Phase-based fast 3D high-resolution quantitative T₂ MRI in 7 T human brain imaging

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Magnetic resonance imaging (MRI) is a powerful and versatile technique that offers a range of physiological, diagnostic, structural, and functional measurements. One of the most widely used basic contrasts in MRI diagnostics is transverse relaxation time (T₂)-weighted imaging, but it provides only qualitative information. Realizing quantitative high-resolution T₂ mapping is imperative for the development of personalized medicine, as it can enable the characterization of diseases progression. While ultra-high-field (≥ 7 T) MRI offers the means to gain new insights by increasing the spatial resolution, implementing fast quantitative T₂ mapping cannot be achieved without overcoming the increased power deposition and radio frequency (RF) field inhomogeneity at ultra-high-fields. A recent study has demonstrated a new phase-based T₂ mapping approach based on fast steady-state acquisitions. We extend this new approach to ultra-high field MRI, achieving quantitative high-resolution 3D T₂ mapping at 7 T while addressing RF field inhomogeneity and utilizing low flip angle pulses; overcoming two main ultra-high-field challenges. The method is based on controlling the coherent transverse magnetization in a steady-state gradient echo acquisition; achieved by utilizing low flip angles, a specific phase increment for the RF pulses, and short repetition times. This approach simultaneously extracts both T₂ and RF field maps from the phase of the signal. Prior to in vivo experiments, the method was assessed using a 3D head-shaped phantom that was designed to model the RF field distribution in the brain. Our approach delivers fast 3D whole brain images with submillimeter resolution without requiring special hardware, such as multi-channel transmit coil, thus promoting high usability of the ultra-high field MRI in clinical practice.
which are simultaneous multi-parametric acquisitions as well as a design for $T_1$ and $T_2$ weighted images in highly inhomogeneous static magnetic fields. These include DESPOT and phase-cycled balanced steady-state free precession (bSSFP). A method called TESS shows promising results for $T_2$ mapping without RF field dependence, however, currently it was demonstrated only as a 2D implementation for brain imaging. Finally, a method analyzing the complex signal of a set of unbalanced GRE scans at 7 T gave $T_1$ and $T_2$ maps, but included a long total scan duration and used parallel transmission to mitigate the transmit field inhomogeneity.

Recently, a new method was introduced based on a steady-state spoiled gradient-echo (SGRE) acquisition that utilizes low flip angles and short repetition times (TRs) to obtain $T_2$ maps at 3 T MRI, assuming a uniform and a priori known flip angle. While most of the GRE-based studies have focused on magnitude images, in this study, phase information was highlighted, which offers a new and attractive method for $T_2$ mapping.

Building on this work we elucidate the dependence of the phase-based method on the (unknown) excitation flip angle in addition to the RF pulse phase, with an eye to design an approach suited for $T_2$ mapping of the brain at 7 T. This new extension to the steady state method includes both $T_2$ and RF field estimation and is designed to cover the relevant flip angle range arising in the brain due to the RF field inhomogeneity at 7 T MRI (see Fig. 1).

The advantage of this approach is its ability to simplify the signal dependencies and reduce the confounding variables. This includes the removal of the static magnetic field ($B_0$) dependence and a reduced dependence on the longitudinal relaxation time ($T_1$).

Building on the phase-based approach by Wang, which departs from the traditional concepts based on spin-echo, our extension introduces a new $T_2$ mapping solution for ultra-high field MRI. This method can deliver quantitative $T_2$ mapping at 7 T MRI without requiring any additional hardware—such as dielectric pads or multi-channel transmit coil—to reduce the RF field inhomogeneity. Another advantage of this method is that it enables whole-brain imaging with high acceleration factors, as it relies on a 3D k-space acquisition.

Our study comprised three main steps (Fig. 1). First, we conducted Bloch simulations of the generated steady state signal for different scan parameters (such as RF flip angle, RF phase, and TR). Then, we looked for parameter combinations that support the range of flip angles, due to the RF field inhomogeneity, in 7 T brain imaging. Next, we developed and assessed an efficient estimation algorithm. Lastly, we performed human brain imaging on a 7 T MRI scanner. The estimation algorithm was assessed on synthetic signals from the Bloch simulations, as well as on actual measurements, in a realistic setting, via a 3D head-shaped phantom, which was designed to model the RF field distribution in the brain. For both the head-shaped phantom and the human brain imaging the phase-based method was compared with the gold-standard single-echo spin echo (SE–SE). Furthermore, we used the phase-based method to acquire whole-brain $T_2$ maps with sub-millimeter resolution.

Figure 1. Schematics of the steady state method for $T_2$ and RF field estimation—its design and verification. Starting from simulations, through assessment of the estimation algorithm, via a 3D head-shaped brain-like phantom, to human imaging. Left—a design of a steady-state configuration based on Bloch simulations that provides $\theta(T_2, \alpha)$ for specific $\varphi_{inc}$ which was thereafter utilized to generate $T_1$ and $\alpha$ in the 2D space $(\theta_1, \theta_2)$. The new space allows to extract $T_1$ and $\alpha$ from $\theta_1$ and $\theta_2$. Center—the estimation algorithm was assessed via simulations and brain-like phantom measurements. In these measurements, a realistic signal $S$ was acquired, providing $|S|$ and $\angle S$, from which the $T_2$ and $\alpha$ (or $B_1$ distribution) were estimated. Right—human imaging at 7 T MRI provided high-resolution whole-brain $T_2$ maps, while coping with the $B_1$ distribution.
Principles of the modified-SGRE sequence for simultaneous $T_2$ and RF field mapping. The foundation for using phase increments during the RF pulse train was provided by Zur et al. in 1988 [31,32]. They showed that an RF pulse train with a quadratic phase $\phi_{RF}(n) = \phi_{inc} \cdot (n^2 + n)/2$ for the $n$-th pulse—using an appropriate $\phi_{inc}$ value in conjunction with a spoiling gradient—can achieve incoherent transverse magnetization, an effective spoiling better than simple gradient spoiling ($\phi_{inc} = 0$ case). This is commonly called RF spoiling. Recent work by Wang [27] at 3 T provided another keystone, in which the authors showed that small $\phi_{inc}$ values have the opposite effect; they introduce coherent transverse magnetization, where the phase of the signal possesses a strong dependence on $T_2$ (Fig. 2a).

