MP3RAGE: Simultaneous mapping of $T_1$ and $B_1^+$ in human brain at 7T

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Purpose: To map $T_1$ and the local flip angle ($B_1^+$) in human brain using a single MP3RAGE sequence with 3 rapid acquisitions of gradient echoes (RAGEs).

Theory and methods: A third RAGE with a relatively high flip angle was appended to an MP2RAGE sequence. Through curve fitting and a rational approximation for small flip angles and short TR, closed form solutions for $T_1$ and $B_1^+$ were derived. The influence of different k-space encoding schemes on precision and whether edge enhancement artifacts could be reduced with a saturation pulse applied prior to the third RAGE were explored. Validation of $T_1$ estimates was performed using single-slice inversion recovery (IR) and a subsequent region-of-interest–based comparison, whereas validation of $B_1^+$ was performed using a whole brain pixelwise comparison to a DREAM flip angle mapping protocol. Lastly, MP3RAGE was compared to $T_1$-mapping by MP2RAGE with separate $B_1^+$ correction.

Results: Whole brain maps of $T_1$ and $B_1^+$ at 1 mm isotropic resolution were obtained with MP3RAGE in 06:37 min. A linear–reverse centric–reverse centric phase-encoding order of the 3 RAGEs improved precision, and artifacts were successfully reduced with the saturation pulse. Estimations of $T_1$ and $B_1^+$ deviated $+2.5 \pm 3.1\%$ and $−1.7 \pm 8.6\%$ from their respective references.

Conclusion: $T_1$ and $B_1^+$ can be mapped simultaneously using MP3RAGE. The approach can be thought of as combining MP2RAGE with a dual flip angle $T_1^-$ mapping protocol. Both maps can be solved for analytically and will be inherently co-registered at the high resolution associated with MPRAGE.

KEYWORDS
7T, $B_1^+$-mapping, dual flip angle, MPRAGE, $T_1^-$-mapping
INTRODUCTION

The MPRAGE sequence is the method of choice for $T_1$-weighted ($T_1$-w) structural brain imaging on clinical MR systems. At ultrahigh field strengths (typically ≥ 7 Tesla [T]), however, signal inhomogeneities due to the spatially heterogeneous $B_0$ field may compromise image quality. The MP2RAGE technique has been proposed as a solution\(^1\) for which a second, predominantly proton density (PD)-weighted RAGE is acquired within the same cycle, albeit at a longer TI. Combining the 2 images produces a $T_1$-w image in which influence from PD, $T_2$, and receive field sensitivity is removed. Bias from the transmit field ($B_1^+$) is reduced to an extent determined by the specific parameter settings. The improved spatial homogeneity has made MP2RAGE popular for brain imaging at high field strengths. In addition, MP2RAGE can provide $T_1$ maps through parameter-specific lookup tables (LUTs) created by forward signal modeling.\(^2\)–\(^4\) Although $B_1^+$ bias is largely compensated, it is not fully eliminated over the whole range of $T_1$ and $B_1^+$ values encountered at 7T.

Here, we suggest a combination of 3 RAGEs, dubbed MP3RAGE, for simultaneous mapping of $T_1$ and $B_1^+$ across the ranges typically encountered at 7T. The third RAGE is acquired at a higher flip angle than what is typically used in MPRAGE or MP2RAGE, which quickly forces the longitudinal magnetization ($M_z$) into a $T_1$-w driven equilibrium. Thus, the signals can be described analytically instead of having to model a 2D LUT, reducing postprocessing time. By minimizing dead time, the additional RAGE can be accommodated without major time requirements compared to the typical MP2RAGE sequence, which comprises substantial periods of free relaxation within each cycle to increase the dynamic range of $M_z$. A preliminary report on this approach has been published in abstract form.\(^5\)

After derivation of the closed-form solutions for $T_1$ and $B_1^+$, refinements to improve the implementation with regards to precision and artifacts are tested. Experimental results are shown to verify assumptions made and acquisition parameters chosen. Validation of both the $T_1$ and $B_1^+$ maps against reference techniques are also performed along with a comparison with an MP2RAGE-based $T_1$-mapping protocol. Finally, a small cohort was studied, and the obtained $T_1$ estimates are discussed in relation to other 7T studies.

THEORY

The MPRAGE cycle begins with an inversion of $M_z$, followed by an optional free recovery period and then a RAGE with a low flip angle, $\alpha_\text{low}$, and short TR. This is followed by another optional free recovery period to increase $M_z$ until the next inversion.\(^6\) The cycle is repeated with differing phase encodings until k-space is sufficiently sampled. The time constant $T_1^*$ describes how fast $M_z$ approaches the driven equilibrium for readout flip angle $\alpha_\text{low}$ and TR\(^1\)\(^3\):\(^8\)

$$T_1^* = \frac{1}{T_1} - \frac{1}{TR} \ln \left( \cos \left( f_1 \alpha_\text{low} \right) \right)^{-1}, \tag{1}$$

where $f_1$ denotes the quotient of the local by the nominal flip angle, that is, the $B_1^+$ bias field. Through Taylor expansion and then a rational approximation for small flip angles and short $TR$,\(^9\) the natural logarithm can be re-written as

$$\ln \left( \cos \left( f_1 \alpha_\text{low} \right) \right) \approx \cos \left( f_1 \alpha_\text{low} \right) - 1 \approx - \left( f_1^2 \alpha_\text{low}^2 / 2 \right).$$

This reduces Equation (1) to:

$$T_1^* = \left( \frac{1}{T_1} + \frac{f_1^2 \alpha_\text{low}^2}{2TR} \right)^{-1}. \tag{2}$$

In the MP3RAGE cycle, 3 RAGES are acquired immediately after each other and with identical TR, resulting in 3 images whose signal intensities are denoted $S_{1,2,3}$ (Figure 1). The first 2 RAGEs are acquired with $\alpha_\text{low}$, whereas the third uses a higher flip angle, $\alpha_\text{high}$ (for which the small flip angle approximations should still apply). Any change in contrast between $S_1$ and $S_2$ is thus governed by $T_1^*$, and the time from inversion to acquisition of the central k-space line, $TI_{1,2}$:

$$S_{1,2} = S_{PD} + \left( S_0 - S_{PD} \right) \exp \left( - TI_{1,2} / T_1^* \right). \tag{3}$$

