Analysis of the Precision of Variable Flip Angle $T_1$ Mapping with Emphasis on the Noise Propagated from RF Transmit Field Maps

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In magnetic resonance imaging, precise measurements of longitudinal relaxation time ($T_1$) is crucial to acquire useful information that is applicable to numerous clinical and neuroscience applications. In this work, we investigated the precision of $T_1$ relaxation time as measured using the variable flip angle method with emphasis on the noise propagated from radiofrequency transmit field ($B_1^+$) measurements. The analytical solution for $T_1$ precision was derived by standard error propagation methods incorporating the noise from the three input sources: two spoiled gradient echo (SPGR) images and a $B_1^+$ map. Repeated in vivo experiments were performed to estimate the total variance in $T_1$ maps and we compared these experimentally obtained values with the theoretical predictions to validate the established theoretical framework. Both the analytical and experimental results showed that variance in the $B_1^+$ map propagated comparable noise levels into the $T_1$ maps as either of the two SPGR images. Improving precision of the $B_1^+$ measurements significantly reduced the variance in the estimated $T_1$ map. The variance estimated from the repeatedly measured in vivo $T_1$ maps agreed well with the theoretically-calculated variance in $T_1$ estimates, thus validating the analytical framework for realistic in vivo experiments. We concluded that for $T_1$ mapping experiments, the error propagated from the $B_1^+$ map must be considered. Optimizing the SPGR signals while neglecting to improve the precision of the $B_1^+$ map may result in grossly overestimating the precision of the estimated $T_1$ values.

Keywords: $B_1^+$ map, $T_1$ map, error propagation, uncertainty, precision, variable flip angle

INTRODUCTION

Measurement of the longitudinal relaxation time ($T_1$) of a sample is of paramount importance as evidenced by the fact that methods for its measurement appeared soon after the invention of NMR (Drain, 1949; Hahn, 1949). In MRI $T_1$ mapping is widely used because it provides insight into the microstructure of brain tissue (Harkins et al., 2016) and can act as a biomarker of myelination (Dick et al., 2012; Lutti et al., 2013; Sereno et al., 2013). Hence, numerous $T_1$ mapping methods are available (Kingsley, 1999). Although, typically taken as the gold standard, the inversion recovery approach is very time consuming (Stikov et al., 2015). Instead, the combination of multiple three
dimensional (3D) spoiled gradient echo (SPGR) (Haase et al., 1986) images with short repetition times, variable flip angles (VFA) (Christensen et al., 1974; Fram et al., 1987) and appropriate spoiling (Zur et al., 1991; Ganter, 2006) offers a means of obtaining whole brain $T_1$ maps in clinically feasible times (Deoni et al., 2005; Helms et al., 2008).

Several factors affect the accuracy and/or precision of $T_1$ measurements obtained via the VFA method (Wang et al., 1987; Deoni et al., 2004; Freibisch and Deichmann, 2009; Schabel and Morrell, 2009; Helms et al., 2011; Wood, 2015). In particular, the bias introduced by the spatial inhomogeneity of the radiofrequency (RF) transmit field ($B_1^+$) is a well-known source of error (Stikov et al., 2015). Numerous methods exist for obtaining a $B_1^+$ map (Insko and Bolinger, 1993; Cunningham et al., 2006; Jiru and Klose, 2006; Dowell and Tofts, 2007; Yarnykh, 2007; Lutti et al., 2010; Sacolick et al., 2010; Nehrke and Börnert, 2012) and incorporating this into the $T_1$ mapping pipeline has been shown to improve the accuracy of the estimated value of the $T_1$ relaxation times (Venkatesan et al., 1998; Deoni, 2007; Helms et al., 2008; Lutti et al., 2013; Liberman et al., 2014). However, the precision of the $B_1^+$ map and how this diminishes the precision of the estimated $T_1$ values has not been thoroughly addressed, especially not in vivo. Recently, a systematic comparison of the precision of different $B_1^+$ mapping methods was performed by Pohmann and Scheffler (2013). They reported the uncertainty in the measurements of the $B_1^+$ maps and found that the error could be up to approximately 30% for 3D variants. The results of their simulations and phantom experiments agreed well, but they did not investigate the precision of the $B_1^+$ mapping methods in vivo (expected to produce higher uncertainty) nor its impact on the estimated $T_1$ relaxation times.

