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Accelerated Radial Diffusion Spectrum Imaging using a Multi-Echo Stimulated Echo diffusion sequence

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Abstract

Purpose—Diffusion Spectrum Imaging (DSI) provides us non-invasively and robustly with anatomical details of brain microstructure. To achieve sufficient angular resolution, DSI requires a large number of q-space samples, leading to long acquisition times. This need is mitigated here by combining the beneficial properties of Radial q-space sampling for DSI with a Multi-Echo Stimulated Echo Sequence (MESTIM).

Methods—Full 2D k-spaces for each of several q-space samples, along the same radially outward line in q-space, are acquired in one readout train with one spin and three stimulated echoes. RF flip angles are carefully chosen to distribute spin magnetization over the echoes and the DSI reconstruction is adapted to account for differences in diffusion time among echoes.

Results—Individual datasets and bootstrapped reproducibility analysis demonstrate image quality and SNR of the more-than-twofold-accelerated RDSI MESTIM sequence. Orientation Distribution Functions (ODF) and tractography results benefit from the longer diffusion times of the latter echoes in the echo train.

Conclusion—A MESTIM sequence can be used to shorten RDSI acquisition times significantly without loss of image or ODF quality. Further acceleration is possible by combination with simultaneous multi-slice techniques.

Keywords

Diffusion Spectrum Imaging; RDSI; radial q-space acquisition; stimulated echo; multi-echo

Introduction

Diffusion Spectrum Imaging (DSI) [1] provides us with robust non-invasive renditions of the complex white matter tract architecture in the human brain [2,3]. DSI achieves this by characterizing the three-dimensional diffusion displacement of water molecules in the diffusion encoding space (also dubbed q-space). Based on these diffusion weighted signal intensities, DSI enables model-free, unbiased estimation of the Orientation Distribution Function (ODF), a measure of complex distribution of intravoxel fiber orientations in each voxel. Resulting voxel-wise ODF information is combined over the brain volume with tractography algorithms to generate estimates of brain connectivity. Although tractography continues to improve, the information it provides is already successfully used to depict

changes in brain connectivity in brain research (e.g. [4, 5]) and pathologically relevant conditions [3].

DSI and other High Angular Resolution Diffusion Imaging (HARDI, [6]) methods such as Q-ball imaging [7] do not rely on prior assumptions about intravoxel fiber distributions in the human brain. Consequently, these methods are well suited to produce accurate depictions of two or more crossing fibers, combinations of dominant and minor fiber bundles, and “kissing” fibers found in each voxel in the human brain [6–9]. These methods thus receive increasing attention over methods which assume single (Diffusion Tensor Imaging, DTI, [9,10]) or multiple [6] fiber bundles as promising tools for detailed visualizations of brain neural connectivity [2,11,12].

The crucial property of DSI in identifying intravoxel fiber crossings is the angular resolution, or the smallest crossing angle that can be resolved between two fibers [11]. The obtained angular resolution depends on the sampling geometry of q-space. In the traditional rectangular q-space grid, increased angular resolution requires larger q-space radii and a larger sampling matrix, resulting in a cubic increase both in the number of required samples and in acquisition time [13]. As a result, for clinical applications using conventional MRI hardware (40–80mT/m, 180mT/m/ms gradients), the maximum angular resolution is a trade-off between scan time and SNR with the optimum maximum q-value limited by gradient performance [14]. Even then, the large number of q-space samples needed leads to long acquisition times [15]. One approach to mitigating these limitations is the use of simultaneous multi-slice or multiband techniques in which several slices are encoded at the same time [16,17]. Here, we choose to explore a complementary approach to improve the time efficiency of DSI by acquiring full 2D k-spaces for each of several q-space samples per readout train.

A recently introduced improvement of DSI, Radial q-space sampling for DSI (RDSI, [13]), succeeds in improving angular resolution at moderately high b-values (e.g. $b = 4000 \text{ s/mm}^2$). RDSI samples q-space on a radial raster and analytically reconstructs the resulting q-space directly (no interpolation) to provide estimates of the ODF at each angular direction via the Central Section Theorem (Fourier Slice Theorem). Not only does this make the nominal angular resolution primarily dependent on the number of radial lines N_r along which samples are acquired (i.e. a quadratic increase of samples with angular resolution instead of a cubic increase) [13]; but it is also more robust against truncation effects due to Gibbs ringing artifacts [13]. The latter can lead to unwanted spurious peaks [13, 18, 19]. RDSI uses multiple shells in q-space, similar to multi-shell q-ball imaging approaches [20,21]. However, it is important to note that the RDSI reconstruction is an exact DSI-reconstruction (i.e. a full Fourier Transform by way of the Fourier Slice Theorem [13]), rather than a fit of orthogonal basis functions on a sphere’s surface as in q-ball imaging.