Here, $S_{PD}$ is the hypotetical signal acquired at the PD-w driven equilibrium ($II \to \infty$), and $S_0$ is the hypothetical signal acquired with $\alpha_\text{low}$ at the start of the cycle ($II = 0$). Note that all signals show the same $T_2^*$ decay. Equation (3) is ill-posed, with only 2 data points to fit a 3-parameter exponential. However, if $S_2$ is acquired immediately prior to inversion, a “synthetic” $S_0$ can be calculated from $S_3$:

$$S_0 = -f_{inv} S_3 \sin \left( f_1 \alpha_\text{low} \right) / \sin \left( f_1 \alpha_\text{high} \right) \approx -f_{inv} S_3 \sin \left( \alpha_\text{low} \right) / \sin \left( \alpha_\text{high} \right). \tag{4}$$

In this work, an inversion efficiency of $f_{inv} = 0.96$ was assumed as in Ref. [1]. The right-hand approximation in Equation (4) is necessary because $f_1$ is unknown at this point but justified for small flip angles. In addition, this approximation has limited influence on the final parameter estimations because $M_z$ at the end of the cycle is small. The same can be said for the exact value of $f_{inv}$. With $S_0$ known, $T_1^*$ and $S_{PD}$ can be obtained from Equation (3) by a nonlinear least-squares fit.

Analogous to $S_{PD}$, $S_{TI}$ is the hypothetical signal acquired with $\alpha_\text{high}$ in a $T_1$-weighted driven equilibrium. If the central k-space lines of $S_3$ are acquired under this condition, $S_{TI}$ is well-represented by $S_3 \left( S_{TI} \approx S_3 \right)$. This can
be accomplished by a relatively high flip angle and short TR, enforcing sufficiently short \( T_1 \) during the third RAGE (as can be seen from Equation (1) but with \( \alpha_{\text{high}} \) as the flip angle). Consequently, both \( S_{\text{PD}} \) and \( S_3 \) correspond to spoiled steady state signals with identical TR but differing flip angles (\( \alpha_{\text{low}} \) and \( \alpha_{\text{high}} \)), that is, a dual flip angle (DFA) experiment from which an “apparent” \( T_1 \) can be obtained:\(^9\)

\[
T_{1,\text{app}} = 2TR \frac{S_{\text{PD}}/\alpha_{\text{low}} - S_3/\alpha_{\text{high}}}{S_3\alpha_{\text{high}} - S_{\text{PD}}\alpha_{\text{low}}}. \tag{5}
\]

The influence of the local flip angle bias on \( T_{1,\text{app}} \) is quadratic:\(^9\)

\[
T_{1,\text{app}} = T_1f_T^2. \tag{6}
\]

Thus, \( T_1 \) can be solved for by substituting \( f_T \) with \( T_{1,\text{app}} \) in Equation (2):

\[
T_1 = T_1^* \left( 1 + T_{1,\text{app}}\frac{\alpha_{\text{low}}^2}{(2TR)} \right), \tag{7}
\]

to finally yield \( f_T \) from Equation (6):

\[
f_T = \sqrt{\frac{T_{1,\text{app}}}{T_1}}. \tag{8}
\]

In principle, \( f_T \) (and hence \( T_1 \)) can be obtained from \( S_{\text{PD}}, S_{T1}, \) and \( T_1^* \) using the Ernst equation, foregoing the
rational approximation for small flip angles. The signal amplitude is eliminated in $S_{PD}/S_{1}$, where the unknown exp $(T_{1}/TR)$ can be substituted using Equation (1). This yields a complicated equation of $f_T$ that can be inverted numerically. Likewise, curve fitting to obtain $T_{1\ast}$ and $S_{PD}$ could be replaced by finding the roots of a second- or third-order polynomial for a linear–linear or linear–reverse centric spacing of the TIs (see the Methods section). The increase in complexity for either of these approaches motivates the approximations presented here.

3 | METHODS

Experiments were performed on an actively shielded 7T MR system (Achieva, Philips Healthcare, Best, NL) using a 32-channel receive head coil with 2 transmit channels at fixed phase settings (Nova Medical, Wilmington, MA). Healthy adult subjects were scanned after giving informed written consent, as approved by the regional ethical review board.

The MP3RAGE sequence was implemented as 3 interleaved scans using Philips interleaved scanning framework (Philips Healthcare), which allows instantaneous switching between multiple scans.\textsuperscript{10} The 3 RAGEs (resulting in the images $S_{1}, S_{2}$, and $S_{3}$) were acquired without any free relaxation delays in the cycle. The first 2 RAGEs ($S_{1}$ and $S_{2}$) used a low flip angle of $\alpha_{low} = 3^\circ$, whereas $S_{3}$ used a higher flip angle of $\alpha_{high} = 16^\circ$. The RF pulse duration was 700 $\mu$s to reduce incidental magnetization transfer effects.\textsuperscript{11} Assuming $T_{1}$ values between $\sim 1100$ ms and $\sim 2200$ ms in brain tissue,\textsuperscript{11} the DFA experiment (Equation (5)) is well posed for normalized $B_{1}^\ast$ values between 44% and 165% at the chosen TR = 7.45 ms (local $\alpha_{low}$ and $\alpha_{high}$ on either side of the Ernst angle). At 100% $B_{1}^\ast$, this flip angle pair minimizes the noise propagation in Equation (5) for $T_{1}$ values around $\sim 1100$ ms, whereas at a $T_{1}$ of 1500 ms, conditions are optimal at $\sim 85\% B_{1}^\ast$.\textsuperscript{12}

