TI s maximizes the SNR of T_1 per unit imaging time. T_1 maps were thus produced from three sets of MPRAGE images acquired with three optimal TI values. We illustrate this method by obtaining whole-brain T_1 maps in the common marmoset at 0.6 mm isotropic resolution. The high accuracy and precision of these T_1 maps facilitate the study of inter-

subject T_1 variations, and we show that T_1 decreases with age in both gray and white matter in the common marmosets.

Using MPAGE for 3D T_1 -mapping

Since its inception 20 years ago (Mugler and Brookeman, 1990), MPAGE has become a standard imaging sequence on commercial scanners for fast, high-resolution T_1 -weighted imaging. However, the idea of using MPAGE or its variants for T_1 mapping was not explored until very recently. In (Wright et al., 2008), MPAGE was acquired at five different TIs with other parameters including TR remaining identical, but the MPAGE signal was not derived as a linear function of $\exp(-TI/T_1)$. Instead, its T_1 estimation required *a priori* knowledge of flip angles and was based on a rather cumbersome nonlinear equation. In (Marques et al., 2010), a new sequence dubbed MP2RAGE was developed that reduces imaging time and is partially insensitive to field inhomogeneity and subject motion. However, this method also requires *a priori* knowledge of flip angles, and is not readily available on commercial scanners.

In contrast, our new method to map T_1 using MPAGE has two important advantages. First, it uses the standard MPAGE sequence without any modifications or technical developments, thus facilitates applications on clinical and commercial scanners. The only technical requirement is that the MPAGE images need to be reconstructed in complex-numbers, and separately for each receive channel. [24] More importantly, our method is immune to deviations of flip angles from their nominal values, because it does not require knowledge of excitation pulse's flip angle θ , or inversion pulse's flip angle α . The flip angle deviations, which often arise from pulse imperfections and field inhomogeneity near tissue boundaries, may introduce significant errors for T_1 -mapping methods that require knowledge of flip angle values. While B_1 mapping can be used to measure flip angles, it requires an additional scan that increases total imaging time and needs to be spatially co-registered to MPAGE images (Wang et al., 2006; Wright et al., 2008).

One intrinsic disadvantage of MPAGE-based methods is the blurring (point-spread function) along the centric phase-encoding direction. This blurring is particularly deleterious to the T_1 -weighted contrast, and consequently the accuracy of T_1 , of a small region that is embedded in a large region with different T_1 values (Deichmann et al., 2000). In the marmoset brain, white matter is such a small region and may have T_1 errors larger than 5%, whereas the majority of voxels are in gray matter and have high T_1 accuracy (Fig. 3C, also see Supplement 2). [25] The blurring in T_1 map can be ameliorated by using variable excitation angles (Mugler et al., 1992) (see Supplement 1), or as in the present study, corrected by high-pass spatial filtering of the images. The filtering decreases the precision of T_1 , though to a level that is still tolerable for our study of age-related T_1 changes. Alternatively, the use of multiple segments can reduce the blurring without spatial filtering, at the expense of increasing imaging time. Another disadvantage of our method is that the acquisitions of the MPAGE images at different TIs are separated by minutes, making the method sensitive to head motion across these acquisitions. This may necessitate the use of motion-correcting algorithms such as those based on mutual information during data processing (Studler et al., 2010). It is important to note that the theory presented here is only valid for perfectly spoiled transverse magnetization, requiring techniques such as RF spoiling for larger excitation pulses and/or for other phase encoding orders. For example, imperfect RF spoiling results in significant errors in T_1 maps obtained with the variable flip angle method (Preibisch and Deichmann, 2009). Here, only gradient spoiling was used. However, the relatively small excitation angles and the use of centric phase encoding minimized the effects of transverse coherences on the MPAGE signal, thus preserving the accuracy of the T_1 maps. [26]

Three inversion times for T_1 mapping

Several studies have explored the optimal number and values of TIs for the IR-based mapping methods that estimate T_1 using the three-parameter model (Crawley and Henkelman, 1988; Ogg and Kingsley, 2004; Zhang et al., 1998). Using the algorithms in these studies, we found that sampling data at just three TIs is more efficient in T_1 SNR per unit time than the conventional approach of sampling at four or more TIs . In particular, we independently sampled each TI value over a large range ($0-10T_1$) and found that, when sampling at more than three TIs , the arrangement that gives the highest SNR is the one in which two or more of the TI values are equal, leaving only three unique TI values. This finding significantly simplifies the optimization of TI , as the three TI values can be easily chosen to map a large range of T_1 values (e.g. more than two folds of T_1 within 80% of maximum SNR). It also reduces the computational load, because with data at just three TIs , T_1 can be computed rapidly using a look-up table for the entire images instead of nonlinear fitting for individual voxels.

