Three-dimensional Multi-parameter Mapping of Relaxation Times and Susceptibility Using Partially RF-spoiled Gradient Echo

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Purpose: MR parameter mapping is a technique that obtains distributions of parameters such as relaxation time and proton density (PD) and is starting to be used for disease quantification in clinical diagnoses. Quantitative susceptibility mapping is also promising for the early diagnosis of brain disorders such as degenerative neurological disorders. Therefore, we developed an MR quantitative parameter mapping (QPM) method to map four tissue-related parameters (T1, T2*, PD, and susceptibility) and B1 simultaneously by using a 3D partially RF-spoiled gradient echo (pRSGE). We verified the accuracy and repeatability of QPM in phantom and volunteer experiments.

Methods: Tissue-related parameters are estimated by varying four scan parameters of the 3D pRSGE: flip angle, RF-pulse phase increment, TR and TE, performing multiple image scans, and finding a least-squares fit for an intensity function (which expresses the relationship between the scan parameters and intensity values). The intensity function is analytically complex, but by using a Bloch simulation to create it numerically, the least-squares fitting can be used to estimate the quantitative values. This has the advantage of shortening the image-reconstruction processing time needed to estimate the quantitative values than with methods using pattern matching.

Results: A 1.1-mm isotropic resolution scan covering the whole brain was completed with a scan time of approximately 12 minutes, and the reconstruction time using a GPU was approximately 1 minute. The phantom experiments confirmed that both the accuracy and repeatability of the quantitative values were high. The volunteer scans also confirmed that the accuracy of the quantitative values was comparable to that of conventional methods.

Conclusion: The proposed QPM method can map T1, T2*, PD, susceptibility, and B1 simultaneously within a scan time that can be applied to human subjects.

Keywords: Bloch simulation, multi-parameter mapping, relaxation time, susceptibility

Introduction

MR parameter mapping is a technique that obtains distributions of parameters such as relaxation time and proton density (PD) through MRI, and it is starting to be used for disease quantification in clinical diagnoses. Quantitative susceptibility mapping (QSM) is also promising for the early diagnosis of brain disorders such as degenerative neurological disorders. MRI multi-parameter mapping obtains spatial distributions of tissue-related parameters such as T1, T2, T2*, PD, and susceptibility. In the past, long scan times were required to obtain multiple quantitative maps, mapping each value individually, so these parameter mapping techniques were rarely used clinically. Note that in MRI it is generally difficult to obtain accurate values for any tissue parameter unaffected by the measurement environment; T2 estimated by fast spin-echo (FSE) can be affected by refocusing pulse imperfections and magnetization transfer, T2* is dependent on field inhomogeneity; and PD includes coil sensitivity.

A number of quantitative imaging methods have been proposed that have reduced the scan time to the extent that they can be used in clinical practice. One of the earliest proposed was DSPOT1/2.1 This method uses spoiled gradient echo and a balanced steady-state free precession (SSFP) pulse sequence to obtain 3D maps of T1 and T2 for the human head...
in less than 15 minutes. Later methods were proposed to obtain 2D maps of T1, T2, PD, and a RF field (B1) in even less time. QRAPMASTER is a method for obtaining 2D maps of T1, T2, PD, and B1 using inversion recovery (IR)-FSE. It can scan a whole human brain in as little as 5 minutes with multi-slice scanning. MR Fingerprinting (MRF) is a method for obtaining single slice maps using a balanced SSFP spiral scan. Quantitative values at a normal spatial resolution are estimated using dictionary-based pattern matching from source images with low spatial resolution. It can be said that the quantitative values and the spatial resolution are included in the unknown. Banding artifacts occur with balanced SSFP, so methods using fast imaging with steady-state precession (FISP) for mapping T1, T2, and PD have become mainstream. 3D scanning methods that stack spiral scans have also been published. 3D quantification using an interleaved Look-Locker acquisition sequence with T2 preparation pulse (3D-QALAS) is another method for 3D mapping of T1, T2, and PD. It combines a T2 preparation pulse and inversion recovery pulse to scan images with a high-speed 3D gradient echo. Initially designed for the heart, this method has been extended to brain imaging, and a scan time of 6 minutes for 1.2 mm isotropic voxels has been reported. In general, the more information that can be acquired simultaneously, the wider the range of clinical applications that can be expected, i.e., the more types of maps there are, the more useful they are, and 3D maps are more advantageous than 2D maps. However, there has been no published method for acquiring a B1 map or a susceptibility map simultaneously with other tissue parameters in 3D.

