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Prospective motion correction enables highest resolution time-of-flight angiography at 7 T

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Abstract

Purpose—Higher magnetic field strengths enable time-of-flight (ToF) angiography with higher resolution to depict small vessel pathologies. However, this potential is limited by the subject's ability to remain motionless. Even small-scale, involuntary motion can degrade the vessel depiction, thus limiting the effective resolution. The aim of this study was to overcome this resolution limit by deploying prospectively motion-corrected (PMC) ToF.

Methods—An optical marker-based in-bore tracking system was used to update the imaging volume prospectively according to the subject's head motion. PMC ToF was evaluated in twelve healthy, cooperative subjects at resolutions of up to $(150\ \mu\text{m})^3$. Image quality was assessed qualitatively through reader rating and quantitatively with the average edge strength metric.

Results—PMC increased significantly the average edge strength and improved qualitatively the vessel depiction in 9 out of 11 cases. Image quality was never degraded by motion correction. PMC also enabled to acquire the highest resolution human brain in vivo ToF angiography to date.

Conclusion—With PMC enabled, high resolution ToF is able to visualize the brain vasculature beyond the effective resolution limit.

Keywords

prospective motion correction; time-of-flight angiography; high resolution MRI; ultra-high field; sparse saturation; lenticulostriate arteries

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Introduction

Time-of-Flight (ToF) angiography employs a gradient recalled echo sequence which uses short repetition times (TR) and large flip angles to suppress the static tissue's signal within a 3D imaging slab. Subsequently, the high signal from the in-flowing, fully relaxed blood is harvested to visualize the vasculature in vivo (1,2). ToF angiography at clinical field strengths is applied in the brain mainly to detect neurovascular diseases, such as intracranial stenosis (3,4) or unruptured aneurysms (5–7). Even though, the non-invasive diagnosis of small vessels such as arteriovenous malformations (AVM), dural arteriovenous fistulas, and detection of arterial feeders of intracranial tumors is possible with ToF, digital subtraction angiography (DSA) has been shown to yield superior sensitivity and specificity due to higher spatial resolution and image quality (8–11). Thus, DSA remains the gold standard imaging modality for small cranial arteries regardless of its related radiation exposure for staff and patients, low but significant risks of neurological deficit, complications, or idiosyncratic reactions due to artery puncture, catheter placement, and iodinated contrast agent (5,12–14).

Ultra-high field (UHF) MRI could provide the necessary spatial resolution for ToF angiography to be competitive with DSA (15). With higher static magnetic fields the signal-to-noise ratio (SNR) increases supra-linearly (16) and T1 relaxation times prolong, enabling higher resolutions and improved background suppression with ToF sequences (17–19). On the other hand, radiofrequency (RF) pulses commonly used at lower field strengths to further suppress the background via magnetization transfer (MT) and venous signal through saturation slabs cannot be transferred to UHF directly due to the increased specific absorption rate (SAR) (17–22). By applying these saturation pulses sparsely, with reduced flip angles or by using the variable-rate selective excitation (VERSE) technique, SAR constraints can be met (20,21,23,24). Initial ToF studies at 7 T showed more than 80% increase in contrast-to-noise ratio, improved visualization of higher order branches and depiction of smaller vessels compared to 3 T due to higher resolutions (15,18,25). For the first time the microvasculature supplying the deep brain structures such as lenticulostriate arteries (LSA) were visualized non-invasively, potentially enhancing the knowledge about lacunar infarcts or small vessel diseases (e.g. leukoaraiosis) (26,27). Aging decreases the vascularization of subcortical nuclei as shown by inter-individual analysis (28). Also, neurodegenerative diseases such as Alzheimer's or Parkinson's disease and Multiple Sclerosis are suspected to have a vascular component (15,25,29,30).

The potential of studying age- and disease-specific vascular changes with submillimeter resolution, however, is limited by the subjects' ability to remain motionless during the examination (31). With increased resolution the vulnerability to subject motion increases, making high resolution scans more prone to motion artifacts. In addition, prolonged scan times increase the likelihood of subject movement (22,32–34). Even with cooperative, healthy subjects, changes in head position or orientation occur due to physiological, involuntary movements or muscle relaxation. This increases the incidence of artifacts due to bulk motion, thus setting a so-called “biological resolution limit” (31,33,35,36). Less cooperative subjects, such as patients suffering from stroke or other neurological impairments, tend to move even more and thus exacerbate this challenge (15,37).

