T₁ Mapping Using Variable Flip Angle SPGR Data With Flip Angle Correction

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Purpose: To improve the calculation of T₁ relaxation time from a set of variable flip-angle (FA) spoiled gradient recalled echo images.

Materials and Methods: The proposed method: (a) uses a uniform weighting of all FAs, (b) takes into account global inaccuracies in the generation of the prescribed FAs by estimating the actual FAs, and (c) incorporates data-driven local B₁ inhomogeneity corrections. The method was validated and its accuracy tested using simulated data, phantom, and in vivo experiments. Results were compared with existing analysis methods and to inversion recovery (IR). Consistency was assessed by means of repeated scans of two subjects. Reference values were obtained from eight healthy subjects from various brain regions and compared with literature values.

Results: The method accurately and consistently estimated T₁ values in all cases. The method was more robust, in comparison with the standard method, to the choice of FA set; to inaccuracies in generation of the prescribed FAs (in simulated data, T₁ estimation error was 12.1 ms versus 235.5 ms); demonstrated greater consistency (in vivo study showed interscan T₁ difference of 80 ms versus 356 ms); and achieved a better agreement with IR on phantom (median absolute difference of 123.8 ms versus 790 ms). Reference T₁ values were 883/801 ms for female/male in white matter and 1501/1349 ms in gray matter, within the range previously reported.

Conclusion: The proposed method overcomes some inaccuracies in FA production, providing more accurate estimation of T₁ values compared with standard methods, and is applicable for currently available data.

Key Words: relaxometry; T₁ mapping; FA correction, SPGR

ACCURATE ESTIMATION OF the longitudinal relaxation time, T₁, of brain tissues has multiple clinical applications, and plays a significant role in the shift toward quantitative analysis of MRI signals. In clinical research of several neurological disorders, such as multiple sclerosis and Parkinson’s disease (1,2), T₁ values improve the delineation of specific brain structures and the differentiation between patients and healthy subjects. In addition, accurate T₁ values are necessary for the extraction of pharmacokinetic parameters, from dynamic contrast enhanced (DCE) data (3). Additionally, knowledge of the T₁ value leads to better approximation of T₂ value in certain methods, such as driven equilibrium single pulse observation of T₂ (DESPOT2) (4).

To this end, various MRI sequences and analysis methods have been proposed to calculate the T₁ value (4–11). One of these methods is the variable flip-angle (VFA) spoiled gradient recalled echo (SPGR) method, that provides high spatial resolution with relatively short acquisition times (1,4), and is commonly used in basic and clinical research. Significant efforts have been devoted to developing a fast and highly accurate analysis (12) of the VFA-SPGR data and to finding the best set of flip angles (FAs) that maximize accuracy and efficiency (in terms of T₁ value to noise ratio per acquisition time unit), for a specific T₁ value or a range of values (4,13,14). There is currently no broadly accepted FA set, and in many institutions, a varied set of angles is used. In addition, most current methods weight each FA dataset by a different factor that depends on the FA, resulting in a nonuniform weighting of the datasets. Thus, the calculated maps are affected by the choice of the FA set (13).

Another limitation of most current analysis methods is that they base their calculation of the T₁ values on the prescribed FA as reported by the MRI system. Yet, the actual FA might deviate from the one reported by the system, both globally, which may occur due to inaccuracy in calibration, and locally, due to inhomogeneity in the radiofrequency (RF) transmit field B₁. Several sequences have been proposed to determine...
the $B_1$ inhomogeneity (5,15,16), with the aim of improving the precision of the $T_1$ value estimate (5). An approximation formula and analysis of $T_1$ error due to $B_1$ inhomogeneities have been separately devised (17). Several sequences have been developed for actual FA imaging (AFI) (16,18) which use SPGR with multiple repetition times (TRs) and multiple FAs, to measure the actual FA along with $T_1$ mapping. However these methods are not always available in clinical systems, and do not deal with global inaccuracies in the production of the prescribed FAs, which are FA dependent.

In the present work, a new method to calculate $T_1$ values from the VFA-SPGR data is proposed with several advantages over existing methods: (i) the method weights the different FAs almost uniformly, resulting in a reduction of the error of fit; (ii) it estimates the global deviation from the prescribed FA due to inaccuracies in FA production, and by using the actual FAs, a better fit is obtained, not only in terms of error of fit, but also in the uniformity of the error of fit maps, indicating that the deviations from the prescribed FAs indeed stem from incorrect report of the actual FAs; and (iii) data-driven $B_1$ inhomogeneities correction is incorporated. The method proposed in this study works with the most commonly available data, acquired using VFA-SPGR, regardless of the way the calibration was performed and of the choice of the FA set. The accuracy and reproducibility of the method was compared with the standard method on simulated data, phantom and in vivo experiments. Finally, reference $T_1$ values of different brain areas of healthy subjects were obtained using the proposed method and compared with literature values.

