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Authors

Ma, Ya-Jun
Jang, Hyungseok
Wei, Zhao
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Brain Ultrashort T_2 Component imaging using a Short TR Adiabatic Inversion Recovery Prepared Dual-Echo Ultrashort TE sequence with Complex Echo Subtraction (STAIR-dUTE-ES)

Ya-Jun Ma[1], **Hyungseok Jang**[1], **Zhao Wei**[1], **Mei Wu**[1], **Eric Y. Chang**[1,2], **Jody Corey-Bloom**[3], **Graeme M. Bydder**[1], **Jiang Du**[1]

[1]Department of Radiology, University of California San Diego, San Diego, CA, USA

[2]Radiology Service, VA San Diego Healthcare System, San Diego, CA, USA

[3]Department of Neurosciences, University of California San Diego, San Diego, CA, USA

Abstract

Long T_2 water contamination is a major challenge with direct in vivo UTE imaging of ultrashort T_2 components in the brain since water contributes most of the signal detected from white and gray matter. The Short TR Adiabatic Inversion Recovery prepared Ultrashort TE (STAIR-UTE) sequence can significantly suppress water signals and simultaneously image ultrashort T_2 components. However, the TR used may not be sufficiently short to allow the STAIR preparation to completely suppress all the water signals in the brain due to specific absorption rate (SAR) limitations on clinical MR scanners. In this study, we describe a STAIR prepared dual-echo UTE sequence with complex Echo Subtraction (STAIR-dUTE-ES) which improves water suppression for selective ultrashort T_2 imaging compared with that achieved with the STAIR-UTE sequence. Numerical simulations showed that the STAIR-dUTE-ES technique can effectively suppress water signals and allow accurate quantification of ultrashort T_2 protons. Volunteer and multiple sclerosis (MS) patient studies demonstrated the feasibility of the STAIR-dUTE-ES technique for selective imaging and quantification of ultrashort T_2 components in vivo. A significantly lower mean UltraShort T_2 Proton Fraction (USPF) was found in lesions in MS patients (5.7±0.7%) compared with that in normal white matter of healthy volunteers (8.9±0.6%). The STAIR-dUTE-ES sequence provides robust water suppression for volumetric imaging and quantitation of ultrashort T_2 component. The reduced USPF in MS lesions shows the clinical potential of the sequence for diagnosis and monitoring treatment in MS.

Corresponding authors: • Ya-Jun Ma, Department of Radiology, University of California San Diego, 9500 Gilman Dr., San Diego, CA 92093, USA, yam013@ucsd.edu, Phone: 858-246-2229 • Jiang Du, Department of Radiology, University of California San Diego, 9500 Gilman Dr., San Diego, CA 92093, USA, jiangdu@ucsd.edu, Phone: 858-246-2248.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Keywords

ultrashort T_2 component; STAIR; dual-echo UTE; complex echo subtraction; Multiple Sclerosis

Introduction

Myelin is a lipid-protein bilayer which is present in the form of a sheath around the axonal fibers of neurons. It contributes to the mechanical and functional structure of nerves. Loss of myelin is a cardinal feature of many neurodegenerative diseases including Multiple Sclerosis (MS) [1]. In the past few decades extensive research has focused on developing Magnetic Resonance Imaging (MRI) techniques to non-invasively assess myelin in the brain [2–4]. Most of these techniques have targeted myelin water which is trapped within the myelin sheath. It has a short T_2 and can be quantified by measuring the Myelin Water Fraction (MWF), defined as the ratio of the signal intensity of the shortest T_2 component to the total signal intensity calculated with a multi-component T_2 fitting model [2]. Multicomponent-Driven Equilibrium Single Pulse Observation of T_1 and T_2 (mcDESPOT) is another technique that has been developed to quantify the water myelin component after characterizing it by measuring its short longitudinal and transverse relaxation times (T_1 and T_2) [3]. Assessment of MWF and its relaxation times is subject to the complex interaction between non-aqueous protons in myelin and water. This is affected by changes unrelated to myelin loss and may result in ambiguities in data interpretation [3,5]. Direct imaging of ultrashort T_2 components in brain may resolve these problems and so improve the specificity of MRI for the assessment and quantification of demyelination [6–10].

However, direct imaging of ultrashort T_2 components is challenging due to their fast signal decays [6,11–15]. As a consequence, this component is not detectable in the brain using conventional Gradient Recalled Echo (GRE) or Spin Echo (SE) based sequences. Ultrashort Echo Time (UTE) sequences with nominal Echo Times (TEs) of less than 50 μs have been used to directly image this ultrashort T_2 components [9,13,16], however one of the major challenges in doing this is the need to minimize water signal contamination, i.e. to provide effective suppression of signals from both intra and extracellular water with their long T_2s, and myelin water with its short T_2. This is essential, as over 90% of the detected UTE total signal originates from water with less than 10% from ultrashort T_2 components [13,17]. Adiabatic Inversion Recovery prepared UTE (IR-UTE) sequences have been employed for this purpose [8,18]. The Adiabatic Full Passage (AFP) pulse used with this sequence for the inversion of the longitudinal magnetization has a relatively broad spectral bandwidth and is insensitive to both B_1 and B_0 inhomogeneities, and so provides uniform inversion of the longitudinal magnetization for long T_2 tissues. During the AFP pulse the longitudinal magnetization of ultrashort T_2 components is largely saturated due to their fast transverse relaxation during the relatively long adiabatic IR pulse [19,20]. The Bloch simulation performed by Horch et al. suggests that there can be substantial detectable ultrashort T_2 signal after use of clinical adiabatic pulses [20]. With the IR-UTE sequence, the longitudinal magnetization of ultrashort T_2 components after applying the AFP pulse is higher when the T_2 is lower due to the weaker inversion efficiency of the AFP pulse. The ultrashortT_2 longitudinal magnetization recovers during TI and a UTE data acquisition at the nulling

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point of the inverted longitudinal magnetization of the long T_2 water components provides direct imaging of ultrashort T_2 components. When a dual echo data acquisition is used residual long T_2 water signals which have not been completely suppressed by the adiabatic IR pulse can be selectively detected on the longer TE image. When the second echo magnitude reconstructed image is subtracted from the first magnitude image, ultrashort T_2 components are seen with high contrast [14]. However, if residual water contamination is demonstrated on the second echo due to incomplete water suppression with conventional IR-UTE technique, this is likely to render measurement of the ultrashort T_2 fraction and its T_2* inaccurate. Water signal contamination arises from patient differences and regional variation in T_1 within the brain. These lead to inappropriate inversion times (TIs) with the IR-UTE sequence for some tissues or parts of them, and, as a consequence, incomplete long T_2 signal suppression.

More recently, a Short TR Adiabatic Inversion Recovery prepared UTE (STAIR-UTE) sequence has been used for trabecular bone imaging to provide efficient suppression of signals from long T_2 tissues with a wide range of T_1s including bone marrow, fat, muscles and fluids [21] and allow selective imaging of ultrashort T_2 components. In this trabecular bone study, a short TR (e.g., 150 ms) together with an optimal TI, determined by an optimization framework, was used for long T_2 signal suppression. In principle, the STAIR-UTE sequence could also be used to suppress water components with different T_1s in whole brain and thus provide selectively imaging of the ultrashort T_2 components contained within it [22]. However, accurate imaging and quantification of ultrashort T_2 components are much more challenging in gray matter (GM) than in white matter (WM) because GM has a much lower myelin proton density. Any residual water signals may particularly affect the efficacy of ultrashort T_2 imaging in GM. In addition, the TR used in STAIR-UTE sequence may not be sufficiently short to allow the STAIR preparation to completely suppress all the water signals due to specific absorption rate (SAR) limitations on clinical MR scanners.