To further understand and quantify the effect of uncertainty (i.e., random variability) in $B_1^+$ maps on the precision of $T_1$ mapping, a theoretical framework that can be applied in vivo and that considers the measurement uncertainty not only in the SPGR signals but also in the $B_1^+$ maps is needed. Hence the aims of this paper are:

a) To theoretically investigate, within the clinically-feasible VFA approach, the propagation of noise from $B_1^+$ measurements to the estimated $T_1$ values and compare this to the error propagated from the SPGR data.

b) To verify that these theoretical estimates are valid for in vivo neuroimaging experiments.

c) To show that decreasing the variability in $B_1^+$ measurements can dramatically increase the precision of estimated $T_1$ values.

**MATERIALS AND METHODS**

**Theory**

Before proceeding with the theoretical framework for analyzing $T_1$ precision, two terms, accuracy and precision, have to be defined clearly. Accuracy represents how close, on average, the measured value is to the true value and is often dependent on the level of systematic error present in the measurement. The deviation of the average measured value from the true value due to the systematic error is termed bias. On the other hand, precision represents how close the values from the repeated measurements are to each other and will depend on multiple factors, e.g., the sensitivity of the measurement device. Thus, the precision is a measure of uncertainty in the measurement irrespective of the true value. Figure 1A shows examples of measurements that are both accurate and precise, which is the target measurement scenario. Measurements can also be accurate but imprecise (Figure 1B), inaccurate but precise (Figure 1C), and neither accurate nor precise (Figure 1D). To collect a single data point with the hope that it is close to the true value, both accuracy and precision are important.

If the transverse magnetization is adequately spoiled before each RF pulse the SPGR signal amplitude is a function of $T_1$, equilibrium magnetization ($M_0$), effective transverse relaxation time ($T_2^*$), and imaging parameters, i.e., the repetition time (TR), flip angle $\alpha$ and echo time (TE) (Fram et al., 1987)

$$S = A \sin(\alpha) \frac{1 - \exp(-\text{TR}/T_1)}{1 - \cos(\alpha) \cdot \exp(-\text{TR}/T_1)}$$

where $A = S_0 \exp\left(-\text{TE}/T_2^*\right)$. Here $S_0$ is defined as $M_0$ multiplied by the receive gain of the system and the receive coil sensitivity. Recently, rational approximation of the SPGR signal for small flip angles and short TR was suggested, which provides a simpler form of Equation (1) (Helms et al., 2008),

$$S \approx A \alpha \frac{\text{TR}/T_1}{\alpha^2/2 + \text{TR}/T_1}$$

By acquiring two SPGR signals, $S_1$ and $S_2$, at two different flip angles, $\alpha_1$ and $\alpha_2$, $T_1$ estimates can be obtained with a simple algebraic expression (Helms et al., 2008),

$$T_1 = 2\text{TR} \frac{S_1/\alpha_1 - S_2/\alpha_2}{S_2\alpha_2 - S_1\alpha_1}$$

**FIGURE 1** Simulation of repeatedly measured data with (A) high accuracy and high precision, (B) high accuracy, but low precision, (C) low accuracy and high precision, and (D) low accuracy and low precision. The dashed lines represent the true value.
Since the VFA method relies on the flip angle dependency of the SPGR signal for $T_1$ estimation, a correction for $B_1^+$ inhomogeneities is necessary in order to obtain unbiased $T_1$ estimates. The spatially dependent $B_1^+$ correction factor, denoted as $f_{B1}$, can be determined by normalizing the $B_1^+$ map such that 1 is the nominal flip angle. By multiplying $\alpha_1$ and $\alpha_2$ by $f_{B1}$ in Equation (3) the $B_1^+$ bias corrected $T_1$ equation can be obtained (Helms et al., 2008),

$$T_1 = 2TR \frac{S_1/\alpha_1 - S_2/\alpha_2}{S_2/\alpha_2 - S_1/\alpha_1} \frac{1}{f_{B1}}$$  

