NeuroImage xxx (xxxx) xxx



Contents lists available at ScienceDirect

# NeuroImage



journal homepage: www.elsevier.com/locate/neuroimage

# Advances in gradient echo myelin water imaging at 3T and 7T

Hyeong-Geol Shin<sup>a</sup>, Se-Hong Oh<sup>b</sup>, Masaki Fukunaga<sup>c</sup>, Yoonho Nam<sup>d</sup>, Doohee Lee<sup>a</sup>, Woojin Jung<sup>a</sup>, Minju Jo<sup>a</sup>, Sooyeon Ji<sup>a</sup>, Joon Yul Choi<sup>a</sup>, Jongho Lee<sup>a,\*</sup>

<sup>a</sup> Laboratory for Imaging Science and Technology, Department of Electrical and Computer Engineering, Seoul National University, Seoul, South Korea

<sup>b</sup> Department of Biomedical Engineering, Hankuk University of Foreign Studies, Yongin, South Korea

<sup>c</sup> Division of Cerebral Integration, National Institute for Physiological Sciences, Okazaki, Japan

<sup>d</sup> Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

### ARTICLE INFO

Keywords: Myelin Myelin water imaging T<sub>2</sub>\* relaxation Bipolar acquisition Multi-echo gradient echo Gradient pairing

### ABSTRACT

Gradient echo myelin water imaging (GRE-MWI) is an MRI technique to measure myelin concentration and involves the analysis of signal decay characteristics of the multi-echo gradient echo data. The method provides a myelin water fraction as a quantitative biomarker for myelin. In this work, a new sequence and post-processing methods were proposed to generate high quality GRE-MWI images at 3T and 7T. In order to capture the rapidly decaying myelin water signals, a bipolar readout GRE sequence was designed with "gradient pairing," compensating for the eddy current effects. The flip angle dependency from the multi-compartmental T<sub>1</sub> effects was explored and avoided using a 2D multi-slice acquisition with a long TR. Additionally, the sequence was tested for the effects of inflow and magnetization transfer and demonstrated robustness to these error sources. Lastly, the temporal and spatial B<sub>0</sub> inhomogeneity effects were mitigated by using the B<sub>0</sub> navigator and field inhomogeneity corrections. Using the method, high-quality myelin water fraction at 3T and 7T were compared, they showed a good correlation (R<sup>2</sup>  $\geq$  0.88; p < 0.001) with a larger myelin water fraction at 7T. The proposed method also opens the possibility of high resolution (isotropic 1.5 mm resolution) myelin water mapping at 7T.

### 1. Introduction

Myelin is a fatty substance found in the microstructure of the vertebrate central nervous system. It fosters the rapid and efficient conduction of action potential along axons (Hildebrand et al., 1993). Myelination is one of the fundamental processes for development (Wang et al., 2009) and neuro-plasticity (McKenzie et al., 2014). Moreover, neurodegenerative disorders such as multiple sclerosis and leukodystrophy are accompanied by the degeneration of myelin (Compston and Coles, 2008; Nave, 2010). Hence, quantifying myelin content *in vivo* has important applications in science and clinic.

In MRI, one approach for quantifying myelin is myelin water imaging (MWI), which measures the signals from the water trapped between myelin lipid bilayers (Mackay et al., 1994). This method provides myelin water fraction (MWF), which is the ratio of the myelin water signal to the total water signal, and is a quantitative assessment of myelin water concentration. The metric has been shown to have a good correlation with histological measurements of myelin, demonstrating the potential of

the method as an *in-vivo* biomarker for myelin (Laule et al., 2006, 2004; Webb et al., 2003).

In conventional MWI, a multi-echo spin echo sequence was utilized to collect multi-compartmental  $T_2$  decays (Mackay et al., 1994). A typical sequence for this method acquires 32 echoes with an echo space of 10 ms, requiring 32 refocusing RF pulses and 320 ms duration (Prasloski et al., 2012). Recently, an alternative approach based on the  $T_2^*$  decay characteristics of myelin water was proposed by utilizing a multi-echo gradient echo sequence (GRE-MWI) (Du et al., 2007). This approach does not require any refocusing RF pulse and, therefore, provides higher data acquisition efficiency and lower specific absorption rate (SAR) than the conventional MWI (Du et al., 2007). In particular, the advantage of the low SAR may help us to apply the method for *in-vivo* human brain imaging at a high field system (7T or higher), in which the conventional MWI has been limited for *ex-vivo* specimens (Laule et al., 2008, 2016).

Over the past few years, several methods have been proposed to acquire high quality GRE-MWI (Alonso-Ortiz et al., 2016; D. Lee et al., 2018; H. Lee et al., 2017; Nam et al., 2015a, 2015b). One of the

E-mail address: jonghoyi@snu.ac.kr (J. Lee).

https://doi.org/10.1016/j.neuroimage.2018.11.040

Received 3 September 2018; Received in revised form 22 November 2018; Accepted 22 November 2018 Available online xxxx

1053-8119/© 2018 Elsevier Inc. All rights reserved.

<sup>\*</sup> Corresponding author. Department of Electrical and Computer Engineering, Seoul National University, Building 301, Room 1008, 1 Gwanak-ro, Gwanak-gu, Seoul, South Korea.

### H.-G. Shin et al.

important technical improvements is the complex model for multi-compartmental analysis, which offers a reliable myelin water estimation (Nam et al., 2015b; Sati et al., 2013; van Gelderen et al., 2011) by including the frequency shift characteristics of the water compartments (Sati et al., 2013; Wharton and Bowtell, 2012). Other methods such as physiological noise (i.e., inflow and respiration noises) compensation (Nam et al., 2015a) and  $B_0$  field inhomogeneity correction (Alonso-Ortiz et al., 2016; D. Lee et al., 2018) have been demonstrated to improve the quality of GRE-MWI results.

