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Super-Resolution Reconstruction of Diffusion Parameters from Diffusion-Weighted Images with Different Slice Orientations

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INTRODUCTION

Diffusion MRI (dMRI) is a noninvasive imaging modality that allows in vivo investigation and characterization of tissue microstructure (1,2). The presence of diffusion of water molecules will attenuate the signal in the diffusion-weighted (DW) images (3). Consequently, the signal-to-noise ratio (SNR) of DW images is relatively low. Also, modelling the 3D diffusion requires many DW images, resulting in long scan times and high risk for subject motion. To obtain DW images with a reasonable SNR within a clinically feasible scan time, it is common to acquire DW images with low spatial resolution compared to structural MRI images. In a clinical setting, DW images are typically acquired at a resolution ranging from 2 to 3 mm isotropic (4). Given that the diameter of an axon is of the order of 1–20 µm, large partial volume effects will occur (4,5). In fact, a recent study has shown that, at the current resolution, the diffusion tensor model (DTI model) is inadequate in the majority of white matter voxels as a result of partial volume effects, posing significant problems for DTI tractography and the interpretation of DTI integrity metrics (6). Even though one is mostly interested in the imaging of bundles of axons, the low spatial resolution limits the use of dMRI to the investigation and characterization of large fiber bundles (7). Increasing the spatial resolution of dMRI would reduce partial volume effects and thereby enable resolving finer structures and smaller bundles of axons.

Improvement of the spatial resolution in an MR image requires sampling of higher frequencies in k-space. However, sampling a large k-space within a reasonable time frame is a challenging task. DW images are preferably acquired with multislice single-shot spin-echo echo planar imaging (8) or single shot fast spin echo sequences (9,10), which image a whole slice in a single excitation. These sequences provide a fast acquisition and are robust to motion and phase shifts caused by micro motion (11,12). The time required to encode the k-space in a single shot is not negligible, so sampling a larger k-space leads to a larger echo time. Since increasing the echo time exponentially decreases the DW signal (13), encoding a larger k-space results in a drop of SNR. Clinical time constraints prohibit the use of extensive averaging to increase the SNR. Hence, there is an inherent trade-off between spatial resolution, SNR, and acquisition time.

Recent work has shown that super-resolution reconstruction (SRR) methods can provide images with an improved trade-off of spatial resolution, SNR, and...
acquisition time (14–25). SRR methods combine multiple low resolution (LR) images to obtain a high resolution (HR) image, where each LR image samples the HR scene in a different way. In dMRI, several SRR methods have been proposed. In [26–28], SRR methods developed for structural MRI were successfully applied to improve the through-plane resolution of DW images. In [26,28], the LR DW images are acquired with three orthogonal slice orientations, while in [27] arbitrary slice orientations are allowed. In addition to this type of SRR methods, several alternative methods to achieve a high spatial resolution in dMRI have been proposed [29,30]. In [30], fiber configurations are recovered on a subvoxel scale by posing the tractography as an inverse problem with regularization and in [29], resolution enhancement is obtained with single image SR techniques exploiting self-similarity across the orthogonal directions that differ in resolution.

This article belongs to the class of SRR methods that require a set of LR DW images with multiple slice orientations [27,28]. Those methods generate a set of HR DW images where each HR DW image is reconstructed from a set of LR DW images with the same diffusion weighting and gradient direction. Consequently, HR diffusion parameters are computed from the reconstructed HR DW images. Consequently, the relationship between the LR DW images from different diffusion gradient directions, that is, the diffusion model, is ignored in the SRR, which may prevent its preservation in the reconstructed HR DW images. Recently, two SRR methods that do include a diffusion model were proposed. One method uses the ball-and-stick model in combination with an SRR model [31]. Although this method shows promising results on simulated data, no clinical data experiments have been reported. Moreover, this method does not provide a solution for EPI distortions nor for motion and eddy current distortions. The other method reconstructs 3D DTI parameters iteratively from motion scattered multislice diffusion-weighted imaging (DWI) sequences acquired from a moving fetal brain [26]. However, the acquisition of both methods is restricted to orthogonal DWI stacks, limiting the resolution gain, as will be explained in the methods section. Additionally, all currently available SRR methods acquire the same set of q-space points for each slice orientation, which, as we will show, does not optimally sample the q-space. To solve these limitations, we propose an SRR method with an integrated diffusion model that directly estimates the diffusion parameters from the LR DW images. Additionally, we propose an optimal k- and q-space sampling scheme for the set of LR DW images. The main advantage of our approach is that the reconstruction algorithm can deal with and even benefit from arbitrary diffusion gradient and slice orientations as LR input.

Early versions of the proposed SRR framework in this article have been presented at ISMRM 2013 [32] and ISMRM 2014 [33].

**METHODS**

In this section, the proposed SRR-DTI method and its acquisition protocol are described. The proposed SRR-DTI method is compared to a recently published SRR method [27], which we will refer to as the SRR DW imaging (SRR-DWI) method.

