Reducing bias in dual flip angle $T_1$-mapping in human brain at 7T

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**Purpose:** To address the systematic bias in whole-brain dual flip angle (DFA) $T_1$-mapping at 7T by optimizing the flip angle pair and carefully selecting radiofrequency (RF) pulse shape and duration.

**Theory and Methods:** Spoiled gradient echoes can be used to estimate whole-brain maps of $T_1$. This can be accomplished by using only two acquisitions with different flip angles, that is, a DFA-based approach. Although DFA-based $T_1$-mapping is seemingly straightforward to implement, it is sensitive to bias caused by incomplete spoiling and incidental magnetization transfer effects. Further bias is introduced by the increased $B_0$ and $B_1^+$ inhomogeneities at 7T. Experiments were performed to determine the optimal flip angle pair and appropriate RF pulse shape and duration. Obtained $T_1$ estimates were validated using inversion recovery prepared echo planar imaging and compared to literature values. A multi-echo readout was used to increase signal-to-noise ratio, enabling quantification of $R_2^*$ and susceptibility, $\chi$.

**Results:** Incomplete spoiling was observed above a local flip angle of approximately 20°. An asymmetric gauss-filtered sinc pulse with a constant duration of 700 μs showed a sufficiently flat frequency response profile to avoid incomplete excitation in areas with high $B_0$ offsets. A pulse duration of 700 μs minimized effects from incidental magnetization transfer.

**Conclusion:** When performing DFA-based $T_1$-mapping one should (a) limit the higher flip angle to avoid incomplete spoiling, (b) use a RF pulse shape insensitive to $B_0$ inhomogeneities and (c) apply a constant RF pulse duration, balanced to minimize incidental magnetization transfer.

**Keywords**
7T, dual flip angle, human brain, longitudinal relaxation, spoiled gradient echo, $T_1$
1 | INTRODUCTION

The longitudinal relaxation time, $T_1$, is related to the concentration of iron and myelin in the brain. $T_1$ is thus a relevant parameter in the process of normal aging but also in pathologies, such as multiple sclerosis and Parkinson’s disease. Quantification of $T_1$ on a voxel-wise basis allows for reproducible maps of a tissue-specific metric that can be compared longitudinally and across sites. The increase in contrast compared to conventional weighted images, due to the removal of confounding contrast sources, may allow for visualization of otherwise invisible pathologies, and is more directly related to tissue properties.

A seemingly straightforward and undemanding way to perform quantification of $T_1$ is by varying the flip angle of a gradient echo sequence under spoiled steady-state conditions. A two-point measurement, that is, a dual flip angle (DFA) approach, is sufficient to determine $T_1$ as well as the signal amplitude reflecting proton density (PD). The DFA approach is the fastest method to acquire high resolution whole-brain maps of $T_1$ and has been applied extensively on clinical MR systems and dedicated processing tools, like the hMRI toolbox have been made available. Besides $T_1$, this toolbox can also provide maps of $R_2^*$, PD, and magnetization transfer (MT) saturation.

Studies employing DFA-based $T_1$-mapping of the whole-brain at 7T have, to our knowledge, not previously been published, although one study has employed three flip angles to map $T_1$ in a single 2D slice. When implementing a DFA protocol at 7T, one must consider the reduced homogeneity of primarily the transmitted radiofrequency (RF) field, $B_1^+$, but also $B_0$, as well as the prolonged $T_1$ compared to 3T. The DFA approach for quantification of $T_1$ is very sensitive to $B_0$ inhomogeneities, thus accurate flip angle mapping becomes more important at 7T for performing a post-hoc correction of $T_1$ estimates. The prolongation of $T_1$ entails an increase in TR and to avoid dead time, a multi-echo readout can be accommodated within TR. This is a time-efficient approach to increase signal-to-noise ratio (SNR) through averaging across echoes, while at the same time enabling quantification of $R_2^*$ and magnetic susceptibility, $\chi$.

In this study, the procedure to optimize a DFA protocol for whole-brain $T_1$-mapping at 7T is described. Primarily, the choice of flip angles as well as RF pulse shape and duration are discussed and motivated by minimizing noise propagation and addressing systematic biases in the $T_1$ estimation. The investigated sources of bias were residual transverse coherences, reduced flip angles due to $B_0$ inhomogeneities, as well as incidental on-resonance MT effects on the longitudinal magnetization.

The absorption of RF by the bound macromolecular pool depends on $(B_1^+)^2$ and will thus cause partial saturation of the bound macromolecular pool. When the bound pool is more saturated than the bulk water, the observed steady state is lowered by MT to the bound pool, which in turn is interpreted as an increase in $T_1$. Such MT induced changes of $T_1$ have been reported for 3T, but can be addressed by choice of pulse shape and duration.

