Accelerated Mapping of Magnetic Susceptibility Using 3D Planes-on-a-Paddlewheel (POP) EPI at Ultra-High Field Strength

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Abstract

With the advent of ultra-high field MRI scanners in clinical research, susceptibility based magnetic resonance imaging (MRI) has recently gained increasing interest because of its potential to assess subtle tissue changes underlying neurological pathologies/disorders. Conventional, but rather slow three-dimensional (3D) spoiled gradient echo (GRE) sequences are typically employed to assess the susceptibility of tissue. 3D echo-planar-imaging (EPI) represents a fast alternative but generally comes along with echo time restrictions, geometrical distortions and signal dropouts that can get severe at ultra-high fields.

In this work we assess quantitative susceptibility mapping (QSM) at 7 T using non-Cartesian 3D EPI with a planes-on-a-paddlewheel (POP) trajectory, which is created by rotating a standard EPI readout train around its own phase encoding axis.

We show that the three-fold accelerated non-Cartesian 3D POP EPI sequence enables very fast, whole brain susceptibility mapping at an isotropic resolution of 1 mm and that the high image quality has sufficient SNR in the phase data for reliable QSM processing. The susceptibility maps obtained were comparable with regard to QSM values and geometric distortions to those calculated from a conventional 4 minute 3D GRE scan using the same QSM processing pipeline.
Introduction

Quantitative susceptibility mapping (QSM) gained a lot of interest recently as it delivers a unique gray matter/white matter contrast (1,2) and potentially novel insights into tissue composition and disease related tissue changes in the human brain (3,4). It can be considered as a novel biomarker based on the magnetic properties of tissue (5). For example, it helps visualizing micro bleeds (6) and differentiating them from calcifications (7) and can potentially be used for measurement of iron and myelin concentrations in the human brain (8,9) as well as electrode placement planning for deep brain stimulation (10). QSM and magnetic susceptibility based magnetic resonance imaging (MRI) in general profit disproportionately from scanning at ultra-high field due to the increase in signal-to-noise ratio and white matter/gray matter contrast (11–16). Compared to lower field strengths (< 3T), improvements for glioma treatment response MRI (17), MRI of microbleeds (18), as well as the characterisation of multiple sclerosis (MS) lesions (19) have been demonstrated.

The current standard acquisition technique for structural T2* weighted, susceptibility weighted MRI and QSM is a three-dimensional (3D) spoiled gradient-echo (GRE) sequence with Cartesian sampling. It can be used with high spatial resolution to detect small structures and lesions and has performed well with respect to SNR and stability. However, the long measurement time can be problematic in terms of head motion during the scan. This is particularly the case in clinical populations, such as Alzheimer’s and Parkinson’s disease, where involuntary head motion is more common than in healthy control participants. The image acquisition can be accelerated using partial Fourier imaging, elliptical scanning and parallel imaging. However, these methods come along with a reduction in SNR due to the acquisition of a reduced amount of k-space data. In addition, parallel imaging – such as simultaneous acquisition of spatial harmonics (SMASH) (20), sensitivity encoding (SENSE) (21) or generalized auto-calibrating partially parallel acquisitions (GRAPPA) (22) – introduce some noise amplification during the reconstruction process characterized by the so-called geometry factor. To a certain extent, this effect can be mitigated by shifting the sampling positions in k-space so that the coil sensitivity variations can be exploited more efficiently in multiple dimensions, resulting in a more robust parallel imaging reconstruction (23–26).

Another strategy to shorten the acquisition is to use echo-planar-imaging (EPI) (27), which increases the efficiency by a factor of 10-100. It is mainly limited by the desired echo time (TE) – and as such the gradient performance. Also the T2* of the tissue of interest can be restricting since long readout trains can lead to spatial blurring. Further limitations include geometric distortions and signal dropouts which are typically worse at higher fields and become more severe at ultra-high field strength. However, recently magnitude and phase images with a very high isotropic resolution of 0.5
mm, excellent tissue contrast and image fidelity have been demonstrated using a 6 minute segmented three-dimensional (3D) EPI scan at 7 T (28). With respect to a 3D GRE measurement of the same duration, this increased the SNR by a factor of 2 and the volume coverage by a factor of 4.5. The 3D EPI images in this study showed limited distortions due to the short echo train length used.