Despite these developments, a few issues still need to be addressed for GRE-MWI. For example, short TR (~60 ms) 3D GRE-MWI has shown an overestimated MWF (H. Lee et al., 2017; Nam et al., 2015b), most likely due to the multi-compartmental  $T_1$  effects (i.e., the  $T_1$  weighting difference between the short  $T_1$  myelin water and long  $T_1$  axonal/extracellular water) (Labadie et al., 2014; S.-H. Oh et al., 2013). This observation suggests that MWF is dependent upon sequence parameters such as TR and flip angle and can be affected by  $B_1$  inhomogeneity, hampering the reliability of the method. Although this issue can be prevented by using a sufficiently long TR as in 2D GRE-MWI, 2D multi-slice imaging may also introduce unexpected effects from magnetization transfer (Chang et al., 2007; Sati et al., 2013; Vavasour et al., 2000), eddy currents (e.g., from a large slice selection rephasing gradient in 2D), and physiological noises.

scheme. Compared to a monopolar readout scheme, the bipolar readout provides a shorter first echo time and echo space and, therefore, captures the rapidly decaying myelin water signal more efficiently (Du et al., 2007; H. Lee et al., 2017). However, the rapid gradient polarity change induces magnitude (Delakis et al., 2005) and phase (Alecci and Jezzard, 2002; Reeder et al., 1999) modulations between odd and even echoes, which may introduce significant artifacts in GRE-MWI (H. Lee et al., 2017) (e.g., artifacts in Fig. 2d). Thus far, only linear phase errors from the readout gradient have been compensated (H. Lee et al., 2017). Hence, the effects of other error sources (e.g., eddy currents from slice rephasing gradient) need to be addressed.

In this study, we proposed a sequence and post-processing methods that generate high quality myelin water images at 3T and 7T. A new 2D GRE sequence was developed, tested, and optimized at 3T. Then, the sequence was applied at 7T to demonstrate the feasibility of high field MWI for the *in-vivo* human brain.

### 2. Material and methods

### 2.1. Pulse sequence for 2D GRE-MWI with gradient pairing

In order to incorporate the bipolar readout scheme while avoiding the magnitude and phase modulations, we modified a multi-echo 2D GRE



**Fig. 1.** (a) The 2D GRE sequence with the gradient pairing. For the gradient pairing, the gradient polarities are reversed (blue to orange or orange to blue) in all three gradients in every TR. The same k-space line is acquired twice (measurement #1 and #2) and averaged. The sequence includes a navigator echo (green) and an optional flow saturation module (dashed box). (b, c) The phase maps from the first four echoes of the two measurements. Between the two measurements, the odd echoes (*TE*<sub>1</sub> and *TE*<sub>3</sub>) show consistent field patterns whereas the even echoes (*TE*<sub>2</sub> and *TE*<sub>4</sub>) show the opposite field pertrubation patterns. (d) The phase maps after combining the two measurements, revealing consistent phase evolution over time.

### H.-G. Shin et al.

sequence to acquire the same k-space line twice with the opposite gradient polarity (Soliman et al., 2016; Yu et al., 2010). This approach is referred to as "gradient pairing," hereafter and can be applied in all three gradients (i.e., the readout, phase encoding, and slice selection gradients). The gradient pairing was performed on every TR to maintain data consistency between the two k-space datasets from potential artifacts (e.g., motion) (Fig. 1a). Therefore, two GRE datasets (Fig. 1, measurement #1 and measurement #2) were acquired simultaneously in a single scan at the cost of twice the total scan time required by the conventional GRE acquisition.

The sequence included a  $B_0$  navigator echo (green trapezoid in Fig. 1a) and an optional flow saturation module (dashed box in Fig. 1a) to test the effects of the physiological noises in 2D GRE-MWI.

### 2.2. Data acquisition at 3T

To generate high quality data, we explored the effects of the following confounding factors: 1) gradient pairing, 2) physiological noises, 3) flip angle effects from the multi-compartmental T<sub>1</sub>, and 4) magnetization transfer from the multi-slice acquisition. Seven healthy volunteers (Subject 1 to 7; mean age =  $27.6 \pm 3.1$  years) were scanned at a 3T Tim Trio MRI scanner (Siemens Healthcare, Erlangen, Germany) using a 32-channel phased array head coil under the approval of the institutional review board.

The default scan parameters of 2D GRE-MWI were as follows: in-plane resolution =  $2 \times 2 \text{ mm}^2$ , slice thickness = 2 mm, number of echoes = 20, TR = 2000 ms, first TE = 2.4 ms, echo spacing = 2.2 ms, bandwidth per pixel = 500 Hz/pixel, field of view =  $256 \times 256 \text{ mm}^2$ , number of slices = 40, flip angle =  $85^{\circ}$  (Ernst angle for T<sub>1</sub> of 840 ms (Wright et al., 2008)), and total scan time = 8 min 24 s. For excitation, a Hanning windowed sinc-shape RF pulse (TBW = 2 and duration = 980 µs) was used with the slice selection gradient amplitude of 28 mT/m. The imaging slices were acquired axially. For all subjects, the scan was conducted using the default scan parameters with the gradient pairing in all axes, flow saturation off, and navigator echo correction on. Additionally, the following experiments were performed to test the effects of the confounding factors by varying a few parameters from the default setting.

### 2.2.1. Experiment 1: gradient pairing

To demonstrate the effects of the gradient pairing, three different gradient pairing conditions were tested: no gradient pairing, readout gradient ( $G_{read}$ ) pairing, and full gradient pairing (i.e., all three gradients are paired) (Fig. 2a-c). These datasets were acquired from Subject 1.

### 2.2.2. Experiment 2: physiological noises

The effects of the physiological noises on 2D MWI were investigated (Subject 2). Two datasets, one with the flow saturation and the other without the flow saturation, were acquired. Since each flow saturation module took 16 ms, the flow-saturated scan had 30 slices instead of 40 to hold the total scan time constant as the default setting. The datasets were then reconstructed with and without the navigator correction.

Additionally, the flow-unsaturated data from all subjects (Subject 1 to 7) were processed with and without the navigator correction to confirm the robustness of our method for physiological noises.

### 2.2.3. Experiment 3: flip angle effects from multi-compartmental $T_1$

To demonstrate the effects of the flip angle on MWF, myelin water images were acquired using two different TRs and two different flip angles (Subject 3, 5, 6, and 7). Two TRs, 70 ms and 2000 ms, which were used in 3D (H. Lee et al., 2017; Nam et al., 2015a) and 2D (Alonso-Ortiz et al., 2018) GRE-MWI, were utilized. Hereafter, TR of 70 ms is referred to as short TR and TR of 2000 ms as long TR. Two long TR (= 2000 ms) 2D images (flip angles:  $45^{\circ}$  vs.  $85^{\circ}$ ;  $85^{\circ}$  is the Ernst angle) and two short TR (= 70 ms) 3D GRE images (flip angles:  $20^{\circ}$  vs.  $40^{\circ}$ ;  $20^{\circ}$  is the Ernst angle) were acquired and compared.

