MAJOR PAPER

Diffusion MR Imaging with T2-based Water Suppression (T2wsup-dMRI)

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Purpose: This study proposes and assesses a new diffusion MRI (dMRI) technique to solve problems related to the quantification of parameter maps (apparent diffusion coefficient [ADC] or mean diffusivity [MD], fractional anisotropy [FA]) and misdrawing of fiber tractography (FT) due to cerebrospinal fluid (CSF)-partial volume effects (PVEs) for brain tissues by combining with the T2-based water suppression (T2wsup) technique.

Methods: T2wsup-diffusion-weighted imaging (DWI) images were obtained by subtracting those images from the acquired multi- b value (b) DWI images after correcting the signal intensities of multiecho time (TE) images using long TE water signal-dominant images. Quantitative parameter maps and FT were obtained from minimum data points and were compared with those using the standard (without wsup) DWI method, and partly compared with those obtained using other alternative DWI methods of applying fluid attenuation inversion recovery (FLAIR), non- b -zero (NBZ) by theoretical or noise-added simulation and MR images.

Results: In the T2wsup-dMRI method, the hyperintense artifacts due to CSF-PVEs in MRI data were dramatically suppressed even at lower b ($\lesssim 500$ s/mm²) while keeping the tissue SNR. The quantitative parameter map values became precisely close to the pure tissue values precisely even in water (CSF) PVE voxels in healthy brain tissues ($T_2 \lesssim 100$ ms). Furthermore, the fiber tracts were correctly connected, particularly at the fornix in closest contact to the CSF.

Conclusion: Solving the problem of CSF-PVE in the current dMRI technique using our proposed T2wsup-dMRI technique is easy, with higher SNR than those obtained with FLAIR or NBZ methods when applying to healthy brain tissues. The proposed T2wsup-dMRI could be useful in clinical settings, although further optimization of the pulse sequence and processing techniques and clinical assessments are required, particularly for long T_2 lesions.

Keywords: *diffusion-weighted imaging, diffusion tensor imaging, water suppression, partial volume effects, cerebrospinal fluid*

Introduction

The diffusion magnetic resonance imaging (dMRI) technique, including diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI), has the potential to provide biomarkers of tissue variation, such as cell density, tissue

anisotropy, and microvascular perfusion.^{1,2} The dMRI has now being regularly implemented in commercial MRI scanners and is being widely used, particularly in the neurological region related to brain stroke, tumor characterization, and neurodegenerative diseases. The dMRI can provide several quantitative parameter maps, including a diffusivity given by apparent diffusion coefficient (ADC) or mean diffusivity (MD) and diffusion anisotropy given by fractional anisotropy (FA) or relative anisotropy (RA), and it can visualize a fiber tractography (FT) to assess neural tracts. Those are calculated using multiple images acquired using different encoding ranges and directions of diffusion denoted by b -values (b).

However, a significant limitation of the dMRI technique is the imaging artifacts, which is essential for identifying tissue neural signatures of diseases and brain-behavior relationships.³⁻⁷ In dMRI, it is extremely important to

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suppress the cerebrospinal fluid (CSF) because the quantitative parameter maps are affected by a partial volume effect (PVE) when the CSF is mixed with the brain's gray matter (GM) or white matter (WM) in the same voxel. This is because the standard dMRI (Std-dMRI) images are usually acquired using T2-weighted spin-echo (SE) with longer TE (=80–100 ms) conditions based on single-shot echo-planar imaging (EPI), and because the ADC for the CSF is several times greater than those for brain tissues. The CSF also provides isotropic diffusion. Therefore, compared with pure tissue volumes, the voxel with CSF-PVE introduces an overestimation of ADC, underestimation of anisotropy indexes of FA or RA, and misdrawing in FT.^{4–6} To solve these problems, various CSF suppression techniques for dMRI have been proposed and assessed.^{8–24}

The first approach is to combine dMRI with a fluid attenuation inversion recovery (FLAIR) sequence to suppress CSF-PVE while using the same range of b as the Std SE sequence, including zero.⁵ The FLAIR technique succeeded in providing pure tissue maps of diffusivity and anisotropy even at the tissue-CSF border^{8–12} and visualizing tracts, such as the fornix and corpus callosum in closest contact to the CSF in the lateral ventricle.^{14,16} Despite these contributions, compared with the Std method without inversion, FLAIR approaches have issues in reducing SNR¹⁴ because of the small longitudinal magnetization (M_z), particularly in the high magnetic field due to T1 extension. This could result in an extension of imaging time or reduction in the number of slices and instability due to CSF inflow artifacts, thereby not providing information about the CSF.

The second approach is the non- b -zero (NBZ) method,^{16,17} in which a greater minimum b , $b_{\min}$ is used to sufficiently reduce water signals because CSF contamination was a source of non-mono exponential decay even in a GM distant from CSF that could be suppressed by removing the $b \sim 0$ data. For example, in the case of Salminen,¹⁶ $b_{\min} = 680 \text{ s/mm}^2$ was used with a TR = 7.8 s and an TE = 86 ms. In the case of Baron,¹⁷ TR optimization was additionally combined with NBZ method, ($b_{\min} = 425 \text{ s/mm}^2$ with a shorter TR = 2.5 s and TE = 60 ms). Those methods require no model compartment assumption and used the same analysis method as the Std method. However, the NBZ method requires several motion probing gradient (MPG) directions for $b_{\min}$ (e.g., minimally three¹⁶ or six¹⁷ to be isotropic but one in the Std DTI). Furthermore, compared with the Std method, it may have the following disadvantages: first, reducing tissue SNR in ADC and FA because the range of b is reduced; and, second, is insufficient water signal suppression depending on the minimum b . Thus, this paper assessed these issues.

The third approach is the free-water elimination (FWE) method, in which Std acquisition data are used to analytically separate free water from tissue components.^{18–24} The method assumes that two subregions exist within a voxel demonstrating characteristic tensor signals for brain tissue and free water. By calculating separate tensors for the CSF and brain tissue, the

FWE method can control CSF contamination. The FWE method has several variations. Two types of methods have been proposed: a single-shell method^{18–23} and a multi-shell method.^{24–25} The multi-shell method can provide better results due to fitting of multiple shells of DWI data, with each shell providing tensor information and having different b . Pasternak et al.¹⁸ showed that their single-shell, bi-tensor model-based FWE technique could separate free water and WM in edema and increase the FA value compared with in the Std DTI method.¹⁸ Their technique is beginning to be used clinically.^{19–26} However, the FWE method requires many data points with non-zero b for multi-shell method, MPG directions, and complicated analysis based on a model assumption.