Unless otherwise stated, remaining acquisition parameters were as follows: The matrix size was $224 \times 224 \times 200$ with 1 mm isotropic voxels, sagittal orientation, readout in the feet–head direction, and a bandwidth/pixel of 212.6 Hz. All RAGEs used a nonselective multi-shot acquisition scheme with a turbo factor (TF) of 256, TR/TE = 7.45/3.40 ms, and a SENSE-factor of 2 in the outer-loop right–left direction. Thus, the duration of each RAGE was TF $\times$ TR $= 1907$ ms, and the respective effective inversion times (time from inversion until acquisition of the central k-space line) were $T_{1}/T_{1\ast}/T_{1\ast}$ $= 960/3821/5738$ ms, with linear–reverse centric–reverse centric k-space phase-encoding orders. Enabling the “3D free factor” made the TF independent of the number of inner-loop phase-encoding steps and allowed an elliptical k-space phase encoding, reducing total acquisition time by a factor of $\sim 1.3$. The matrix size in the outer-loop right–left direction was varied somewhat between subjects so that the FOV encompassed the ears. For inversion of the magnetization prior to acquisition of $S_{1}$, an adiabatic TR-FOCI pulse of 13 ms was used.\textsuperscript{13} Further, a composite adiabatic saturation pulse of 8.9 ms was applied prior to $S_{1}$ to reduce high-frequency artifacts (see Section 3.2).

Maps of $S_{0}, T_{1\ast}, S_{PD}, T_{1\ast}$—and finally $T_{1}$ and $B_{1}^\ast$ (represented by $f_T$ in percent units)—were obtained from the data as described in the Theory section using MatLab R2020b (MathWorks, Natick, MA). The following subsections describe different experiments addressing the effect of different sequence parameter settings and assumptions, as well as validating MP3RAGE by independent reference techniques. When applicable, co-registration of images was performed using FSL 6.0 FLIRT,\textsuperscript{14} whereas segmentation of white matter (WM), gray matter (GM), and CSF was performed using SPM where the GM segmentations contained a mixture of cortical and deep brain GM.

3.1 | Optimizing TIs by a reverse centric phase-encoding order

According to Ogg and Kingsley,\textsuperscript{15} the precision regarding an IR-based $T_{1}$ estimate increases monotonically with the maximum TI until full relaxation at approximately $5 \times T_{1}$. The minimum TI should be set as short as possible, whereas remaining TIs should be spaced geometrically. Here, the minimum TI of 0 ms was achieved by the synthetic $S_{0}$ of Equation (4). The range of expected $T_{1\ast}$ estimates in tissue was (assuming $\sim 2200$ ms $\geq T_{1\ast} \geq \sim 1100$ ms) $\sim 2100$ ms $\geq T_{1\ast} \geq \sim 700$ ms for local flip angles in the range $1.2^\circ \leq f_T \times \alpha_{low} \leq 5.1^\circ$ (40%–170% $B_{1}^\ast$). Hence, $T_{1\ast}$ should be as long as possible, which can be achieved by a reverse centric phase-encoding order of $S_{2}$. Thus, the center of k-space was acquired at the end of the RAGE at $T_{1\ast} = 3821$ ms. A linear order was chosen for $S_{1}$ so that the center of k-space was acquired in the middle of the RAGE at $T_{1\ast} = 960$ ms. This rendered the spacing of TIs as close to a geometric spacing as possible for the set TR $\times$ TF and without extensive scanner software modifications. The $T_{1\ast}$-w $S_{3}$ is not used for curve-fitting, but its phase-encoding order is still relevant to ensure that the central k-space lines are acquired at the $T_{1\ast}$-w driven equilibrium to obtain $S_{3} \approx S_{T_{1\ast}}$. Hence, a reverse centric order was chosen also for $S_{3}$ ($T_{1\ast}$ = 5738 ms).

To evaluate the effect of the chosen phase-encoding orders on the fitted $T_{1\ast}$ and $S_{PD}$ maps (Equation (3)), 2 MP3RAGE data sets with either a linear–linear or linear–reverse centric order for $S_{1}$ and $S_{2}$ were acquired on a subject. Derived $T_{1\ast}$ and $S_{PD}$ maps were inspected visually to appreciate any change in precision/SNR.
3.2 | Artifact reduction by a saturation pulse prior to $S_3$

High-frequency artifacts may appear due to strong changes in $M_z$ at the start of a RAGE. This issue was initially seen in the $T_1$-w $S_3$ image, that is, when applying $\alpha_{\text{high}}$ and a reverse centric phase-encoding order. In our implementation, these artifacts are reduced by applying a saturation pulse before the third RAGE, which prepares $M_z$ closer to the driven equilibrium for $f_T \times \alpha_{\text{PD}} \geq 1.38^\circ$ (46% $B_1^+$) and $T_1 \geq 1100$ ms. Figure 1 shows the steep initial decline of $M_z$ for $T_1 = 1500$ ms and $f_T \times \alpha_{\text{PD}} = 3^\circ$ (100% $B_1^+$) during acquisition of $S_3$ when a saturation pulse is not applied (blue dotted line). To illustrate these artifacts in $S_3$, 2 MP3RAGE scans were acquired on a subject with and without a saturation pulse.

3.3 | Validation of $S_3$ and $S_{\text{PD}}$

To experimentally determine whether the $T_1$-w and PD-w driven equilibriums were estimated reliably with the MP3RAGE approach, 2 spoiled gradient echo scans with $\text{TR} = 7.45$ ms and $\alpha_{\text{low}}/\alpha_{\text{high}} = 3^\circ/16^\circ$ were acquired on 1 subject along with an MP3RAGE scan. The 2 gradient echo scans were thereafter independently co-registered to the MP3RAGE images. The $T_1$-w gradient echo ($\alpha_{\text{high}} = 16^\circ$) was compared to $S_3$, whereas the PD-w gradient echo ($\alpha_{\text{low}} = 3^\circ$) was compared to $S_{\text{PD}}$, as derived from curve fitting of the MP3RAGE signal (Equation (3)). The comparison was performed pixelwise in segmented WM, GM, and CSF. A region-of-interest (ROI)-based comparison was also performed to specifically study areas of low $B_1^+$. Further, maps of $T_1$ and $B_1^+$ were derived by replacing $S_3$ and $S_{\text{PD}}$ with the externally acquired gradient echoes. These maps were then compared to those derived only from the MP3RAGE data. For the ROI analysis, this reference $B_1^+$ map was used to denote the local flip angle.

