Double inversion recovery imaging of the brain: deriving the most relevant sequence through real images

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Abstract We propose a practical method for setting the optimal inversion times (TI) for double inversion recovery (DIR) sequences. Our method used the measurement of signal intensity (SI) from real images to set the optimal TI for white-matter (WM) and gray-matter (GM)-attenuated inversion recovery (WAIR and GAIR, respectively) images. 3D-DIR images of healthy volunteers were obtained on 1.5- and 3.0-T magnetic resonance (MR) scanners and the SIs of GM, WM, and cerebrospinal fluid (CSF) were evaluated on real images. We found TI2 at which the SI of WM or GM was null. Then, we found T1 = T1 + T2 at which the SI of CSF was null. We defined the two TIs as optimal Tls. We assessed the utility of these Tls with additional volunteers and patients, and similar images were obtained with the determined Tls. Optimal Tls for DIR images could be efficiently determined using this method.

Keywords Magnetic resonance imaging · Inversion recovery · Double inversion recovery · White-matter-attenuated inversion recovery (WAIR) · Gray-matter-attenuated inversion recovery (GAIR)

1 Introduction

In inversion recovery (IR) sequences in magnetic resonance imaging (MRI), the signal intensity of a specific tissue is suppressed to null by one inversion pulse. For instance, the fluid-attenuated inversion recovery (FLAIR) sequence, used for brain imaging, suppresses the signal intensity of the cerebrospinal fluid (CSF) [1, 2], while the short-inversion time (TI) inversion recovery (STIR) sequence suppresses the signal of fat tissue [3]. Recent developments in technology enable double inversion recovery (DIR) sequences, in which two different inversion pulses are applied and a signal is obtained with the fast spin echo (FSE) method, thereby enabling the signals of two different tissues with two greatly different T1 relaxation times to be simultaneously suppressed. Some investigators have reported the application of DIR sequences in the diagnoses of multiple sclerosis (MS) [4–8], brain tumors [9], and brain infarctions [10]. In the diagnostic criteria for MS, the report by Barkhof et al. is especially well known [11]. It was reported that “the presence or absence of subcortical lesions” is one of the diagnostic criteria for the spatial dissemination of MS. It was reported that DIR sequences enabled increased intracortical lesion detection in MS, as well as improved distinction between juxtacortical and white-matter–gray-matter lesions [4].

The DIR sequence was first reported as a method to selectively image white matter (WM) or gray matter (GM) [12]. According to this report, the longitudinal magnetization (MA) immediately prior to the imaging pulse in a spin echo DIR sequence is as follows:

\[ M_A = M_0 (1 - 2E_2 + 2E_1E_2 - E_x(2E_1^{-1} - 1)), \]  

where
Here, $M_0$ is the signal intensity of the longitudinal magnetization in the thermal equilibrium state, $T_1$ is the tissue $T_1$ value, $T_1$ is the inversion time (TI) from the first inversion recovery pulse to the second inversion recovery pulse, and $T_1$ is the TI from the second inversion recovery pulse to the 90° pulse. TR is the repetition time, TE is the echo time, and $\tau$ is TE/2. Equation (1) shows that the signal intensity $M_A$ changes according to the $T_1$ value of tissue, two inversion times ($T_{11}$, $T_{12}$), TR, and TE. The authors concluded that the inversion times ($T_{11}$, $T_{12}$), optimal for selective white-matter or gray-matter images could be defined using this theoretical formula [9].

The CSF-suppressed and white-matter-suppressed images were called “white-matter-attenuated IR (WAIR)” images, while the CSF-suppressed and gray-matter-suppressed images were called “gray-matter-attenuated IR (GAIR)” images for DIR. In previous reports on the DIR method, TIs were calculated from the theoretical formula [13, 14] and the TI optimized by the vendor for human brain imaging was used [10]. Initially, we scanned using the TI calculated from the suggested theoretical formula; however, this did not satisfactorily suppress the two tissues.