In this study, we combine the STAIR preparation and dual-echo Ultrashort TE data collection with complex Echo Subtraction (ES) (STAIR-dUTE-ES) for both morphological and quantitative imaging of ultrashort T_2 components in the whole brain. Dual-echo acquisition is employed with each spoke of the STAIR-dUTE sequence (STAIR-dUTE-1 for the first echo and STAIR-dUTE-2 for the second echo). The complex ES algorithm provides much better suppression of residual water components after the STAIR preparation with STAIR-dUTE-ES imaging. Numerical simulation as well as in vivo MS patient and healthy volunteer studies were conducted to assess the feasibility of the STAIR-dUTE-ES technique for robust imaging of ultrashort T_2 components in the whole brain. Quantitative UltraShort T_2 Proton Fraction (USPF) maps were also generated to compare ultrashort T_2s seen in lesions in MS patients with those seen in Normal White Matter (NWM) in healthy volunteers.

Materials and methods

The STAIR-UTE sequence

Figure 1 shows key features of the 3D STAIR-dUTE sequence [21,22]. Following an AFP inversion pulse, a series of UTE k-space spokes (N_{sp}) with identical time separation is used

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for fast data acquisition. TI is defined as the time from the center of the AFP pulse to the center of the multispoke acquisition (Figure 1A). A short rectangular pulse with duration 20–120 μs is used for signal excitation. After 3D spiral trajectories using conical view ordering (Figure 1B) dual-echo acquisition is performed [23,24]. Figure 1C shows the contrast mechanism for ultrashort T_2 component imaging with the STAIR-dUTE sequence. The longitudinal magnetizations of the long T_2 components in both WM (WM_L) and GM (GM_L) are inverted by the AFP pulse and start to recover at the end of it. Due to the fast transverse relaxation of ultrashort T_2 protons during the relatively long AFP pulse, the longitudinal magnetization of ultrashort T_2 component is largely saturated. The ultrashort T_2 signal recovers quickly after the AFP pulse due to its relatively short T_1 (around 300 ms) [10,25], and can be acquired at the specific TI (e.g. TI = 64 ms, TR = 140 ms) at which the long T_2 components are nulled. As reported in Ma et al. [21], the signal nulling points for different long T_2 water components (e.g. WM_L and GM_L) converge as TR is shortened when using the STAIR sequence. Determination of the optimal TI for long T_2 water suppression over a range of T_1s with STAIR type sequence can be found in the Appendix.

Complex Echo Subtraction (ES)

Though all water signals can be significantly suppressed with the STAIR-dUTE sequence when using an optimal TR/TI combination as described in the Appendix, a certain amount of residual water signal may remain due to the fact that the TR cannot be shortened to much less than 140 ms because of Specific Absorption Rate (SAR) limitations for brain imaging using clinical scanners. In this study, complex subtraction of the second echo from the first one was utilized to further reduce water signal contamination. The signal obtained with STAIR-dUTE imaging can be expressed as follows:

$$S(TE) = S_m e^{-TE/T^*_{2,m}} e^{i(\varphi + \gamma \Delta B_0 TE)} + S_w e^{-TE/T^*_{2,w}} e^{i(\varphi + \gamma \Delta B_0 TE)}. \quad [1]$$

where S_m and S_m are the ultrashort T_2 component and residual water signals, respectively. S_m can be positive or negative. This is determined by the TI used for the STAIR-dUTE data acquisition. For example, if TI is chosen at the nulling point of WM_L, the residual GM_L signal S_m is negative due to its longer T_1 than GM_L. $T^*_{2,m}$ and $T^*_{2,w}$ are the T^*_2 values of ultrashort T_2 component and water, respectively. φ is the phase offset induced by the receive coil. ΔB_0 is the inhomogeneity of the B_0 field. At the second echo, the TE (e.g. 2.2 ms) is much longer than $T^*_{2,m}$ but much shorter than $T^*_{2,w}$. By the time of the second echo the ultrashort T_2 signal has decayed to zero, while the short and long T_2 water signals maintain nearly the same signal intensity as they had on the first echo image. As a result, the signal equations for the first and second echo images (i.e. S_1 at TE_1 and S_2 at TE_2) can be simplified as follows:

$$S_1 = S_m e^{i\varphi} e^{i\gamma \Delta B_0 TE_1} + S_w e^{i\varphi} e^{i\gamma \Delta B_0 TE_1}, \quad [2]$$

$$S_2 = S_w e^{i\varphi} e^{i\gamma \Delta B_0 TE_2}. \quad [3]$$

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ΔB_0 can be measured before the complex ES, and be used to calculate the ultrashort T_2 signal intensity given by the following equation:

$$|S_m| = \left|S_1 - S_2 e^{-i\gamma \Delta B_0 \Delta TE}\right|. \quad [4]$$

where $\Delta TE = TE_2 - TE_1$ and $|\cdot|$ is the operator used to generate an absolute value. In the STAIR-dUTE-ES process, no phase unwrapping is needed since the term $e^{i * phase}$ is used for the phase calculation instead of directly using phase.

Magnitude dual-echo subtraction can also be determined for comparison with the complex echo subtraction described above. The signal equation for the magnitude echo subtraction is as follows:

$$|S_1| - |S_2| = |S_m + S_w| - |S_w|. \quad [5]$$

UltraShort T_2 Proton Fraction (USPF) determination

USPF is defined as the ratio of the transverse magnetization of the ultrashort T_2 component to the total transverse magnetization of the brain. To generate an USPF map, the ultrashort T_2 signal intensity map and an image with both ultrashort T_2 components and water signals present (i.e., without long T_2 signal suppression) needs to be produced. The ultrashort T_2 signal is given by Eq. [4] and the total image signal including both signals from ultrashort T_2 components and water can be obtained with a proton density weighted UTE (PDw-UTE) scan. Moreover, considering the spin evolution difference between the STAIR-dUTE-1 and UTE sequences, their signal equations can be utilized to calibrate them and extract the equilibrium state magnetization (i.e. M_0). USPF can be calculated as the ratio of the signal intensity of ultrashort T_2 component, or M_0 of ultrashort T_2 component (i.e. $M_{0,m}$) derived from STAIR-dUTE-ES images, to the total M_0 including both ultrashort T_2 component and water (i.e. $M_{0,all}$) generated from PD_w-UTE images.

In the STAIR-dUTE sequence, the ultrashort T_2 magnetization starts to recover from zero at the end of AFP pulse following its saturation during the AFP pulse. From Eq. [A1] with $Q_q \sim 0$, the ultrashort T_2 signal at the i^{th} spoke can be expressed as follows [21,22]:

$$M^i_{STAIR} = M_{0,m}\sin(\alpha)\{(1-E)[e_1\cos(\alpha)]^{i-1} + (1-e_1)\left\{1 - [e_1\cos(\alpha)]^{i-1}\right\}/[1 - e_1\cos(\alpha)]\}, \quad [6]$$

The definitions of E, e_1 and α can be found in the Appendix. The ultrashort T_2 signal in the final STAIR-dUTE-1 image can then be expressed as the signal average over the N_{sp} spokes:

$$S_{STAIR} = \sum_{i=1}^{N_{sp}} M^i_{STAIR}/N_{sp}. \quad [7]$$

The signal expression for the PD_w-UTE signal is as follows:

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$$S_{PD} = M_{0,all}\sin(\theta), \quad [8]$$

where θ is the excitation flip angle used for the PD_w-UTE imaging.