On the other hand, several computational imaging techniques, including computed DWI or synthetic MRI, have been proposed to provide several quantification parameter maps (e.g., T2, T1, proton density [PD], and ADC maps). The images obtained using these techniques are combined with the weighted images, which are difficult to acquire directly due to hardware limitation or noise effects.^{26–29} DWI images with high b and high contrast-to-noise ratio can be obtained using the ADC maps calculated by combining DWI images with relatively lower b .^{26,27} As for derivative methods, a short TE DWI method including zero TE was proposed by additionally using T2 maps,²⁹ which can reduce T2 shine-through effects,³⁰ and a method to provide FLAIR–DWI images with higher SNR was proposed by additionally using T1 maps.³¹ Furthermore, a new synthetic imaging technique was proposed on the basis of the proposed T2-based water-suppression (T2wsup)³² method (a modified version of the high-intensity reduction [HIRE] technique³³), which provides synthetic FLAIR or SE images that are free of hyperintense artifacts due to CSF-PVE problematic in conventional synthetic MRI method.^{34–35}

This study assesses the effectiveness of proposed wsup technique for dMRI called T2wsup-dMRI in solving the problems existing in several conventional approaches by combining with the proposed T2wsup technique.

Materials and Methods

Signal model

Here, we assume that a single voxel in a brain MRI SE image is modeled by a two-compartment model, in which the single voxel includes two components of water and tissue, and each of the components is described as a single-compartment model with a single T2 relaxation time and with Gaussian diffusion ellipsoid representation of a single tensor model.^{1,2} In addition, the T2 and ADC in CSF are assumed to be constant in the entire brain, the motion effects are negligible, and MRI SE image acquired with very long TE can be regarded as a water signal dominant, where the signal intensities (SIs) over a certain threshold are assumed to be from pure (100%) water.

Figure 1 shows a schematic diagram of a two-compartment model for SE DWI signal with TE and b -factor, b , SI, and $S(TE, b)$ in a single voxel. The $S(TE, b)$ is a mixture of

Fig. 1 Schematic of DWI signal space, $S(TE, b)$, assuming a two-compartment model that contains tissue and water in a unit voxel. The gray dashed line means tissue signal, S_t ; thin gray dotted line means water signal, S_w ; and black solid line means total signal, $S = S_w + S_t$. The minimum number of data points to obtain $T2_t$ and D_t is four points of $S(TE_1, b_0)$, $S(TE_2, b_0)$, $S(TE_3, b_0)$, and $S(TE_2, b_1)$, where TE_3 is selected as water signal dominant ($TE_3 = TE_{\text{long}}$). Obtaining only the D_t requires three points, except for $S(TE_1, b_0)$. Besides, several directions of MPGs are required as b_1 to obtain diffusion directions; for example, three points for isotropic DWI and ADC or six points for DTI. Here TR is assumed to be long enough and constant. b , b-value; D , apparent diffusion coefficient (ADC); DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; MPG, motion probing gradient; PD , proton density; S , signal intensity; t , tissue; $T2$, transverse relaxation time; V , unit voxel volume; w , water.

tissue SI, $S_t(TE, b)$, and water SI, $S_w(TE, b)$, given using the following equation:

$$S_i(TE, b) = S_{w_i}(TE, b) + S_{t_i}(TE, b) \quad (1)$$

where subscripts w , t , and i are water, tissue compartment, and MPG direction, respectively. Water and tissue SIs are obtained using the following equation adding MPG direction:

$$S_{w_i, t_i}(TE, b) = Mz_{w, t} \cdot \text{Decay}T2_{w, t} \cdot \text{Decay}D_{w_i, t_i} \quad (2)$$

where

$$Mz_{w, t} = V_{w, t} \cdot PD_{w, t} \cdot \text{Decay}T1_{w, t} \quad (3)$$

$$\text{Decay}T1_{w, t} = \begin{cases} 1 - \exp[-TR/T1_{w, t}] & (SE) \\ 1 - 2 \cdot \exp[-TR/T1_{w, t}] + \exp[-TR/T1_{w, t}] & (FLAIR) \end{cases} \quad (4)$$

$$\text{Decay}T2_{w, t} = \exp[-TE/T2_{w, t}] \quad (5)$$

$$\text{Decay}D_{w_i, t_i} = \exp[-b_i \mathbf{g}_i^T \mathbf{D}_{w, t} \mathbf{g}_i] \quad (6)$$

where $Mz_{w, t}$ is the water or tissue longitudinal magnetization, $V_{w, t}$ is the water or tissue volume in unit voxel V ($V = V_w + V_t = 1$), $PD_{w, t}$ is the water or tissue PD, $T2_{w, t}$ is the water or tissue transverse relaxation time, $T1_{w, t}$ is the water or tissue longitudinal relaxation time, and b_i and $\mathbf{g}_i$ are the diffusion-weighting amplitude (b-value) (in s/mm^2) and unit gradient encoding vector, respectively, and $\mathbf{D}_{w, t}$ is the water or tissue diffusion tensor, described by

$$\mathbf{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \quad (7)$$

Fig. 2 Process flow for the currently proposed technique of T2wsup-dMRI. General whole process (a), detailed process for water suppression for the acquired image (b), and the process flow b shown with typical output images in each process using $b = 0$ images (c), where TR and TI in process b are abbreviated because those are common. b , b-value; DWI, diffusion-weighted imaging; TI, inversion time.

T2wsup

Here, we consider the problems associated with simply obtaining DWI images and parameter maps of only tissue components by eliminating water components. To reduce the CSF-PVE in the acquired DWI images, we used the T2wsup technique,³² a modified version of the HIRE technique.³³ The basic flow for T2wsup for an image with $b = 0$ (b_0) image is almost similar to that reported by Kimura et al.³² We used a Std SE-DWI sequence for imaging.

For imaging, we acquired Std images of $b = b_0$ (~ 0) with $TE = TE_m$ ($m = 1, \dots, M$) at spatial position r in all imaging spaces R , $S_{\text{acq}}(TE_m, b_0, r)$ and DWI images of $b_n > 0$ ($n = 1, 2, \dots, N$) with the same TE, $S_{\text{acq}}(TE_m, b_n, r)$, images of $b = b_0$ with long TE ($TE_M = TE_{\text{long}}$) assumed to be pure water (neglecting tissue) signals, $S_{\text{acq}}(TE_{\text{long}}, b_0, r)$.

Figure 2a shows the general total processing flow of our T2wsup-dMRI technique, and Fig. 2b shows the key flow of wsup for the acquired DWI images, with its example shown in Fig. 2c. The following is the detailed algorithm for the T2wsup-dMRI method:

First, obtain the water volume ratio map, $V_w(r)$ ($0 \leq V_w(r) \leq 1$) and normalize it by dividing the pure water (CSF) SI in the long TE image, $S_{\text{acq}}(TE_{\text{long}}, b_0, r)$, in which the easiest way is using a maximum value of the long TE image as follows:

$$S_{\text{acq, max}}(TE_{\text{long}}, b_0) = \max_{r \in R} [S_{\text{acq}}(TE_{\text{long}}, b_0, r)] \quad (8)$$

$$V_w(r) = \frac{S_{\text{acq}}(TE_{\text{long}}, b_0, r)}{S_{\text{acq, max}}(TE_{\text{long}}, b_0)} \quad (9)$$

where $\max_{r \in R} [\]$ is an operator to obtain the maximum value for all r in R . Optionally, it is possible to make it robust by enlarging the pure CSF portion as follows:

$$V_w(r) = \begin{cases} 1 & (S_{\text{acq}}(TE_{\text{long}}, b_0, r) \geq ThV_{w_{\text{max}}}) \\ \frac{S_{\text{acq}}(TE_{\text{long}}, b_0, r)}{ThV_{w_{\text{max}}} \cdot S_{\text{acq, max}}(TE_{\text{long}}, b_0)} & (\text{otherwise}) \end{cases} \quad (9')$$

where $ThV_{w_{\text{max}}}$ is the threshold to be included in the pure CSF portions. If $ThV_{w_{\text{max}}} = 1$ in Eq. (9'), then Eq. (9') becomes Eq. (9).