The q-space sampling strategy of RDSI can be accelerated by acquisition of full 2D k-spaces for each of several q-space samples per readout train because RDSI calls for the acquisition of multiple q-space samples along a set of radial lines. All, or several, of the samples along the same radial line can be measured in one readout train of multiple spin and stimulated echoes (Figure 1c). This single-readout approach accelerates the acquisition relative to the

conventional Twice Refocused Spin Echo (TRSE) diffusion sequence (Figure 1a). Indeed, the Multi-Echo Stimulated Echo Sequence (MESTIM) presented here measures full 2D k-spaces for each of 4 q-space samples per readout. Taking into account the longer readout train, the MESTIM sequence speeds up RDSI acquisition by more than a factor of two.

In this work, we show the feasibility of accelerating RDSI acquisitions using a MultiEcho Stimulated echo sequence *in vivo* in a clinical 3T scanner. We detail the sequence layout and the echo signal distribution, discuss implications for RDSI reconstruction, compare reproducibility metrics with a TRSE sequence, and show *in vivo* ODF and tractography results for the MESTIM and TRSE sequences.

Methods

Q-space sampling

Radial Diffusion Spectrum Imaging (RDSI) samples q-space on a radial grid [13]. Indeed, several q-space samples are acquired on each of a number of radial lines N_l (Figure 1). Note that this radial sampling of q-space is independent of the k-space sampling scheme, which is Cartesian in this paper. Whereas the conventional rectangular acquisition of q-space samples [2] in DSI uses a three-dimensional Fourier Transform to reconstruct the Probability Density Function (PDF) from q-space, radially sampled DSI benefits from the geometry of its sampling scheme. That is, the three-dimensional Fourier Transform is rewritten using the Fourier slice theorem to the one-dimensional radial Fourier Transform of a three-dimensional Radon transform [13]. In this reconstruction, both q-space and the PDF are sampled on radial grids, and the Orientation Distribution Function (ODF) can be easily calculated without interpolation. From these ODFs, the PDF is integrated radially outward, weighted by the square of the displacement L [11]. The preservation of radial geometry has the advantage that every radial line in q-space generates a value of the ODF at the same angular location in the spatial domain [13]. Hence, the nominal angular resolution is mainly determined by the number of lines intersecting the unit sphere and not by the largest q-space value sampled [13].

An additional benefit of the radial geometry of RDSI reconstruction is the avoidance of the Gibbs ringing artifacts [22], which arise from the Discrete Fourier Transformation (DFT) of truncated datasets. The Gibbs ringing artifacts of a three-dimensional DFT (Cartesian DSI) affect different radial directions differently and may lead to spurious peaks, a phenomenon usually mitigated in conventional Cartesian DSI by application of a Hanning filter, although at the cost of blurring the PDF [14, 23]. However, one-dimensional DFT in RDSI has the benefit that its reduced Gibbs ringing artifacts appear along the radial direction, thus not interfering with directional information in the PDF.

Multi-Echo Stimulated Echo Sequence

Here we present a Multi-Echo Stimulated Echo Sequence (MESTIM) for Radial DSI. In each TR, this sequence generates four echoes using five RF-pulses (Figure 2a): one spin echo after the second RF-pulse and three stimulated echoes after each of the subsequent RF-pulses. The magnetization of the stimulated echoes is only affected by the initial excitation

pulse, the second RF-pulse which stores the magnetization along the longitudinal axis and the RF-pulse directly before the echo which flips the magnetization back to the transverse plane. In addition, given the storage of their magnetization along the longitudinal axis, the stimulated echoes are also unaffected by the diffusion and readout gradients of earlier echoes which occur between the second RF-pulse and the RF-pulse directly before the readout of the echo. The sequence layout allows for the encoding of subsequent echoes with increasing diffusion weighting along a line in q-space (Figure 1bc); thus for acquiring a full 2D k-space for each of multiple q-space samples in each TR. This translates to a significant acceleration of the DSI acquisition. To our knowledge, this is the first application for DSI acquisitions of the technique of generating and acquiring multiple echoes [24–29].