**Acquisition Scheme for SRR-DTI**

In SRR, a HR image is reconstructed from a set of LR images that sample the HR scene in different ways, by acquiring the LR DW images with different slice orientations [19,23,26–28]. As only the resolution in the slice direction can be improved [34], the LR DW images are acquired with an isotropic in-plane resolution and a slice thickness larger than the in-plane resolution. Increasing the slice thickness improves the SNR in multislice image acquisitions. Throughout the article, we will quantify the anisotropy of the voxels by the anisotropy factor, $AF = \frac{b}{a}$ with $b$, the slice thickness and $a$, the voxel size in the frequency encoding direction and thus also in the phase encoding direction.

In practice, the LR DW images are often acquired with an single-shot spin-echo echo planar imaging sequence because of its short measuring times and robustness to phase shifts. Unfortunately, single-shot spin-echo echo planar imaging images generally suffer from geometric distortions along the phase encoding direction. Hence, if the LR DW images would be acquired with different phase encoding directions, the distortions would, for each LR DW image, show up in a different direction, which would result in blurring of the HR image. To avoid phase encoding direction-dependent distortions, we acquire the LR DW images with identical phase encoding directions and thus rotate the frequency and slice encoding axis around the phase encoding axis (Fig. 1).

**k-Space Sampling**

Improving the spatial resolution requires sampling higher frequencies in k-space, so an optimal coverage of k-space is desirable. Since we choose to rotate only around the phase encoding ($k_y$) axis, the k-space can only be sampled in a cylinder with radius $\frac{k}{2}$. To ensure a short acquisition time, the minimal number of slice orientations that maximally covers the k-space by rotating about the center, is chosen. Preferably, the cylinder is completely sampled while the overlap between the different k-spaces is as small as possible. Hence, the number of acquisition directions, $n$, is given by

$$n = \left\lceil \frac{\pi}{2}AF \right\rceil. \quad [1]$$

Figure 1 schematically shows the coverage of the k-space for $AF = 4$. In Figure 1a, the k-space coverage of one LR DW image is shown, while in Figure 1b, the k-space coverage of seven LR DW images, each with a different slice orientation, is shown.

**q-Space Sampling**

In dMRI, not only the spatial resolution is important, but also the angular resolution in q-space [35]. Note that for our method, in contrast to [27] and [28], it is not necessary to use the same set of diffusion gradient directions for each slice orientation. Indeed, the integration of the
DTI model into the reconstruction allows LR DW images to be acquired with an arbitrary mix of diffusion gradient directions and slice orientations. As such, each LR DW image can be acquired with a different gradient direction (sample a different point in $q$-space), resulting in a denser sampling of the $q$-space. This denser sampling leads to increased angular resolution and rotation invariant diffusion parameter estimation (36). To obtain uniform $q$-space sampling, not only the $q$-space of all the acquired LR DW images combined, but also of each group of LR DW images with the same slice orientation needs to be sampled uniformly as each group also samples a different part of $k$-space. The uniform sampling at both levels is achieved with the method of electrostatic repulsion in multiple shells (37). Figure 1 shows the classic $q$-space sampling as used in SRR-DWI (Fig. 1c) and our proposed $q$-space sampling (Fig. 1d).

**SRR-DTI Method**

**DTI Model**

Any diffusion model can be combined with our SRR model. Nevertheless, for the sake of simplicity, the methodology and experiments will be explained using the DTI model as it is one of the simplest and widely used diffusion models.

In each voxel $j$, the diffusion tensor $\mathbf{D}(j)$ is a $3 \times 3$ symmetric, positive-definite tensor, characterized by six elements. Let $r_m(v_m \times 1)$ denote the $m$th HR DW image represented as a vector, with $m \in \{1, \ldots, N\}$, the image index and $N$ the number of DW images. Let $f \in \{1, \ldots, v_m\}$ be the voxel index of $r_m$ and $v_m$ the number of voxels in image $r_m$. Then, the noise free DW image intensity of $r_m$ in voxel $f$ is:

$$r_m(f) = a(f)e^{-b_m g_m^T \mathbf{D}(f)/g_m}, \quad [2]$$

where $g_m$, $b_m$, and $a$ are the diffusion gradient direction, diffusion weighting strength, and the non-DW signal, respectively. To ensure that the result of the SRR-DTI is a positive-definite tensor and to simplify the regularization, we reparametrize the diffusion tensor $\mathbf{D}(j)$ in Eq. [2] by its matrix logarithm (38)

$$\tilde{\mathbf{D}}(j) = \log \mathbf{D}(j). \quad [3]$$

**Signal Generating Model**

Assume that $r_m$ is a vector of intensities representing the HR DW image, which serves as the ground truth (GT) image from which an LR image $s_m$ is acquired. Let $s_m(u_m \times 1)$ be a noise free LR DW image simulated from