Second, obtain water scaling factors for T2 decay, $\alpha(TE_m)$, and for ADC decay, $\alpha(b_n)$, to convert SI at the acquired condition of water image, $S_{\text{acq}}(TE_{\text{long}}, b_0, r)$ to the DWI image, $S_{\text{acq}}(TE_m, b_n, r)$, as follows.

a) The $\alpha(TE_m)$ is obtained using the T2 of water, T_{2w} , or using the SI ratio at pure CSF portion when the T_{2w} is unknown, respectively, as

$$\alpha(TE_m) = \exp[-(TE_m - TE_{\text{long}})/T2_w], m = 1, 2, \dots, M - 1 \quad (10)$$

and

$$\alpha(TE_m) = \frac{S_{\text{acq.mean}}(TE_m, b_0)}{S_{\text{acq.mean}}(TE_{\text{long}}, b_0)} \quad (10')$$

where

$$S_{\text{acq.mean}}(TE_m, \text{long}, b_0) = \text{mean}_{r' \in V_w(r)=1} [S_{\text{acq}}(TE_m, \text{long}, b_0, r)]$$

and $\text{mean}[\]$ is an operator to obtain the averaged value for $r \in V_w(r)=1$

all r satisfying $r \in V_w(r) = 1$.

b) The $\alpha(b_n)$ is obtained using water ADC, D_w , which is measured at stationary pure water (CSF) portions or assumed to be isotropic ($D_{xx} = D_{yy} = D_{zz} = D_w$) and literature value of approximately $3.0 \times 10^{-3} \text{ mm}^2/\text{s}$ as follows:

$$\alpha(b_n) = \exp[-(b_n - b_0)D_w] \quad (11)$$

Third, obtain a spatial mask, $Mask(r)$, to keep the SNR of tissue portions after subtraction as follows:

$$Mask(r) = \begin{cases} 1 & (V_w(r) \geq ThV_{w\min}) \\ 0 & (otherwise) \end{cases} \quad (12)$$

where $ThV_{w\min}$ is a threshold value (0–1) when pure (100%) water is 1 and decided experimentally, dependent on TE_{long} ; however, it can be commonly used once it is decided. Then, a spatial smoothing filter is applied to the $Mask(r)$ to smooth the boundary of 0 and 1 in the mask.

Fourth, obtain water images after SI correction from (TE_{long}, b_0) to (TE_m, b_n) and masking from the standard b_0 images as follows:

$$S_{\text{acq.mask}}(TE_m, b_n, r) = Mask(r) \cdot \alpha(TE_m) \cdot \alpha(b_n) \cdot S_{\text{acq.mask}}(TE_{\text{long}}, b_0, r) \quad (13)$$

Finally, our proposed water-suppressed DWI (T2wsup DWI) images, $S_{\text{acq.wsup}}(TE_m, b_n, r)$, are obtained by subtracting the corrected water images with the same TE and b in Eq. (13) as follows:

$$S_{\text{acq.wsup}}(TE_m, b_n, r) = S_{\text{acq}}(TE_m, b_n, r) - S_{\text{acq.wsup}}(TE_m, b_n, r) \quad (14)$$

When only the T2wsup DWI images with a single MPG direction are required, the minimum number of data is three ($M = 2$ and $N = 1$). In contrast, when it optionally requires synthetic wsup images, except for DWI (i.e., water-suppressed quantitative parameter maps of PD and T2), the minimum required number of data is four ($M = 3$ and $N = 1$), as shown in the closed circles in Figure 1.

After obtaining the T2wsup DWI images under the same condition as the standard DWI images, we can obtain the quantitative parameter maps of ADC (MD), FA, and FT using those T2wsup DWI images for the entire range of b , including $b = 0$ by the same way as the Std (w/o wsup) dMRI method.

Quantitative parameters in dMRI

When the DWI images are acquired using the two-point method using the $b =$ and $b =$ data with the same TE and MPG direction, we can calculate the ADC for each direction i , D_i as follows:

$$D_i = \frac{\ln[S_i(TE, b_0)/S_i(TE, b_n)]}{b_0 - b_n} \quad (15)$$

When using multiple point b SIs ($n = 1, 2, \dots$), a linear least-square method is used to obtain D_i . In standard clinical DTI,^{1,2} an ellipsoid diffusion tensor model is assumed, and the three eigenvalues of DTI tensor ellipsoid, $\lambda_{1,2,3}$ ($\lambda_1 \geq \lambda_2 \geq \lambda_3$), are obtained using a diagonalization process after obtaining DWI images in the laboratory frame (x, y, z) with several MPG directions ($i \geq 6$). Thus, MD and FA can be obtained as follows:

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} = \frac{D_{xx} + D_{yy} + D_{zz}}{3} \quad (16)$$

$$FA = \sqrt{\frac{1}{2} \frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}} \quad (17)$$

where D_{xx} , D_{yy} , and D_{zz} are diffusion constants obtained at each direction of the laboratory frame (x, y, z). The MD can be obtained from only three-axis measurements ($i = 1, 2, 3$) because it is obtained only using the diagonal elements of D_{xx} , D_{yy} , and D_{zz} of 3×3 tensor matrix before the diagonalization process, as shown in Eq. (16).

SNR of the ADC map

The SNR of the ADC map with a single MPG direction calculated by the two-point method in Eq. (15) is given as follows.^{36–37} The standard deviation (SD) of D ($=D_i$), σ_D is obtained by

$$\begin{aligned} \sigma_D^2 &= \sigma_0^2 \left(\frac{\partial D}{\partial S(b_0)} \right)^2 + \sigma_n^2 \left(\frac{\partial D}{\partial S(b_n)} \right)^2 \\ &= \frac{1}{(b_n - b_0)^2} \left[\left(\frac{\sigma_0}{S(b_0)} \right)^2 + \left(\frac{\sigma_n}{S(b_n)} \right)^2 \right] \end{aligned} \quad (18)$$

Finally, the SNR of D is obtained as

$$SNR(D) = \frac{D}{\sigma_D} = \frac{-\ln \left[\frac{S(b_n)}{S(b_0)} \right] \left[\frac{S(b_0)}{\sigma_0} \right]}{\sqrt{1 + \frac{\left(\frac{\sigma_n}{\sigma_0} \right)^2}{\left[\frac{S(b_n)}{S(b_0)} \right]^2}}} \quad (19)$$

where $S(b_0)$ and $S(b_n)$ indicate the SIs of $b = b_0$ and $b = b_n$ images ($b_n > b_0$), σ_0 and σ_n are the SDs of noise in $S(b_0)$ and $S(b_n)$ assuming Gaussian noise.