(4)

Measurement of a $B_1^+$ map and inclusion of the correction factor, $f_{B1}$, in Equation [4] is intended to ensure the accuracy of the $T_1$ estimates (Stikov et al., 2015). This correction is assumed to correspond to going from Figure 1C to Figure 1A. However, unless the precision of the $B_1^+$ map is high, the actual correction may correspond to going from Figure 1D to Figure 1B, or worse going from Figure 1C to Figure 1B thereby lowering the precision of the $T_1$ estimate.

In the general VFA case, an expression for the variance of the estimated $T_1 (\sigma_{T1}^2)$ can be calculated for a set of SPGR signals ($S_1$, $S_2$, …, and $S_N$) measured with $N$ different flip angles and a $B_1^+$ map ($f_{B1}$) (Bevington and Robinson, 2003). Assuming statistically independent measurements of each signal the variance in the $T_1$ estimate is

$$\sigma_{T1}^2 = \sum_{i=1}^{N} \left( \left( \frac{\partial T_1}{\partial S_i} \right)^2 \sigma_i^2 \right) + \sigma_{f_{B1}}^2 \left( \frac{\partial T_1}{\partial f_{B1}} \right)^2$$  

(5)

where $\sigma_i$ and $\sigma_{f_{B1}}$ are the noise levels in $S_i$ and $f_{B1}$ respectively. For the VFA $T_1$ mapping technique proposed by Helms et al. (2008) only two SPGR signals are acquired ($N = 2$) and $T_1$ is calculated from Equation (4). Hence the variance of the estimated $T_1$ propagated from a $B_1^+$ map expressed by the second term in Equation (5) is determined by the noise in a $B_1^+$ map ($\sigma_{f_{B1}}$) and the partial derivative term which can be obtained from Equation (4):

$$\frac{\partial T_1}{\partial f_{B1}} = \frac{4TR}{f_{B1}} \cdot S_2/\alpha_2 - S_1/\alpha_1$$  

(6)

The $T_1$ variance propagated from the two SPGR signals can be determined in the same way by the partial derivative terms with respect to $S_i$:

$$\frac{\partial T_1}{\partial S_i} = \frac{2TR}{f_{B1}} \cdot S_i/\alpha_i - S_i/\alpha_1$$  

(7)

$$\frac{\partial T_1}{\partial S_2} = \frac{2TR}{f_{B1}} \cdot S_2/\alpha_2 - S_1/\alpha_1$$  

(8)

Each partial derivative term in Equations (6–8) is a weighting factor for the noise in the corresponding input signal (i.e., $S_1$, $S_2$, and $f_{B1}$) in Equation (5).

**MR Data Collection**

Data were collected on four adult volunteers using a 3T MRI scanner (Achieva Platform, Philips Healthcare, Best, The Netherlands). Four different experiments were performed. The first two experiments involved all four volunteers and the input variable $f_{B1}$ was repeatedly measured either with small (Experiment 1) or with large spoiler gradients (Experiment 2) to assess two different levels of variance in the $B_1^+$ measurements. On one of the volunteers, the other two input variables, $S_1$ and $S_2$, were also repeatedly measured (Experiments 3 and 4 respectively) to assess their variances and compare them with the variance introduced by the $B_1^+$ measurements.