![FIG. 1. Sampling strategy for $k$-space (a-b) and $q$-space (c-d). a: $k$-space sampling of one LR image, with $k_x$ the frequency encoding direction, $k_y$ the phase encoding direction, and $k_z$ the slice selection direction. b: $k$-space sampling of seven LR images, all acquired with a different slice orientation. The shaded area denotes the sampled $k$-space, while the white region is not sampled. c: Classic $q$-space sampling. d: Proposed $q$-space sampling. Each slice orientation is differently color coded, so the diffusion gradient directions with the same slice orientation belong to the same slice orientation.](image-url)
\( r_m(v_m \times 1) \), where the signal in voxel \( l \in \{1, \ldots, u_m\} \) of \( s_m \) is given by (19, 27):

\[
    s_m(l) = \sum_{j=1}^{v_m} X_m(j, l) r_m(j) \tag{4}
\]

with \( X_m \) a \((u_m \times v_m)\) linear operator defining the transformation of the HR DW image into the LR DW image. The acquired image \( S_m \) can be modeled as \( S_m(l) = s_m(l) + e_m(l) \), with \( e_m(l) \) the measurement noise in voxel \( l \). Note that the image is Rician distributed but that for high SNR (SNR >5), the noise can be assumed to be Gaussian distributed (39).

The transformation \( X_m \) can be split into different steps. First, motion and eddy current effects are modeled with an affine transformation \( M_m \). Next, the geometric transformation \( T_m \) maps the points in the HR space, \( x_j \), to the space of the \( m \)th LR image, \( y_j \). The slice selection and in-plane sampling are modeled by the point spread function \( \omega \), which is defined by the MR image acquisition method. In the frequency and phase encoding direction, the sampling functions are defined by a rectangular area in k-space, and hence \( \omega \) is modeled by a windowed sinc function. In the experiments in this work, a windowed sinc RF pulse was used for slice selection, so the slice selection, part of \( \omega \), was modeled by a smoothed box function (19). The projection matrix \( X_m \) can be written as,

\[
    X_m(j, l) = \omega(T_m(M_m(x_j)) - y_j). \tag{5}
\]

As the acquisition time of one LR DW image is short, it can be assumed that the motion during the acquisition of this LR DW image is negligible. The transformation \( M_m \) that models the motion in between the different LR DW images and the eddy current effects, is obtained by affinely registering the LR DW images to each other, for example, using Elastix (40). By incorporating the motion and eddy current distortions in the acquisition model, the original acquired LR DW images can be used as input for the SRR-DTI method. So, in contrast with (28), the HR DTI parameters are estimated from the acquired LR DW images and not from interpolated LR DW images, resulting in a more accurate model. From the affine transformation, \( M_m \), the corresponding rotation matrix is derived, which in turn is used to rotate the diffusion gradient directions (41). As the proposed SRR-DTI method can deal with arbitrary diffusion gradient directions, compared to (17) and (28), no interpolation in q-space is needed. \( M_m \) and \( T_m \) are both affine transformations and are combined into one affine transformation. The multiplication with \( X \), which is specified by this combined transformation, is applied efficiently using shear transformations as described in (19).

Reconstruction of the HR DTI Parameters

By substituting Eqs. [3] and [2] into Eq. [4], the LR DW images \( s_m \) are predicted from the HR non-DW image intensity \( a \) and the matrix logarithm of the HR diffusion tensor \( D \):

\[
    s_m(l) = \sum_{j=1}^{v_m} X_m(j, l) a(j) e^{-b_s s_m^w \exp(D(l))} \tag{6}
\]

The HR DTI parameters can be estimated by

\[
    \hat{D}, \hat{a} = \arg\min_a \sum_{m=1}^{N} \sum_{l=1}^{u_m} \|s_m(l) - S_m(l)\|^2 + \lambda R(D, a). \tag{7}
\]

where \( s_m \) is a function of \( D \) and \( a \) as given by Eq. [6], \( R(D, a) \) is a regularization function and \( \lambda \) its corresponding weighting factor. The regularization term \( R(D, a) \) is required since the HR grid generally contains spatial frequencies that are not sampled by any of the LR DW images (the white region in Fig. 1b). Since the log diffusion tensor is estimated, the regularization is performed in the Log-Euclidean domain (42). As such, the same regularization as in (27) can be used. In this regularization term, the high frequencies are minimized by computing the squared Laplacian of the reconstructed log diffusion tensor \( D \) and the logarithm of the non-DW image intensity \( a \).

The nonlinear least squares problem stated in Eq. [7] is solved using a trust-region Newton method (43). The problem is very “large-scale” due to the large number of parameters and the coupling between the parameters. The combination of the LR data, the reconstructed HR DTI parameters and the gradients and Hessians needed in the optimization method, requires a large amount of memory. To reduce memory consumption and the number of iterations required by the optimization, the region of interest (ROI), for example, the brain in human brain scans, is split in several blocks, where the HR DTI parameters are reconstructed in each block separately. In the experiments, the blocks were \( 30 \times 30 \times 30 \) voxels and had an overlap of 5 voxels in each dimension to avoid block edge artifacts. To initialize \( D \) and \( a \), first all LR DW images were transformed to the HR grid with the adjacent transformation \( X_m \). Next, the logarithm of the diffusion tensor was estimated from these images by a nonlinear Log-Euclidean framework (38). Finally, the logarithm of the HR diffusion tensor (Eq. [3]) and the non-DW signal \( a \) served as the initialization for the reconstruction.