In our study, however, the combined $(T_2, \alpha)$ dependence of the signal’s phase $\theta$ was exploited to cope with the RF field inhomogeneity at ultra-high field MRI. Neglecting, for now, the small $T_1$ dependence of the phase—for $T_1$ values relevant to brain tissues at 7 T, see Fig. 2a—the phase $\theta$ of the signal depends on the $T_2$ at the voxel and on the actual flip angle $\alpha$ there. This $\alpha$ is the target flip angle of the scan $\alpha_{scan}$ scaled by the RF field ratio at each voxel: $\alpha = \alpha_{scan} \cdot RF_{ratio}$, where $RF_{ratio}$ is the normalized RF field distribution. As the phase $\theta(T_2, \alpha)$ (see Fig. 2a) is not a one-to-one map of $(T_2, \alpha)$ to $\theta$, at least two measurements, $\theta_1$ and $\theta_2$, are needed; thus defining a 2D space $(\theta_1, \theta_2)$. To extract $T_2$ and $\alpha$ from $\theta(T_2, \alpha)$, we need a convenient 2D space to represent $T_2$ and $\alpha$ in each voxel. Based on the Bloch simulations, such a 2D space can be generated by two scans with two flip angles, $\alpha_{scan1}$ and $\alpha_{scan2} = RFA \cdot \alpha_{scan1}$ (RFA is a user set multiplication factor; for example, $RFA = 2$). Furthermore, we found that varying $\phi_{inc}$ between the two scans—one scan with $(\phi_{inc1}, \alpha_{scan1})$ and a second with $(\phi_{inc2}, RFA \cdot \alpha_{scan1})$—provides greater flexibility in controlling the 2D $(\theta_1, \theta_2)$ space and its mapping to $(T_2, \alpha)$. Figure 2b shows that different combinations of phase increment and flip angle pairs can be useful to adjust the range of viable flip angles and the $T_2$ of interest.

The two phase measurements, $\theta_1$ for scan parameters $(\phi_{inc1}, \alpha_{scan1})$ and $\theta_2$ for scan parameters $(\phi_{inc2}, \alpha_{scan2})$, are functions of $\phi_{inc1}$, $\phi_{inc2}$, $T_2$, and the (actual) flip angles, i.e., $\theta_1 = \theta(\phi_{inc1}, \alpha_{scan1}, T_2)$ and $\theta_2 = \theta(\phi_{inc2}, \alpha_{scan2}, T_2)$, where $\alpha_1$ and $\alpha_2$ are the actual flip angles. Although $\alpha_1$ and $\alpha_2$ are unknown, their ratio must obey $\alpha_2/\alpha_1 = \alpha_{scan2}/\alpha_{scan1} = RFA$. Thus, renaming $\alpha_2$ as $\alpha$, we have $\theta_1 = \theta(\phi_{inc1}, \alpha_{scan1}, T_2)$ and $\theta_2 = \theta(\phi_{inc2}, RFA \cdot \alpha_{scan1}, T_2)$, or in a shorthand notation $\theta_1 = \theta_1(\alpha, T_2)$ and $\theta_2 = \theta_2(\alpha, T_2)$, where the functions $\theta_1()$ and $\theta_2()$ contain the known $\phi_{inc1}$, $\phi_{inc2}$, and $RFA$ parameters. One can now map $T_2$ and $\alpha$ to the new $(\theta_1, \theta_2)$ 2D space, written as $T_2(\theta_1, \theta_2)$ and $\alpha(\theta_1, \theta_2)$. Figure 2b shows that equi-$T_2$ and equi-$\alpha$ lines are nearly orthogonal, when we are well inside the “balloon” (the support region), which is an indication of the robust estimation for a given set of $(\theta_1, \theta_2)$ there. At the “balloon” edges of low or high $\alpha$ values the solution is ill-posed and can provide more than one solution, thus increasing the variability and
of 10 ms provided a practical tradeoff. Our examination of the effect of the RFA on the flip angle range showed be made by balancing between SAR limitations, on the one hand, and scan duration, on the other hand. A TR -(Fig. S4a). As the change in relative variability as a function of TR (Fig. S4b) is insignificant, the choice of TR can 30 < T2 < 50 ms and 5° < α < 17°, and both the minimal and maximal flip angles that provide std(T2 includes four scans: the two scans (φinc1, αscan1) and (φinc2, αscan2) and their repetition with a negative phase incre- of the “balloon” (Fig. 2b), a region where interpolation is an ill-posed problem. Low flip angles tional step was established for low flip angles because low flip angles result in (θ 1,θ2) measurement pairs close (2.4–35°), in practice, φinc1 = 1° generates a high CSF signal. This can result in an extra signal and a residual artifact important to explore and characterize optimal choices of flip angles and φinc to achieve minimal variability and bias. Figure 2b shows that the set (φinc1 = 3°, αscan1) and (φinc2 = 1.5°, αscan2 = 2αscan1) covers a larger flip-angle range than set (φinc1 = 2°, αscan1) and (φinc2 = 2°, αscan2 = 2αscan1). We performed a detailed analysis to determine the optimal regime for whole-brain imaging, the results of which are summarized in Fig. S1–S4.

