Myelin Imaging Using 3D Dual-echo Ultra-short Echo Time MRI with Rosette k-Space Pattern

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Abstract

Purpose: This study aimed to develop a new 3D dual-echo rosette k-space trajectory, specifically for applications of ultra-short echo time (UTE) magnetic resonance imaging (MRI). The direct imaging of the myelin bilayer, which has ultra-short transverse relaxation time (uT_2), was acquired to test the performance of the proposed UTE sequence.

Theory and Methods: The rosette trajectory was developed based on rotations of a 'petal-like' pattern in the k_x-k_y plane, with oscillated extensions in k_z-direction for 3D coverage. Five healthy volunteers were recruited and underwent ten dual-echo rosette UTE scans with varied echo times (TEs). Dual-exponential model fitting was performed to separate uT_2 signals, with the output of uT_2 fraction, uT_2 value and long T_2 value.

Results: The reconstructed images' signal contrast between white matter (WM) and grey matter (GM) increased with longer TEs. The WM regions had higher uT_2 fraction values than GM (10.9%$\pm$1.9% vs. 5.7%$\pm$2.4%). The uT_2 value was about 0.12 milliseconds in WM.

Conclusion: The higher uT_2 fraction value in WM compared to GM demonstrated the ability of the proposed sequence to capture rapidly decaying signals.

Keywords: non-Cartesian, ultra-short echo time, rosette trajectory, k-space, microstructure

Introduction

Conventional ^{1}H-MRI sequences are widely used for *in vivo* imaging with relatively long spin-spin (transverse) relaxation time (T_2). However, depending on the surrounding chemical environment, some protons in specific tissues in the human body have an ultra-short T_2, which conventional MRI can hardly detect due to the relatively long echo time (TE) in the order of milliseconds (ms). For example, the myelin bilayer in cerebral white matter (WM) (1), cortical and trabecular bones (2), ligaments (3), tissues with high iron concentration (4), etc. On the other hand, ultra-short echo time (UTE) MRI (5) sequences are capable of acquiring data with TE in the order of microseconds (µs), which can provide images of tissues with ultra-short T_2 directly.

For UTE sequences, the readout gradients are applied immediately after the completion of the RF pulses. Therefore, to achieve minimum possible TE, each data acquisition in UTE sequences needs to follow a center-out trajectory. Although 2D UTE methods are available, they have limitations making it difficult to achieve an appropriate slice selection and a minimum TE due to eddy currents and imperfect gradients (6,7). Alternatively, the most common k-space trajectory used in UTE MRI applications is a 3D radial center-out readout. However, sampling the outer k-space with a radial pattern may not be efficient (8). Novel 3D k-space trajectories with greater curvature per spoke have been proposed for a more efficient sampling strategy, e.g., the spiral-like extended cones sampling (7,8). Rosette k-space trajectories, which allow a center-out sampling pattern while providing more samples in the outer k-space per spoke than radial trajectories, are also potential candidates for 3D UTE MRI. In addition, the rosette k-space trajectory samples data in a more incoherent pattern than the radial trajectory. Therefore, it offers the potential for further acceleration using higher under-sampling factors and the compressed sensing technique for reconstruction (9). However, to date, 3D rosette k-space patterns have not yet been demonstrated in UTE applications.

Alternatively, a similar MRI-based technique, zero echo time (ZTE) MRI, has also been proposed for imaging ultra-short T_2 tissue. However, unlike UTE imaging, the readout gradients are applied before the RF pulse and are always on in ZTE sequences (10). In

addition, the center k-space in the ZTE sequence is empty because of the dead time due to the switching from RF pulse excitation to data receiving (10), which requires additional scans or interpolation based on an over-sampling strategy to fill in the missing k-space (11). Nevertheless, a recent comparison study has shown that UTE and ZTE MRI sequences provide similar results in terms of image quality and signal-to-noise ratio (SNR) (12).

One of the important applications of 3D UTE and ZTE sequences is imaging the myelin bilayer in brain white matter (WM). Myelin constituents are water and dry mass, in which the dry mass is composed of about 80% lipids and 20% protein (13). Since transverse relaxation of the lipid proton signal becomes shorter in this geometrically restricted environment, T_2 values vary from a few microseconds to milliseconds, where 75% of the myelin lipid signal manifests T_2 values below 100 μs (14). Thus, conventional MRI sequences with TEs in the order of milliseconds or longer can hardly capture the rapid signal decay of the lipid bilayer.

Many alternative MRI-based methods have been proposed for myelin imaging, e.g., the methods based on magnetization transfer (MT) effects, separation of myelin water signals, susceptibility imaging, and cortical myelin mapping (15-18). However, while those methods provide an indirect measurement of myelin (19), UTE MRI can provide a direct measure of myelin, which may be more specific and more precise (7).

UTE MRI methods have shown great promise for imaging the signals arising from the phospholipid chains of myelin sheaths. Common techniques for the separation of myelin signals based on UTE acquisitions are the combination of inversion recovery (IR) suppression (1) and dual-echo subtraction (20). Even though those methods showed the potential to suppress signals originating from long-T_2 components in both grey matter (GM) and WM, the inversion time (TI) of IR suppression is difficult to choose because of the wide range of longitudinal relaxation time (T_1) reported in WM (700 to 1100 ms at 3T) (21,22). An alternative method to quantify myelin signals was using a

dual-exponential model fitting with data input based on a multiple TEs acquisition, ranging from microseconds to milliseconds.