Experiments

Both synthetic and clinical datasets were used to evaluate the reconstruction quality of the proposed SRR-DTI method and the previously proposed SRR-DWI method in terms of SNR and resolution.

Synthetic Data

The Numerical Fiber Generator (44) was used to simulate a noiseless \( 48 \times 48 \times 48 \) DW dataset with one non-DW image \((b = 0s/mm^2)\) and 64 DW images \((b = 1000s/mm^2)\). From this DW dataset, DTI parameters were calculated, which served as GT dataset. Based on Eq. [6], Rician distributed datasets with anisotropic voxel size and a noise level of \( \sigma = 0.2 \) were simulated from this GT dataset. Table 1 shows the detailed settings of the simulated images. For each dataset, the total number
Table 1
Overview of the Simulated HR and LR DW Datasets

<table>
<thead>
<tr>
<th>Dataset</th>
<th>AF</th>
<th>(n_b)</th>
<th>(n)</th>
<th>(N_{DW})</th>
<th>(N)</th>
<th>SNR of (a)</th>
<th>(q)-Sampling</th>
<th>SRR method</th>
<th>SRR result</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT</td>
<td>1</td>
<td>48</td>
<td>1</td>
<td>64</td>
<td>65</td>
<td>(\infty)</td>
<td>Classic (DTI model)</td>
<td>GT DTI</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1</td>
<td>48</td>
<td>1</td>
<td>14</td>
<td>15</td>
<td>5</td>
<td>Classic (DTI model)</td>
<td>HR DTI</td>
<td></td>
</tr>
<tr>
<td>LR AF2</td>
<td>2</td>
<td>24</td>
<td>1</td>
<td>31</td>
<td>32</td>
<td>10</td>
<td>Classic (DTI model)</td>
<td>LR DTI AF2</td>
<td></td>
</tr>
<tr>
<td>LR AF2c</td>
<td>2</td>
<td>24</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>Classic (DTI model)</td>
<td>SRR-DWI</td>
<td>SRR DWI AF2c</td>
</tr>
<tr>
<td>LR AF2p</td>
<td>2</td>
<td>24</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>Proposed</td>
<td>SRR-DWI</td>
<td>SRR DWI AF2p</td>
</tr>
<tr>
<td>LR AF4</td>
<td>4</td>
<td>12</td>
<td>1</td>
<td>62</td>
<td>63</td>
<td>20</td>
<td>Classic (DTI model)</td>
<td>LR DTI AF4</td>
<td></td>
</tr>
<tr>
<td>LR AF4c</td>
<td>4</td>
<td>12</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>20</td>
<td>Classic (DTI model)</td>
<td>SRR-DWI</td>
<td>SRR DWI AF4c</td>
</tr>
<tr>
<td>LR AF4p</td>
<td>4</td>
<td>12</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>20</td>
<td>Proposed</td>
<td>SRR-DTI</td>
<td>SRR DTI AF4p</td>
</tr>
<tr>
<td>LR AF6</td>
<td>6</td>
<td>8</td>
<td>1</td>
<td>95</td>
<td>96</td>
<td>30</td>
<td>Classic (DTI model)</td>
<td>LR DTI AF6</td>
<td></td>
</tr>
<tr>
<td>LR AF6c</td>
<td>6</td>
<td>8</td>
<td>12</td>
<td>7</td>
<td>96</td>
<td>30</td>
<td>Classic (DTI model)</td>
<td>SRR-DWI</td>
<td>SRR DWI AF6c</td>
</tr>
<tr>
<td>LR AF6p</td>
<td>6</td>
<td>8</td>
<td>12</td>
<td>7</td>
<td>96</td>
<td>30</td>
<td>Proposed</td>
<td>SRR-DTI</td>
<td>SRR DTI AF6p</td>
</tr>
</tbody>
</table>

\(n_b\) is the number of slices per image, \(n\) is the number of slice orientations, \(N_{DW}\) is the number of DW images per slice orientation, \(N\) is the total number of LR images, and \(a\) is the non-DW image.

of slices \((N \cdot n_b, n_b\) being the number of slices per image) and the in-plane resolution are equal. So, given that the acquisition time of one slice, \(T_a\), is independent of the slice thickness, the total acquisition time, \(T_{acq} = N_n T_a\), is equal for all datasets. The number of slice orientations, \(n\), was chosen according to Eq. [1], with the exception of the dataset with AF = 6, where \(n = 12\) was chosen to obtain a more similar acquisition time. Table 1 also defines the naming scheme of the simulated datasets and the corresponding DT estimates. The first part of the name refers to the type of DW dataset, the second part refers to the AF. A “c” at the end means the classic \(q\)-space sampling is used, a “p” means the proposed \(q\)-space sampling is used. The names of the reconstructed datasets are built in the same way, where the first part indicates the used SRR method. When no SRR method is used, the first part of the name is kept the same as for the simulated datasets.