Other than that, several non-Cartesian readout trajectories were proposed to overcome the undesired effects of EPI. Multi-shot PROPELLER (29) based readout schemes for example were employed for various applications (30–32), including susceptibility weighted imaging (33). By rotating echo trains with reduced readout or echo train length about the k-space centre, high spatio-temporal resolutions and reduced distortions can be achieved. Moreover, the trajectories’ self-navigation properties can be used for motion and advanced phase correction.

In this proof-of-principle study we combine a segmented as well as accelerated EPI readout (high sampling efficiency) with the beneficial properties of radial acquisitions (minimal distortion in radial direction, motion robustness) and propose a non-Cartesian 3D EPI sequence with a paddlewheel-shaped readout scheme (34–37) for quantitative susceptibility mapping at ultra-high field. The so-called planes-on-a-paddlewheel (POP) trajectory is realized by rotating 2D readout planes about the phase encoding axis, which comes with its specific challenges for phase correction, but lends itself to the use of advanced undersampling patterns and acceleration techniques.
Experimental

All measurements were performed on a 7 T whole body MRI scanner (Magnetom 7 T, Siemens Healthcare, Erlangen, Germany) equipped with a SC72 gradient system providing a maximum gradient strength of 70 mT/m and a slew rate of 200 T/m/s. A 7T Tx/32 channel Rx head array (Nova Medical, Wilmington, MA, USA) was used for radio frequency (RF) transmission and signal reception. To improve the B0 field homogeneity 3rd order shimming was employed. For the human in vivo experiments written informed consent was obtained before the examination as approved by the local ethics committee.

Sequence Design

A 3D EPI sequence was equipped with a planes-on-a-paddlewheel (POP) readout trajectory (34–37) sampling a cylinder-shaped k-space. As displayed in Fig. 1a and b, the 3D POP trajectory consists of multiple standard two-dimensional (2D) EPI readout trains rotating about the phase encoding axis. Per excitation a single plane on this paddlewheel is sampled, with the slab selection performed along the rotation/phase encoding axis.

Phantom experiments and measurements on 3 volunteers were performed to probe different azimuthal distributions of the planes/projections in terms of practicability, gradient delay and phase error removal as well as eddy-current behaviour. In addition to conventional radial sampling patterns using a uniform projection distribution also golden angle type projection orders were considered (38,39). Besides this, the sequence timing as well as the RF and gradient spoiling were optimized to improve the results (40,41).

Based on these results and to facilitate the parallel imaging calibration (see below) a homogeneous azimuthal distribution of the planes was chosen and achieved by employing an interleaved radial projection order as shown in Fig. 1c. The azimuthal angle $\Theta$ of the $j^{th}$ plane is thereby calculated by:

$$\Theta_j = (j-1) \cdot 2\pi / N + \vartheta(j),$$

with $N$ denoting the number of planes. $\vartheta(j)$ is given by:

$$\vartheta(j) = \begin{cases} 0 & \text{for } 1 \leq j \leq N/2 \\ \pi / N \cdot \left( (N-1) \text{ mod } 2 \right) & \text{for } N/2 < j \leq N \end{cases}$$
and ensures correct interleaving for even numbers of planes. Recently it was shown that distributing the planes over $2\pi$ rather than over $\pi$ allows for an improved gradient delay correction (42).

**In Vivo Study**

To evaluate the performance of the 3D POP EPI sequence for QSM in vivo, brain imaging was performed in 3 healthy volunteers.

Three basic protocols with 3 different echo-times were set up by employing 3 different partial Fourier factors and images were obtained at an isotropic resolution of 1 mm using the following acquisition parameters: field of view (FOV) = $212 \times 212 \times 108$ mm³, 330 projections, partial Fourier factor (PF) = 5/8, 6/8, 7/8, repetition time (TR) = 35 ms, 39 ms, 44 ms, echo time (TE): 12 ms, 16 ms, 21 ms, echo spacing (ES) = 1.0 ms, flip angle = 11°, 12°, 13°. Data sampling was performed with a readout bandwidth (BWRO) of 1180 Hz/pixel incorporating ramp sampling. A 3.2 ms water excitation RF pulse with a bandwidth time product of $\text{BWT}_{tx}=25$ was employed for slab selection. To facilitate the correction of gradient delays (43) and to reduce Nyquist ghosting, three non-phase-encoded navigator echoes (44,45) were acquired between each RF excitation and EPI readout.
To achieve the echo-times stated above and to minimize geometric distortions, k-space was segmented by a factor of $R_E = 3$ (Fig. 1b) along the phase encoding direction, yielding effective echo-train-lengths (ETL) of 35, 39 and 44 for the three different echo-times. To mitigate potential influences of physiological effects (46), the k-space for each plane was fully covered using 3 interleaved shots before incrementing the azimuthal angle. Acquisition times per volume were 35 s, 39 s and 43 s. Repeating the measurements 9, 9 and 8 times, resulted in overall acquisition times of 312 s, 347 s and 349 s, respectively.