One assumption implicit in the optimization of TI is that the longitudinal relaxation is monoexponential. Recently, biexponential longitudinal relaxation in the rat brain has been reported to include both slow- and fast-relaxation components (Prantner et al., 2008). The latter resulted from magnetization transfer between free water and bound protons, which produced very short longitudinal relaxation times (23 ms at 4.7 T and 53 ms at 11.7 T for *in-vivo* rat brain). Therefore, we used a relatively long $TI_{\min}$ (150 ms at 7 T for *in-vivo* marmoset brain, see Table 1), [127] in order to make the fast-relaxation component negligible and allow for the use of the three-parameter model for T_1 -mapping of the brain.

Age-related T_1 changes in the marmoset brain

Quantitative relaxometry studies of the human brain have established that T_1 changes with age. Specifically, T_1 in both gray and white matter decrease significantly from birth to adulthood (20 years), with the most dramatic decreases in the first 2 years, followed by more gradual decreases until adulthood. After reaching adulthood, T_1 in gray matter continues to decrease throughout life, albeit at an even slower rate, but T_1 in white matter does not decrease, and may even increase as the person reaches senescence (> 60 years) (Ogg and Steen, 1998; Saito et al., 2009; Suzuki et al., 2006). The decrease of T_1 with age correlates well with the increase of iron concentration, which is described by an exponential function of age. Therefore, iron deposition is presumably the main contributor of age-related T_1 changes in the brain (Ogg and Steen, 1998).

Here, we measured 3D whole-brain T_1 maps from a cohort of common marmosets, a small non-human primate that has been increasingly used in neuroscience research. We observed significant decreases of T_1 with marmoset age throughout the age span of 1.8 to 15.8 years, which covers mainly the adulthood and senescence period of the marmoset (Abbott et al., 2003), but only the juvenile period of the human. Specifically, the marmoset gray matter's T_1 decrease rate during this age span is 0.39 %/year, close to the human gray matter's T_1 decrease rate ($\approx 0.3\%$ per year, see (Ogg and Steen, 1998; Saito et al., 2009)) during the same age span (human juvenile period), but much larger than the decrease rate ($\approx 0.1\%$ per year, see (Suzuki et al., 2006)) during human adulthood and senescence period (>20 years). In addition, the marmoset white matter's significant T_1 decrease with age also makes it similar to the human white matter during juvenile period rather than adulthood. [128] Thus, compared to the human studies, our results in marmosets suggest that age-related T_1 changes in the brain are ruled by the amount of time elapsed since birth, and are not scaled by life expectancy, which is about five times longer in humans than in marmosets. They also suggest that iron deposition in neural tissues, the presumed cause of T_1 decrease, may have similar temporal dynamics across primate species. Future studies with a larger number of

marmosets covering the entire lifespan (including before 2 years) may clarify whether the temporal dynamics is identical to that in human.

T_1 maps were high reproducible in the same subject over sessions separated by a few months, with precision similar to that in phantom measurements, and with high spatial resolution (0.60 mm) to alleviate partial volume effects and dissociate gray and white matter. This was achieved despite that the total T_1 -mapping imaging time in each marmoset was very short (11 min.), in an effort to simulate demands of time efficiency in clinical settings. [29] On the other hand, we observed a large inter-subject variation of the T_1 histograms, which has potential implications to the use of absolute T_1 values in clinical studies. For example, quantitative T_1 values have been used to diagnose a subgroup of multiple sclerosis (MS) patients that have normal-appearing T_1 -weighted images but elevated T_1 values in white matter (Vrenken et al., 2006). If T_1 value is the only measure used to make the diagnosis, our results suggest that taking age-related T_1 changes into account is necessary to avoid misdiagnosis that may arise from the high inter-subject variability in T_1 . In addition, the use of non-human primate models of MS, in particular the marmoset (t'Hart and Massacesi, 2009), may help elucidate the role of T_1 in neurological diseases because quantitative T_1 values can be obtained from each subject before onset of the disease.

In conclusion, we developed a new method to obtain 3D T_1 maps using a standard MPRAGE sequence and sampling the data at only three TIs . The method can be optimized to measure T_1 over a broad range, and to obtain whole-brain T_1 maps with high spatial resolution within clinically acceptable imaging time. We demonstrated significant advantages of the new method over other IR-based T_1 -mapping approaches, and used it to study age-related T_1 changes in the marmoset brain. The use of this method to obtain T_1 maps with high spatial resolution, precision and accuracy promotes the use of quantitative anatomical MRI in basic neuroscience research as well as in the clinical setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Computer simulation results of the noise function $f(N, T I_j / T_1)$. **(A)** At $N = 3$ (three $T I$ s), the noise function f versus $T I_2$ (the medium $T I$) at three different values of $T I_3$ (maximum $T I$): $2 T_1$, $3 T_1$ and $5 T_1$ (see top legend). **(B)** At $N = 4$ (four $T I$ s), the noise function f versus of $T I_2$ and $T I_3$ (the two medium $T I$ s), at the same three maximum $T I$ as in **A** (see bottom legend).