Before each measurement the scanner performed a full preparatory phase of shimming, center frequency determination and RF transmit power calibration. The repeated measurements approach adopted here captured all noise sources, e.g., thermal/physiological noise, scanner stability, etc. In summary, the four different experiments were designed as follows:

**Experiment 1:** one $S_1$, one $S_2$, and six $B_1^+$ maps with small spoiler gradients.

**Experiment 2:** one $S_1$, one $S_2$, and six $B_1^+$ maps with large spoiler gradients.

**Experiment 3:** six $S_1$, one $S_2$, and one $B_1^+$ map with large spoiler gradients.

**Experiment 4:** one $S_1$, six $S_2$, and one $B_1^+$ map with large spoiler gradients.

The 3D SPGR sequence had 0.8 mm isotropic voxels, TR/TE1/TE2/TE3 = 25.0/4.6/11.5/18.3 ms, sensitivity encoding (SENSE) (Pruessmann et al., 1999) factor = 2.0, and scan time = 11.6 min. The SPGR images acquired at three different echo times were averaged to increase the signal-to-noise ratio (SNR) (Helms et al., 2008). The $S_1$ and $S_2$ images were acquired with the nominal flip angles of $\alpha_1 = 6^\circ$ and $\alpha_2 = 20^\circ$ respectively, resulting in images with predominantly proton-density (PD) weighting or $T_1$ weighting. The $B_1^+$ maps were acquired at 4.0 mm isotropic resolution using the actual flip angle imaging (AFI) method (Yarnyk, 2007) with either small ($A_{G1}/A_{G2}=45.33/761.2$ mT.ms/m and TR1/TR2/TE = 20/100/2.2 ms) or large ($A_{G1}/A_{G2}=931.8/1971.0$ mT.ms/m, TR1/TR2/TE = 46/138/2.2 ms) spoiler gradients. $A_{G1}$ and $A_{G2}$ are the spoiler gradient areas on one axis for the interleaved acquisitions with TR1 and TR2, respectively. A nominal flip angle of $60^\circ$ was used for this AFI $B_1^+$ map. To match the scan time (5.2 min) of the AFI acquisitions, the protocol using large spoilers also used a SENSE factor of 1.7. The six repetitions were chosen with consideration of the subject’s ability to stay still during the measurements. To ascertain that six repetitions were adequate for a reliable estimate of the variability of input signals, variance was also calculated from the first three, first four and first five repetitions separately. The variance distribution converged after five measurements indicating that the estimate was stable and valid (data not shown).
Data Analysis

All images \((S_1, S_2, \text{and } B_1^+ \text{ map})\) were aligned to the first PD weighted image (i.e., the first of the six \(S_1\) in Experiment 3) using rigid body registration as implemented in SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, UK). The \(B_1^+\) maps were aligned by using the transformation matrix obtained in the alignment of the corresponding short TR AFI image to the first PD weighted image. Data were evaluated in two different ways to compare the \(T_1\) variances estimated from the in vivo measurements and the theoretical framework:

**Experimental variance evaluation:** Using Equation (4) six \(T_1\) maps were calculated for each of Experiments 1–4. The voxel-wise variance across these six \(T_1\) maps was then calculated. With this approach, the experimental noise level in the \(T_1\) map, \(\sigma_{T_1,\text{exp}}\) was obtained.

**Theoretical variance evaluation:** The voxel-wise variance of the repeated \(S_1, S_2, \text{or } B_1^+\) scans (i.e., \(\sigma_{S_1}^2, \sigma_{S_2}^2, \text{or } \sigma_{B_1^+}^2\)) was calculated and inserted into the theoretical noise propagation framework [Equations (5–8)], while assuming zero variance for the other two input signals. For example, in Experiment 1 we assumed \(\sigma_{S_1}^2 = \sigma_{S_2}^2 = 0\) and evaluated \(\sigma_{T_1}^2\) by multiplying \(\sigma_{B_1^+}^2\) (obtained from the repeated in vivo experiments) by the square of the expression given in Equation (6). \(\sigma_{T_1}^2\) was similarly evaluated for Experiments 2–4. \(\sigma_{T_1}\) calculated by this approach is the theoretically-predicted voxel-wise noise level in the \(T_1\) map and is denoted by \(\sigma_{T_1,\text{theo}}\).

Subsequently, coefficient of variation (CV = 100 × standard deviation / mean) maps were calculated to ease comparison of results across Experiments 1–4. Note that CV is inversely proportional to SNR.