In addition to that, measurements were performed with the $TE = 16$ ms ($PF = 6/8$) protocol employing parallel imaging with an undersampling factor of $R_E = 3$ instead of k-space segmentation along the phase encoding direction (Fig. 1b). A TGRAPPA (47) like sampling scheme was employed to facilitate the image reconstruction from the acquired data itself. Keeping all other acquisition parameters unchanged, the protocol allows covering a 3-fold undersampled k-space within 13 s.

For comparison, brain imaging was performed using a 3D multi-echo GRE sequence. Again, the images were acquired at an isotropic spatial resolution of 1 mm$^3$. The acquisition parameters included: $FOV = 212 \times 212 \times 120$ mm$^3$, 104 partitions, slice oversampling = 15.4%, $TR = 29$ ms, 7 echoes, first echo time ($TE_1$): 4.36 ms, $ES = 2.86$ ms, flip angle = 13°, $BW_{RO} = 600$ Hz/pixel. Parallel imaging was applied along the phase encoding direction with an acceleration factor of $R_E = 3$ and 24 auto-calibration lines additionally acquired for image reconstruction.

For both the 3D POP EPI and the 3D GRE measurements, slab selection was performed along the same oblique axis within the central sagittal plane. Consequently, the phase encoding direction of the 3D POP EPI measurements matched the partition encoding direction of the 3D GRE scan. Slices positioned perpendicular to this axis (x-z plane) will be referred to as “axial”, slices positioned parallel to the x-y and y-z plane as “coronal” and “sagittal”, respectively.

**Image Reconstruction**

Image reconstruction for the 3D POP EPI data was performed using Matlab (The Mathworks, Natick, MA, USA). At first, all ramp-sampling induced non-linearities along the readout axis were removed by interpolating the data onto equidistant sampling points. Hereafter, a gradient delay and Nyquist ghost correction was performed: For each plane, the gradient delay induced shift along the readout axis was estimated according to (48) using the average of the first and third (45) and the second navigator as the two opposed calibration lines. To minimize the influence of noise and eddy currents in the estimation, the shifts obtained at all angles $\Theta$ were fitted using the appropriate gradient delay.
The fit values were finally used to correct for the linear phase errors between the odd and even phase encoding lines. Constant phase errors were corrected as described by Heid et al. (45). The phase correction was carried out individually for each acquired data subset, i.e. before combining individual segments to a measurement or reference dataset. If required, GRAPPA (22) was employed to reconstruct the missing phase encoding lines with the weight sets determined plane-wise from the combined acquired data subsets. After zero-filling and applying the Fourier transform along the phase encoding direction, the non-Cartesian data of each axial slice was reconstructed using the non-uniform fast Fourier transform (NUFFT) software published by Fessler et al. (49) (http://www.eecs.umich.edu/~fessler/code/index.html). Finally, the multiple receiver channels were combined by calculating the root-sum-of-squares.

The images for the 3D GRE measurement were calculated online using the reconstruction pipeline provided by the manufacturer. For the parallel imaging reconstruction GRAPPA was utilized with 36 autocalibration lines for weight set calculation. Again, a root-sum-of-squares receiver channel combination was employed to finalize the reconstruction.

**Quantitative Susceptibility Mapping**

For susceptibility mapping, the image phase was extracted from the uncombined single channel data and processed using the total generalized variation (TGV) method recently proposed by Langkammer et al. (50). The mapping procedure incorporates phase unwrapping, background field removal and dipole inversion in a single step. The required brain mask was generated based on root-sum-of-squares-combined magnitude data using the segmentation and image calculator module of SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/). To ensure comparability between all 3D POP EPI and the 3D GRE protocols, the mask was obtained from the 3D POP EPI dataset with TE = 21 ms and used for processing all 3D POP EPI and 3D GRE data. The single channel susceptibility maps were finally combined by computing the mean across all channels (51).