In Std DWI methods including FLAIR and NBZ methods, the σ_0 and σ_n are independent of b , becoming the same as the noise SD in original acquired image, σ , i.e., $\sigma_0 = \sigma_n = \sigma$. In contrast, in T2wsup-DWI method, the noise SDs become the same as in the Std DWI when the masking process in Eq. (13) was performed. However, when the *Mask* in Eq. (13) is not zero, those become to be

$$\sigma_0 = \sqrt{\{1 + \alpha(TE_m)\}} \sigma \text{ and } \sigma_n = \sqrt{\{1 + \alpha(TE_m)\alpha(b_n)\}} \sigma.$$

Note that the σ_n becomes close to σ with increasing b_n in DWI images even when the masking was not performed.

Simulation

Here, both the theoretical and noise-added simulations were performed. It is assumed in this stimulation that the axes of three MPGs ($i = 1, 2, 3$) coincide with the three axes of eigenvectors in tensor ellipsoid. Thus, the isotropic diffusion model for water becomes $\lambda_{w1} = \lambda_{w2} = \lambda_{w3}$ and WM of the cylinder tensor model² for tissue becomes $\lambda_{t1}(\text{long axis}) > \lambda_{t2}(\text{short axis}) = \lambda_{t3}$. Therefore, the errors, including SNR changes in diagonalization process in actual DTI process, are not included in our noise-added simulation. Table 1 shows the simulation parameters.

For theoretical simulations, first, the PVE degree was quantitatively compared with the Std (w/o wsup) methods including NBZ and T2wsup methods, and MD and FA were then calculated on the basis of a single-compartment model from the averaged SIs as a parameter of V_w . Second, the SIs as a function of b were compared among the three DWI methods, namely, Std, FLAIR, and our T2wsup, each as a parameter of water volume ratio (V_w). Third, the SNRs of ADC obtained using Eq. (19) were compared for the four DWI methods assuming the short axis of pure nerve fiber tissue volume ($V_w = 0$). Furthermore in T2wsup method, the masking effects were compared between with (*Mask* = 0) and without (*Mask* = 1).

For noise-added simulations, Gaussian noises of $\sigma = 0.029$ were added to the SIs and absolute values were taken, where the SNR ($\frac{S(b_0)}{\sigma}$ in Eq. [19]) was 100 at $S(b_0 = 0)$ of $V_w = 0$. The mean and SD values were

calculated after a trial of 10,000 times to calculate the four tissue parameters of Mz_t , $T2_t$, MD_t , and FA_t . In the T2wsup method based on the proposed algorithm with $ThV_{w\min} = 0.1$, tissue $T2$, $T2_t$, and water volume, V_w were varied from 0 to 0.9 to assess errors in calculated model parameters. Note that the SNRs for $S(b_0 = 0)$ in T2wsup method were reduced with increasing V_w due to the tissue SIs are proportional to $V_t (=1-V_w)$. Next, the SNRs in pure tissue signals ($V_w = 0$) with 4 methods, including NBZ method, were compared. For the $S(b_0)$ data, a single datum was used in the Std and T2wsup methods because of $b_0 = 0$, but the different noise-added 3-axes data were used for $b_0 = 500$ and 1000 s/mm^2 in the NBZ methods.

MRI experiments

A healthy volunteer study was performed on an MRI machine (Galan 3T ZGO; Canon Medical Systems, Tochigi, Japan) with a 32-channel head coil after obtaining written informed consent. This study was approved by the Institutional Review Board of the Shizuoka College of Medical Care Science (Shizuoka, Japan) and Canon Medical Systems Corp. The SE-EPI sequence was used, in which the common acquisition parameters were as follows: parallel imaging of speed-up factor 3; the number of slices was selected at the maximum for long TE images; the number of average = 1, FOV = 23 cm, acquisition matrix = 192×256 (phase encode $\times$ read out); display matrix = 512×512 after sinc interpolation; and software-based correction of geometric distortion due to eddy current was performed to maintain spatial fidelity. The analysis parameters were as follows: $\alpha(TE)$ was measured using the SI ratio with $ThV_{w\max} = 1$, $D_w = 3 \times 10^{-3} \text{ mm}^2/\text{s}$,¹⁶ and experimentally determined $ThV_{w\min} = 0.1$. The two cases of data were assessed with and without our T2wsup technique in each case.

Case 1

Three-axis DWI and contrast weighted images: $5 \text{ mm} \times 16$ slices; $TR_1 = 8000 \text{ ms}$; $TE_1 = 25 \text{ ms}$; $TE_2 = 80 \text{ ms}$; $TE_{\text{long}} = 300 \text{ ms}$; $TI = 1000 \text{ ms}$; and $b = 0, 250, 500, 1000, 1500$, and 2000 s/mm^2 . In addition to synthetic T2wsup images of $b = 0$, isotropic DWI and isotropic ADC (MD) images were obtained for various b combinations.

Case 2

Six-axis DTI: $3 \text{ mm} \times 50$ slices; $TR_1 = 10000 \text{ ms}$; $TE_{\text{long}} = 500 \text{ ms}$; $TE_2 = 48 \text{ ms}$; and $b = 0, 1000 \text{ s/mm}^2$. Isotropic DWI, MD, FA, color FA, and FT images were obtained. T2 maps were additionally calculated from the images with $TE=25$ and 80 ms . dTV-II.SR and Volume-One v.1.72 (<http://medimg.info.hiroshima-cu.ac.jp/dTV.II.15g/>) were used for DTI data analysis. Tractography analysis was performed after iso-voxel interpolation to $256 \times 256 \times 350$ (voxel volume = 0.9 mm^3), followed by drawing the tracts by

Table 1 Simulation conditions of quantitative parameters and imaging parameters for 3 water suppression DWI methods

Quantitative parameter ^{a)}	Water (CSF)	Tissue (WM)
<i>PD</i>	0.97	0.8
<i>T1</i> (ms)	4000	1000
<i>T2</i> (ms)	1910	100
λ_1 (mm ² /s)	3.0×10^{-3}	1.2×10^{-3}
λ_2 (mm ² /s)	3.0×10^{-3}	0.6×10^{-3}
λ_3 (mm ² /s)	3.0×10^{-3}	0.6×10^{-3}
<i>MD</i> (mm ² /s)	3.0×10^{-3}	0.8×10^{-3}
<i>FA</i>	0.00	0.41