This study aims to develop a novel rosette k-space pattern for 3D UTE MRI and test the sequence by directly and non-invasively measuring the myelin bilayer with the whole-brain coverage. With the novel k-space design, dual-echo data is sampled in a single acquisition, allowing multiple TEs 3D images in a clinically acceptable total scan time. In addition, compressed sensing and low-rank de-noising were applied to reconstruct images from the acquired non-Cartesian k-space data.

Theory

Rosettes are non-Cartesian k-space trajectories with high design flexibility (23). The shape of the rosette trajectory depends highly on the parameters, which could be identical to rings or radial patterns in extreme cases. The rosette trajectories are well known for the multiple crossings of k-space origin (24), which suggests the potential for multiple-echo acquisition.

The following equations define the 3D rosette k-space trajectory (25):

$$K_{xy}(t) = Kx(t) + i * Ky(t) = (Kmax * \cos(\varphi)) * \sin(\omega_1 * t) * e^{i\omega_2 t + \beta}$$

$$K_z(t) = (Kmax * \sin(\varphi) * \sin(\omega_1 * t)$$

where $Kmax$ is the maximum extent of k-space, ω_1 is the frequency of oscillation in the radial direction, ω_2 is the frequency of rotation in the angular direction, φ determines the location in the z-axis, and β determines the initial phase in the angular direction.

In Figure 1A, a rosette trajectory is shown for the specific case where ω_1 and ω_2 are set to be equal. Origin of the k-space is sampled at the beginning and the end of each repetition time (TR), forming a petal-like sampling pattern (Figure 1A). With a manual separation at the middle of each data readout, dual-echo images can be achieved within a single acquisition (Figure 1A and 1B). TE values are separately determined by the time of two crossings of the k-space origin. The gradients of one petal trajectory are shown in Figure 1B. The amplitude of the readout gradient began at zero to avoid any potential delays caused by the gradients' ramp-up (details in discussion).

The parameters for the UTE acquisition were: $Kmax$=250/m, ω_1=ω_2=1.611 kHz, number of total petals= 36100, samples per petal=210, φ was sampled uniformly in the range of $[-\pi/2, \pi/2]$, and β was sampled uniformly in the range of [0,2π]. With ten μs readout dwell time, the difference between first TE (TE_1) and second TE (TE_2) is equal to $210 \times 10\ \mu s = 2.1\ ms$ (details of other scan parameters are stated in Methods). Crusher gradients in all three directions were applied at the end of each readout gradient (not shown in Figure 1B).

The 3D radius (including all x, y, and z directions) of the rosette trajectory is expressed with a sine function ($Kmax * \sin(\omega_1 * t)$), which varies within [0, $Kmax$]. In addition, the 3D radius of the rosette trajectory has a fast rate of change at small radii of k-space but a slow velocity at large radii of k-space. With the constant readout dwell time, the k-space velocity difference led to increased samples with the radii of k-space for each readout spoke (about 43% samples at radii of k-space larger than 0.75$Kmax$). However, for each readout spoke, the 3D radius of the standard radial trajectory has a constant change rate, which led to a uniform sampling with the 1D radii of k-space (25% samples at radii of k-space larger than 0.75$Kmax$). A 2D example is illustrated in Figure 1C.

Methods

The study was approved by the Institutional Review Boards (IRBs) of Purdue University. Five healthy subjects underwent brain scans with a whole-body 3T MRI scanner (Siemens Healthineers, Erlangen, Germany). A vendor-supplied 20-channel receiver head coil was used for all volunteers. An MPRAGE sequence was performed before the UTE sequence for the anatomical reference. The parameters used in the 3D dual-echo UTE sequence with rosette k-space sampling were: field of view (FOV)=240x240x240 mm^3, matrix size=120x120x120, readout dwell time=10 μs, flip angle=7-degree, TR=7 ms, readout duration=2.1 ms. Ten repeated dual-echo UTE scans were performed with varied TEs. The first TEs were 20 μs, 40 μs, 60 μs, 80 μs, 100 μs, 150 μs, 300 μs, 600 μs, 1ms, and 1.5 ms. The second TEs were 2.12, 2.14, 2.16, 2.18, 2.2, 2.25, 2.4, 2.7, 3.1, and 3.6 ms. For one dual-echo UTE acquisition, 36100 petals were acquired (full k-space acquisition without acceleration factor), resulting in a scan duration of 4.2 minutes (36100x7 ms). The ten repeated UTE scans lasted 42 minutes, and the total scan time was about 50 minutes for each volunteer.

Image reconstruction and post-processing steps were performed in MATLAB (MathWorks, USA) platform. Non-uniform fast Fourier transform (NUFFT) was used to calculate the forward encoding transform of the acquired k-space data (26). A compressed sensing approach was used for image reconstruction, using total generalized variation (TGV) as the sparsifying penalty (27). The post-processing procedure was performed using FSL (FMRIB Software Library) and SPM (Statistical Parametric Mapping) software. The workflow of post-processing steps was summarized in Figure 2, including registration to T1-weighted anatomy images (28,29), brain skin and skull removal (30), bias-field correction (31), voxel-wised LORA (low-rank approximations) correction (32), and voxel-wised dual-exponential fitting based on the real part of the complex free induction decay (FID) signal. The model for dual-exponential fitting was expressed as the equation:

$$S(TE) = S_{0,short} \exp\left(-\frac{TE}{T_2{}^*{}_{short}}\right) + S_{0,long} \exp\left(-\frac{TE}{T_2{}^*{}_{long}}\right)$$

where $S_{0,short}$ and $S_{0,long}$ are the proton density with short T_2^*($T_2^*{}_{short}$), and long T_2^*($T_2^*{}_{long}$), respectively. After the fitting, the voxel-wised ratio between $S_{0,short}$ and the total proton density ($S_{0,short}$ + $S_{0,long}$) was reported as ultra-short T_2 fraction map, and $T_2^*{}_{short}$ and $T_2^*{}_{long}$ were reported as ultra-short T_2 value and long T_2 value maps, correspondingly. All maps were registered to a standard brain atlas (MNI-152) for better visualization and then were averaged across subjects for statistical analysis. The ultra-short T_2 fractions in total WM and total GM were reported individually and as mean across subjects. A two-sample t-test was used to test whether the ultra-short T_2 fractions were statistically different between GM and WM. In addition, the ultra-short T_2 fractions were quantified based on selected regions of interest (ROIs), including cingulum, corona radiata (CR), internal capsule (IC), corpus callosum (CC), external capsule, fornix, and sagittal stratum.

Results

In Figure 3A, brain image slices from a volunteer are shown for five representative TEs, 20 μs, 100 μs, 2.1 ms, 2.4 ms, and 3.6 ms. There was little or no contrast between WM and GM at the minimum ultra-short TE (TE=20 μs), whereas the difference between WM and GM increased at longer TE. In addition, strong cortical bone contrast was highlighted at shorter TEs.

Figures 3B and 3C show the differences in signal decay between WM (Figure 3B) and GM (Figure 3C). The signal intensities with different TEs were normalized based on the detected signal at the shortest TE of 20 μs. After LORA de-noising, WM and GM signal decay curves showed signal drop at ultra-short TE period (below 0.1 ms). The signal curve of WM continued to drop, while the signal curve of GM had a slower decay at longer TEs.

Table 1 summarizes the ultra-short T_2 components (uT_2) fraction in GM and WM individually and as mean across the subjects. All subjects and the average indicated a significantly higher uT_2 fraction in WM than GM (P<0.0001 for all subjects and the mean). The average WM uT_2 fraction across subjects was 10.9%$\pm$1.9%, and the average GM uT_2 fraction across subjects was 5.7%$\pm$2.4%.

Figure 4 shows the mean uT_2 fraction map (Figure 4A), the mean ultra-short T_2 value map (Figure 4B), and the mean long T_2 value map (Figure 4C) in MNI-152 space. The uT_2 fraction map (Figure 4A) indicated a generally homogeneous uT_2 fraction among voxels in WM, which is higher than the uT_2 fraction among voxels in GM. The ultra-short T_2 value in WM was around 0.12 ms, and the ultra-short T_2 value in GM was slightly faster than WM (0.08 ms). The long T_2 components T_2 value map indicated an increased T_2 value across GM and the CSF compared to the WM, which is in line with previous literatures (33,34).

Figure 5 summarizes the mean and standard deviation (SD) of the uT_2 fraction among different ROIs, quantified based on the uT_2 fraction map shown in Figure 4A. All the

ROIs were identified as WM-rich regions and reported about 10% as the uT_2 fraction. The lowest reported ROI-based uT_2 fraction value was 8.8%$\pm$0.5%, as in the cingulum. The highest reported ROI-based uT_2 fraction value was 12.7%$\pm$0.4%, as in the fornix.

Discussion

In this study, a novel 3D dual-echo UTE sequence based on rosette k-space trajectory was proposed. The advantages of this novel design included: 1) increased sampling density in the outer k-space; 2) shorter TE due to the gradient design without ramp-up time; 3) a smooth transition between the two echoes in dual-echo acquisition. A statistically significantly higher uT_2 fraction value was found in WM compared to GM. In addition, the uT_2 fraction value was homogeneously distributed among WM voxels.

The achievement of the shortest TE in UTE sequences is limited by the system hardware, not only by the dead time (10), but also the slew rate limitation if the initial gradient amplitude is high in any direction. In this specific 3D rosette k-space design, the initial gradient amplitude was zero and gradually increased to overcome the slew rate limitation in all acquisitions. The strategy was to gradually increase the ω_1 and ω_2 to the designed value of 1.611 kHz at the beginning of each TR. With this strategy, the maximum slew rate was about 140 mT/m/ms for all three directions, separately. In addition, the initial sampled data still followed the originally designed rosette trajectory, which was used for image reconstruction. This resulted in an over-sampling at the center k-space (about 20% samples located in radii of k-space smaller than 0.25$Kmax$), which could provide an extra signal-to-noise ratio (SNR). Similar to ZTE applications, this study used a small flip angle (7 degrees). Although large flip angles are allowed in UTE acquisition, a small flip angle could minimize the T_1 influence on the detected signals (35).

The volume of 3D k-space is in proportion to the cube of the radius of the acquired k-space. The volume of radii larger than 0.75 $Kmax$ (considered as peripheral k-space) occupied about 58% (= $(1^3-0.75^3)/1^3$) of the entire volume of 3D k-space with the radius of $Kmax$. However, the volume of radii smaller than 0.25 $Kmax$ (considered as center k-space) only occupied about 2% (= $0.25^3/1^3$) of the entire volume of k-space. This resulted in a much larger peripheral k-space than the center k-space volume in 3D cases. The conventional radial acquisition, which samples uniformly along with the 1D radius of k-space (25% of samples at center k-space, and 25% of samples at peripheral

k-space), may not be efficient at the large radii of 3D k-space. The newly proposed 3D rosette trajectory has increased samples at larger radii of k-space, which provides greater sampling density in peripheral k-space. It may have the potential for further acceleration by acquiring fewer petals without losing imaging quality.

