Model-Based Super-Resolution Reconstruction of T2 Maps

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ABSTRACT:

Purpose: High-resolution isotropic T_2 mapping of the human brain with multi-echo spin-echo (MESE) acquisitions is challenging. When using a 2-D sequence, the resolution is limited by the slice thickness. If used as a 3-D acquisition, specific absorption rate (SAR) limits are easily exceeded due to the high power deposition of non-selective refocusing pulses. A method to reconstruct 1-mm^3 isotropic T_2 maps is proposed based on multiple 2-D MESE acquisitions. Data were undersampled (10-fold) to compensate for the prolonged scan time stemming from the super-resolution acquisition.

Method: The proposed method integrates a classical super-resolution with an iterative model-based approach to reconstruct quantitative maps from a set of undersampled low-resolution data. The method was tested on numerical and multipurpose phantoms, and in-vivo data. T_2 values were assessed with a region-of-interest analysis using a single-slice spin-echo and a fully sampled MESE acquisition in a phantom, and a MESE acquisition in healthy volunteers.

Results: Numerical simulations showed that the best trade-off between acceleration and number of low-resolution datasets is 10-fold acceleration with four acquisitions (TA=18 mins). The proposed approach showed improved resolution over low-resolution images for both phantom and brain. Region-of-interest analysis of the phantom compartments revealed that at shorter T_2, the proposed method was comparable with the fully sampled MESE. For the volunteer data, the T_2 values found in the brain structures were consistent across subjects (8.5-13.1ms standard deviation).

Conclusion: The proposed method addresses the inherent limitations associated with high-resolution T_2 mapping and enables the reconstruction of 1mm^3 isotropic relaxation maps with a ten times faster acquisition.

Introduction

Spin-spin relaxation characterised by its relaxation time T_2 is one of the two principal relaxation mechanisms in Magnetic Resonance Imaging (MRI). Its quantification, typically referred to as T_2 mapping, provides important information about the tissue of interest. Previous studies have demonstrated the importance of T_2 mapping to study various neurological conditions such as stroke (1), epilepsy (2) multiple sclerosis (3), and tumour detection (4).

Conventionally, T_2 is measured by sequentially acquiring several spin-echo (SE) images, each with a different echo time (TE) and subsequently fitting a mono-exponential decay. This is commonly acknowledged as a gold standard despite residual diffusion effects affecting the T_2 quantification. Nonetheless, the long acquisition times of around 50 min for whole-brain coverage in 2-D is impractical for clinical applications. As an alternative approach, the multiple-echo spin-echo (MESE) sequence in the Carr-Purcell-Meiboom-Gill (CPMG) condition (5) uses subsequent refocusing pulses to acquire multiple echoes for each excitation, reducing the total acquisition length. However, the quantitative accuracy of the sequence is compromised by imperfect refocusing. The imperfect refocusing results in the formation of stimulated (secondary) echoes that disrupt the T_2 decay of the primary spin echoes (6). The effect of the stimulated echoes can be reduced by ignoring the first echo (since this pure spin echo biases the fitting of the subsequent stimulated-echo-contaminated data) while fitting the relaxation curve (7). However, it has been shown that skipping echo approaches still yield highly variable results with errors that depend on flip angle, T_2 and echo train length (8). Therefore, more complex signal models are required to accurately estimate T_2 (6).

The ability to accurately and precisely map T_2 at high resolution (e.g. 1-mm^3 isotropic voxel size) in large volumes may help to improve the quantification of small focal changes such as multiple sclerosis lesions or brain areas causing focal seizure onset in epilepsy. However, using thin slices in a 2-D MESE acquisition is challenging due to the reduced signal-to-noise ratio (SNR) and increasing difficulties to achieve a good slice profile. Furthermore, radio-frequency (RF) pulses with long duration are required to excite thin slices leading to longer echo spacings (ΔTE) (9). The increased ΔTEs aggravate and inhibit an accurate quantification of short T_2 values. In addition, true T_2-weighting is difficult to obtain in reasonable acquisition times with 3-D acquisition methods since a long repetition time (TR) is required to fully recover the magnetization to equilibrium between excitations. Since all spins in the FOV of a 3-D acquisition are excited by every pulse, the recovery time cannot be used for interleaved slice

sampling, rendering the sequence less efficient (10). Furthermore, a 3D acquisition is also limited by specific absorption rate (SAR) safety constraints. A large amount of power is deposited if multiple non-selective 180° pulses are used which can easily exceed the SAR limits (11).