DWI method	Imaging parameters
T2wsup-DWI	$S(TR_1, TE_1, b_0)^{b)}$ $S(TR_1, TE_2, b_0)$ $S(TR_1, TE_3, b_0)^{c)}$ $S(TR_1, TE_2, b_n)$ (b_0, b_n) (s/mm ²) (0, 1500)
FLAIR-DWI	$S(TR_1, Tl_2, TE_2, b_0)$ $S(TR_1, Tl_2, TE_2, b_n)$ (b_0, b_n) (s/mm ²) (0, 1500)
NBZ-DWI	$S(TR_1, TE_2, b_0)$ $S(TR_1, TE_2, b_n)$ (b_0, b_n) (s/mm ²) (500, 1500); (1000, 1500) TR_1 (ms) 10000 TE_1, TE_2, TE_3 (ms) 20, 100, 500 Tl_2 (ms) 2350

a) quantitative parameters were referred to Ref. #34 and Ref. #23.

b) need for T2, no need for ADC.

c) need for water image, TE_3 correspond to TE_{long} .
 CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; FA, fractional anisotropy; FLAIR, fluid attenuation inversion recovery; MD, mean diffusivity; NBZ, non-*b*-zero; PD, proton density; T2wsup, T2-based water suppression; WM, white matter.

setting two seed ROIs on the portion of the fornix crus with the threshold parameters of FA to stop drawing commonly at 0.25.

Results

Simulation

Figures 3–6 and Table 2 show the simulation results. For the DTI quantitative parameter maps of MD and FA as a function of V_w (Fig. 3), the Std DWI method became close to each

pure water value with increasing V_w . Larger b_0 values corresponding to the NBZ–DWI method reduced water effects but were not sufficient even at $b_0 = 1000$ s/mm². In contrast, the MD and FA with the T2wsup were kept constant with the ground truth tissue values being independent of V_w , except when V_w was 100%.

For the SIs as a function of b for three DWI methods, each as a parameter of water volume ratio (V_w) (Fig. 4), the Std method provided bi-exponential decay for $V_w = 25\%$ – 75% . The water components were relatively reduced by increasing b but remained at a b of 1000. In contrast, the FLAIR method and our proposed T2wsup method provided the SI decay of pure tissue component thorough the entire b , and those SIs were proportional to tissue volume ($V_t = 1 - V_w$), whereas the SIs in T2wsup–DWI were 24% better than those in FLAIR–DWI, reflecting a difference in SI ($b = 0$).

For the theoretical SNRs of the ADC values of pure tissue as a function of b_n for three DWI techniques using the two-point method (Fig. 5), the Std SE method (Std($b_0 = 0$)) and our T2wsup with masking method provided the best performance through the entire range of b_n .

Our noise-added simulation results at $b_n = 1500$ s/mm² in pure tissues ($V_w = 0$) (Table 2) provided almost the same SNRs between the T2wsup and the Std because the subtraction processes were eliminated in our T2wsup method due to the thresholding effects when $V_w < ThV_{wmin}$. The SNRs in NBZ method were lower than the Std or T2wsup methods. Those results were almost the same as in the theoretical simulation in Fig. 5.

For noise-added simulation with the T2wsup method (Fig. 6), the errors in the quantitative parameters at $T2_t = 100$ ms were reasonable, but the errors for $V_w = 10$ – 90% became greater as the $T2_t$ became longer (closer to TE_{long}) since the components of tissue SIs were relatively greater with increasing $T2_t$ at $TE = TE_{long}$ and could not be sufficiently separated in our current T2wsup–dMRI algorithm. In this simulation, the SDs were kept $\sigma = 0.0029$ (SNR = 100 at $T2_t = 100$ ms) corresponding original added noise at $V_w = 10\%$ but the SDs were increased to $\alpha(TE) = 1.5\sigma = 0.0043$ at $V_w \geq 25\%$ for $T2_t = 100$ – 150 ms. The SDs in T2wsup SIs at $V_w = 10\%$ for $T2_t = 100$ – 150 ms and $V_w = 0\%$ for $T2_t = 200$ ms were further increased due to the instability of the thresholding (mixed with or without subtraction in trials) in the current algorithm. Those errors were transformed to the errors in quantitative parameters calculated afterwards.

Anyway, these simulation results indicate that the Std–dMRI along with wsup technique, that is, T2wsup–dMRI, provides the best results among the three methods evaluated in terms of both SNR and wsup effects.

MRI experiments

Figure 7–8 and Table 3 show the results of case 1. Comparing the DWI images with the Std method and those with our T2wsup method (Fig. 7a), the CSF signals for T2wsup

Fig. 3 Theoretical simulation results of MD and FA as a function of V_w (%) for standard (w/o wsup) DWI (Std) and T2-based water suppression DWI (T2wsup) obtained by the two-point method for WM with denoted combinations of $b = (b_0, b_n)$ s/mm². Note that the MD and FA for standard respectively increased and decreased with the increasing V_w . The greater b_0 values corresponding to the NBZ-DWI reduced water effects but were not sufficient even at $b_0 = 1000$ s/mm². In contrast, the MD and FA with T2wsup-DWI were kept constant to the theoretical tissue values ($MD = 0.8 \times 10^{-3}$ mm²/s, $FA = 0.41$) through whole V_w , expect for $V_w = 100\%$ (no tissue signal). Simulation parameters were shown in Table 1. b , b-value; DWI, diffusion weighted imaging; FA , fractional anisotropy; MD , mean diffusivity; NBZ, non- b -zero; Std, standard; T2wsup, T2-based water suppression.

Fig. 4 Theoretical simulation results of SIs as a function of b for three DWI methods (a–c) each as a parameter of water volume ratio (V_w), and overlapped version of the Std (w/o wsup) and T2wsup DWI methods with magnification (d). b , b-value; FLAIR, fluid attenuation inversion recovery; DWI, diffusion-weighted imaging; Std, standard; T2wsup, T2-based water suppression.

were well suppressed in the entire range of b , including $b = 0$, particularly in the CSF-PVE portions, such as the cerebral cortex and cerebellum. The CSF signals remained constant until a b of 1000 s/mm² for the Std method. The CSF signals, such as those in the Monroe foramen at a b of 250–500 s/mm² for the Std method, were lower than those in the lateral ventricle because of the effects of CSF. Therefore, the CSF signals for T2wsup were negative because of the overestimation of subtracted CSF signals (underestimation of the estimated D_w) at those portions. Comparing the characteristics of $\ln[S(b)]$ with b (Fig. 7b), those in the cerebellum and temporal portions for the Std method were not linear because of CSF-PVE. In contrast,

those for the T2wsup method had higher linearity, and the gradients corresponding to ADC (MD) values became close to the pure tissue values even at the ROIs, including CSF and tissue (Table 3).