In this paper, we propose a 3D quantitative parameter mapping (QPM) method to simultaneously map four tissue-related parameters (T1, T2*, PD, and susceptibility) and B1, which increases the number of map types compared with previous methods. A partially RF-spoiled gradient echo (pRSGE) with multi-echo acquisition is used to improve the efficiency of 3D acquisition. The quantitative value reflecting the transverse relaxation obtained in this method is T2* rather than T2 because pRSGE affects the transverse magnetization during a scan. Instead of T2, which is obtained in many conventional methods, the gradient multi-echo images are used to obtain the susceptibility, which is difficult to obtain using conventional methods. Furthermore, the gradient multi-echo images can be applied to water-fat separation.

The tissue-related parameters are estimated by taking multiple image scans while varying a set of four scan parameters (flip angle [FA], RF-pulse phase increment [θ], TR, and TE) and finding a least-squares fit for the intensity function, which expresses the relationship between scan parameters and intensity values. Scan parameters are optimized using the law of error propagation to increase the SNR. Estimating quantitative values with the least-squares fit of an intensity function has the advantage of a shorter computation time. However, the intensity function of the pRSGE sequence includes very complex case divisions, so it was previously used only for the estimation of T2, and it has been difficult to generalize for estimating multiple quantitative values. As such, we built a numerical intensity function using a Bloch simulation, enabling us to estimate multiple quantities simultaneously. Phantom and volunteer studies were conducted to clarify the usefulness of QPM, and quantitative and visual evaluations were performed for comparison with the conventional methods.

### Materials and Methods

The estimation of quantitative parameters using QPM consists of the following three procedures.

#### Create intensity function using Bloch simulation

We first use a Bloch simulation to compute echo intensities for a wide range of T1 and T2* for human tissues by varying scan parameters discretely and broadly. We then create an intensity function using third-order linear interpolation. This intensity function only needs to be created once and can then be used for any QPM conditions. As described in the following, the range of T1 and T2* used in this paper was set to adequately cover the relaxation times assuming scans of head tissue with 0.3 T to 3 T.

Scan parameters that can be varied with pRSGE are the FA, TR, and θ. In conventional RF-spoiled GE (RSGE), θ is generally fixed at 117 or 123 degrees to obtain T1-weighted images with low dependence on T2*. Equivalent to another high-speed scanning method called FLASH, varying this θ is known to alter the dependence of image contrast on T2 greatly.

The pRSGE intensity function, $f$, is a function of variables $T_1$, $T_2^*$, FA, TR, and θ, as shown in the following.

$$f = f(T_1, T_2^*, FA, TR, \theta)$$

The range and increments used for tissue-related parameters ($T_1$ and $T_2^*$) and scan parameters (FA, θ, and TR) when creating this intensity function numerically are given in Table 1. A total of 248400 parameter combinations were computed.

To obtain a simulated signal intensity in a steady state, echo center signals from repetition 3001 to 3100 were averaged and used as an intensity function value. For the pRSGE acquisition used in this study, scanning for four times longer than $T_1$ is sufficient to obtain a steady-state signal. As the maximum $T_1$ used to calculate the intensity function was 5.6s, the time-to-steady-state in this study was 22.4s. Since the shortest TR in this study was 10 ms, more than 2240 repetitions were required to obtain a steady-state signal. In the phantom and volunteer imaging described in the following, the k-space was scanned sequentially starting from the high-frequency region and the preparation pulses were applied for 10s so that the echoes near the center of the k-space would be in a steady state.

