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Optimal combination of FLAIR and T2-weighted MRI for improved lesion contrast in multiple sclerosis

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Abstract

Purpose—Post-acquisition combination of three-dimensional T2-weighted (T2w) and fluid-attenuated inversion recovery (FLAIR) images can improve the visualization of brain lesions in multiple sclerosis (MS). However, an optimal way to combine these images has not been described so far. The main objective of this study is to investigate an optimal combination of T2w and FLAIR to improve the conspicuity of MS lesions.

Methods—We determined the parameters for a generalized multiplicative image combination which maximize the contrast-to-noise ratio (CNR) between lesions and normal-appearing brain tissue through simulations and verified experimentally. MRI Data from 11 MS patients acquired at 3T were retrospectively analyzed using the proposed approach and compared to conventional FLAIR, and to images obtained by direct multiplication of T2w and FLAIR (FLAIR²). Image quality was assessed by region-of-interest analysis. In addition, to evaluate the degree of cerebrospinal fluid (CSF) suppression, CSF-to-gray matter (CSF/GM) ratio was calculated. Reduction in global image contrast was assessed by computing the reduction in the contrast of mid-level intensity values.

Results—An optimal combination was found to be the third order expression: $FLAIR_3 = FLAIR^{1.55} \times T2w^{1.45}$. Compared to FLAIR, the lesion CNR was significantly increased by 1.9x (P<0.005) and 2.5x (P<0.001) using FLAIR² and FLAIR₃, respectively. CSF/GM ratio was increased by 1.7x in FLAIR² (P<0.001) compared to FLAIR, while it was reduced to 0.7x on FLAIR₃ (P<0.05). The mid-intensity contrast was preserved on FLAIR² (P=0.2), and decreased by 29% on FLAIR₃ (P<0.001).

Conclusion—These results show that the optimized combination of FLAIR and T2w can improve MS lesion conspicuity.

Keywords

MS lesions; cortical lesions; image contrast; fluid suppression; inversion recovery

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that affects more than 2 million people world-wide ¹. MS predominantly affects females and young adults aged 20-50 years ¹. MS is characterized by CNS lesions that are disseminated in space and time. Magnetic resonance imaging (MRI) is the primary imaging modality used to image MS lesions. MS lesions as visualized by standard MRI, are characterized by their distinctive appearances and topography, characteristics that provide supportive evidence to fulfill current clinical diagnostic criteria for the disease ². T2-weighted (T2w) MRI scans provide high lesion-to-brain contrast, and are included routinely in MS scan protocols. However, T2w images suffer from the presence of intense cerebrospinal fluid (CSF) signal, which interferes with the visualization of periventricular lesions. In addition, sulcal CSF is a major source of partial-volume artifacts that reduces the ability to detect cortical and subcortical lesions ³. Suppressing CSF in the fluid-attenuated inversion recovery (FLAIR) pulse sequence enhances lesion visualization. Both T2w and FLAIR are routinely acquired in clinical investigation of MS.

Due to the necessary tradeoffs made when selecting the MRI pulse sequence parameters, no single sequence can generate all the desired tissue contrast characteristics in one image. Hence, post-acquisition combination of images acquired with different scan parameters is a potential strategy to obtain images with enhanced quality compared to the individually acquired images. A recent work demonstrated this approach by combining T2w and FLAIR images to enhance the detection of MS lesions ⁴. This method multiplies the two image volumes to produce a volume with the desirable properties of high lesion-brain contrast and CSF suppression ⁴. However, methods to further optimize combining these two contrasts have not been reported so far. This is important because the level of lesion-brain contrast, even at the same echo time, is not the same in the two images. Unlike T2w, FLAIR introduces a moderate T1 weighting, which counteracts the effect of a prolonged T2 relaxation in lesions, thus reducing the lesion-to-brain contrast. On the other hand, only FLAIR produces CSF-nulled images. Hence, combining the two images with equal weighting may be suboptimal.

In this work, we seek to find an optimal combination of T2w and FLAIR images to maximize the contrast between MS lesions and normal-appearing brain tissues, based on simulations and experimental verification.