Motion-induced blurring reduces the level of detail, thus, the effective resolution is lower than the nominal image resolution. Improvement in effective image resolution through reduction of rigid body motion-induced blurring can be achieved with prospective motion correction (PMC) (33). Previously, PMC significantly improved the ToF vessel depiction at 1.5 T in presence of deliberate head motion (37) and a motion-corrected, high resolution, single subject ToF acquisition at 7 T without additional saturation pulses showed the potential of motion correction for studying the microvasculature (31). Nevertheless, a comprehensive study of the biological resolution limit in high resolution ToF angiography with cooperative, healthy subjects was never investigated. Therefore, the aim of this study was to develop a motion-corrected ToF sequence with sparse saturation (sSat) to enable high resolution ToF angiography and to evaluate the effect of small-scale, involuntary subject motion on vessel depiction. Additionally, we attempted to acquire the highest resolution human in vivo ToF angiogram to date.

Methods

Prospective motion correction (PMC)

In this study, an optical, marker-based, tracking system with an in-bore camera (Metria Innovation, Milwaukee, Wisconsin, USA) — which previously showed good performance for high resolution imaging (31) — was used to correct rigid body motion by updating the imaging volume position and orientation prospectively according to the subject's head movement during scanning. The $15 \times 15 \text{ mm}^2$ marker was attached to the subjects' teeth via individually made mouth pieces (based on dental impressions), providing rigid coupling of the marker to the upper jaw and, therefore, to the skull and brain (38). The camera was positioned above the subject's head in the scanner and tracked the marker at 80 frames per second. The video stream was processed by a dedicated computer to calculate marker, thus subject, position and orientation with 0.01 mm and 0.01 degree precision (33). This information was sent to the MRI scanner to update the imaging volume every TR. The motion estimates from the tracking system are stored in log files for motion-corrected and uncorrected scans to allow quantification of head movement during each scan.

To enable tracking in six degrees of freedom with a single marker, single camera setup, the marker has lithographically printed layers which generate Moré patterns. These patterns change under rotation, allowing out-of-plane-rotation estimates by fitting sinusoidal functions to the grey level of the pixels along the Moiré patterns (so-called cosine ambiguity recovery). The remaining four degrees of freedom are estimated using standard photogrammetric techniques (33). A detailed description and validation of the motion correction system can be found elsewhere (31,33,39).

Sparse saturation (sSat)

Different approaches to meet the SAR constraints at UHF for background and venous saturation with ToF angiography have been published (20,21,23,24). In this study a variation of the approach by Schmitter et al. was implemented (21): First, the peak voltage of the 90 degrees venous saturation pulse was reduced by approximately 65% with the vendor-implemented VERSE routine. This was achieved by setting the gradient amplitude of the

side lobes to 250% of the center amplitude, and by specifying the gradient center length as 40% of the whole gradient duration. Secondly, the venous saturation slab was applied sparsely every 7th or 10th TR (see Table 1). Lastly, the MT pulse was applied only during scanning of the central 10% of k-space lines, yielding the best trade-off between increase in SAR and background suppression (21). These parameters were retained throughout this study whenever sSat was applied.

In vivo measurements

Twelve healthy and compliant subjects consented to participate in the study, which was approved by the local ethics committee. A 7 T whole body MRI (Siemens Healthcare, Erlangen, Germany) with a quadrature transmit and 32-channel receive head coil (Nova Medical, Wilmington, Massachusetts, USA) was used to acquire ToF angiography at three different resolutions: 300 μm , 250 μm , and 150 μm isotropic voxel size. The sequence parameters are summarized in Table 1. For the excitation, TONE pulses (40) with 80% ramp were applied. If venous suppression was used, a 40 mm thick saturation slab was positioned 7 mm above the imaging slab. Accelerated ToF scans used GRAPPA (41) with 32 auto-calibration signal lines. All sequences used partial Fourier. The missing k-space information was zero-filled prior to the image reconstruction.

ToF at 250 μm isotropic resolution—As a demonstration, a single subject (male, 34 years) was scanned with PMC and sSat as well as without any alteration of the sequence (product sequence configuration) at a resolution of 250 μm isotropic. Axial maximum intensity projections (MIP) of both scans were assessed qualitatively.

ToF at 300 μm isotropic resolution—To further investigate the potential of motion-corrected high resolution ToF angiography eleven, cooperative subjects (30.83 ± 4.71 years, 4 females) were scanned with and without PMC at an isotropic resolution of 300 μm and were instructed to hold still during acquisition. Sparse saturation was applied for corrected as well as uncorrected scans to improve background and venous suppression. For all scans axial MIPs were generated and evaluated qualitatively through reader rating (by an experienced MR physicist, stating whether image quality with PMC was improved, similar, or degraded) as well as quantitatively with the average edge strength metric (AES). The AES is defined as the total edge energy divided by the number of edge pixels and was computed as introduced in (42)

$$AES = \frac{\sqrt{\sum E(I)[G_x(I)^2 + G_y(I)^2]}}{\sum E(I)} \quad [1]$$

where $E(I)$ is the sum of edges detected in the MIP and $G_{x/y}$ are the gradient images of the MIP along the x- and y-direction.