Based on Eqs. [5] to [7], the USPF can be calculated from the following equation:

$$\frac{M_{0,m}}{M_{0,all}} = \frac{S_{STAIR}sin(\theta)}{S_{PD}\sin(\alpha)f}, \quad [9]$$

where $f = \sum_{i=1}^{N_{sp}} \left\{(1-E)[e_1\cos(\alpha)]^{i-1} + (1-e_1)\left\{1-[e_1\cos(\alpha)]^{i-1}\right\}/[1-e_1\cos(\alpha)]\right\}/N_{sp}$. S_{STAIR} is the signal of the STAIR-dUTE-1 image (i.e. Eq. [4]). In addition, the T_1 of the ultrashort T_2 components was set to 300 ms for the USPF calculation [10,25].

Numerical simulation

Numerical simulation was performed to investigate the efficiency of long T_2 signal suppression and the accuracy of ultrashort T_2 quantification with the STAIR-dUTE-ES approach. Simulated USPFs ranged from 1% to 10% and ultrashort T_2* and T_1 values were set to 0.3 ms and 300 ms respectively [9,10]. Both myelin water and intra/extracellular water were considered in this simulation since they have quite different T_1s and T_2s [3]. The simulated myelin water fraction ranged from 1.25% to 12.5%. T_2* and T_1 values of myelin water were set to 10 ms and 400 ms respectively [3,26]. The intra/extracellular water has a relatively long T_2* of 60 ms and its proton fraction changed according to the fractions of ultrashort T_2 component and myelin water. All the simulated tissue properties used in this study are listed in Table 1.

For the STAIR-dUTE sequence, α, τ, and N_{sp} were set to 32°, 5.7 ms, and 5 respectively, which were identical to the parameters used in the following in vivo study. A dual-echo acquisition with TEs of 0 and 2.2 ms was employed in the simulation. A product AFP pulse, with a duration of 8.64 ms, bandwidth of 1.15 kHz and maximum B_1 value of 12 μT, was used for longitudinal magnetization inversion. The myelin water magnetization was not completely inverted due to its relative short T_2* (i.e. around 10 ms) [27]. An inversion efficiency factor Q (defined as the ratio of inverted magnetization to the initial magnetization) of −0.75 was estimated for myelin water using Bloch equation simulation. The Q of intra/extracellular water was set to −1 (i.e. full inversion) as its T_2* is much longer than the duration of the AFP pulse. After this, the optimal TI for STAIR-dUTE imaging needed to minimize the average signal from all the water components with T_1 values ranging from 250 to 1800 ms was determined from Eq. [A6].

Both the magnitude of the first echo signal and the signal from magnitude subtraction of the dual echoes were calculated to provide a comparison with the ultrashort T_2 quantification obtained by complex ES.

In vivo study

The 3D STAIR-dUTE sequence was implemented on a 3T GE MR750 scanner (GE Healthcare Technologies, Milwaukee, WI). Four healthy volunteers (21–47 years of age,

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three males, one female) and four patients with MS (49–69 years of age, four females) were recruited for this feasibility study. Informed consent was obtained from all subjects in accordance with guidelines from the local Institutional Review Board. A 12-channel head coil was used for signal reception.

The sequences and corresponding parameters used for the in vivo brain study were: 1) the 3D STAIR-dUTE sequence: field of view (FOV) = 22×22×30 cm^3, matrix = 140×140×60, TR/TI = 140/62 ms, TE = 0.032/2.2 ms, N_{sp} = 5, τ = 5.7 ms, flip angle (FA) = 32°, bandwidth (BW) = 125 kHz, oversampling factor = 2.4, scan time = 10 min; 2) the 3D dual-echo PDw-UTE (PDw-dUTE) sequence: FOV = 22×22×30 cm^3, matrix = 140×140×60, TE = 0.032/2.2 ms, TR = 7 ms, FA = 2°, BW = 125 kHz, and scan time = 1 min 30 sec; 3) the 3D MP-RAGE sequence: TR = 7 ms, TE = 3 ms, TI = 450 ms, FOV = 22×22×16 cm^3, matrix = 256×256×136, scan time = 4.2 min; 4) the 3D T_2-FLAIR sequence: FOV = 25.6×25.6×25.6 cm^3, matrix = 256×256×256, TR/TI = 7600/2162 ms, TE = 117 ms, acceleration factor = 2, scan time = 6.9 min. Both the STAIR-dUTE and PDw-dUTE sequences were performed three times in one of the healthy volunteers (38-year-old male) to test the repeatability of the USPF measurement.

Data analysis

All data analysis algorithms were written in Matlab 2018b (The MathWorks Inc., Natick, MA, USA). In numerical simulation, a proton fraction difference ratio was determined. This was defined as the difference between the measured proton fraction and that of the reference, divided by the reference. A ΔB_0 field map was generated before complex ES (see Eq. [4]) for all the subjects by phase subtraction of the dual-echo UTE images. The USPF in lesions was measured in each of the MS patients. The USPF of NWM in the same anatomical regions as the MS lesions was also measured in the healthy volunteers for comparison. ANOVA analysis was performed to test the USPF difference between lesions in MS patients and NWM in healthy volunteers.

Results

Figure 2 shows results from the numerical simulation. As can be seen from column two (i.e. STAIR-dUTE-1) in panel A, the signal from long T_2 components is largely suppressed with the STAIR preparation as demonstrated by the similarity of USPFs on the first echo with those of the reference, especially for high USPFs. However, some residual long T_2 signals are seen on the second echo (column three in panel A). These are also present on the first echo. Magnitude ES with Eq. [5] is not very useful for removing this long T_2 signal contamination as ultrashort T_2 components with low proton fractions shows negative signals in column five of panel A. However, with the complex ES shown in column six, the USPFs are almost identical to the true fractions. The corresponding fraction and fraction difference ratio curves are shown in Figs. 2B and 2C respectively. It is clear that USPFs obtained with complex ES are much more accurate than USPFs obtained from the magnitude of the first echo alone, or magnitude subtraction of dual echoes, especially for phantoms with low USPFs. The signal dynamic ranges of both the first echo magnitude signal and the magnitude echo subtracted signal are wider than those of the complex echo subtracted

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signals. This may be useful for high contrast morphological imaging of ultrashort T_2 component.

Figure 3 shows a volunteer study (21-year-old male) with the images used to generate ultrashort T_2 signals employing the methods described above. In the white matter region, the STAIR-dUTE-1 image shows a high ultrashort T_2 signal. This signal almost completely disappears on the STAIR-dUTE-2 image, consistent with effective water suppression and selective imaging of ultrashort T_2 component. However, there are still some residual GM signals (i.e. GM_L) on the STAIR-dUTE-2 image (panel B) and these signals are negative as evidenced by the π difference between GM and WM on the second echo phase image (panel D). Since the ultrashort T_2 signals should always be positive, there must have been signal cancellation between residual GM_L and ultrashort T_2 components on the first echo image. Panel E shows the ΔB_0 field map generated for complex ES. The magnitude of the first echo, magnitude echo subtracted, and complex echo subtracted images using the STAIR-dUTE sequence are shown in panels F to H respectively. Similar to the simulation, the magnitude first echo and the magnitude echo subtracted images show higher contrast between white and gray matter than the complex echo subtracted image.