Using the classic \(q\)-space sampling, at least six noncollinear diffusion gradient directions need to be acquired per slice orientation to avoid that the DTI parameter estimation problem becomes underdetermined. This is not the case for the proposed \(q\)-space sampling as for each slice orientation a different set of diffusion gradient directions can be used. As such, the total number of noncollinear diffusion gradient directions can still exceed six when less than six diffusion gradient directions per slice orientation are used. To highlight the impact of the proposed \(q\)-space sampling, LR DW datasets with AF = 2 and a different number of diffusion gradient directions per slice orientation, \(N_{DW}\), ranging from 2 to 20, were simulated from the GT dataset. As these LR DW datasets have a different number of LR DW images, their acquisition time will not be the same.

From each LR DW dataset, HR DTI parameters were reconstructed on a HR grid of \(48 \times 48 \times 48\) using the SRR-DTI method. Additionally, from the LR DW datasets with classic \(q\)-space sampling, \(N_{DW} = 48 \times 48 \times 48\) HR DW images were reconstructed with the SRR-DWI method. From these HR DW images, HR DTI parameters were estimated with the Log-Euclidean framework. The regularization factor \(\lambda\) was chosen so that the total root-mean-square error (RMSE) on the DT parameters was minimal. HR DTI parameters were estimated from the HR dataset with the Log-Euclidean framework.

To quantify the reconstruction results, each dataset was simulated with 50 noise realizations. Using the GT dataset, for each of the 50 reconstructions, the RMSE of the fractional anisotropy (RMSE FA), the RMSE of the mean diffusivity (RMSE MD) and the median angular error of the first eigenvector (MAE FE) were calculated. These errors incorporate both the variance and the bias of the reconstruction and are often used to quantify the uncertainty of DTI parameter estimation (27,29).

### Clinical Data

For the evaluation of the proposed SRR-DTI method with human in vivo data, six datasets of a single healthy 27-years old volunteer were acquired with a Trio Scanner (3T; Siemens AG, Siemens Medical Solution, Erlangen, Germany) with a 32-channel head coil. The acquisition parameters were chosen such that the acquisition time was similar for all DW datasets. The in-plane resolution of all DW datasets, except the isotropic LR dataset, was \(1.5 \times 1.5\) mm\(^2\) and the slice thickness was AF-1.5 mm. All the DW datasets were acquired with a multislice single-shot spin-echo echo planar imaging sequence without a slice gap and no averaging. As many acquisition parameters as possible were kept the same in each dataset: the field of view \(237 \times 237 \times 192\) mm\(^3\), acquisition matrix \(158 \times 158\) with 119 phase encoding steps, 100% sampling and the pixel bandwidth 1666 Hz. The non-DW images were acquired with \(b = 0\) s/mm\(^2\), the DW images with \(b = 1000\) s/mm\(^2\). Datasets ending with \(c\) were acquired with the classic \(q\)-space sampling, those ending with \(p\) with the proposed \(q\)-space sampling. The subsets were acquired with a different slice orientation rotated around the phase encoding axis (Fig. 1).

- **LR AF2p and LR AF2c**: LR DW datasets with voxel dimensions \(1.5 \times 1.5 \times 3\) mm\(^3\) (AF = 2) consisting of
FIG. 2. Three orthogonal views of the DEC FA map of the simulated phantom, with directions left—right (red), up—down (blue), and back—front (green) for different datasets which all have the same acquisition time.
four subsets of LR DW images. Each subset included one non-DW image and seven DW images and each LR DW image had a TR = 9700 ms, TE = 97 ms and 64 slices. The total scanning time was 5.17 min.

- **LR AF4p and LR AF4c**: LR DW datasets with voxel dimensions 1.5 mm x 1.5 mm x 6 mm (AF = 4) consisting of 7 subsets of LR DW images. Each subset included 1 non-DW image and 8 DW images and each LR DW image had a pulse repetition time (TR) = 4900 ms, echo time (TE) = 97 ms and 32 slices. The total scanning time was 5.14 min.

- **HR DTI**: Direct isotropic HR dataset with voxel dimensions 1.5 x 1.5 x 1.5 mm³, consisting of 7 subsets of LR DW images. Each subset included 1 non-DW image and 14 DW images. Each DW image had a TR = 19,426 ms, TE = 97.4 ms and 128 slices. The total scanning time was 4.85 min.

- **LR DTI**: Isotropic LR dataset with voxel dimensions 2.5 x 2.5 x 2.5 mm³ and acquisition matrix 104 x 104, consisting of one non-DW image, and 15 DW images. Each DW image had a TR = 16,900 ms, TE = 98 ms and 69 slices. The total scanning time was 4.51 min.