Computation points (spins) in the subject model were placed within 1 pixel in the plane and the center 5% of the slice thickness in the slice direction. To ensure an adequate computation time. However, the intensity function of the pRSGE sequence includes very complex case divisions, so it was previously used only for the estimation of T2, and it has been difficult to generalize for estimating multiple quantitative values. As such, we built a numerical intensity function using a Bloch simulation, enabling us to estimate multiple quantities simultaneously. Phantom and volunteer studies were conducted to clarify the usefulness of QPM, and quantitative and visual evaluations were performed for comparison with the conventional methods.
and B1 were derived from the quadratic approximation of the intensity function from Eqn. 1 with variables T1, T2*, PD, and B1. To improve the SNR for these four values, we optimized the scan parameter set using the combination of values of FA ranging over 10, 20, 30, and 40 degrees, 0 ranging from 2 to 22 degrees in 1-degree increments, and TR ranging from 10 to 40 ms in 5 ms increments. To suppress flow artifacts, 0 and 1 degrees were excluded from the range of \( \theta \). Since there are four parameters to be estimated: T1, T2*, PD, and B1, the number of scans must be 4 or more. Therefore, the range was set from 4 to 6. TR combinations were selected such that the total TR of the scans was 130 ms, which is roughly the same as the product of the mean TR (25 ms) and the average number of scans (5). The shorter the total TR, the shorter the scan time. However, since the number of combinations is reduced, the accuracy of quantitative value estimation will decrease.

Note that the optimized scan parameter set does not depend on MRI equipment or the subject, and it can be used even for different magnetic field strengths if T1 and T2* of the tissues are roughly the same. However, when scanning different body parts, it will be necessary to find a scan parameter set optimized for T1 and T2* of the tissues in the part being scanned.

### Optimize scan parameter set using intensity function

Quantitative values given by QPM using the intensity function are T1, T2*, PD, and B1. To improve the SNR for these four values, we optimized the scan parameter set using the law of error propagation. As such, we rewrite the intensity function from Eqn. 1 with variables T1, T2*, PD, and B1 and add a term for T2* decay to obtain the following.

\[
f_s = PD \times f(T_1, T_2^*, B_1 \times FA, TR, \theta) \exp(-TE/T_2^*)
\]

The perturbations of the quantitative values T1, T2*, PD, and B1 were derived from the quadratic approximation of the intensity function \( f_s \) using the gradient vector and Hessian matrix. The perturbations of each quantitative value of the tissues to be optimized were calculated for each scanning parameter set (FA, TR, and \( \theta \)), and the scanning parameter set that minimized the sum of the perturbations was searched among all sets. The multi-echo TEs in Eqn. 2 were fixed for each TR. Each perturbation was normalized by its quantitative value and evaluated as a relative error in summation. The resulting set of scanning parameters was used as the optimal one for QPM in this study.

The tissues to be optimized (Target Tissues) were white matter (WM), gray matter (GM), fat, and cerebrospinal fluid (CSF), which are the main types of tissues in the human head. The T1 and T2* values were set on the basis of those at 0.3 T to 3 T. These are shown in Table 2.

For the optimization, we searched for the optimal combination of values of FA ranging over 10, 20, 30, and 40 degrees, \( \theta \) ranging from 2 to 22 degrees in 1-degree increments, and TR ranging from 10 to 40 ms in 5 ms increments. To suppress flow artifacts, 0 and 1 degrees were excluded from the range of \( \theta \). Since there are four parameters to be estimated: T1, T2*, PD, and B1, the number of scans must be 4 or more. Therefore, the range was set from 4 to 6. TR combinations were selected such that the total TR of the scans was 130 ms, which is roughly the same as the product of the mean TR (25 ms) and the average number of scans (5). The shorter the total TR, the shorter the scan time. However, since the number of combinations is reduced, the accuracy of quantitative value estimation will decrease.