3.4 | Validation of $f_{\text{inv}}$

To determine the validity of an assumed global $f_{\text{inv}} = 0.96$, a subject was scanned using a modified MPRAGE-based experiment where 4 RAGES were acquired with the same low flip angle of 2°, linear phase-encoding orders, and without a saturation pulse. To further increase precision, the voxel size was increased to (1.25 mm)$^3$. Remaining parameter settings were kept identical. A slightly lower flip angle than $\alpha_{\text{low}} = 3^\circ$ was chosen to increase the signal difference between the RAGES. By a pixelwise 3-parameter fit, a map of $f_{\text{inv}}$ was obtained (besides $T_1^*$ and $S_{\text{PD}}$). The whole brain mean of $f_{\text{inv}}$ was calculated, excluding perceived noise pixels of either $f_{\text{inv}} < 0.6$ or $f_{\text{inv}} > 1.0$. The whole brain means in segmented WM, GM, and CSF were also compared. Further, maps of $T_1$ and $B_1^+$ were estimated and compared assuming either $f_{\text{inv}} = 0.96$ or the whole brain mean $f_{\text{inv}}$ derived here.

3.5 | Validation of $S_3$ and $S_{\text{PD}}$

Simulations were performed to explore the theoretical limitations of the suggested MP3RAGE protocol, specifically regarding the $T_1$-w driven equilibrium and the rational approximation for small flip angles. The progression of $M_z$ during the proposed MP3RAGE cycle was simulated using Equation (1), an assumed $f_{\text{inv}} = 0.96$ and a saturation pulse prior to the third RAGE for different $T_1$ values ranging from 1 ms to 5000 ms (step size of 1 ms) and different $f_T$ values ranging from 0.01 to 2.00 (step size of 0.01). The simulation was continued to include the third cycle. At this point, an outer-loop steady state had been established even when the $T_1$-w driven equilibrium was not reached by the end of each cycle. The signals $S_1(T_1, f_T) = M_z(T_1, f_T, T_{1,\text{est}}) \sin(f_T \alpha_1)$; $S_2(T_1, f_T) = M_z(T_1, f_T, T_{1,\text{est}}) \sin(f_T \alpha_2)$; and $S_3(T_1, f_T) = M_z(T_1, f_T, T_{1,\text{est}}) \sin(f_T \alpha_3)$ were then calculated for the 2D parameter space. From these, estimated maps of $T_1$ and $f_T$ were derived ($T_{1,\text{est}}$ and $f_{T,\text{est}}$), as described in the Theory section. Ground truth values ($T_{1,\text{true}}$ and $f_{T,\text{true}}$) were then compared to $T_{1,\text{est}}$ and $f_{T,\text{est}}$ to visualize the expected bias.

3.6 | Validation of $B_1^+$ and $T_1$: Experimental

A validation experiment of the derived $T_1$ and $B_1^+$ maps was performed on a single subject.

For $B_1^+$ validation, 3 multi-slice DREAM acquisitions with a spatial resolution of 3.75 × 3.75 and a slice thickness of 3.50 mm (slice gap of 0.25 mm) were acquired with preparation flip angles of 25°, 40°, and 60° and then combined into a single $B_1^+$ map. This map was co-registered to MP3RAGE space. The $B_1^+$ estimates were then compared by calculating a map of their difference (MP3RAGE–DREAM), whole brain histograms, and linear regression as well as a Bland–Altman plot. The comparison was further complemented by ROI analysis as for the $T_1$ validation (see following paragraph).

For $T_1$ validation, a transverse, single-slice, single-shot IR-EPI sequence with TR = 10 s, echo train length of 51, and bandwidth in the phase-encoding direction of 29.5 Hz/px was used. The sequence was repeated with 18 inversion times of TI = 200, 300, 400, 600, 800, 900, 1000,
3.7 | \( T_1 \) cohort study

The MP3RAGE protocol was run on a cohort of 5 healthy volunteers (3 females, 24–36 years old). For each subject, “clipped” mean values and SD of \( T_1 \) for segmented WM, GM, and CSF were calculated from the fifth to 95th percentiles.

3.8 | Comparison to MP2RAGE

Because MP3RAGE can be seen as an extension to MP2RAGE, \( T_1 \) maps derived using either approach were compared in a single subject. The MP3RAGE sequence was acquired with an acquisition voxel size of (0.8 mm)\(^3\) and a matrix size of 288 × 288 × 250, resulting in an acquisition duration of 10:15 min. The MP2RAGE sequence had a voxel size of (0.7 mm)\(^3\), a matrix size of 320 × 320 × 264 (15 mm smaller FOV in the outer loop direction). Further, a flip angle pair of \( \alpha_1/\alpha_2 = 5^\circ/3^\circ \), \( T_{\text{I1}}/T_{\text{I2}} = 911/2761 \) ms, TR/TE = 6.80/2.45 ms, cycle duration of \( T_{\text{C}} = 5 \) s, and TF = 256\(^{18} \) were used. The bandwidth/pixel was 326 Hz. Like MP3RAGE, a SENSE factor of 2 was applied in the outer loop direction as well as an elliptical phase encoding. Unlike MP3RAGE, a partial Fourier factor of 75% was also applied in the same direction, resulting in an acquisition duration of 08:35 min. A LUT-based \( T_1 \) map was derived from the MP2RAGE data using MatLab R2020b (MathWorks) scripts with the default setting of \( f_{\text{inv}} = 0.96 \) as made available by the authors.\(^1\) Correction of residual \( B_1^+ \)-induced bias was performed using a separate DREAM flip angle map, bringing the total acquisition time for the MP2RAGE protocol to 09:47 min. Comparison through histogram analysis was performed after co-registration and subsequent interpolation of the slightly lower resolution MP3RAGE volume to the MP2RAGE volume.