For 3D, data were collected using the following parameters: resolu-

tion =  $2 \times 2 \times 2$  mm<sup>3</sup>, TR = 70 ms, field of view =  $256 \times 256 \times 80$  mm<sup>3</sup>, and total scan time = 10 min 30 s. The gradient pairing was applied in the readout and phase encoding gradients. The physiological noises were compensated (Nam et al., 2015a). The other parameters were identical to the default parameters for 2D.

# 2.2.4. Experiment 4: magnetization transfer (MT) effects from multi-slice acquisition

To test the MT effects from the multi-slice acquisition, single-slice data were acquired using the same scan parameters as the default setting except for the number of slices (Subject 4, 5, 6, and 7). The results were compared with those from the multi-slice data.

### 2.3. Data acquisition at 7T

The proposed GRE sequence was implemented on a 7T MRI scanner (Magnetom, Siemens Healthcare, Erlangen, Germany). Five subjects (Subject 8 to 12; mean age = 29.6  $\pm$  4.3 years) were scanned using a 1-channel circularly polarized head coil for RF transmission and 32-channel phased array coil for signal reception (Nova Medical, Wilmington, MA). All subjects signed a consent form approved by the institutional review board.

GRE data were obtained using the same parameters used for the 3T default scan except for the following parameters: first TE = 2 ms, echo spacing = 1.4 ms, bandwidth per pixel = 840 Hz/pixel, and flip angle = 80° (Ernst angle for T<sub>1</sub> of 1100 ms (Wright et al., 2008)). The first TE and the echo spacing were reduced from those of 3T to reflect the T<sub>2</sub>\* shortening at 7T.

To compare the 7T MWI results with those from 3T, the same subjects (Subject 8 to 12) were scanned at a 3T MRI scanner (Verio, Siemens Healthcare, Erlangen, Germany). All scans were conducted using the default scan parameters of the 3T Tim Trio scanner, except for the first TE which was adjusted to 2.5 ms due to the difference in the gradient system.

In one subject (Subject 8), high resolution GRE-MWI was acquired using the following parameters: in-plane resolution =  $1.5 \times 1.5 \text{ mm}^2$ , slice thickness = 1.5 mm, first TE = 2.2 ms, field of view =  $288 \times 288 \text{ mm}^2$ , number of slices = 64, and total scan time = 12 min 50 s. All the other parameters were the same as in the lower resolution scan at 7T.

### 2.4. Data processing

As the first step for image reconstruction, the k-space data were processed to compensate for the respiration-induced  $B_0$  field fluctuation using the navigator echo (except for Experiment 2). Each k-space line of the navigator echo was Fourier-transformed and averaged along the readout direction. Subsequently, the phase of the averaged value was divided by the navigator echo time to calculate the frequency shift. This frequency shift was scaled for each echo data, and the resulting phase was subtracted to correct for the  $B_0$  field fluctuation (Nam et al., 2015a). The navigator-corrected k-space data were weighted by a Tukey window (window parameter = 0.4) to reduce ringing artifacts. The data were then processed to generate the channel-combined magnitude (via root-sum-of-squares) and phase images (via MCPC-3D-I (Robinson et al., 2011)). In the MCPC-3D-I processing, the first and third echoes were utilized to calculate the phase offset.

After the coil combination, the two images from the gradient pairing were combined into a single image using the following formula:

$$|I(TE_n)| = \sqrt{|I_1(TE_n)|^2 + |I_2(TE_n)|^2}$$
(1)

$$\measuredangle I(TE_n) = \measuredangle \left(\frac{I_1(TE_n) + I_2(TE_n)}{2}\right)$$
<sup>(2)</sup>

where  $I_1(TE_n)$ ,  $I_2(TE_n)$ , and  $I(TE_n)$  denote the nth echo complex images



**Fig. 2.** (a-c) The sequence diagrams of the three gradient pairing conditions. The corresponding MWF (d, f, h) and frequency shift (e, g, i) maps. When the gradients are not paired (a, no pairing), the MWF (d) and frequency shift (e) maps show substantial artifacts. For the readout gradient pairing (b,  $G_{read}$  pairing), the artifacts along the readout direction are removed but the artifacts along the slice selection persist (f, g). When all gradients are paired (c, full pairing), both MWF (h) and frequency shift (i) maps show high quality images.

from measurement #1, measurement #2, and combined data, respectively (Fig. 1). Finally, the combined multi-echo complex images were fitted by a modified version of the three pool complex model (Nam et al., 2015b):

$$S(t) = \left[A_{my} \cdot e^{-t/T_{2,my}^{*} - i2\pi \cdot \Delta f_{my\&bg} \cdot t} + A_{ax} \cdot e^{-t/T_{2,ax}^{*} - i2\pi \cdot \Delta f_{ax\&bg} \cdot t} + A_{ex} \\ \cdot e^{-t/T_{2,ex}^{*} - i2\pi \cdot \Delta f_{ex\&bg} \cdot t}\right] \cdot e^{-i\phi_{0}} \cdot sinc(\alpha t)$$

$$(3)$$

### H.-G. Shin et al.

where *my*, *ax*, *ex*, and *bg* represent the myelin water, axon water, extracellular water, and background offset, respectively. Correspondingly, *A*,  $T_2^*$ , and  $\Delta f$  denote the signal amplitude,  $T_2^*$ , and the frequency offset.  $\phi_0$ is a phase offset. The sinc function with a coefficient of  $\alpha$ , which was not included in the original Nam et al.'s model, serves to compensate for the signal loss from macroscopic B<sub>0</sub> field inhomogeneity (Alonso-Ortiz et al., 2016; Fernández-Seara and Wehrli, 2000).

The model parameters were estimated using iterative non-linear least square fitting ('lsqnonlin' function in MATLAB, step tolerance = 1e-5, function tolerance = 1e-5). The initial values and the upper/lower boundaries for the fitting are summarized in Table 1. The initial values were set based on the previous studies (Nam et al., 2015b; Sati et al., 2013). For  $\alpha$ ,  $\alpha_{init}$  is defined as  $\gamma D_z/2$  where  $\gamma$  indicates the gyromagnetic ratio and  $D_z$  denotes a directional derivative of unwrapped phase maps along the slice selection direction (Alonso-Ortiz et al., 2016).

To demonstrate the effects of the  $B_0$  field inhomogeneity, MWI fitting was processed with and without the sinc correction (see Supplementary Information).