**MATERIAL AND METHODS**

**The Standard Method for Estimating the $T_1$ Value From VFA-SPGR Data**

The signal $S$ detected with an SPGR sequence depends on: the equilibrium longitudinal magnetization ($M_0$) which relates to the proton density; the repetition time TR; the $T_1$ value of the tissue; and the FA [$\alpha$]:

$$S = M_0 \frac{1 - \exp(-TR/T_1)}{1 - \exp(-TR/T_1)\cos(\alpha)}\sin(\alpha). \quad [1]$$

Other multiplicative factors, such as $T_2$, $T_2^*$ and $B_0$ inhomogeneity effects are assumed to remain constant while the FA is changed. These factors will affect the estimation of $M_0$, but not of $T_1$. A common method to calculate the $T_1$ values from a given set of acquisitions with different FAs was suggested by Blüm [19], assuming constant TR values. In this method, a linear equation system is constructed, where each equation is a linearization of Eq. [1] for a different FA. The linearization is performed by multiplying Eq. [1] by $c_\alpha = (1 - \exp(-TR/T_1)\cos(\alpha))/\sin(\alpha)$ and rearranging, resulting in:

$$\frac{S}{\sin(\alpha)} = S \cdot \frac{\exp(-TR/T_1)}{\tan(\alpha)} + M_0 \cdot (1 - \exp(-TR/T_1)). \quad [2]$$

Written in matrix form for different FAs, this becomes

$$\begin{pmatrix}
S_1 \\
\sin(\alpha_1)
\end{pmatrix} =
\begin{pmatrix}
S_1 \\
\sin(\alpha_2)
\end{pmatrix} = \cdots =
\begin{pmatrix}
S_n \\
\sin(\alpha_n)
\end{pmatrix} =
\begin{pmatrix}
1 \\
\frac{\exp(-TR/T_1)}{\tan(\alpha_1)} \\
\frac{\exp(-TR/T_1)}{\tan(\alpha_2)} \\
\vdots \\
\frac{\exp(-TR/T_1)}{\tan(\alpha_n)}
\end{pmatrix} \cdot
\begin{pmatrix}
M_0 \cdot (1 - \exp(-TR/T_1))
\end{pmatrix} \quad [3]
$$

where $n$ is the number of FAs acquired. The resulting equation system [3] has a line form (\(y_i = a x_i + b\)), where the $T_1$ value can be simply extracted from the slope coefficient of this linear regression problem. We will refer to this method as the line fit method. Note that the line fit method aims to fit Eq. [2], rather than Eq. [1]. As $c_\alpha$ is FA dependent, it is different for each instance of Eq. [2] in the equation system [3]. Thus it operates as a weighting factor, giving different weights for the different FA datasets, resulting in a suboptimal fit to the actual signal data.

**The Proposed Method**

Here, we propose three modifications to the method to improve the estimation of the $T_1$ value.

**Uniform Weighting of All Flip Angles**

Aiming for a linear equation with uniform weighting, we would like to have a new weighting coefficient $c_\alpha$ to be only weakly dependent on $\alpha$. As the numerator of $c_\alpha$, $1 - \exp(-TR/T_1)\cos(\alpha)$, is used for the linearization, we change the denominator to be a good approximation of it, $1 - \exp(-TR/T_1')\cos(\alpha)$, where $T_1'$ approximates the real $T_1$ value. This results in our weighting factor:

$$c_\alpha' = (1 - \exp(-TR/T_1)\cos(\alpha))/(1 - \exp(-TR/T_1')\cos(\alpha)) \approx 1, \forall \alpha \quad [4]$$

which leads to the following equation system:
A linear equation system which can be solved with the same complexity as the standard method. In this case, \( T_1' \) needs to be defined. It can be predefined to an accepted value detected in the brain, eg, 1200 ms. Note that this is a constant and a priori known value, and thus does not harm linearity. An additional iteration is performed to optimize this value, where \( T_1' \) used in the second iteration is the \( T_1 \) value calculated in the previous step. For a wide range of \( T_1 \) values (300–2500 ms), two iterations were found to be enough for convergence, leading to \( c' \approx 1 \), for any reasonable \( a \). We will refer to these stages of analysis as the one- and two-step methods, respectively (for pseudo-code, see Supp. Material S1, which is available online).