To highlight the impact of the proposed q-space sampling, datasets with less than six diffusion gradient directions per slice orientation were created from the LR AF2p and LR AF4p datasets. For each acquisition orientation the appropriate number of diffusion gradient directions were selected from the existing 7 or 8 diffusion gradient directions. It is important to notice that in this way, the datasets will have a suboptimal q-space sampling. Moreover, these LR DW datasets will have a reduced acquisition time as they contain less DW images.

- **LR AF2p D5**: LR AF2p dataset with for each of the four subsets one non-DW image and five DW images. The total scanning time would be 3.88 min.

- **LR AF4p D5**: LR AF4p dataset with for each of the seven subsets one non-DW image and five DW images. The total scanning time would be 3.43 min.

- **LR AF4p D4**: LR AF4p dataset with for each of the seven subsets one non-DW image and four DW images. The total scanning time would be 2.86 min.

The lowest TR = 4900 ms is still substantially larger than the T₁ of gray and white matter in the brain [0.9–1.4 s, (45)]. Hence, no significant influence of incomplete T₁ relaxation is expected. Each of the anisotropic LR DW datasets was used to construct HR DTI parameters, with voxel dimensions 1.5 x 1.5 x 1.5 mm³. For the two datasets with classic q-space sampling, LR AF2c and LR AF4c, the SRR-DWI method was used, resulting in SRR DWI AF2 and SRR DWI AF4 maps, respectively. The datasets, LR AF2p (D5) and LR AF4p (D4 and D5), acquired with the proposed q-space sampling, were reconstructed with the SRR-DTI method, resulting in the SRR DTI AF2p (D4) and SRR DTI AF4p (D4 and D5) estimates, respectively. DTI parameters were directly estimated from the acquired isotropic HR and isotropic LR dataset using the log-Euclidean framework. For each reconstruction, the FA and directionally encoded (DEC) FA map were calculated. Furthermore, whole brain deterministic DTI tractography was performed using MRtrix3 (46). For each dataset, a streamline was launched from fixed equidistant seed points throughout the brain. The minimum fiber length was set to 10 mm, the FA threshold to 0.1 and the step size to 0.15 mm. The SNR of the non-DW image of each of the acquired DW datasets was computed by calculating the ratio of the mean and standard deviation of a uniform region in the corpus callosum.

To quantify the resolution of the (reconstructed) volunteer datasets, the FA along a line segment was plotted for several line segments crossing a border between...
structures with different FA. The FA on the line segments is obtained by cubic spline interpolation on the FA image. As resolution proxy the apparent width of the anatomically step wise transition in FA is used. This width is defined as the distance between 10 and 90% of the step in FA value. Additionally, to quantify the noise in the FA images, the standard deviation ($\sigma$) of the HR FA maps was computed in a uniform region in the corpus callosum.

RESULTS

Synthetic Data

Figure 2 shows the DEC FA maps constructed from the different simulated datasets. As can be seen in Figure 2b, the HR DTI dataset suffers from a low SNR in comparison to the other datasets. Compared to the HR DTI dataset, the anisotropic LR datasets (Fig. 2c, g, k) have a higher SNR. However, due to the lower through-plane resolution, partial volume effects appear and fine details are lost. These partial volume effects increase with increasing AF. From Figure 2d–f, h–j, and l–n, it is clear that all the SRR datasets show an improvement in details compared to the LR DW datasets they stem from. Furthermore, compared with the HR DTI dataset, smaller details are no longer concealed by the noise. The images closely resemble the GT data (Fig. 2a). This is confirmed by the quantitative evaluations given in Figure 3, where the error bars represent the 95% confidence interval based on 50 noise realizations. The RMSE FA, MAE FE, and RMSE MD are significantly higher for the HR DTI dataset than for the SRR datasets.

When the SRR DWI AF2c map (Fig. 2d) is compared with the SRR DTI AF2c and SRR DTI AF2p maps (Fig. 2e, f), small differences can be observed. Figure 3 shows that the RMSE FA and MAE FE are significantly smaller for SRR-DTI than for SRR-DWI for all AFs. The RMSE MD is not significantly different when LR DW images with AF = 4 or 6 are used, combined with SRR-DTI or SRR-DWI. The quantitative measures also point out that using datasets with a higher AF results in a better reconstruction, as all the quantitative measures decrease with increasing AF.

When comparing the SRR-DTI maps with classic (Fig. 2e, i, m) and proposed q-space sampling (Fig. 2f, j, n), the differences are small and hard to observe. The differences in the quantitative measures (Fig. 3) are more clear: the RMSE FA and MAE FE are significant smaller for the SRR-DTI reconstructions with the proposed q-space sampling. In the RMSE MD, no significant differences can be observed between the proposed and classic q-space sampling. With increasing AF, the differences in RMSE FA and MAE FE between the classic and proposed q-space sampling decrease.

In Figure 4, the RMSE FA, MAE FE, and RMSE MD are shown as a function of the number of diffusion gradient directions per slice orientation ($N_{DW}$) for the different SRR methods if $AF = 2$. The acquisition time scales linearly with $N_{DW}$.