Figure 1 shows the schematic diagrams of the $T_1$ recovery curve for WAIR parameters and two types of WAIR images. In appropriate TIs, the signals of WM and CSF are null at $T_{11}+T_{12}$ (i.e., $T_{11}+T_{12}$) after two inversion pulses. IR sequences use an inversion pulse, thereby producing a negative signal, but IR images are usually displayed as magnitude images. On magnitude images, the signal intensity is represented as an absolute value on a

\[
E_1 = \exp(-T_{11}/T_1) \\
E_2 = \exp(-T_{12}/T_1) \\
E_c = \exp(-TR/T_1) \\
E_\tau = \exp(-\tau/T_1) \quad \text{and} \quad \tau = TE/2.
\]
gray scale, such that a null signal is black, and a negative signal is brighter than the null signal (Fig. 1a, b). Therefore, the magnitude image cannot show a negative signal. In real images, a negative signal appears darker than a null signal. Figure 1c, d depicts both positive and negative signals accurately and intuitively. Therefore, we measured the signal intensities on real images, plotted the values on a graph, and observed the extent of the longitudinal recovery. We propose this method using real images as a practical method for setting optimal inversion times (TI1, TI2) of WAIR and GAIR images.

2 Materials and methods

2.1 Equipment and subjects

We used a 1.5-T MR scanner (Achieva 1.5T, Philips Medical Systems, Best, The Netherlands) with an 8-channel receiver head coil and a 3.0-T MR scanner (Ingenia 3.0T, Philips Medical Systems, Best, The Netherlands) with a dS-HeadSpine receiver head coil. Measurements of signal intensity were made on a workstation (ViewForum R 6.1. Philips Medical Systems, Best, The Netherlands).

We performed DIR imaging on 11 healthy volunteers (3 men and 2 women: age 45.6 ± 6.4 years, range 38–53 years at 1.5 T; 2 men and 4 women: age 34.6 ± 9.2 years, range 25–39 years at 3.0 T) and 34 patients (3 men and 4 women: age 61.8 ± 11.8 years, range 44–76 years at 1.5 T; and 13 men and 16 women: age 61.7 ± 21.1 years, range 12–85 years at 3.0 T). This study was approved by our institutional review board and all volunteers and all patients provided written informed consent prior to their participation in this study.

2.2 MR imaging sequences

We acquired sagittal images using a 3D-turbo spin echo (TSE) DIR sequence with volume-isotropic TSE acquisition (VISTA). We chose to acquire images in 3D because of the clinical need to evaluate high-resolution images in multiple directions. We used TR (5500 ms) based on the report of Li et al. [10].

The scanning parameters on the 1.5 T scanner were as follows: TR 5500 ms, effective TE 169 ms, field of view (FOV) 250 × 168 × 250 mm (anterior to posterior: AP × right to left: RL × foot to head: FH), matrix 208 × 208 (phase × frequency direction), reconstruction matrix 224 × 224 (phase × frequency direction), slice thickness 2.4 mm (1.2-mm zero-fill interpolation), echo spacing 3.9 ms, and echo train length (ETL) 80, refocusing flip angle 60°. To suppress artifacts caused by blood and CSF flow, flow compensation on the “sensitized” setting was used. This is the setting recommended by the manufacturer. The k-space order was “Linear-Radial” (sequential-radial). The total acquisition time was 4 m and 40 s.

The scanning parameters on the 3.0-T scanner were as follows: TR 5500 ms, effective TE 286 ms, FOV 221 × 195 × 250 mm (AP × RL × FH): matrix 208 × 208 (phase × frequency direction), reconstruction matrix 256 × 256 (phase × frequency direction), slice thickness 1.2 mm (0.6-mm zero-fill interpolation), echo spacing 3.0 ms, and ETL 173. The refocusing flip angle was set to “brainview-DIR,” which is the variable flip angle (VRFA) recommended by the manufacturer for the brain DIR sequence. Using VRFA optimized for DIR, even if effective TE was extended by ETL increase, high contrast and blurring reduction were possible, and the acquisition time was shortened [15]. We performed flow compensation in the “sensitized” setting. The k-space order was “Linear-Y” (sequential–sequential). The acquisition time was 5 m 52 s. Axial images were reconstructed for evaluation.