Methods

Generalized image combination

We consider a general multiplicative combination of the two images of the form:

$$f(x, y) = Ax^{\alpha}y^{\beta} \quad (1)$$

where x and y represent the two input images, here representing FLAIR and T2w, respectively; A is an arbitrary scale factor, and α and β are two positive exponents. Setting $\alpha = 1$ and $\beta = 1$, we obtain the FLAIR² reconstruction⁴. The conventional FLAIR and T2w signals for a tissue with equilibrium magnetization M_0 , and longitudinal/transverse relaxation times of T_1/T_2 are given by:

$$\begin{aligned} S_{\text{FLAIR}} &= k_f \cdot M_0 \cdot \left(1 - 2e^{-\frac{TI_F}{T_1}} + e^{-\frac{(TR_F - TE_{\text{last}, F})}{T_1}} \right) \cdot e^{-\frac{TE_F}{T_2}} + n_f \\ S_{\text{T2w}} &= k_T \cdot M_0 \cdot \left(1 - e^{-\frac{(TR_T - TE_{\text{last}, T})}{T_1}} \right) \cdot e^{-\frac{TE_T}{T_2}} + n_T \end{aligned} \quad (2)$$

where n is additive image noise, k is the image scaling factor, TE_{last} is the time of the last echo, and the subscripts F and T denote the FLAIR and T2w acquisitions. Although these signal expressions can be used to derive an optimal solution, these equations may not exactly describe the signal in modern pulse sequences such as volumetric T2w sequences (SPACE, CUBE, VISTA) where a large train of small-flip-angle refocusing pulses are used, changing the signal decay^{5, 6}. In addition, any preparation pulses (such as T2-preparatoin pulses to enhance T2-weighting) must be included. Therefore, we utilize the FLAIR and T2w signal values obtained from Bloch equation simulation of the MRI pulse sequences, utilizing the extended phase graph algorithm for multi-echo sequences^{7, 8}.

Here, we seek to find the exponents α and β which optimize the tissue contrast as defined below. The effect of random noise in the two input images on the final image f is simulated with the following error propagation rule,

$$\sigma_f = \sqrt{|\partial f / \partial x|^2 \sigma_x^2 + |\partial f / \partial y|^2 \sigma_y^2} \quad (3)$$

where σ denotes the standard deviation of the noise in the image. Under the condition that $\sigma_x = \sigma_y = \sigma$, this expression reduces to:

$$\sigma_f = \sigma A x^\alpha y^\beta \sqrt{\alpha^2 / x^2 + \beta^2 / y^2} \quad (4)$$

We choose to maximize a weighted sum of the CNR measured between the white matter lesions (WML) and normal-appearing WM, and between cortical lesions (CL) and normal-appearing GM:

$$\psi = (f_{\text{WML}} - f_{\text{WM}}) / \sigma_{\text{WM}} + \lambda (f_{\text{CL}} - f_{\text{GM}}) / \sigma_{\text{GM}} \quad (5)$$

where λ is a weighting parameter that biases the optimization to one type of lesions. In this work, we did not favor a particular lesion type, and equal weighting for WML and CL ($\lambda = 1$) was assumed.

CSF suppression

As stated above, besides the contrast between lesions and brain tissue, the degree of CSF suppression is another factor that affects the visualization of periventricular as well as cortical and subcortical lesions. Therefore, CSF signal intensity must be kept at a low level. We define the CSF suppression metric as the CSF/GM ratio:

$$\xi_{\text{CSF}} = f_{\text{CSF}} / f_{\text{GM}} \quad (6)$$

This ratio is preferred over the ratio of CSF to (GM+WM), because multiplying T2w and FLAIR, with both having GM signal higher than WM signal, results in large WM suppression, leading to images that resemble the double inversion recovery (DIR) images⁹. We empirically found that $\xi_{\text{CSF}} \sim 0.2$ provides visually excellent suppression of CSF, which was similar to the value of 0.22 calculated for FLAIR using Bloch equation simulation with our 3D FLAIR site protocol (see the MR imaging protocol for sequence parameters). However, the acceptable ratio remains as a design parameter, and may be traded for higher lesion contrast.

