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Measuring intra-axonal T_2 in white matter with direction-averaged diffusion MRI

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Abstract

Purpose: To demonstrate how the T_2 relaxation time of intra-axonal water (T_{2a}) in white matter can be measured with direction-averaged diffusion MRI.

Methods: For b-values larger than about 4000 s/mm², the direction-averaged diffusion MRI signal from white matter is dominated by the contribution from water within axons, which enables T_{2a} to be estimated by acquiring data for multiple TE values and fitting a mono-exponential decay curve. If given a value of the intra-axonal diffusivity, an extension of the method allows the extra-axonal relaxation time (T_{2e}) to be calculated also. This approach was applied to estimate T_{2a} in white matter for 3 healthy subjects at 3 T, as well as T_{2e} for a selected set of assumed intra-axonal diffusivities.

Results: The estimated T_{2a} values ranged from about 50 ms to 110 ms, with considerable variation among white matter regions. For white matter tracts with primarily collinear fibers, T_{2a} was found to depend on the angle of the tract relative to the main magnetic field, which is consistent with T_{2a} being affected by magnetic field inhomogeneities arising from spatial differences in magnetic susceptibility. The T_{2e} values were significantly smaller than the T_{2a} values across white matter regions for several plausible choices of the intra-axonal diffusivity.

Conclusion: The relaxation time for intra-axonal water in white matter can be determined in a straightforward manner by measuring the direction-averaged diffusion MRI signal with a large b-value for multiple TEs. In healthy brain, T_{2a} is greater than T_{2e} and varies considerably with anatomical region.

Keywords

brain; diffusion MRI; direction-averaged; intra-axonal; T_2 ; white matter

1 | INTRODUCTION

Measurements of transverse relaxation in white matter can distinguish 3 different compartments, which may be identified as intra-axonal water, extra-axonal water, and myelin water.¹ The T_2 relaxation time for myelin water is typically in the range of 10 ms to 20 ms, whereas the intra-axonal and extra-axonal T_2 values are substantially longer.² Knowledge of compartmental T_2 values is important for understanding how tissue microstructure affects MRI signal data.

Most previous studies have been based on multi-exponential fits for spin echo signal decay curves over a broad range of TE values.^{1,3–9} Recently, an alternative approach (known as TEDDI) has been demonstrated that uses diffusion MRI (dMRI) data, acquired with multiple b-values and TEs, that are fit with a specific model for the diffusion-weighted signal.¹⁰ An advantage of TEDDI is that the extra information provided by applying diffusion-sensitizing gradients helps to separate the intra-axonal and extra-axonal compartments, which is hard to do from spin echo signal decay curves alone.

Here we describe a straightforward method of estimating the intra-axonal T_2 ($\equiv T_{2a}$) relaxation time from direction-averaged dMRI data obtained with multiple TEs but only a single b-value. Moreover, the signal is fit with a mono-exponential decay rather than the more complicated model used in TEDDI. The key idea is that the direction-averaged dMRI signal is dominated by intra-axonal water for sufficiently large b-values and TEs. As discussed in previous studies, b-values of about 4000 s/mm² or higher should be sufficient to suppress most of the signal from extra-axonal water.^{11–14} The TE need only be large enough to suppress the signal from myelin water. In practice, this implies TEs greater than about 80 ms for the myelin signal to be reduced by at least a factor of 50. On clinical scanners, TEs for dMRI sequences with large b-values are typically greater than this because of the gradient pulse durations required to generate strong diffusion weightings.¹⁵

To demonstrate our technique, we used data acquired from 3 healthy volunteers. Most of our data were collected using a monopolar (i.e., Stejskal-Tanner) diffusion pulse sequence, as this allows for shorter TEs than a bipolar (i.e., twice-refocused) sequence. However, for 1 subject, we also obtained data with a bipolar sequence to reduce eddy currents, which could conceivably confound our T_{2a} measurements.

2 | THEORY

With increasing b-value (b), the direction-averaged dMRI signal in white matter has been observed to decay approximately as $b^{-1/2}$ for b-values greater than about 4000 s/mm² and TEs greater than about 80 ms.^{12–14} This scaling behavior is the signature of water confined to thin cylindrical pores, which presumably correspond to axons. It is only evident at high b-values for 2 reasons. First, the condition $bD_a \gg 1$, in which D_a is the intra-axonal diffusivity, must be satisfied for the signal decay from the intra-axonal water to decrease as $b^{-1/2}$.¹¹ Because $D_a \approx 2 \mu\text{m}^2/\text{ms}$,^{14,16} this implies that $b \gg 500 \text{ s/mm}^2$. Second, the b-value must be sufficiently high to suppress the signal from the more mobile pool of extra-axonal water within the extra-cellular space, glial cells, blood, and possibly cerebrospinal fluid.