The MESTIM sequence generates four echoes. The existence and properties (echo times, relaxation and diffusion weighting) of these echoes are calculated using the coherence pathway formalism [27,30,31] (Figure 2b). This formalism is used to optimize the RF-flip angles as to minimize variations in echo amplitudes between the coherence pathways generating the echoes [26,29]. In this optimization, the T_1 , T_2 and diffusion D of human brain tissue (white matter at 3T, $T_1 = 1.084$ s, $T_2 = 0.069$ s [32], $D = 0.705 \cdot 10^{-3} \text{mm}^2/\text{s}$ [33]) are taken into account. Optimal angles are calculated to be 90° , 75.6° , 33.6° , 44.6° and 90° . Unwanted echoes are spoiled by adding spoiler gradients before the third, fourth and fifth RF-pulses in the slice directions and to the de- and rephasors of the slice-selective gradients.

Although some of the echoes in the MESTIM-sequence have formation times (TE+TM) up to 250ms (Table 1), they retain sufficient signal for imaging (Figure 2bc) even taking into account the loss of signal due to the stimulated echo mechanism. The time between the first excitation and the formation of the echo includes both the Mixing Time TM where the signal suffers from T_1 -relaxation and the time TE where T_2 relaxation reduces the signal. As a result, the signal of each echo S , not accounting for diffusion effects, can be expressed as

$$S = M \cdot \exp^{-\frac{TM}{T_1}} \cdot \exp^{-\frac{TE}{T_2}} \quad (1)$$

with the magnetization M , TE and TM specific to this echo (Table 1). Hence, even though the stimulated echoes have long echo formation times (TE+TM), the majority of that time (TM) the echoes are only subject to the more benign T_1 -relaxation rather than suffering from T_2 -relaxation during the whole echo time as in the TRSE-sequence (Figure 2bc). The echoes amplitudes, accounting for T_1 , T_2 and diffusion relaxation, in the MESTIM sequence are 68, 46, 46 and 44% of their respective counterparts with similar b-values in the TRSE sequence (Figure 2 with sequence parameters in Table 1).

DSI calculates the average propagator $p(\vec{R}, \Delta)$, which indicates the probability that within the diffusion time Δ a water proton would diffuse a distance $\vec{R}$ within the voxel, from the normalized diffusion weighted images $S(\vec{q}, \Delta)$ [1]

$$p(\vec{R}, \Delta) = \int S(\vec{q}, \Delta) e^{-i2\pi \vec{R} \cdot \vec{q}} d\vec{q} \quad (2)$$

with $\vec{q} = \gamma \vec{G} \delta / 2\pi$ the q-space diffusion weighting, γ the gyromagnetic ratio and $\vec{G}$ and δ the strength and duration of the diffusion-encoding gradient. In the next step, this Probability Density Function (PDF) $p(\vec{R}, \Delta)$ is compiled across a range of displacements L to the Orientation Distribution Function (ODF) [11]

$$ODF(\theta, \phi, \Delta) = \int p(L\hat{u}, \Delta) L^2 dL \quad (3)$$

with L the diffusion sampling length and $\hat{u}$ the unit vector in the direction specified by (θ, ϕ) .

The q-space samples acquired with the MESTIM sequence cover a similar range of b-values

$$b = \left(\frac{\gamma}{2\pi}\right)^2 \vec{G}^2 \delta^2 \left(\Delta - \frac{\delta}{3}\right) = (\vec{q})^2 \left(\Delta - \frac{\delta}{3}\right) \quad (4)$$

as the TRSE-sequence (Table 1). In contrast, since the $\vec{G}$ and δ of the diffusion gradients are identical for all echoes in one TR, the q-values of these echoes are the same. However, these echoes experience different diffusion times which means the DSI reconstruction of the MESTIM sequence refines to

$$p(\vec{R}_\Delta, q) = \int S(q, \vec{\Delta}) e^{-i2\pi \vec{R}_\Delta \cdot \vec{\Delta}} d\vec{\Delta} \quad (5)$$

with $\vec{\Delta}$ in the direction of $|\vec{\Delta}| = \Delta$, $q = |\vec{q}|$ and $\vec{R}_\Delta$ now expressed in units of inverse time and spatial directionality similar to $\vec{R}$. The units of inverse time of $|\vec{R}_\Delta|$ indicate that at different distances from the origin the PDF is probed at different diffusion times. From $p(\vec{R}_\Delta, q)$, we can then calculate $ODF(\theta, \phi, q)$ as before (Eq. 3). Figure 3 illustrates this for one-dimensional isotropic diffusion. It shows that the diffusion weighted signal drops with increasing diffusion time in a manner sufficiently similar to the signal drop with increasing q-values. Indeed, both approaches (Eq. 2, TRSE and Eq. 5, MESTIM) preserve a one-to-one correspondence between diffusion coefficients and estimated ODF-values (Figure 3c). This correspondence safeguards the ODF peak identification although ODF values and their interpretation might differ. In addition, increasing diffusion times in the MESTIM sequence lead to increased anisotropy (steady longitudinal diffusion vs. decreasing radial diffusion) which improves peak identification over the TRSE sequence [34–37].