Figure 4 shows STAIR-dUTE results from two MS patients (first row: 49-year-old female; second row: 69-year-old female). Clinical MP-RAGE and T_2-FLAIR images are shown for comparison. Lesions detected with the two clinical sequences show signal loss on the three groups of STAIR-dUTE images (see last three columns in Fig. 4). Both GM and MS lesions show higher contrast on the magnitude first echo and the magnitude echo subtracted images as compared with the complex echo subtracted images.

Though complex ES showed the lowest image contrast, it is the most accurate method for ultrashort T_2 quantification because of its minimal water contamination. Figure 5 shows representative USPF maps from the same volunteer as in Fig. 3. The USPF maps were generated from the STAIR-dUTE-ES and PDw-UTE images using Eq. [9]. Higher contrast is seen on the USPF maps compared to the STAIR-dUTE-ES images. This is because the PD contrast is added in the USPF map. GM has a higher PD than WM [28]. Thus, the signal ratio between STAIR-dUTE-ES and PDw-UTE images will reduce the GM signal more than it does the WM signal. This leads to higher WM and GM contrast in USPF than with STAIR-dUTE-ES. The USPF values ranged from 3.1% for gray matter to 11.5% for white matter in the normal brain, which are in good agreement with reported values (i.e. close to 10% for WM) [9]. The maximum USPF difference ratio among the test-retest experiments (three scans) in eight white matter regions (i.e. left and right centrum semiovale, subcortical white matter and periventricular region, as well as the splenium and genu of corpus callosum) was less than 2%, which demonstrates excellent repeatability for the technique.

The lesions in MS patients showed a lower mean USPF value (5.7±0.7%) compared with that of NWM (8.9±0.6%) in healthy volunteers, as is shown in Figure 6. The difference was statistically significant ($p < 0.0001$). Normal GM (NGM) had a USPF value of 5.9±0.3%. These results show that STAIR-dUTE-ES measurement of USPF may be a useful as a biomarker for determining the ultrashort T_2 content in MS lesions for diagnosis and monitoring therapy.

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Discussion

We demonstrated that the STAIR-dUTE-ES technique can effectively suppress water signals and accurately quantify USPF. The effectiveness of water suppression with the original STAIR-UTE sequence is limited by the relatively long TR that needs to be used as a result of the SAR limitations on clinical scanners. STAIR-dUTE acquisition coupled with complex ES increases the water suppression. Numerical simulation shows that complex ES with the STAIR-dUTE sequence results in much more accurate measurement of USPF than use of the magnitude of the first echo or magnitude ES. Despite the inaccuracy of quantification with both the magnitude of the first echo and the magnitude ES, these sequences generate higher contrast ultrashort T_2 images than complex ES as shown both by simulation and in vivo studies. Clear ultrashort T_2 component loss was shown on the STAIR-dUTE images generated with all three methods.

For quantification of ultrashort T_2 protons in vivo, an USPF map was generated from the STAIR-dUTE-ES and PDw-UTE images. The lesions in MS patients showed a significantly lower mean USPF (5.7±0.7%) compared with that of NWM (8.9±0.6%) in the healthy volunteers. This demonstrates the clinical potential of the STAIR-dUTE-ES sequence for evaluation of demyelination in disease.

Water contamination is the major problem in accurate ultrashort T_2 quantification [16]. The STAIR-dUTE sequence effectively suppresses signal from long T_2 components with a wide range of T_1 values in brain. The optimized sequence parameters (TR and TI) can be used in all subjects without specific adjustment. This is not possible with the conventional IR-UTE sequence since optimal nulling TIs vary in different subjects due to change in T_1 with age and disease [14] as well as in different regions of the brain due to normal variation in T_1. As a result, the STAIR-dUTE-ES technique has considerable potential for general clinical use.

Another challenge for ultrashort T_2 imaging of the brain is its low proton density, especially in gray matter [8,9]. As can be seen in Figure 3, the ultrashort T_2 signal in brain close to the pad is much lower than that of the skull and its associated tissues. To improve signal to noise ratio (SNR), a relatively high flip angle of 32° was used with the shortest RF duration (i.e. 100 μs, limited by the peak power of the RF amplifier) for signal excitation. More densely acquired k-space data with an oversampling factor of 2.4 also helped improve SNR.

The STAIR-dUTE-ES technique improved long T_2 water signal suppression for ultrashort T_2 imaging of white matter and gray matter of the brain. The ultrashort T_2 components may include non-aqueous protons (from myelin and/or non-myelin related components (e.g. glial cells)) and some water tightly bound to the lipid bilayer of myelin membrane [7–9,12,29]. Specifically, recent studies have reported that the non-aqueous protons in myelin have extremely short T_2 values (i.e. < 0.1 ms) with a super-Lorentzian lineshape [7,12,29]. We will investigate multi-component fitting (including both super-Lorentzian and Lorentzian lineshapes) of the 3D STAIR-UTE data with more densely distributed TEs especially for the ones less than 0.2 ms [12]. There is no doubt that it is very challenging to image the components with T_2 <0.1 ms using clinical whole-body scanners due to limitation of RF peak power and gradient systems (e.g. gradient slew rate and maximum amplitude). In

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imaging these components there would be significant signal decay of non-aqueous myelin components during the relatively long excitation pulse and significant short T_2 blurring during the relatively long data acquisition window. To improve the non-aqueous proton imaging in human brain, efforts have been made to develop a powerful gradient insert with a maximum strength of 200 mT/m and a fast slew rate of 600 mT/m/ms at 100% duty cycle [12,30]. This type of gradient insert and a dedicated RF system would help STAIR-dUTE-ES imaging of ultrashort T_2 components in the brain.

To further investigate the accuracy of the proposed STAIR-dUTE-ES technique in USPF quantification, we also performed simulations for ultrashort T_2 protons with five shorter T_2 values (i.e. 10, 20, 30, 40 and 50 μs) [12]. Similar results were found between the simulations of the ultrashort T_2 component with a T_2 of 300 μs (see Figure 2) and T_2s of 10 to 50 μs (not shown in this paper). The proposed STAIR-dUTE-ES still shows the most accurate quantification of ultrashort T_2 density.

PDw-UTE images with a flip angle of 2° and a TR of 7 ms were utilized for USPF calculations. However, there was still some long T_1 contrast contamination on these PDw-UTE images as evidenced by the fact that CSF is shown with a lower signal intensity than white and gray matter (see Fig. 5B) which is erroneous. Thus, the proton fraction measured in CSF is overestimated. In future studies, a lower flip angle, or longer TR could be used for PDw-UTE imaging to reduce the residual T_1 contrast.

Though ultrashort T_2 proton quantification was improved in this study, image blurring due to the fast T_2 signal decay and the limited gradient performance of clinical MR systems may reduce the accuracy of ultrashort T_2 imaging. The proton fractions in both gray matter and MS lesions could be overestimated as a result of this blurring. A higher performance gradient system could allow improvement of the resolution of the ultrashort T_2 imaging and lead to more accurate quantification [30].