2.3 Experimental TI settings

We estimated the TIs needed to image a 41-year-old healthy male volunteer. To determine the TIs that would nullify the signal of CSF and WM or CSF and GM to obtain appropriate WAIR and GAIR images, we used real images for the measurement of signal intensity instead of the commonly used magnitude images (Fig. 1).

First, we performed imaging using the TIs derived by the theoretical Eqs. (1)–(5) [12]. Incidentally, there are two types of TI setting parameters in the equipment used: “IR delay” and “dual delay.” “IR delay” is the total time of TI1 and TI2, and “dual delay” is TI2. Since these two parameters varied, the total time of TI1 and TI2 was expressed as TI1+2 in this study. When the TR = 5500 ms and TE = 169 ms, the T1 values of WM, GM, and CSF were 580, 980, and 4300 ms, respectively, at 1.5 T [13]. The theoretical TIs were derived as TI1+2 = 2455 ms, TI1 = 2098 ms, and TI2 = 357 ms for WAIR, and TI1+2 = 2782 ms, TI1 = 2227 ms, and TI2 = 555 ms for GAIR. When TR = 5500 ms and TE = 286 ms, the T1 values of WM, GM, and CSF were 830, 1250, and 4300 ms, respectively, at 3.0 T [13]. The theoretical TIs were derived as TI1+2 = 2681 ms, TI1 = 2168 ms, and TI2 = 513 ms for WAIR and TI1+2 = 2932 ms, TI1 = 2269 ms, and TI2 = 663 ms for GAIR.

Furthermore, using the theoretically derived TIs as in [12], we performed multiple scans while gradually changing the TIs and measured the signal intensities of each tissue on both 1.5 and 3.0 T images. For WAIR images, we varied TI1+2 from 2400 to 2650 ms at 50-ms intervals and TI2 from 380 to 440 ms at 20-ms intervals on...
the 1.5-T scanner (420–480 ms on the 3.0-T scanner). For GAIR images, we varied TI₁ from 2750 to 3000 ms at 50-ms intervals, and TI₂ from 550 ms to 700 ms at 50-ms intervals on the 1.5-T scanner (650–800 ms on the 3.0-T scanner).

2.4 Measurement of signal intensity and TI optimization

Signal intensity was measured on axial images reconstructed from sagittal images at the level of the bodies of the lateral ventricles using a workstation. Regions of interest (ROIs) in the CSF, GM, and WM were selected elliptically at the same position and size on each real image by one author. We chose the ROIs considering field inhomogeneity and the effect of the surface coil of non-uniformity of signal intensity in the area imaged. The ROIs were carefully selected so as to not include other tissue. The signal intensity of the CSF was measured in two locations (in the subarachnoid space and in the lateral ventricle, size of ROI: about 30 mm²), and the two values were averaged. GM ROIs were set in the frontal, temporal, and parietal lobes (size of ROI: about 20 mm²), and the three values were averaged. A WM ROI was selected to be as large as possible without containing tissues other than WM (size of ROI: about 400 mm²). We plotted the signal intensities on a graph, and calculated the TIs at which the signal intensities for CSF and WM were null for WAIR images and CSF and GM were null for GAIR images. We determined TI₂ at which WM was null and TI₁ = TI₂ at which CSF was null. We defined these TIs as “measured TIs” (TI₁ = 2580 ms, TI₂ = 420 ms). (TI inversion time, SI signal intensity, CSF cerebrospinal fluid, WM white matter, GM gray matter)

2.5 Comparison among volunteers

We performed the initial optimization studies on a single volunteer. To evaluate the reliability of the TIs obtained from the above study, we assessed the utility of these TIs on additional volunteers. The DIR images of additional healthy volunteers were obtained using the theoretical and measured TIs. The signal intensities of CSF and WM on WAIR and CSF and GM on GAIR were evaluated.
2.6 Comparison between volunteers and patients

The clinical utility of these TIs was evaluated on patients. We obtained WAIR images from patients using the measured TIs and the signal intensities of the CSF were compared with that of the healthy volunteers. These patients underwent brain MRI for various clinical reasons, although there were no mass lesions or large vascular diseases on conventional T1-weighted, T2-weighted, and FLAIR images. Five patients (1 man and 4 women: age 61.8 ± 11.8 years, range 44–76 years) were imaged at 1.5 T and 27 patients (12 men and 15 women: age 62.6 ± 23.0 years, range 12–85 years) were imaged at 3.0 T. However, only the CSF signal intensity was compared, because these patients may have abnormal signal intensities in the brain parenchyma. In addition, since GAIR was not routinely used in clinical practice, we did not consider GAIR this study.