To compare the corrected to the uncorrected subject motion, 3D mean $\pm$ standard deviation for translational and rotational movement was computed per subject. Paired *t*-tests (significance level 5%) were performed to test if subject motion during corrected and

uncorrected scans differed significantly as well as to test if PMC significantly improved the AES of the axial MIPs. All processing was performed with MATLAB 2015b (The MathWorks, Natick, Massachusetts, USA).

ToF at 150 μm isotropic resolution—In the effort to acquire the highest resolution human in vivo brain ToF angiogram to date, a single motion-corrected 150 μm isotropic resolution scan was acquired of the same subject as for the 250 μm resolution. Due to extended scan duration (>2h) no uncorrected 150 μm ToF angiogram was incorporated for comparison. Compared to the 250 μm protocol, MT pulses were omitted since they prolong the TR by 15 ms. Also, the number of slices per slab and number of slabs were not increased to prevent longer acquisition, resulting in lower coverage than for the 250 μm protocol.

To evaluate the vessel depiction with respect to imaging resolution the fully sampled 150 μm data were compared to 1.) the previously acquired 250 μm data set and 2.) 250 μm data synthesized from the 150 μm data set itself. For the first evaluation, the following data sets were generated and compared: 150 μm acquired without image acceleration, 150 μm retrospectively reconstructed with 3-fold undersampling, 250 μm acquired with 3-fold undersampling, and the 250 μm data set interpolated to 150 μm using zero-filling (43).

The retrospective undersampling of the 150 μm data set was done with an in-house reconstruction pipeline consisting of the following steps: First, channel-wise raw data were read (approx. 100 GB), 32 auto-calibration signal lines were stored for each slice, and 3-fold undersampling in phase encoding direction was performed. Then, GRAPPA reconstruction (based on (41)) was used to estimate the missing k-space, followed by zero-filling to account for partial Fourier during the acquisition. Afterwards, inverse fast Fourier transform yielded channel-wise image data. Adaptive combination (44) provided four partially overlapping slabs which were merged into the final volume.

Interpolation with zero-filling was reported to improve vessel contrast and vessel continuity (43). Therefore, the 250 μm image data were interpolated to 150 μm by transforming it back to k-space, zero-filling, and then transforming it into the image domain again.

For the second evaluation, a 250 μm data set was synthesized from the fully sampled 150 μm by transforming the 150 μm data back to k-space, setting the corresponding high frequency components to zero and generating images from the zero-filled k-space. Thus, the synthesized data had 150 μm voxel spacing but contained only measured k-space information for 250 μm resolution.

For comparison of vessel depiction the data based on the previous 250 μm scan was coregistered to the fully sampled 150 μm ToF with ANTs 2.1 (45) using ‘antsRegistrationSyN.sh’ for affine registration. For all data sets sagittal MIPs over 60 mm (400 slices) were produced. Additionally, axial MIPs were generated over the whole imaging volume to compare 150 μm and measured 250 μm , and coronal MIPs over 30 mm (200 slices) to compare 150 μm and synthesized data. Vessel-to-background ratios were estimated for the anterior cerebral arteries (ACA), LSA, and residual venous blood by dividing the mean vessel signal intensity by the mean surrounding background signal intensity. The ROIs

for the vessel and background were selected manually in the sagittal MIPs, featuring only vessels visible with 150 μm and 250 μm . As an anatomic reference for this highest resolution ToF angiogram, a prospectively motion-corrected MPRAGE (46) was acquired with the following parameters: $0.45 \times 0.45 \times 0.45 \text{ mm}^3$ resolution; FoV $225 \times 225 \times 187.2 \text{ mm}^3$, TR/TI/TE 2820/1050/2.8 ms, 5 degrees flip angle, bandwidth 170 Hz/Px, GRAPPA 3 with 24 auto-calibration signal lines, 6/8 slice partial Fourier, scan duration 12:11 min. After bias field correction with SPM12 (47), the MPRAGE was coregistered to the 150 μm ToF with FSL FLIRT (48). MeVisLab 2.8.2 (MeVis Medical Solutions AG, Bremen, Germany) was used for 3D volume rendering of the 150 μm data set with the MPRAGE in the background. A vesselness filter (Hessian computation with 4 sigmas in the interval of 1 to 5 voxels) was applied to extract the arteries in the ToF data.