In Vivo Measurements

DSI datasets were acquired using both a Twice-Refocused Spin Echo sequence (TRSE, Figure 1a) and the proposed custom-made Multi-Echo Stimulated Echo (MESTIM, Figure 1c) diffusion sequence on a 3T scanner (Prisma, Siemens, Erlangen; 80mT/m, 180mT/m/ms gradients), using a 64-channel head coil. The protocol was approved by an Institutional

Review Board. Both sequences sampled k-space using a standard Echo Planar Imaging (EPI) readout for all echoes. Image reconstruction was performed on the scanner in a nearly identical fashion for both sequences. An extra B_1 -receive field correction (Prescan Normalize, Siemens) was performed for the TRSE sequence (improved image homogeneity, see anterior part of the brain in Figure 5). This reconstruction difference does not have an effect on SNR (Figure S4) and is cancelled in later analysis when normalizing the diffusion weighted images with b_0 -images. Q-space was sampled according to the recently proposed radial q-space sampling scheme (Figure 1b, [13]) as discussed above. For this sampling scheme 236 samples were acquired on 59 radial lines N_j , evenly distributed on a radius 4 half sphere. To facilitate eddy current correction, the radial lines N_j are divided over the whole sphere. For each volunteer, in one session, either whole brain covering or limited coverage DSI datasets were acquired using both the TRSE and MESTIM sequences. The limited coverage DSI datasets used for bootstrapping were repeated 5 times, alternating between both sequences (i.e. 10 limited coverage DSI datasets, 5 for each sequence). For image correction an extra b_0 -dataset was acquired for each DSI dataset with PA phase encoding rather than AP phase encoding. The sequence parameters were (Table 1): $b_{max} = 4000 \text{ s/mm}^2$, TR = 2000(bootstrap) / 8500(full, TRSE) / 7300(full, MESTIM) ms, TE = 86(TRSE), TE+TM = 40,110,180,250(MESTIM) ms, 10(bootstrap) / 46(full) slices, $2.5 \times 2.5 \times 2.5 \text{ mm}$ resolution, field of view $200 \times 200 \text{ mm}$, Partial Fourier 5/8, full dataset acquisition time 33:43(TRSE) / 15:34(MESTIM) min. A T_1 -weighted gradient-echo sequence (MPRAGE) was acquired as a reference for image registration: TR= 2300 ms, TR/TE = 2300 / 2.87 ms, 192 slices, $1 \times 1 \times 1 \text{ mm}$ resolution, TI=900 / 1000 ms, 5:03 min.

Phantom Measurements

For SNR calculation and b-value verification, DSI datasets were acquired of a homogeneous cyclooctane phantom ($D = 0.4799 \cdot 10^{-3} \text{ mm}^2/\text{s}$, 23°C [38]) using the same parameters as above (bootstrap). In this phantom, cyclooctane (99%, Sigma-Aldrich, St. Louis, MO, USA) in a glass bottle is suspended in a larger plastic bottle (both bottles, McMaster, Princeton, NJ, USA) filled with distilled water (Absopure Water Co. Plymouth, MI, USA) to reduce susceptibility artifacts. The surrounding water is doped with a Gd-agent to suppress its signal (1 mmol/L, Gadavist, Bayer, Whippany, NJ, USA).

Data Processing

Post-processing is performed offline. In a first step, the raw diffusion images are denoised using the Random Matrix Theory [39]. Then, eddy currents and movements are corrected using the programs *topup* and *eddy* from the FMRIB Software Library [40]. These programs are applied separately on image sets containing all unweighted and diffusion weighted images with the same TE+TM for the MESTIM sequence. This is necessary since eddy current distortions differ for each TE+TM (Figure 4). Subsequently, the diffusion datasets are registered to the subject's MPRAGE images using *elastix* and *transformix* [41]. The b-matrices were reoriented according to the transformation rotations.

RDSI reconstruction was performed using custom-made software (Matlab, Mathworks) and the resulting DSI datasets were displayed using Matlab and DSI Studio [42]. For the different mixing times TM in the MESTIM sequence, each diffusion weighted image was

normalized with an unweighted b_0 -image with identical mixing time TM acquired with the same sequence in order to isolate the diffusion weighting from T_1 , T_2 , proton density effects and flip angle inhomogeneities. This normalization ensures accurate reconstruction of the diffusion weighted information.