Effect on global image contrast

Raising the image to a positive power γ is a nonlinear intensity transformation that alters the image contrast. In the image and video literature, this operation is known as γ -encoding, or correction¹⁰. For $\gamma > 1$, the contrast is accentuated for structures with large intensity such as MS lesions, providing better depiction of lesion heterogeneity, while the contrast of the low-intensity structures is diminished. Without loss of generality we assume that the image intensity is normalized in the range [0, 1]. When the human eye is adapted to the average intensity of the image, its contrast sensitivity is reduced at the bright and dark ends of the display range¹¹. Thus, we require that the contrast of mid-intensity gray levels not be substantially reduced. We consider the contrast changes for the intensity range [0.5-d, 0.5+d], for some positive d. This range of intensity in the input image is mapped to [(0.5-d) $^\gamma$, (0.5+d) $^\gamma$] in the output image (Fig. 1), and the contrast is modulated by a factor [(0.5+d) $^\gamma$ -(0.5-d) $^\gamma$]/[(0.5+d)-(0.5-d)]. The contrast modulation is plotted against γ in Fig. 1. Note that the contrast of mid-intensity levels is not reduced for $1 \leq \gamma \leq 2$. However, for $\gamma > 2$, the contrast decreases gradually. Hence, it is recommended to keep γ small enough ($\gamma \leq \gamma_{\text{max}}$) such that the contrast is not compressed beyond a certain threshold. For example, to preserve approximately 80% of the contrast of mid-intensity levels, the sum ($\alpha + \beta$) should be restricted below $\gamma_{\text{max}} = 3$.

Contrast optimization

The contrast optimization problem can now be written as the following constrained optimization:

$$\begin{aligned} & \underset{\alpha, \beta}{\text{maximize}} \quad (f_{\text{WML}} - f_{\text{WM}}) / \sigma_{\text{WM}} + (f_{\text{CL}} - f_{\text{GM}}) / \sigma_{\text{GM}} \\ & \text{s.t.} \quad (\alpha + \beta) \leq \gamma_{\text{max}} \text{ and } f_{\text{CSF}} / f_{\text{GM}} \leq \xi_{\text{CSF}} \end{aligned} \quad (7)$$

We use the term FLAIR_x to denote the solution to this problem, with x representing the value of $(\alpha + \beta)$. A subscript, rather than a superscript, is used to avoid confusion with exponentiation. However, to be consistent with published literature⁴ we will retain the notation FLAIR^2 to denote the $\text{FLAIR} \times \text{T2w}$ image.

Computer simulations

MS lesions do not show a uniform relaxation pattern across the brain or with different degrees of lesion severity^{1213 1415}. Therefore, WML and CL were assumed to have T1 and T2 relaxation times with conservative 15% higher values than those of normal-appearing WM or GM. The proton density of lesions was assumed similar to that of GM, based on their similar appearance on PD-weighted images. Simulations were performed with the brain tissue parameters listed in Table 1. The clinical protocol at our site uses a VISTA sequence for 3D single-slab turbo-spin-echo for both 3D FLAIR and 3D T2w. To match the signal levels expected in practice, the FLAIR and the T2w signal intensities were calculated using the extended phase graph algorithm^{7, 8} to account for the multiple refocusing pathways in the signal evolution (see the section on MR imaging protocol for sequence details). Noise in the reconstructed image (σ_f) was calculated using Eq. 4, with the standard deviation of both the T2w and FLAIR signals taken as 10% of the average of the T2w and FLAIR signals. The sum of tissue CNR was calculated using Eq. 5. The simulations were performed for values of α and β between 0.01 and 3, with a step of 0.002.

Study Subjects

Eleven datasets from MS patients (10 females, age 47 ± 11 years, 1 clinically isolated syndrome, 8 relapsing-remitting MS, and 2 secondary progressive MS) were included in this study. The MRI study was approved by our Institutional Review Board and all subjects provided written informed consent. The inclusion criterion was the availability of three-dimensional T2w and FLAIR data from subjects scanned in the prior three months at our center.