This study has other limitations. First, a 10 min scan time is relatively long for clinical practice. Compressed sensing with randomized gradient encoding could be used to accelerate the scan without significant SNR reduction [31]. Second, only four MS patients were scanned in this study and no lesions were found in the GM of their brains. A further study involving a larger number of MS patients will be conducted to investigate whether the proposed technique can detect signal change in lesions in GM.

Conclusion

The 3D STAIR-dUTE-ES technique provides robust water suppression within the whole brain and allows accurate ultrashort T_2 proton quantification. USPF reduction in MS lesions suggests that the STAIR-dUTE-ES technique has potential for evaluation of demyelination and remyelination in the diagnosis and treatment of patients with MS.

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FUNDING INFORMATION

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Appendix

Signal equation and long T_2 suppression

At steady state, the longitudinal magnetization of the i^{th} ($i = 1, 2, 3, ..., N_{sp}$) spoke is expressed as follows [21,32]:

$$M_z^i = A(i)M_p + B(i), \quad [A1]$$

where

$$A(i) = E(e_1\cos(\alpha))^{i-1}, \quad [A2]$$

$$B(i) = M_0(1-E)(e_1\cos(\alpha))^{i-1} + M_0(1-e_1)(1-e_1\cos(\alpha))^{i-1}/(1-e_1\cos(\alpha)), \quad [A3]$$

$$M_p = \frac{Q_q\left[E_1 B_{N_{sp}}\cos(\alpha) + M_0E(1-E_1)\right]}{1-Q_qE_1A_{N_{sp}}\cos(\alpha)}, \quad [A4]$$

using the following definitions:
$A_{N_{sp}} = A(N_{sp}), B_{N_{sp}} = B(N_{sp}), \quad e_1 = \exp(-\tau/T_1), \quad E = \exp\left\{-\left[TI - 0.5\tau(N_{sp}-1)\right]/T_1\right\}$ and $E_1 = \exp\{-[TR - TI - 0.5\tau(N_{sp}-1)]/T_1\}$. Q_q is defined as the inversion efficiency factor for tissue q (q = 1, 2, 3, ..., N), where N is the total number of tissue components. α is the excitation flip angle. M_p is the longitudinal magnetization after the AFP pulse and its explicit derivation can be found in Ma et al. [21,32].

The signal intensity acquired with the STAIR-dUTE sequence is proportional to the longitudinal magnetization averaging of the multispoke acquisitions:

$$M_z = \sum_{j=1}^{N_{sp}} M_z^j/N_{sp}. \quad [A5]$$

A general framework to determine the optimal TI for minimizing the signals of long T_2 components with a STAIR type sequence is as follows:

$$TI = \text{argmin}\left\{\sum_{q=1}^{N}\left[M_z(TI, TR, \alpha, \tau, N_{sp}, T_{1q}, Q_q)\right]\right\}, \quad [A6]$$

where T_{1q} is the T_1 of the q^{th} long T_2 component. An N of 1000 is used for optimization in this study. When the TR is sufficiently short, this framework is used to suppress a group of long T_2 components with a broad range of T_1s [21].

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Highlights :

- 3D STAIR-dUTE-ES technique can efficiently suppress long T_2 water components in whole brain
- 3D STAIR-dUTE-ES technique allows quantitation of ultrashort T_2 components in brain volumetrically
- The reduced USPF in MS lesions shows the clinical potential of the sequence for diagnosis and monitoring treatment in MS

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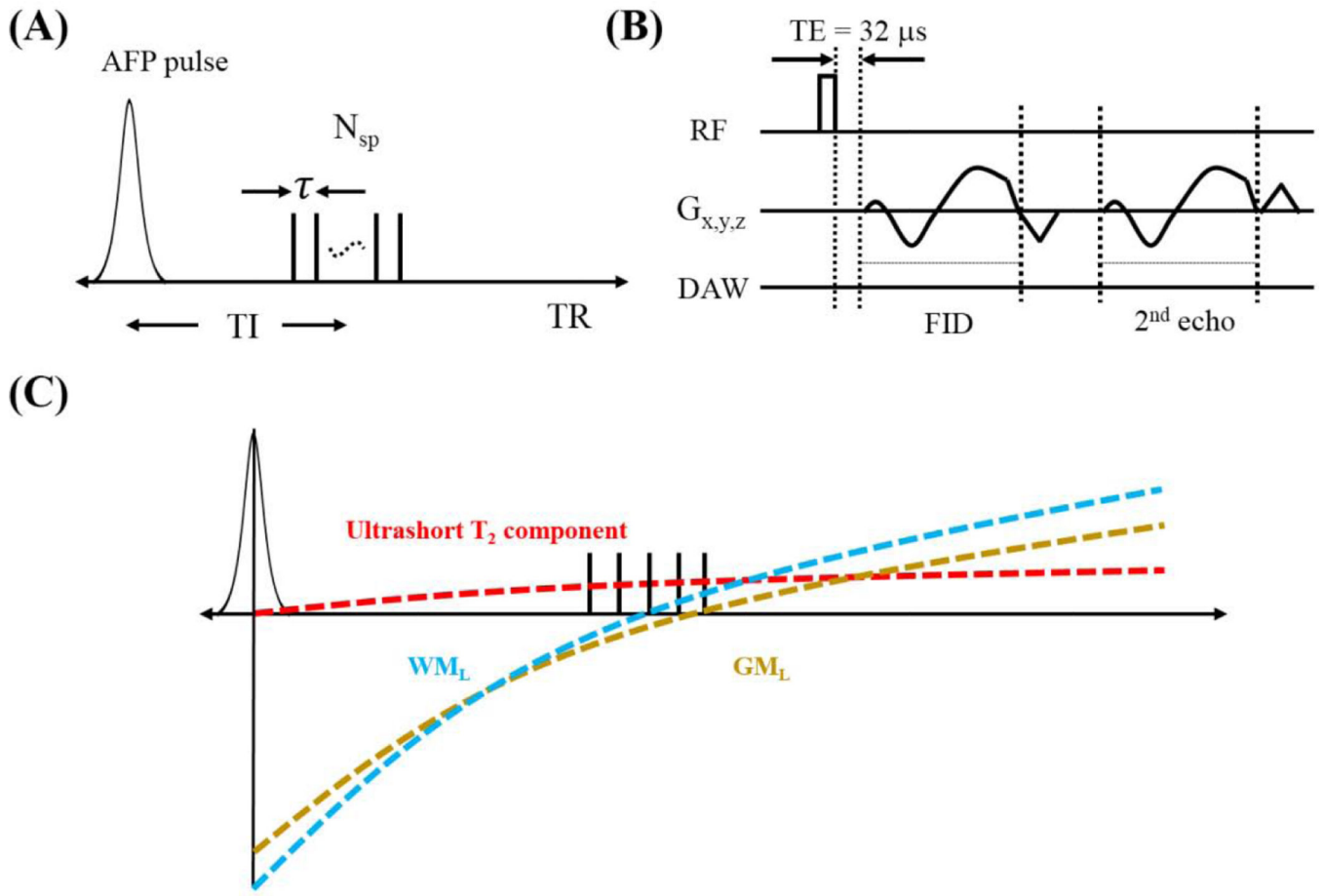

Figure 1.