A fundamental consideration in any MRI experiment is to optimally balance image resolution, SNR, and acquisition time. Various methods have been published to accelerate quantitative mapping methods, for example applying model-based reconstructions(7,12-14), low-rank approaches (15,16) or sparsity constraints (17,18) to highly undersampled acquisitions. However, these methods experience a low SNR and use low spatial resolution to counteract this effect. On the other hand, it has been shown that super-resolution (SR) reconstruction provides a better trade-off between acquisition time, spatial resolution, and SNR (9,10). The earlier SR methods (19,20) focused on the improvement of the in-plane resolution of MR images. To achieve this in-plane resolution improvement, several images with a subpixel shifted FOV in the in-plane directions were acquired. However, the subpixel shift of the FOV in the in-plane directions correspond to a linear phase modulation in the k-space and does not acquire new frequency information (21). Thus, the apparent improvement in the in-plane resolution in this case is due to an improvement in the SNR. Later, most SR methods focused on decreasing the slice thickness and reaching voxel isotropy by exploiting the aliasing as a result of downsampling in the slice-select direction (22). The resolution is thereby enhanced by acquiring multiple low-resolution images with a shift of the field of view (FOV) in the slice direction (10), three orthogonal slice orientations (22) or rotated slice orientations (23), and subsequently combining the images by solving a non-linear inverse problem. In quantitative MRI, SR reconstruction benefits from combining the parametric model with the SR model. This has been shown in T_1 mapping (24) where the relaxation model was combined with the SR model allowing the direct estimation of a high-resolution T_1 map from low-resolution images. However, the acquisition of multiple low-resolution images results in long scan times (TA>20 mins), hence limiting its use for clinical applications.

Both the SR and model-based reconstructions are based on solving an inverse problem using iterative optimisation methods. The present work investigates the combination of SR and model-based reconstruction to exploit the respective advantages (i.e., high-resolution and fast acquisition time) in the application of quantitative T_2 mapping. The proposed method is based on multiple 2-D MESE acquisitions which were highly undersampled to compensate for prolonged scan time. The method was tested on a phantom and four healthy volunteers. An

early version of this framework was presented at the Annual Meeting & Exhibition of the ISMRM in 2017 (25).

Theory

Super-resolution reconstruction is a method to obtain a high-resolution image from a series of low-resolution images, where each low-resolution has a different FOV or orientation. Each FOV or orientation can be expressed as a different geometric transform T_j (with $j = 1,...,J$, and J the number of transformations) from the high-resolution image to the low-resolution image. The resolution is enhanced since the different FOVs or orientations contain complementary information. The reconstructed high-resolution image on the other hand benefits from the high SNR of the low-resolution images, which are typically acquired with a high in-plane resolution and a low through-plane resolution, i.e. thick slices.

Let x_n (with $n = 1, ..., N$, and N the number of spin-echoes) represent a high-resolution T_2-weighted series of vectorized images and $y_{j,n,c}$ (with $c = 1,...,C$, and C the number of coils) be the undersampled low-resolution k-space measurements acquired with a MESE sequence. The acquisition of the undersampled low-resolution $y_{j,n,c}$, can be modelled by:

$$y_{j,n,c} = PF\{S_{j,c} \downarrow T_j x_n\} + \eta_{j,n,c}, \qquad [1]$$

where T_j is the geometric transformation representing a rotation or translation of the FOV (Figure 1), $\downarrow$ is a down-sampling operator that maps the high-resolution grid to the low-resolution grid, $S_{j,c}$ are the complex coil sensitivities calculated separately for each transformation, F is the forward discrete Fourier operator and P is a binary under-sampling mask. According to (26), the noise $\eta_{j,n,c}$ in MRI can be assumed to be additive, white and Gaussian when the SNR > 3, which is what we assume here. Using pertinent SR techniques, the high-resolution image x_n can be estimated by solving the inverse problem of Eq. [1]:

$$\underset{x_n}{argmin} \sum_c^C \sum_j^J \| PF\{S_{j,c} \downarrow T_j x_n\} - y_{j,n,c} \|^2, \qquad [2]$$

where the choice of the least- squares criterion is motivated by the assumption that the noise is Gaussian distributed. The greater the number of acquisitions, J, with complementary information of the same object, the better the problem becomes conditioned. However, the problem in Eq. [2] is often still ill-posed due to the downsampling operator, since several different intensity combinations in the high-resolution image can lead to the same intensity in the low-resolution image.