Bootstrapped DSI datasets (500) were generated from the 5 original datasets with limited brain coverage for each sequence using repetition bootknife sampling [43]. From these bootstrapped datasets reproducibility and performance metrics were calculated in order to compare the two methods: normalized RMSE (NRMSE) and Jensen-Shannon Divergence (JSD) [43] of the bootstrapped ODFs relative to the average ODF in each voxel; 95% Confidence Intervals (CI) and coherence κ [44] of the main identified fiber directions in each voxel. To separate the effects of differences in SNR and other sequence and reconstruction parameters, a second bootstrap analysis was performed on the TRSE-datasets where noise (Rician distribution) was added to match the SNR of the MESTIM sequence at each shell in q-space.

Fiber tractography is performed using a deterministic fiber tracking algorithm [45], as implemented in DSI Studio using tractography parameters, as suggested in literature [3]. More specifically, random seeding points were uniformly distributed in the whole brain or in user-defined seeding regions until a predetermined number of fibers was generated ($1 \cdot 10^5 / 10^4$ tracts (whole brain/seed region)). The tracking was performed in the most prominent fiber direction with a stepsize of 1.15 mm, and the fiber trajectories were smoothed by averaging the propagation direction with 20% of the previous direction. Fiber propagation was halted when the turning angle $> 60^\circ$ or anisotropy $QA < 0.125/0.08$ (whole brain/seed region). Fibers shorter than 20 mm or longer than 300 mm were discarded.

SNR of the images before denoising in the phantom and in vivo was calculated with noise levels estimated using the Random Matrix Theory [46].

Results

Unprocessed diffusion weighted images from both a TRSE and the MESTIM sequence at similar b-values (Figures 5, S2 (Volunteer #1) and S3 (Volunteers #1–4)) illustrate the feasibility of acquiring a full 2D k-space for each of several q-space samples per readout train. Indeed, the image quality of both sequences is similar, notwithstanding the shared magnetization of the echoes in the MESTIM sequence nor the longer time to echo formation (TE+TM) (40, 110, 180 and 250 ms vs. 86 ms). The latter effect is largely compensated by the slower T_1 relaxation during TM (Figure 2). Phantom measurements (Supporting Figure S4a) show that the b-values are encoded as expected. This illustrates that in the MESTIM sequence the later echoes are not affected by the EPI readout trains of the earlier echoes. Figure 5 also indicates the SNR in the diffusion weighted images. This SNR is higher for the first echo of the MESTIM sequence, but then drops slightly below the SNR of the TRSE sequence for the latter three echoes *in vivo* (SNR 105, 65, 60 and 50% relative to the TRSE sequence) although the image quality remains high. In the phantom with its low diffusion coefficient ($D = 0.4799 \cdot 10^{-3} \text{ mm}^2/\text{s}$, 19°C [38]) the SNR in the MESTIM sequence is higher: 120, 104, 110, 72% (Supporting Figure S4b) relative to the TRSE sequence. Reconstructions

of these datasets (Figure 6) show that DTI and DSI parametric maps of ADC, FA, the eigenvalues λ_1 , λ_2 and λ_3 and Quantitative Anisotropy (QA) of the prominent fiber orientation are comparable for both sequences. Moreover, both FA and QA-maps of the MESTIM sequence of Figure 6 reveal more details than the TRSE sequence (see e.g. the areas indicated by arrows in Figure 6).

Figures 7 and S5 summarizes the reproducibility of RDSI *in vivo* in healthy volunteers using a TRSE (top row) and the MESTIM sequence (bottom row) as evaluated by an analysis of 500 bootstrapped datasets. Although the reproducibility metrics NRMSE, JSD and the 95% confidence interval (CI) of the TRSE sequence are lower than those of the MESTIM sequence, it is clear that both variations of RDSI perform well in this reproducibility analysis. In order to tease out the impact of the slightly reduced SNR of the *in vivo* MESTIM diffusion weighted images, we added noise to the TRSE datasets to match the SNR of the MESTIM datasets. The bootstrap analysis of these SNR-adjusted TRSE datasets (Figures 7 and S5, middle row) show that, at similar SNR levels, the MESTIM sequence outperforms the TRSE sequence to minor extent in white matter and to a larger extent in gray matter in the NMRSE metric. Indeed, when comparing similar *in vivo* SNR levels (middle row and top row) the reproducibility metrics NRMSE, JSD and CI-distributions of the MESTIM sequence match up or improve over the distributions of the TRSE sequence. Furthermore, the QA-maps and histogram analysis on the left side of Figure 7 (e.g. area indicated by an arrow) show that higher QA-values and sharper delineation of the fiber tracts are obtained with the MESTIM sequence.