### 2.5. Data analysis

Region of interest (ROI) analyses were performed for quantitative comparisons of the different conditions (i.e., different flip angles; 3T vs. 7T; single-slice vs. multi-slice). All ROIs were manually segmented in the MWF maps. For the comparison between 3T and 7T, the mean MWF and frequency shift values were measured in five ROIs: forceps minor, genu of the corpus callosum, posterior limb of the internal capsule (PLIC), splenium of the corpus callosum, and forceps major. A representative figure of the ROIs is displayed in Supplementary Information (Fig. S2). One of the five datasets acquired at 7T (Subject 8 to 12) was discarded due to motion artifacts. Correlation analyses were performed between 3T and 7T for the MWF and frequency shift. For the MT effects from the multislice acquisition, a paired *t*-test was performed, comparing the MWF maps from the single- and multi-slice acquisitions in a white matter mask. The mask was determined by a range of MWF (5% < MWF < 30%).

All data processing was performed using MATLAB (MathWorks, Natick, MA).

### 3. Results

Fig. 1b and c demonstrate the effects of the bipolar readout gradient scheme on the GRE phase. When comparing the two measurements of the opposite gradient polarities (Fig. 1b vs c), the phase maps from the odd echoes ( $TE_1$  and  $TE_3$ ) are found to have similar field distributions. On the other hand, the maps from the even echoes ( $TE_2$  and  $TE_4$ ) show the opposite field perturbation patterns. Once the two measurements are combined, the resulting phase maps (Fig. 1d) display consistent phase evolution over time, suggesting the successful compensation of the errors.

The effects of the gradient pairing on MWI are summarized in Fig. 2. When the gradient pairing is not used (Fig. 2a, no pairing), the MWF and myelin water frequency shift maps  $(\Delta f_{my-ex} = \Delta f_{my-kbg} - \Delta f_{ex,kbg})$  do not reveal the characteristics of the myelin water distribution (Fig. 2d and e). When the readout gradients are paired (Fig. 2b,  $G_{read}$  pairing), the MWF NeuroImage xxx (xxxx) xxx



**Fig. 3.** The magnitude (a, b) and phase images (c, d) (TE = 39.8 ms), and MWF maps (e, f) before and after the navigator correction. After the correction, the ghost artifacts observed in the magnitude and phase images are reduced. The asymmetry in the MWF map is also removed (e and f, red arrows).

maps show substantial improvements (Fig. 2f). However, the upper and lower slices show erroneous MWF and frequency shift patterns from the unpaired slice selection and phase encoding gradients (Fig. 2f and g). When gradients are paired in all three axes (Fig. 2c, full pairing), both MWF and frequency shift maps show no apparent artifacts, demonstrating the utility of the gradient pairing (Fig. 2h and i).

Fig. 3 shows the effects of the navigator correction. Without the navigator correction, ghosting artifacts are observed in both magnitude and phase images along the phase encoding direction (left-to-right) (Fig. 3a and c). The corresponding MWF map shows asymmetric MWF distribution (red arrow in Fig. 3e). When the navigator correction is applied, the ghosts are reduced (Fig. 3b and d), and the asymmetry is removed (Fig. 3f). These results demonstrate the necessity of the navigator correction in 2D GRE-MWI (See Fig. S3 in Supplementary Information for consistent results of all subjects).

The effects of the flow saturation are explored using the navigatorcorrected data (Fig. 4). The MWF map without the flow saturation shows no conspicuous artifacts outside the vessels (Fig. 4a) and provides an image quality similar to that of the map with the flow saturation (Fig. 4b). The results were consistent in all subjects (see Fig. S3 in

Table 1

The initial values and the upper/lower boundaries for the three pool fitting process.  $I_1$  denotes the first echo GRE image.  $\Delta f_{bg,init}$  indicates a frequency shift of the background field (Nam et al., 2015b).

		$A_{my}$	A <sub>ax</sub>	A <sub>ex</sub>	$T_{2,my}^{*}$ (ms)	$T_{2,ax}^{*}$ (ms)	$T_{2,ex}^{*}$ (ms)	$\Delta f_{my\&bg}$ (Hz)	$\Delta f_{ax\&bg}$ (Hz)	$\Delta f_{ex\&bg}$ (Hz)	$\alpha$ (Hz)
3Т	upper bound initial value lower bound	$egin{array}{l}  I_1  imes 2\  I_1  imes 0.1\ 0 \end{array}$	$egin{array}{c}  I_1  imes 2\  I_1  imes 0.6\ 0 \end{array}$	$egin{array}{c}  I_1  imes 2\  I_1  imes 0.3\ 0 \end{array}$	24 10 3	1000 64 24	1000 48 24	$\Delta f_{bg,init} + 75$ $\Delta f_{bg,init}$ $\Delta f_{bg,init} - 75$	$\Delta f_{bg,init} + 25$ $\Delta f_{bg,init}$ $\Delta f_{bg,init} - 25$	$\Delta f_{bg,init} + 25$ $\Delta f_{bg,init}$ $\Delta f_{bg,init} - 25$	$lpha_{ ext{init}}+10 \ lpha_{ ext{init}} \ lpha_{ ext{init}}-10$
7T	upper bound initial value lower bound	$egin{array}{c}  I_1  imes 2 \  I_1  imes 0.1 \ 0 \end{array}$	$egin{array}{c}  I_1  imes 2 \  I_1  imes 0.6 \ 0 \end{array}$	$egin{array}{c}  I_1  imes 2 \  I_1  imes 0.3 \ 0 \end{array}$	14 6 2	800 40 14	800 30 14	$\Delta f_{bg,init} + 175$ $\Delta f_{bg,init}$ $\Delta f_{bg,init} - 175$	$\Delta f_{bg,init} + 60$ $\Delta f_{bg,init}$ $\Delta f_{bg,init} - 60$	$\Delta f_{bg,init} + 60$ $\Delta f_{bg,init}$ $\Delta f_{bg,init} - 60$	$lpha_{ ext{init}}+10 \ lpha_{ ext{init}} \ lpha_{ ext{init}} -10$



Fig. 4. The MWF maps without (a) and with (b) the flow saturation. The 2D GRE-MWI shows no substantial inflow artifacts even without the flow saturation. Flow signals are largely confined to large vessels (red arrows).

Supplementary Information), yielding no substantial flow artifacts in the default scan (i.e., flow saturation off).