To further improve the conditioning of the problem, we can incorporate a signal model into the cost function. Given the task of T_2 quantification, it is natural to use the physical constraints

imposed across the sequence of images, x_n to further regularize the optimization. The signal model in its simplest form is typically described with a mono-exponential decay depending on the relaxation time map $\mathbf{T_2}$ and proton density map $\mathbf{M_0}$:

$$x_n = \mathbf{M_0}.exp(-t_{n.}/\mathbf{T_2}), \qquad [3]$$

where the above equation represents the pixel-wise scalar non-linear function for M_0 and T_2 and t_n being the echo time. In this work, the first echo is ignored to alleviate the effect of stimulated echoes(27). However, even with ignoring the first echo, the standard exponential fitting will result in an overestimation of T_2 (8). A more complex model that includes effects such as $B1^+$, slice profiles, multiple T2 compartments, diffusion and magnetization transfer is required to accurately fit the data. Since the present work aims at a proof of concept for super-resolution for T2 mapping, the common approach of ignoring the first echo is used due to its simplicity and easy implementation.

In the next step of the algorithm, the most intuitive step might be to substitute the high-resolution image x_n in Eq. [2] with the signal-model (Eq. [3]) and solving directly for $\mathbf{M_0}$ and $\mathbf{T2}$, resulting in the following cost-function:

$$\underset{T2,M0}{argmin} \sum_j^J \sum_n^N \sum_c^C \parallel PF\,\{S_{j,c} \downarrow T_j\,(\mathbf{M_0}.exp(-t_{n.}/\mathbf{T_2}))\,\} - y_{j,n,c}\parallel^2. \qquad [4]$$

However, minimizing Eq. 4 often requires special techniques such as gradient scaling and repeated restarts of the optimization algorithm to achieve a fast convergence (7,27). Therefore, in this work, we rather formulate the minimization problem as:

$$\underset{T2,M_0,\{x_{n_{n=1}}^N}{argmin} \sum_n^N \sum_c^C \sum_j^J \parallel PF\{S_{j,c} \downarrow T_j x_n\} - y_{j,n,c}\parallel^2 + \lambda \parallel x_n - \mathbf{M_0}.exp(-t_{n.}/\mathbf{T_2})\parallel^2, \qquad [5]$$

where the first term ensures data-consistency of the high-resolution image with the acquired data as in Eq. [1] and an additional term ensures model-consistency, i.e. forces the signal intensities to decay exponentially across the different echoes N. In order to balance between the data- and model-consistency, a regularization parameter λ is introduced.

The above cost function in Eq. [5] can be minimized using a split algorithm that estimates quantitative $\mathbf{T_2}$ by minimizing data- and model- consistency terms alternately (20). By fixing $\mathbf{T_2}$ and $\mathbf{M_0}$, solving Eq. [5] with respect to x_n amounts to a standard linear least-squares problem with a closed form solution. On the other hand, for solving Eq. [5] fixing variable x_n corresponds to fitting a mono-exponential decay onto x_n, intrinsically estimating $\mathbf{T_2}$ and $\mathbf{M_0}$.

Methods

Numerical Simulation

Numerical noiseless T_2 and PD maps were generated from a segmentation of grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) in a single axial slice (1x1 mm^2 resolution) of a numerical phantom (28). For the three main tissues, the following T_2 values were used: 0.1 s for grey matter, 0.06 s for white matter, and 2 s for CSF (29). From these maps, T_2-weighted high-resolution images x_n were simulated, each with equidistant TEs [TE=10…,160 ms]. The T_2-weighted images were down-sampled to the desired low-resolution using eq. [1] and different transformations T_j. These different shifted images were then down sampled to low-resolution. Complex coil sensitivities for each of these transformations were simulated using the Parallel MRI Noisy Phantom Simulator (30). These simulations exploit the fact that the reconstruction is separated into multiple 2-D problems along the read-out direction (i.e. head-feet direction in this case). Therefore, for the phantom, a sagittal acquisition with phase-encoding in anterior-posterior and slice-encoding in left-right directions can be simulated. For the number of repetitions, the low-resolution single slice of the numerical phantom was shifted in the slice encoding direction (left-right). For the rotation, the FOV was rotated around the read-out (i.e. head-feet) axis for each repetition. Therefore, the applied transformations were not in-plane since the slice plane is sagittal/coronal but the numerical phantom is axial. Three different types of transformations were tested: linear (where the images were shifted along the slice direction (25)), orthogonal (images were rotated to two orthogonal positions 0 and 90 degrees) and diagonal (two orthogonal rotations plus two rotations at 45 and -45 degrees). An illustration of the different transformations is shown in Figure 1. The images were transformed to k-space and then ten-fold undersampled with a mixed parallel imaging and block undersampling pattern described in (31). The high-resolution images were reconstructed with the proposed SR model-based reconstruction. Root mean square error (RMSE) was calculated between ground truth and reconstructed T_2 maps for all the orientations.