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### Estimate MR parameters using source image and intensity function

The intensity function is used to estimate T1, T2*, PD, and B1 as follows. Multiple optimized scan parameters are used to scan multiple images, and T1, T2*, PD, and B1 are computed by finding the least-squares fit of \( f \) to the intensity values, \( I \), in accordance with the following equation.

\[
\arg\min \sum_{i=1}^{n} \left( I_i - PD \exp \left[ -\frac{TE_i}{T_2^*} \right] f(T_1^i, T_2^i, B_1 \times FA, TR, \theta) \right)^2
\]

\[
0.05 < T_1 < 5.6, 0.01 < T_2 < 2.8, 0.3 < B_1 < 1.5, 0 < PD
\]

Here, \( i \) is the source image number, \( n \) is the number of source images, and \( TE \) is the echo time. Note that PD is the spin density, including receiver-coil sensitivity.

### Table 1 Range and increments used for tissue parameters (T1 and T2*) and scan parameters (FA, \( \theta \), and TR) when creating this intensity function numerically

<table>
<thead>
<tr>
<th>Tissue and scan parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (ms)</td>
<td>50, 70, 98, 140, 190, 270, 380, 530, 740, 1000, 1400, 2000, 2800, 4000, 5600</td>
</tr>
<tr>
<td>T2* (ms)</td>
<td>13, 18, 25, 36, 50, 70, 98, 140, 190, 270, 380, 530, 740, 1000, 1400, 2000, 2800</td>
</tr>
<tr>
<td>FA (degree)</td>
<td>5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60</td>
</tr>
<tr>
<td>( \theta ) (degree)</td>
<td>0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>10, 20, 30, 40</td>
</tr>
</tbody>
</table>

A total of 248400 parameter combinations were computed. FA, flip angle.

### Table 2 Target tissues and T1 and T2* values for optimizing QPM scan parameter set

<table>
<thead>
<tr>
<th>Approximate ranges of literature values</th>
<th>Target values for optimizing QPM scan parameter set</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (ms)</td>
<td>T2* (ms)</td>
</tr>
<tr>
<td>GM</td>
<td>1000–1500</td>
</tr>
<tr>
<td>WM</td>
<td>600–850</td>
</tr>
<tr>
<td>fat</td>
<td>280–300</td>
</tr>
<tr>
<td>CSF</td>
<td>2500–4600</td>
</tr>
</tbody>
</table>

Main tissues of human head were chosen as target tissues. Target values were set according to those from 0.3 T to 3 T. CSF, cerebrospinal fluid; GM, gray matter; QPM, quantitative parameter mapping; WM, white matter.
The $B_1$ distribution in the human head is smooth. This fact can improve the SNR of the quantitative parameter maps with the following process.

Step 1: Create intermediate images with 1/4 the resolution on each axis by decimating voxels at equal intervals on each of the three axes.

Step 2: Apply Eqn. 3 to the intermediate images and estimate the quantitative values $T_1$, $T_2^*$, PD, and $B_1$.

Step 3: Return the estimated low-resolution $B_1$ map to the original resolution by fitting it with a homogeneous polynomial of degree six or less.

Step 4: Estimate the quantitative values ($T_1$, $T_2^*$, and PD) again at the original resolution using Eqn. 3. Use the value of $B_1$ from Step 3 as a known value.

A susceptibility map is estimated using a conventional method\textsuperscript{12} from the multi-echo image obtained by the QPM scan.

**Phantom studies**

To verify the accuracy of tissue-related parameter estimates using QPM, we performed experiments using four phantoms with different $T_1$ and $T_2^*$ values on a 3 T MR scanner with a 32-channel head coil (FUJIFILM Healthcare, Tokyo, Japan). Each phantom vessel was a cylindrical polyvinyl chloride bottle of approximately 200 mm in height and 80 mm in diameter. The composition of the phantoms was a mixture of manganese chloride and nickel chloride aqueous solutions. To cover $T_1$ and $T_2^*$ as widely as possible, as shown in Table 2, the concentrations of manganese chloride and nickel chloride in phantoms A, B, C, and D were (0.14 and 0), (0.24 and 0), (0.17 and 3.6), and (0.005 and 0) mM, respectively. The scan parameters were as follows: FOV, 192 mm; FA, 90; matrix size, $256 \times 128$; slice thickness, 5 mm; inversion time ($T_I$), 200, 400, 700, 1000, 1600 ms; TE, 12 ms; TR, $3s + TI$; and total scan time, 41 minutes. For RSGE, they were as follows: FOV, $167 \times 167$ mm$^2$; FA, 90; matrix size $148 \times 148$; slice thickness, 1.1 mm; number of signal averages (NSA), 4; TE, $7, 12, 17, 22, 27, 32, 37, 42, 47, 52, 57, 62, 67, 72, 77, 82$ ms; TR, $2s$; and total scan time, 22 minutes.