The PD weighted image \((S_1)\) was segmented using SPM8 to extract the gray matter (GM) and white matter (WM) segments, which were subsequently thresholded at 0.9 (i.e., 90% probability of belonging to the respective tissue types). The resulting GM and WM masks were used to extract voxel-wise values from the three input images, the \(T_1\) maps and the corresponding CV maps. The median and interquartile range (IQR) of the CV values were then calculated for each tissue type independently.

RESULTS

Example images used to calculate \(T_1\) maps in the work described here, namely two SPGR images \((S_1 \text{ and } S_2)\) and a \(B_1^+\) map (in this case with large spoiler gradients) are shown in Figure 2 along with the resulting \(T_1\) map.

Figure 3 provides the results of both methods of variance estimation for Experiments 1–2. Column 1 shows the CV maps calculated from the variance across the repeated \(B_1^+\) measurements, i.e., \(\sigma_{B_1^+}^2\), with small (Figure 3a) and large (Figure 3e) spoiler gradients. The experimental and theoretical evaluations of the noise level in the \(T_1\) map propagated from the variance in the \(B_1^+\) map (i.e., \(\sigma_{T_1,\text{exp}}\) and \(\sigma_{T_1,\text{theo}}\)) are shown in column 2 and 3 respectively. Increased spoiling resulted in improved precision of the \(B_1^+\) maps (compare Figure 3a with Figure 3e), which in turn reduced the variance of the \(T_1\) estimates both experimentally and theoretically (compare Figure 3b with Figure 3f and Figure 3c with Figure 3g). Column 4 shows the percentage difference map between the experimentally-measured \((\sigma_{T_1,\text{exp}})\) and the theoretically-predicted \((\sigma_{T_1,\text{theo}})\) noise levels in \(T_1\). In general the discrepancy between \(\sigma_{T_1,\text{exp}}\) and \(\sigma_{T_1,\text{theo}}\) was small. For Experiment 1 (small spoiler), the mean discrepancies (average of absolute percentage difference values) were 1.97 and 1.44% in GM and WM respectively. For Experiment 2 (large spoiler) these mean discrepancies were reduced to 0.52 and 0.46% respectively. The discrepancy maps (Figures 3a,h) show that, if the noise in the input signal is small, the theoretical prediction works better. This is expected from Equation (5).

Figure 4 shows the results of Experiments 3 and 4 where \(S_1\) and \(S_2\) were measured repeatedly as a comparison to the repeated acquisitions of the \(B_1^+\) maps. Figure 4a,e show the CV maps across the repeated measurements of \(S_1\) and \(S_2\) (i.e., PD-weighted and \(T_1\)-weighted signal respectively). The results of Experimental and Theoretical variance evaluations and
the percentage difference map between them are shown in Figures 4b–d, f–h respectively. The mean discrepancies between $\sigma_{T_1, \text{exp}}$ and $\sigma_{T_1, \text{theo}}$ in GM/WM were 0.62/0.37% and 3.03/1.73% for Experiments 3 and 4 respectively. The larger discrepancy between theory and experiment in Experiment 4 (Figure 4h) compared to Experiment 3 (Figure 4d) could be attributed to the larger input noise in the repeated $S_2$ measurements (Figure 4e) than in the repeated $S_1$ measurements (Figure 4a). Nonetheless, the fact that the overall discrepancies are small (column 4 of Figures 3, 4) demonstrates the validity of the theoretical framework presented in Equations (5–8) for estimating the variance in $T_1$ maps measured in vivo.

Histograms of the CV maps for GM and WM are shown in Figure 5 from the voxel-wise variance in the input images (solid lines), CV maps obtained with Experimental variance evaluation (dashed lines) or Theoretical variance evaluation (circles) for Experiments 1–4. The histogram of the theoretically-predicted CV values agreed well with that of the experimentally-calculated CV values. Note that the histograms for Experiment 2 (cyan) shifted toward lower CV values and sharpened significantly compared to those for Experiment 1 (red), indicating that the $T_1$ precision was greatly improved by the increased spoiler gradients, across the entire brain. Except for the distributions from Experiment 1 with small spoiler gradients (solid red) where neither of the distributions from GM nor WM is symmetric, the distributions of CV values in WM are closer to the normal distribution than those in GM.