Figure 8 shows the contrast-enhanced weighted images and the quantitative parameter maps for the Std (without wsup) and the currently proposed T2wsup methods. Comparing the ADC (MD) values for the T2wsup ($b = 0, 1500$) with those for NBZ ($b = 500, 1500$), the tissue SNRs and CSF suppression effects for the current method were greater compared with those for the NBZ. The SNR measured at the uniform tissue portions in the MD map

Fig. 5 Theoretical SNRs of ADC values as a function of the second b , b_n of pure tissue ($V_w = 0$, $D_t = 0.6 \times 10^{-3} \text{ mm}^2/\text{s}$) for five DWI techniques using the two-point method when the SNR of SE b_0 SI ($\text{Std}(b=b_0)$) for $V_w = 0$ ($S(b_0)/\sigma_0 = 100$). The NBZ method was shown by $b_0 = 500$ and 1000 s/mm^2 . Note that $\text{Std}(b_0 = 0)$ and $\text{T2wsup_with mask}(b_0 = 0)$ provided the best performance through the entire range of b_n . The SNR ratios to the $\text{Std}(b_0 = 0)$ at $b_n = 1500 \text{ s/mm}^2$ in six cases were 33.9 (1.00), 33.9 (1.00), 31.1 (0.92), 24.7 (0.73), 21.4 (0.63), and 9.8 (0.29) in a descending order. ADC, apparent diffusion coefficient; b , b -value; FLAIR, fluid attenuation inversion recovery; DWI, diffusion-weighted imaging; NBZ, non- b -zero; SE, spin-echo; SI, signal intensity; Std, standard; T2wsup, T2-based water suppression.

was nearly 50–80% for the NBZ compared with the current T2wsup (Fig. 8 and Table 3). This result was almost theoretically comparable with that of our simulation, as shown in Fig. 5. These results showed that the tissue SNRs were preserved (Table 3) even by subtraction because of the masked subtraction technique of this study.

Figures 9 and 10 show the results of the DTI in case 2. Comparing the Std and T2wsup images (Fig. 9) with those numerical results in the CSF-PVE portions (Fig. 10), the T2, MD, and FA values became close to pure tissue values, i.e., the T2 and MD became lower and the FA values became closer to 1 in the T2wsup images, typically at the portion of the fornix crus or genu of the corpus callosum where CSF-PVE was greater because of the ventricle. Furthermore, FT for the T2wsup method at the central portions of two seed ROIs was thicker and better connected than that for the Std DWI.

Discussion

The currently proposed T2wsup-dMRI technique was assessed using the simulation of the current study and MRI *in vivo* study. Moreover, the currently proposed technique was demonstrated to sufficiently suppress the water signals in DWI images through the entire range of b , including $b = 0$. Furthermore, the quantitative parameter values of T2, ADC (MD), and FA were demonstrated to be close to pure tissue

values under certain limitations even when the CSF-PVE portions were included in the ROI or voxels. Moreover, the fiber tracts of the fornix were correctly visualized even in the CSF-PVE portions because the FA values for the T2wsup technique became greater than those for the Std (without wsup) method. The following section compared this technique with several alternative methods and discussed the modifications and future of the proposed technique.

Comparison between the T2wsup method and other alternative methods

Regarding the comparison of the T2wsup method with the FLAIR method, CSF-PVE in FLAIR method was perfectly suppressed at the optimal TI, but the tissue SNR was lower in the FLAIR method than in our SE-based T2wsup method even using w/o masking, as shown in our theoretical simulation of $V_w = 0$ (Table 2). In addition, it has been verified using MRI data that the T2wsup- b_0 images with masking have higher SNR than the FLAIR- b_0 images,³² and that the ratio of SNR between the two methods is perceived to be independent of b .

When comparing the NBZ with our method, the SNR of ADC was roughly proportional to the difference of the two b , b_0 and b_n , in the two-point method if background noises were retained. Therefore, when b_n is fixed and the water signal is ignored, the smaller the b_0 , the better the SNR of ADC. In this case, the SNR of ADC for the NBZ method with $b_0 = 500 \text{ s/mm}^2$ was 0.64 times that for the Std method with a b_0 value of 0 in this simulation. In addition, it is nearly 0.67 ($[1500-500]/[1500-0]$) times that of our method. Figure 8 shows that MD map with our T2wsup method is visually better than with the NBZ method because of the effects of keeping tissue SNRs on b_0 images between our T2wsup and the Std. Furthermore, the b of approximately 500 s/mm^2 used in the NBZ was not sufficient because it required that a $b > 1000 \text{ s/mm}^2$ reduces the CSF signals almost perfectly ($< 5\%$) in our results. The biggest advantage of our T2wsup method is that the entire range of b (> 0) can be used to calculate the dMRI parameters without loss of tissue SNR.

In terms of the FWE method, although not compared yet, our T2wsup method has of imaging time and analysis simplicity if similar results can be provided. However, FWE method using a single-shell method can use a Std imaging protocol but requires multiple MPG directions; furthermore, some regularization techniques must be introduced to become robust because the original approach is ill-posed, resulting in poor tissue specificity due to smoothing effects.^{16,17} The basic theory of separating free water and tissue in the FWE technique using a single-shell method is based on the assumptions that the free-water ADC is isotropic and having fixed value ($D_w = 3 \times 10^{-3} \text{ mm}^2/\text{s}$). In contrast, our method can provide water-suppressed DWI images just using at least three different images (two $b = 0$ and one $b > 0$ with a single MPG direction) and does not require special analysis once T2wsup- b_0 images are obtained because our method is based

Table 2 Noiseadded simulation results for $V_w = 0$ (pure tissue signal) with 4 methods.

Index	Parameter	DWI method (b_0, b_1)			
		Std(0,1500)	T2wsup(0,1500)	NBZ(500,1500)	NBZ(1000,1500)
Ideal value	$T2_t$ (ms)	100.0		NA	
	$\lambda_{t1} \times 10^{-3}$ (mm ² /s)			1.200	
	$\lambda_{t2}, t_3 \times 10^{-3}$ (mm ² /s)			0.600	
	$MD_t \times 10^{-3}$ (mm ² /s)			0.800	
	FA_t			0.408	
Mean	$T2_t$ (ms)	100.15	100.19	NA	
	$\lambda_{t1} \times 10^{-3}$ (mm ² /s)	1.201	1.202	1.201	1.203
	$\lambda_{t2}, t_3 \times 10^{-3}$ (mm ² /s)	0.600	0.600	0.600	0.601
	$MD_t \times 10^{-3}$ (mm ² /s)	0.801	0.801	0.800	0.801
	FA_t	0.409	0.409	0.408	0.408
SD	$T2_t$ (ms)	1.37	1.37	NA	
	$\lambda_{t1} \times 10^{-3}$ (mm ² /s)	0.041	0.041	0.063	0.138
	$\lambda_{t2}, t_3 \times 10^{-3}$ (mm ² /s)	0.018	0.018	0.028	0.061
	$MD_t \times 10^{-3}$ (mm ² /s)	0.0169	0.016	0.0249	0.0544
	FA_t	0.0213	0.0214	0.0337	0.0733
SNR	$T2_t$ (ms)	73.08	73.22	NA	
	$\lambda_{t1} \times 10^{-3}$ (mm ² /s)	29.23	29.30	18.94	8.70
	$\lambda_{t2}, t_3 \times 10^{-3}$ (mm ² /s)	33.90	33.91	21.43	9.83
	$MD_t \times 10^{-3}$ (mm ² /s)	47.37	47.37	32.14	14.73
	FA_t	19.18	19.09	12.12	5.56