Key features of the 3D STAIR-dUTE sequence for ultrashort T_2 imaging. Following an AFP pulse, a series of k-space spokes (N_{sp}) separated by an identical time interval τ is used for fast data acquisition (A). TI is defined as the time from the center of the AFP pulse to the center of the multispoke acquisition. Dual-echo acquisition is utilized with each spoke which utilizes spiral gradient encoding and 3D conical view ordering (B). C shows the contrast mechanism for ultrashort T_2 imaging in the first echo of STAIR-dUTE. The longitudinal magnetizations of both WM_L and GM_L are inverted by the AFP pulse and start to recover at the end of it. The longitudinal magnetization of ultrashort T_2 is largely saturated during the relatively long AFP pulse due to its fast transverse relaxation. Pure ultrashort T_2 signals can be acquired at a specific TI when the long T_2 component is effectively nulled.

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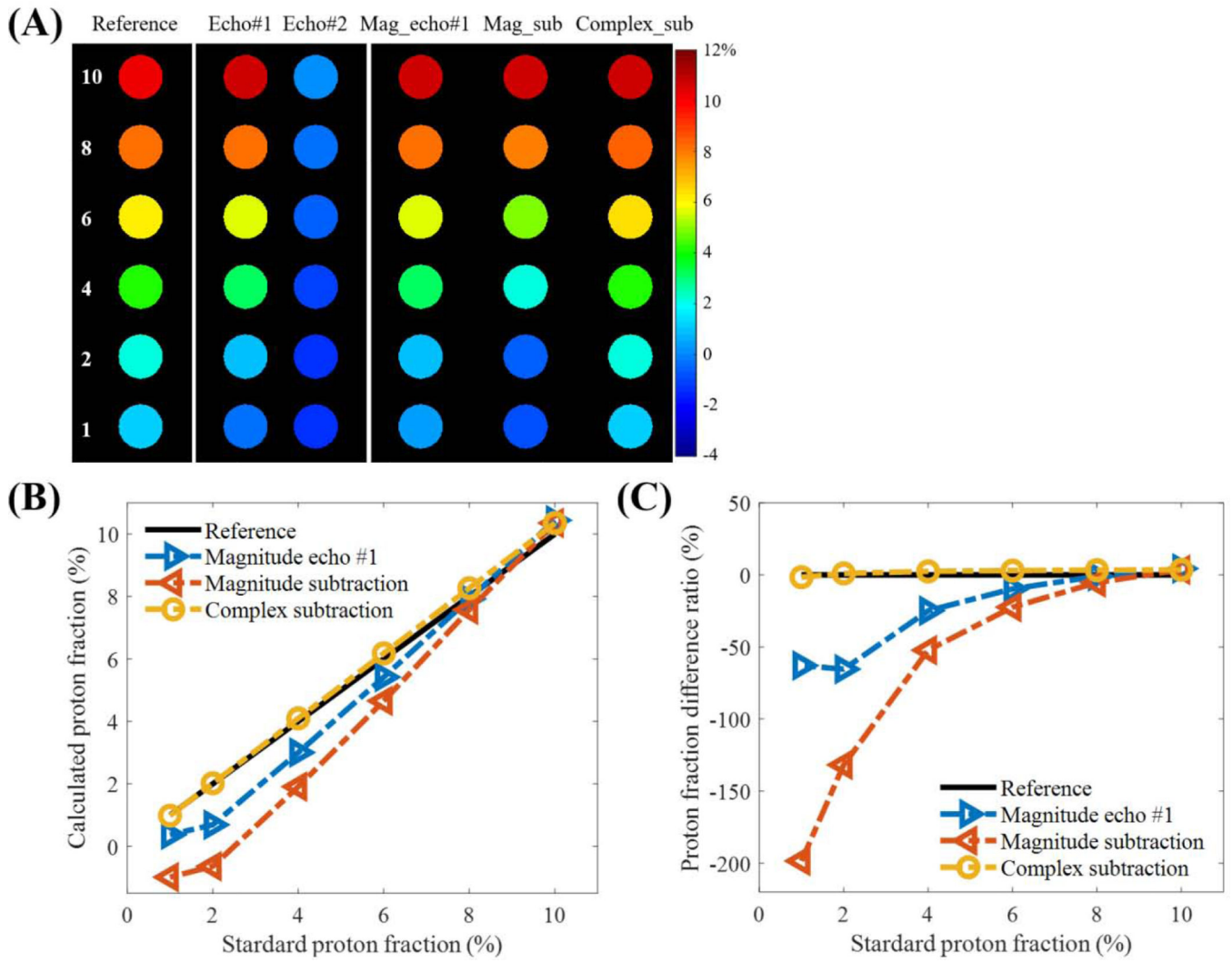

Figure 2.

Numerical simulation to investigate the accuracy of quantifying USPF with different methods. A reference standard is shown in the first column in A. Echo signals with STAIR-dUTE imaging are shown in columns 2 (first echo) and 3 (second) respectively. The last three columns show USPFs derived from the magnitude of first echo, magnitude subtraction and complex ES of the dual echoes respectively. The corresponding fraction and fraction difference ratio curves are shown in B and C respectively. The most accurate results are obtained with complex ES.

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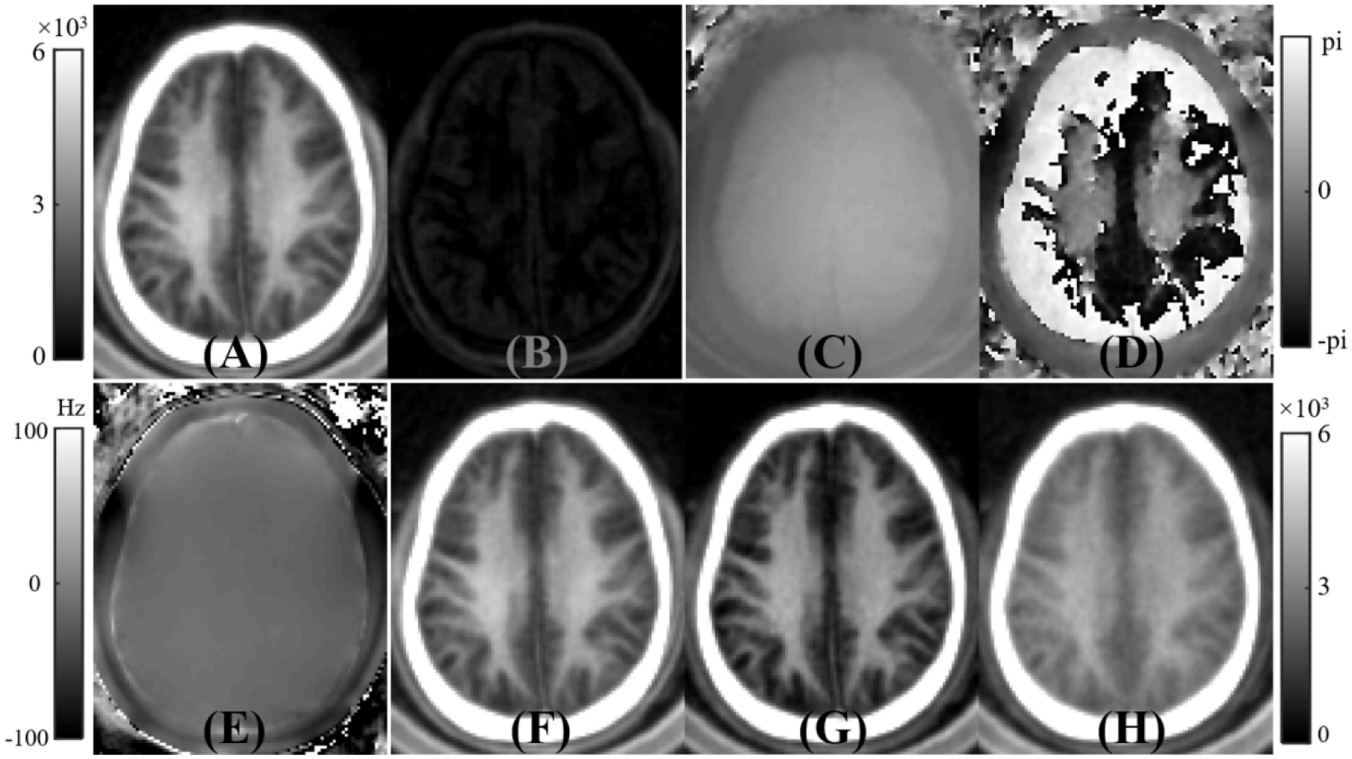