Variability and bias evaluation + SAR considerations. We examined the variability and bias of the method in the range of flip angles relevant for brain imaging. To do so, noise was added to the simulated signal and the variability and bias of the method were examined as a function of T2 and α. The noise in the simulations was calibrated so the resulting synthetic signal to noise ratio (SNR) matched the measured SNR in agar tubes for the same α and T2, where the agar T2 was in a range matching white matter (WM) and gray matter (GM) at 7718. The signal dependence on flip angle and phase increment showed that the phase of the signal is high for low φinc (φinc < 10°) (Fig. S1). It can be seen that the combination (φinc1 = 3°, αscan1) and (φinc2 = 1.5°, αscan2 = 2αscan1) provides a lower variability (i.e., lower std(T2est)) and a smaller bias (i.e., lower |ave(T2est) − T2true|) for a larger range of flip angles (Fig. S2). We also examined three criteria (Fig. S3): the average estimation variability for 30 < T2 < 50 ms and 5° < α < 17°, and both the minimal and maximal flip angles that provide std(T2est) < 5 ms. The result of a combined minimization of the three criteria (shown in Fig. S3d) is a pair of scans with (φinc1 = 3°, αscan1) and (φinc2 = 1.5°, αscan2 = 2αscan1) that provides a good combination of the lowest average std(T2est) and supports a flip angle range of 3.7–35° (in which std(T2est) < 5 ms).

Figure S4 shows three additional aspects that were included to establish the final configuration, including the repetition time (TR), the RFA in a realistic experiment and reduction of the cerebrospinal fluid (CSF) signal. Although the combination (φinc1 = 3°, αscan1) and (φinc2 = 1°, αscan2 = 2αscan1) provides a better flip angle range (2.4–35°), in practice, φinc1 = 1° generates a high CSF signal. This can result in an extra signal and a residual artifact in the proximity of the ventricles. To reduce the CSF signal’s effect, it was found worthwhile to use φinc2 = 1.5° (Fig. S4a). As the change in relative variability as a function of TR (Fig. S4b) is insignificant, the choice of TR can be made by balancing between SAR limitations, on the one hand, and scan duration, on the other hand. A TR of 10 ms provided a practical tradeoff. Our examination of the effect of the RFA on the flip angle range showed that the higher the RFA, the better (Fig. S4c). However, to keep SAR within the “Normal” level, it was found that RFA in the range of 1.6–2 (with TR = 10 ms) provides a suitable flip angle range. In case of adopting “First level” SAR limit, one can increase the range of the flip angles.

Global phase corrections. In practice, the phase (∠S) of the signal S at a voxel is comprised of the steady-state phase θ(α, T2, T1) plus a global phase θ0. The global phase θ0 arises from several factors, with a dominant contribution from B0. It can be eliminated by repeating the scan twice, once with φinc and once with −φinc, and setting θ(α, T2, T1) = (∠Sφ+ − ∠Sφ−) / 2 (as was shown in Ref. 27). The implemented acquisition thus includes four scans: the two scans (φinc1, αscan1) and (φinc2, αscan2) and their repetition with a negative phase incre-ment to remove θ0. Calculating the θ1 and θ2 in this method does not result in phase wrapping, since after the global phase removal, the signals’ phase is in the range of 0° to 50°.

Estimation algorithm. The actual estimation algorithm included two main steps, per voxel, namely the removal of the global phase (θ0) and an estimation of T2 and α from (θ1, θ2) using linear interpolation. An additional step was established for low flip angles because low flip angles result in (θ1, θ2) measurement pairs close to the edges of the “balloon” (Fig. 2b), a region where interpolation is an ill-posed problem. Low flip angles are relevant for whole-brain imaging because despite the flip angle of the first scan being set to αscan1 = 15°, the are typically reached are the cerebellum, midbrain, and brainstem, as well as some regions in the temporal lobe. The added step to handle low flip angles takes advantage of two aspects: i) that α changes slowly in space, and ii) that for small flip angles (α < 20°) the phase

T2 corrections. As mentioned, phase dependence on T1 is small, but it can account for ~15% of the final T2 estima- tion. To reduce the error due to T1 in human imaging voxels were classified as either “high” or “low” T1 by empirically thresholding |Sscan1| / |Sscan2| . Separate maps—T2(θ1, θ2) and α(θ1, θ2)—were used for each clas-sification, based on T1 = 1 s (representing WM) and T1 = 2 s (the rest). With this correction, the error was further reduced (shown in Fig. S6). A detailed description of the algorithm is provided in the “Materials and methods” section.

Results

To examine the estimation bias and estimation variability we conducted two imaging experiments with phantoms, one with tubes filled with agarose suspension, the other with a 3D head-shaped phantom. In the first experiment (Fig. 3a), the variability was ×1.4 smaller than with SE–SE (0.5 ms compared to 0.7 ms). The a_{slope} and the relative deviation error (see Eq. 1) calculated between the T2 from this method and the T2 from SE–SE were 1.01 and
0.5%. Thus, the phase-based method provides a small bias and a lower variability compared to SE–SE, while the scan duration is ×2.3 faster.