**Volunteer experiments**

Upon receiving written informed consent, all of the human brain data were acquired in accordance with the study, which the ethics committee approved.

To evaluate the application of QPM to human brain 3D imaging, we performed healthy volunteer experiments on a 3 T MR scanner with a 32-channel head coil (FUJIFILM Healthcare). The scan parameters were the same as those in the phantom study.

$T_1$ and $T_2^*$ values for WM and GM estimated using QPM were evaluated through comparison with reference values.\textsuperscript{13,14} To evaluate the QSM obtained using QPM, we examined the correlation with QSM acquired at the same spatial resolution as QPM and the same imaging conditions as in the reference: FA = 15 degrees, TR = 35 ms, and TE = (7.0, 11.6, 16.2, 20.8, 25.4, and 30.0) ms.\textsuperscript{15}

**Results**

Four subsets of the intensity function created through the Bloch simulation are shown in Fig. 1. The figure shows...
changes in intensity for $\theta$ and FA for four combinations of $T_1$ and $T_2^*$. The intensity of the function changed smoothly for its variables, so the least-squares fit for estimating quantitative values was relatively easy to accomplish. Computing the echo intensities for all 248400 scan parameters required approximately five weeks using 30 PCs (Xeon E5, 2.7 GHz, 6-Core; Intel, Santa Clara, CA, USA) operating in parallel with a program written in C.

A QPM scan parameter set optimized using this intensity function and the law of error propagation is shown in Table 3. The scan parameter set consisted of 5 scans, resulting in 12 images. The SNR for the estimated quantitative values increases with the number of source images. Therefore, we increased the number of source images by multi-echo imaging for scans 1 and 2. However, for scans 3, 4, and 5, which had a small $\theta$, flow artifacts were quite prominent in the multi-echo images, so we used single-echo images. Note that the five multi-echo images from scan 1 were also used for QSM.

Figures 2 and 3, respectively, show $T_1$ and $T_2^*$ values obtained in the phantom experiments using conventional methods and 10 repetitions of QPM. Table 4 shows a comparison of $T_1$ and $T_2^*$ values from the conventional methods and QPM and the QPM coefficient of variation (CV). The difference between the conventional and QPM values for $T_1$ was 10% for phantom D, which was the longest, and less than 5.9% for the others; the difference in $T_2^*$ values was −35% for D and less than 1.9% for the others. The QPM CV values varied from 2.4% to 4.9% for $T_1$, 0.87% to 4.4% for $T_2^*$, and 1.6% to 2.1% for PD.

The correlation between the conventional and QPM values for $T_1$ and $T_2^*$ is shown in Fig. 4. Figure 4a shows the correlations for phantoms A, B, C, and D, and Fig. 4b shows the correlations excluding phantom D. Figure 4a shows a strong correlation, with coefficients of determination of 0.9997 and 0.9998 respectively for $T_1$ and $T_2^*$ for all phantoms. Also, the slopes for $T_1$ and $T_2^*$ were 1.133 and 0.6295, respectively. In addition, these strong correlations were maintained in Fig. 4b, with phantom D excluded, and

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Scan parameter set optimized for multi-parameter mapping of brain tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan No.</td>
<td>FA (deg.)</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
</tr>
</tbody>
</table>

Scan parameter set consists of 5 scans, resulting in 12 images. $\theta$, RF-pulse phase increment; FA, flip angle.

Fig. 2 Evaluation of reproducibility of QPM $T_1$ values. Thin horizontal lines indicate values obtained by the conventional method. QPM, quantitative parameter mapping.