When the two maps with the short TR are compared, the map using the large flip angle (40°) shows larger MWF than that using the small flip angle (20°) across the slice (Fig. 5a and b). The quantitative comparison in ROIs (the superior longitudinal fasciculus, red circle in Fig. 5) confirms this observation, yielding a statistically significant difference between the two results (Fig. 5c from Subject 3: MWF =  $14.2 \pm 1.7\%$  for 20° and MWF =  $16.9 \pm 2.0\%$  for 40°, p < 0.001; when averaged over all four subjects: MWF =  $15.5 \pm 1.8\%$  for 20° and MWF =  $18.3 \pm 2.2\%$  for 40°,

p<0.001). On the other hand, the two MWF maps from the long TR (flip angles:  $45^{\circ}$  vs.  $85^{\circ}$ ) reveal similar MWF distribution (Fig. 5d and e). No statistically significant difference is reported in the ROI analysis (Fig. 5f from Subject 3: MWF =  $13.9\pm1.3\%$  for  $45^{\circ}$  and MWF =  $13.9\pm1.3\%$  for  $85^{\circ}, \ p=0.391$ ; when averaged over all four subjects: MWF =  $14.4\pm1.4\%$  for  $45^{\circ}$  and MWF =  $14.4\pm1.4\%$  for  $85^{\circ}, \ p=0.727$ ).

Fig. 6 compares the MWF maps from the single-slice and multi-slice acquisition to test the MT effects. The two maps demonstrate similar MWF distribution and the difference map also displays no structured pattern, suggesting that the MT effects from the multi-slice acquisition



**Fig. 5.** The short TR (= 70 ms) 3D MWF maps using the flip angles of  $20^{\circ}$  (a) and  $40^{\circ}$  (b). The larger flip angle induces larger MWF. (c) The ROI analysis confirms a significant MWF increase in the larger flip angle result (p < 0.001). On the other hand, the long TR (= 2000 ms) 2D MWF maps from the two different flip angles (d, e) reveal no statistically significant difference (p = 0.391) (f).



Fig. 6. Comparison of the MWF maps from the single-slice (a) and multi-slice (b) acquisition. The difference map (c) reveals no white mater structure.

are negligible. The quantitative analysis of all subjects (Subject 4 to 7) in the white matter mask does not reveal a statistically significant difference between the MWF maps from the single-slice and multi-slice acquisitions (p = 0.879).

Finally, the MWI maps at 3T and 7T with the default setting (i.e., full gradient pairing, navigator correction, no flow saturation, and  $B_0$  field inhomogeneity correction) are displayed in Fig. 7. The results show high quality MWF and frequency shift maps at both field strengths. A few regions of non-white matter, such as globus pallidus (at 7T), vessels, skull, and falx cerebri, reveal unexpectedly high MWF and the regions close to air/tissue boundaries also show artifacts (e.g., the frontal lobe in the bottom slice of Fig. 7b).

The ROI measurements of the MWF and frequency shift values are summarized in Table 2. The 3T results report a MWF range similar to those in the previous works (see Discussion) (Alonso-Ortiz et al., 2018; H. Lee et al., 2017; Prasloski et al., 2012). The frequency shift results suggest that fibers perpendicular to the B<sub>0</sub> field have large positive frequency shifts (splenium:  $9.5 \pm 1.0$  Hz, and genu:  $11.0 \pm 1.1$  Hz) whereas fibers parallel to the B<sub>0</sub> field reveal a frequency shift close to zero  $(1.3 \pm 2.4$  Hz in PLIC). These results are in agreement with the previous works (Sati et al., 2013; Wharton and Bowtell, 2012). Compared to the 3T results, the 7T MWI demonstrates increased MWF and frequency shift across the brain (Fig. 7b and d). When the ROI values are plotted for 3T and 7T (Fig. 7e and f), both MWF and frequency shift show strong correlations



Fig. 7. The MWF and frequency shift maps at 3T (a, c) and 7T (b, d). The correlations between 3T and 7T (e, f) demonstrate strong correlations (MWF:  $R^2 = 0.88$ ; frequency shift:  $R^2 = 0.96$ ). The error bars denote the inter-subject standard deviation.

### NeuroImage xxx (xxxx) xxx

### Table 2

The summary of the MWF and frequency shift values (mean  $\pm$  standard deviation) in the five ROIs at 3T and 7T.

		forceps major	forceps minor	splenium	genu	PLIC
myelin water fraction (%)	3T 7T	$\begin{array}{c} 13.0 \pm 1.3 \\ 13.4 \ \pm 3.6 \end{array}$	$\begin{array}{l} 9.9 \pm 2.0 \\ 11.6 \ \pm 1.2 \end{array}$	$\begin{array}{c} 16.4 \pm 0.3 \\ 20.9 \ \pm 1.5 \end{array}$	$\begin{array}{c} 13.5 \ \pm 2.3 \\ 17.5 \ \pm 1.7 \end{array}$	$\begin{array}{c} 9.5 \ \pm \ 0.6 \\ 11.3 \ \pm \ 1.6 \end{array}$
frequency shift (Hz)	3T 7T	$\begin{array}{c} 6.7 \ \pm 1.7 \\ 15.1 \ \pm 5.7 \end{array}$	$\begin{array}{c} 4.5 \ \pm 1.7 \\ 14.0 \ \pm 3.3 \end{array}$	$\begin{array}{c} 9.5 \ \pm 1.0 \\ 23.0 \ \pm 1.0 \end{array}$	$\begin{array}{c} 11.0 \ \pm 1.1 \\ 25.1 \ \pm 4.6 \end{array}$	$\begin{array}{c} 1.3 \ \pm 2.4 \\ 2.1 \ \pm 6.5 \end{array}$

(MWF: slope = 1.2,  $R^2$  = 0.88, and p < 0.001; frequency shift: slope = 2.4,  $R^2$  = 0.96, and p < 0.001).

Fig. 8 illustrates the 1.5 mm isotropic resolution MWF maps at 7T, revealing high quality images.

### 4. Discussion and conclusion

In this study, we developed a new 2D GRE-MWI sequence and optimized it by testing the effects of eddy currents, physiological noises, flip angles, MT and  $B_0$  field inhomogeneity. This new approach generated high quality myelin water images at 3T and 7T. In particular, the 7T results demonstrated the feasibility of acquiring high resolution (1.5 mm isotropic resolution) MWI at the ultra-high field.

One important advantage of 2D MWI is the flip-angle-insensitive MWF from the use of a long TR, as demonstrated in Fig. 5. The long TR provides sufficient relaxations for all water compartments and may also induce substantial compartmental water exchange (Harkins et al., 2012; Kalantari et al., 2011; Sati et al., 2013). As a result, 2D GRE-MWI with a long TR becomes insensitive to the flip angle and B<sub>1</sub> field inhomogeneity and, therefore, can be a robust approach for quantitative MWI. On the other hand, when a short TR is used as in 3D GRE-MWI, the myelin water signal with short T<sub>1</sub> recovers more rapidly than the axonal/extracellular water signals with long T<sub>1</sub>, introducing an overestimation of the MWF (Fig. 5a-c). This overestimation also suggests sensitivity to B<sub>1</sub> inhomogeneity, hampering reliable measurement of the MWF. Further investigation is necessary to determine minimum TR and corresponding flip angle that prevent the MWF overestimation.