A finalized DFA $T_1$-mapping protocol with multi-echo readout is produced, from which $R_2^*$, $\chi$, and PD estimates are also derived by the multi-parametric hMRI toolbox. $T_1$ values, estimated using a rational approximation of the Ernst equation, are reported in subregions of normal brain tissue for nine healthy volunteers and compared to literature values. Validation experiments were performed, both in a multi-$T_1$ phantom and in-vivo, using an inversion recovery (IR) prepared echo planar imaging (EPI) sequence. The total measuring time for a whole-brain multi-parameter map with isotropic 0.9 mm resolution was under 8 min including flip angle mapping.

2 | THEORY

2.1 | $T_1$ estimation via a rational approximation of the Ernst equation

The dependence of the steady-state signal on the flip angle, $\alpha$, in a spoiled gradient echo with perfectly spoiled transverse coherences is given by the Ernst equation:

$$S(\alpha) = |A| \sin(\alpha) \frac{1 - \exp(-TR/T_1)}{1 - \cos(\alpha) \exp(-TR/T_1)}$$  \hspace{1cm} (1)

where $A$ denotes the complex signal amplitude at echo time (TE), that is, the signal obtained for $\alpha = \pi/2$ and fully relaxed conditions, that is, repetition time (TR) $TR >> T_e$. $A$ is a function of TE, thus allowing quantification of $R_2^*$ and $\chi$. For small flip angles ($\alpha << 1$) and short TR $<< T_e$, the expression in Equation 1 can be approximated by:

$$S(\alpha) \approx |A| \alpha \frac{TR/T_1}{\alpha^2/2 + TR/T_1}$$.  \hspace{1cm} (2)

This equation immediately shows the change from $T_1$-weighting ($T_1$-w) to PD-w with decreasing flip angles when $\alpha^2/2$ becomes smaller than $TR/T_1$ and the quotient in the right-hand term approaches unity.

The Ernst angle, $\alpha_E$, defined by $\cos \alpha_E = \exp(-TR/T_1)$, for a given TR and $T_1$, is correspondingly approximated by:

$$\alpha_E \approx \sqrt{2TR/T_1}$$.  \hspace{1cm} (3)

Lastly, Equation 2 can be rewritten as

$$\frac{S(\alpha)}{\alpha} = |A| - \frac{T_1}{2TR} \cdot S(\alpha) \alpha$$.  \hspace{1cm} (4)
revealing a linear relationship when $S(\alpha)/\alpha$ is plotted against $S(\alpha) \cdot \alpha$, $|A|$ can thus be derived as the intercept and $T_1$ from the slope of a regression line. This also provides a simple way to visually inspect variable flip angle (VFA) data for systematic biases such as those resulting from residual transverse coherences.\textsuperscript{20}

In the DFA-based $T_1$ estimation, two flip angles ($\alpha_{T1}, \alpha_{PD}$) are used to provide two signals $S_{T1}$ and $S_{PD}$, which are predominantly $T_1$-w and PD-w. Use of the nominal flip angles in Equation 2 ($\alpha_{nom}$ as defined on the user interface) yields an apparent $T_1$,\textsuperscript{15}

$$T_{1,app} = 2TR \frac{S_{PD}/\alpha_{PD} - S_{T1}/\alpha_{T1}}{S_{T1}\alpha_{T1} - S_{PD}\alpha_{PD}}, \quad (5)$$

as well as an apparent signal amplitude,

$$|A_{app}| = \frac{S_{T1}S_{PD}(\alpha_{T1}/\alpha_{PD} - \alpha_{PD}/\alpha_{T1})}{(S_{T1}\alpha_{T1} - S_{PD}\alpha_{PD})}. \quad (6)$$

Note that apparent stands for "without correcting for $B_1^+$ inhomogeneities". Correspondingly, replacing $T_1$ with $T_{1,app}$ in Equation 3 yields the apparent $\alpha_{E}$, that is, the nominal flip angle at which the signal maximum would be observed in this voxel.