Figure 3.

A volunteer study (21-year-old male) showing the generation of ultrashort T_2 signals with the methods used in this study. The first row shows magnitude images for the first echo (A) and the second echo (B), as well as the corresponding phase images for the first echo (C) and second echo (D). Panel E shows the ΔB_0 field map used for the complex ES. Magnitude of the first echo (F), magnitude echo subtracted (G), and complex echo subtracted (H) images obtained with the STAIR-dUTE sequence are shown. The magnitude of the first echo image (A) is displayed again in (F) for closer comparison with (G) and (H). Four different color bars are used for images (A and B), images (C and D), image (E), as well as images (F to H). Images (F) and (G) show higher GM-WM contrast than (H).

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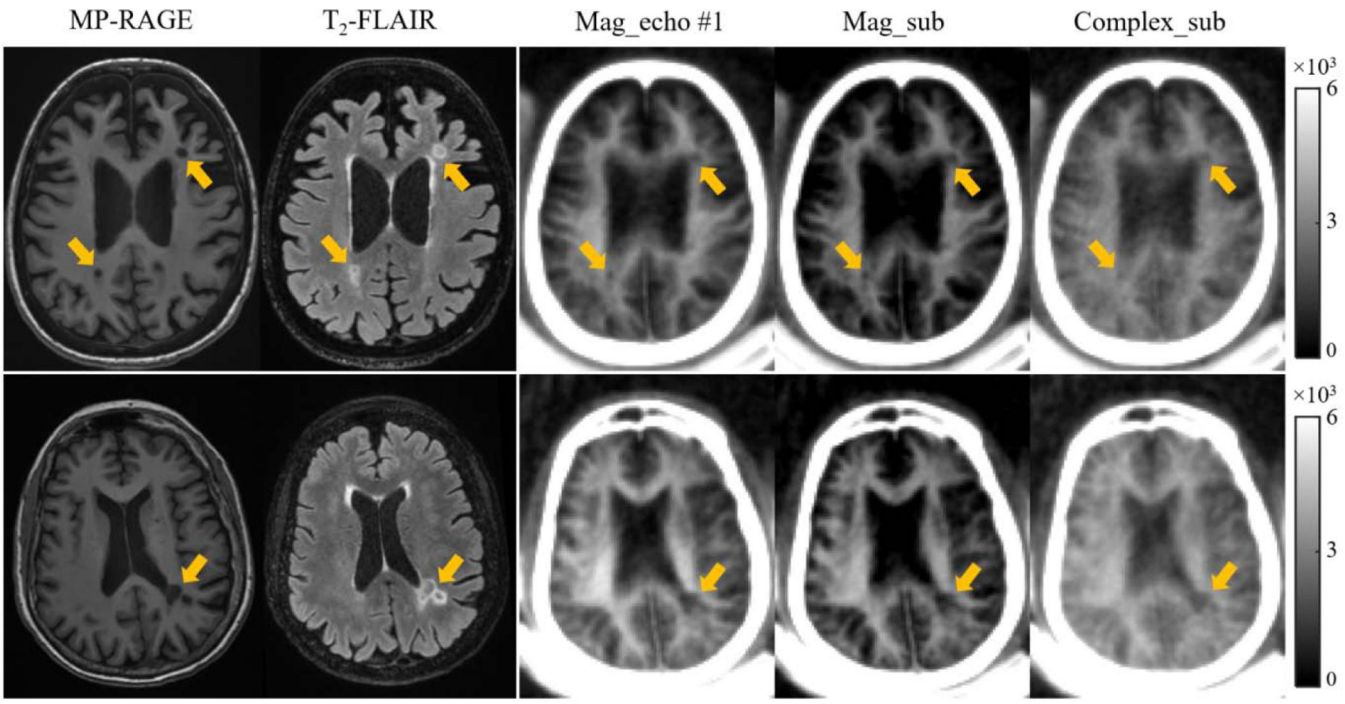

Figure 4.

Selective clinical MP-RAGE (first column), T_2-FLAIR (second column) and STAIR-dUTE (last three columns) images of two representative patients with MS (first row: a 49-year-old female; second row: a 69-year-old female). MS lesions appeared hypointense on the MP-RAGE image and hyperintense on the T_2-FLAIR image as indicated by the yellow arrows. These lesions also show signal loss on the magnitude images in the first echo images (third column), magnitude echo subtracted images (fourth column) and complex echo subtracted images (last column) using the STAIR-dUTE sequence.