Fig. 3 The relationships between inversion time $T1_{1+2}$ and SI for each $T2$ for gray-matter-attenuated IR (GAIR) images acquired on the 1.5-T scanner. a $T2$ 550 ms, b $T2$ 600 ms, c $T2$ 650 ms, d $T2$ 700 ms. The SI was measured on the real images and we plotted the values on a graph. We determined $T2$ at which GM was null and $T1_{1+2}$ (= $T1 + T2$) at which CSF was null. We defined these TIs as “measured TIs” ($T1_{1+2}$ 2970 ms, $T2$ 670 ms). ($T1$ inversion time, $SI$ signal intensity, $CSF$ cerebrospinal fluid, WM white matter, GM gray matter)

2.7 Clinical DIR imaging

Using the DIR sequences with the parameters determined by the method described in this study, we imaged various patients with disorders for which DIR has been suggested to be useful.

2.8 Statistical analyses

The data were expressed as mean ± SD and the paired $t$ test and Mann–Whitney $U$ test were used for statistical analyses. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). It is a modified version of R commander designed to add statistical functions frequently used in biostatistics [16].
3 Results

3.1 Measurement of signal intensity and TI optimization

The signal intensity changes in WAIR and GAIR images acquired on the 1.5-T MR scanner are shown in Fig. 2 [TI2 were: (a) 380 ms, (b) 400 ms, (c) 420 ms, and (d) 440 ms] and Fig. 3 [TI2 were: (a) 550 ms, (b) 600 ms, (c) 650 ms, and (d) 700 ms]. Signal intensities of WM and GM were fairly constant, while CSF signal intensity decreased when TI1 were increased. The signal intensity changes in WAIR and GAIR images were acquired on the 3.0-T MR scanner and showed similar trends.

From these measurements, we determined TI2 at which WM or GM were null and TI1 TI2 (=TI1 + TI2) at which CSF was null. We defined these TIs as “measured TIs.” The measured TIs were found to be as follows: TI1 +2 = 2580 ms, TI1 = 2160 ms, and TI2 = 420 ms at 1.5 T; TI1 +2 = 2550 ms, TI1 = 2070 ms, and TI2 = 480 ms at 3.0 T for WAIR images; TI1 +2 = 2970 ms, TI1 = 2300 ms, and TI2 = 670 ms at 1.5 T; and TI1 +2 = 3100 ms, TI1 = 2300 ms, and TI2 = 800 ms at 3.0 T for GAIR.

When the healthy volunteers were scanned using the theoretical and measured TIs, the measured TIs showed better suppression of both target tissues (Figs. 4, 5).