Results

ToF at 250 μm isotropic resolution

The modified sequence was tested in a single subject with an isotropic voxel size of 250 μm to evaluate qualitatively the performance of PMC and sSat. Even though instructed to hold still, the subject moved $3.52 \pm 1.44 \text{ mm}$; 3.72 ± 0.62 degrees during the corrected and $7.05 \pm 3.03 \text{ mm}$; 1.95 ± 0.85 degrees during the uncorrected scan. The axial MIPs in Figure 1 show that PMC and sSat considerably improve the vessel depiction: background tissue is suppressed better and vessels appear sharper, resulting in higher vessel contrast, longer vessel continuity, and increased visibility of small vessels. Veins are suppressed effectively with sSat.

ToF at 300 μm isotropic resolution

To evaluate the effect of motion on the vessel depiction in MIPs, eleven trained, healthy subjects (instructed to hold still) were scanned with and without PMC. Sparse saturation was used for corrected and uncorrected scans. The tracked motion, AES results, and reader ratings are shown in Table 2. Additionally, zoomed MIPs for subject 2 and 8 are shown in Figure 2. Comparisons for all subjects with and without PMC can be found in Supporting Figure S1. Even though, the mean observed subject motion during corrected and uncorrected scans did not differ significantly (p -values of 0.199 for translation and 0.643 for rotation), subject-wise comparison can yield large differences between scans, e.g. subject 3 moved almost one order of magnitude more during the corrected scan compared to the uncorrected one. If uncorrected, the movement in the range of a few millimeters and degrees blurred the MIPs. PMC improved visually the sharpness and brightness of the vessels in the MIP, enabling the visualization of smaller and more distal vessels. The quantitative analysis with AES revealed an improvement with PMC in 8 out of 11 cases (Table 2). Additionally, the group median increased from 22098 a.u. without PMC to 23543 a.u. with PMC. The paired t -test for the AES indicated that PMC on and off differ significantly ($p=0.016$). The subjective reader rating showed a similar trend: 9 out of 11 cases show an improved MIP, for subject 9 and 10 the image quality is similar. PMC never degraded the vessel depiction.

ToF at 150 μm isotropic resolution

The subject from the 250 μm scan was measured again with 150 μm isotropic voxel size to investigate the potential of PMC. Due to the very long scan time for this scan only motion-corrected data were acquired, during which the subject moved 2.69 ± 1.14 mm; 2.25 ± 0.44 degrees, respectively.

Besides the fully sampled 150 μm and 3-fold undersampled 250 μm data, a 3-fold undersampled version of the 150 μm data and zero-filled interpolation of the 250 μm data to 150 μm voxel size were reconstructed retrospectively. After coregistering all data sets to the fully sampled 150 μm data the axial and sagittal MIPs in Figure 3 and Figure 4 were created. The fully sampled 150 μm provided superior vessel-to-background ratios (see Table 3) and vessel depiction (see Figure 3 and Figure 4) compared to the other volumes. Vessel-to-background ratios were approximately identical for all undersampled volumes, independent of the resolution. Undersampling reduced the ratios by approximately 16% in the ACA, 19% in the LSA, and 9% for residual venous blood compared to the fully sampled data. Even though the undersampled 150 μm data showed increased noise compared to the fully sampled data, they still enabled the delineation of more LSAs, and longer tracking of arteries extending to the occipital lobe compared to the volumes originating from 250 μm data (see Figure 3 and Figure 4). With 3-fold undersampling the 150 μm scan would require approximately the same scan time as the 250 μm scan (49:03 min vs 48:05 min), while providing 40% less slice coverage, more than 4-fold decrease in voxel size, and increased inflow effect due to thinner slabs. Zero-filling of the 250 μm to 150 μm could not improve vessel contrast, vessel continuity, or recover vessels not visible prior to the interpolation. Thus, visualization of small vessels like the LSA benefited the most from the higher acquired resolution, increased inflow effect due to thinner slabs, and decreased imaging acceleration. However, venous contamination increased in the fully sampled 150 μm data as well due to overall increased vessel-to-background ratios. Additionally, reduced slab oversampling for both 150 μm volumes caused residual slab boundary artifacts (compare Table 1 and Figure 4). Since the 150 μm and 250 μm data were acquired in different sessions, careful subject repositioning was used to minimize potential bias due to different orientations of the imaging volume with respect to the anatomy and blurring due to interpolation by the registration process. The difference in head orientation as estimated by the registration was 4.87 degrees in pitch, 6.12 degrees in roll, and 0.70 degrees in yaw. To evaluate potential bias due to interpolation the fully sampled 150 μm data set was coregistered to the zero-filled 250 μm data set (see Supporting Figure S2). Again, the 150 μm data showed superior vessel depiction.