The propagation of noise from the signals $S_{T1}$ and $S_{PD}$ into the calculated $T_{1,app}$ is minimized for the following flip angles\textsuperscript{19,}\textsuperscript{20,}\textsuperscript{23}

$$\alpha_{T1, opt} \approx \alpha_E \cdot 2.414, \quad (7)$$

$$\alpha_{PD, opt} \approx \alpha_E / 2.414. \quad (8)$$

2.2 Correcting for $B_1^+$ inhomogeneities

In the presence of $B_1^+$ inhomogeneities, the local flip angle is described by the transmit field bias, $f_T$, as

$$\alpha = f_T \cdot \alpha_{nom}. \quad (9)$$

Inserting this into Equation 4, $f_T$ appears in the intercept and the slope, yielding the $f_T$-corrected parameter values\textsuperscript{15,}\textsuperscript{19,}\textsuperscript{23}

$$T_1 = T_{1,app} / f_T^2 \quad (10)$$

$$|A| = |A_{app}| / f_T. \quad (11)$$

Thus, $f_T$ cannot be derived from a VFA experiment at low flip angles but must be mapped independently. From $|A|$, PD can be derived by numerically approximating the receive field.\textsuperscript{13}

3 METHODS

Experiments were performed on an actively shielded 7T MR system (Achieva, Philips Healthcare, Best, NL), using a head coil with two transmit and 32 receive channels (Nova Medical, Wilmington, MA). Healthy adult subjects were scanned after giving informed written consent as approved by the regional Ethical Review Board.

A non-selective 3D multi-echo spoiled gradient echo ("T1-FFE") sequence was used. Sagittal volumes of $230 \times 230$ mm$^2$ in-plane field of view and 200 mm in the right-left direction (with some variation due to subject size) were acquired at isotropic voxel size of (0.9 mm)$^3$ with readout in the head-feet direction. Within TR = 18 ms, eight equidistant gradient echoes were acquired with fat and water in-phase (at multiples of TE = 1.97 ms) at a bandwidth of 670 Hz/px using alternating readout gradient polarity to reduce eddy currents, peripheral nerve stimulation, and gradient heating. The scan time was 3:23 min using a SENSE-factor\textsuperscript{21} of 2 in both phase-encoding directions and an elliptical k-space coverage.

A series of experiments were performed to determine the optimal settings for the PD-w and $T_1$-w acquisitions. A VFA experiment was performed to identify bias caused by incomplete spoiling\textsuperscript{20} and to minimize noise propagation.\textsuperscript{19} To mitigate effects of $B_0$ inhomogeneities, Bloch equation simulations were performed to determine a suitable RF pulse shape with a flat frequency response profile for the excitation. The duration of the RF pulse was varied to reduce the effect of incidental on-resonance MT effects on the $T_1$ maps.\textsuperscript{18}

The dual refocusing echo acquisition mode (DREAM)\textsuperscript{22} optimized for 7T\textsuperscript{23} was used for $B_1^+$ mapping. Eighty transverse slices with field of view of $240 \times 240$ mm$^2$, voxel size of $3.75 \times 3.75 \times 3.50$ mm$^3$, and readout bandwidth of 4796 Hz/px were acquired. Three $B_1^+$ maps with preparation angles of 25°, 40°, and 60° were acquired to account for the variation of $B_1^+$ at 7T.\textsuperscript{24} Total duration for $B_1^+$-mapping was 3 × 10 s. In brief, voxels showing low SNR (at local $\alpha < 25^\circ$) or bias (at local $\alpha > 50^\circ$) were masked out and the remaining overlapping maps averaged, resulting in a single composite $f_T$ map.\textsuperscript{24}

3.1 Data processing

DICOM images were exported, pseudo-anonymized and converted to 4D NIfTI files using an in-house modification of the dicom2nii tool.\textsuperscript{25} In brief, voxel intensities were scaled back to physical signal [a.u.] using private DICOM tags, phase maps were converted to radians, and spatial dimensions were re-ordered to conform to radiological convention (right-left) in the standard transverse orientation.
Processing was performed in FSL and MATLAB. For each scan, voxel intensities were averaged across TEs. Rigid-body co-registration of the separate scans was performed using FLIRT. The brain mask was derived from the PD-w scan using BET. Apparent T1 maps were calculated using Equation 5 and corrected post-hoc with the composite DREAMT1 map using Equation 10.

To account for any residual effects of imperfect spoiling on the T1 estimates arising in high B+ areas, the fT1 map was modified based on simulations performed by Baudrexel et al. In this work, voxel-wise correction factors for incomplete spoiling are calculated based on the RF phase difference increment which was 150° in this work.

For PD and R2* maps, processing was done by the hMRI toolbox to exploit the built-in functions of data-driven receive field estimation and normalization of PD maps to white matter (WM) where the mean PD value is assumed to be 69 percentile units (p.u.) as well as the use of ESTATICS for R2* calculations. The multi-scale dipole inversion (MSDI) algorithm was used for QSM on the T1-w multi-echo dataset.