**Estimation of the Actual Flip Angles**

Actual FAs can vary from prescribed ones. Using linear approximations and the half-angle substitution, Helms et al (17) derived a simple approximation to Eq. [1]: as:

\[
S \approx M_0 \alpha \frac{TR/T_1}{\alpha^2/2 + TR/T_1}. \tag{S, Eq. 7 in (15)}
\]

The \( T_1' \) and \( M_0' \) resulting from local inhomogeneity in \( B_1 \), i.e., dividing all of the FAs by a constant factor to be \( \alpha \approx \alpha/k \) are as follows:

\[
T_1' \approx T_1 \cdot k^2, \quad M_0' \approx M_0 \cdot k. \tag{7a,b, Eq. 11a,b in (15)}
\]

The signal of a voxel with these parameters and the FA affected by the \( B_1 \) inhomogeneity will be as follows:

\[
S' \approx M_0' \alpha' \frac{TR/T_1'}{\alpha'^2/2 + TR/T_1'} = (M_0 \cdot k') \frac{TR/(T_1 \cdot k^2)}{\alpha^2/(2k^2)} = M_0 \alpha \frac{TR/T_1}{\alpha^2/2 + TR/T_1} \approx S. \tag{8}
\]

thus, the changes in the \( T_1 \) and \( M_0 \) values completely compensate at the signal level for the constant multiplicative change in the FA, for any of the FAs, and the two configurations are indistinguishable in VFA-SPGR data at the voxel level. This claim was also numerically validated. Thus using the prescribed FAs in the calculation will lead to inaccuracy in the \( T_1 \) estimation, while the error of fit in the equation system (ie, either [3] or [5]) will be insignificant.

However, if each FA deviates from its prescribed value differently, using the prescribed values will result in both inaccuracy in the \( T_1 \) estimation and in a significant error of fit (due to the fact that the 2 free parameters, \( T_1 \) and \( M_0 \), cannot capture the higher dimensional space spanned by the FA deviations, assuming more than 2 FAs).

We suggest a search in the FA additive deviation space to minimize the error of fit. As a consistent multiplicative change in the FAs does not affect the error of fit, one degree of freedom is reduced by fixing one of the FAs to some value (eg, in this study, the median FA to its prescribed value). In other words, we propose a search in the \((n-1)\)-dimensional space for deviation from the prescribed FAs, where \( n \) is the number of FAs given, while keeping one FA fixed. The optimization problem can be formalized as:

\[
\Theta^* = (d_1, \cdots, d_{n-1}) = \arg \min \left( \sum_{\nu \in \text{Samples}} \text{RMS}_\nu(S_\nu, \Theta) \right) \tag{9}
\]

where \( S_\nu \) is the vector of \( n \) VFA-SPGR signal values corresponding to the acquisition in the voxel \( \nu \), and \( \text{RMS}_\nu(S_\nu, \Theta) \) is the root-mean-square error of fit criteria between \( S_\nu \) and a signal simulated using the FAs with deviations \( \Theta \) (where, for each \( \Theta \) evaluated during the search, the \( T_1 \) and \( M_0 \) values used are the ones found by the two-step method presented above (Pseudo-code is provided in S2)).

This part of the method is insensitive to local inhomogeneity, which appears as a constant multiplicative change in the FAs (eg, the effective value for all of the FA in a specific voxel might be 70% of their global value). Therefore, compensation for \( B_1 \) inhomogeneity is applied, as described next.

**B1 Inhomogeneity Correction**

In the last step, a data-driven extraction of the change in the localized actual FA, due to the \( B_1 \) inhomogeneity, is proposed. Data-driven \( B_1 \) inhomogeneity correction algorithms are based on various assumptions. The N3 algorithm (20) presupposes: (a) a smooth multiplicative field, and (b) smoothing of an originally multimodal histogram which results from the field (formally described as reduction of the high frequency content of the intensity distribution). These hold for the \( T_1 \) map: (a) as can be seen by the approximation developed by Helms et al (17) (see Eq. 7a here), a multiplicative change in the FA values leads to an approximately inverse squared multiplicative change in the \( T_1 \) value. Thus the \( B_1 \) field is reflected in the \( T_1 \) map as a smooth multiplicative field. (b) The real \( T_1 \) value histogram is expected to contain distinct peaks corresponding to the various tissues.

Given that these two assumptions hold, we propose to apply the N3 algorithm to the calculated \( T_1 \) map, rather than to the raw data. This gives more accurate \( T_1 \) values, by correcting for the \( B_1 \) inhomogeneity, without the need for additional scans (for pseudo-code, see S3). Note that the inhomogeneity estimation is true up to a global multiplicative factor (eg, it estimates that the field in voxel \( a \) is 20% weaker than in voxel \( b \), but it does not tell if we should thus compensate the value in \( a \) accordingly, leave it as it is and compensate the value in \( b \), or compensate both to some degree). Therefore, a global multiplicative factor is chosen such that it fixes a value at a given region of interest (ROI) to an a priori known value (in this study, the value of the white matter (WM) was set to 830 ms) (21).

**Validation of the Method and Obtaining Reference Values**

**Simulated Data**

**Dataset 1**

VFA-SPGR signals were simulated using Eq. [1], with \( TR = 5.6 \) ms, \( M_0 = 10,000 \) (a.u.), FAs in the range...
[2–50], and several T1 values: 300, 1200, and 2500 ms. For the two-step method, the FA set used was {2, 9, 20} and Gaussian noise with \( \sigma = 30 \), corresponding to a signal to noise ratio (SNR) of around 10, was added to the data. These data were used to calculate the weights on the different FAs using the proposed method, in comparison to the line fit method.