In this work, the evaluation of the flow effects demonstrates that flow signals are largely confined to vessels in 2D GRE-MWI (Fig. 4). This allows us to omit the flow saturation module in our sequence, increasing the data acquisition efficiency by 33%. The result is in contrast to the 3D GRE-MWI results (Nam et al., 2015a), which reported substantial inflow artifacts when the flow saturation was not applied (see Fig. 2 in Nam et al., 2015a). The difference between 2D and 3D may be explained by the size of the tissue signal, which is comparable to the inflow signal in a

long TR but is smaller in a short TR.

Our results demonstrate that the MT effects from the multi-slice acquisition do not affect the myelin water quantification despite the differential impacts of the MT effects among the water compartments (Vavasour et al., 2000). This can be explained by the water exchange between the water compartments during the long TR, as suggested in the previous study (Sati et al., 2013).

The new sequence requires twice the scan time of a conventional GRE sequence due to the use of the gradient pairing. This may seem to be a disadvantage of the proposed method. However, considering the low SNR of myelin water images due to the small fraction of the myelin water signal ( $\sim$ 10%), the signal averaging during the gradient pairing helps us to gain SNR and improve image quality. If the scan time needs to be reduced, one may apply a parallel imaging method.

Recently, an MWI study has suggested the use of a linear phase error compensation method for the bipolar readout scheme, reducing phase errors along the readout direction (H. Lee et al., 2017). However, remaining phase errors from an anisotropic gradient delay (Alecci and Jezzard, 2002; Reeder et al., 1999) or high order eddy currents (Yu et al., 2010), and magnitude modulations from a non-ideal receiver frequency response (Delakis et al., 2005) may introduce artifacts in GRE-MWI. In case of 2D GRE-MWI, the large slice selection rephasing gradient induces substantial errors in MWI, which cannot be corrected using the conventional linear phase error compensation method. On the other hand, the gradient pairing has shown robustness to the remaining errors (Soliman et al., 2016; Yu et al., 2010).

In our work, the  $B_0$  field inhomogeneity correction compensated for the linear field inhomogeneity along the through-plane. Further improvement may be achieved by a method that corrects for both in- and through-plane field inhomogeneity (Yablonskiy et al., 2013).

The comparison of our 3T MWF values with those from the previous studies is summarized in Supplementary Information (Table S1) (Alonso-Ortiz et al., 2018; H. Lee et al., 2017; Prasloski et al., 2012). The MWF values reported by Prasloski et al. and Alonso-Ortiz et al. have a MWF range similar to that in our study in all ROIs except for PLIC. The



Fig. 8. High resolution (1.5 mm isotropic resolution) MWF maps at 7T, displaying eight slices out of 64 slices. The method covers a large field of view ( $288 \times 288 \times 96 \text{ mm}^3$ ) in 12 min 50 s.

### H.-G. Shin et al.

difference may originate from the choice of the ROIs (PLIC vs. internal capsule) and the overestimated MWF in the conventional MWI (Russell-Schulz et al., 2013). In our study, PLIC was chosen instead of the internal capsule to have a uniform fiber orientation within the ROI. When compared to our study, the 3D GRE-MWI results with a TR of 60 ms demonstrate overall larger MWF values (H. Lee et al., 2017), suggesting the flip angle effect.

Our study reports that the 7T MWF values are larger than those of 3T. This may be explained partially by the increased  $T_1$  of axonal/extracellular water at 7T, which may have led to reduced magnetization recovery and generated an overestimated MWF. When assuming the parameters used in this study (TR: 2000 ms; flip angle: 85° at 3T and 80° at 7T; myelin water  $T_1$ : short enough for full relaxations; axonal/extracellular water  $T_1$ : 840 ms at 3T and 1150 ms at 7T (Wright et al., 2008)) and no water exchange, the increased  $T_1$  can explain up to 6.1% of the MWF overestimation. This is not sufficient to explain our observation. Thus, further exploration is necessary to understand the higher MWF values at 7T. Interestingly, the previous studies also reported higher MWF values at a higher field strength system (1.5T vs. 3T) (Kolind et al., 2009; J. Oh et al., 2006). In contrast to the MWF, the increased frequency shift at 7T by 2.4 times reflects the field strength ratio (7/3 = 2.33), which is in agreement with the theory (Wharton and Bowtell, 2012).

In both 3T and 7T, the hyper-intense MWF values are observed in non-white matter regions, including large vessels, skull, falx cerebri, and deep grey matter. These errors may originate from the miscategorization of fast decaying signals from the origins such as susceptibility effects or short  $T_2^*$  of fat into the myelin water. In the previous studies using the GRE-MWI (Alonso-Ortiz et al., 2016; H. Lee et al., 2017) and the conventional MWI (Prasloski et al., 2012), similar instances of the miscategorization have been observed. Nevertheless, these artifacts are highly localized and can be distinguished from white matter.

The experiments in this study on the confounding factors were conducted at 3T, and then the optimized sequence and processing were applied at 7T. While further research may be necessary to confirm the effects of the confounding factors at 7T, the high image quality of the 7T MWF maps suggest that our approach is still valid at 7T.

In MWI, alternative approaches such as T<sub>2</sub>-prepared imaging (Nguyen et al., 2012), multicomponent driven-equilibrium single-pulse observation of T<sub>1</sub> and T<sub>2</sub> (mcDESPOT) (Deoni et al., 2008), direct visualization of short transverse relaxation time component (ViSTa) (S.-H. Oh et al., 2013), and longitudinal relaxographic imaging (Labadie et al., 2014) exist. Applying these methods at a high field strength (>7T) can be challenging due to the high SAR and the B<sub>1</sub> field inhomogeneity. On the other hand, as demonstrated in this work, GRE-MWI is a good option for high field MWI.

In conclusion, we proposed an efficient and reliable approach to measure the myelin water fraction using GRE-MWI. One of the advantages of the method, a low SAR, enables us to acquire *in-vivo* human brain myelin water images at an ultra-high field strength. Our method may have potential in scientific and clinical applications by reliably quantifying myelin changes *in vivo*.