One disadvantage of the 3D rosette k-space pattern is that more samples per acquisition were needed (1.5 times samples compared to radial). In addition, the long readout duration of this rosette trajectory (2.1 ms for dual-echo acquisition, which means 1.05 ms for the first echo acquisition), may suffer image blurring caused by the fast signal decay (6). A previous study has shown that the ideal sampling duration is $0.81*T_2$ of the imaging tissue for radial UTE (36). However, such a short sampling duration would result in spatial resolution loss (6). Therefore, typically, the sampling duration of two to four times T_2 of the imaging tissue was used (6). For the myelin imaging applications, the sampling duration was usually set to 0.3 to 1 ms (1,20,37).

Instead of combining IR suppression and dual-echo subtraction, which provides myelin maps with arbitrary signal intensities (7), dual-exponential fitting was performed in this study, which offers uT_2 fraction and uT_2 value maps as results. Although the quantitative analysis of myelin by the uT_2 fraction and value maps still needs validation (7), this method showed a potential way to compare across subjects. The setback of this method was the need for a multiple TEs acquisition, which increased total scan time. However, with the dual-echo rosette sequence proposed in this study, twenty images with different TEs could be acquired in a clinically acceptable/feasible total scan time (about 50 minutes per subject). In addition, with further optimization of the image reconstruction, further reduction of the total scan time would be feasible with an under-sampling strategy.

Overall, the reconstructed images with different TEs and the uT_2 fraction maps agree with previous publications (7,38). The contrast between WM and GM was higher at longer TEs, and the uT_2 components were mainly distributed in WM voxels. Previous publications were using the IR suppression (7,38) approach, which caused WM signal

loss creating contrast between WM and GM at short TEs. In this study, little or no contrast at short TEs was achieved without IR suppression. Additionally, the uT_2 fraction values based on ROIs also aligned with previous publications (39-41), which is around 10% to 12% in most WM-rich brain regions.

Recent publications showed that the brain iron content led to inaccurate results of the myelin water fraction (MWF) (about 26%-28% decrease after iron extraction by reductive dissolution of brain slice samples) by myelin water imaging technique (MWI) (42). Although 3D UTE rather than MWI was used in this study, the influence of iron content on the results was not ruled out. Myelin concentrations could be higher than expected since iron decreased the signal, especially within substantia nigra (43), putamen (44), and globus pallidus (45) regions, which have potential age-related iron accumulation. Those regions had high signal intensities in our reconstructed images with the shortest TE (~ 20 μs). A new model for fitting could regress the iron effect out (46). In addition, quantitative susceptibility mapping (47) may be applied for iron measurement since the proposed sequence allows a dual-echo acquisition.

There are some other limitations of this study. Firstly, the newly designed rosette k-space pattern was only compared to the conventional radial acquisition roughly through theoretical calculations. Thus, there was no data acquired by 3D UTE sequences with the radial acquisition in this study for *in vivo* performance comparison, which was limited by the total scan time. Secondly, other macromolecules with similar uT_2 values may contribute to the detected signals (48). Therefore, an *in vivo* comparison between radial acquisition and rosette pattern will be proposed for future studies. In addition, patients (and/or animals) with different stages of myelination diseases will be recruited to test the performance of this novel rosette k-space trajectory.

In conclusion, this study proposed a novel 3D rosette k-space trajectory, specifically for UTE applications. The higher uT_2 fraction value in WM compared to GM demonstrated the ability of this sequence to capture rapidly decayed signals. In addition, the fitting

based on the dual-exponential model provided quantitative results of the uT_2 fraction, which could be used for myelination assessment in the future.

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Tables

Table 1. Mean and standard deviation of the ultra-short T_2 components (myelin) fraction in the grey matter (GM) and white matter (WM)

Subject number	Total GM	Total WM	*P*-values
1	7.5%±1.1%	11.6%±0.9%	*P<0.0001*
2	3.7%±1.4%	9.9%±1.3%	*P<0.0001*
3	3.9%±2.1%	9.1%±1.0%	*P<0.0001*
4	8.7%±1.4%	13.8%±1.2%	*P<0.0001*
5	5.4%±1.6%	10.5%±1.1%	*P<0.0001*
Total	5.7%±2.4%	10.9%±1.9%	*P<0.0001*

Table captions

Table 1. Individual and mean across subjects ultra-short T_2 fractions in total white matter (WM) and total grey matter (GM). All values of ultra-short T_2 fractions are shown as mean$\pm$standard deviation. A two-sample t-test was used to test whether the ultra-short T_2 fractions were statistically different between GM and WM, which *P*-values were calculated.