Long TEs are also needed to suppress the signal from myelin water, which has a relatively low diffusivity¹⁷; however, at least on clinical scanners, this will automatically be the case for large b-values, as the time to play out the diffusion-sensitizing gradients typically forces the TE to be about 80 ms or longer.¹⁵ Thus, with an appropriate choice of imaging parameters, the direction-averaged dMRI signal is dominated by the contribution of intra-axonal water. Consequently, the TE dependence of the direction-averaged dMRI signal for a fixed large b-value will simply be given by

$$\bar{S}(TE) = C_a \cdot e^{-TE/T_{2a}}, \quad (1)$$

where C_a is a constant. Equation 1 is the basis of our proposed method for estimating T_{2a} . Provided data for 2 TEs, TE_1 and TE_2 , we then have the explicit formula

$$T_{2a} = \frac{TE_2 - TE_1}{\ln[\bar{S}(TE_1)/\bar{S}(TE_2)]}. \quad (2)$$

When data for more than 2 TEs are available, Eq. 1 could instead be fit numerically to find T_{2a} , which reduces to a linear problem after taking the logarithm of both sides.

If one also acquires the MRI signal, $S_0(TE)$, without diffusion weighting (i.e., $b = 0$) for the same TEs, and if one has a prior estimate for D_a , then the extra-axonal T_2 ($\equiv T_{2e}$) relaxation time may be calculated from

$$F(TE) \equiv S_0(TE) - 2\bar{S}(TE)\sqrt{\frac{bD_a}{\pi}} = C_e \cdot e^{-TE/T_{2e}}, \quad (3)$$

where C_e is a constant and b is the b-value for which the direction-averaged signal is measured. A derivation of Eq. 3 is given in the Appendix. In the special case of 2 TEs, the extra-axonal relaxation time is

$$T_{2e} = \frac{TE_2 - TE_1}{\ln[F(TE_1)/F(TE_2)]}. \quad (4)$$

However, the accuracy of Eqs. 3 and 4 will depend on the accuracy of the estimate for D_a , which puts these equations on a less firm foundation than Eqs. 1 and 2.

3 | METHODS

3.1 | Imaging

Three healthy adult volunteers (26 to 30 years old) were scanned on a 3T Prisma MRI system (Siemens Healthineers, Erlangen, Germany) using a 32-channel head coil under a

protocol approved by the institutional review board of the Medical University of South Carolina.

Diffusion-weighted data were acquired for all 3 subjects using a monopolar dMRI pulse sequence and 64 diffusion-encoding directions with a b-value of 6000 s/mm² for TE = 90, 100, 110, 120, 130, 140, and 150 ms. Other imaging parameters were TR = 3800 ms, voxel size = 3 mm³, number slices = 42, FOV = 222 mm², acquisition matrix = 74 × 74, slice acceleration = 2, phase-encoding acceleration = 2, coil combine mode = adaptive combine, and bandwidth = 1438 Hz/px. The diffusion time (Δ) and gradient pulse duration (δ) of the monopolar sequence both depended on TE, with each increasing by 5 ms for every 10-ms increase in TE. Thus, Δ varied from 44.1 ms for TE = 90 ms to 74.1 ms for TE = 150 ms, whereas δ varied from 24.9 ms for TE = 90 ms to 54.9 ms for TE = 150 ms. For every TE, we obtained 5 additional images with the same parameters except that the b-value was set to zero (b0 images). For TE = 90 ms, diffusion-weighted data were also collected using the same monopolar sequence except with 30 diffusion-encoding directions, b-values of 1000 and 2000 s/mm², and an additional 5 b0 images. These low b-value data were used to calculate standard diffusion measures to support our analysis, but not for estimating T_{2a} . For anatomical reference, T₁-weighted images were acquired with isotropic 1-mm voxels, TE = 2.26 ms, and TR = 2300 ms. The total scan time for all of these sequences was 42 minutes 47 seconds.