In the second experiment, a specially designed 3D head-shaped brain-like phantom was used to examine the capability to cope with an RF field distribution similar to that in the brain. The “brain” had a uniform $T_2$, which helped to separate the two parameters we sought to estimate, $\alpha$ and $T_2$. Our results show low variability in $T_2$ ($\text{std}(T_2 \text{ phase-based-method}) / \text{std}(T_2 \text{ SE–SE}) = 0.46$) and an RF field map estimation with little bias (a 4% average deviation from the map acquired with the vendor’s pulse sequence), see Fig. 3b. Even low flip angles, in the ill-posed area of the “balloon”, were well determined using the implemented estimation algorithm (Fig. S8).

The contribution of the $B_1$ correction to the $T_2$ estimate can be seen in Fig. 4. It compares $T_2$ maps extracted from a set of four scans (two pairs) to $T_2$ maps extracted from a single pair—as in Ref. 27—using either of the pairs (either pair 1: $\phi_{\text{inc}1} = 3^\circ$ and $\phi_{\text{inc}1} = -3^\circ$, with $\alpha_{\text{scan}1}$; or pair 2: $\phi_{\text{inc}2} = 1.5^\circ$ and $\phi_{\text{inc}2} = -1.5^\circ$, with $\alpha_{\text{scan}2}$). It can be seen that for both phase increments the RF field inhomogeneity results in either underestimated or overestimated $T_2$ values, depending on the actual flip angle in each voxel (see Fig. 2a for phase dependence on flip angle). The 4-scans result, which combines both phase increments, provides a uniform $T_2$ map of the “brain” tissue in the 3D-head shaped phantom, as expected by the design.

Figure 4 also shows the estimated $T_2$ maps, for human imaging, based on either 4-scans or a single scan-pair. Although more challenging to observe, due to the heterogeneous $T_2$ distribution in the brain and to the very high $T_2$ values in the CSF regions, it can also be seen that $T_2$ estimated from a single pair, is either underestimated or overestimated compared to 4-scans. This can be observed, for example, in regions such as the cerebellum and the temporal lobes. Table 1 summarizes the results by giving sample $T_2$ values in white matter, grey matter and CSF. For each tissue 2 sampled regions were chosen as shown in Fig. 4—WM1 and WM2 in white matter tissue, GM1 and GM2 in the grey matter tissue and CSF1, CSF2 in the CSF. The table also shows $T_2$ values reported in Ref. 18. Note: the CSF values are underestimated with the current method, as further elaborated in the Discussion section.

Continuing with human imaging, Fig. 5 compares the phase-based method with 1.5 mm isotropic voxels to the gold standard SE–SE, for a $T_2$ mapping comparison, and to the vendor RF mapping, for an RF field mapping comparison. The map in Fig. 5c was smoothed by $3 \times 3$ filter to reduce the effect of local CSF signals (see Fig. S13 for original high resolution $B_1$ map). The RF field map extracted with the phase-based approach shows a distribution similar to the separately acquired vendor map with, however, noticeable deviations in the ventricles, as well as in some of the CSF region. The ratio of the $T_2$ values and the relative deviation error between the phase-based method and SE–SE is shown in Fig. 6, for the different volunteers. Over all volunteers the $T_2$ ratio
Finally, high-resolution whole-brain $T_2$ mapping was performed with the phase-based method, with 1 mm and 0.85 mm isotropic voxels. To acquire whole-brain high-resolution images, $\times 5.11$ acceleration was used—combining elliptic sampling and $\times 2$ acceleration in both phase encoding directions. Each of the four scans with 1 mm resolution was 1:13 min giving a total scan time of 4:52 min. For 0.85 mm each scan was 1:42 min long and the total scan time was 6:48 min. Figure 7 shows the estimated $T_2$ maps for the 0.85 mm scan (Fig. S12)

**Table 1.** Estimated $T_2$ in sample regions of white matter, grey matter and CSF (see Fig. 4).

| Region | Single pair $(\phi_{inc1}, \alpha_{scan1})$ | Single pair $(\phi_{inc2}, \alpha_{scan2})$ | 4-scans | From Ref.18 |
|--------|---------------------------------|---------------------------------|---------|-------------|
| WM1    | 19.00 ± 0.86                    | 40.02 ± 2.34                    | 28.83 ± 1.47 | 33.7 ± 0.7   |
| WM2    | 16.28 ± 1.21                    | 37.84 ± 4.04                    | 26.74 ± 2.49 | 49.2 ± 3.8   |
| GM1    | 30.02 ± 5.77                    | 60.67 ± 14.52                   | 45.05 ± 10.23 | 49.2 ± 3.8   |
| GM2    | 25.37 ± 3.10                    | 59.05 ± 14.97                   | 41.95 ± 9.52  | 49.2 ± 3.8   |
| CSF1   | 341.93 ± 105.73                 | 447.95 ± 31.76                  | 422.75 ± 33.30 | 408.35 ± 15.73 |
| CSF2   | 280.25 ± 3.10                   | 436.36 ± 14.64                  | 408.35 ± 15.73 | 408.35 ± 15.73 |

($T_2$ phase-based method/$T_2$ SE–SE) and relative deviation error are 0.80 and 15.45% for WM, and 0.85 and 19.76% for GM (detailed description is in Supplementary Information S4).
shows the 1 mm resolution images). To provide even higher robustness following the reduced SNR of the high-resolution datasets, we also incorporated denoising based on a DnCNN deep-learning network (provided in MATLAB, The Mathworks, Natick MA, for Gaussian noise removal). This entailed denoising of $\theta_1$ and $\theta_2$ before the estimation of $T_2$. The denoising greatly improved the observed details of the cerebellum structure, a region with especially low flip angles (Fig. 7b).