Figure captions

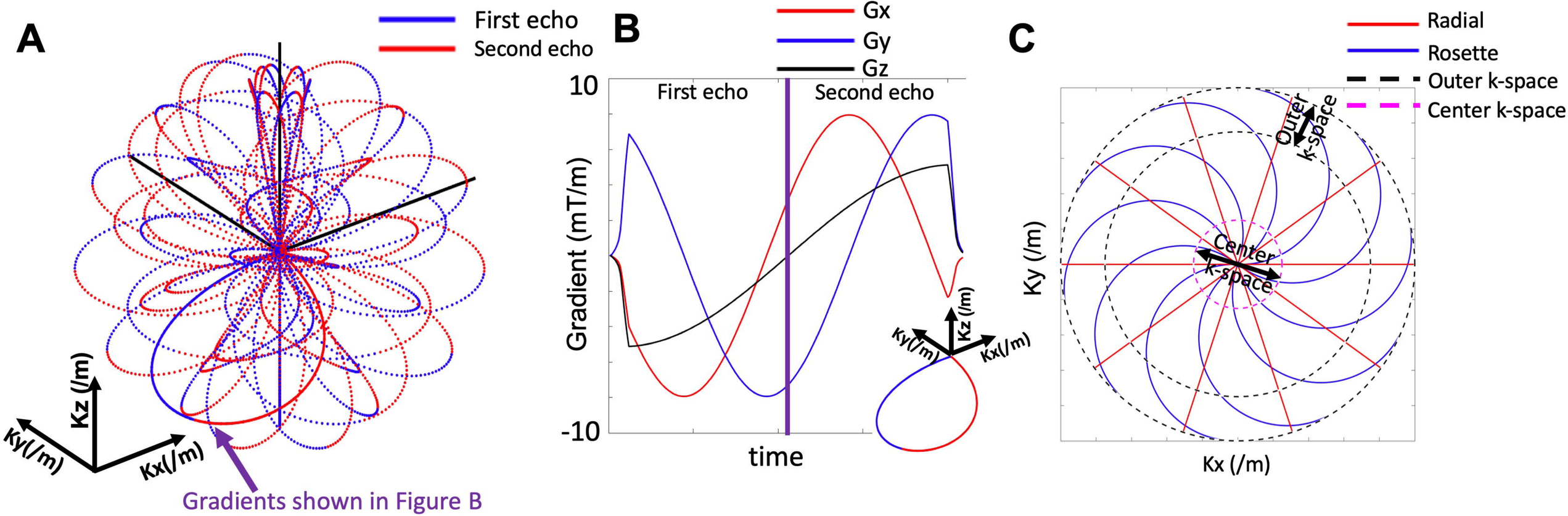
Figure 1. Illustrations of the 3D rosette k-space design. A) Selective spokes with varied rotations in the k_x-k_y plane and varied extensions in the k_z-axis are shown. Each spoke crosses the origin of k-space at the beginning and the end, forming a 'petal-like' pattern. The dual-echo acquisition (blue: first echo, red: second echo) was generated based on manual separation at the middle of each 'petal-like' pattern. B) The gradients in all three directions (red: gradients in the x-axis, Gx; blue: gradients in the y-axis, Gy; black: gradients in the z-axis, Gz) of a selective spoke as shown in Figure 1A. All gradients began at zero amplitude to avoid any potential delays caused by the gradients' ramp-up. C) A 2D example to illustrate the differences between rosette (blue) and radial (red) acquisitions in peripheral (outer) k-space coverage (regions between black dash lines). With greater curvature, rosette trajectory provides more samples in the peripheral k-space than radial trajectory.

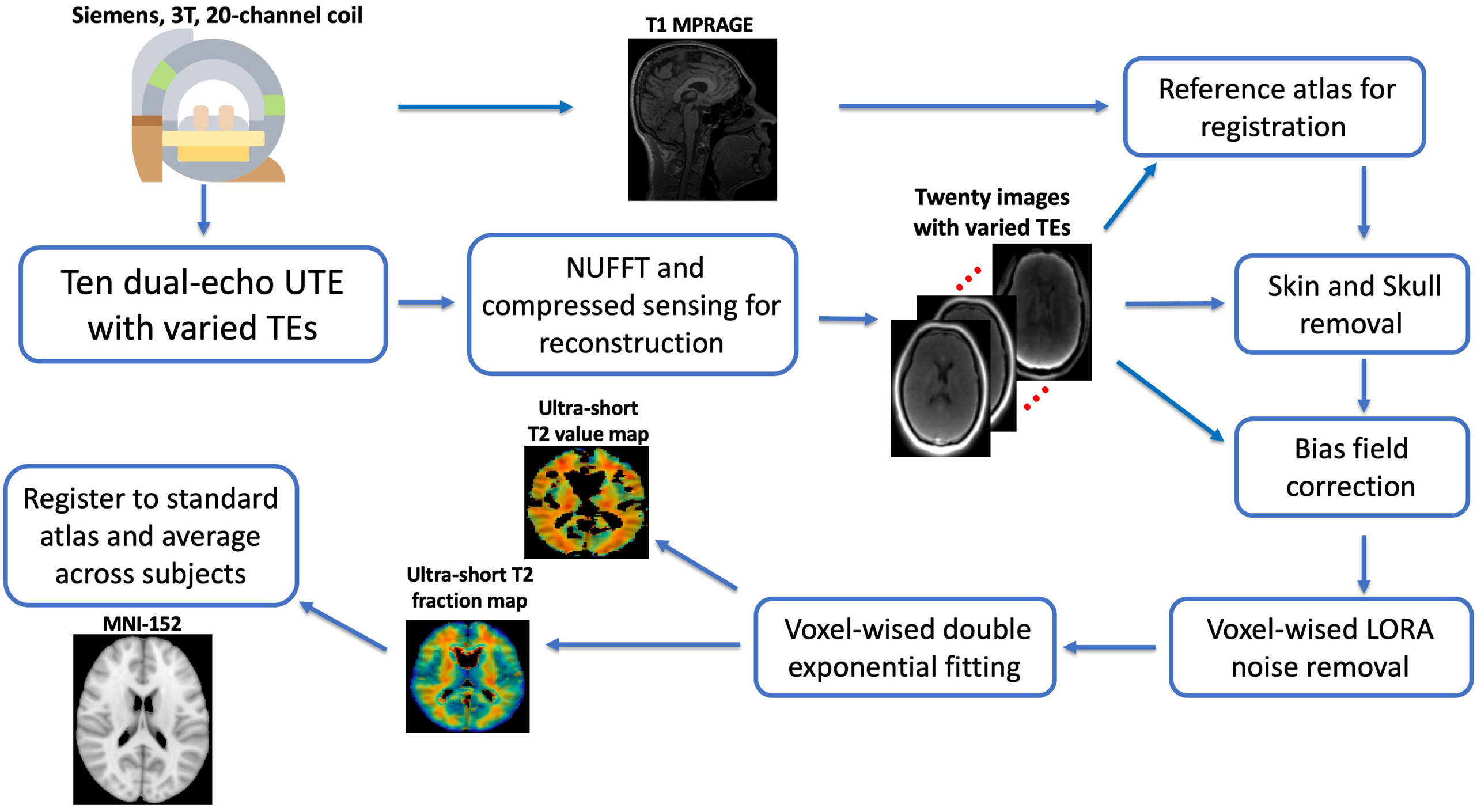
Figure 2. Workflow from data acquisition, image reconstruction to post-processing. NUFFT: non-uniform fast Fourier transform.