**Dataset 2**

The three-dimensional (3D) VFA-SPGR images were simulated using M0 and T1 values obtained from a healthy subject for the FA set \{1.4, 2.6, 4.8, 7.8, 13.3, 15.1, 17.6\}. These M0, T1 maps and FA values will be referred to as “actual.” The related “prescribed” FAs given to the algorithm were {2, 3, 5, 9, 16, 20, 25}. A Gaussian noise with \( \sigma = 10 \) was added, a realistic standard deviation in our data. These data were used to assess the method’s accuracy in estimating the actual FAs.

**Phantom Data**

A phantom of a chicken leg was scanned using inversion recovery (IR) with inversion time TI = {200, 500, 1000, 1400, 3000} ms and TR/TE = 10000/13 ms, and with VFA-SPGR with FA set {2, 10, 15, 20, 30} and TR/TE = {5.64 to 5.82}/2.1 ms. The data were used to test the accuracy of the suggested method. The VFA-SPGR data were analyzed twice, using the standard and the proposed methods. Errors of fit measurements are presented for voxels for which the signal was above 100 (a.u.) in all FA datasets. Comparison to IR were done after reslicing into the IR space, on a mask containing voxels for which all of the IR signals were above 100 (a.u.), and eroded by a disk kernel of 11 voxels radius to exclude margin effects.

**In Vivo Experiment**

Ten healthy subjects were scanned on a 3 Tesla (T) GE HDxt scanner (GE Signa EXCITE, Milwaukee, WI, USA) using 3D FSPGR sequences, with separate calibration for each FA acquisition.

Subjects were scanned using head quad coil, with field of view (FOV) / acquisition matrix: 24 × 18 cm / 256 × 128, bandwidth of 31.25 kHz, slice thickness of 5 mm and two averages, unless otherwise specified. Scan time (for each FA) was in the range of 12–38 s depending on the number of slices acquired.

One subject (subject number 1; male) was scanned using the FA set \{2, 3, 5, 8, 10, 12, 2, 3, 5, 8, 10, 12, 15, 18, 25\} with repetition time/echo time (TR/TE) = 5.86/2.1 ms. This subject was scanned with an 8 channel head coil, acceleration factor of 2 and slice thickness of 4mm. These data were used to evaluate the inaccuracy in prescribed FA production.

One subject (subject number 2; male) was scanned twice, on 2 consecutive days, with an eight-channel head coil, acceleration factor of 2 and slice thickness of 5 mm using the FA set \{3, 5, 12, 20\} with TR/TE = 5.56/1.61 ms on the first day and TR/TE = 5.768/1.65 ms on the second day. These data were used to test the consistency of the proposed method.

Eight subjects (five males, three females) were scanned using the FA set \{3, 5, 12, 20\} with TR/TE = 4.96–5.55/1.57–2.1 ms. These data were used to obtain reference T1 values from different brain areas. The study was approved by the Hospital’s Institutional Review Board, and written informed consent was obtained from all subjects.

**Data Analysis**

T1 values were calculated using the described two-step method, using the prescribed and actual FA values extracted by the method, and with and without B1 correction using the N3 algorithm (20) applied to the resulting T1 map. For validation of accuracy, results were compared between all analyses. For the healthy subjects’ data, preprocessing included brain extraction performed using the BET module of the FSL toolbox (http://www.fmrib.ox.ac.uk/fsl) (22), and coregistration of all FA datasets of each subject was performed using the mutual-information criteria, to the median FA data, by SPM8’s rigid coregistration module (23). When measuring the T1 values in the various brain areas, the two-step method was used, using the extracted FAs with the B1 inhomogeneity correction. The global multiplicative factor on the FAs was estimated by multiplying the T1 map such that the mean value for WM ROIs would correspond to 830 ms, as reported by Wansapura et al (21).

**Brain Area Definition**

Several regions of interest (ROIs) were defined on the median FA volume to measure the T1 values in the different brain areas. ROIs were defined in the same areas as in (21): frontal, parasagittal frontal, insular, parietal, parasagittal occipital and occipital gray matter (GM); frontal, parietal, and occipital WM and additionally in the corpus callosum and thalamus. The median T1 values were calculated for each ROI in each subject to minimize partial volume and mislabeling effects. The average values of all eight subjects were calculated.

**Minimization Procedure**

The error of fit minimization in the FA deviation space was performed by running the Broyden-Fletcher-Goldfarb-Shanno algorithm (24) on several sample sets (10 sets of 1000 randomly chosen voxels), and choosing the corrected FA set which produced minimal error of fit for the whole volume (for pseudo-code, see S2).