MR imaging protocol

All imaging studies were performed on a Philips 3.0T Ingenia MRI scanner using a 15-channel SENSE-compatible head coil. The exam included 3D FLAIR acquired with the following parameters: TR/TE = 4800/302 ms (minimum effective TE, scanner-reported equivalent TE = 131 ms), inversion times TI = 1650 ms, 125-ms T2-preparation pre-pulse, field-of-view, FOV = 256 mm×256 mm×180 mm, voxel size = 1 mm×1mm×1mm, SENSE factor of 2.5×2.5, turbo-spin readout read-out echo train length = 167, echo-spacing = 3.3 ms, and a final flip angle of 40°. The total 3D FLAIR scan time was 5:31 min. A 3D T2w sequence was acquired with a similar TSE pulse sequence with matching FOV and voxel size and TR/TE = 2500/252 ms, effective TE = 106 ms, and total scan time 4:33 min.

Data Analysis

The FLAIR and T2w images were corrected for intensity non-uniformity using the N4ITK method¹⁶ in the Advanced Normalization Tools (ANTs; <http://www.picsl.upenn.edu/ANTs>) software, and then co-registered using a rigid-body routine in SPM (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) using mutual information as the cost function. After registration, the images were combined in two ways: $\text{FLAIR}^2 = \text{FLAIR} \times \text{T2w}$ and using the optimized combination method (described in the Results section).

Region-of-interest (ROI) analysis was performed on matching locations on FLAIR and all reconstructed images (FLAIR^2 and FLAIR_x images). ROIs were placed in the ventricular CSF, frontal GM, frontal WM, and up to 10 WM lesions and the neighboring normal appearing WM. From the ROI measurements, the following parameters were calculated: (1) the CNR between WM lesions and neighboring WM, calculated as the difference of the average signals divided by the signal standard deviation in WM; (2) the GM/WM CNR calculated similarly from the frontal lobe measurements; and (3) the ratio of CSF to frontal GM. The average lesion CNR was also calculated.

To evaluate the effect of the reconstruction method on the global image contrast in the reconstructed images, all intensities were normalized to [0, 1]. A mask was created on the FLAIR image for all voxels with intensity in the range 0.5 ± 0.2 . This mask was applied to all reconstructed images, and the standard deviation of the intensity of the voxels within this mask was calculated. The ratio of the standard deviation of each image to that of FLAIR was used as a measure of the global contrast compression. All image analysis was performed with in-house developed software written in Matlab (The Mathworks, Natick, MA). The ROI analysis was performed with ImageJ software (1.48v, National Institutes of Health, USA).

Statistical analysis was conducted with the Matlab Statistics Toolbox. Differences in tissue contrast or CSF suppression between different image types was evaluated by one-way analysis of variance (ANOVA), followed by post-hoc t-test. The results were considered significant for p-values less than 0.05.

Results

Figure 2 shows a contour plot of the optimization cost function and the total power and CSF suppression surfaces. At $\gamma_{\max} = 3$ and $\xi_{\text{CSF}} = 0.2$, the CNR cost function is maximized at $\alpha = 1.55$ and $\beta = 1.45$, giving the FLAIR_3 combination expressed as:

$$\text{FLAIR}_3 = \text{FLAIR}^{1.55} \times \text{T2w}^{1.45} \quad (8)$$

The optimal (α, β) values calculated for the whole range of $\gamma_{\max}$ and ξ_{CSF} is plotted in Fig. 3. Fig. 4A shows the optimal (α, β) values for a range of $\gamma_{\max}$ at a constant $\xi_{\text{CSF}} = 0.2$. At small values of $\gamma_{\max}$, FLAIR receives more weighting to satisfy the CSF suppression constraint. This weighting is diminished with higher $\gamma_{\max}$ until both T2w and FLAIR receive the same weighting at $\gamma_{\max} \approx 3.2$ ($\alpha = \beta = 1.6$). Afterwards, T2w gets more