Fig. 3 Evaluation of reproducibility of QPM $T_2^*$ values. Thin horizontal lines indicate values obtained by the conventional method. QPM, quantitative parameter mapping.
the slopes for $T_1$ and $T_2^*$ were 1.060 and 0.9963, respectively, in which both were very close to one. Note that the temperatures of the phantoms immediately after the scans were in the range of around 20.0±0.4 degrees.

The results from the volunteer QPM experiments are shown in Fig. 5. The figure shows PD including the receiver-coil sensitivity, $T_1$, $T_2^*$, $B_1$, and susceptibility ($\chi$) maps in the sagittal, coronal, and axial planes. There are two images from different slice positions for the sagittal and coronal maps and three images for the axial map. The gray-scale ranges for the $T_1$, $T_2^*$, $B_1$, and $\chi$ maps were 0 to 3s, 0 to 0.2s, 0 to 1, and −0.2 to 0.2 ppm, respectively.

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Table 4 Accuracy and repeatability of QPM $T_1$ and $T_2^*$

<table>
<thead>
<tr>
<th>Phantom No.</th>
<th>$T_1$ IR-SE (ms)</th>
<th>QPM mean ± SD (ms)</th>
<th>Difference (%)</th>
<th>QPM CV (%)</th>
<th>$T_2^*$ RSGE (ms)</th>
<th>QPM mean ± SD (ms)</th>
<th>Difference (%)</th>
<th>QPM CV (%)</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>711</td>
<td>725 ± 35.9</td>
<td>+2.0</td>
<td>4.9</td>
<td>60.0</td>
<td>59.7 ± 1.15</td>
<td>−0.51</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>B</td>
<td>463</td>
<td>436 ± 10.3</td>
<td>−5.9</td>
<td>2.4</td>
<td>35.5</td>
<td>35.2 ± 0.343</td>
<td>−0.94</td>
<td>0.98</td>
<td>2.1</td>
</tr>
<tr>
<td>C</td>
<td>244</td>
<td>231 ± 8.41</td>
<td>−5.2</td>
<td>3.6</td>
<td>42.4</td>
<td>42.5 ± 0.370</td>
<td>0.25</td>
<td>0.87</td>
<td>2.1</td>
</tr>
<tr>
<td>D</td>
<td>2352</td>
<td>2598 ± 71.6</td>
<td>+10</td>
<td>2.7</td>
<td>879</td>
<td>570 ± 25.3</td>
<td>−35</td>
<td>4.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Shown are comparison of $T_1$ and $T_2^*$ values from conventional method and QPM and QPM CV. CV, coefficient of variation; IR-SE, inversion recovery spin-echo; PD, proton density; QPM, quantitative parameter mapping; RSGE, RF-spoiled gradient echo; SD, standard deviation.

Fig. 4 Correlation between conventional and QPM values for $T_1$ and $T_2^*$; a: All phantoms, b: Excluding phantom D. There was a strong correlation between the conventional method and QPM for both $T_1$ and $T_2^*$. QPM, quantitative parameter mapping.

Table 5 shows the results of comparing $T_1$ and $T_2^*$ values for WM and GM with the reference values. Figure 6 shows circles indicating the ROIs for WM and GM. QPM $T_1$ was 889 ± 43 ms for WM and 1610 ± 156 ms for GM, and $T_2^*$ was 47.0 ± 3.9 ms for WM and 63.6 ± 5.1 ms for GM. The $T_1$ values were within the range of the reference values, and the $T_2^*$ values were almost the same as the reference values.

Figure 7 shows the susceptibility maps obtained with QPM and the conventional QSM at the same spatial resolution, and the correlation between the two. There were no noticeable differences in quality between the images. The
The processing time for estimating the $T_1$, $T_2^*$, $B_1$, and PD maps in the volunteer QPM experiments was approximately 5 minutes with a program written in Visual C# (Microsoft, Redmond, WA, USA) using 11 cores of Xeon E5 at 2.7 GHz (Intel) and about 1 minute using a GeForce RTX 2080 Ti (NVIDIA, Santa Clara, CA, USA). The processing time for QSM was about 5 minutes using 1 core of Xeon E5 at 2.7 GHz (Intel).