Figure 5. Human imaging—$T_2$ from the phase-based method or SE–SE, and $\alpha$ from the phase-based method or the vendor’s scan. (a) SE–SE Sagittal magnitude image at $TE = 30$ ms and the estimated $T_2$ maps in three main cross-sections. (b) An $\alpha$ map using the vendor’s pulse sequence. (c) Sagittal magnitude image with $\phi_{inc} = 3$ and $\alpha = 15^\circ$, as well as the estimated $T_2$ and $\alpha$ maps in three main cross-sections. $\alpha$ map shown here was smoothed by a $3 \times 3$ filter to reduce the effect of local CSF signal. Orange arrows point to the cerebellum and brainstem regions suffering from low flip angles due to $B_1$ inhomogeneity; their inner structure is much more pronounced—and clearly visible—in the phase-based $T_2$ images. Purple arrows point to a region in the CSF that resulted in a low magnitude signal.

Figure 6. Comparison of $T_2$ estimation between the phase-based method and SE–SE. The plot shows the ratio $T_2$ phase-based method/$T_2$ SE–SE per volunteer, both for WM and for GM. The error bars depict the relative deviation error [see Eq. (1)].
Discussion

The expected rewards of pushing the limits and moving to 7 T MRI are increased spatial resolution and shorter scan durations. Both these features are essential for clinical and research imaging, all the more so for quantitative methods. However, scanning at 7 T also poses new challenges, including high power deposition and severe RF field inhomogeneity. The extended phase-based method shown here delivers high-resolution brain $T_2$ imaging while overcoming the above challenges. This is achieved by relying on a modified 3D SGRE sequence, using the phase of the signal to encode the $T_2$ dependence. The 3D SGRE images are also highly robust to $B_0$ inhomogeneity. This can be seen in the magnitude images of both the phantom example (Fig. 3a) and the human images (Fig. 5). The SE–SE is more distorted both at the edges of the agar tubes and near the nasal areas in the human images. The $B_0$-dependent phase is reliably canceled out by the two scans with opposite phase increments ($\phi_{inc}$) of the RF pulse train. However, shifts in the global phase between scans may occur, which will require corrections. Similarly, the scans may be sensitive to movements, which will affect the phase. Incorporating a second echo acquisition could be used to correct for both the phase shifts and motion34. Aiming to shorten the total scan duration, one can also consider estimation of the global phase from a single pair, thus reducing the number of scans to three. However, in this case careful analysis and phase unwrapping will be required in the third, non-paired, scan. Incorporating a second echo acquisition could be used to correct for both the phase shifts and motion34. Aiming to shorten the total scan duration, one can also consider estimation of the global phase from a single pair, thus reducing the number of scans to three. However, in this case careful analysis and phase unwrapping will be required in the third, non-paired, scan. Incorporating a second echo acquisition could be used to correct for both the phase shifts and motion34. Aiming to shorten the total scan duration, one can also consider estimation of the global phase from a single pair, thus reducing the number of scans to three. However, in this case careful analysis and phase unwrapping will be required in the third, non-paired, scan.

The current implementation used a non-selective hard pulse for the 3D acquisition. Although this works well for whole brain acquisition as in this study, in other cases it can be a limitation. For faster acquisition and to limit potential aliasing, the use of slab-selective pulses is beneficial. Figure S9 shows that as long as the slab is thick enough, compared to the slice thickness, the estimated $T_2$ is correctly estimated. However, for a single slice-selective acquisition, the estimation by which the $T_2$ and RF field maps are estimated must also account for the slice profile. This was already demonstrated in other $T_2$ mapping methods such as balanced SSFP19.

Another sensitivity of the method that requires discussion is the sensitivity to movement and potential inaccuracy in the RF pulse phase. Although we did not observe noticeable movement in our human scanning, a simulation to examine these vulnerabilities was performed (see Supplementary Information, Section S5). The movement was simulated assuming a constant velocity during the scan, which will result in an additional parabolic phase term accumulated during the scan. Examining the error due to potential head movement of 1–2 voxels during the scan, it resulted in a small error, less than 1% for a movement of up to 5 mm/min. However,
for large movement within a voxel, such as due to flow, the error of the estimated $T_2$ can be significant; reaching 20%, for a velocity of 0.5 mm/s.

Two simulations were also performed to analyze possible hardware inaccuracies: (i) a constant error in the actual RF-phase increment, (ii) a randomly distributed error in the actual phase of the RF pulse. In the first case, a constant error of 0.1° resulted in <4% error. In the second, a randomly distributed error with $\sigma = 0.2°$ resulted in a negligible error with standard deviation of 0.07 ms in the estimated $T_2$. It is also important to note that the estimation of the $T_2$ in the CSF and other tissues with high $T_2$ values (> 0.5 s) is challenging with this method, since the signal's phase curve slowly converges for $T_2 > 100$ ms (see Fig. 2a) and so the $T_2$ contours in the ($\theta_1, \theta_2$) space grow denser with $T_2$ (see Fig. 2b). In addition, local intensity drops in CSF voxels, resulting in low SNR voxels, can occur due to fluid movement (purple arrows in Fig. 5 point to such area), thus further limiting $T_2$ estimation of CSF.