Median and IQR values were used to quantitatively summarize the CV histograms given that they were not all normally distributed. Table 1 shows the results for Experiments 1 and 2 on four different subjects and Table 2 for Experiments 3 and 4 on one subject. These results indicate that the noise in
S1, S2, and fB1 propagated similarly into the T1 maps, such that the CV approximately doubled between the input signals and the calculated T1 maps. Also, the CV values of the T1 maps calculated via Experimental and Theoretical variance evaluations were similar in both GM and WM. As noted previously, the CV values decreased dramatically going from Experiment 1 with small spoiler to Experiment 2 with large spoiler. This was the case for subjects 1–3 (see Table 1). For subject 4, however, the CV values did not decrease (gray cell background in Table 1). This was likely due to instability in the RF transmit chain and it demonstrates the validity of the theoretical framework for different sources of error.

DISCUSSION

Using the VFA method, the precision of T1 relaxation time measurements depends not only on the SNR of the SPGR images but, crucially, also on the error propagated from the B1+ map that is used to correct the bias caused by spatial inhomogeneity in the achieved flip angle. The precision of the B1+ map is often overlooked as a source of uncertainty in T1 measurements. Here we have derived analytical solutions for the error propagated to the T1 relaxation time estimates (Equations 5–8). This analysis indicates that the three signal sources (the two SPGR images with different flip angles and the B1+ map) propagate noise into the T1 estimates to approximately the same degree, with the CV approximately doubling between each of the three signal sources and the T1 estimate (Tables 1, 2). By examining two distinct noise levels in the B1+ maps (by manipulating the degree of spoiling), we could show that the precision of the T1 map can be greatly improved by increasing the precision of the B1+ mapping procedure.

We have experimentally validated the analytical framework by performing repeated experiments to estimate the voxel-wise
variance of the $T_1$ maps. We found overall agreement between the theoretical predictions ($\sigma_{T_1,\text{theo}}$) and the experimental measures ($\sigma_{T_1,\text{exp}}$), especially when the input noise, and accordingly $T_1$ noise, is small as in Experiments 2 and 3. For example, Figure 4d shows discrepancy of less than 1% inside GM and WM and relatively high discrepancy only in voxels containing cerebrospinal fluid (CSF), which we attribute to the fact that CSF has a significantly longer $T_1$ than GM and WM, for which the VFA sequence was optimized. With higher input noise the discrepancy between theory and measurement tended to increase (Figures 3d, 4h). This is because Equation (5) predicts the propagated error correctly only when $\sigma_S$ and $\sigma_{f_B}$ are small enough that the constant slope approximation (i.e., constant partial derivative) is valid over the ranges of $\sigma_S$ and $\sigma_{f_B}$ in the $S/f_B$ vs. $T_1$ graph. Nonetheless, in the range of experimentally measured noise from our in vivo experiments, the discrepancies were small inside both GM and WM.

Subject 4 had high variability in $f_B$ and therefore in the estimated $T_1$, even in Experiment 2, which used big spoiler gradients to minimize the variance. This may be due to one of the parameters associated with the determination of the RF transmit voltage, which were observed to fluctuate more across the six $B_1^+$ acquisitions in subject 4 than across the acquisitions from the other three subjects. This fluctuation might be due to hardware instability in the RF transmit chain. The necessity to keep the RF transmit voltage constant for reliable quantification of $T_1$ has been reported previously in Lutti and Weiskopf (2013). Therefore, it is reasonable to consider the RF transmit instability as a reason behind the reduced precision of the repeated $B_1^+$ map acquisitions in this case. This observation demonstrates that not only the acquisition method, e.g., degree of spoiling used, but also the hardware settings need to be considered when optimizing the precision of $B_1^+$, and by extension $T_1$, measurements.