For 1 subject (subject 1), we also obtained, during the same scan session, diffusion-weighted data using a bipolar dMRI pulse sequence in order to suppress eddy currents.¹⁸ The imaging parameters were set in the same way as for the monopolar sequence except no data were collected with TE = 90 ms, which was not possible for the bipolar sequence due to the time needed to include the extra refocusing pulse. The bipolar diffusion scans required 27 minutes 57 seconds of additional scan time.

To test the dependence of our T_{2a} estimates on the choice of b-value, subject 2 was scanned, in a separate session, using the monopolar sequence and 64 diffusion-encoding directions for b-values of 1000, 2000, 4000, 6000, and 8000 s/mm², both with TE = 100 ms and with TE = 140 ms. The remaining imaging parameters were set to be the same as for the other monopolar diffusion-weighted data. For each combination of b-value and TE, 5 b0 images were also acquired. A T₁-weighted anatomical scan was also obtained using the same imaging parameters as in the previous scan session. The total scan time for this session was 51 minutes 48 seconds.

3.2 | Data analysis

Signal noise in all diffusion-weighted images was reduced by applying a denoising algorithm based on principal components analysis.¹⁹ The denoising algorithm also yielded noise maps, which were used with the method of moments²⁰ to correct positive signal bias arising from noise rectification in magnitude images. Gibbs ringing artifacts were mitigated by using the approach of Kellner et al.²¹ Image coregistration was accomplished through the standard techniques,^{22,23} which included correction of image distortion due to eddy currents (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy>).

Conventional diffusion metrics, such as mean kurtosis, mean diffusivity, and fractional anisotropy (FA), were calculated from the diffusion-weighted data obtained with the monopolar sequence for TE = 90 ms and b-values of 0, 1000, and 2000 s/mm² by applying in-house software (<https://www.nitrc.org/projects/dke/>).²⁴ White matter masks for each subject were defined as all cerebral voxels with a mean kurtosis greater than 1 and mean diffusivity less than 1.5 $\mu\text{m}^2/\text{ms}$.²⁵ In addition, we located specific anatomical regions of interest by reference to a white matter atlas.²⁶ Eleven white matter regions were considered: the posterior limb of the internal capsule, the genu of the corpus callosum, the posterior thalamic radiation, the anterior corona radiata, the anterior limb of the internal capsule, the superior longitudinal fasciculus, the external capsule, the body of the corpus callosum, the splenium of the corpus callosum, the superior corona radiata, and the posterior corona radiata.

To estimate T_{2a} , Eq. 1 was fit in each voxel, using least squares, to the direction-averaged signal with a b-value of 6000 s/mm², for the monopolar data with TE ranging from 90 ms to 150 ms (subjects 1–3) and for the bipolar data with TE ranging from 100 ms to 150 ms (subject 1). To assess the extent to which the measured T_{2a} depends on the choice of b-value, we used Eq. 2 together with the direction-averaged data from the second scan session for subject 2, with b-values of 4000, 6000, and 8000 s/mm² and TEs of 100 ms (TE_1) and 140 ms (TE_2).

We also generated parametric maps of T_{2e} for all subjects by fitting Eq. 3 to monopolar data with b-values of 0 s/mm² and 6000 s/mm² and TE ranging from 90 ms to 150 ms. The assumed values for D_a were 1.0, 1.5, 2.0, and 2.5 $\mu\text{m}^2/\text{ms}$, which are representative of estimates obtained from microstructural modeling.^{10,27–29}

Because T_2^* in white matter is known to depend on orientation,^{30,31} we investigated the relationship of T_{2a} and the angle of the principal diffusion tensor eigenvector relative to the main magnetic field. We restricted our comparison to voxels with a coefficient of linearity greater than 0.4, because these represent white matter with largely collinear axonal fiber bundles for which any angular variation is most likely to be apparent. Here we defined the coefficient of linearity as $c_l = (\lambda_1 - \lambda_2)/\lambda_1$, where λ_1 and λ_2 are, respectively, the first and second largest eigenvalues of the diffusion tensor.³² For this analysis, T_{2a} was estimated by using the monopolar data of all 3 subjects with a b-value of 6000 s/mm² and the 7 TE values from 90 ms to 150 ms.

4 | RESULTS

The direction-averaged signal with a b-value of 6000 s/mm² as a function of TE is plotted in Figure 1 for representative white matter voxels from subject 1. The error bars indicate standard errors calculated as the SD of the signal noise divided by the square root of the number of diffusion-encoding directions. The lines show mono-exponential fits with Eq. 1. The quality of the fits is similar for the monopolar data (A) and bipolar data (B), although T_{2a} is slightly longer for the bipolar data.