The vessel depiction with respect to imaging resolution was also investigated by synthesizing 250 μm data from the 150 μm data by setting corresponding high frequencies to zero in k-space. Comparison of measured and synthesized data in Figure 5 and Supporting Figure S3 shows similar depiction of the imaged vasculature. The vessel sharpness benefited visually from higher acquired resolutions. However, noise decreased after removing the measured high frequency components. Thus, vessel-to-background ratios (see Table 3) increased by 14% (ACA), 12% (LSA), and 6% (residual venous blood) for synthesized 250 μm data.

The potential of the fully sampled 150 μm data set for small vessels visualization is shown in Figure 6: The coronal MIP clearly shows small vessels such as the LSA and their branching as well as pontine branches of the basal artery. Additionally, 3D rendering of the 150 μm ToF scan with a coregistered MPRAGE scan enables studying the arterial vasculature and its surrounding anatomic structures at the cost of reduced depiction of very small vessels due to limitations in the automated segmentation.

Discussion

We present the first systematic study of high resolution, motion-corrected ToF angiography at 7 T. Motion correction employed tracking information from an optical, marker-based, in-bore camera to update the imaging volume position and orientation during acquisition according to the subject's motion, thus correcting motion prospectively. Additionally, a sparse saturation scheme was implemented to enable improved venous and background suppression under SAR constraints similar to previously reported approaches (20,21,23,24). With motion correction enabled, the implemented sequence never compromised image quality, showed qualitatively improved vessel depiction at different imaging resolutions (10 out of 12 cases), increased significantly the MIP edge strength, and was used to acquire the highest resolution human brain in vivo ToF angiography to date.

Comparison of the modified and product ToF sequence for a single subject shows improved vessel depiction and venous as well as background suppression with PMC and sSat enabled (see Figure 1). The selected isotropic 250 μm resolution increased the susceptibility to motion artifacts and required approximately 50min of scanning, thus, increased the likelihood of subject motion. Even though, the trained and cooperative subject was instructed to hold still, movements one order of magnitude larger than the voxel size were observed, resulting in image blurring and loss of detail if not corrected for. PMC successfully prevented motion artifacts, enabling higher effective resolution compared to the uncorrected scenario.

Venous suppression was applied in 500 ms intervals (every 10th TR), resulting in an effective saturation (T1 relaxation of venous blood at 7 T is approximately 2450 ms (49)). The qualitatively improved background suppression with PMC and sSat could originate from the sparsely applied MT pulses, the sharper vessel depiction due to motion correction, or both. Distinguishing between both — potentially complementary — techniques was beyond the scope of this study, which focuses on the effect of PMC on ToF angiography. Thus, sparse saturation with MT pulses was used for corrected and uncorrected scans in eleven cooperative subjects to further evaluate the potential of PMC. During these scans only small-scale, involuntary head motion — in the order of a few millimeters/degrees (see Table 2). — occurred, enabling the depiction of the Circle of Willis vessels with and without motion correction. Nevertheless, PMC improved depiction particularly of small and distal arteries in more than 80% of the subjects qualitatively, and the edge strength of the MIPs increased significantly (see Table 2, Figure 2 and Supporting Figure S1). While this study focused on motion correction for small vessels at 7 T, Kopeinigg et al. showed that PMC improves depiction of the Circle of Willis vessels greatly at 1.5 T (37). In contrast to the current study, they used an approximately 18-times lower resolution (0.502 mm³ vs 0.027 mm³) and

instructed the subjects to move. Nevertheless, they reported the best vessel depiction if no deliberate head motion was present, thus, indicating that involuntary movement can degrade also lower resolution angiograms. Furthermore, the application of PMC never impaired the image quality in their and our study. Thus, PMC showed great potential for ToF angiography for low and high resolution independent of the presence of deliberate subject movement. Translation to clinical routine, where higher resolutions are demanded but increased patient motion is likely, should be the next step to prove the diagnostic value of PMC for angiography.