The $CV$ maps from Experiment 1 had asymmetric left-right distributions as shown in Figures 3a-c for subject 1. While three out of four subjects manifested asymmetric distributions, one of them showed a strong pattern of left-right symmetry (data not shown), indicating that the spatial distribution of precision is subject-specific. This may be due to susceptibility effects from the air-tissue interface, how well the shimming procedure can correct for local field distortions, positioning of the subject in the scanner and interaction with the transmit field. We also found that the histograms of $CV$ values in GM did not tend to be normally distributed compared to those in WM. This may be due to the fact that more GM voxels suffer partial volume effects with CSF and the VFA acquisition was optimized for the $T_1$ of CSF. The non-normal distributions in the histograms from Experiment 1 for both GM and WM show that the $B_1^+$ maps with small spoiler gradients are dominated by noise sources other than thermal noise.

Because the transmit RF field map is smoothly varying, a commonly recommended practice for reducing noise in $B_1^+$ maps is spatial smoothing. As an example see Figure 6 where the 6 $B_1^+$ maps from Experiment 1 were smoothed by a 3D Gaussian kernel with standard deviation of $4 \times 4 \times 4$ mm$^3$. It is evident from the profile extracted from the white line in Figure 6a that spatial smoothing of the 6 individual $B_1^+$ maps separately leaves a systematic offset uncorrected (Figures 6c,d). In such cases, when thermal noise does not dominate the error sources but the systematic offset is random in the different repetitions, a more appropriate procedure is averaging multiple acquisitions. Although, repeated
measurement of the $B_1^+\text{ map}$ requires additional time, it is usually still the more efficient way to proceed because high-resolution SPGR images take significantly longer to acquire (in our case more than twice as long). This recommendation is further supported by our finding that the $B_1^+\text{ maps}$ propagate approximately the same error as either of the two SPGR images. When optimizing $T_1\text{ mapping protocols},$ previous work has focused mainly on optimizing acquisition parameter settings, most notably the flip angles used to acquire the SPGR images, that minimize uncertainty in the measured $T_1\text{ value} \text{ (Weiss et al., 1980; Wang et al., 1987; Schabel and Morrell, 2009; Helms et al., 2011; Wood, 2015). Although bias resulting from the spatial non-uniformity of the transmit RF transmit field is also well known and is commonly corrected by incorporating a $B_1^+\text{ map}$ into the calculations (Helms et al., 2008; Yarnykh, 2010; Lutti et al., 2013; Stikov et al., 2015), the precision with which the $B_1^+\text{ map}$ is obtained is typically ignored. Pohmann and Scheffler compared the precision of several $B_1^+\text{ mapping methods}$ and found widely varying results depending on the method used and the nominal flip angle to be measured (Pohmann and Scheffler, 2017).
2013). Our results further demonstrate the necessity to consider the precision of $B^+_1$ mapping when using these to correct bias in the $T_1$ relaxation time maps. Rather than the assumed high precision estimate of $T_1$ (Figure 1A), one may arrive at a result that on the average is correct but may also have a high level of uncertainty (Figure 1B). This will have the greatest impact in vivo where there are more sources of noise (e.g., physiologically driven noise) and will reduce the detectable effect size in both cross-sectional and longitudinal studies in which $T_1$ measurements are used as a biomarker (Lutti et al., 2013).

In this study we used the AFI method for $B^+_1$ mapping, which was proposed and optimized by Yarnykh (Yarnykh, 2007, 2010) and has been shown to perform comparatively well (Pohmann and Scheffler, 2013). From Experiments 1–2, we showed that increasing spoiler gradients makes the estimation of $T_1$ not only more accurate as previously reported (Yarnykh, 2010) but also more precise due to the complete spoiling of the transverse magnetization. Pohmann and Scheffler (2013) found that for a 60° nominal flip angle their implementation of the AFI method had an uncertainty of 3° (5%) in simulations and 4° (7.5%) in phantom experiments. The CV of approximately 3% in the $B^+_1$ map that we observed in vivo (Tables 1, 2) is in line with these findings, and may even underestimate the $B^+_1$-related variance that can be expected to propagate into common $T_1$ mapping protocols from the map. However, the theoretical framework presented here makes no assumption on the choice of $B^+_1$ mapping approach. These findings are equally applicable, regardless of the $B^+_1$ mapping method used or how it was optimized to have high precision.