4 | RESULTS

4.1 | Optimizing TIs by a reverse centric phase-encoding order

When using a linear–linear phase-encoding order for \( S_1 \) and \( S_2 \), the fitted maps of \( T_1^* \) and \( S_{\text{PD}} \) showed “specks” of deviating values, most evident in the \( S_{\text{PD}} \) maps. These were not seen when using a linear–reverse centric combination (Figure 2). This confirmed the choice of a linear–reverse centric combination of phase-encoding orders. Figure 2 also illustrates the general appearance of the \( T_1^* \) maps, which are similar to normal \( T_1 \) maps, albeit with shorter values as well as a decreased WM-GM contrast in high \( B_1^+ \) areas such as the centrally located thalamus.

4.2 | Artifact reduction by a saturation pulse prior to \( S_3 \)

Figure 3 shows 2 \( S_3 \) images, both with a reverse centric phase encoding acquired without and with a saturation pulse prior to \( S_3 \) (red arrow) is reduced with the linear–reverse centric combination. This is indicative of improved precision. The red arrow in the \( T_1^* \) map from the linear–linear combination denotes a particularly noisy area between the posterior horns of the ventricles. Note the reduction of WM/GM contrast in the high \( B_1^+ \) thalamic area that is characteristic of the \( T_1^* \) maps. GM, gray matter; WM, white matter.
pulse applied prior to the third RAGE. High-frequency artifacts, especially in cortical areas close to the brain–skull boundary (red arrow), were greatly reduced by the saturation pulse.

### 4.3 Validation of $S_3$ and $S_{PD}$

The average difference in $S_3$ compared to the externally acquired reference was $-3.0 \pm 4.1\%$, $-4.3 \pm 5.1\%$, and $-4.9 \pm 13.9\%$ in WM, GM, and CSF, respectively. Larger deviations were generally observed in low $B_1^+$ areas ($<50\%$). In 2 example ROIs, the underestimation was $-6.4 \pm 3.1\%$ in the low $B_1^+$ ($f_T \times \alpha_{\text{high}} < 8.3 \pm 0.7^\circ$) right temporal lobe and $-3.4 \pm 4.0\%$ in the more typical ($f_T \times \alpha_{\text{high}} = 14.0 \pm 0.7^\circ$) right frontal WM. Corresponding deviations for $S_{PD}$ were $-1.7 \pm 3.2\%$ and $-2.2 \pm 4.9\%$ in the WM and GM segmentations, respectively. The median difference in the CSF segmentation was $-4.7\%$. For the ROIs, the deviations in $S_{PD}$ were $-2.8 \pm 4.3\%$ in the temporal lobe and $-3.1 \pm 2.8\%$ in frontal WM. Lower values of $S_{PD}$ are correlated to shorter $T_1^*$, whereas a proportionally stronger underestimation in $S_3$ compared to $S_{PD}$ results in longer $T_{1,\text{app}}$. This in turn translates into somewhat shorter $T_1$ and higher $B_1^+$ estimates. In the resulting $T_1$ maps, the difference was thus $-36 \pm 103$ ms and $-36 \pm 228$ ms in the WM and GM segmentations. The median difference in the CSF segmentation was $-151$ ms. The ROI analysis showed a deviation of $-25 \pm 93$ ms in the temporal lobe and $-75 \pm 88$ ms in frontal WM. In the $B_1^+$ maps, the corresponding absolute differences ($100 \times \left[ f_T - f_{T,\text{ref}} \right]$) were $+2.1 \pm 2.6\%$, $+2.2 \pm 2.8\%$, and $+1.7\%$ in the segmentations and $+2.5 \pm 1.2\%$ and $+2.7 \pm 2.3\%$ in the ROIs. The median (rather than the mean) is reported for CSF because SDs were very high, which reflects a lower precision for long $T_{1,\text{app}}$ values from the DFA experiment (Equation (5)) and for long $T_1^*$ values when fitting Equation (3).

### 4.4 Validation of $f_{\text{inv}}$

A map of $f_{\text{inv}}$ as well as a whole brain histogram can be seen in Figure 4. The mean $f_{\text{inv}}$ of the whole brain was $0.87 \pm 0.43$, that is, substantially lower than the expected 0.96. Using $f_{\text{inv}} = 0.87$ instead of $f_{\text{inv}} = 0.96$ increased $T_1$ by $2.1 \pm 0.71\%$ in segmented WM and by $+3.7 \pm 1.8\%$ in GM with larger deviations in low $B_1^+$ areas. The estimated $B_1^+$ was virtually independent of $f_{\text{inv}}$ ($-0.73 \pm 0.055\%$/$-0.83 \pm 0.075\%$ for WM/GM). Supporting Information Figure S1 shows maps of $100 \times \left( T_1(f_{\text{inv}} = 0.87) - T_1(f_{\text{inv}} = 0.96) \right)/T_1(f_{\text{inv}} = 0.96)$
and $100 \times (f_t(f_{inv} = 0.87) - f_t(f_{inv} = 0.96))$ as well as corresponding histograms. The mean $f_{inv}$ was slightly lower in WM (0.86 ± 0.038) compared to GM (0.88 ± 0.030) and CSF (0.88 ± 0.040).

### 4.5 Validation of $B_1^+$ and $T_1$: Simulations

Maps of $100 \times (T_{1,est} - T_{1,true})/T_{1,true}$ and $100 \times (f_{T,est} - f_{T,true})$ as a function of $T_{1,true}$ and $f_{T,true}$ can be seen in Supporting Information Figure S2. At high $B_1^+$, there is an overestimation of primarily $T_1$ due to the rational approximation for small flip angles. The approximation affects primarily the $T_{1,app}$ calculation in Equation (5) via $\alpha_{high} = 16^\circ$. At low $B_1^+$, there is an overestimation of both $T_1$ and $B_1^+$ when the $T_1$-w driven equilibrium is not reached by the end of the cycle. Pixels with a deviation of 3% are marked in black to denote the limit beyond which the approach cannot be considered reliable. For 3 representative $T_1$ values of 1300, 1900, and 4300 ms (expected in WM, GM, and CSF), the respective ranges of $B_1^+$ values within the 3% limit are $f_T \geq 0.45$, $0.48 \leq f_T \leq 1.86$ and $0.52 \leq f_T \leq 1.52$.