The ODFs and resolved fiber directions resulting from the RDSI reconstructions (Figure 8) reconstructed from RDSI datasets acquired with both sequences succeed in identifying the fiber bundles. This is the case for both repeated (black/white fiber directions and ODF outlines) and averaged datasets (colored fiber directions and ODF renderings). As suggested in the reproducibility metrics in Figure 7 there is slightly more variability in the identified fiber directions of the repeated acquisitions for the RDSI datasets acquired with the MESTIM sequence due to the lower *in vivo* SNR (e.g. the area indicated by an arrow in Figure 8). This increased variability in the MESTIM RDSI datasets does not seem to harm tractography analysis. Both whole-brain tractography (Figure 9a) and tractography from a seed region (Left superior region of the internal capsule, Figure 9) adequately identify common fiber bundles. The sharper delineation of fiber tracts in the MESTIM RDSI datasets (Figure 6, FA and QA; Figure 7, left column) leads to better defined fiber bundles. This is apparent both in the whole-brain tractography where the gyri of the cortex are better separated and in the seeded tractography where the Corticospinal tract stands out relative to the TRSE RDSI dataset.

Discussion

In this paper we combine the recently introduced radially symmetric sampling scheme for DSI acquisitions, Radial DSI [13], with a Multi-Echo Stimulated Echo Diffusion sequence. By acquiring several samples along a single line in q-space, as RDSI prescribes, the MESTIM diffusion sequence is able to significantly speed up acquisition of RDSI datasets. In each readout train, the MESTIM sequence acquires one spin echo and three stimulated

echoes. Notwithstanding the distribution of the magnetization signal over these echoes and the longer echo formation times of the stimulated echoes, we demonstrate that the resulting diffusion weighted images (Figure 5, Supporting Figures S2, S3 and S4) contain sufficient SNR to perform DSI reconstructions (Figure 6) and that the reproducibility of the reconstructed ODFs is similar to that of datasets acquired with the more traditional TRSE sequence (Figure 7, taking into account the slightly lower SNR of the MESTIM sequence). The direct (ODFs and resolved fiber directions, Figure 8) and indirect results (tractography, Figure 9) of the RDSI reconstructions further demonstrate the feasibility of the MESTIM sequence for RDSI.

Radial q-space sampling for DSI calls for the acquisition of several q-space samples along a number of radially outward lines in q-space [13]. This q-space sampling, as demonstrated before [13], needs less samples to attain the same angular resolution as the traditional Cartesian sampling for q-space. As RDSI also avoids interpolation and truncation artifacts, it is more reproducible than Cartesian sampled DSI [13]. The radial sampling of q-space forms an ideal opportunity for acceleration of the acquisition by multiple echo readout trains [24–29]. The multiple (stimulated) echoes in such a readout train can be easily encoded with identical diffusion direction and increasing diffusion weighting due to the increasingly longer diffusion times for the latter echoes. Here, we chose to acquire four echoes per readout train (Figure 1), though one might envision acquiring more or fewer echoes to optimally balance SNR and q-space coverage depending on the acquisition demands. Similarly, the MESTIM sequence q-space sampling density is easily adapted by spacing out the stimulated echoes differently. Although RDSI and the Multi-Echo Stimulated Echo acquisition scheme form an ideal combination given the geometry of the problem, similar approaches can also accelerate other q-space sampling schemes, such as the ones used in multi-shell q-ball imaging [7,20, 21].

The Multi-Echo Stimulated Echo sequence for RDSI presented in this paper accelerates the standard RDSI protocol by more than a factor of two. Although MESTIM acquires 4 echoes per readout train, the maximum acceleration of four is not reached because of the longer readout train which leads to a longer slice TR (Figure 1). The more than twofold acceleration of RDSI achieved here can be further extended by combination with other acceleration approaches such as the use of simultaneous multi-slice or multiband techniques [16, 17, 47] and by the undersampling of q-space in combination with compressed sensing reconstruction [48,49]. For instance, incorporating simultaneous multi-slice techniques, we might accelerate by another factor 3 or 4, reaching the 5 min mark.

Notwithstanding the achieved acceleration, MESTIM succeeds in maintaining the quality of acquired datasets. The raw diffusion weighted images (Figures 5, S2 and S3) display similar image quality even though the SNR of the MESTIM images with longer TM is slightly lower. Also the reproducibility of the reconstructed ODFs (Figure 7) reaches similar levels when comparing equivalent SNR levels. The higher anisotropy measures in the MESTIM sequence (Figure 6 and 7) might even improve tractography results (Figure 9). These higher anisotropy measures originate in the longer diffusion times experienced by some of the coherence pathways in the MESTIM sequence [34–37].