3.2 Comparison among volunteers

On WAIR images at 1.5 T (Fig. 6a, b), the signal intensity of the CSF was found to be $-0.36 \pm 4.08$ using the measured TIs and $106.90 \pm 15.98$ using the theoretical TIs (paired t test, $p < 0.05$) and the signal intensity of the WM was $1.14 \pm 3.82$ using the measured TIs and $-355.74 \pm 16.70$ using the theoretical TIs (paired t test, $p < 0.05$), suggesting that the signals of CSF and WM were significantly better when suppressed with the measured TIs than the theoretical TIs. On GAIR images (Fig. 6c, d), the signal intensity of the CSF was $-18.20 \pm 4.92$ using the measured TIs and $32.98 \pm 11.22$ using the theoretical TIs (paired t test, $p < 0.05$), and the signal intensity of the GM was $1.74 \pm 9.05$ using the measured TIs and $-593.0 \pm 108.13$ using the theoretical TIs (paired t test, $p < 0.05$), suggesting that the signals of GM were better suppressed with the measured TIs than the theoretical TIs.
At 3.0 T, on WAIR images (Fig. 7a, b), the signal intensity of the CSF was found to be 16.23 ± 13.12 using the measured TIs and 90.42 ± 20.04 using the theoretical TIs (paired \( t \) test, \( p < 0.05 \)) and the signal intensity of the WM was 6.05 ± 12.63 using the measured TIs and 106.72 ± 27.93 using the theoretical TIs (paired \( t \) test, \( p < 0.05 \)), suggesting that the signals of CSF and WM were significantly better suppressed with the measured TIs than the theoretical TIs. On GAIR images (Fig. 7c, d), the signal intensity of the CSF was -28.88 ± 13.50 using the measured TIs and 67.00 ± 23.75 using the theoretical TIs (paired \( t \) test, \( p < 0.05 \)), and the signal intensity of the GM was -0.68 ± 5.18 using the measured TIs and -164.65 ± 44.89 using the theoretical TIs (paired \( t \) test, \( p < 0.05 \)), suggesting that the signals of CSF and GM were better suppressed with the measured TIs than the theoretical TIs.

### 3.3 Clinical DIR imaging

We imaged clinical cases at the TIs derived by the method described in this study. Figure 9 shows images of a patient with MS [a 43-year-old woman, (a) FLAIR, (b) WAIR].

Figure 10 shows images of a patient with B-cell Lymphoma [a 56-year-old man, (a) FLAIR, (b) WAIR].

### 4 Discussion

We assessed the optimal TIs for WAIR and GAIR images using the measurement of signal intensity from images instead of the commonly used magnitude images. The use of real images is the key novelty of our practical method. The current study also suggested an efficient method to obtain the optimal TIs for DIR images. \( T_1 \) values of WM and GM were small. The signal had already recovered and was fairly constant. However, CSF has a large \( T_1 \) value, since longitudinal relaxation takes time to recover. Therefore, CSF signals were decreased with a larger \( T_{1+2} \) (Figs. 2, 3). It is efficient to first obtain the optimal \( T_2 \) at which the WM or GM signal is null. This step is an important concept in our practical method. Then, once \( T_2 \) is established, \( T_{1+2} \) can be determined by plotting the signal intensity of the CSF, \( T_{1+2} \) at which the CSF signal is null is the optimal one. However, the TR must be large enough to set these TIs.
The TIs derived from this method differed from those calculated from the theoretical equation [12]. We suspect two possible reasons: (1) other sequence parameters may also affect the results and (2) since magnetic field intensity affects the $T_1$ relaxation time, it may also affect appropriate TIs.

TSE with a VRFA has many uses, such as reducing specific absorption rate (SAR) or blurring [17]. On the 1.5-T scanner we used, the flip angle of the first pulse was 160°, and that of subsequent pulses was an input value. For this study, we set the refocusing flip angle at 60°. This was so that a large angle could create an increased flow void and the addition of signal from blood vessels [18] and a small angle would create a phase scatter owing to transverse relaxation, causing decreased tissue contrast [19]. On the 3.0-T scanner that we used, the “Brainview-DIR” input was available. This function enabled a variable flip angle (VRFA) ideal for brain DIR sequences. The refocusing flip angle may affect longitudinal recovery, although the theoretical equation considers this. Thus, attention should be paid to the influence of RFA, as the variable flip angle techniques available may vary with the MR scanner used. Using the present method, acquiring the optimal TI without considering these effects can be easy. We expect that DIR images of optimum image quality will soon be used in medical imaging.