The implemented sequence was used to acquire the highest resolution human brain in vivo MR angiography to date. Previously, Stucht et al. acquired ToF angiography of a 28 mm thick slab with a voxel volume of 0.008 mm^3 without venous saturation (31). We reduced the voxel volume to 0.003 mm^3 and acquired a 46.8 mm thick slab with venous saturation. The acquired MIP for the fully sampled $150 \mu\text{m}$ isotropic resolution is shown in Figure 3 and Figure 4 along with a retrospectively undersampled version of the $150 \mu\text{m}$ data and the previously acquired $250 \mu\text{m}$ data of the same subject with and without zero-filling. The fully sampled $150 \mu\text{m}$ data provided the best vessel depiction compared to all other volumes. The vessel-to-background ratio decreased in presence of undersampling and independent of the resolution (see Table 3). For the identical undersampling factors (and approximately same scan time), vessel visibility improved with higher acquired resolution and reduced slabs thickness (see Figure 3 and Figure 4), regardless of the smaller reconstructed voxel size. Zero-filling could not recover more vessels, in contrast to previously reported results (43).

Comparing the measured $250 \mu\text{m}$ and $150 \mu\text{m}$ data did not account for difference in slab thickness. The $150 \mu\text{m}$ data employed thinner slabs (motivated by long scan duration), thus, had an increased inflow effect. By zero-filling high frequency components in the measured $150 \mu\text{m}$ k-space synthesized $250 \mu\text{m}$ data with $150 \mu\text{m}$ voxel spacing were created. Zero-filling did not impair the detection of small vessels due to decreased imaging resolution or improve their detection due to increased vessel-to-background ratios (see Table 3). Overall, visual differences between both data sets are subtle. The measured $150 \mu\text{m}$ data provided visually sharper vessels while the synthesized $250 \mu\text{m}$ data showed reduced image noise (see Figure 5 and Supporting Figure S3). Applying no imaging acceleration and using thinner slabs resulted in intrinsically high vessel-to-noise ratio of the measured $150 \mu\text{m}$ data. Therefore, setting high frequency components to zero retrospectively did decrease the level of detail, since the vessel signal remained the dominant signal source within the voxel volume. Regardless of the imaging matrix, without PMC such detailed vessel depiction might not have been possible due to inevitable subject motion during the two hours of scanning

In this study, the vessel depiction depended on the imaging resolution, inflow effect, and imaging acceleration. On the one hand, inflow effect and imaging acceleration determine the vessel-to-background ratio. Therefore, vessels smaller than the voxel resolution could be visualized, if the vessel signal is sufficiently higher than the surrounding tissue within the same voxel. On the other hand, higher imaging resolution enables sharper vessel depiction and reduces the voxel volume. Thus, the vessel signal is less affected by partial volume effects of the background tissue within the same voxel.

The coronal MIP of the Circle of Willis and the 3D volume rendering of the fully sampled 150 μm data in Figure 6 outline the potential of imaging the microvasculature non-invasively at such high resolution. Even though, the vesselness filter for the 3D rendering loses small details, an improved segmentation algorithm could enable vessel morphology to advance our understanding of the neurovascular structure – function relationship (50). Motion-prone cohorts could be studied in vivo to visualize previously not detectable changes in vascularization of e.g. the striatum or hippocampus, potentially improving the knowledge about neurodegenerative diseases, stroke, and aging (15,25,26,28–30,51). Furthermore, motion-corrected ToF angiography could improve functional magnetic resonance angiography (52), which detects changes of the arterial microvasculature due to stimuli at high spatial resolutions. Uncorrected subject motion could blur the arterial response and, therefore, may result in decreased activation patterns.

The main limitation of the presented approach is the excessively long scan time. Even with 1D GRAPPA sufficient vessel-to-background ratios were achieved. Thus, 2D GRAPPA could reduce the scan time considerably while maintaining depiction of small vessels.

Also, compressed sensing (53,54), CAIPIRINHA (32), or multiband, multi slice imaging (55) could further decrease the scan duration. Potential residual motion artifacts, due to large motion (gradient and static magnetic field inhomogeneity, relative changes in coil sensitivity profiles) or imperfect motion correction (cross-calibration errors, latency, pseudo motion) could be addressed retrospectively (35,56–59). In less experienced cohorts, large motion could increase residual artifacts due to e.g. relative changes in the receiver sensitivity profiles or gradient non-linearities, which cannot be corrected by PMC. Yarach et al. have extended the PMC system with retrospective sensitivity profile and gradient correction to address these challenges (57).

The biological resolution limit, originating from inevitable, small-scale bulk motion due to e.g. breathing and muscle relaxation, could be overcome with PMC. However, this biological resolution limit, i.e. the ability to lie still, does not consider non-rigid motion. Correction of non-rigid motion, such as pulsations of the vascular and ventricular system, is not supported by the implemented approach as rigid body motion is assumed. For example a shift of the thalamus of more than 100 μm had been reported (60) due to cerebrospinal fluid pulsation. As a result, the effective resolution might be decreased even with PMC. Analysis of this potential physiological resolution limit due to non-rigid motion remains a task for the future.