Parametric maps of T_{2a} for 1 anatomical slice from subject 1 are shown in Figure 2, along with the corresponding color FA map. The T_{2a} values are only meaningful in white matter regions, where the theory underlying our method is expected to hold. The maps generated from the monopolar data and from the bipolar data are qualitatively similar, although a tendency toward higher T_{2a} for the bipolar data is apparent. Figure 3 shows a scatter plot of the monopolar and bipolar T_{2a} values for all of the white matter voxels from the same slice as in Figure 2. The dashed line has a slope of 1 and an intercept of 0; thus, points lying above this line have a higher T_{2a} for the bipolar data. The solid line is a best fit with a slope of 1.1 and a y-intercept of 3.6 ms, indicating that the bipolar T_{2a} values are, on average, about 10% larger than the monopolar T_{2a} values. The Pearson correlation coefficient is 0.9, reflecting a strong correlation between the monopolar and bipolar data.

Histograms of T_{2a} from all white matter voxels for each subject are shown in Figure 4. The data are for the monopolar sequence with a b-value of 6000 s/mm² and 7 TE values. Most voxels have T_{2a} between 50 ms and 110 ms, and the average values are 78 ± 11 , 81 ± 12 , and 78 ± 11 ms for subjects 1, 2, and 3, respectively. The median T_{2a} for selected white matter regions is shown in Figure 5, with median values being used instead of averages to reduce the effect of outliers. Considerable regional variation is evident, with a lowest median value of 64 ± 7 ms (external capsule, subject 3) and a highest median value of 94 ± 17 ms (posterior limb of the internal capsule, subject 2). There are no significant differences in T_{2a} among the 3 subjects.

Figure 6 shows a plot of T_{2a} in white matter from subject 2 as a function of FA, for b-values of 4000, 6000, and 8000 s/mm². The data points represent median values, and the error bars indicate the first and third quartiles for each bin, which spanned an FA interval of 0.05. For $0.2 < \text{FA} < 0.6$, which includes most of the white matter voxels, similar results are obtained for all 3 b-values. Some minor differences are apparent for $\text{FA} < 0.2$ and $\text{FA} > 0.6$, although these might well reflect noise and/or coregistration errors, as there are a relatively small number of voxels in these bins. The average T_{2a} values ($\pm$ SD) over all white matter voxels are 81 ± 12 , 81 ± 13 , and 83 ± 13 ms for b-values of 4000, 6000, and 8000 s/mm², respectively.

The averages of the median T_{2e} and T_{2a} for all 3 subjects as a function of FA are shown in Figure 7. The data are for the monopolar sequence with a b-value of 6000 s/mm², with the error bars indicating intersubject SDs. We calculated T_{2e} for several different choices of the intra-axonal diffusivity, as this has been a difficult quantity to estimate accurately,³³ although recent work indicates that it is most likely in the range of 2 $\mu\text{m}^2/\text{ms}$ to 2.5 $\mu\text{m}^2/\text{ms}$.¹⁶ In all of the cases considered, T_{2a} is substantially longer than T_{2e} , which is consistent with previous studies.^{5,7,9,10} Interestingly, T_{2e} is markedly shorter for the higher FA values than for lower FA values. Over all white matter voxels, the median values are 64, 62, 59, and 56 ms for T_{2e} with $D_a = 1.0, 1.5, 2.0$, and 2.5 $\mu\text{m}^2/\text{ms}$, respectively, whereas the median T_{2a} is 78 ms.

The dependence of T_{2a} on the angle θ between the main magnetic field and the principal diffusion tensor eigenvector, for white matter voxels with coefficients of linearity greater than 0.4, is shown in Figure 8. The colored lines are median values for individual subjects,

using a bin size of 5° . The black line is the average of the median values for the 3 subjects and demonstrates a significant negative correlation between T_{2a} and θ ($r = 0.41$, $p < .0001$). The plot indicates that T_{2a} tends to be longer for axonal fiber bundles that are parallel to the main field than for bundles that are perpendicular. This is similar to previous observations of a longer T_2^* in white matter bundles that are parallel to the main field,^{30,31} which has been attributed to variations in subvoxel magnetic susceptibility.³¹