The susceptibility maps calculated from the echoes 4, 5 and 7 (TE = 12.9 ms, 15.8 ms and 21.5 ms) of the 3D GRE measurement were extracted for comparison with corresponding 3D POP EPI based susceptibility maps (TE = 12 ms, 16 ms and 21 ms). For the 3D POP EPI approach, each measurement was processed independently yielding an individual susceptibility map for each time point. For post processing, the maps were motion corrected with respect to each other using the Oxford FMRIB
Software Library (FSL) MCFLIRT toolbox (52). To avoid bias, we abstained from referencing the computed susceptibility values to any specific structure. All values presented in the following were directly obtained after the outlined QSM computation.

**Evaluations**

Effects of the gradient delay and Nyquist ghost correction were assessed by comparing the images obtained with the new EPI trajectory to images reconstructed from the same data without applying the phase correction. Single volume and k-space averaged multi-repetition images were also compared to corresponding images reconstructed from the 3D GRE data. To assess geometric distortions, the reconstructed images were co-registered using FMRIB’s Linear Image Registration Tool (FLIRT) (52,53) with 6 degrees of freedom and, subsequently, tissue boundaries were extracted from the GRE images using an edge detection algorithm in Matlab (The Mathworks, Natick, MA, USA) and overlayed on the POP EPI data. Visual comparisons were also made for the QSM images obtained using the two different sequences. A detailed analysis was performed on the susceptibilities measured within the corpus callosum and the three iron-rich sub-cortical structures caudate, putamen and pallidum. All anatomical regions were manually outlined in susceptibility maps using the ITK-SNAP software (54).
Results

Effects of the gradient delay and Nyquist ghost correction are displayed in Fig. 2 where the reconstructions of representative axial and sagittal slices obtained without (left column) and with employing the phase correction (center column) are compared. The utilization of the phase correction does not only remove Nyquist ghost artifacts, it also decreases signal inhomogeneities with low spatial frequencies. Additionally, the combination of individual segmentation subsets significantly benefits from the correction. Similar effects are observed for GRAPPA reconstructed datasets. The improved combination of segmentation subsets in the TGRAPPA calibration data leads to substantially reduced residual undersampling artifacts in the sagittal views.

Figure 2: Images reconstructed from an in vivo 3D POP EPI dataset (subj. 1, 27, female) without (left) and with (middle) Nyquist ghost correction and the difference between both reconstructions (right). Apart from removing Nyquist ghosting (red arrows) the correction improves the signal homogeneity (white arrows) and has a significant influence on the combination of individual segmentation subsets (orange arrows). For better visibility all difference images were multiplied by a factor of 5.
Images obtained from the 3D GRE and the first repetition of the 3D POP EPI measurements are displayed in Fig. 3 on the left and right, respectively. For each sequence, 8 of the 108 reconstructed axial slices obtained at echo-times around 12 ms, 16 ms and 21 ms are shown. As expected for the high spatial resolution, the smaller features of the brain are well depicted and the images are free of significant segmentation and streaking artifacts. Typical EPI signal dropouts are particularly visible in the proximity of the paranasal sinuses, within inferior slices and the cerebellum. As expected, their extent increases with the echo-time. Although providing a lower signal-to-noise ratio (SNR), the EPI images provide slightly higher contrast. This is particularly visible in the bottom left slice for the measurement with TE = 21 ms. The geometry of the GRE and EPI images compares well.

Figure 4 compares images obtained using the different 3D POP EPI protocols with TE = 16 ms and the 3D GRE sequence at TE = 15.8 ms. The strongest signal boundaries found within the 3D GRE images (left column) were extracted and superimposed on top of the single-volume 3-fold segmented 3D POP EPI images (center column). Only very small deviations can be identified within the axial plane, increased distortions are found along the y-axis as expected, as this is the phase encoding direction of the 3D POP EPI scan. The most prominent distortions are depicted by arrows. The k-space averaged reconstruction of all 3-fold segmented 3D POP EPI repetitions (right column, top) shows significantly improved SNR over the single volume reconstruction (centre column). As expected from the short overall acquisition time, the SNR is decreased for the 3-fold accelerated 3D POP EPI measurement (right column, bottom) resulting in slightly reduced contrast. Substantial non-local signal variations as well as higher order effects of non-linear phase differences (55) are also visible.