weighting. The optimal values for (α, β) were also calculated at different levels of CSF suppression ($\xi_{\text{CSF}} = S_{\text{CSF}}/S_{\text{GM}}$; Fig. 4B). A ratio $\xi_{\text{CSF}} \sim 0.22$ was the crossover point that produces equal weighting for FLAIR and T2w ($\alpha = \beta = 1.5$), and at this point we obtain the special case $\text{FLAIR}_3 = (\text{FLAIR}^2)^{3/2}$. Figure 5 shows co-registered and nonuniformity-corrected FLAIR and T2w images in three representative MS patients (patients 1, 2, and 4) and the images reconstructed using FLAIR^2 and FLAIR_3 . Note the improved image contrast and visibility of the lesions in the reconstructed images. Note also the progressive suppression of WM from FLAIR to FLAIR^2 to FLAIR_3 . Fig. 6 shows the images from one MS patient (Patient 3), where the reconstructed images (FLAIR^2 and FLAIR_3) show successive improved visibility of an intra-cortical lesion (top row and arrow to bottom row detail). However, a small juxtacortical lesion can be topographically distinguished with confidence only on the FLAIR_3 image (top row and arrow to middle row detail). This lesion does show a slightly higher signal on the FLAIR, T2w, and FLAIR^2 images that might otherwise be easily overlooked. Fig. 7 illustrates the improved lesion contrast and enhanced visualization of intra-lesion heterogeneity on the FLAIR_3 images.

Results of the ROI analysis in the 11 MS patients are summarized in Table 2. The results confirm the visual progressive increase in GM-WM and WML-WM contrast, and the reduction CSF/GM with higher exponent sum. When compared to FLAIR, the CNR between WM lesions and normal-appearing WM significantly increased in FLAIR^2 by a factor of 1.9 ($P < 0.005$) and FLAIR_3 by a factor of 2.5 ($P < 0.001$). Moreover, the WML-WM CNR was significantly higher by 40% on FLAIR_3 compared to FLAIR^2 ($P < 0.05$). However, the improved contrast comes at a reduced contrast in the mid-gray levels. Compared to FLAIR, the mid-intensity levels lost, on average, 29% of the contrast in the FLAIR_3 reconstruction ($P < 0.001$). On the other hand, this contrast was preserved on FLAIR^2 ($P = 0.2$). CSF suppression on FLAIR^2 was inferior to FLAIR, with CSF/GM ratio increasing by 70% ($P < 0.001$). On the other hand, CSF suppression significantly improved on FLAIR_3 compared to both FLAIR ($P < 0.05$) and FLAIR^2 ($P < 0.001$), with the CSF/GM ratio reduced by 30% and 59%, respectively. Fig. 8 shows the average lesion CNR in 11 subjects obtained with different reconstruction methods. Progressively higher contrast is obtained with higher $(\alpha + \beta)$.

Discussion

Optimization of image contrast for the visualization of WML and CL remains an active area of research in MS^{4, 17}. Recent advances in multiple approaches for identification and characterization of MS lesions include the use of high field imaging^{18, 19}, nonconventional pulse sequences such as the double inversion recovery²⁰ and phase-sensitive inversion recovery²¹, patient-customized protocols²², and post-processing techniques that are aimed at combining images with different contrasts^{4, 23}.

Post-processing techniques utilize existing images acquired with conventional imaging methods and synthesize new images for improved contrast. The method described in this report, based on simulations and experimental verification, proposes a generalized image combination approach to optimally combine these images. The results obtained demonstrate improved lesion contrast using simple algebraic operations. Compared to FLAIR and the

FLAIR² approach⁴, the optimized FLAIR₃ image, in agreement with the simulations, shows higher lesion-brain contrast and better CSF suppression.

One of the promising tools to detect CL in MS is DIR^{20, 21, 24–27}. However, DIR images tend to be noisy and show high inter-rater variability²⁵. Combining FLAIR and T2w produces images with relatively good suppressed WM. This approach was suggested to produce images with a contrast similar to DIR, but with better image quality⁴. The results presented here show that optimized combination of conventional MRI contrast images produces high-quality images with improved lesion contrast, and may be useful for visualizing CL.

We expect that the improved lesion-brain contrast obtained with the proposed image combination may improve the detection, delineation, and classification of MS lesions. Further studies are needed to assess the performance of this method. If this combination is to be considered as an alternative to DIR for the detection of CL, its performance must be assessed by direct comparison to DIR images.