5 | DISCUSSION AND CONCLUSIONS

In microstructural models for white matter based on dMRI data, differences in the intra-axonal and extra-axonal T_2 values have typically been ignored.³⁴ This is understandable, considering that the daunting task of linking brain microstructure to dMRI data necessitates simplifying assumptions to obtain a tractable mathematical description capable of yielding useful predictions. However, as recent work has shown, intra-axonal and extra-axonal T_2 values do differ significantly, enough to cause a noticeable bias in estimates for the compartmental water fractions if neglected.¹⁰

In this paper, we proposed a simple technique for estimating T_{2a} from mono-exponential fits to direction-averaged dMRI data for b-values exceeding about 4000 s/mm^2 . The key idea underlying this method is that the direction-averaged signal is dominated by the contribution from intra-axonal water for large b-values, which is supported by the observed $b^{-1/2}$ scaling behavior.^{12–14} Our results for T_{2a} are largely consistent with those obtained by Veraart et al using the TEdDI method, even though TEdDI differs markedly from our approach in being based on a detailed model for both the intra-axonal and extra-axonal spaces and in requiring complex nonlinear fitting.¹⁰ We have shown here that neither a comprehensive tissue model nor advanced numerical methods are necessary for determining T_{2a} . The advantage of TEdDI, however, is that it also estimates T_{2e} along with several diffusion parameters. Another approach for estimating compartmental T_2 is the recently proposed b-tensor method.³⁷

An important observation is that T_{2a} has a strong regional variation. At first this might seem surprising, as the chemical composition of axoplasm is presumably relatively uniform. However, a possible explanation is that T_{2a} is altered by spins diffusing across microscopic magnetic field inhomogeneities, generated by adjacent myelin, tissue iron, and deoxyhemoglobin within small blood vessels, which depend on both the local arrangement of axons as well as their orientation with respect to the main magnetic field. This hypothesis is supported by our observation that T_{2a} is correlated with the angle between the main magnetic field and the principal diffusion tensor eigenvector for voxels with coefficients of linearity exceeding 0.4, which is consistent with previous work on the orientation dependence of T_2^* .^{30,31} It is also conceivable that T_{2a} may be affected by the axon diameter, due perhaps to exchange or surface relaxation effects.^{35–37} Axons with larger diameters would then be expected to have a longer T_{2a} , which is roughly consistent with our results. For example, the cortical spinal tract, which runs through the posterior limb of the internal capsule, contains many thick axons, whereas axons in frontal white regions, such as the anterior corona radiata, have smaller average diameters.³⁸ Accordingly, we find a

significantly longer T_{2a} in the posterior limb of the internal capsule as compared with the anterior corona radiata (Figure 5).

A potential confounding effect for our method is that the eddy currents induced by the strong diffusion-sensitizing gradients will vary across TEs, thereby conceivably altering the signal decay curves due to TE-dependent image distortions. To mitigate this, we applied eddy current correction to all of our diffusion-weighted images.²² In addition, for 1 subject we acquired data with a bipolar sequence, which is designed to strongly suppress eddy currents,¹⁸ as well as with the monopolar sequence used for most of our scans. Any eddy current effects should manifest themselves as differences in the monopolar and bipolar T_{2a} values. Qualitatively, we found a good correspondence between the T_{2a} maps obtained with the 2 sequences, and the T_{2a} values were strongly correlated. Thus, eddy current effects are likely to be small for our experiments. We did observe a somewhat larger T_{2a} for the bipolar sequence, but that may be attributed, at least in part, to the extra refocusing pulse for the bipolar sequence, which reduces the effects of magnetic field inhomogeneities. This is similar to the known increase, as measured using a multiple spin echo sequence of white matter T_2 with a decrease of interecho time.^{39,40} We chose to use the monopolar sequence for most of our scans, because it allows for a shorter minimum TE, thereby supporting more precise measurements of T_{2a} .

In applying our method, a chief consideration is the choice of b-value. Below about 4000 s/mm², systematic errors may be expected because of the contribution to the signal from extra-axonal water, whereas above 8000 s/mm² accurate quantification of T_{2a} is challenging as a result of a low SNR. For this reason, we used a b-value of 6000 s/mm² for most of our experiments, although we found good consistency with results obtained at 4000 s/mm² and 8000 s/mm². The optimal b-value may also depend somewhat on scanner hardware and the details of the imaging protocol.