In principle, we assume that adding more rotations (e.g. orthogonal with two rotations versus diagonal with four rotations) will increase the accuracy of the SR reconstruction but at the expense of increased acquisition time. To that end, various numbers of rotations (two, four, and five) were tested in combination with different acceleration factors (6-fold, 10-fold, 14-fold) to determine a trade-off between accuracy and acquisition time. Approximate acquisition times were calculated for all the simulations with the following parameters: 1 x 1 mm^2 resolution, matrix size 210 x 53 and TR= 5 sec, two concatenations. The root mean square error

(RMSE) between the ground truth and the estimated T2 map was calculated to quantify the reconstruction quality.

Image Acquisition

The proposed approach was tested on a standardized multipurpose phantom (E 38 19 195 K2130, Siemens) with five compartments of different concentration of MnCl2·4H2O in distilled water and four healthy subjects. Permission from the Institutional Review Board was obtained for all the in-vivo imaging studies and written informed consent for the study and its publication was obtained from all participants prior to the experiments. The datasets were acquired with a standard 20-channel head/neck coil using a ten-fold undersampled GRAPPATINI (31) prototype sequence at 3T (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). The sequence implements a block undersampling pattern (7) which samples the k-space in blocks (or segments) which are shifted across the echoes. A classic parallel imaging scheme with two-fold acceleration is used additionally where only every other (phase-encoding) line inside each block is acquired. For the first dataset, 50 sagittal slices with 4 mm thickness and 1x1 mm^2 in-plane resolution were acquired. The FOV was moved by 1 mm in the slice-encoding direction with four shifts implementing the linear transformation. The total time of acquisition for this dataset was 16 minutes. For the second dataset, 60 slices each in two orthogonal orientations (sagittal and coronal) and two diagonal orientations (sagittal > coronal 45° and -45°) with the same slice thickness and in-plane resolution were acquired. The acquisition time for this dataset was 18 minutes. Additional data was acquired in the same setup (i.e. orthogonal and diagonal) with 14-fold acceleration which reduced the acquisition time to eleven minutes. Of note, the dataset with orthogonal orientation was not acquired separately, but rather the two diagonal orientations were removed during reconstruction to create a third dataset. Spectral fat suppression was enabled, and other relevant acquisition parameters were: TR=5.4 s, 16 echoes, ΔTE=10 ms. For reference T2 values, a fully sampled MESE dataset with 16 echoes and 29 slices and a resolution of 1.1 x 1.1 x 4 mm^3 was acquired. In addition, for the phantom, a conventional single-slice single-echo SE sequence with 16 TEs (10, 20, …, 160 ms) was acquired as reference. It should be noted that the single-echo SE sequence is not a gold standard since it is still affected by diffusion, but is commonly used as a reference acquisition (32,33). Detailed overview of the acquisition parameters of these datasets can be found in Table 1.

Image Reconstruction

The reconstruction was implemented using Matlab (MATLAB2017a, The Mathworks Inc., Natick, USA). First, GRAPPA (34) was used to fill the missing lines in each block of the acquired k-space according to (31). Using the k-space samples available at different echo times, composite fully sampled images were reconstructed and up-sampled to the high-resolution grid. Subsequently, an initial guess of a T_2 and M_0 map was estimated by non-linear least-square fitting of these magnitude high-resolution images. This estimate of the maps was then used in the algorithm for SR T_2 estimation by alternately solving Eq. [5] fixing T_2 and M_0 first as described in the theory section. Complex coil sensitivities were approximated for each of the transformations by summing k-spaces across echoes. The k-space is then transformed into coil images by inverse Fourier transform and then divided by the sum of squares to obtain coil sensitivities (35) . The regularization parameter was heuristically set to $\lambda = 1$, establishing equal contributions from model- and data-consistency in the cost function. The reconstruction was performed iteratively until no improvement was achieved in the previous two consecutive iterations:

$$\frac{\|X^{(i)} - X^{(i-1)}\|}{\|X^{(i)}\|} < \varepsilon \qquad [6]$$

where $X^{(i)}$ was the reconstructed signal series at i^{th} iteration and $\varepsilon = 1e^{-04}$. In addition, the maximum number of iterations was fixed to 30 after it was experimentally tested at what iteration the algorithm typically convergences (results not shown). The reconstruction scheme is illustrated in Figure 2.

Validation

To evaluate the performance of the proposed SR model-based method, T_2 maps were qualitatively compared to T_2 maps from two other methods using the numerical phantom and one in-vivo dataset. The two approaches were as follows:

- Low-resolution model-based + SR reconstruction: It is pertinent to assess whether minimizing the cost function jointly contributes to the better reconstruction. For this purpose, both the data consistency and model consistency were enforced one after the other rather in a joint cost function. Firstly, low-resolution T_2 maps were reconstructed from individual low-resolution orientations using model-based reconstruction, followed by a SR algorithm to up-sample to a high-resolution T_2 map.