The sparse saturation scheme applied in this study included VERSE for the saturation pulse, sparse venous saturation every 7th or 10th TR, and MT pulses during acquisition of the center 10% k-space lines. Even though, this approach enabled effective venous saturation and sufficient excitation flip angles, residual venous contamination occurred in some subject scans. Potentially, subject-specific differences in the vasculature or venous flow velocity could cause these residuals. The increased venous residuals in the intra-subject comparison of fully sampled 150 μm to undersampled data sets is caused likely by the overall increased vessel-to-background ratio, originating from the reduced imaging acceleration in the fully sampled 150 μm scan (see Table 3, Figure 3, and Figure 4). Improved saturation could be

achieved by applying VERSE to the excitation pulse to further reduce SAR, thus, enabling shorter TRs, increased excitation flip angles or more frequent saturation to increase the vessel-to-background ratio further (20,21). Nevertheless, VERSE should be applied moderately to control distortions of the excitation slab profile (21), a challenge potentially more severe for high resolution ToF angiography. Furthermore, improved B1 transmit field shimming can improve the venous, fat, and background suppression (61).

The proposed motion-corrected ToF sequence enables similar spatial resolution as the gold standard technique DSA, without the drawbacks of X-ray imaging, contrast agents and invasive catheterization. DSA detectors have commonly a 1024×1024 matrix while using a 170 – 220 mm FoV (4,6,62), resulting in nominal pixel size of e.g. 0.21×0.21 mm (4) (note that imaging parameters such as magnification factors can change the nominal resolution). Therefore, UHF ToF angiography with PMC can produce spatial resolution superior to clinically used DSA. Additionally, ToF angiography provides 3D information, rather than projections only, but provides no temporal resolution (9,10). Combining ToF angiography and 4D flow MRA (10) with PMC could provide high spatial and temporal resolution of small vessel diseases non-invasively.

In summary, we presented a prospective motion-corrected ToF sequence with sparse saturation for high resolution angiography at 7 T. The results indicate that with the proposed sequence, the biological resolution limit, originating from small-scale, involuntary bulk head motion, could be overcome to enable detailed depiction of the brain's microvasculature in vivo with improved venous and background suppression under SAR constraints. Thus, the method provides non-invasive in vivo high resolution angiograms, potentially closing the gap to DSA and enhancing the knowledge about aging and neurodegenerative diseases in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Maximum intensity projections (MIP) of time-of-flight angiography with 250 μm isotropic voxel size (a) with prospective motion correction (PMC) as well as sparse saturation (sSat) and (b) without PMC and no sSat (MIPs have identical windowing). PMC improved the vessel depiction and sharpness of the MIP. Venous contamination, such as the superior sagittal sinus (large vessel in the bottom of the MIPs), was saturated by sSat.

Figure 2.

Comparison of regional maximum intensity projections (MIP) for two subjects with and without prospective motion correction (PMC) in the presence of small-scale, involuntary movements. All MIPs of the 300 μm data sets have the same windowing. With PMC the vessel depiction qualitatively improves. Arrows indicate exemplary regions with improved vessel depiction.

Figure 3.

Axial maximum intensity projections (MIP) for (a) fully sampled 150 μm , (b) 150 μm with retrospective 3-fold undersampling, (c) 250 μm zero-filled to 150 μm , and (d) 250 μm isotropic voxel size (all reconstructed from motion-corrected scans of the same subject; MIPs have identical windowing). The 250 μm data sets were coregistered to the 150 μm scan prior to the MIP to ensure the same coverage and orientation. Arrows indicate the lenticulostriate arteries (blue), arteries extending towards the occipital lobe (green), and residual venous signal (yellow).

Figure 4.

Sagittal maximum intensity projections (MIP) (a, c, e, g) and zoomed MIPs of the blue regions (b, d, f, h) for (a, b) fully sampled 150 μm , (c, d) 150 μm with retrospective 3-fold undersampling, (e, f) 250 μm zero-filled to 150 μm , and (g, h) 250 μm isotropic voxel size (all reconstructed from motion-corrected scans of the same subject; MIPs have identical windowing). Arrows indicate the anterior cerebral arteries (pink), the lenticulostriate arteries (blue), arteries extending towards the occipital lobe (green), and residual venous signal (yellow). The 250 μm data sets were coregistered to the 150 μm scan prior to the MIP to ensure the same coverage and orientation.

Figure 5.

Sagittal maximum intensity projections (MIP) (a, c) and zoomed MIPs of the blue regions (b, d) for (a, b) fully sampled 150 μm , and (c, d) 250 μm synthesized from the 150 μm by setting the corresponding high frequency components to zero in k-space (all MIPs have identical windowing). Arrows indicate the anterior cerebral arteries (pink), the lenticulostriate arteries (blue), arteries extending towards the occipital lobe (green), and residual venous signal (yellow).