A limitation of our experimental design is that the diffusion time and the gradient pulse duration δ for the monopolar sequence varied with TE, which could, in principle, alter the T_{2a} estimates even with a fixed b-value. This is a built-in feature of our vendor-supplied sequence, which is constructed so as to allow the maximum possible b-value for any chosen TE. However, changing and δ has little effect on measured diffusion parameters in healthy white matter.^{41,42} As a result, the signal attenuation in our experiments caused by the diffusion-sensitizing gradients should primarily be determined by the b-value, and we do not expect the variable and δ to appreciably affect our results. Similar considerations hold for the bipolar sequence, although the diffusion time and gradient pulse duration are less well-defined in this case due to the more complicated pulse sequence design.¹⁸

Although the focus of this paper has been on T_{2a} , we have also shown how T_{2e} can be estimated in a similar way, provided that some additional information is available. First, one needs signal data acquired without diffusion weighting for the same TEs used to calculate T_{2a} . Second, an independently determined value for the intrinsic intra-axonal diffusivity is required, as could be found using any of several proposed dMRI-based microstructural modeling methods.^{14,16,27,29,34,43} Given these, T_{2e} may once again be obtained from simple mono-exponential fits, according to Eq. 3. For a range of plausible values for the intra-

axonal diffusivity, we find that the T_{2a} exceeds T_{2e} in most of the white matter voxels, which is consistent with the previous studies.^{5,7,9,10} The reader should be aware, however, that there has been some controversy regarding the accurate measurement of the intra-axonal diffusivity.^{16,28,33}

An important reason for estimating T_{2a} and T_{2e} is that knowledge of these 2 parameters can be used to correct values for the axonal water fraction obtained from dMRI-based microstructural modeling, which would typically be T_2 -weighted as suggested by Eq. A3, when the difference between T_{2a} and T_{2e} is neglected. Specifically, the corrected axonal water fraction is given by

$$f = \frac{f^* \cdot e^{-TE/T_{2e}}}{f^* \cdot e^{-TE/T_{2e}} + (1 - f^*)e^{-TE/T_{2a}}}, \quad (5)$$

where f^* is the uncorrected (apparent) axonal water fraction determined with dMRI data acquired at an echo time TE . Equation 5 can be derived by solving Eq. A3 for f .

For our experiment, we can estimate f^* for any given value of D_a by applying the following expression^{11,12}:

$$f^*(TE) = 2\sqrt{\frac{bD_a}{\pi}} \cdot \frac{\bar{S}(TE)}{S_0(TE)}, \quad (6)$$

which follows from Eq. A2. Using the monopolar data with $TE = 90$ ms, we obtain $f^* = 0.418 \pm 0.004$, 0.512 ± 0.004 , 0.591 ± 0.005 , and 0.661 ± 0.006 , where the values are averages ($\pm$ SD) across all 3 subjects for $D_a = 1.0$, 1.5 , 2.0 , and $2.5 \mu\text{m}^2/\text{ms}$, respectively. Thus, the intra-axonal and extra-axonal water fractions should be comparable in size, as has also been found in previous work^{10,27,29} employing dMRI-based microstructural modeling. If we set, for example, $f^* = 0.6$, $T_{2a} = 78$ ms, $T_{2e} = 60$ ms, and $TE = 90$ ms in Eq. 5, we find $f \approx 0.515$, which is a correction of about 14%.

In summary, we have demonstrated how T_{2a} in white matter can be found from mono-exponential fits of direction-averaged dMRI data acquired with large b-values and 2 or more TEs. Our results show a substantial regional variation in T_{2a} . We propose that this is at least partially attributable to the effects of microscopic magnetic field inhomogeneities, as is known to be the case for T_2^* ,³¹ although other effects may well be important too. We also confirm the conclusion of previous studies that $T_{2a} > T_{2e}$. Our method may find application in improving the predictions of dMRI-based microstructural models of white matter.

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APPENDIX

Neglecting myelin water, the MRI signal without diffusion weighting can be written as

$$S_0(TE) = A \left[f \cdot e^{-TE/T_{2a}} + (1 - f) \cdot e^{-TE/T_{2e}} \right], \quad (A1)$$

where f is the intra-axonal water fraction and A is a constant. For large b -values, the theory underlying fiber ball imaging¹¹ predicts

$$\bar{S}(TE) = \frac{1}{2} f^*(TE) S_0(TE) \sqrt{\frac{\pi}{bD_a}}, \quad (A2)$$

where

$$f^*(TE) = \frac{f \cdot e^{-TE/T_{2a}}}{f \cdot e^{-TE/T_{2a}} + (1 - f) \cdot e^{-TE/T_{2e}}} \quad (A3)$$

is the “apparent” axonal water fraction for a given TE .¹⁰ By combining Eqs. A1–A3, one sees that

$$\bar{S}(TE) = \frac{Af}{2} e^{-TE/T_{2a}} \sqrt{\frac{\pi}{bD_a}}. \quad (A4)$$

From Eqs. A1 and A4, it then follows that

$$F(TE) = A(1 - f) \cdot e^{-TE/T_{2e}}, \quad (A5)$$

which is identical to Eq. 3 after identifying C_e with $A(1 - f)$.