In the MESTIM sequence, all diffusion gradients have the same diffusion gradient amplitude and duration. Here, b-values increase by increasing the diffusion time. Hence, although the resulting b-values in the MESTIM sequence cover a similar range to that covered by the TRSE sequence, the q-values are the same for all echoes (Table 1). This equivalence gives us the opportunity to refine the DSI reconstruction for the MESTIM sequence from the classic form given in Eq. 2 to Eq. 5. The diffusion weighted signal exhibits a similar decrease as a function of increasing q-value and as a function of increasing diffusion time. Both weighting mechanisms sample ever larger displacements. This makes both weighting mechanisms suitable for correct estimations of the Orientation Distribution Functions (Figure 3). The MESTIM derived ODFs indeed identify the correct fiber directions, even though the ODF values might differ due to the different weighting mechanism. The different diffusion displacements for the different echoes in the MESTIM-sequence form a limitation on the interpretation of the MESTIM ODFs compared to more traditional sequences. On the other hand, the range of diffusion times can possibly be incorporated in a diffusion model [50, 51] and be exploited to extract other microstructural information and generate new diagnostic measures [34,52,53].

The microstructural information available could further be extended by assuming water pools with different T_1 . These T_1 -pools might have different contributions to the different echoes. Correct modelling might allow insight in T_1 -pools present in tissue, though the presence of multiple T_1 -pools can also be a limitation to the MESTIM-method when insufficiently accounted for.

In conclusion, we demonstrated the use of a Multi-Echo Stimulated Echo sequence to accelerate the acquisition of Radially sampled DSI. This innovative sequence design allows for a more than twofold acceleration. Combination of this acceleration with multi-slice or multiband techniques [16, 17] can bring DSI acquisition times down to clinically feasible scan times.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

DFT	Discrete Fourier Transformation
DSI	Diffusion Spectrum Imaging
DTI	Diffusion Tensor Imaging
HARDI	High Angular Resolution Diffusion Imaging

JSD	Jensen-Shannon Divergence
NMRSE	Normalized Root Mean Square Error
ODF	Orientation Distribution Function
PDF	Probability Distribution Function
MESTIM	Multi-Echo Stimulated Echo Sequence
QA	Quantitative Anisotropy
RDSI	Radial Diffusion Spectrum Imaging
SNR	Signal to Noise Ratio
TRSE	Twice Refocused Spin Echo
TM	Mixing Time

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Figure 1.

Radially sampled DSI (b) acquires several q-space samples (n_{shell} , e.g. 4) along several radial lines N_t . When using a conventional Twice Refocused Spin Echo (TRSE) diffusion sequence (a), the sequence train has to be repeated n_{shell} times. In contrast, the multi-echo stimulated echo diffusion sequence (c) naturally acquires a full 2D k-space for each of the n_{shell} echoes along the same radial line in q-space in one readout train. Once acquired, each radial line in q-space can be transformed to the value of the ODF at the same radial line using the Fourier slice theorem (b).

Figure 2.

The multi-echo stimulated echo diffusion sequence acquires n_{shell} echoes along the same radial line in q -space in one readout train (a). As a result, the available signal from the first excitation RF-pulse is distributed over the n_{shell} echoes (4 in this example). Each echo forms at a different time and has a T_1 -relaxation time TM and T_2 -relaxation time TE. Echo signal amplitudes (S , taking into account T_1 and T_2 -relaxation S_{T_1, T_2} and diffusion $DS_{T_1, T_2, D}$) are calculated using the coherence pathway formalism for the Multi-Echo Stimulated Echo (b, MESTIM) and the conventional Twice Refocused Spin Echo (c, TRSE) diffusion sequences.

Figure 3.

Signal ($S(q, \Delta)$), a), Probability Density Function (Figure S1) and Orientation Distribution Function values (ODF, b) of one-dimensional isotropic diffusion as sampled by a conventional Twice Refocused Spin Echo (TRSE, left, $\tau=50$ ms, $\delta=41$ ms, $G=7.4\text{--}33$ mT/m, $q=80\text{--}3601/\text{mm}$) and the Multi-Echo Stimulated Echo (MESTIM, right, $\tau=19\text{--}229$ ms, $\delta=6.7$ ms, $G=74.8$ mT/m, $q=1301/\text{mm}$) sequences for a relevant range of diffusion coefficients (D ranges from $0.3 \cdot 10^{-3}$ to $1.2 \cdot 10^{-3}$ in steps of $0.1 \cdot 10^{-3} \text{ mm}^2/\text{s}$). Whilst the TRSE sequence samples $S(q, \Delta)$ at different q -values (80–360 $1/\text{mm}$), the MESTIM sequence samples $S(q, \Delta)$ at different diffusion times (20–230 ms). Both approaches preserve a one-to-one correspondence between diffusion coefficients and estimated ODF-values, thus enabling ODF peak identification.