Clinical Data

The SNR values of the non-DW images are $SNR_{HR \text{ DTI}} = 4.7$, $SNR_{LR \text{ AF2}} = 8.4$, and $SNR_{LR \text{ AF4}} = 15.2$. These values demonstrate that, as expected on theoretical grounds, the SNR in actual acquisitions is proportional to the slice thickness.
Figure 5 shows orthogonal slices of the DEC FA map for the HR acquisition, LR acquisition and the SRR DTI AF4p reconstruction. The DEC FA map of the isotropic HR DTI data (Fig. 5a) shows fine structures but clearly suffers from a low SNR. As a result, some of the fine details are lost in the noise. Although acquiring the data with a lower isotropic resolution (Fig. 5b) does improve the SNR, smaller structures are harder to distinguish due to partial volume effects. Figure 5c demonstrates that the SRR-DTI method successfully recovers HR information while preserving the high SNR of the anisotropic LR dataset they stem from. This can be even more appreciated from Figure 6, which zooms in on the FA map for the different acquisitions and reconstructions. Figure 6 shows the differences between the SRR-DWI and SRR-DTI reconstruction results. Although the SRR-DWI method (Fig. 6c, d) recovers most HR information, some structures are more clear in the SRR-DTI FA maps (Fig. 6e, f).

The standard deviations, $\sigma$, on FA are given in Figure 6. The HR DTI FA map (Fig. 6a) has the highest $\sigma$ due to the presence of noise. The $\sigma$ of the FA maps of both SRR methods are lower than the one of the HR DTI FA map and of the LR DTI FA map (Fig. 6b). The SRR-DTI FA maps (Fig. 6e, f) have a lower $\sigma$ than the SRR-DWI FA maps (Fig. 6c, d). As the SNR increases with increasing AF, $\sigma$ decreases with increasing AF.

Figure 7 shows the FA along a line segment for several line segments crossing a border between structures with different FA. The HR DTI FA increases fast over a short distance, which is underpinned by the small width of the FA transition, but fluctuates due to the low SNR. The LR DTI FA shows less fluctuations, but has a slower increase and the width of the FA transition is larger. Both the SRR-DWI FA and the SRR-DTI FA increase faster than the LR DTI FA and show less fluctuations than the HR DTI FA. The width of the FA transition is
also smaller for SRR-DWI and SRR-DTI than for LR DTI. Comparing the reconstructions derived from datasets with the same AF, the width of the FA transition is smaller for SRR-DTI than for SRR-DWI. Between different AFs, overall, the width of the FA transition is smaller for datasets with a higher AF.

In Figure 8, orthogonal slices of the DEC FA maps for the SRR-DTI reconstruction on the datasets with less than six diffusion gradient directions per slice orientation are shown. It is important to notice that the datasets from which these DEC FA maps are reconstructed, have a suboptimal q-space sampling. As these datasets are a subset from the LR AF2p and LRAF4p datasets, their acquisition time is shorter than the one of the DEC FA maps shown in Figure 5. Although these datasets have shorter acquisition time than the LR DTI dataset, their DEC FA maps show more details than the LR DTI DEC FA map (Fig. 5b) and the width of the FA transition across the borders of two structures is smaller than for the LR DTI dataset (Fig. 7b). The standard deviation on FA is lower than the standard deviation on the HR DTI FA.

Figure 9 shows a slab visualization of the whole brain tractography results. The HR dataset (Fig. 9a) provides a poor result with many short tracts due to the low SNR. The track density of the isotropic LR dataset (Fig. 9b) and the SRR datasets (Fig. 9c–i) is higher, due to their high SNR. The tracks are also longer for these datasets.

DISCUSSION

Increasing the spatial resolution in DTI is a challenging task because of the trade-off between spatial resolution, SNR, and acquisition time. To improve this trade-off, we have proposed an SRR-DTI method that reconstructs HR diffusion tensor fields from multiple anisotropic LR DW images acquired with different slice orientations and diffusion gradient directions. By extending the SRR method with the DTI model, it is ensured that the solution of the reconstruction satisfies the DTI model. Moreover, the reconstruction of the HR DTI parameters is now performed in one step instead of two. Therefore, errors will not propagate through the different steps of the reconstruction. Another advantage of the SRR-DTI method is that the diffusion gradient directions and slice orientations can be arbitrarily selected. Opposed to the methods by (27) and (28), it is not required to acquire the same set of diffusion gradient directions for each slice orientation. The possibility to use a different diffusion gradient direction for each LR DW image results in a more extended sampling of the q-space. The experiments demonstrate an improved RMSE of the SRR diffusion tensor parameters compared to those obtained from a HR DW acquisition with the same acquisition time. They also show an improvement compared to previously published reconstruction methods.