### Acknowledgment

This work was supported in part by National Research Foundation of Korea grant funded by the Korea government (MSIP) (NRF-2017R1C1B2007258), Creative-Pioneering Researchers Program through Seoul National University, Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) from Japan Agency for Medical Research and Development (AMRD), and the Grants-in-Aid for Scientific Research (KAKENHI JP16H03305) from Japan Society for the Promotion of Science.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2018.11.040.

#### References

- Alecci, M., Jezzard, P., 2002. Characterization and reduction of gradient-induced eddy currents in the RF shield of a TEM resonator. Magn. Reson. Med. 48, 404–407. https://doi.org/10.1002/mrm.10226.
- Alonso-Ortiz, E., Levesque, I.R., Paquin, R., Pike, G.B., 2016. Field inhomogeneity correction for gradient echo myelin water fraction imaging. Magn. Reson. Med. 78, 49–57. https://doi.org/10.1002/mrm.26334.
- Alonso-Ortiz, E., Levesque, I.R., Pike, G.B., 2018. Multi-gradient-echo myelin water fraction imaging: comparison to the multi-echo-spin-echo technique. Magn. Reson. Med. 79, 1439–1446. https://doi.org/10.1002/mrm.26809.
- Chang, Y., Bae, S.J., Lee, Y.J., Hwang, M.J., Lee, S.H., Lee, J., Lee, S.K., Woo, S., 2007. Incidental magnetization transfer effects in multislice brain MRI at 3.0T. J. Magn. Reson. Imag. 25, 862–865. https://doi.org/10.1002/jmri.20867.
- Compston, A., Coles, A., 2008. Multiple sclerosis. Lancet 372, 1502–1517. https:// doi.org/10.1016/S0140-6736(08)61620-7.
- Delakis, I., Petala, K., De Wilde, J.P., 2005. MRI receiver frequency response as a contributor to Nyquist ghosting in echo planar imaging. J. Magn. Reson. Imag. 22, 324–328. https://doi.org/10.1002/jmri.20365.
- Deoni, S.C.L., Rutt, B.K., Arun, T., Pierpaoli, C., Jones, D.K., 2008. Gleaning multicomponent T<sub>1</sub> and T<sub>2</sub> information from steady-state imaging data. Magn. Reson. Med. 60, 1372–1387. https://doi.org/10.1002/mrm.21704.
- Du, Y.P., Chu, R., Hwang, D., Brown, M.S., Kleinschmidt DeMasters, B.K., Singel, D., Simon, J.H., 2007. Fast multislice mapping of the myelin water fraction using multicompartment analysis of T<sub>2</sub>\* decay at 3T: a preliminary postmortem study. Magn. Reson. Med. 58, 865–870. https://doi.org/10.1002/mrm.21409.
- Fernández-Seara, M.A., Wehrli, F.W., 2000. Postprocessing technique to correct for background gradients in image-based R<sub>2</sub>\* measurements. Magn. Reson. Med. 44, 358–366.
- Harkins, K.D., Dula, A.N., Does, M.D., 2012. Effect of intercompartmental water exchange on the apparent myelin water fraction in multiexponential T<sub>2</sub> measurements of rat spinal cord. Magn. Reson. Med. 67, 793–800. https://doi.org/10.1002/mrm.23053.
- Hildebrand, C., Remahl, S., Persson, H., Bjartmar, C., 1993. Myelinated nerve fibres in the CNS. Prog. Neurobiol. 40, 319–384.
- Kalantari, S., Laule, C., Bjarnason, T.A., Vavasour, I.M., MacKay, A.L., 2011. Insight into in vivo magnetization exchange in human white matter regions. Magn. Reson. Med. 66, 1142–1151. https://doi.org/10.1002/mrm.22873.
- Kolind, S.H., M\u00e4dler, B., Fischer, S., Li, D.K.B., MacKay, A.L., 2009. Myelin water imaging: implementation and development at 3.0T and comparison to 1.5T measurements. Magn. Reson. Med. 62, 106–115. https://doi.org/10.1002/mrm.21966.
- Labadie, C., Lee, J.H., Rooney, W.D., Jarchow, S., Frécon, M.A., Springer, C.S., Möller, H.E., 2014. Myelin water mapping by spatially regularized longitudinal relaxographic imaging at high magnetic fields. Magn. Reson. Med. 71, 375–387. https://doi.org/10.1002/mrm.24670.
- Laule, C., Kozlowski, P., Leung, E., Li, D.K.B., MacKay, A.L., Moore, G.R.W., 2008. Myelin water imaging of multiple sclerosis at 7 T: Correlations with histopathology. Neuroimage 40, 1575–1580. https://doi.org/10.1016/j.neuroimage.2007.12.008.
- Laule, C., Leung, E., Lis, D.K.B., Traboulsee, A.L., Paty, D.W., MacKay, A.L., Moore, G.R.W., 2006. Myelin water imaging in multiple sclerosis: quantitative correlations with histopathology. Mult. Scler. 12, 747–753. https://doi.org/10.1177/ 1352458506070928.
- Laule, C., Vavasour, I.M., Moore, G.R.W., Oger, J., Li, D.K.B., Paty, D.W., MacKay, A.L., 2004. Water content and myelin water fraction in multiple sclerosis. J. Neurol. 251, 284–293. https://doi.org/10.1007/s00415-004-0306-6.
- Laule, C., Yung, A., Pavolva, V., Bohnet, B., Kozlowski, P., Hashimoto, S.A., Yip, S., Li, D.K., Moore, G.W., 2016. High-resolution myelin water imaging in post-mortem multiple sclerosis spinal cord: a case report. Mult. Scler. 22, 1485–1489. https:// doi.org/10.1177/1352458515624559.
- Lee, D., Lee, J., Lee, J., Nam, Y., 2018. Single-scan z-shim method for reducing susceptibility artifacts in gradient echo myelin water imaging. Magn. Reson. Med. 80, 1101–1109. https://doi.org/10.1002/mrm.27127.
- Lee, H., Nam, Y., Lee, H.-J., Hsu, J.-J., Henry, R.G., Kim, D.-H., 2017. Improved threedimensional multi-echo gradient echo based myelin water fraction mapping with phase related artifact correction. Neuroimage 169, 1–10. https://doi.org/10.1016/ j.neuroimage.2017.11.058.
- Mackay, A., Whittall, K., Adler, J., Li, D., Paty, D., Graeb, D., 1994. In vivo visualization of myelin water in brain by magnetic resonance. Magn. Reson. Med. 31, 673–677. https://doi.org/10.1002/mrm.1910310614.
- McKenzie, I.A., Ohayon, D., Li, H., de Faria, J.P., Emery, Ben, Tohyama, K., Richardson, W.D., 2014. Motor skill learning requires active central myelination. Science 346, 318–322. https://doi.org/10.1126/science.1254960.
- Nam, Y., Kim, D.-H., Lee, J., 2015a. Physiological noise compensation in gradient-echo myelin water imaging. Neuroimage 120, 345–349. https://doi.org/10.1016/ j.neuroimage.2015.07.014.
- Nam, Y., Lee, J., Hwang, D., Kim, D.-H., 2015b. Improved estimation of myelin water fraction using complex model fitting. Neuroimage 116, 214–221. https://doi.org/ 10.1016/j.neuroimage.2015.03.081.
- Nave, K.-A., 2010. Myelination and support of axonal integrity by glia. Nature 468, 244–252. https://doi.org/10.1038/nature09614.
- Nguyen, T.D., Wisnieff, C., Cooper, M.A., Kumar, D., Raj, A., Spincemaille, P., Wang, Y., Vartanian, T., Gauthier, S.A., 2012. T<sub>2</sub> prep three-dimensional spiral imaging with efficient whole brain coverage for myelin water quantification at 1.5 tesla. Magn. Reson. Med. 67, 614–621. https://doi.org/10.1002/mrm.24128.
- Oh, J., Han, E.T., Pelletier, D., Nelson, S.J., 2006. Measurement of in vivo multicomponent T<sub>2</sub> relaxation times for brain tissue using multi-slice T<sub>2</sub> prep at 1.5 and 3 T. Magn. Reson. Imag. 24, 33–43. https://doi.org/10.1016/j.mri.2005.10.016.