Discussion

The proposed method, QPM, can obtain 3D maps of four tissue-related parameters ($T_1$, $T_2^*$, PD, and susceptibility) and $B_1$ using multi-echo pRSGE. While the $T_2$ map, which is commonly obtained with conventional methods, is not available, the advantage of QPM over conventional MRF or QALAS is that the susceptibility map can be obtained simultaneously with $T_1$, $T_2^*$, and PD maps. This is because QSM can be applied directly because of the use of multi-echo pRSGE. For the same reason, water-fat separation and fat fraction can also be applied.

Another advantage of QPM is that $B_1$ inhomogeneity correction is not necessary because the $B_1$ map is estimated simultaneously with other quantitative values. In contrast, MRF requires the $B_1$ map to be obtained and corrected for $B_1$ inhomogeneity to improve the repeatability of $T_2$ values. In addition, as described in the following, QPM, which uses the least-squares method for quantitative value estimation, has the advantage of a much shorter reconstruction time compared with MRF, which uses pattern matching.
However, the scan time of QPM in this study is 12.4 minutes. This is rather long for human imaging, so errors due to subject motion may occur. The solution to this problem includes reducing the scanning time by applying compressed sensing17 (CS) and using image registration for each scan. CS has already been applied to MRF and QALAS, and when applied to QALAS, the imaging time is reduced from 11.2 minutes to 5.9 minutes.18,19 The same effect can be expected for QPM.

The phantom QPM experiments yielded accurate estimations of $T_1$ and $T_2^*$ close to those of brain parenchyma and within 6% of the values from the conventional methods (IR-SE and RSGE). However, the estimation accuracy was lower for phantom D, which had relaxation times significantly longer than brain parenchyma. The difference from the conventional methods was 10% for $T_1$ and ~35% for $T_2^*$. This may be due to the fact that more items with a relaxation time closer to brain parenchyma were used when optimizing the scan parameter set for QPM. The reason for the larger difference in $T_2^*$ may be the vibration and diffusion of the phantom solution. When a liquid phantom with a long relaxation time is imaged with an FISP sequence without RF spoiling, the diffusion reduces the MR signal, which results in a reduction in $T_2$ in MRF-FISP.20 pRSGE is not completely RF spoiled, so a similar phenomenon is likely to occur.

Regardless of the length of relaxation time, CV was $3.4 \pm 1.1\%$ for $T_1$, $2.1 \pm 1.7\%$ for $T_2^*$, and $1.9 \pm 0.25\%$ for PD. Since the CV of MRF is about 5%,21 the repeatability of QPM in the phantom experiments in this study was sufficiently high. In general, a PD map obtained by quantitative mapping includes the sensitivity distribution of the receiver coil. To obtain a PD map that is not affected by the coil sensitivity, it is necessary to measure and correct the coil sensitivity distribution separately.

$T_1$ and $T_2^*$ values from the conventional methods and QPM showed a strong correlation when excluding phantom D, which had $T_1$ and $T_2^*$ values close to those of CSF. The slope was also very close to 1, showing that the QPM quantitative value estimation accuracy was high. Even when including phantom D, the correlation was strong, but the slope for $T_1$ was somewhat larger than 1, and for $T_2^*$, it was somewhat smaller than 1. This was due to the effects of

### Table 5 Comparison of $T_1$ and $T_2^*$ with published values

<table>
<thead>
<tr>
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<th>$T_1$ (ms)</th>
<th>$T_2^*$ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QPM (13 and 14)</td>
<td>QPM (14)</td>
</tr>
<tr>
<td>White matter</td>
<td>889 ± 43</td>
<td>750–1084</td>
</tr>
<tr>
<td></td>
<td>47.0 ± 3.9</td>
<td>53.2 ± 1.2</td>
</tr>
<tr>
<td>Gray matter</td>
<td>1610 ± 156</td>
<td>1209–1820</td>
</tr>
<tr>
<td></td>
<td>63.6 ± 5.1</td>
<td>66 ± 1.4</td>
</tr>
</tbody>
</table>

QPM, quantitative parameter mapping.