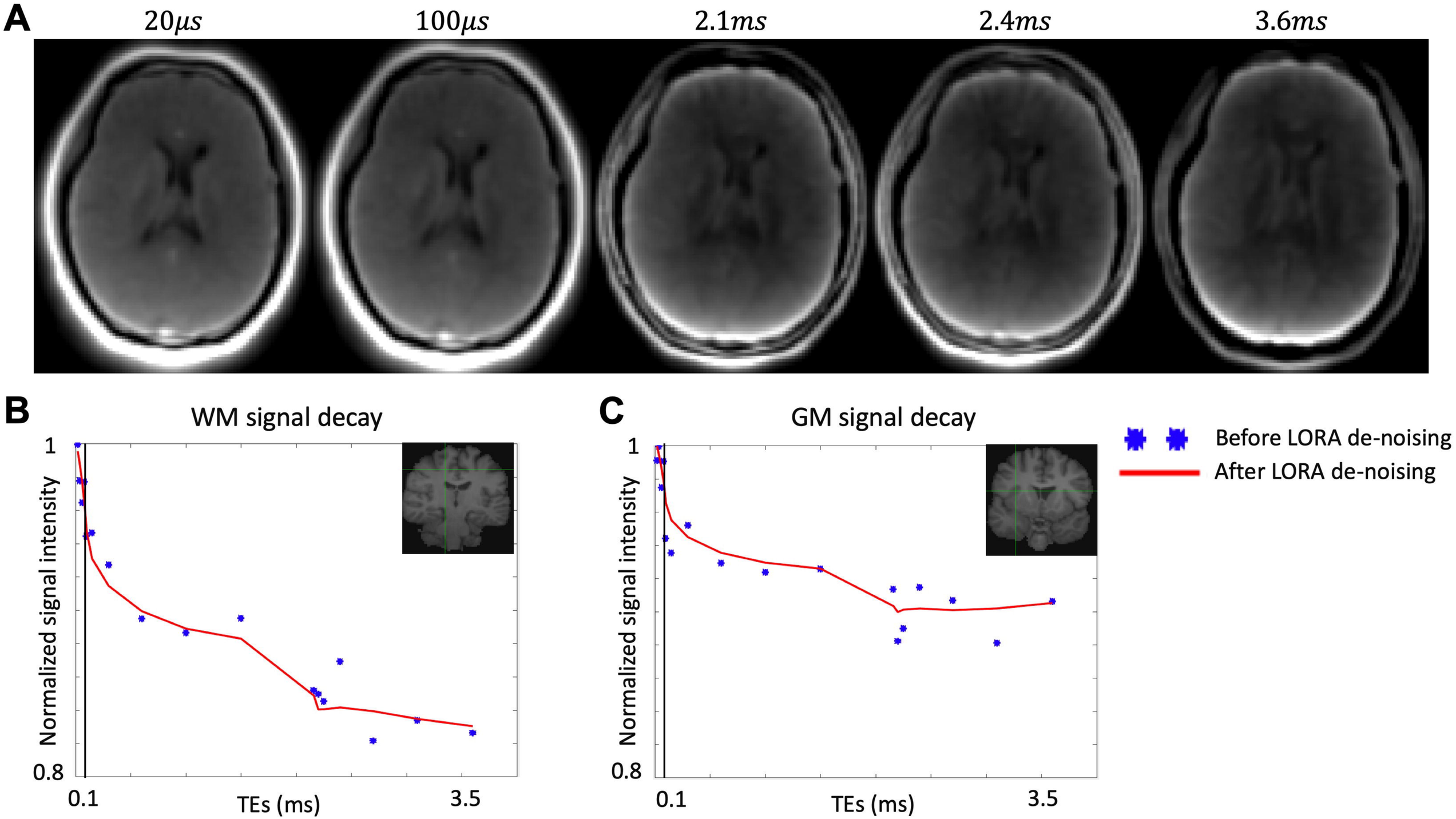
Figure 3. A) Five brain image slices with 20 μs, 100 μs, 2.1 ms, 2.4 ms, and 3.6 ms TEs from a volunteer are shown. B, C) Signal decay curves from arbitrary voxels, which are identified as B) white matter (WM) and C) grey matter (GM). All signals were normalized based on the shortest TE (~20 μs). The blue stars show the distribution of signals with different TEs before LORA (low-rank approximations) de-noising. The red curves show the signal decay after LORA de-noising. Black lines were used to identify the ultra-short TEs region (below 0.1 ms).