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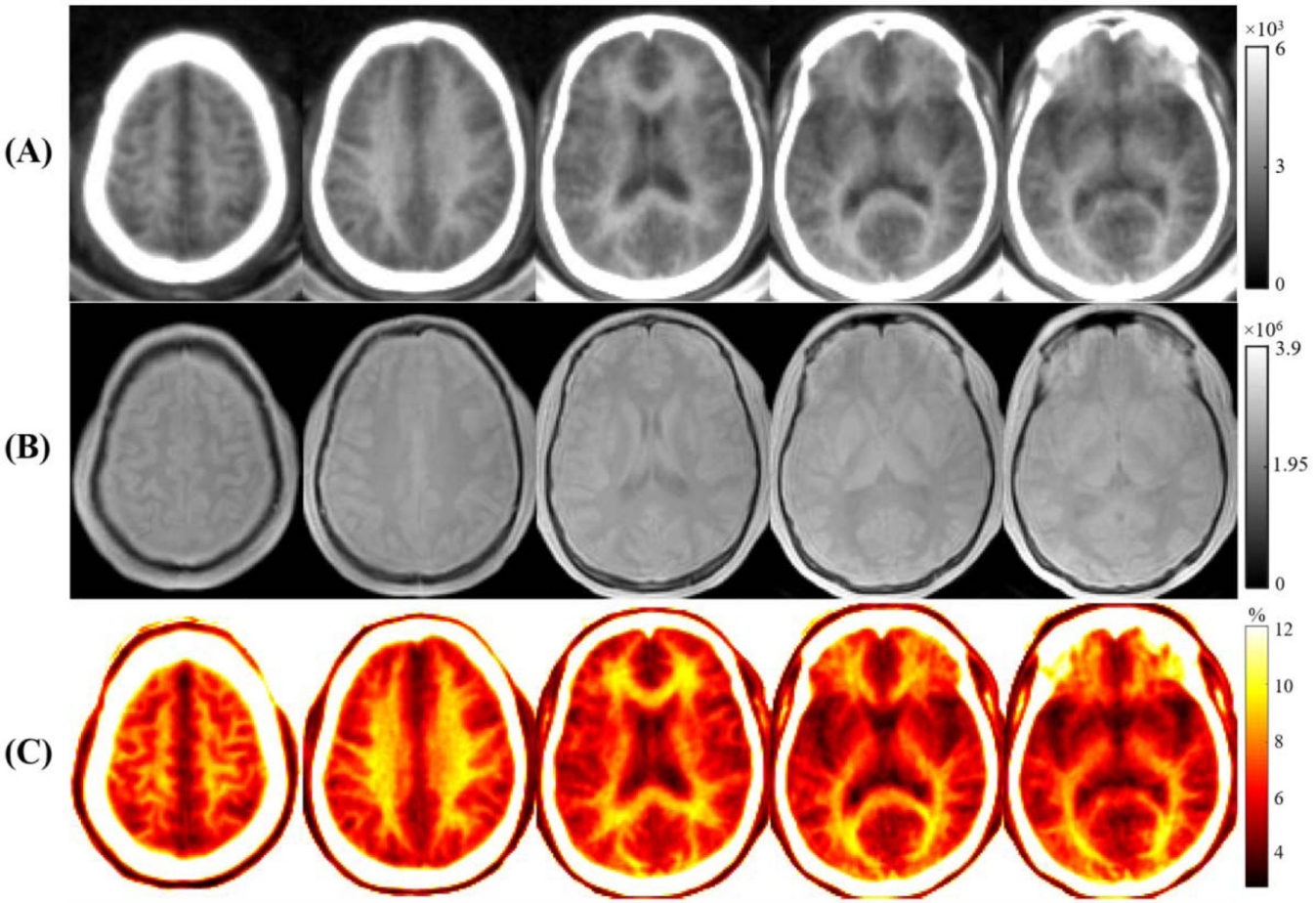

Figure 5.

Representative STAIR-dUTE-ES images (A), PDw-UTE images (B) and USPF maps (C) from the same volunteer as shown in Figure 3. The images in (B) show CSF in the lateral ventricles with lower signal than white or gray matter due to residual T_1-weighting. Higher contrast is seen on the USPF maps (C) compared to the STAIR-dUTE-ES images (A).

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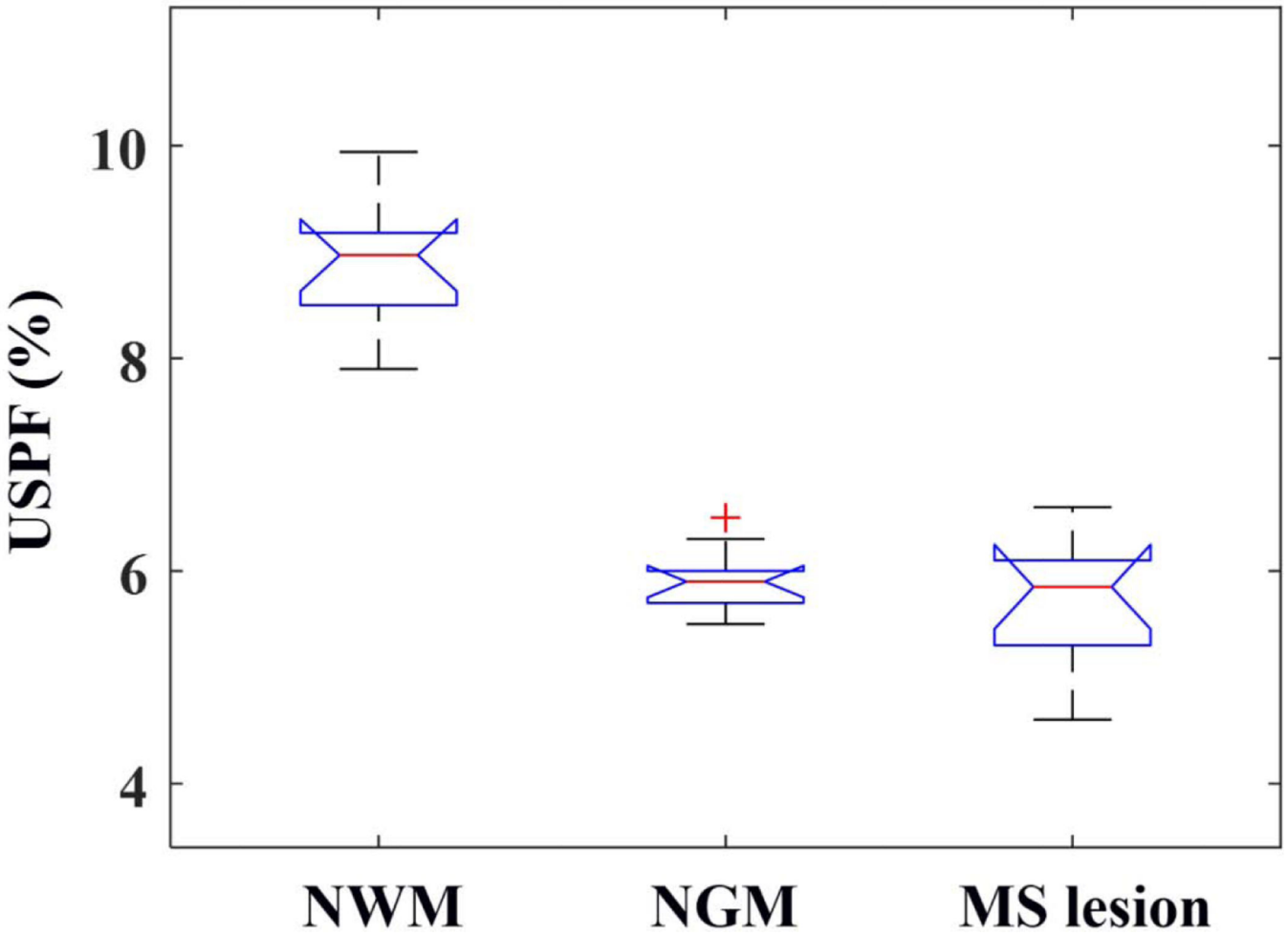

Figure 6.

Statistical analysis for USPF measurement with the STAIR-dUTE-ES method. The lesions in MS patients showed a lower USPF (5.7±0.7%) compared with that of NWM (8.9±0.6%) in healthy volunteers ($p < 0.0001$). The NGM has a USPF value of 5.9±0.3%. The central mark in each boxplot indicates the median. The bottom and top edges of each box indicate the 25th and 75th percentiles, respectively.

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Table 1

Simulated tissue properties used in this study.

MR property \ Tissue Component	Ultrashort T_2	Myelin water	Intra/extracellular water
T_2* (ms)	0.3	10	60
T_1 (ms)	300	400	850/850/1000/1200/1500/1800
Proton fraction (%)	10/8/6/4/2/1	12.5/10/7.5/5/2.5/1.25	77.5/82/86.5/91/95.5/97.75