### 4.6 Validation of $B_1^+$ and $T_1$ maps: Experimental

Maps of normalized $B_1^+$ in percent ($100 \times f_T$) derived from either MP3RAGE or DREAM are shown in Figure 5. The DREAM map subtracted from the MP3RAGE map is also shown. There was a general tendency toward MP3RAGE resulting in a larger range of $B_1^+$ estimates, that is, slightly higher values in higher $B_1^+$ areas (center of brain) and lower values in low $B_1^+$ areas (most notably in or close to the cerebellum). This is also reflected by the histograms, which show that MP3RAGE contained more pixels above 140%, but especially below 60%. A scatter plot with a linear regression indicates that 100% $B_1^+$ using DREAM corresponded to 98% using MP3RAGE. The Bland-Altman plot also revealed a tendency toward somewhat lower estimates using MP3RAGE, with an average difference of

![Figure 5: $B_1^+$ validation. (A) MP3RAGE $B_1^+$ map. (B) DREAM $B_1^+$ map. (C) MP3RAGE–DREAM difference map. (D) Whole brain histograms peak at 103% for both MP3RAGE and DREAM. (E) A density plot also showing the line of identity (solid line) and linear regression (dotted line). (F) Bland-Altman plot showing the mean deviation of −1.7% (solid line) and the 95% interval (± 1.96 × SD = ± 17%) (blue). High $B_1^+$ areas tend to have slightly higher estimates, whereas low $B_1^+$ areas tend to have somewhat lower in MP3RAGE compared to DREAM. This is noticeable in occipital regions close to the cerebellum.](image-url)
−1.7 ± 8.6% across the whole brain. The ROI analysis (excluding areas of very low $B_1^+$) yielded an average deviation of +0.9 ± 3.7% (Table 1).

Two $T_1$ maps derived from either MP3RAGE or IR-EPI can be seen in Figure 6. Mean values and SDs of the outlined ROIs are given in Table 1. The relative differences were within ±5%, except for the CSF and the thalamus. The average relative difference across all tissue ROIs (excluding the CSF) was +2.5 ± 3.1% relative to IR-EPI. The tendency toward higher estimates using MP3RAGE was stronger in GM ROIs (+3.3 ± 3.4%) than WM ROIs (+1.6 ± 2.8%). The mean inversion efficiency in the IR-EPI slice was $f_{\text{inv}} = 0.89 ± 0.062$.

### 4.7 | $T_1$ cohort study

The mean $T_1$ estimates for segmented WM, GM, and CSF for each subject are listed in Table 2. Across subjects, the average $T_1$ was 1394 ± 31 ms in WM, 2027 ± 70 ms in GM, and 3340 ± 281 ms in CSF (average of the means ± SD of the means).

Example maps of $T_1$ and $B_1^+$ of an example subject with corresponding whole brain histograms are shown in Figure 7. The maps are shown in all 3 projections to illustrate the whole brain coverage of MP3RAGE. A sharp increase in $B_1^+$ is discernible in ventricular CSF, and the WM/GM modes are clearly separated in the $T_1$ histogram.

### 4.8 | Comparison to MP2RAGE

Maps of $T_1$ derived using MP2RAGE with/without $B_1^+$ correction and MP3RAGE as well as the corresponding whole brain histograms are shown in Figure 8. The residual $B_1^+$ bias in MP2RAGE corresponds to lower $T_1$ estimates in central high $B_1^+$ regions and higher $T_1$ estimates in peripheral low $B_1^+$ regions, as well as an absence of a well-defined GM mode in the histogram. MP3RAGE estimates of $T_1$ were higher than for MP2RAGE with WM modes peaking at 1325 ms and 1185 ms respectively (12% increase, bin size of 10 ms). The increase in GM was smaller with the peaks of the histogram modes situated at 1885 ms and 1825 ms (3.3% increase).

### 5 | DISCUSSION

We propose a novel technique to obtain whole brain maps of $T_1$ and $B_1^+$ from a single sequence. The technique, dubbed “MP3RAGE,” is based on adding a third RAGE to the well-established MP2RAGE method, although the approach to obtain the parametric maps is quite different.

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**Table 1** ROI analysis of the $T_1$ maps (Figure 6) derived using IR-EPI or MP3RAGE and their relative difference (100 × (MP3RAGE−IR-EPI)/IR-EPI)

| ROI                        | IR-EPI [ms] | MP3RAGE [ms] | $T_1$ Relative Difference [%] | $B_1^+$ Difference [%] |
|----------------------------|-------------|--------------|------------------------------|------------------------|
| Frontal WM (L)             | 1317 ± 78   | 1347 ± 85    | +2.3                         | +1.8 ± 2.5             |
| Frontal WM (R)             | 1318 ± 85   | 1329 ± 90    | +0.8                         | +4.2 ± 3.2             |
| Posterior WM (L)           | 1352 ± 65   | 1355 ± 81    | +0.2                         | −7.8 ± 2.2             |
| Posterior WM (R)           | 1340 ± 50   | 1296 ± 92    | −3.3                         | −0.7 ± 1.6             |
| Genu                       | 1309 ± 129  | 1369 ± 110   | +4.6                         | +5.1 ± 4.0             |
| Splenium                   | 1501 ± 293  | 1578 ± 126   | +5.1                         | +1.3 ± 5.7             |
| Caudate nucleus (L)        | 1826 ± 196  | 1876 ± 162   | +2.7                         | +0.7 ± 4.2             |
| Caudate nucleus (R)        | 1903 ± 266  | 1896 ± 169   | −0.4                         | +6.0 ± 4.3             |
| Putamen (L)                | 1583 ± 111  | 1646 ± 121   | +4.0                         | +1.4 ± 3.5             |
| Putamen (R)                | 1609 ± 122  | 1623 ± 154   | +0.8                         | +2.3 ± 3.7             |
| Thalamus (L)               | 1868 ± 654  | 2043 ± 235   | +9.4                         | +2.5 ± 6.0             |
| Thalamus (R)               | 1819 ± 343  | 1876 ± 204   | +3.2                         | +2.9 ± 5.0             |
| CSF (L)                    | 4156 ± 1367 | 4569 ± 2737  | +9.8                         | −5.1 ± 8.0             |
| CSF (R)                    | 3666 ± 740  | 3932 ± 1918  | +7.3                         | −2.2 ± 5.8             |

**Note:** Mean $T_1$ relative difference in tissue (excluding CSF) was +2.5 ± 3.1%. The last column shows the difference between the normalized $B_1^+$ maps (MP3RAGE−DREAM) shown in Figure 5 using the ROIs defined in MP3RAGE space. The mean difference in the $B_1^+$ comparison was +0.9 ± 3.7%.