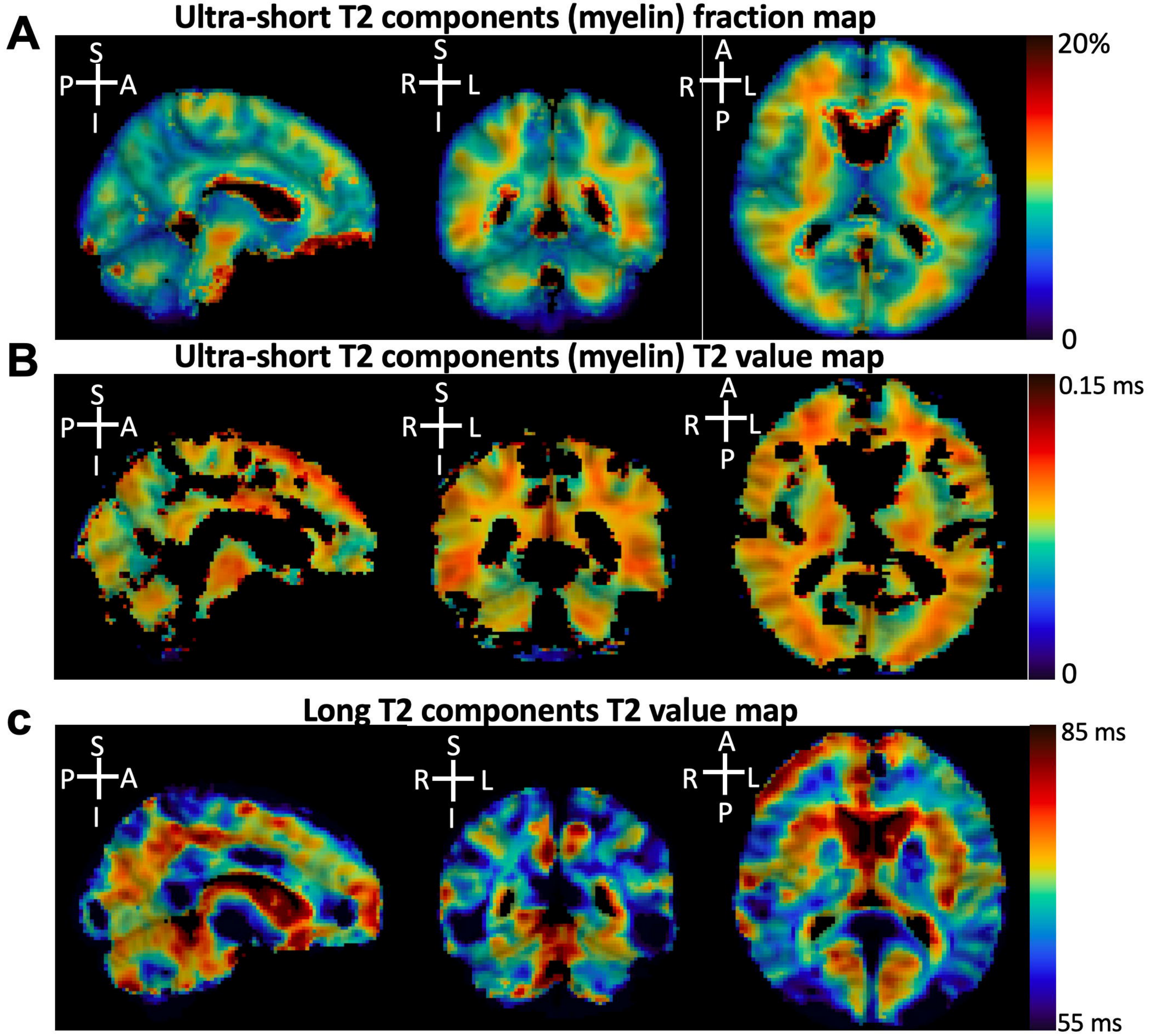
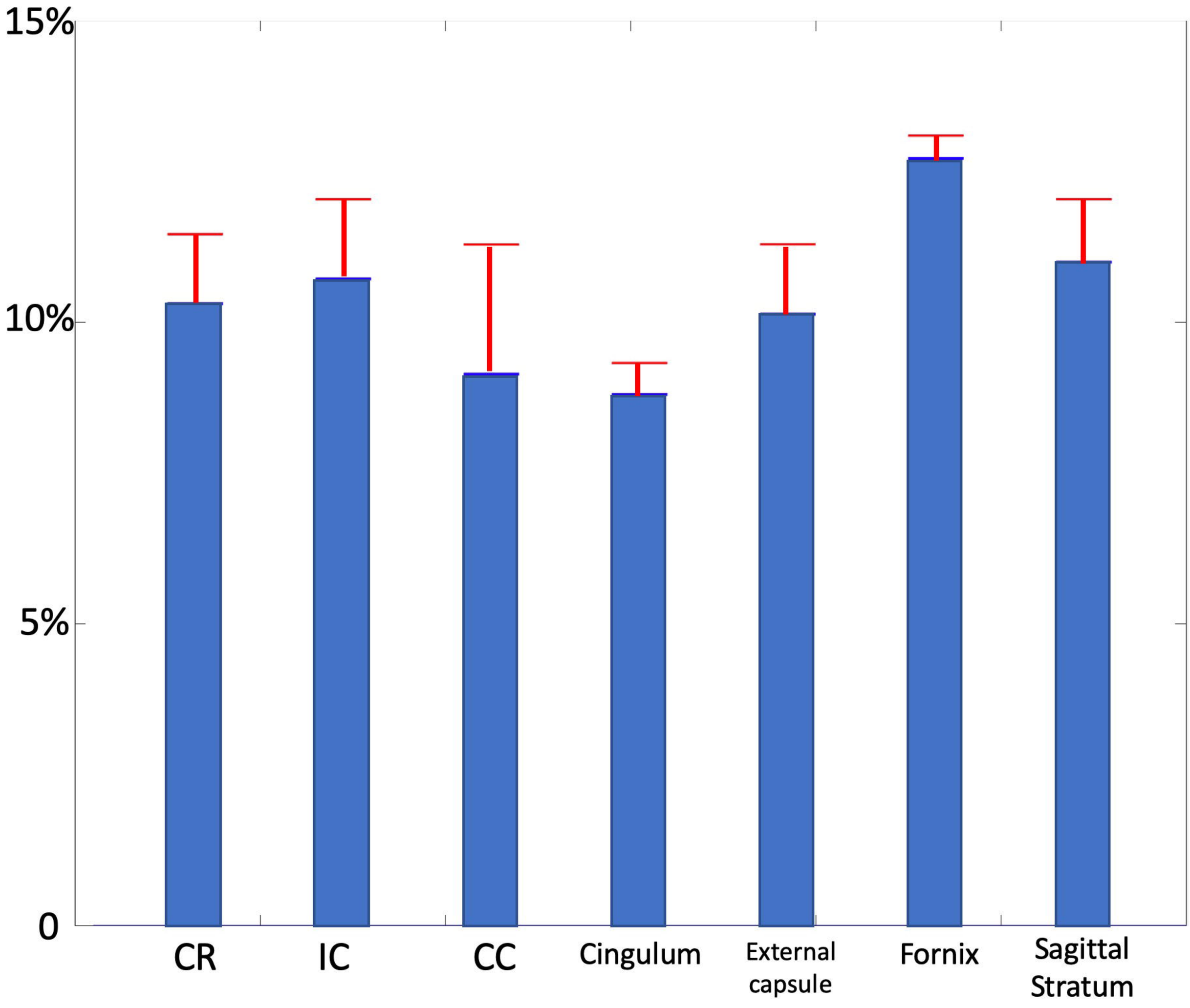
Figure 4. The results of dual-exponential fitting: A) The mean ultra-short T_2 components (uT_2) fraction map; B) The mean uT_2 value map; C) The long T_2 value map. A: anterior, P: posterior, L: left, R: right, S: superior, I: inferior. Please note that some voxels show black color in Figure 4B (mostly located in cerebrospinal fluid and grey matter), which is caused by high uT2 values reaching the top threshold of the color bar.