These simulated conditions were shown in Table 1. The tissue SNR was the same as in Fig. 4. (SNR = 100 for SI [$TE = 100$ ms, $b_0 = 0$]). Note that the SNR of each parameter in T2wsup method was almost the same as in the Std method and better than the two NBZ methods. The other parameters were the same as in Fig. 3. The major simulation parameters are shown in Table 1. The other parameters are: $ThV_{wmin} = 0.1$, SNR = 100 (SNR = $S[TE = 100\text{ms}, b = 0]/\sigma$). b , b-value; DWI, diffusion-weighted imaging; NBZ, non-b-zero; SD, standard deviation; SI, signal intensity; Std, standard; T2wsup, T2-based water suppression.

on just the T2 difference between free water and tissue. Furthermore, the water motion in the FWE method will introduce difficulty in separating water from the tissue components because the diffusion anisotropy of the CSF introduces a divergence from their model assuming stationary water.⁸ In contrast, our T2wsup method is robust to water motion because it uses non-DWI ($b = 0$) images for separating water and tissue.

More recently, a new wsup technique providing multiple T2 components of tissue, including water without using diffusion model, was proposed.³⁸ Their technique is similar to the T2wsup method of this study wherein the data on multi-TE with a single b value were combined. However, the blind source separation technique without model assumption was used there. Furthermore, future assessments will need to be informative and usable whether with TE or b or both for separating multiple tissue components in clinical use.

Modification of the proposed technique

Errors in quantitative parameters in T2wsup method and the solution

The simple analytical algorithm in the T2wsup method was applied to obtain several quantitative parameter maps by using minimum data of combining TE and b . However, when $T2_t$ becomes long and/or TE_{long} is not sufficiently long, errors in tissue T2 and $T2_t$ with the T2wsup method will be introduced. Therefore, errors in MD_{wsup} and FA_{wsup} become greater as shown in Fig. 6. The accuracies of the quantitative parameters in the proposed T2wsup method are almost decided in the T2wsup data of $b = 0$. The use of longer TE_{long} reduces the T2wsup errors even using the current algorithm to reduce the errors (Fig. 11). Moreover, the TE_{long} of ~1,000 ms is not extremely unrealistic in the EPI sequence. A technique of masking with thresholding to reduce the problems associated with the fast-spin-echo (FSE)-based T2wsup technique has been proposed.³² The

Fig. 6 Noise added simulation results (mean $\pm$ SD) for water suppressed SIs for SE with 2 TE, and quantitative tissue parameters of M_z , T_2 , MD, and FA as parameters of water volume, V_w (%) and tissue T_2 , T_2 (ms), each obtained with T2wsup method under Rician noise of SNR=100 on SI ($TE=100$ ms, $b=0$, and $V_w=0$). Ground truth (g.t.) values were also shown. TE_{long} was commonly 500 ms. All parameters for tissue ($T_2=100$ ms) provided the tissue specific values except for $V_w=100$ %, however those errors were increased with increasing T_2 . All errors at $V_w=0$ (pure tissue) were smaller because of the effects of the subtracting threshold with $ThV_{w_{\min}}=10\%$. The SNRs in all parameters for T2wsup method became worse with increasing V_w due to the lower tissue volume ($\propto M_z$) in a voxel. Other simulation parameters were shown in Table 1. b , b -value; FA, fractional anisotropy; g.t., ground truth; MD, mean diffusivity; M_z , magnetization; NBZ, non- b -zero; SD, standard deviation; SE, spin-echo; SI, signal intensity; T2wsup, T2-based water suppression.

very small $ThV_{w_{\min}}$ introduces tissue SNR reduction. By contrast, extremely large $ThV_{w_{\min}}$ introduces insufficient water suppression. The experiments with $TE_{\text{long}} = 300\text{--}500$ ms and $ThV_{w_{\min}} = 0.1$ for healthy volunteers provided reasonable results. Although it is difficult for the current T2wsup method with a similar $ThV_{w_{\min}}$ setting to perfectly preserve the accuracy when $V_w < 0$, subtracting tissue components can be less than the $ThV_{w_{\min}}$ ($< 10\%$ in this case).

Otherwise, nonlinear least square regression approach may be useful to simultaneously obtain unknown parameters of T_2 , D_t , and M_z in the model equation defined by $S(TE, b)$ in Fig. 1 or in addition to the tensor model despite of computing cost and the number of image data. All FWE methods assumed that TE is constant. The number of data along the b axis may be reduced while maintaining the same accuracy or improving the accuracy of the obtained parameters if the FWE methods are extended to different TEs.

Decay correction for water SI in DWI images

Regarding the decay correction of water SI due to b , the computing cost is low; however, it is not always necessary that when the b is sufficiently high (e.g., $b > 1000$ s/mm²),

the water SI falls to $< 5\%$. The correction for DWI images with greater b may not be performed because calculating ADC or FA correctly is impossible when the SI is negative or below Rician noise,³⁹ resulting in noise or requirements for masking.

CSF motion introduces the overestimation of water ADC, D_w when it is assumed to be the value for stationary water. The portion of negative SI at the ventricle for a b of 250–500 mm²/s in Fig. 6a was due to those effects. However, it is not an important problem because our T2wsup reduces the error in the ADC or FA maps due to CSF-PVE; those effects are major in the voxel of pure CSF portions but weak in the voxel of smaller V_w because of slow CSF motion. If necessary, the portions of negative SIs are set to 0 after T2wsup correction. Applying a DWI sequence with a gradient moment nulling is desirable to reduce motion effects when the errors introduced using fixed D_w are reduced.

Applying to T2wsup-dMRI to synthetic MRI

If the clinical purpose is only for dMRI with wsup, the additional data are only the long TE images in our T2wsup method. Current synthetic MRI is based on the

Fig. 7 Healthy brain DWI imaging results for case 1. **a:** DWI images as a parameter of b for the Std (w/o wsup) method, our water suppression (T2wsup) method, and subtractions (Std – T2wsup) in case 1. Here, all images were shown with the same window level and width. The CSF signals in T2wsup were well suppressed even at small b ($< 500 \text{ s/mm}^2$) (arrows), although the CSF signals in the Std and T2wsup methods were almost comparably decreased with the increasing b ($> 1000 \text{ s/mm}^2$). Moreover, the tissue SNRs in the T2wsup method were maintained similarly to those in the Std method because of our masking technique. **b:** ROI analysis results for the Std (left) and T2wsup (right) methods, each shown by $\ln[S(b)]$ vs. b with linear fitting by $\ln[S(b)] = A \times b + B$. The gradients (A) corresponding to the ADC or MD were increased in the cerebellum or temporal lobe and those B s for Std were not zero, reflecting CSF–PVE, in the standard method. By contrast, the gradients became almost similar even at CSF–PVE ROIs, and the B s became almost zero due to the effects of CSF suppression in the T2wsup method. The numerical values are shown in Table 3. ADC, apparent diffusion coefficient; b , b -value; CSF, cerebral spinal fluid; DWI, diffusion-weighted imaging; MD, mean diffusivity; PVE, partial volume effect; Std, standard; T2wsup, T2-based water suppression; WM, white matter.