### 3.2 | Experiment 1: Nominal flip angle pair and spoiling bias

The nominal flip angle was varied from 4° to 32° in increments of 4° with otherwise constant parameter settings. This VFA experiment allowed to visualize the signal bias caused by incomplete spoiling through deviations from linearity in Equation 4 and minimize noise propagation as in Equations 7 and 8.

Incomplete RF spoiling depends on the RF phase difference increment and can affect the signal in a spoiled steady-state gradient echo acquisition and thus lead to systematic bias in the T1 estimation. The effect increases with the local flip angle and is negligible beneath a certain threshold. To identify the onset of bias due to incomplete spoiling, region of interest (ROI) analysis was performed in a high and low B+ area, respectively. This way, a suitable upper limit on αT1 could be determined.

A voxel-wise whole-brain map of the apparent Ernst angle was calculated from the slope of the linear regression, excluding nominal flip angles higher than the upper limit set on αT1. To achieve a compromise regarding noise progression over the whole brain, choice of αT1 and αPD was based on the whole-brain median of the apparent Ernst angle.

Recognizing that some incomplete spoiling likely occurred in high B+ areas regardless of the conservative choice of flip angles, further steps were taken to reduce bias in the T1 estimation. The correction factor derived by Baudrexel et al. was superimposed onto the composite fT1 map. This modified fT1 map was then used for correction of T1 estimates.

### 3.3 | Experiment 2: RF pulse shape

To avoid a decrease in the local flip angle in areas with a high proton resonance frequency (f0) offset, different RF pulse shapes, available at the MR system, were evaluated. High B+ amplitudes (close to 20 μT) are to be avoided to preclude incidental MT effects (experiment 3), which comes at the cost of reduced bandwidth of the frequency response. Thus, the flatness of the frequency response profile for the pulse shapes was evaluated with special attention paid to the interval of the expected f0 variation after shimming (±500 Hz). Frequency response profiles were simulated using RF Pulse Wizard tool ignoring relaxation. We compared pulse shapes with a small time-bandwidth product to maintain a short TE. The frequency response profile of a rectangular pulse (default for the non-selective T1-FFE sequence) and an asymmetric (single side-lobe) gauss-filtered sinc pulse were evaluated more closely. The simulations were performed for a flip angle of 16° (from experiment 1) and with identical maximum B+ for the two pulse shapes. A map of the f0 offset was acquired on an example subject. Based on this map and the frequency response profile, the reduction in flip angle was simulated.

### 3.4 | Experiment 3: RF pulse duration

The influence of incidental MT effects on the T1 estimation was varied via the duration of the asymmetric sinc pulse as τ = 210, 700, 2000 μs. In all scans, the first echo of the readout was omitted to accommodate the longest pulse. The nominal flip angle pair was kept constant and both RF pulses used identical τ within the DFA acquisition. T1 estimates were evaluated through histogram analysis and compared to literature values.

### 3.5 | Phantom validation

To validate the T1 estimates, 13 gel samples with unique T1 values (taken from the Eurospin II set, Diagnostic Sonar Ltd) were attached to a 2000 mL flask containing Marcol oil, thus reducing B+ inhomogeneities compared to in vivo. As a reference T1 measurement, a single slice, IR-prepared, multi-shot EPI sequence with 3 k-space lines acquired per shot was used to measure nine inversion times of TI = 120, 200, 400, 600, 900, 1500, 2100, 3000, 4000 ms at TR = 10 s. The minimum relaxation delay was thus 6 s. Other acquisition parameters were as follows: In-plane voxel size of 2.50 × 2.50 mm², slice thickness of 4.50 mm, bandwidth in the phase-encoding direction of 404 Hz/pixel, transverse field of view of 200 × 200 mm², SENSE-factor of 2.5, and TE = 7.68 ms. Total scan time was 20 min. T1 estimates were then derived.
by mono-exponential three-parameter fitting of the signal dependence on TI. These reference T₁ estimates were compared to those acquired with the DFA protocol for the separate gel samples through ROI analysis.

3.6 | In vivo validation

The protocol was also validated in vivo. To reduce motion sensitivity, a single-shot, single-slice EPI was used with a resulting echo train length of 29, bandwidth in the phase-encoding direction of 55 Hz/pixel and TE = 22.83 ms. The shortest and longest TI were excluded due to incomplete MT after inversion and incomplete relaxation after readout. The total scan time was 2 min 20 s. Correction of EPI distortions were done in-plane in the phase encoding direction using FSL FUGUE. After upsampling the EPI-based T₁ map to 0.83 x 0.83 x 0.9 mm³ resolution the DFA-based T₁ map was co-registered and then down-sampled to the original 2D EPI to mimic partial volume effects before a voxel-wise comparison.