- SR reconstruction only: As described in the theory section, the signal model is used as a regularizer to better condition the minimization problem. To assess the significance of the signal model, the cost function was minimized without the model consistency

term, which is equivalent to classical SR approach.

To ascertain the accuracy of the calculated T_2 values, a ROI analysis was performed on the phantom and in-vivo T_2 maps for both accelerated and fully sampled datasets. T_2 values from different compartments of the phantom were compared with the T_2 values obtained from the conventional non-linear least-squares fitting of the fully sampled MESE and gold standard SE data. The same comparison was made for the healthy brain where ROIs were drawn in the frontal white matter, deep grey matter (putamen and caudate nucleus), and corpus callosum. ROI labelling and segmentation was conducted using ITK-SNAP (36) (www.itksnap.org). The segmentation was performed in the native space of the fully sampled T_2w images. Subsequently, the fully sampled T_2w image was pairwise registered rigidly onto the T_2 maps of the other datasets using Elastix (37). The resulting transformation was then applied to the label map of the ROIs to provide a similar segmentation among datasets. The datasets of the four healthy volunteers who were scanned with both a 10- and 14-fold accelerated acquisition with diagonal orientations and a fully sampled MESE were used in a ROI analysis as well. The T_2 values from four ROIs were compared across all the volunteers to ascertain the consistency of T_2 values across subjects.

Results

Numerical Phantom

T_2 maps and images obtained from the SR model-based reconstruction in the numerical phantom using different orientations (linear, orthogonal, and diagonal) are shown in Figure 3 in comparison to the ground truth. The diagonal rotations were better able to resolve the brain structures as compared to the linear and orthogonal datasets. This can be better appreciated in the zoomed images of the same area that demonstrates the diagonal rotation results in better delineation of the small structures in brain (Figure 3, bottom). The comparison between the three orientations in reconstructed T_2-weighted images also shows sharper edges in the high-resolution images when using the diagonal orientation.

The trade-off between the number of rotations and the acceleration is demonstrated in Figure 4. The numerical simulation demonstrated that adding more rotations results in reduced error around the edges for all the acceleration factors (from left to right). At the same time, an increased acceleration factor influences the T_2 accuracy i.e. an increased difference from the

ground truth (top to bottom). Considering the prolonged acquisition time with the number of rotations, the best trade-off is a 10-fold accelerated scan with four rotations (RMSE=7.8 ms, TA=14mins). Five rotations and 6-fold acceleration showed the least error (RMSE=3.2 ms) but required an acquisition time of 29 minutes. 14-fold acceleration with five rotations had an acquisition time of 10 minutes but an RMSE of 12.5 ms. The details of the RMSE for all the accelerations and rotations are provided in Supporting Table S1.

Phantom and In-vivo Data

Figure 5 shows the reconstructed T_2 maps and T_2-weighted images from one low-resolution acquisition, and the SR model-based reconstructed maps for linear, orthogonal, and diagonal orientations. The low-resolution T_2 maps and weighted images (Figure 5a) show partial-volume effects within the compartments of the phantom and blurring of the fine structures in the brain. Estimating T_2 maps with SR model-based reconstruction enhances the spatial resolution, reducing the partial-volume effect. However, with linear shifting, there is still blurring of the edges around the compartments of the phantom and brain structures (Figure 5b). For orthogonal rotations, the compartment edges in the phantoms appear sharper in both orthogonal directions (Figure 5c, white arrows) whereas the diagonal orientation improves the sharpness further, especially in the diagonal direction (Figure 5d, black arrows). The same can be observed for the human brain where diagonal rotation improved the spatial resolution and delineation of the brain structures.

Figure 6 shows the axial and coronal views of the reconstructed T_2-weighted images from a 10-fold accelerated low-resolution dataset with diagonal orientations and the fully sampled MESE data. It is evident that the SR-T_2 mapping allows satisfactory 3D visualization due to isotropic resolution as compared to conventional MESE which inherently has low through-plane resolution. This can be appreciated even more from the zooms shown in Figure 6. A transversal zoom on the caudate nucleus head and the putamen is shown where the interface between different structures is well delineated in both SR-T_2-weighted and MESE-T_2-weighted images. However, for the coronal zoom, the interface between grey and white matter is better defined for SR-T_2-weighted image.