The $T_1$ relaxation times of the intended tissue (WM and GM) may differ among patients [20, 21]. However, in the 11 volunteers we scanned, the distribution of the signal intensity using the “measured TIs” of not only CSF, but also WM and GM, scarcely recognized individual differences. Previous studies have suggested that the $T_1$ values of WM and GM are 832 ± 10 and 1331 ± 13 ms, respectively, and show small individual variations [22]. We suspected that the difference in $T_1$ relaxation times of WM and GM among individuals may not be a significant factor.
Fig. 7  Boxplots of SI at 3.0 T of 6 healthy volunteers (a CSF on WAIR, b CSF on GAIR, c WM on WAIR, and d GM on GAIR). The WAIR-CSF, WAIR-WM, GAIR-CSF, and GAIR-GM SIs obtained using the measured and theoretical TIs were significantly different (paired t test, *p < 0.05). In measured TIs, all signals were appropriate suppressed. (SI signal intensity, CSF cerebrospinal fluid, WAIR white-matter-attenuated inversion recovery, GAIR gray-matter-attenuated inversion recovery, WM white matter, GM gray matter, TI inversion time, NS not significant)

Fig. 8  Boxplots of SI of CSF on WAIR of a 5 healthy volunteers and 5 patients at 1.5 T and b 6 healthy volunteers and 27 patients at 3.0 T. No statistically significant difference in either signal intensities was detected (Mann–Whitney U test). (SI signal intensity, CSF cerebrospinal fluid, WAIR white-matter-attenuated inversion recovery, NS not significant)
However, in the relativity study with multiple healthy volunteers, there were tissues that could not be suppressed in WAIR and GAIR images using the theoretical TIs. The theoretical TIs were calculated using the $T_1$ value of the previous report [13]. Although the influence of the individual difference of the $T_1$ value is limited, we suspected that the $T_1$ value used deviates from the actual value. However, the tissue $T_1$ values in the volunteers were not measured in this study, so details are unknown; this could be investigated in future studies.

In the comparison between volunteers and patients, the signal intensity of the CSF was $-0.36 \pm 4.08$ in the healthy volunteers (the value shown in Sect. 3) and $3.3 \pm 12.2$ in the patients at 1.5 T and the signal intensity of the CSF was $16.23 \pm 13.12$ in the healthy volunteers (the value shown in Sect. 3) and $13.19 \pm 24.19$ in the patients at 3.0 T; in the distribution of CSF signal intensity using the “measured TIs,” we found no significant difference between patients and controls (Mann–Whitney $U$ test, Fig. 8). This suggests that optimized WAIR and GAIR can be applied to the imaging of all patients. Further investigation is required to answer questions such as these, particularly in individuals with diseases.

In this study, we determined the optimal TI by measuring the signal intensity of each tissue. However, we must recognize a few limitations of our approach. ROIs were manually set on the images by the authors. The cortex is a thin tissue, allowing the partial volume effect to influence the signal intensity. These effects are not considered in our study. The comparison among volunteers examined 12 volunteers and the comparison between volunteers and patients examined only WAIR images. GAIR images were not examined; this could be investigated in future studies.

For clinical cases, the WAIR image showed the cortical and subcortical lesions of MS more conspicuously than the FLAIR image (Fig. 9). In B-cell lymphoma, the WAIR image showed the cortical tumor more clearly than did the FLAIR image (Fig. 10). By adding DIR images optimized by the present method to routine clinical brain MRI, the
diagnostic ability for various disorders may improve. Objective and more extensive evaluation of the clinical utility of our method may be a topic of further investigation.

Using the method described in our study, we were able to efficiently obtain optimal TIs for use in DIR imaging. Briefly, the methods were as follows: (1) calculating the theoretical TIs from the equation; (2) obtaining images at several TI1 at 50–100-ms intervals, and determining TI1 at which the signal of the intended tissue (WM or GM) is null (optimal TI1); (3) obtaining images for the derived TI2 at several TI1+2 at 50–100-ms intervals, and plotting the signal intensities on a graph; and (4) selecting TI1+2 at which the CSF signal is null as optimal. In addition, our findings suggest that real images (instead of the commonly used magnitude images) should be used to evaluate signal intensities. Using this approach, we were able to derive optimal TIs for DIR imaging even when the T1 relaxation time of a tissue at which the signal intensity becomes null is unknown, and the extent of involvement of other imaging parameters on signal intensity cannot be predicted.

5 Conclusions

We optimized TIs for WAIR and GAIR images using the measurement of signal intensity from real images.

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Compliance with ethical standards

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no conflicts of interest.

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