**Abbreviations:** IR, inversion recovery; L, left; R, right; ROI, region of interest.
Here, we estimated the effective $T_1^*$ time constant followed by closed-form rational approximations of the signal equations to derive $T_1$ and $B_1^+$ instead of employing a LUT. The MP3RAGE technique is quite sampling-efficient because data is continuously acquired throughout the cycle without any period of free relaxation. It should be acknowledged that adding a third RAGE to MP2RAGE as well as the name “MP3RAGE” has been reported previously by others in abstract form: First, to determine the inversion efficiency locally and hence improve the accuracy in the subsequent LUT-based $T_1$-mapping; secondly, to perform LUT-based $T_1$- and $B_1^+$-mapping using pair-wise combinations of the 3 RAGEs where each pair was designed to be sensitive to either variations in $T_1$ or $B_1^+$. In this context, one should also note SA2RAGE, which is a LUT-based approach for $B_1^+$-mapping similar to MP2RAGE but with a saturation pulse and parameter settings designed to maximize $B_1^+$-sensitivity and minimize $T_1$-sensitivity.

To derive unbiased $T_1$ values, it is often necessary to use an independently acquired map (to obtain the local flip angle). Maps of $B_1^+$ are typically acquired at quite low spatial resolutions, like in the $3.75 \times 3.75 \times 3.50$ mm$^3$ DREAM protocol used here. The low resolution is justified based on the supposedly smoothly varying $B_1$ field. However, $B_1^+$ is higher in the ventricles, as shown by Brink et al. due to the higher conductivity of CSF compared to tissue. This could lead to partial volume effects in areas close to the ventricles when a $B_1^+$ map with low spatial resolution is used for quantitative parameter mapping. Although Brink et al. exclusively mention

### TABLE 2  Cohort $T_1$ estimations in WM, GM, and CSF

| Subject | WM     | GM     | CSF    |
|---------|--------|--------|--------|
| 1       | 1387 ± 82 | 1910 ± 283 | 2931 ± 1320 |
| 2       | 1356 ± 94  | 1996 ± 240 | 3445 ± 1466  |
| 3       | 1450 ± 82  | 2089 ± 187 | 3635 ± 1202  |
| 4       | 1399 ± 92  | 2036 ± 263 | 3088 ± 1643  |
| 5       | 1378 ± 82  | 2104 ± 242 | 3599 ± 1358  |
| Mean*  | 1394 ± 31  | 2027 ± 70  | 3340 ± 281   |

Note: Averages of each tissue-class segmentation is presented. The segmentations consisted of pixels with a probability ≥0.50, which was then eroded by a $3 \times 3$ kernel. Top/bottom 5% of estimates were clipped from reported values to avoid the very long tail of the CSF $T_1$ values.

Abbreviations: GM, gray matter; WM, white matter.

*Mean ± SD across subject averages.

**FIGURE 6** $T_1$ maps derived from MP3RAGE and IR-EPI. Outlines of the ROIs used for $T_1$ validation (Table 1) are outlined in purple. IR, inversion recovery; ROI, region of interest

**FIGURE 7** Example maps of $T_1$ and $B_1^+$ with corresponding whole brain histograms. Higher local $B_1^+$ values in CSF can be appreciated in both the ventricles and sulci in the colormap. Vessels are affected by flow artifacts, however, visible in the coronal view
ventricular CSF, one can assume that the same will apply to sulcal CSF close to cortical GM. With MP3RAGE, both the $T_1$ and $B_1^*$ map is acquired simultaneously at the higher resolution associated with MPRAGE. Hence, no partial volume or interpolation effects from co-registration are introduced into the $T_1$ map through a separately acquired low resolution $B_1^*$ map.

To reduce scan time, it could be possible to acquire the $B_1^*$ map at a lower resolution while maintaining the same high resolution in the $T_1$ map (albeit with some PVE effects as described above). This could be done by reducing the spatial resolution of $S_3$ and solving for $f_T$ in Equation (8) first where $T_1$ is substituted according to Equation (7). To avoid introducing artificial tissue contrast in the $B_1^*$ map, $S_{PP}$ in Equation (5), and $T_1^*$ in the new Equation (8) would have to be downsampled to the resolution of $S_3$. Lastly, a high-resolution $T_1$ map is calculated by solving Equation (2). Note, however, that reducing the length of the third RAGE will adversely affect the ability to reach the $T_1$-w driven equilibrium by the end of the cycle.

Some underestimation of $S_3$ was observed in low $B_1^*$ areas (<−50%) compared to a separately acquired $S_{TI}$ image with identical acquisition parameters. This can be explained by $S_3$ not quite reaching the $T_1$-w driven equilibrium in these areas $(5 \times T_1^*(\alpha_{T1}) > TR \times TF)$, as further indicated by simulations (Supporting Information Figure S2). However, this contradicts the observed lower $B_1^*$ estimates in the cerebellum/temporal lobe visible in the sagittal view in Figure 5. In this context, it should be mentioned that a similar discrepancy has previously been observed between DREAM and the actual flip angle technique.\cite{16,23}

The point-spread function (PSF) is an important consideration when implementing MPRAGE sequences.\cite{8} Here, the dynamic change of $M_z$ during the first RAGE is limited via its starting point given by the inverted $T_1$-w driven equilibrium. This will benefit the PSF of the linearly ordered $S_1$ but reduce precision when fitting Equation (3). The dynamic change of $M_z$ during the second RAGE is even smaller. This could explain the lack of discernible PSF effects (such as blurring at the boundary of the ventricles) in Figure 2, where a linear phase-encoding order of $S_2$ arguably should manifest in a narrower PSF. The saturation pulse is beneficial to the PSF of $S_3$, although in this case the initial changes of $M_z$ manifest as high-frequency artifacts instead of blurring (Figure 3).