To study the conformity of T₁ estimates in WM, cortical gray matter (GM) and ventricular cerebrospinal fluid (CSF), segmentation was performed using FAST. To avoid partial volume effects and noise voxels, probability maps were masked so that only voxels with a probability of 1 were included and then eroded by one voxel. Guided by segmentation, manual ROIs were placed symmetrically (right-left) and compared in the caudate nucleus, putamen and thalamus.

3.7 | Cohort data

T₁ maps of nine healthy volunteers (25 to 52 years old, four males and five females) were obtained with the optimized protocol. To analyze T₁ in various brain tissues and to assess the validity of the estimates, ROIs were manually defined in the frontal WM, frontal cortical GM, caudate nucleus, thalamus, putamen, globus pallidus, and ventricular CSF. Efforts were made to place the ROIs as in the work by Rooney et al.

4 | RESULTS

4.1 | Experiment 1: Nominal flip angle pair and spoiling bias

Signal bias caused by incomplete spoiling and manifested as deviations from the expected linearity of Equation 4 was analyzed in a high and a low f₁ area (Figure 1). Deviations can be seen for nominal flip angles > 16° in the high B₁⁺ area (f₁ = 1.23) but not until 32° in the low B₁⁺ area (f₁ = 0.73). This corresponds to local flip angles of 16° · 1.23 ≈ 20° and 32° · 0.73 ≈ 23°, respectively.

A map of the apparent Ernst angle obtained from flip angles ≤16° with an accompanying whole-brain histogram is shown in Figure 2. The apparent Ernst angle is dominated by the influence of B₁⁺ inhomogeneities, with some local contrast between GM, WM, and CSF. Accordingly, the whole-brain histogram shows a smooth variation with no well-defined tissue specific modes. The whole-brain median of the apparent

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**FIGURE 1** Linear plot of VFA signal in a high B₁⁺ ROI (f₁ = 1.23) situated in the splenium (A) and a low B₁⁺ ROI (f₁ = 0.73) situated in frontal WM (B). The line fitted to α = 4°, 8°, 12° is plotted (as in Equation 4) to highlight deviations from the Ernst equation. Residual transverse coherences become apparent at nominal flip angles of 16° and 32° in the low and high B₁⁺ area, respectively. Taking f₁ into account, these nominal flip angles convert to a local flip angle of approximately 20°. The bottom row (C) shows the spoiled gradient echo signal for each nominal flip angle in a transversal slice.
Ernst angle was $\alpha E = 9.5^\circ$ which would yield an optimal nominal flip angle pair of $\alpha_{PD} = 4^\circ$ and $\alpha_{T1} = 23^\circ$ regarding noise propagation. Due to the incomplete spoiling observed in high $\mathbf{B}_1^+$ areas, however, $\alpha_{T1} = 23^\circ$ was reduced to $\alpha_{T1} = 16^\circ$.

4.2 | Experiment 2: RF pulse shape

Bloch equation simulations of the two evaluated RF pulse shapes can be seen in Figure 3. With the maximum $\mathbf{B}_1^+$ amplitude of 4.317 $\mu$T, the asymmetric sinc pulse shows a flatter frequency response around the center, despite the shorter pulse duration of the rectangular pulse. For this pulse, simulations based on an $f_0$ offset map showed a reduction in local flip angle by 1° to 6° (6 to 63% of nominal flip angle) in 6% of the brain voxels in orbitofrontal and inferior temporal regions. Therefore, the asymmetric sinc was preferred over the rectangular pulse.

4.3 | Experiment 3: RF pulse duration

The effect of varying the RF pulse duration, $\tau$, on estimated $T_1$ maps can be seen in Figure 4. An increase in estimated $T_1$ when decreasing $\tau$ is visible both in the color maps and in the histograms. For example, the peak $T_1$ estimates in the WM mode were 1128, 1253, 1373 ms for $\tau =$ 2000, 700, 210 $\mu$s, respectively corresponding to nominal $\mathbf{B}_1^+$ amplitudes of 1.50, 4.32, 14.26 $\mu$T for $\alpha_{T1}$, and 0.38, 1.08, 3.57 $\mu$T for $\alpha_{PD}$. A smaller increase in the GM mode was observed while CSF appeared unaffected. Since the values obtained with the 700 $\mu$s asymmetric sinc pulses were well in agreement to
literature and could later be validated using IR-prepared EPI, this pulse duration was chosen for the protocol.