Figure 5. The mean (blue columns) and standard deviation (SD) (red lines above blue columns) of ultra-short T_2 components (uT_2) fraction among different regions of interest (ROIs), quantified based on the uT_2 fraction map in Figure 4A. CR: corona radiata, IC: internal capsule, CC: corpus callosum.


A
First echo
Second echo
Kz (/m)
Ky(/m)
Kx(/m)
Gradients shown in Figure B
B
Gx
Gy
Gz
10
-10
First echo
Second echo
Gradient (mT/m)
time
Kz (/m)
Ky(/m)
Kx(/m)
C
Radial
Rosette
Outer k-space
Center k-space
Outer k-space
Center k-space
Ky (/m)
Kx (/m)


Siemens, 3T, 20-channel coil
T1 MPRAGE
Reference atlas for registration
Twenty images with varied TEs
Ten dual-echo UTE with varied TEs
NUFFT and compressed sensing for reconstruction
Skin and Skull removal
Bias field correction
Ultra-short T2 value map
Register to standard atlas and average across subjects
Ultra-short T2 fraction map
MNI-152
Voxel-wised double exponential fitting
Voxel-wised LORA noise removal


A
20μs
100μs
2.1ms
2.4ms
3.6ms
B
WM signal decay
Normalized signal intensity
1
0.8
0.1
TEs (ms)
3.5
C
GM signal decay
Normalized signal intensity
1
0.8
0.1
TEs (ms)
3.5
Before LORA de-noising
After LORA de-noising


A
Ultra-short T2 components (myelin) fraction map
S
P
A
I
S
R
L
I
A
R
L
P
20%
0
B
Ultra-short T2 components (myelin) T2 value map
S
P
A
I
S
R
L
I
A
R
L
P
0.15 ms
0
C
Long T2 components T2 value map
S
P
A
I
S
R
L
I
A
R
L
P
85 ms
55 ms

Ultra-short T2 components (myelin) fraction based on different ROIs