A correct spatial alignment of the LR DW images is crucial for SRR. Incorrect registration of the images leads to blurring in the reconstruction and affects the estimated diffusion tensors. Therefore, motion correction with the corresponding b-matrix rotation is included in the SRR-DTI method. Currently, the LR DW images are first affinely registered and the resulting transformation parameters are then used in the acquisition simulation of the LR DW images, to simulate the motion and eddy current effects. By doing so, the SRR-DTI method starts from the original acquired LR DW images rather than from resampled LR DW images as in (28). The eddy current distortion correction is modeled together with the motion as an affine transformation. Assuming that the eddy currents induce affine deformations is common (47–49), even though it is known that the deformations depend on slice position (50).

In contrast to (26,28,31,51), the LR DW images are not acquired with three orthogonal slice orientations. In this work, the slice orientations are rotated around the phase encoding axis to prevent blurring due to EPI-distortions. This acquisition set up leads to a nonuniform sampling of the k-space, with a higher density in the center of k-space.
This oversampling of the center of k-space, which leads to a high SNR of the low frequency range, is often used in MRI as it reduces sensitivity to motion artifacts (52). Due to the lower density in the higher frequency range, some high frequencies might not be sampled by any of the LR DW images. Therefore, regularization is used to force the amplitude of these under sampled high frequencies to zero. Furthermore, due to this sampling scheme...
super-resolution is not possible along the phase encoding direction. Note, however, that this acquisition strategy is only used to avoid inconsistencies due to EPI distortions and is not an inherent limitation of the proposed SRR method. The rotation of the slice orientations enables the reconstruction of a HR DTI map from LR DW images with arbitrary slice thicknesses. The simulation and clinical data experiments compared the reconstruction results of LR datasets with AFs. Increasing the AF leads to an increased partial volume effect, as the voxels are larger. However, data with a higher AF has a shorter acquisition time, and thus, more LR DW images can be acquired in the same acquisition time. Moreover, the increase in AF also leads to an increased SNR of the measured data, which, in turn, leads to a more precise estimation of the HR DTI parameters. The increased AF and large partial volume effects may complicate accurate motion correction. Moreover, constraints in the hard and software of the MRI scanner limit the choice of the AF in clinical practice.

A major advantage of the proposed SRR-DTI method over the SRR-DWI method, is its flexibility in acquisition set up. In contrast to (27) and (28), it is no longer required to acquire the same set of diffusion gradient directions per slice orientation and as such a minimum of six diffusion gradient directions per slice orientation. Acquiring a different set of diffusion gradient directions for each slice orientation results in a denser $q$-space sampling. The experiments show that the SRR-DTI method benefits from this denser $q$-space sampling. With the SRR-DTI method and proposed $q$-space sampling, HR DTI parameters can be estimated with the same quality, in terms of RMSE FA, MD, and MAE FE, within a shorter scan time compared to the SRR-DWI method or

FIG. 8. Axial, sagittal, and coronal slice of DEC FA maps with isotropic voxels (1.5 mm; red: left–right, green: anterior–posterior, blue: superior–inferior) for different reconstructions from datasets with a limited number of diffusion gradient directions per slice orientation.
direct HR acquisition. The impact of the proposed $q$-space sampling reduces when more LR DW images are used. This is expected as an increase in LR DW images results in a denser $q$-space sampling.

In the proposed method, distortions of the EPI images due to off-resonance effects are not corrected. To prevent problems due to these distortions, the LR DW images are acquired with the same phase encoding directions. Due to this choice, the EPI-distortions will not affect the registration of the images and thus will not cause inconsistencies between the diffusion model and acquired data. However, since the distortions are not corrected, the resulting DTI parameter maps will show the EPI-distortions in the phase encoding direction. The use of a field map (53) or reversed phase encoding (54,55) on the LR DW images could reduce these problems (28). Those correction methods are fully compatible with the proposed reconstruction method, but application of them is beyond the scope of this article.

Although in this work the DTI model was used, we would like to point out that the proposed SRR framework is generic as other diffusion models can be incorporated analogously. We foresee that models relying on high angular resolution diffusion data would benefit even more from the proposed $q$-space sampling.

FIG. 9. Coronal slab visualization (thickness: 3 mm) through the corticospinal tracts of the whole brain tractography (red: left–right, green: anterior–posterior, blue: superior–inferior) for different reconstructions. The two top rows have the same acquisition time, the acquisition time of the bottom row is shorter.
CONCLUSION

In this article, we proposed an SRR-DTI method that reconstructs HR diffusion parameters from LR DW images with different slice orientations and diffusion gradient directions. Including the DTI model allows denser sampling of the q-space as well as integration of motion and eddy current distortion correction and the corresponding b-matrix rotation in the reconstruction. Furthermore, we proposed a method to select an optimal sampling scheme of the q-space. Experiments with synthetic and in vivo data demonstrate that with the SRR-DTI method, HR DT parameters can be estimated with a significantly lower RMSE compared to a direct HR acquisition in the same scanning time and that the reconstruction benefits from the integration of the DTI model and the proposed q-space sampling scheme.

Overall, the SRR-DTI method is more flexible than the existing methods. The experiments have shown that SRR substantially increases the spatial resolution and/or SNR of DTI obtainable in a clinically acceptable scan time.

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