**Statistical Analyses**

Statistical analyses were performed using MATLAB software (25). t-tests were performed to assess differences between maps obtained using the various methods. An analysis of variance (ANOVA) analysis was performed to assess the contribution of the prescribed FA value and subset chosen to the estimation of the FA, on all of the extracted FA values in Table 2.
RESULTS

The proposed method to analyze the VFA-SPGR data produced a more uniform weighting of the different FAs, as shown in the following subsection. By using the actual FAs, as estimated by the method, we obtained more accurate and consistent estimation of the T1 values on the simulated data, on the phantom, and on consecutive scans of a healthy subject. Furthermore, we calculated T1 values in various anatomical locations in healthy subjects and compared them with literature values, obtained using various acquisition and analysis methods, including IR. The comparison indicated a good agreement between our results and literature values.

Uniform Weighting of All Flip Angles

Simulated Dataset 1

The standard and suggested coefficients on S (\(c_a = (1 - \exp(-TR/T_1)\cos(\alpha))/\sin(\alpha)\)) and \(c'_a = (1 - \exp(-TR/T_1)\cos(\alpha))/(1 - \exp(-TR/T_1)\cos(\alpha))\), respectively) were calculated on simulated dataset 1. Figure 1 shows the weights on each FA data using the standard line-fit method (black), the suggested one-step method (blue, using \(T_1' = 1200\) ms) and the two-step method (red). As can be seen, the weights using the two-step method are uniform for the whole range of FAs, for the full range of T1 values tested. For example, for \(T_1 = 1200\) ms, the 25' data are weighted \(\sim 2.4\) times more than the 5' data using the line-fit method, while less than 5% more using the proposed two-step method. The coefficients in the proposed method are virtually independent of the FA. In our data, this step alone had a small effect on the T1 estimation and the error of fit, yet the suggested mathematical elaboration may prove useful in devising better analyses.

![Weighting schemes](Image)

**Figure 1.** Weighting of the flip angle data: Black, using the commonly used line-fit weighting method. Blue, using the suggested one-step weighting method where \(T_1' = 1200\) ms. Red, using the suggested two-step weighting method, using the \(T_1'\) from the first step.

Estimation of the Actual Flip Angles

Simulated Dataset 2

Several subsets of FAs, ie, different FA datasets, were taken from the full set \(\{1.4, 2.6, 4.8, 7.8, 13.3, 15.1, 17.6\}\) of the simulated 3D MR images. The algorithm was initialized by the corresponding "prescribed" FA values: \(\{2, 3, 5, 9, 16, 20, 25\}\) and estimated values for the actual FAs were extracted by minimizing the error of fit on the data. The results are presented in Table 1. The extracted FAs were accurate in all cases except for minor deviation in the first subset, which included only small flip-angles.

<table>
<thead>
<tr>
<th>Effective FA Values*</th>
<th>Extracted FA Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4, 2.60, 4.80</td>
<td>1.46, 2.73, 5.33</td>
</tr>
<tr>
<td>1.4, 4.80, 13.30</td>
<td>1.40, 4.80, 13.32</td>
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<tr>
<td>1.4, 7.80, 17.60</td>
<td>1.40, 7.77, 17.56</td>
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<tr>
<td>1.4, 8.80, 10.70</td>
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<td>1.4, 6.80, 15.10, 17.60</td>
<td>1.40, 2.61, 4.82, 13.30, 17.61</td>
</tr>
<tr>
<td>1.4, 8.80, 15.10, 17.60</td>
<td>1.40, 4.80, 7.82, 15.10, 17.58</td>
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<tr>
<td>1.4, 2.60, 4.80, 8.80, 13.30</td>
<td>1.40, 4.80, 7.81, 13.30, 15.10, 17.59</td>
</tr>
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<td>1.40, 2.60, 4.81, 7.81, 13.30, 15.10</td>
</tr>
<tr>
<td>1.4, 7.80, 12.60, 15.10</td>
<td>15.10 17.60</td>
</tr>
</tbody>
</table>

*The left column shows the effective FA values used for simulating MR signal. The right column shows the FA values extracted by the algorithm, when given the simulated signal and the corresponding nominal FAs from the set \(\{2, 3, 5, 9, 16, 20, 25\}\).

In Vivo Experiment

The first subject was scanned with many prescribed FAs including some FAs that were repeated (\(\{2, 3, 5, 8, 10, 12, 2, 3, 5, 8, 10, 12, 15, 18, 25\}\)). For several subsets of the data, we searched for the actual FAs by minimizing the error of fit. The prescribed and extracted FAs for several subsets of the data are shown in Table 2. The algorithm consistently extracted the same values independently of the FA subset used with only minor variations. In addition, different values were consistently extracted for
repeated acquisitions with the same prescribed values, for example, $11.62 \pm 0.15$ for $10^a$ and $10.10 \pm 0.07$ for $10^b$. The method showed high consistency and robustness to the FA subset used. An ANOVA analysis on the actual FA values shows significance for prescribed FA value ($P < 1.e-10$) but not for the subset chosen ($P > 0.05$).