Validation

A comparison between the SR model-based reconstruction and the SR-only and low-

resolution model-based + SR reconstruction is shown in Figure 7. For numerical phantom, nRMSEs showed that the proposed approach outperforms the SR-only and model-based + SR reconstruction. The nRMSE for SR only reconstruction was 0.50, for model-based + SR reconstruction was 0.23 and for proposed reconstruction was 0.12. The SR-only reconstruction showed visible artefacts due to the undersampling as no prior information from the signal model (mono-exponential decay) was incorporated in the reconstruction. The low-resolution model-based + SR reconstruction showed improvement in the reconstruction; however, blurring around the edges is evident in both numerical phantom and in-vivo data. In comparison, SR model-based reconstruction demonstrated that combining SR and model knowledge jointly in one cost function improves the reconstruction.

ROI Analysis

The ROI analysis of the phantom compartments revealed that at shorter T_2, 10-fold accelerated data was comparable with the fully sampled MESE (Figure 8a). For compartment 1, the mean T_2 value for 10-fold accelerated data was $31.1.0 \pm 1.6$ ms, for 14-fold it was 29.25 ± 1.7 ms, whereas the T_2 value for the MESE was 25.41 ± 1.5 ms and for SE was 18.22 ± 0.5 ms. For compartment 2, the mean T_2 value for 10-fold, 14-fold, MESE and the SE was 29.19 ± 0.8 ms, 31.00 ± 0.9 ms, 30.57 ± 0.7 ms and 25.58 ± 1.1 ms respectively. However, the error increased with higher T_2 values, with compartments 3 and 4 showing a relative difference of 10-12%. For compartment 3, the mean T_2 values for 10-fold was 47.70 ± 2 ms, for 14-fold was 43.0 ± 1.5 ms, for MESE was 51.50 ± 0.5 and for SE was 41.0 ± 0.3 ms. The mean T_2 values for compartment 4 for 10-fold, 14-fold, MESE and SE were 89.00 ± 2.3, 94.42 ± 2.1, 96.98 ± 2.7 and 79.96 ± 3.6 ms respectively. For compartment 5, a greater difference (> 15%) was observed with mean T_2 values of 161.7 ± 2.5 ms, 147.5 ± 2.6 ms, 184.3 ± 2.3 ms and 155 ± 23.4 ms for 10-fold, 14-fold, MESE and SE respectively. All values derived with a MESE sequence were overestimated in comparison to T_2 values derived from a SE sequence. This overestimation is well known and caused by the stimulated echoes formed in the MESE sequence (6).

For the in-vivo data, the T_2 values in different regions of the brain showed good agreement with the fully sampled MESE acquisition (Figure 9b). For frontal white matter, the mean T_2 value for the 10-fold acceleration was 80.0 ± 1.3 ms, for 14-fold it was 76.5 ± 5.1, and for MESE fully sampled it was 83.0 ± 2.1 ms. For putamen, the mean T_2 value for 10-fold, 14-

fold, and MESE fully sampled was 69.8 ± 1.2, 66.2 ± 1.3 and 73.0 ± 3.1 ms, respectively. In the corpus callosum (MESE T2 = 94 ± 2 ms), the 14-fold acceleration showed increased difference (80 ± 2.4 ms) as compared to 10-fold (87 ± 1.8 ms). The T_2 value for the caudate nucleus with the 10-fold acceleration (74.8 ± 2.0 ms) was closest to the MESE acquisition (75 ± 1.8), whereas the T_2 at 14-fold acceleration was 67 ± 2.8 ms. Comparing the mean T_2 values for 10-fold accelerated data from all the four ROIs across volunteers demonstrated consistent values with some natural variation (Figure 9c). The average T_2 value across all volunteers were 70.8 ± 8.5 ms for the frontal white matter, 81.3 ± 10.5 ms for the putamen, 79.8 ± 9.5 ms for the corpus callosum, and 79.66 ± 13.6 ms for the caudate nucleus.

Discussion

The proposed work aims to address the challenges associated with high-resolution T_2 mapping with the widely used MESE sequence. The method combines SR and model-based reconstruction for T_2 estimation into one integrated approach, enabling the direct estimation of an isotropic high-resolution T_2 map from a set of anisotropic, undersampled, low-resolution k-spaces.

Numerical simulations demonstrated that rotating the slice orientations around the phase-encoding results in better image quality of the SR reconstruction than linear sub-pixel shifts in the slice-encoding direction. These results were confirmed by the phantom and the in-vivo acquisitions where the rotation resulted in much sharper images. Low-resolution images with different slice orientations appear to better sample different spatial information than shifting the low-resolution images by subpixel distances along the slice selection direction (9). This is because acquiring low-frequency information in the slice-selective direction limits the additional information available in the subpixel shift. In contrast, the different orientations populate the 3D k-space much better (similar to PROPELLER (38) sequences). The optimal number of slice orientations ensures that the low-resolution images contain enough spatial information to reconstruct the high-resolution image without extensively prolonging the acquisition time. The comparison between number of rotations and acceleration factors showed that four slice orientations (0°,90°,45°, -45°) with a 10-fold acceleration was the optimum in this application with an acquisition time of 18 minutes.