Figure 4.

Raw images (b_0), uncorrected (top row) and corrected (bottom row) for susceptibility and eddy currents, acquired with a TRSE (left) and a Multi-Echo Stimulated Echo (right) diffusion sequence. Field maps (middle row) are estimated for each TE+TM. Contours (red) of the corrected images with lowest TE+TM for each sequence are drawn on the respective uncorrected images at different TE+TM.

Figure 5.

Raw diffusion weighted images (b0 and 4 shells, Volunteer #1) acquired with a TRSE (left) and a Multi-Echo Stimulated Echo (right) diffusion sequence. Next to each respective image the b-value, echo formation times TE or TE+TM and SNR are indicated. Additional slices are included in Figure S2

Figure 6.

DTI and RDSI reconstructions of a human brain volunteer acquired using a TRSE and a Multi-Echo Stimulated Echo Sequence (MESTIM). Shown are DTI metrics ADC, FA and eigenvalues and the quantitative anisotropy (QA) of the prominent fiber orientation. Arrows indicate examples of areas with higher detail in the MESTIM sequence.

Figure 7.

Comparisons of reproducibility metrics of bootstrapped RDSI datasets acquired using a TRSE (top), a multi-echo stimulated echo (MESTIM, bottom) and a TRSE with *in vivo* SNR similar to a MESTIM (middle) sequence. Compared parameters are Quantitative Anisotropy (QA) of the prominent fiber direction, Normalized Root Mean Square Error (NRMSE) and Jensen-Shannon Divergence (JSD, [43]) of the bootstrapped ODF's relative to the average ODF (the 95% confidence intervals (CI) and coherence κ of the main identified fiber direction, and the number of identified fiber directions are included in Figure S5). The distribution of these parameters in white matter is illustrated in the histograms on the bottom row (used white matter map in Figure S5). Arrows indicate areas discussed in the text.

Figure 8.

Quantitative Anisotropy maps (a,b,g,h), resolved fiber directions (c,d,i,j) and ODFs (e,f,k,l) of individual and averaged RDSI datasets (5 repetitions on a single volunteer) acquired using a TRSE (left) and a multi-echo stimulated echo (MESTIM, right) sequence in selected regions of axial (a-f) and coronal (g-l) slices through the centrum semiovale. The ODFs and resolved fiber directions of the average datasets are color coded (red: left-right, green: anterior-posterior, blue: superior-inferior), whilst the ODF-outlines and resolved fiber directions of the individual datasets are displayed in black and/or white. The arrow indicates an area of higher variability in the MESTIM sequence.

Figure 9.

Tractography of the (a) whole brain and (b) seeded from the left superior region of internal capsule (including the left Arcuate Fasciculus and Corticospinal tract) of RDSI datasets acquired using a TRSE (top) and a multi-echo stimulated echo sequence (MESTIM, bottom) as seen in sagittal, coronal, transversal and oblique views. Arrows indicate areas discussed in the text.

Table 1

Experimental parameters used for the Twice Refocused Spin Echo (TRSE) and the Multi-Echo Stimulated Echo (MESTIM) sequences in this paper. Note that all imaging parameters were kept consistent. Median SNR was calculated over a cyclooctane phantom and in vivo using the Random Matrix Theory method [46].

	TRSE	MESTIM
$TE + TM$ ms	86	40, 110, 180, 250
TE ms	86	40, 40, 40, 40
TM ms	–	–, 70, 140, 210
ms	49.9	19.4, 89.4, 159.4, 229.4
b s/mm ²	200, 1466, 2722, 3989	289, 1550, 2811, 4071
q 1/mm	80, 216.9, 295.5, 357.7	134.2
TR ms	8500	7300
TA min	33:43	15:34
Median SNR (<i>in vivo</i>)	162, 77, 43, 28	171, 50, 26, 14
Median SNR (phantom)	111, 54, 28, 15	112, 48, 27, 17
Diffusion sampling	59 directions, 4 shells	
Seq param	2.5×2.5×2.5 mm resolution, partial fourier 5/8 Bandwidth 2000, 50 slices, 200×200 mm	