Figure 6. Zoomed visualization of the 150 μm isotropic voxel size scan using (a) maximum intensity projection and (b) 3D volume rendering. The 3D volume rendering features also MPRAGE data to show the anatomical region close to the vessels. The pathways of small vessels like the lenticulostriate arteries into deep gray matter (see blue arrows) and pontine branches of the basal artery to the brain stem (see red arrows) are depicted in detail.

Table 1
Sequence parameters for different acquisitions

Parameters	Sequence		
Resolution	$250 \times 250 \times 250 \mu\text{m}^3$	$300 \times 300 \times 300 \mu\text{m}^3$	$150 \times 150 \times 150 \mu\text{m}^3$
FoV x,y,z	$196 \times 147 \times 78 \text{ mm}^3$	$216 \times 189 \times 58.5 \text{ mm}^3$	$196 \times 147 \times 46.8 \text{ mm}^3$
Slabs	4	4	4
Slab encoding matrix	784×588×96	720×630×60	1296×972×96
Slab oversampling	16.7%	20.0%	8.3%
Slab overlap	-25%	-25%	-25%
TR/TE	50 ms/6.63 ms	50 ms/6.63 ms	35 ms/6.63 ms
Flip angle	25 degrees	25 degrees	23 degrees
Bandwidth	78 Hz/Px	78 Hz/Px	102 Hz/Px
Venous saturation	every 10 th TR	every 7 th TR	every 7 th TR
GRAPPA factor	3	3	none
Partial Fourier	6/8 (phase & slice)	6/8 (phase & slice)	6/8 (phase & slice)
Scan duration	0:48:05 h	0:33:08 h	2:14:21 h

Subject-wise motion quantification and image quality assessment: Mean and standard deviation of the 3D translational and rotational movement is given as well as the average edge strength (AES) and reader quality rating with and without prospective motion correction (PMC).

Table 2

Subject	Translational motion [mm]		Rotational motion [deg]		AES [a.u.]		Reader quality rating
	PMC on	PMC off	PMC on	PMC off	PMC on	PMC off	
1	0.96 ± 0.59	4.63 ± 1.23	0.43 ± 0.1	1.79 ± 0.38	28924	23500	improved
2	2.47 ± 1.30	2.25 ± 0.90	0.77 ± 0.38	2.50 ± 0.41	20187	13715	improved
3	12.70 ± 6.25	1.63 ± 0.59	5.27 ± 1.93	0.67 ± 0.20	14121	13816	improved
4	1.40 ± 0.52	0.70 ± 0.40	0.45 ± 0.15	0.47 ± 0.04	21530	22098	improved
5	3.44 ± 0.81	1.20 ± 0.56	1.66 ± 0.53	2.20 ± 0.21	29944	19463	improved
6	1.36 ± 0.82	2.47 ± 2.04	0.73 ± 0.40	1.53 ± 0.68	40715	32568	improved
7	1.73 ± 0.45	2.44 ± 0.50	0.65 ± 0.15	0.53 ± 0.17	19964	15569	improved
8	1.72 ± 0.82	0.21 ± 0.42	0.65 ± 0.40	3.31 ± 0.16	32272	21891	improved
9	3.82 ± 1.65	0.66 ± 0.40	0.75 ± 0.34	1.28 ± 0.12	21606	22619	similar
10	2.32 ± 0.81	0.54 ± 0.29	0.60 ± 0.15	0.59 ± 0.05	26353	27758	similar
11	3.27 ± 1.73	1.68 ± 0.45	0.95 ± 0.51	0.95 ± 0.12	23543	22459	improved

Table 3

Vessel-to-background ratios for the anterior cerebral arteries (ACA), the lenticulostriate arteries (LSA), and residual venous blood at different resolutions.

Volume	Vessel-to-background ratio		
	ACA	LSA	Veins
Fully sampled $(150\ \mu\text{m})^3$	4.18	2.04	1.61
$(150\ \mu\text{m})^3$ with retrospective 3-fold undersampling	3.59	1.66	1.48
$(250\ \mu\text{m})^3$ with 3-fold undersampling and zero-filled to $(150\ \mu\text{m})^3$	3.46	1.69	1.45
$(250\ \mu\text{m})^3$ with 3-fold undersampling	3.46	1.65	1.45
$(250\ \mu\text{m})^3$ synthesized from $(150\ \mu\text{m})^3$ by setting corresponding high frequency components to zero in k-space	4.78	2.29	1.71