To confirm the finding that for the same prescribed FAs, the actual values were different; we focused on the fifth FA subset (marked in bold in Table 2). The mean absolute signal differences between the two acquisitions with the same prescribed FA were $53.16$ (a.u.) for $10^a/C14$ and $65.06$ (a.u.) for $2^b/C14$. These large differences in the signal between two almost consecutive acquisitions of the same prescribed FA can be explained by the fact that different actual FAs were applied, as detected by the algorithm. Furthermore, images were simulated using the extracted FA values ($11.65$, $10.04$, and $2.62 , 2.27$) based on the $T_1$ and $M_0$ maps obtained from this subject. These images were subtracted from the corresponding acquired MR images. Mean absolute differences were $10.49$, $10.24$ for $10^a,10^b$ and $4.76$, $4.59$ for $2^a,2^b$ (a.u., respectively). The smaller differences indicate that the simulation indeed captures the nature of the difference between the acquisitions, i.e., the deviations from the prescribed FAs.

A similar analysis was performed on the data of the second subject, who was scanned twice on 2 consecutive days, with similar results; of note, the same prescribed FAs yielded different actual ones.

B1 Inhomogeneity Correction and Consistency of $T_1$ Maps

*In Vivo Experiment*

Subject number 2 was scanned on 2 consecutive days with the same prescribed FAs. $T_1$ maps were calculated for each dataset using the standard method and the proposed method, using the extracted FAs and B1 inhomogeneity correction, and the interscan differences were calculated (Fig. 3). Using the proposed method, the $T_1$ maps showed higher interscan consistency in comparison with the standard method (mean absolute difference between the $T_1$ maps of the 2 days: $80.8$ ms and $356.7$ ms, respectively); the interscan $T_1$ difference map was more uniform and lacked spatial anatomical structure. These results indicate that by accounting for inaccuracy in prescribed FA production and B1 inhomogeneity, higher consistency in calculated $T_1$ maps can be achieved.

**Accuracy of the Method**

The phantom was scanned using both IR and VFA-SPGR and $T_1$ values were estimated from both datasets. $T_1$ value estimation from the VFA-SPGR data was performed using the standard and the proposed methods. Relative root-mean-square ($r$RMS, coefficient

<table>
<thead>
<tr>
<th>Nominal</th>
<th>Extracted</th>
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<tbody>
<tr>
<td>$10^a$</td>
<td>$2^a$ $10^b$ $2^b$ $25$ $11.66$ $2.62$ $10.05$ $2.27$ $18.60$</td>
</tr>
<tr>
<td>$10^a$</td>
<td>$2^a$ $3$ $12$ $25$ $11.57$ $2.63$ $3.36$ $9.98$ $18.53$</td>
</tr>
<tr>
<td>$10^b$</td>
<td>$2^b$ $3$ $12$ $25$ $10.10$ $2.27$ $3.35$ $10.10$ $18.66$</td>
</tr>
<tr>
<td>$10^b$</td>
<td>$2^b$ $10^a$ $2^a$ $25$ $10.06$ $2.27$ $11.65$ $2.62$ $18.57$</td>
</tr>
<tr>
<td>$10^b$</td>
<td>$2^b$ $10^b$ $2^b$ $25$ $11.65$ $2.62$ $10.04$ $2.27$ $18.58$</td>
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<td>$10^b$</td>
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<td>$10^b$</td>
<td>$2^b$ $25$ $11.37$ $2.67$ $18.36$</td>
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<tr>
<td>$10^b$</td>
<td>$2^b$ $25$ $10.09$ $2.28$ $18.69$</td>
</tr>
</tbody>
</table>

*The left column shows the nominal flip angle values, as reported by the MRI system. The right column shows the flip angle values extracted by the method. Repeated acquisitions using the same flip angles are marked by superscript "a" and "b".*
of variation of the RMS of the errors) values were calculated per voxel using both methods, with the results showing a much lower rRMS value using the actual FAs than using the standard method (mean rRMS of 0.01 versus 0.12, F-test P-value < 1e-10). T1 maps estimated from IR data (considered as gold-standard) and from the VFA-SPGR data using the standard and proposed methods, are presented in Figure 4a,b,c, along with the differences in T1 estimation between IR and the two VFA-SPGR analyses (Fig. 4e,f). The proposed method achieved a better agreement with IR estimations (median absolute difference of 123.8 versus 790.0 ms). Note that similarly high differences to IR have been previously reported using the standard analysis method of VFA-SPGR on a 3T system (5). The proposed analysis overcomes much of this inaccuracy. Figure 4d shows a scatter plot of the T1 values obtained using IR and VFA-SPGR with the suggested

Figure 3. Consistency of T1 maps. T1 maps from both days, using the standard and the proposed methods, along with the corresponding interscan differences.