4.4 | Phantom validation

Figure 5 shows a comparison of the T₁ estimates in each of the 13 gel samples acquired with either the IR-prepared EPI or the DFA protocol. Across the samples, T₁ estimates varied between approximately 500 ms and 1700 ms, with good agreement between IR-EPI and DFA. However, a small systematic underestimation of DFA-derived T₁ estimates is observable with a mean deviation of −1.6%.

4.5 | In-vivo validation

A 2D comparison of an IR-derived and DFA-derived downsampled T₁ map of an example subject can be seen in Figure 6. The maps are accompanied by a linear regression plot and a Bland-Altman plot. The regression line has a slope of 0.90 and the Bland-Altman plot shows a mean deviation in T₁ of +0.5% and a standard deviation of ±34%. The ROI analysis (Table 1) shows that DFA T₁ values correspond well to the IR-EPI results in segmented WM (+2%), thalamus (+1%), and putamen (+0%), but were slightly lower in cortical GM (−3%) and caudate nucleus (−4%). Both methods show rather high standard deviations in CSF.

4.6 | Cohort data

Regional T₁ values across nine healthy subjects are presented in Table 2, together with literature values. The estimates derived in this study are within the span of previously reported estimates, except for cortical GM (6% lower than the mean of previous estimates). Figure 7 illustrates a typical 3D T₁ map by two sets of orthogonal views, one centered on the basal ganglia and the other on the motor cortex. A distinct distribution of T₁ with GM can be seen. The histogram shows clearly delineated modes representing WM (~1280 ms) and GM (~1830 ms), whereas the broad CSF mode is discernible around 4000 ms. Finally, Figure 8 shows maps of T₁, R₂, PD and χ, to illustrate the multi-parametric capability of the finalized protocol.
In this study, we report on whole-brain T1-mapping at 7T using the DFA approach with special focus on addressing known sources of bias by the choice of RF excitation. Firstly, the influence of incomplete spoiling was mitigated by limiting the higher flip angle and applying a post-processing correction algorithm. Secondly, the use of an RF pulse shape with a flat frequency response profile removed the influence of B0 inhomogeneities. Thirdly, the duration of the RF pulse was adjusted so that MT between the bound and free water pool was minimized. Bias minimization is particularly important when using only two flip angles, since it is impossible to identify bias from just two data points. Hence, in experiment 1, the flip angle was varied over a wide range. Due to the non-selective implementation, there was no need to account for slice profile effects as described in a 2D VFA study at 7T.14

T1 quantification by the finalized protocol was validated: (1) in a multi-T1 phantom using a gold standard IR-prepared EPI protocol; (2) in a single subject, again comparing to an IR-derived reference; and (3) in a cohort of healthy volunteers, relating the T1 estimates obtained by ROI analysis to the literature. In all these experiments, the DFA protocol generally yielded estimates well in agreement with the respective reference. The only notable deviation was observed in cortical GM, where the DFA protocol resulted in 3% lower T1 estimates relative the IR-prepared EPI protocol and 6% lower than the mean of previously reported estimates.14,37-39

Regarding validation experiment 2, even though attempts were made to mimic the partial volume effects obtained in the low-resolution EPI images through down-sampling (increasing cortical GM T1 estimates), it is possible that this was not fully compensated due to slice profile effects and an imperfect co-registration. On a similar note, the single-slice studies with larger slice thickness14,37 have reported higher cortical GM estimates than studies with smaller slice thickness38,39 implying that partial volume effects from the CSF has led to overestimation of cortical GM T1.

Although DFA-based T1 quantification appears fairly straightforward to implement, it is more sensitive to B1+ inhomogeneities than the IR-based measurements often used as reference.37,39 Local flip angles typically varied between 30% and 130% of the nominal flip angle across the brain. Biases introduced by the more severe B1+ inhomogeneity compared to 3T are corrected post-hoc with accurate flip angle mapping.24 However, there are some exceptions in areas of low B1+ amplitude such as the temporal lobes where T1 appears underestimated. The B1+ inhomogeneity could possibly be mitigated using dielectric pads40 and/or multi-channel transmit RF technology. The choice of only two flip angles for whole brain coverage thus implies a compromise to allow shorter scan times and to make the protocol compatible with the hMRI13 toolbox. Of course, it is possible to optimize the flip angle pair for B1+ and T1 in target regions, sacrificing...
Table 2  Regional $T_1$ data averaged across nine subjects compared to literature