Susceptibility maps obtained from the 3D GRE and the first 3D POP EPI measurement are presented in Fig. 5. Shown are the same measurements and axial slices as in Fig. 3. All susceptibility maps were reconstructed using the same regularization parameters for the TGV-QSM algorithm and the same brain mask. In general, the susceptibility maps are highly comparable across the echo-times and modalities. Also finer brain structures are similarly well depicted.

Figure 6 displays the susceptibility values attained in one volunteer using different 3D POP EPI protocols in the selected regions of interest after averaging the mapping results of different numbers of repetitions (blue, black). In all four regions, the number of averages do basically not affect the mean and standard deviation. For comparison, the corresponding susceptibilities calculated from the 3D GRE data are depicted as well (red) and match those measured with the 3D POP EPI approach. Significant differences between the different echo-times are not observed. The standard deviation, which represents the variability within a region of interest, is very similar between the 3D GRE and 3D POP EPI measurements.
Figure 3: Images reconstructed from the 3D multi-echo GRE measurement (subj. 1, 27, female) at TE = 12.9 ms, 15.8 ms and 21.5 ms (left) and the first repetition of the 3-fold segmented 3D POP EPI measurements with TE = 12 ms, 16 ms and 21 ms (right). For each echo-time, 8 of the 108 reconstructed axial slices are depicted. Echo-times, partial Fourier factors and total acquisition times are given in the images (bottom left to right).

Mean susceptibilities and corresponding standard deviation across the individual repetitions of the 3D POP EPI measurements are summarized for all volunteers in Table 1. The standard deviations derived within the corpus callosum and the three sub-cortical structures are typically low, indicating a high reproducibility of the mapping results across repetitions. Slightly higher standard deviations are observed for the third volunteer, particularly within the putamen and pallidum. Here, the mean susceptibility also varies significantly across the different protocols. Larger deviations across the protocols can also be found for all structures of subject 2. We note that the 3-fold accelerated 3D
POP EPI measurement tends to show the largest deviations compared to the segmented acquisitions.

The generally high reproducibility of the susceptibility values across the protocols can also be seen in Fig. 7. It depicts the mean susceptibilities as a function of the corresponding susceptibility obtained using the 3D GRE sequence and shows a generally high correspondence between the different sequences.

Figure 4: Geometric distortion and effects of averaging and acceleration in the 3D POP EPI data (subj. 1, 27, female). Representative non-registered views of the axial (top row), coronal (middle), and sagittal (bottom row) planes reconstructed from the 3D GRE dataset at TE = 15.8 ms (left column) and the 3-fold segmented (seg) 3D POP EPI dataset with TE = 16 ms (center column). The contours (red) of the GRE images are displayed on top of the POP EPI images for reference. To allow for a better comparison, an affine co-registration algorithm was applied to the GRE-images before calculating the contours. Distortions are only observed along the phase encoding direction. Arrows indicate areas with major geometric distortions. The same axial slice is also depicted for the 9-fold k-space average (avg) of all 3D POP EPI repetitions (right column, top) as well as the 3-fold accelerated and GRAPPA reconstructed 3D POP EPI measurement (right column bottom). The overall acquisition time is given in the bottom right of each image.
Discussion

For the medical application of high resolution mapping approaches it is essential to keep the acquisition time as short as possible as it greatly reduces the probability of subject motion during acquisition. In this study we explored the potential for fast susceptibility mapping at ultra-high field using a non-Cartesian 3D POP EPI trajectory with multiple acquisition protocols. The proposed readout scheme provides significantly shorter acquisition times compared to standard 3D multi-echo GRE imaging with minimal geometric distortions present in the radial plane (x-z), which is particularly important at ultra-high field as the distortion scales linearly with field strength.