![Fig. 6 ROIs for comparing $T_1$ and $T_2^*$ with published values. GM, gray matter; WM, white matter.](image)

![Fig. 7 Comparison of susceptibility maps. a, QPM; b, QSM; c, Correlation between both. QPM, quantitative parameter mapping; QSM, quantitative susceptibility mapping.](image)
the somewhat lower accuracy of QPM for phantom D, as previously described.

In volunteer evaluations, the QPM $T_1$ and $T_2^*$ values for WM and GM were equivalent to the reference values. With the volunteer scans, it was difficult to evaluate simultaneously with conventional IR-SE, SE, or GE, which have longer scan times. For this reason, we performed the phantom experiments to compare the accuracy and evaluate the repeatability against conventional methods, and with the volunteer scans, we evaluated the validity of the quantitative values obtained within the scan time applicable to human subjects.

The QPM susceptibility map was strongly correlated with QSM. However, since the spatial resolution of the QPM susceptibility map is lower than that of normal QSM, it is necessary to verify whether it can be used for the same applications as the normal QSM.

The intensity function of the pRSGE has been obtained analytically, but the analytically derived function is extremely complex, so while it can be used to estimate $T_2$ alone, it is difficult to generalize to the estimation of multiple quantitative parameters. In this paper, we estimated multiple quantitative values by building the intensity function numerically with a Bloch simulation and using least-squares fitting. This made it possible to obtain a multi-parameter mapping, simultaneously mapping $T_1$, $T_2^*$, PD, $B_1$, and susceptibility by using gradient echo sequences that require relatively short scan times.

The intensity function was numerically constructed by a Bloch simulation to enable the least-squares method to be applied, which also contributes to reducing processing time; the processing time for QPM was about 5 minutes on a central processing unit (CPU) and about 1 minute on a graphics processing unit (GPU) for $148 \times 186 \times 148$ voxels. These can be considered short processing times for quantitative multi-parameter mapping. For example, the reconstruction time for MRF$^5$ with the number of voxels used for QPM is approximately 62 minutes. This difference can be attributed to QPM’s use of least-squares fitting rather than pattern matching.

To optimize the scan parameter set, the total TR was set to 130 ms. If there is a margin in the SNR of the system, the total TR can be shortened to reduce the scan time. For example, if a map with a high SNR can be obtained even when the acceleration factor of the parallel imaging is increased to the limit applicable for the receiver coil, the scan time can be further reduced by shortening the total TR and re-optimizing the scan parameter set.

A limitation of this study was that only healthy volunteers were used to validate the QPM. Further studies on clinical usefulness, such as lesion detectability, are needed to demonstrate the value of QPM. In particular, it is important to evaluate the effect of obtaining $T_2^*$ and susceptibility instead of $T_2$. Other quantitative mapping methods have shown improved clinical usefulness using their relaxation times; however, QPM should further improve the usefulness by leveraging the susceptibility of tissues, which sensitively reflects iron deposition, calcification, and demyelination.

Conclusion

We proposed QPM, which can map four tissue-related parameters ($T_1$, $T_2^*$, PD, and susceptibility) and $B_1$ simultaneously in 3D. We completed a 1.1 mm isotropic scan covering the whole brain in 12.4 minutes. The accuracy and repeatability of the quantitative values were confirmed with phantom experiments. Volunteer experiments also confirmed that the quantitative values were comparable with values from the conventional methods. QPM simultaneously mapped $T_1$, $T_2^*$, PD, susceptibility, and $B_1$ within a scan time applicable for human subjects.

Acknowledgments

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Conflicts of Interest

All authors (Yo Taniguchi, Suguru Yokosawa, Toru Shirai, Ryota Sato, Tomoki Amemiya, Hisaaki Ochi, Yoshihisa Soutome, and Yoshitaka Bito) are salaried employees of FUJIFILM Healthcare Corporation.

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