| Tissue              | This study  | Rooney37 Look-Locker | Marques38 MP2RAGE | Wright39 MPRAJE | Dieringer14 2D-VFA |
|---------------------|-------------|----------------------|-------------------|-----------------|-------------------|
| WM                  | 1218 ± 44   | 1220 ± 36            | 1150 ± 60         | 1130 ± 100      | 1284 ± 22         |
| Cortical GM         | 1898 ± 43   | 2132 ± 103           | 1920 ± 160        | 1939 ± 150      | 2065 ± 69         |
| Caudate nucleus     | 1686 ± 64   | 1745 ± 64            | 1630 ± 90         | 1684 ± 76       | –                 |
| Thalamus            | 1659 ± 124  | 1656 ± 84            | 1430 ± 100        | –               | –                 |
| Putamen             | 1646 ± 84   | 1700 ± 66            | 1520 ± 90         | 1643 ± 167      | –                 |
| Globus pallidus     | 1415 ± 81   | 1347 ± 52            | –                 | –               | –                 |
| CSF                 | 4435 ± 432  | 4425 ± 137           | –                 | –               | –                 |

Mean ± SD in ms across subjects. Note that Rooney et al37 and Wright et al39 used fitting of the signal dependence on TI while Marques et al38 used a look-up table. Overall, good agreement is observed considering the large variation in previously reported estimates.

Figure 7  $T_1$ maps of a representative subject with accompanying whole-brain histogram using the finalized protocol. The color scale is centered on the GM peak (gray) to highlight variations across GM represented by gray/dark blue. WM appears red/bright orange and the CSF is shown in light blue. Orthogonal views in the upper row are centered on the basal ganglia and the lower on the motor cortex. The asymmetry in the right cerebellum is caused by the two-channel transmit/receive coil locally yielding weak $B_1^+$ coverage and low SNR. The whole brain $T_1$ histogram shows clearly delineated WM/GM modes and a long tail corresponding to voxels of predominantly CSF.

Figure 8  Example multi-parametric maps of $T_1$, $R_2^*$, PD and $\chi$ from a representative subject using the finalized protocol. Note, the well-defined structures in the visual cortex on the $\chi$ map compared to the $R_2^*$ map.

Performance in other areas. In this work, a general optimization of the whole brain was aimed for, based on the median apparent Ernst angle.

Based on RF pulse simulations, we chose to change the RF pulse shape from a rectangular pulse to an asymmetric sinc pulse, to obtain a flat frequency response within the
typical $f_0$ range in the brain at 7T. With a rectangular pulse, a sufficiently broad frequency response entailed a high $B_1^+$ amplitude (close to 20 $\mu$T) and thus considerably stronger MT effects (not shown). Contrary to the standard settings, the RF pulse duration, $\tau$, was kept constant between the two flip angles, rather than the maximum $B_1^+$ amplitude, $B_{1,max}^+$. This approach was chosen because, for a certain pulse, it allows to balance the partial saturation of the free and the bound pool over a range of sufficiently small flip angles and thus reduce incidental MT effects.18 The partial saturation of the free water pool is $\delta_i = 1 - \cos \alpha \approx \alpha^2 / 2$. When the saturation of the bound pool is small, it can be approximated by $\delta_b \approx q \alpha^2 / \tau$ where $q$ depends on the RF pulse shape. Thus, with $\tau$ being the same for the two pulses, $\tau$ can be chosen to match the saturation of each pool independent of flip angle, $q \alpha^2 / \tau = \alpha^2 / 2 \Rightarrow q / \tau = 1 / 2$. When instead $B_{1,max}^+$ is kept constant, the saturation of the bound pool can be approximated as $\delta_b \approx q B_{1,max}^+ \alpha$ and the balance with $\delta_i$ can only be obtained for a single flip angle, $q B_{1,max}^+ \alpha = \alpha^2 / 2$. This will result in MT effects in the $T_1$ maps which are difficult to control, especially with large $B_1^+$ inhomogeneities.

MT effects on $T_1$ estimation have rarely been considered,41,42 but the present results show that the influence on $T_1$ estimates can be about 10%. Experiment 3 aimed to determine the $\tau$ which minimizes this MT-related bias. Too short pulses disproportionately saturated the bound pool relative to the free pool, leading to MT from the free pool and thus a decrease in the steady-state signal and, in turn, an overestimation of $T_1$. Conversely, too long pulses create the opposite situation, leading to an underestimation of $T_1$. For the asymmetric sinc pulse, a duration of $\tau = 700$ $\mu$s yielded $T_1$ estimates consistent with literature and IR-prepared EPI. Still, $T_1$ was systematically underestimated in WM of the inferior temporal lobes and cerebellum, where $B_1^+$ was quite low (~50%). Since the composite $f_2$ maps were specifically designed for a wide range of $B_1^+$, the tentative explanation is that the approximation of MT given above may be an oversimplification. While our empirical adjustment of $\tau$ gives correct $T_1$ for moderate deviations of $B_1^+$, it may still imply bias where the local $B_1^+$ power is low. Despite this, overall $T_1$ estimates in WM agree well with those obtained using IR-prepared EPI (Table 1) and literature (Table 2). Assessment of $T_1$ in different cortical regions will be covered elsewhere.