In this context it is noteworthy that minimizing the echo train length and echo time can help reducing geometric distortions or signal dropouts (28). To obtain a suitable echo time for susceptibility mapping and to reduce distortion also in the phase encoding direction (y), partial Fourier imaging was applied in addition to k-space segmentation. Employing a partial Fourier factor of PF = 6/8 enabled whole brain susceptibility mapping at an isotropic resolution of 1 mm in less than 39 seconds per volume. This temporal footprint could be further reduced to below 13 seconds, using parallel imaging instead of segmentation. An echo time of 16 ms was achieved by employing segmentation or parallel imaging with a factor of RPE = 3, and, as demonstrated in Fig. 4, the major differences in distortions between GRE and POP EPI were within the range of a few pixels.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Measurement</th>
<th>Acquisition time / s</th>
<th>Susceptibility / $10^{-3}$ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (26, female)</td>
<td>TE = 12, PF = 5/8</td>
<td>312</td>
<td>caudate: 26.05 ± 0.15, putamen: 23.41 ± 0.66, pallidum: 56.51 ± 0.67, corpus callosum: -27.8 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>TE = 16, PF = 6/8</td>
<td>347</td>
<td>caudate: 28.02 ± 0.24, putamen: 21.56 ± 0.49, pallidum: 51.36 ± 0.77, corpus callosum: -23.48 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>TE = 21, PF = 7/8</td>
<td>349</td>
<td>caudate: 29.25 ± 0.19, putamen: 18.83 ± 0.67, pallidum: 50.06 ± 1.73, corpus callosum: -23.28 ± 0.11</td>
</tr>
<tr>
<td>2 (35, male)</td>
<td>TE = 12, PF = 5/8</td>
<td>312</td>
<td>caudate: 28.92 ± 0.57, putamen: 21.99 ± 0.67, pallidum: 51.51 ± 0.87, corpus callosum: -28.58 ± 0.23</td>
</tr>
<tr>
<td></td>
<td>TE = 16, PF = 6/8</td>
<td>347</td>
<td>caudate: 32.37 ± 0.39, putamen: 21.62 ± 0.67, pallidum: 74.46 ± 0.69, corpus callosum: -21.99 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>TE = 21, PF = 7/8</td>
<td>349</td>
<td>caudate: 35.27 ± 0.36, putamen: 20.45 ± 1.01, pallidum: 67.61 ± 0.75, corpus callosum: -16.32 ± 0.33</td>
</tr>
<tr>
<td></td>
<td>TE = 16, PF = 6/8, RPE = 3</td>
<td>116</td>
<td>caudate: 28.02 ± 0.92, putamen: 15.97 ± 1.11, pallidum: 62.16 ± 1.35, corpus callosum: -20.2 ± 0.33</td>
</tr>
<tr>
<td>3 (23, male)</td>
<td>TE = 12, PF = 5/8</td>
<td>312</td>
<td>caudate: 20.19 ± 0.81, putamen: 0.83 ± 1.9, pallidum: 60.7 ± 5.63, corpus callosum: -19.12 ± 0.43</td>
</tr>
<tr>
<td></td>
<td>TE = 16, PF = 6/8</td>
<td>347</td>
<td>caudate: 21.6 ± 0.71, putamen: -5.77 ± 2.83, pallidum: 89.51 ± 2.56, corpus callosum: -21.73 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>TE = 21, PF = 7/8</td>
<td>349</td>
<td>caudate: 22.34 ± 0.88, putamen: -4.46 ± 2.08, pallidum: 71.27 ± 7.74, corpus callosum: -20.51 ± 0.44</td>
</tr>
<tr>
<td></td>
<td>TE = 16, PF = 6/8, RPE = 3</td>
<td>116</td>
<td>caudate: 17.57 ± 1.16, putamen: 2.22 ± 3.26, pallidum: 51.43 ± 2.4, corpus callosum: -17.37 ± 0.63</td>
</tr>
</tbody>
</table>

Table 1: Mean susceptibilities and corresponding standard deviations across repetitions for the different 3D POP EPI acquisition protocols and volunteers.
Figure 5: Susceptibilities obtained from the 3D GRE data (subj. 1, 27, female) at TE = 12.9 ms, 15.8 ms and 21.5 ms (left), and the first repetition of the 3-fold segmented 3D POP EPI measurements with TE = 12 ms, 16 ms and 21 ms (right). Shown are the same axial slices as in Fig. 3. Echo-times, partial Fourier factors and total acquisition times are given in the images (bottom left to right).