The important advantage of the phase-based approach for $T_2$ mapping is its whole-brain coverage ability. The method shows robust results in the brainstem region and even in parts of the spinal cord (see Fig. 5). These results are achieved without the need for additional hardware to reduce the RF field inhomogeneity, such as dielectric pads or multi-channel transmit coil. Naturally, the method can also benefit from a dielectric pad or multi-channel transmit coils to improve the SNR, especially in regions with low flip angles. The current configuration ($\phi_{\text{scan}1}$, $\phi_{\text{scan}2}$, $\alpha_{\text{scan}1}$, $\alpha_{\text{scan}2}$, $\alpha_s$) was designed for the RF field distribution in the brain, and was shown to robustly extract the RF field distribution in the 3D head-shaped phantom (which has a slightly larger RF field inhomogeneity than in vivo). If another region will be of interest, the configuration—the RF pulse phase increments and the scan RF field distribution in the 3D head-shaped phantom (which has a slightly larger RF field inhomogeneity than in vivo)—can be adapted accordingly.

It is worth noting that $\theta_1$, on its own, calculated from the first pair of scans (with $\phi_{\text{scan}1}=\pm 3°$), achieves a "$T_2$ weighted" image (see Fig. S10 for the 0.85 mm case), unlike the magnitude of these scans. $\theta_1$, however, suffers from pronounced RF field inhomogeneity, which is removed by using two sets of scans (giving $\theta_1$ and $\theta_2$), as was implemented here, allowing the generation of $T_2$ maps.

In our study, the estimation algorithm is based on an interpolation procedure, where the simulated data serves as the ground-truth. This method is similar to the dictionary-based approach in MRF, but is based on two measurement points ($\theta_1$, $\theta_2$) that allow us to represent the parameters of interest, $T_2$ and $\alpha$ in the ($\theta_1$, $\theta_2$) 2D space. This offers the advantage of mapping the $T_2$ of interest by a simple linear interpolation. An improvement in the estimation algorithm was implemented in the low flip angles' range, which extended the viable flip angles (Figs. S5 and S8). In this study, we demonstrated the low variability and small bias of the estimations in both simulations and phantom experiments. In the phantom experiment with agar tubes, the method provides $T_2$ estimation with low variability—a × 3.2 (1.4 × 2.3) lower variability-to-scan-time factor than that of SE–SE. The $T_2$ values were estimated by the phase-based method with a small bias ($a_{\text{bias}} = 1.01$ and relative deviation error of 0.5% compared to SE–SE).

However, the in-vivo $T_2$ ratio of the phase-based method to SE–SE was 0.79 ± 0.16 for WM and 0.86 ± 0.19 for GM. Similarly, there is a ratio of 0.82 and 0.88 between the reported values with 4-scans in Table 1 to the values in Ref. 18. This result is also similar to the results in Ref. 22,24. Possible reasons for the different ratios found for WM and GM are a partial volume of GM and CSF as well as deviations due to $T_2$. Although $T_2$ has a small impact on the phase of the signal and its effect was reduced in our implementation. The ~0.8 ratio between the $T_2$ estimated by the phase-based approach and by SE–SE could arise for several reasons, among which are a contribution due to exchange and magnetization transfer, diffusion, and different contributions of the fast and slow $T_2$ components to the two methods.'
Materials and methods

Bloch simulations. 1D single voxel simulations based on the Bloch equations were performed with a custom MATLAB (The Mathworks, Natick MA) code to examine the signal in steady state. The simulations included an excitation pulse, an acquisition and a net total spoiler (including the area of the acquisition) of 3/Δx (Δx the 1D voxel size). The number of initial repetitions to reach steady-state (“dummy scans”) was set to 500, which was verified to provide reliable steady states. Following the dummy scans, a single acquisition was simulated. The simulation was repeated over a grid of flip angles and T2 values, for different values of T1, φinc, and TR. The grid covered T2 from 0 to 200 ms with a resolution of 4 ms, and flip angles from 0° to 70° with a resolution of 1°. The resulting θ(T2, α) map was interpolated prior to its use in the estimation algorithm with 1 ms in T2 and 0.1° in alpha, generating θ1(T2, α) and θ2(T2, α) for relevant φinc and RFA factors.

Estimation algorithm. The estimation algorithm included the following steps:

Preparatory step #0.1: global phase removal. In practice, the phase (∠S) of the signal S at a voxel is comprised of the steady-state phase θ0, plus a global phase θg. The global phase θg arises from several factors, with a dominant contribution from B0. It can be eliminated by repeating the scan twice, once with +φinc and once with -φinc, and setting θ(α,T2,T1) = ∠(S+φinc · conj(S−φinc))/2 (as was shown in Ref.25). The implemented acquisition thus includes four scans: the two scans (φinc1, αscan1) and (φinc2, αscan2), and their repetition with a negative phase increment to remove θ0.

Preparatory step #0.2 (optional): denoising. For high-resolution human imaging, a denoising procedure based on a DnCNN deep-learning network (provided in MATLAB 2021a, for Gaussian noise removal) was incorporated. The denoising procedure was implemented on the measured θ1, θ2 with the command denoised_θ1 = denoiselmage(θ1, net), where the net was set by the command net = denoisingNetwork(dncnn).