### H.-G. Shin et al.

### NeuroImage xxx (xxxx) xxx

- Oh, S.-H., Bilello, M., Schindler, M., Markowitz, C.E., Detre, J.A., Lee, J., 2013. Direct visualization of short transverse relaxation time component (ViSTa). Neuroimage 83, 485–492. https://doi.org/10.1016/j.neuroimage.2013.06.047.
- Prasloski, T., Rauscher, A., MacKay, A.L., Hodgson, M., Vavasour, I.M., Laule, C., Mädler, B., 2012. Rapid whole cerebrum myelin water imaging using a 3D GRASE sequence. Neuroimage 63, 533–539. https://doi.org/10.1016/ j.neuroimage.2012.06.064.
- Reeder, S.B., Atalar, E., Faranesh, A.Z., McVeigh, E.R., 1999. Referenceless interleaved echo-planar imaging. Magn. Reson. Med. 41, 87–94. https://doi.org/10.1002/(SICI) 1522-2594(199901)41:1<87::AID-MRM13>3.0.CO;2-X.
- Robinson, S., Grabner, G., Witoszynskyj, S., Trattnig, S., 2011. Combining phase images from multi-channel RF coils using 3D phase offset maps derived from a dual-echo scan. Magn. Reson. Med. 65, 1638–1648. https://doi.org/10.1002/mrm.22753.
- Russell-Schulz, B., Laule, C., Li, D.K.B., MacKay, A.L., 2013. What causes the hyperintense T<sub>2</sub>-weighting and increased short T<sub>2</sub> signal in the corticospinal tract? Magn. Reson. Imag. 31, 329–335. https://doi.org/10.1016/j.mri.2012.07.003.
- Sati, P., van Gelderen, P., Silva, A.C., Reich, D.S., Merkle, H., de Zwart, J.A., Duyn, J.H., 2013. Micro-compartment specific T<sub>2</sub>\* relaxation in the brain. Neuroimage 77, 268–278. https://doi.org/10.1016/j.neuroimage.2013.03.005.
- Soliman, A.S., Wiens, C.N., Wade, T.P., McKenzie, C.A., 2016. Fat quantification using an interleaved bipolar acquisition. Magn. Reson. Med. 75, 2000–2008. https://doi.org/ 10.1002/mrm.25807.
- van Gelderen, P., de Zwart, J.A., Lee, J., Sati, P., Reich, D.S., Duyn, J.H., 2011. Nonexponential T<sub>2</sub>\* decay in white matter. Magn. Reson. Med. 67, 110–117. https:// doi.org/10.1002/mrm.22990.

- Vavasour, I.M., Whittall, K.P., Li, D.K.B., MacKay, A.L., 2000. Different magnetization transfer effects exhibited by the short and long T<sub>2</sub> components in human brain. Magn. Reson. Med. 44, 860–866. https://doi.org/10.1002/1522-2594(200012)44:6<860:: AID-MRM6>3.0.CO;2-C.
- Wang, Y., Wu, C., Caprariello, A.V., Somoza, E., Zhu, W., Wang, C., Miller, R.H., 2009. In vivo quantification of myelin changes in the vertebrate nervous system. J. Neurosci. 29, 14663–14669. https://doi.org/10.1523/JNEUROSCI.4082-08.2009.
- Webb, S., Munro, C.A., Midha, R., Stanisz, G.J., 2003. Is multicomponent T2 a good measure of myelin content in peripheral nerve? Magn. Reson. Med. 49, 638–645. https://doi.org/10.1002/mrm.10411.
- Wharton, S., Bowtell, R., 2012. Fiber orientation-dependent white matter contrast in gradient echo MRI. Proc. Natl. Acad. Sci. U.S.A. 109, 18559–18564. https://doi.org/ 10.1073/pnas.1211075109.
- Wright, P.J., Mougin, O.E., Totman, J.J., Peters, A.M., Brookes, M.J., Coxon, R., Morris, P.E., Clemence, M., Francis, S.T., Bowtell, R.W., Gowland, P.A., 2008. Water proton T<sub>1</sub> measurements in brain tissue at 7, 3, and 1.5 T using IR-EPI, IR-TSE, and MPRAGE: results and optimization. Magma 21, 121–130. https://doi.org/10.1007/ s10334-008-0104-8.
- Yablonskiy, D.A., Sukstanskii, A.L., Luo, J., Wang, X., 2013. Voxel spread function method for correction of magnetic field inhomogeneity effects in quantitative gradient-echobased MRI. Magn. Reson. Med. 70, 1283–1292. https://doi.org/10.1002/ mrm.24585.
- Yu, H., Shimakawa, A., McKenzie, C.A., Lu, W., Reeder, S.B., Hinks, R.S., Brittain, J.H., 2010. Phase and amplitude correction for multi-echo water-fat separation with bipolar acquisitions. J. Magn. Reson. Imag. 31, 1264–1271. https://doi.org/10.1002/ jmri.22111.