Acquiring and averaging data for about 3.5 minutes, images of comparable quality were obtained using 3D POP EPI and 3D GRE. Evidently, the significantly reduced acquisition times stated above come along with a reduction of SNR. While effects are indiscernible for the acquisitions with 3-fold segmentation, employing an acceleration factor of $R_{PE} = 3$ leads to visible image noise and a reduction of image details. Nevertheless, as can be seen from Figures 6-7 and Table 1, even for this
accelerated protocol, the 3D POP EPI approach delivered sufficient SNR within the phase data for the QSM reconstruction. The susceptibilities estimated in the brain and particularly in three iron-rich sub-cortical structures were very similar to those obtained using the 3D multi-echo GRE technique and comparable to previously reported values (16,50,56,57). This is in line with similar reports that compared EPI- and GRE-based susceptibility mapping (50,58). Apart from that, the generally low variability of the susceptibility values across the multiple repetitions indicates a high stability of the technique. As displayed in Fig. 8, higher variabilities across repetitions in volunteer 3 were found to be a consequence of head motion introducing a misregistration between anatomy and brain mask used for QSM processing. The associated susceptibility drift mostly affects smaller and more inferior brain regions like the pallidum. While this drift is considered reversible by adjusting the brain mask for every single volume, the significant amount of blurring observed for the time-averaged with respect to the single-volume reconstruction underlines the importance of keeping the acquisition time short and highlights the advantage of the proposed POP EPI acquisition over a standard GRE scheme.

A regular azimuthal distribution of the planes was chosen in this work. However, as pointed out by other groups, POP trajectories provide a high adaptability and the most suitable sampling and reconstruction technique can be chosen according to the desired application. A golden angle plane order (38) as well as sliding window or filtered reconstruction techniques for example may be used to enhance the spatio-temporal flexibility (34,37) in applications like functional MRI. POP trajectories are also considered to support higher undersampling factors than comparable Cartesian trajectories (35,59). Another major benefit of the radial character of the 3D POP EPI trajectory is its robustness to motion (60,61). Also sampling the center of k-space with each plane opens up opportunities for advanced phase and motion corrections (33,62), which can be particularly helpful when scanning patient populations. The slight contrast increase that was found for 3D POP EPI with respect to 3D GRE tends to be more obvious for the protocols with longer repetition time and is most likely the result of the longer readout in the EPI protocols.

To achieve the results presented in this work, careful optimizations of the sequence timing were required and accurate 3rd order shimming turned out to be of major importance. As in conventional Cartesian EPI a gradient delay or Nyquist ghost correction is essential. Besides correcting for echo shifts within each individual readout plane it also helps aligning the central readout points of all planes on top of each other (43). In this study, the correction was based on additional navigator lines that were acquired for every plane prior to the actual echo-planar readout. To improve the fit stability for the gradient delay estimation an azimuthal distribution of the planes over 2π rather than π was chosen (42). The phase correction successfully removed Nyquist ghosting and increased the
signal homogeneity across the brain. It also had a major positive effect on the image reconstruction. Skipping the phase correction leads to discontinuities in k-space when combining the segmentation or GRAPPA calibration subsets introducing residual artifacts either directly or through miscalibration of the GRAPPA kernel. Minor other effects that are considered to be a result of improving the trajectory alignment were a slight reduction in background noise and some slight removal of blurring artifacts. However, these effects appeared to be rather small. If more severe gradient delays or major eddy current induced trajectory errors are present, prospective correction techniques (63), a gradient field camera (64), or designated data driven methods (65,66) may be employed to improve results. For simplicity, ramp sampling regridding was performed before the phase correction, which can introduce edge ghosting (67). While no significant effects were observed in this work, incorporating the ramp sampling regridding step into the non-uniform fast Fourier transform could enhance the reconstruction quality.

Figure 6: Susceptibility values (mean and standard deviation) measured within the caudate (1st row), pallidum (2nd row), putamen (3rd row) and corpus callosum (4th row) of one volunteer (subj. 1, 27, female) using the different non-accelerated segmented 3D POP EPI protocols with TE = 12 ms (left column), TE = 16 ms (center column) and TE = 21 ms (right column). The values are plotted in blue against the overall acquisition time of the data included in the evaluation for each region. For comparison, corresponding susceptibility values obtained using the accelerated 3D POP EPI protocol and the 3D GRE sequence are depicted in black and red, respectively. For each subfigure, the brain region and echo time are given at the top.
Certainly beyond the scope of this work, further improvements in image quality are expected from employing field map approaches (68,69) or non-linear image registration algorithms (70), which provide a means to overcome geometric distortions. 3D POP EPI is essentially compatible to those corrections.