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FIGURE 1.

Direction-averaged diffusion MRI (dMRI) signal as function of TE for individual voxels from selected regions of interest using a monopolar (MP) sequence (A) and a bipolar (BP) sequence (B). All data points were obtained from a single subject (subject 1) with a b-value of 6000 s/mm^2 . The lines are best fits using the mono-exponential form of Eq. 1. The error bars indicate the standard error for the signal noise. Abbreviations: ACR, anterior corona radiata; GCC, genu of corpus callosum; PLIC, posterior limb of internal capsule; PTR, posterior thalamic radiation

FIGURE 2.

Parametric maps of T_{2a} for a single anatomical slice from subject 1, as determined with a monopolar sequence (center) and a bipolar sequence (right), along with the corresponding color fractional anisotropy (FA) map (left) for anatomical reference. The 2 T_{2a} maps are qualitatively similar, although somewhat higher values are apparent for the bipolar sequence in most white matter voxels. Note that T_{2a} values are only meaningful in white matter regions, because the assumptions underlying the estimation method are invalid in gray matter

FIGURE 3.

Scatter plot of T_{2a} for white matter voxels from the same anatomical slice as in Figure 2. The monopolar and bipolar values are strongly correlated ($r = 0.9$), but those for the bipolar sequence are mostly higher, with the best fit line having a slope of 1.1. Thus, the extra refocusing pulse of the bipolar sequence tends to increase the apparent T_{2a} .

FIGURE 4.

Histograms of T_{2a} for all white matter voxels from 3 healthy subjects. The dMRI data were acquired with a monopolar sequence and a b-value of 6000 s/mm². Most of the T_{2a} values lie between 50 ms and 110 ms

FIGURE 5.

Bar graphs showing the median T_{2a} for selected regions of interest from all 3 subjects, as acquired with a monopolar sequence and a b-value of 6000 s/mm². The median values range from a low of about 64 ms to a high of about 94 ms, and the error bars indicate SDs.

Abbreviations: ALIC, anterior limb of internal capsule; BCC, body of corpus callosum; EC, external capsule; PCR, posterior corona radiata; SCC, splenium of corpus callosum; SCR, superior corona radiata; SLF, superior longitudinal fasciculus

FIGURE 6.

The T_{2a} in white matter as a function of FA for b-values of 4000, 6000, and 8000 s/mm from subject 2. Similar results are found for all 3 diffusion weightings, with some small deviations being apparent for very low and very high FA. The dMRI data were acquired with a monopolar sequence. The data points indicate median values, and the error bars reflect the first and third quartile of T_{2a} values within each bin (bin size = 0.05)

FIGURE 7.

The T_{2e} in white matter as a function of FA for assumed intra-axonal diffusivities of $D_a = 1.0, 1.5, 2.0,$ and $2.5 \mu\text{m}^2/\text{ms}$, together with T_{2a} . The dMRI data were acquired with a monopolar sequence and a b-value of 6000 s/mm^2 . The data points are the averages of the median values from all 3 subjects, with the error bars indicating intersubject SDs. For all choices of D_a , T_{2e} is found to be substantially shorter than T_{2a} over the full range of considered FA values

FIGURE 8.

The T_{2a} in white matter voxels with a coefficient of linearity exceeding 0.4 as a function of the angle θ between the principal diffusion tensor eigenvector and the direction of the main magnetic field. The broken colored lines are median values for individual subjects, whereas the solid black line shows the average of these medians. The intersubject averages of T_{2a} are significantly correlated with θ ($r = 0.41$, $p < .0001$), suggesting that T_{2a} might be influenced by magnetic field inhomogeneities generated by spatial variations in magnetic susceptibility. The dMRI data were acquired with a monopolar sequence and a b-value of 6000 s/mm^2 .