The advantage of combining SR with model-based reconstruction has already been demonstrated for T_1 mapping (24). This work was performed in the image domain without k-

space undersampling, whereas the proposed approach addresses a more complex problem by reconstructing quantitative maps from undersampled k-space data. It is important to ascertain whether model-based SR-T2 mapping performs better than the sequential application of model-based and SR reconstructions. The comparison of the proposed approach to the SR reconstruction without prior model and to the low-resolution model-based reconstruction followed by SR reconstruction demonstrated that incorporating the model information in the reconstruction yields improved results.

Comparing a T_2 map estimated with model-based SR to a T_2 map estimated with a conventional non-linear least-square fitting on a fully sampled MESE dataset proved that T2 values are comparable between the two methods. For the phantom, the compartments with longer T_2 had a higher bias as compared to shorter T_2 compartments, which may be attributed to an imperfect signal model. One contributing factor, as already reported in the literature (6) is that the T_2 values derived from MESE-type acquisitions are overestimated in comparison to single-echo SE acquisitions due to stimulated-echo signal contributions which mostly stem from an imperfect slice profile of the refocusing pulses. This can be addressed by using a different signal model which accounts for slice profile shape and B1 inhomogeneity, e.g. by using an analytical (6,27) or numerical (33,39,40) signal model. The current model of the proposed method does not account for the slice profile. It is assumed that incorporating it in the reconstruction will not only allow addressing stimulated-echo issues but also lead to a more realistic downsampling/upsampling operator between high-resolution and low-resolution images. Since this more accurate model will potentially further improve the spatial resolution, the slice profile is subject of future investigation.

An alternative formulation of the reconstruction problem proposed here can be as follows: the signal in a low-resolution voxel may consist of different tissue types, e.g. at a WM/GM boundary. Neglecting microstructural T_2 components, this partial volume effect yields a multi-exponential signal decay. The fitting of a mono-exponential decay in a high-resolution voxel corresponds to a multi-exponential fitting in the low-resolution image space due to the downsampling operator. The resulting ill-posed problem becomes better conditioned because the different orientations provide selective high-resolution information which allows us to separate out the multi-exponential components within a voxel.

Currently, the optimal-quality 10-fold accelerated acquisition lasts 18 minutes. Despite the high acceleration, the acquisition time is too long to be acceptable for clinical routine or clinical studies. A higher acceleration factor (14-fold) was tested which reduced the acquisition time to 11 minutes but decreased the sharpness of brain structures. Nevertheless, this long acquisition time is still too long for clinical applications where a typical sequence requires 3 minutes. Various other techniques can be applied to further accelerate the acquisition time, such as simultaneous multi-slice (41,42). Moreover, the same sampling pattern was used in each slice and orientation. Varying the sampling across slices and orientations may improve the reconstructed T_2 maps and will be further investigated.

SR approaches require several acquisitions with different orientations, and the reconstruction method assumes that each voxel corresponds to the same anatomical location in all the orientations. Subject motion and image distortions (e.g. due to imperfect gradient performance) violate this assumption and may not perfectly align the multiple orientations for model fitting. This model violation will lead to image artefacts and wrong T_2 values which is a limitation of the proposed method. In the frame of this study, motion correction schemes were not explored, but could be used to facilitate a better alignment of different orientations and improve the reconstruction. The area of motion correction and compensation has been well studied specifically for SR reconstruction in foetal imaging (43,44). Future work will aim to incorporate these strategies to further improve the robustness of the SR-T_2 mapping. In addition, incorporating a spatial regularization of the T_2 maps will potentially further improve the reconstruction.

Conclusion

We propose a technique that uses four 10-fold undersampled low-resolution MESE 2-D acquisitions to iteratively reconstruct a high-resolution T_2 map. The proposed technique enables high-resolution 1 mm^3 isotropic whole-brain T_2 mapping in 18 min. The proposed technique may allow the assessment of T_2 values in small brain structures valuable for the search of imaging biomarkers in the future.

Acknowledgement

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Tables and Figures

Dataset	In-plane resolution (mm²)	Slice thickness (mm)	Acquisition Matrix	Slices	Bandwidth (Hz)	TR (ms)	TE (ms)	No. of shifts/ rotations	Acceleration Factor	No. of echoes	Scan time (mins)
Linear	1x1	4.0	240 x 256	50	227	4490	10	4	10	16	16
Orthogonal	1x1	4.0	240 x 256	60	227	5390	10	2	10	16	9
Diagonal	1x1	4.0	240 x 256	60	227	5390	10	4	10	16	18
Diagonal Fast	1x1	4.0	224 x 240	56	227	4750	10	4	14	15	11
MESE-Fully Sampled	1.1x1.1	4.0	192 x 160	29	221	5000	10	-	-	16	14
SE- Fully Sampled	0.9x0.9	4.0	224 x 256	1	164	2500	10, 20, …, 160	-	-	16	113

Table 1: Overview of the relevant protocol parameters of acquired datasets.