In both the in vivo experimental variance (Experimental variance evaluation) and the theoretical framework (Theoretical variance evaluation) we considered the noise propagating from the three input signals separately (Equations 5–8 and Experiments 1–4). This provides a convenient way in which to compare the effect of the three noise sources on the uncertainty of the final $T_1$ map. In practice, however, the errors propagating from the three sources are summed (Equation 5). Although CVs for the averaged SPGR signals and the $B^+_1$ maps were similar in our in vivo experiments, the precision of $B^+_1$ maps can vary significantly depending on the $B^+_1$ mapping approach (see for example Figure 6 in Pohmann and Scheffler, 2013), which shows that in phantom measurements some of the $B^+_1$ mapping methods, especially the 2D variants, can suffer higher uncertainty for certain acquisition parameter sets. Therefore, neglecting the uncertainty in the $B^+_1$ map can lead to significant erroneous overestimation of the precision of the calculated $T_1$ value.

Also note that including more than two SPGR images with more than two different flip angles for the $T_1$ estimation may even lead to the increased variability in $T_1$ since the noise from the additional SPGR images is additive to the total variance in $T_1$ ($\sigma_{T_1}^2$) according to Equation (5). This is also reflected by the fact that previous evaluations of uncertainty within the VFA regime conclude that when acquiring additional images the optimal approach is to acquire at the same flip angle and average (Wang et al., 1987; Helms et al., 2011).

To assess the uncertainty in the measurements of SPGR images and $B^+_1$ maps we performed repeated in vivo experiments for each of the input images. In such an approach, the uncertainty in each variable includes all sources, e.g., thermal noise, scanner instability, scanner drift, physiological noise and the test/re-test variability (e.g., differences in the optimized shim currents, or power amplifier calibration etc.), whereas usually only the thermal noise components are considered (Cheng and Wright, 2006). Had we simply estimated the thermal noise component by extracting the standard deviation of pixels in the background the theoretically-predicted uncertainty (Theoretical variance evaluation) would have seriously underestimated the uncertainty found in the in vivo $T_1$ relaxation time measurement (Experimental variance evaluation). In addition we would have confounds due to the Rician noise distribution of magnitude images and the image reconstruction scheme chosen (Constantinides et al., 1997).

A wide array of methods exists for measuring the $T_1$ relaxation time (Kingsley, 1999). A recently proposed method (Helms et al., 2008) was chosen here because it has been broadly used (Dick et al., 2012; Sereno et al., 2013; Callaghan et al., 2014) and optimized (Helms et al., 2011). However, our findings regarding the dependence of the precision of the $T_1$ measurement on the level of uncertainty in the $B^+_1$ map is not expected to be unique to this method of $T_1$ relaxation time measurement.

We conclude that when estimating the uncertainty of $T_1$ mapping methods, the error propagated from the $B^+_1$ map must also be considered. Optimizing the SPGR signals while neglecting to improve the precision of the $B^+_1$ map will result in a significant underestimation of the final uncertainty in the calculated $T_1$ relaxation time. Maximizing the precision of the adopted $B^+_1$ mapping approach is crucial for studies using $T_1$ as an imaging biomarker, which require high sensitivity (minimum variance), e.g., to investigate subtle differences in the micro-architectural organization of the brain.

**ETHICS STATEMENT**

This study was carried out in accordance with the recommendations of The Kantonale Ethics Komitee.
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and ZN analyzed data, interpreted the results and wrote the manuscript.

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AUTHOR CONTRIBUTIONS

YL, MC, and ZN designed the study; YL and ZN acquired the data; MC provided software for data analysis; YL, MC,
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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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