Figure 2.

The spatial SNR of T_1 measured in a doped water phantom at (A) a range of TI_{med} values with fixed TI_{min} (70 ms = $0.2T_1$) and TI_{max} (1494 ms = $4.4T_1$), and (B) a range of TI_{max} values with fixed TI_{min} (70 ms = $0.2T_1$) and total imaging time, and with an optimized value of TI_{med} for each TI_{max} (see Table 2). In each panel, dots represent measurements, and the curve represents the best fit of the SNR per unit time function expressed by Eq. [8] to the measurements.

Figure 3.

(A) A single sagittal slice in the 3D T₁ maps measured by standard IR, four-segment and one-segment MPAGE in the fixed marmoset brain phantom. (B) A high-pass spatial filter along the dorsal-ventral (vertical) direction applied to the one-segment MPAGE data, and the same slice in the T₁ map computed from the filtered MPAGE images. (C) The T₁ difference between MPAGE and standard IR, normalized by T₁ in standard IR, shown for four-segment MPAGE (dotted line), and one-segment MPAGE before (dashed line) and after (solid line) high-pass spatial filtering. (D) The temporal SNR of T₁ using four-segment MPAGE and one-segment MPAGE before and after filtering.

Figure 4.

(A) Whole-brain T_1 histograms obtained from 3D T_1 maps in marmosets ($n = 20$), normalized by the total number of voxels. Thin gray lines show individual data, and the thick black line shows the distribution of T_1 averaged across subjects. (B) T_1 histograms including only the voxels in the cerebrum ROI, in which the white matter T_1 is better characterized. The top-left insets use the same sagittal slice of a T_1 map as example to illustrate the anterior-posterior and dorsal-ventral boundaries of the cerebrum ROI.

Figure 5.

(A) T_1 histograms of the cerebrum ROI obtained from one subject in two sessions (solid and dotted lines). (B) histograms of the cerebrum ROI obtained from two subjects of similar age (the solid line identical to that in A, and the dotted line for the other marmoset). (C) An exemplary axial slice from one subject (left image: solid line; right image: dotted line in panel A). (D) An exemplary axial slice from the other subject (dotted line in B).

Figure 6.

(A) Mean whole-brain T_1 , (B) cerebral gray matter T_1 and (C) cerebral white matter T_1 obtained from 20 marmosets of different ages show significant age-dependent decreases. Black symbols represent subjects from which a single T_1 measurement was obtained, whereas each set of gray symbols connected by gray lines represents several measurements in the same subjects over time. Square and round symbols represent male and female marmosets, respectively. Thick black line constitutes the linear fit of all data points in each panel.

Table 1

MPRAGE sequence parameters used in four types of measurements. Field-of-view and matrix are shown in (anterior-posterior) $\times$ (left-right) $\times$ (dorsal-ventral) format.

	Doped water phantom	Brain phantom	Marmoset in-vivo
Field-of-view (mm)	4 $\times$ 32 $\times$ 27	38.4 $\times$ 26.4 $\times$ 38.4	
Acquisition matrix	8 $\times$ 64 $\times$ 54	64 $\times$ 44 $\times$ 64	
Isotropic resolution (mm)	0.50	0.60	
<i>TR</i> (ms)	Varied	2180	4535
<i>TI</i> values (ms)	Multiple, with a minimum of 70	60, 480, 1600	150, 1200, 4000
<i>n</i> (number of excitation pulses after each inversion)	18 (3-segment) 1 (standard IR)	64 (1-segment) 16 (4-segment) 1 (standard IR)	64
Nominal flip angle θ (deg)	10 (MPRAGE) 90 (standard IR)	9 (MPRAGE) 90 (standard IR)	9
<i>TRE</i> (ms)	9.00	8.45	
Acquisition time (min)	Varied	5.2 (1-segment) 21 (4-segment) 308 (standard IR)	10.3

Table 2

The list of parameter sets used for $TI_{\max}$ optimization measurement. TR and the number of repeats, N_{repeat} , were adjusted such that their product remained the same. $TI_{\max}$ was 180 ms shorter than TR . The optimal TI_{med} value optimized from simulation was used for each $TI_{\max}$. The numbers in parentheses were the TIs normalized by T_1 (341 ms).

TR (ms)	N_{repeat}	$TI_{\max}$ (ms)	TI_{med} (ms)
857	35	677 (1.99)	284 (0.83)
968	31	788 (2.31)	306 (0.90)
1111	27	931 (2.73)	329 (0.97)
1250	24	1070 (3.14)	345 (1.01)
1428	21	1248 (3.66)	361 (1.06)
1579	19	1399 (4.10)	370 (1.09)
1765	17	1585 (4.65)	378 (1.11)
1875	16	1695 (4.97)	381 (1.12)
2000	15	1820 (5.34)	384 (1.13)
2143	14	1963 (5.76)	387 (1.14)