Estimation step #1: T2 and α estimation by interpolation. First, using Matlab’s scatteredInterpolant(), we generated two interpolants, T2(θ1, θ2) and α(θ1, θ2), which map (θ1, θ2) to the desired quantities T2 and α. These interpolants were then used to estimate T2 and α from any (θ1, θ2) pair, at each voxel.

As mentioned, phase dependence on T1 is small, but it can account for ~15% of the final T2 estimation. Thus, in human imaging, to reduce the error due to T1, voxels were classified as either “high” or “low” T1 by empirically thresholding |Sscan1|/|Sscan2| (Δx the 1D voxel size). Separate maps—T2(θ1, θ2) and α(θ1, θ2)—were used for each classification, based on T1 = 1 s (representing white matter—WM) and T1 = 2 s (the rest). With this correction, the error was further reduced (see simulation results in Fig. S6).

Estimation step #2: T2 estimation update for low flip angles. First, the flip angles α found in the previous step were smoothed, generating αsmoothed. For low flip angle voxels with αsmoothed < 4.5°, the flip angles were temporarily set to αtemp = 4.5°, and the matching temporary T2 quantities, T2-temp, were found by interpolation—using αtemp and θ (the phase from the scan using the higher flip angle, αscan2 = RFA · αscan1). The final T2 was found through the linear connection T2 = (αtemp/αsmoothed) ∙ T2-temp.

Estimation step #3: handling of negative θ1 or θ2. For θ1 < 0 (and θ2 > 0), the θ2 from step #1 together with αsmoothed from step #2 were used to estimate T2; using the above simulated θ(T2, α) for the known α. Similarly, for θ1 < 0 (and θ2 > 0), θ1 and αsmoothed were used to estimate T2.

Validation of the estimation algorithm was performed by generating N = 100 noisy repetitions of each point in the simulated datasets of θ1(T2, α) and θ2(T2, α). This was done using a fixed noise which resulted in the SNR varying with T2 and α, depending on the intensity at each point. The noise was fixed to produce an SNR of 180 for the simulated data at T2 = 38 ms and α = 13°; resembling the SNR in the human images acquired with 1.5 mm resolution. The SNR was set as an average SNR over the two signals |Sαscan1| and |Sαscan2|. Separate maps—T2(θ1, θ2) and α(θ1, θ2)—were used for each classification, based on T1 = 1 s (representing white matter—WM) and T1 = 2 s (the rest). With this correction, the error was further reduced (see simulation results in Fig. S6).

Pulse sequence considerations. The sequence is based on a Siemens 3D GRE sequence that was modified to enable control over both the φinc and the gradient spoiler moment. The RF pulse used was a hard pulse. An important aspect to consider is the gradient spoiler moment intensity and its effect on the T2 estimation, as well as on image artifacts (in the form of residual signals from spurious echoes). A set of scans was performed to examine the spoiler effect. The gradient spoiler moment needs to provide complete dephasing inside a voxel, which defines a preferable gradient moment size to be $\Delta t \geq \frac{1}{\Delta r} (\Delta t = \sqrt{(\Delta x^2 + \Delta y^2 + \Delta z^2)})$. We found it useful to add a parameter to the pulse sequence that directly controls the net gradient spoiler moment (after all previous gradients had been rephased). The net spoiler was set to be equally distributed in all three directions, which was found useful in reducing artifacts. However, our experiments also showed that the gradient moment affected the measured phase, and thus the estimated T2. Figure S7a shows this dependence. Phantom experiments were used to calibrate the gradient spoiler moment to provide the T2 estimate closest to that from SE–SE. Accordingly, the gradient moment was set in all experiments to 0.015 [mT/m·sec] in each direction. This moment is expected to
provide dephasing for $\Delta r \lesssim 0.9$ mm. As shown in Fig. S7b, under this moment, the estimated $T_2$ did not change for the voxel sizes tested.

**MRI scanning.** All scans in this study were performed on a 7 T MRI system (MAGNETOM Terra, Siemens Healthcare, Erlangen) using a commercial 1T/32Rx head coil (Nova Medical, Wilmington, MA).

When comparing the results of the phase-based method to SE–SE, inside a region, the relative deviation error from the fit was calculated as

$$\text{rel. dev. err.} = 100 \cdot \frac{\sum_{i=1}^{N} \left( T_2^{\text{(phase-based-method)}} - a_{\text{slope}} T_2^{\text{(SE-SE)}} \right)}{N} / \text{ave}(a_{\text{slope}} T_2^{\text{(SE-SE)}})$$

where $a_{\text{slope}}$ is the slope found for each fit, and $N$ is the number of voxels in the comparison.

**Phantom imaging.** Five tubes with agar concentrations of 1.5, 2, 2.5, 3 and 3.5% were used to compare the phase-based $T_2$ estimation to the gold standard SE–SE, using three TE values (10, 30 and 50 ms). A 3D head-shaped phantom that was designed to model the RF field distribution in the brain was used to examine the $T_2$ and RF field estimation. This phantom was originally designed to include three sub-compartments, suitable for mimicking brain, muscle and lipid tissues. However, the version used in this study was filled with two "tissue" types: the inner compartment mimicked the "brain" and the outer one, "muscle" (the planned lipid layer was also filled with "muscle"). Both compartments contained 0.1 mM gadopentetate dimeglumine (GdDTPA), for a $T_1$ close to that of human white matter, and consisted of an agarose suspension of 2.5% and 3% for the "brain" and "muscle" compartments, respectively. NaCl (5.5 gr/L) was used to achieve an in-vivo-like RF field distribution.