Figure 1: Illustration of the linear shifting (Left) and rotation (Right) experiment. The dashed lines within the boxes indicates the slice encoding direction, the frequency encoding direction is from head to toe. For the linear shifting each low-resolution scan (colours) is shifted by a known subpixel distance along the slice encoding direction (which in this case is sagittal). For illustration purposes, the shifting of the FOV (coloured boxes) has been exaggerated. For rotation, each of the low-resolution scans are rotated ($45°$) across the common encoding direction. The red box represents sagittal section, green box represents coronal section, the blue and yellow box represents diagonal sections.

Figure 2: The schematic flowchart for the model-based SR reconstruction: a) k-space data with block undersampling; b) Zero-filled image using the inverse FFT in the phase-encoding direction; c) Sensitivity maps estimation; d) Composite images are formed and up-sampled to high-resolution grid; f) Data consistency is imposed as a first step of alternating minimization; g) T_2 maps estimated by imposing model consistency in the second step. With the new estimate of T_2, step 1 and step 2 are repeated iteratively. SR – super-resolution, FFT – Fast Fourier Transform, HR – high resolution.

Figure 3: Super-resolution T_2 maps (upper row), reconstructed T_2-weighted images (middle row) and the zoomed-in T_2 maps (bottom row) for three different orientations and 10-fold undersampling. a) Ground Truth, (b) linear shifting, (c) orthogonal rotation, (d) diagonal rotation.

Figure 4: The gain in the quality of super-resolution (SR) -T_2 reconstruction as a function of number of rotations and acquisition time in a numerical phantom. The corresponding acquisition times are mentioned with the T_2 maps. Adding more rotations results in reduced error around the edges for all acceleration factors (from left to right). At the same time, the acceleration factor affects the quality of the reconstruction (top to bottom), especially for high T_2 values in the cerebral spinal fluid. Considering the increase in acquisition time with the

number of rotations, it can be deduced that the optimal configuration is 10-fold with four rotations.

Figure 5: Reconstructed T_2 maps and M_0 for phantom and human brain from (a) low-resolution, (b) interpolated to HR grid, (c) linear, (d) orthogonal, and (e) diagonal datasets with respective acquisition times. For the phantom, orthogonal rotation improved the resolution as can be seen in around the edges of the compartments in two directions (white arrows) whereas diagonal orientation improved the resolution in four directions (black arrows). This can be observed in the in-vivo data as well where the diagonal orientation demonstrated better resolution in brain structures as compared to orthogonal rotation and linear shift.

Figure 6: Axial and coronal views of T_2-weighted images reconstructed with super-resolution (SR)-T_2 mapping ($1 \times 1 \times 1$ mm^3) (left) and T_2-weighted image from fully sampled MESE ($1 \times 1 \times 4$ mm^3) for TE = 80 ms. The zoomed regions show the improved resolution in both planes for SR compared to the conventional sequence. MESE – Multi-Echo Spin-Echo.

Figure 7: Reconstructed T_2w images (TE = 80 ms) from the numerical phantom and in-vivo data using the diagonal orientations (TA = 18 mins). The images are shown from (a) a low-resolution dataset, (b) SR reconstruction only, (c) low-resolution model-based followed by SR reconstruction, and (d) proposed SR model-based reconstruction. The SR only reconstruction showed visible artifacts due to the undersampling as no prior information from the signal model (mono-exponential decay) was incorporated in the reconstruction. The low-resolution model-based + SR reconstruction showed improvement in the reconstruction; however, blurring around the edges is evident in both numerical phantom and in vivo data.

Figure 8: ROI Analysis for the accuracy of T_2 estimation for different dataset in different compartments of the phantom. a) T_2 map of the phantom with different compartments labels. b) The bar chart represents the mean of the T_2 values of the ROI, and the error represents the standard deviation for 10-fold, 14-fold and fully sampled MESE and SE T_2 values.

Figure 9: a) Different ROIs drawn in axial, coronal and sagittal sections of a model-based SR T2w (TE=80 ms) image. b) The bar chart represents the mean T_2 values and standard deviation for accelerated and fully sampled dataset in four different regions of brain. c) The mean and standard deviation T_2 values from model-based SR reconstruction (diagonal orientations, 10-fold acceleration) found in all subjects grouped by brain structures, each bar representing a subject.