QSM processing was performed for every single channel in this study, which in contrast to coil-combined approaches (71–73) can be considered computationally expensive. However, using parallel computing on a dedicated computing cluster, the processing time could be kept within a reasonable range. Employing POP-type trajectories usually involves rotating the phase encoding direction with respect to standard 3D GRE and comparable Cartesian readout schemes. As a consequence, the minimum echo time is limited rather by the matrix size in head-foot (usually partition direction in conventional 3D imaging) than in anterior-posterior (usually phase encoding direction in conventional 3D imaging) direction. In high resolution whole brain applications this provides a significant benefit to minimize echo time since the matrix size along the head-foot direction (number of slices or slabs) is usually smaller due to the geometry of the brain.

In this study, 3-shot segmentation or parallel imaging with an undersampling factor of $R_{PE} = 3$ was applied along the phase encoding direction. Thus, whole brain coverage at echo times of $TE = 12$ ms, $16$ ms and $21$ ms could be achieved by making use of partial Fourier undersampling factors of $PF = 5/8$, $6/8$ and $7/8$, respectively. The associated zero-filling in the reconstruction did generally not affect the image quality. However, for the protocol with the highest partial Fourier undersampling ($TE = 12$ ms) signal dropouts in the inferior brain regions slightly increased. Here improvements may be achieved using phase constrained reconstruction approaches (74). For the accelerated protocol, images could be reconstructed without significant residual artifacts. Apart from the decreased SNR, higher order effects of non-linear phase differences appeared loosely near areas of high susceptibility gradients. These effects, which are particularly known for high resolution, ultra-high field EPI can be corrected for by employing a sophisticated parallel imaging reconstruction (54). Major noise enhancement has not been observed. For reasons of simplicity a TGRAPPA like interleaved acquisition scheme was chosen which allowed extracting the calibration data from the scan data itself. Thus, additional calibration scans were not required and artifacts related to different levels of distortion in calibration and scan data (75) could be avoided. A recent study has shown that in terms of temporal SNR a GRE calibration approach might be superior to the EPI based calibration used in this work (76).
Regarding the susceptibility mapping results no substantial differences are found when comparing the different ultra-high field 3D POP EPI protocols used in this study. Considering the image quality and taking into account the time required for scan and calibration, using the accelerated protocol is potentially most beneficial in cases where subject motion is highly likely. Apart from that, employing a partial Fourier factor of PF = 6/8 is considered to provide the best trade-off between echo-time minimization on the one hand and image quality on the other. Regarding the susceptibility deviations across the different protocols that were discussed in Table 1, future research and a higher number of subjects is needed to fully uncover the origin of the slight variations. At lower field strengths like 1.5 T or 3 T, where longer echo-times are usually acceptable and adverse effects such as distortions are less pronounced, partial Fourier undersampling may not be necessary. Taking into account the results of other studies (34,36,37), the proposed readout scheme should be well suitable for those field strengths, too.

As mentioned earlier, the non-Cartesian character of the POP trajectory facilitates the application of more advanced undersampling patterns and acceleration techniques. Thus, future work will exploit further undersampling and calibration schemes including acceleration along the azimuthal direction.

In conclusion, we have demonstrated that high resolution accelerated QSM can be performed using non-Cartesian 3D POP EPI at ultra-high field. The proposed technique is considerably faster than the conventional Cartesian 3D multi-echo GRE approach while yielding comparable susceptibility values in subcortical structures. The proposed non-Cartesian POP readout scheme allows for an echo time suitable for susceptibility mapping, reduced echo train lengths and reduced distortions with respect

![Figure 7: Susceptibility measured with 3D POP EPI as a function of the susceptibility obtained using 3D GRE for subjects 1 (27, female), 2 (35, male) and 3 (23, male) and the different protocols. The line of identity is given in black (dashed).](image-url)
to conventional Cartesian EPI. Providing high flexibility in terms of undersampling renders POP EPI also interesting for other applications such as functional MRI.

**Figure 8:** Effects of motion observed for the 3-fold segmented 3D POP EPI measurement with TE = 12 ms in volunteer 3 (23, male). Axial slice of the k-space averaged reconstruction of all volumes (left image), single-volume reconstructions of repetition 1 (central image) and repetition 9 (right image) and calculated susceptibility within the pallidum plotted against the overall acquisition time of the data included in the evaluation (graph, right). Head motion during the acquisition leads to significant blurring and a loss of details in the averaged reconstruction and an increasing drift of the calculated susceptibility. The overall acquisition time is given in the bottom right of each image.

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