For details, see Ref. 30.

$\alpha$ maps from the phase-based method were compared to the equivalent $\alpha$ maps generated by the vendor. As the RF field maps provided by the vendor are scaled to 90°, they were rescaled to the $\alpha_{\text{scan}}$ of the phase-based method, before comparison. The average deviation between the $\alpha$ maps by the phase-based method and by the vendor were calculated in two main planes (Sagittal and Axial).

The common scan parameters for the phase-based method and SE–SE used in the agar-tube experiments in Fig. 3a) were: FOV 200 × 200 × 104 mm$^3$, resolution 1.1 × 1.1 × 2 mm$^3$, acquired matrix size 176 × 176 × 52. The phase-based method specific parameters were ($\phi_{\text{inc}} = 3°$, $\alpha = 15°$) and ($\phi_{\text{inc}} = 1.5°$, $\alpha = 30°$), TR/TE 10/2.2 ms, using 4 scans with a total scan duration of 6.06 min. The specific scan parameters for SE–SE: TR—6500 ms, 3 scans with TE = 10, 30, 50 ms, × 3 in-plane acceleration, with a total scan duration of 19:04 min. The $T_2$ and $\alpha$ maps were estimated based on Bloch simulation with $T_1 = 2$ s.

The common scan parameters for the phase-based method and SE–SE that were used for the 3D head-shaped phantom in Fig. 3b): FOV 220 × 220 × 144 mm$^3$, isotropic resolution of 1.5 mm, bandwidth per pixel 400 Hz. The phase-based method specific parameters were acquired matrix size 150 × 148 × 96, ($\phi_{\text{inc}} = 3°$, $\alpha = 15°$) and ($\phi_{\text{inc}} = 1.5°$, $\alpha = 30°$), TR/TE 10/2.1 ms, using 4 scans with a total scan duration of 9.28 min. The specific scan parameters for SE–SE (Fig. 3c) were: acquired matrix size 144 × 144 × 96, TR—6500 ms, 3 scans with TE = 10, 30, 50 ms, × 3 acceleration, with a total scan duration of 21:12 min. The vendor RF field map scan parameters (Fig. 3d): FOV 220 × 220 × 144 mm$^3$, resolution 2.3 × 2.3 × 4 mm. The $T_2$ and $\alpha$ maps were estimated based on Bloch simulation with $T_1 = 1.5$ s (based on estimated $T_1$ of the "brain" tissue).

**Human imaging.** All methods were carried out in accordance with the Weizmann Institute of Science guidelines and regulations. This study was approved by the Internal Review Board of the Wolfson Medical Center (Holon, Israel) and all scans were performed after obtaining informed suitable written consents. Human guidelines and regulations. This study was approved by the Internal Review Board of the Wolfson Medical Center (Holon, Israel) and all scans were performed after obtaining informed suitable written consents.

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Scan parameters for the phase-based method and SE–SE comparison with isotropic 1.5 mm voxel. Phase-based method: FOV 220 × 220 × 144 mm$^3$, acquired matrix size 150 × 148 × 96, bandwidth per pixel 400 Hz, TR/TE 10/2.1 ms, ($\phi_{\text{inc}} = 3°$, $\alpha_{\text{scan}} = 15°$), ($\phi_{\text{inc}} = 1.5°$, $\alpha_{\text{scan}} = 24–26°$) ($\alpha_{\text{scan}}$ varied from $24°$ to $26°$ according to the specific volunteer’s 100% “Normal” SAR level), with duration of 4 scans—9:28 min. SE–SE: FOV 220 × 220 × 132 mm$^3$, acquired matrix size 144 × 144 × 86, bandwidth per pixel 400 Hz, TR—6500 ms, TE = 10, 30, 50 ms, using 3 scans with a total scan duration of 21:12 min. Vendor RF field map scan parameters: FOV 220 × 220 × 192 mm$^3$, resolution 3 × 3 × 4 mm.

Phase-based method 1 mm resolution parameters. FOV 220 × 220 × 160 mm$^3$, bandwidth per pixel 400 Hz, TR/TE 10/2.7 ms, ($\phi_{\text{inc}} = 3°$, $\alpha_{\text{scan}} = 15°$), ($\phi_{\text{inc}} = 1.5°$, $\alpha_{\text{scan}} = 25°$), duration of 4 scans—4:52 min.

Phase-based method 0.85 mm resolution parameters. FOV 220 × 220 × 163 mm$^3$, bandwidth per pixel 400 Hz, TR/TE 10/2.7 ms, ($\phi_{\text{inc}} = 3°$, $\alpha_{\text{scan}} = 15°$), ($\phi_{\text{inc}} = 1.5°$, $\alpha_{\text{scan}} = 25°$), duration of 4 scans—6:49 min.
Data availability
All scans collected in this study were performed according to procedures approved by the Internal Review Board of the Wolfson Medical Center (Holon, Israel). Since this protocol was not defined as an open repository, the data is not provided, to provide the ethics and privacy issues of clinical data. The code will be made available via a request to the corresponding author.

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**Author contributions**

The theoretical analysis and manuscript drafting were carried out by R.S. and A.S. The data collection and experiment analysis were carried out by R.S.

**Competing interests**

A.S. is employed by Siemens Healthcare Ltd, Israel; all other authors declare no competing financial interests.

**Additional information**

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