In this implementation, a global efficiency of $f_{inv} = 0.96$ for the adiabatic inversion pulse was assumed in all calculations as in the original MP2RAGE work.\cite{1} However, the experimentally determined $f_{inv} = 0.87 \pm 0.43$ was substantially lower than expected but agreed well with the range 0.8–0.9 reported for the same inversion pulse shape and duration at 9.4T.\cite{24} This discrepancy may be explained if the simulated $f_{inv} = 0.96$ does not account for relaxation effects during inversion and/or MT effects immediately after inversion when equilibrium between the inverted free pool and non-inverted bound pool is restored. The experimentally determined $f_{inv}$ will be influenced by MT effects, and it is this “apparent” $f_{inv}$ that should be used in the monoexponential models of MP3RAGE or MP2RAGE to avoid underestimation of $T_1$. This is in accordance with Rioux et al., who showed that WM $T_1$ estimates may be underestimated in IR-based techniques where monoexponential recovery after inversion is assumed. This underestimation is especially pronounced at higher field strengths and for MP2RAGE, which tend to yield WM $T_1$ estimates at the lower end of reported values.\cite{25} In MP3RAGE, however, the effect of an overestimated $f_{inv}$ on calculating $S_0$ (Equation (4)), and subsequent fitting of $T_1^*$ (Equation (3)), is limited. The inversion pulse in the MP3RAGE cycle acts on $M_z$ in the driven $T_1$-w equilibrium that is strongly

![Figure 8](image-url) Comparison of $T_1$ maps derived from an MP2RAGE protocol with/without $B_1^*$ correction by a separately acquired flip angle map and MP3RAGE. Adjoining whole brain histograms are also displayed. Residual $B_1^*$ bias in MP2RAGE without correction is evident. Higher $T_1$ estimates of MP3RAGE, particularly in WM, compared to MP2RAGE can also be observed.
saturated, whereas for MP2RAGE the magnetization is almost fully relaxed prior to inversion. Thus, the absolute error in modeling the inverted $M_z$ will be considerably less in MP3RAGE compared to MP2RAGE. Indeed, the WM $T_1$ estimates reported here (Table 1) are in good agreement with the 1349 ms of the long component reported by Rioux et al.\textsuperscript{25} Our estimates were generally in the upper range of values reported for $7T$\textsuperscript{1,26–29} or somewhat longer. These longer $T_1$ estimates in WM were confirmed by an IR-EPI experiment that excluded TIs below 200 ms, beyond which relaxation can safely be considered monoexponential.\textsuperscript{17} The discrepancy between $T_1$ estimates from MP2RAGE and MP3RAGE was verified experimentally, and the increase in $T_1$ compared to MP2RAGE was indeed stronger in WM than in GM (12\% vs. 3.3\%) (Figure 8). Further, applying $f_{inv} = 0.87$ instead of $f_{inv} = 0.96$ in MP3RAGE (Supporting Information Figure S1) yielded a much smaller increase in $T_1$ compared to MP2RAGE, which after this adjustment produced WM $T_1$ estimates closer to those obtained using other techniques (data not shown). Although $f_{inv} = 0.87$ was obtained for a weakly saturated $M_z$, and thus not entirely representative for MP3RAGE, it is still likely a better estimate than $f_{inv} = 0.96$ and should be used in future experiments for improved accuracy.

In our preliminary report,\textsuperscript{5} we showed the existence of a unique solution in 2D parameter space. Thus, forward modeling and a 2D search would remove the prerequisite of attaining a driven equilibrium at very low $B_0^+$ (imposed by the analytical inversion). This is also expected to restore experimental flexibility beyond the specific protocol described here.

6 | CONCLUSION

Whole brain maps of $T_1$ and $B_0^+$ can be obtained from a single MP3RAGE experiment. By forcing the spin system into a $T_1$-w driven equilibrium before inversion, the MP2RAGE sequence is effectively merged with a DFA protocol. This allows to solve for $T_1$ and $B_0^+$ analytically, without employing forward modeling. The inherently co-registered maps are acquired at the high resolution associated by MP3RAGE.

CONFLICT OF INTEREST

Mads Andersen is employed as a Clinical Physicist by Philips Healthcare, Copenhagen, Denmark.

DATA AVAILABILITY STATEMENT

The data acquired for this paper, as well as the standard 1 mm3 MP3RAGE examcard protocol, is freely available at https://osf.io/rn4gk/. A MatLab R2020b (MathWorks) script that can be used for calculation of the $T_1$ and $B_0^+$ map is available at https://github.com/OlssonHampus/MP3RAGE.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

**FIGURE S1** Difference in estimated parameter maps when assuming either $f_{inv} = 0.87$ or $f_{inv} = 0.96$. Using a lower of $f_{inv} = 0.87$ resulted in higher $T_1$ estimates reflected in the relative difference $(100 \times (T_1(f_{inv} = 0.87) - T_1(f_{inv} = 0.96))/T_1(f_{inv} = 0.96))$ map (A) and the whole brain histograms (B). The difference was higher in low $B_1^+$ areas. The difference in the estimated $B_1^+$ maps $(100 \times (T_1(f_{inv} = 0.87) - T_1(f_{inv} = 0.96)))$ were virtually null (C, D)

**FIGURE S2** Simulated bias in the $T_1$ and $B_1^+$ estimates ($T_1,est$ and $f_{T,est}$) and its dependency on the true $T_1$ and $B_1^+$ ($T_1,true$ and $f_{T,true}$). The black lines denote where the bias exceed +3%.

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