Figure 4. Accuracy of T1 maps. T1 maps estimated from IR and SPGR data (a) using the standard (b) and the proposed (c) methods, along with T1 estimation difference maps between IR and the standard method (e), and IR and the proposed method (f). d: Scatter plot of the T1 values estimated using IR and SPGR with the proposed method.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Subjects</th>
<th>Blood / CSF</th>
<th>WM</th>
<th>GM</th>
<th>Splenium</th>
<th>Thalamus</th>
<th>Other</th>
<th>Age (yr)</th>
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<tbody>
<tr>
<td>This study</td>
<td>VFA-SPGR - Proposed analysis</td>
<td>3 Females</td>
<td>6873 (CSF)</td>
<td>883</td>
<td>1501</td>
<td>1064</td>
<td>1699</td>
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<tr>
<td>This study</td>
<td>VFA-SPGR - Proposed analysis</td>
<td>5 Males</td>
<td>4184 (CSF)</td>
<td>801</td>
<td>1349</td>
<td>906</td>
<td>1404</td>
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<tr>
<td>Wansapura et al., 1999 (20)</td>
<td>* Saturation recovery</td>
<td>19 (8F, 11M)</td>
<td>832 (893 female, 788 male)</td>
<td>1331 (1393 female, 1286 male)</td>
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<td>28–51, 29–47</td>
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<td>Gelman et al., 2001 (27)</td>
<td>TOMROP</td>
<td>12 (7F, 5M)</td>
<td>847 (FWM)</td>
<td>1763 (PC)</td>
<td>1218</td>
<td>1147 (SN), 1043 (GP), 1337 (PT), 1483 (CN)</td>
<td>22–38</td>
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<td>Chen et al., 2001 (25)</td>
<td>IR-FSE</td>
<td>10 (4F, 6M)</td>
<td>4163 (CSF)</td>
<td>791</td>
<td>1445</td>
<td>1271</td>
<td></td>
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<td>31 ± 10</td>
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<td>Ethofer et al., 2003 (26)</td>
<td>* Progressive saturation - MRS</td>
<td>8 (4F, 4M)</td>
<td>960 (FPWM), 1110 (OWM)</td>
<td>4121</td>
<td>1421</td>
<td>746, 724 (Genu)</td>
<td>1034</td>
<td>1129 (PT), 1190 (CN)</td>
<td>34 ± 9</td>
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<td>Zhu and Penn, 2005 (31)</td>
<td>Adiabatic TESO-IR-FSE</td>
<td>12 (5F, 7M)</td>
<td>790, 761 (FWM), 791 (PWM)</td>
<td>1932b (Blood)</td>
<td>1820</td>
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<td>Stanisz et al., 2005 (30)</td>
<td>IR</td>
<td>Bovine samples</td>
<td>1932b (Blood)</td>
<td>1084</td>
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<td>Lu et al., 2005 (28)</td>
<td>aIR</td>
<td>10 (4F, 6M)</td>
<td>699 (FWM), 758 (OWM)</td>
<td>1209 (FGM), 748, 721 (Genu)</td>
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<td>1102 (PT), 1122 (OC), 1258 (CN)</td>
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<td>Cheng and Wright, 2006 (13)</td>
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<td>1703, 1732</td>
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<td>Rooney et al., 2007 (29)</td>
<td>Modified Look-Locker, estimated value for 3T.</td>
<td>3 (3M)</td>
<td>1961 (Blood)</td>
<td>887</td>
<td>1293 (IGM)</td>
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<td>32–59</td>
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<td>Deoni, 2007 (5)</td>
<td>VFA-SPGR-B1, IR; Analyzed by DESPOT1-HIFI, estimated from graph</td>
<td>3 (2F, 1M)</td>
<td>~1060</td>
<td>~1495</td>
<td>~1230 (GP), ~1570 (PT), ~1610 (CN)</td>
<td>30,32, 26</td>
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<td>Helms et al., 2008 (15)</td>
<td>FLASH, Two angles (7,20)</td>
<td>8 (4F, 4M)</td>
<td>4181 (CSF)</td>
<td>801</td>
<td>1349</td>
<td>778</td>
<td>1408 (OC), 1269 (CN)</td>
<td>25–31</td>
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</table>

*Image of ROIs.

1Ref. to ~1550 Greenman 2003.

1Note that the values were fixed such that WM value is the same as that reported by Wansapura, using the extra degree of freedom.

CC = corpus callosum; PC = prefrontal cortex; IGM = internal GM; OWM = occipital WM; FPWM = frontoparietal WM; M1 = motor cortex; CL = cerebellum; SN = substantia nigra; GP = globus pallidus; PT = putamen; OC = occipital cortex; CN = head of the caudate nucleus.
method. While a good agreement was achieved, the correlation slope deviates from the 1:1 line (gray). This deviation might be the result of inaccuracies relating to IR measurements (such as incomplete inversion), and to the global factor on the $B_1$ inhomogeneity field.