Hypothetically, the small flip angle approximation ($\alpha \ll 1$ rad) could have contributed to the deviation from linearity in experiment 1. At the highest local flip angle of 39° in Figure 1 ($\alpha_{nom} = 32^\circ$ and $f_2 = 1.23^\circ$) the deviation to the exact solution19 is below 4% assuming a reasonably low $T_1$ and TR = 18 ms. At 20° local flip angle, the deviation to the exact solution is below 1%, which is much smaller than the observed deviation.

Apart from attempting to avoid effects from incomplete spoiling altogether by limiting the upper flip angle, we also applied a linear correction algorithm.30 Generally, the effect of this correction on the $T_1$ estimates was small compared to MT effects. Yet, in central regions of high $B_1^+$ such as the splenium and thalamus, $T_1$ estimates were reduced, and better matched the estimates observed with IR-prepared EPI and literature. Consistent with this, high $B_1^+$ areas showed deviation from the Ernst equation at a nominal flip angle of 16° (experiment 1). The correction method was developed with 3T data in mind and simulations were therefore performed on a limited range of $T_1$'s from 700 to 1800 ms.30 Although barely, this should cover the range of $T_1$'s found in the basal ganglia in the center of the brain where $B_1^+$ is at its highest. It would perhaps be possible to rely completely on the post-correction thus not reducing the higher flip angle. It was deemed more prudent, however, to limit the effect of residual transverse coherences at a modest cost in SNR.19

Another way to ensure sufficient spoiling could have been to exploit the long TR at 7T to implement long crusher gradients43 instead of doing a multi-echo readout. Again, since the effect of residual transverse coherences can be effectively limited by the upper flip angle and/or correction, subject comfort and the benefit of the $R_2^*$ and susceptibility quantification may be considered more important. Longer $T_1$ times at 7T favor a longer TR compared to 3T, which was used to accommodate a multi-echo readout. This leads to improved SNR15 with the added benefit of additional parameter quantification from the evolution of transverse magnetization (Figure 8). The timing of the echo train was similar to an established 3T multi-parametric protocol3,8 but the shorter $T_2^*$ at 7T (~15-25 ms) will yield a higher precision in the $R_2^*$ estimates. The PD values obtained by the hMRI toolbox appeared reasonable, despite the conversion from $l|a|$ to PD being optimized for 3T. The hMRI toolbox assigns a PD of 69 p.u. to WM, which could result in errors especially in very young, elderly, or diseased subjects where a large part of WM deviates from this value.8

In combination with a MT-w acquisition, the maps of $T_1$ and $l|a|$ can be used to calculate the MT saturation,44 although this is challenging at 7T due to specific absorption rate restrictions.45 Thus, accurate $T_1$ mapping will reduce the bias of $l|a|$ and hence MT saturation. In addition to magnitude-based multi-parametric data, $\chi$ maps were estimated from the phase images by QSM reconstruction.32 A detailed discussion of these multi-parametric 7T maps is outside the scope of this paper, however.

Another $T_1$-mapping technique is MP2RAGE,38 which has become popular due to the inherent compensation of $B_1^+$ inhomogeneity and interleaved acquisition of the $T_1$-w and PD-$w$ images. Derivation of $T_1$ is performed using a look-up table, and the readout train will somewhat limit the capability of simultaneous mapping of $R_2^*$ and $\chi$.46 The main benefit of the VFA approach for whole-brain $T_1$-mapping is the speed of acquisition due to the lack of recovery intervals. When compared
to IR-based techniques, this reduction of scan time is particularly large at 7T due to the prolongation of $T_1$. Measurement time can thus be spent to increase spatial resolution.

6 | CONCLUSIONS

$T_1$-mapping at 7T using a DFA-based approach in a multi-parameter mapping context is feasible, but care should be taken to address systematic bias due to residual transverse coherences, incomplete excitation in areas with high $B_0$ deviations, $B_1^+$ inhomogeneities as well as incidental on-resonance MT effects. It is suggested to limit the upper flip angle to avoid incomplete spoiling, using an RF pulse shape that is insensitive to $B_0$ inhomogeneities as well as adjusting the RF pulse duration to reduce incidental MT effects.

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