Although in this work we targeted the optimization of FLAR-T2w combination for improved lesion contrast in MS, the same approach may be used to combine FLAIR and T2w, or other contrast types, to optimize image contrast in other neurological disorders. However, this needs to be verified.

The limitations of this study include its retrospective nature and the relatively small sample size. Future prospective studies should include a larger number of subjects. While this study focused on MS patients with definite clinical diagnosis, some of the lesions could be from etiologies other than MS. A limitation of all image combination methods, including this work, is the need for image registration, which introduces image blurring. In addition, errors in the registration could be mistaken for lesions. In this work we did not notice these problems. However, the need for registration introduces a degree of complexity and delay in obtaining the combined image. Executing the protocol with minimal delay between the two acquisitions, and using identical graphical prescription should reduce the inter-scan motion, to minimize registration constraints. In addition, integrating the image analysis into the scanner and using efficient computation techniques would help to obtain the combined image on the scanner, facilitating the incorporation of the image into the patient database²⁸.

The proposed method does not account for differences in the images due to inhomogeneity of the static (B0) or the radio-frequency (B1) magnetic fields. To address this problem, the formulation in Eq. 1 may be extended such that the scaling factor A and the exponents α and β become spatially-varying, and to include explicit expression on the field. However, this solution requires the availability of B0/B1 maps. Here, we considered an alternative approach where the images were first bias field- corrected using nonparametric nonuniform normalization¹⁶.

In conclusion, the proposed method for a generalized combination of FLAIR and T2w images shows increased lesion contrast in MS, a desired goal for improved MRI support of the diagnosis and increased accuracy of new lesion detection when assessing the effects of modern MS disease modifying therapies.

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Fig. 1. Intensity mapping of mid-gray voxel values (in the range 0.3 to 0.7) for linear and cubic mapping (A). Contrast scaling of mid-gray contrast as a function of the image power γ (B)

Fig. 2. Isocontour plot as a function of the exponents of each image: objective optimization function (A), the maximum exponent (B), and CSF suppression (C)

Fig 3. Optimal image powers at different total exponent $\gamma_{\max}$ and CSF suppression level ξ_{CSF}

Fig 4. Optimal image exponents (A) at different total power γ_{max} , at constant $\zeta_{\text{CSF}} = 0.2$, and (B) at different levels of CSF suppression at constant $\gamma = 3$

Fig. 5. Representative images from 3 MS patients (rows) showing T2w (A), FLAIR (B), and the reconstructed FLAIR² (C), and FLAIR₃ (D)

Fig. 6. Cortical (arrowhead) and subcortical (arrow) lesions substantially improved with the image combination. (A) T2w, (B) FLAIR, (C) FLAIR², and FLAIR³ (D)

Fig. 7. Lesion heterogeneity (arrowhead) is most easily depicted on FLAIR₃ (D), compared to T2w (A), FLAIR (B), or FLAIR² (C)

Fig. 8. Average lesion CNR obtained by the different methods in all patients

Table 1
Tissue parameters used in simulations

Tissue	Relative PD	T1 (ms)	T2 (ms)
WM	0.71	850	85
GM	0.83	1400	100
CSF	1.0	4000	2000
WML	0.83	978	98
CL	0.83	1610	115

Table 2
Quantitative ROI analysis in the brains of MS patients (n=11) for different images (mean $\pm$ SD). Asterisk (*) denotes significant differences compared to FLAIR. Dagger ($\dagger$) denotes significant differences compared to FLAIR²

	T2w	FLAIR	FLAIR ²	FLAIR ₃
CNR _{GM-WM}	12.4 $\pm$ 3.7	6.9 $\pm$ 3.4	12.9 $\pm$ 5.0*	15.3 $\pm$ 6.3*
CNR _{WML-WM}	19.7 $\pm$ 5.9	15.1 $\pm$ 3.0	28.3 $\pm$ 9.2*	38.4 $\pm$ 13.6* $\dagger$
CSF/GM	1.70 $\pm$ 0.17	0.10 $\pm$ 0.03	0.17 $\pm$ 0.04*	0.07 $\pm$ 0.03* $\dagger$
Preserved mid-intensity contrast	NA	1.0	1.06 $\pm$ 0.13	0.71 $\pm$ 0.12 $\dagger$