**Reference T1 Values**

$T_1$ maps were calculated in several brain areas of eight healthy subjects using the actual FAs, $B_1$ inhomogeneity correction and estimation of the consistent multiplicative coefficient. The values were normalized such that the mean WM ROIs value was set to 830 ms (as reported by Wansapura et al) (21), due to the extra degree of freedom related to the overall $B_1$ inhomogeneity coefficient. Note that this shift, ie, the effect of the overall amplitude of the $B_1$ inhomogeneity, is an inherent phenomenon, and not particular to the suggested analysis. In this study, the normalization resulted in a change of less than 5% in the $T_1$ values. Mean $T_1$ values in the various brain areas are presented in Table 3, along with literature values (5,13,17,21,26–32). The $T_1$ values, calculated using the proposed method, are within the interstudy range. The differences in $T_1$ values between male and female subjects detected in this study (see Table 3) support previous findings (21). Table 3 presents a comprehensive report of reference (3T) $T_1$ values measured in various studies. A large interstudy variability is evident, suggesting that true universal $T_1$ reference values for brain tissues are still unknown.

**DISCUSSION**

The current study proposed a method for calculating $T_1$ maps based on the commonly used VFA-SPGR method. This method weighs the different FAs uniformly, uses corrected FAs rather than the prescribed FA values and corrects for $B_1$ inhomogeneity. The method shows high consistency in the actual FA value estimation regardless of the FA set used; in the calculation of $T_1$ maps in longitudinal scans; and higher accuracy than the standard method (33).

The problems considered in this study, ie, the biased weighting of the FA data, the inaccuracy in the production of the prescribed FA value and the overall amplitude of the $B_1$ field, are inherent to the VFA-SPGR acquisition, and many other acquisition methods. This study proposes an investigation of these parameters, usually perceived as fixed between acquisitions. Other factors, such as gain and baseline level, were investigated in a preliminary study and found to be unchanged during the VFA-SPGR acquisitions. This approach should be further applied to other sequences and analyses such as AFI mapping and $T_2$ measurements, and $T_1$ measurements through IR scans. Furthermore, we highlight the importance of the neglected error of fit maps for evaluation of the quality of a model.

When a single calibration is performed and applied to all FAs, their actual values may deviate by a constant multiplicative factor from the prescribed ones. However, when each acquisition is calibrated separately, the actual values may deviate by a different factor from the corresponding prescribed values. The proposed method is insensitive to both the choice of FA set and the calibration method used, not requiring any additional data such as $B_1$ mapping, and is therefore applicable to most available data. These advantages, in addition to the high accuracy and reproducibility, make the proposed method ideal for multi-center, longitudinal studies and applicable to retrospective data. While $B_1$ inhomogeneity is usually neglected in 1.5T systems, in 3T systems local changes in the actual FA due to $B_1$ inhomogeneity were shown to be significant (5). In this study, a data-driven algorithm was used to account for $B_1$ inhomogeneity, yet direct $B_1$ mapping methods, such as AFI (16), DESPOT1-HIFI (5), and DREAM (15) are recommended when available.

The approach of uniform weighting of the different FA data can be applied in other studies, to achieve a more accurate parameter estimation. Such schemes may give higher weights for specific data points (i.e., flip angle data) that were acquired with lower noise, or for which a greater a priori belief is assumed (for example, see Cheng and Wright) (13), with weights proportional to signal. Our weighting scheme does not contradict such considerations, but may serve as a basis for equalizing the weight of each data point before application.

Currently reported $T_1$ values obtained from healthy brain tissue show broad interstudy variation even between studies using the same or similar acquisition and analysis methods (5,13,17,21,26–32). This variability can result from the inaccuracy of the prescribed FA used, $B_1$ inhomogeneity and partial volume effect due to the ambiguity of ROI definition. Although our results showed general agreement with literature values, the variability between studies indicates that $T_1$ estimations should be currently considered as method-dependent, and maybe even system-, configuration-, and patient-group-dependent, rather than universal. By using the proposed method and selecting the median value for a set of several voxels (rather than the average of an area) for each ROI, more consistent and accurate $T_1$ values may be obtained.

Several limitations to the proposed method should be considered. The method uses data-driven analysis to estimate acquisition parameters for which a direct measurement is more accurate, indeed a direct measurement of the actual FA is preferable. For the $B_1$ inhomogeneity field mapping, several methods have been proposed (5,15,16) which are preferable when available. Another limitation is the need for a reference tissue with known $T_1$ value for normalization. However, we have shown that this limitation, while not always acknowledged, exists in other $T_1$ analysis methods, and is due to the system’s inaccuracies, as detailed above, rather than being analysis-dependent.

In conclusion, we demonstrate that inaccuracies in production of the prescribed FAs may lead to significant $T_1$ estimation errors. We further propose a
method that can extract the actual FAs and compensate for these changes, as well as compensating for \( B_1 \) inhomogeneity effects and providing a more uniform weighting of the different FA data, leading to a more consistent and robust \( T_1 \) value estimation. A complete pseudo-code is presented in the supplementary material, and the source-code is available upon request. This method is widely applicable to currently available data, providing a valuable tool for accurate measurements of \( T_1 \) values.

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