FSE sequence because the output is only T1, T2, and PD maps and contrast images with their combinations.^{34–35} However, the advantages of combining T2wsup-dMRI with Std synthetic MRI are that the total MR acquisition time for a single patient is reduced and the comparison of different information becomes easier. The biggest advantage of this combined technique is obtaining CSF-PVE-free maps and images, particularly of FLAIR, almost the same as the FLAIR images obtained just by calculation. Finally, the CSF-PVE-free quantitative maps of PD, T1, T2, ADC, and FA and contrast images with an arbitral parameter combination of TR, TE, TI, and b were simultaneously obtained using the same anatomical positions.

Limitations

Some limitations exist in applying the current technique to actual clinical use.

The first is the increased risk of insufficient wsup or errors in quantitative parameters for long T2 lesions depending on setting parameters in the proposed T2wsup algorithm as discussed above. Thus, the current method has to be carefully applied to actual clinical use. Moreover, how long tissue T2 must be supported in the actual clinical use of dMRI with water suppression must be separately made clear. Thereafter, better solutions are prepared depending on the issue of tissue T2.

The second is the increased risk of misregistration between b_0 and long TE images. Separate acquisitions of

Fig. 8 Contrast-enhanced weighted images and parameter maps for the Std (w/o wsup) method and our water suppression (T2wsup) method for case 1. The hyperintense artifacts due to the CSF-PVE shown in the Std method were well reduced in the T2wsup method, especially at the temporal cortex and cerebellum (circle ROIs). For MD maps, the CSF-PVE artifacts were reduced in the standard method with $b = 500$ and $1,500 \text{ s/mm}^2$ corresponding to the NBZ method and persisted compared with those in the currently proposed T2wsup method with $b = 0$ and $1,500 \text{ s/mm}^2$. The tissue SNRs for the T2wsup method with $b = 0$ and $1,500 \text{ s/mm}^2$ were visually better than those for the standard method of $b = 500$ and $1,500 \text{ s/mm}^2$ (NBZ), particularly in the center portion. ROI analysis results are shown in Table 3. *b*, b-value; CSF, cerebral spinal fluid; MD, mean diffusivity; NBZ, non-*b*-zero; PD, proton density; PDW, proton density weighted image; PVE, partial volume effect; Std, standard; T2W, T2 weighted image; T2wsup, T2-based water suppression.

Fig. 9 Comparison of DTI images, quantitative maps, and fiber tractographies, for standard (Std [w/o wsup]) and for our water suppression (T2wsup) in case 2. The T2wsup provided better tissue-specific values for the tissues close to the boundary regions of the ventricle, as the body of fornix (orange arrows), or genu of corpus callosum (red arrows). Those numerical values at several ROIs were shown in Fig. 10. For the tractographies of fornix, the fibers at the central portions of two seed ROIs (yellow arrows) for T2wsup was thicker and better connected than for the standard, and artifactual fibers were drawn for the standard (blue arrow). Here the FA threshold is commonly 0.25, and the seed ROIs were set at two positions of the top of the body on this slice and the right crus of fornix on the bottom axial slice (not shown). *b*, b-value; FA, fractional anisotropy; DTI, diffusion tensor imaging; MD, mean diffusivity; Std, standard; T2-based water suppression.

Fig. 10 Histogram of whole slice (top) and the ROI analysis results (mean $\pm$ SD) (bottom) of T2, MD and FA for Std (w/o wsup) and water suppression (T2wsup) at several representative ROIs in case 2. The histograms of T2, MD and FA for T2wsup show the increase of the number of tissue specific pixels (thick arrows) compared with the standard. For the ROI analysis, the values of T2, MD and FA for T2wsup were respectively reduced, reduced and increased in fornix (open arrows), temporal lobe and cerebellum regions compared with those in the standard. By contrast, the pure tissue ROIs for CC, GM, and WM provide almost comparable values. CC, corpus callosum; FA, fractional anisotropy; GM, gray matter; MD, mean diffusivity; SD, standard deviation; Std, standard; T2wsup, T2-based water suppression; WM, white matter.

Fig. 11 a: REs in T_{2wsup} and ADC (D_{wsup}) vs. TE_{long} and T_{2t} when using no thresholding with $ThVw_{min}$ ($ThVw_{min} = 1$) in T2wsup method. The errors in the tissue T2 and ADC with T2wsup method become smaller with increasing TE_{long} or decreasing T_{2t} . **b:** SI ratio of pure tissue ($V_w = 0$) and pure water ($V_w = 1$), S_t/S_w vs. TE_{long} . The S_t/S_w ratio corresponds to the maximum $ThVw_{min}$ to preserve the tissue signals w/o subtraction under the given T_{2t} and TE_{long} in our T2wsup method. For example, when $ThVw_{min} = 0.1$, the minimum TE_{long} (ms) values without errors were 243, 515, and 820, when T_{2t} (ms) values are 100, 200, and 300, respectively, as shown in dotted vertical line. ADC, apparent diffusion coefficient; REs, relative errors; SI, signal intensity; T2wsup, T2-based water suppression.

different TEs were used for the pulse sequence to obtain T2wsup images with $b = 0$. A multiecho (> 2) EPI sequence may be desirable to make it robust against the misregistration artifacts in T2wsup- b_0 images and to reduce the total acquisition time.

Future

Our technique is useful in reducing the number of different compartments in a multi-compartment model. The original model of intra-voxel coherent motion (IVIM)⁴⁰ assumes the two compartments of perfusion and

Table 3 DWI ROI analysis results (mean $\pm$ SD) of T2, isotropic DWI SIs, and MD mm²/s for Standard-DWI (a) and for T2wsup-DWI (b) in a volunteer study case 1.

(a) Standard (w/o wsup)-DWI						
Subject	Imaging parameters	CSF + tissue		Tissue: GM	Tissue: WM	CSF 100%
		Temporal	Cerebellum	Putamen	Frontal WM	Ventricle
T2 (ms)	TE = (25, 80) (ms)	101 $\pm$ 76	71 $\pm$ 14	53 $\pm$ 3	57 $\pm$ 2	1302 $\pm$ 647
DWI S.I. (a.u.)	$b = 0$ (s/mm ²)	260.3 $\pm$ 54.9	235.3 $\pm$ 38.0	179.4 $\pm$ 14.8	162.9 $\pm$ 12.0	617.4 $\pm$ 18.8
	$b = 250$	179.7 $\pm$ 24.3	177.8 $\pm$ 17.4	147.5 $\pm$ 5.1	132.1 $\pm$ 8.6	268.9 $\pm$ 15.5
	$b = 500$	134.8 $\pm$ 27.6	143.0 $\pm$ 12.1	125.5 $\pm$ 6.6	108.2 $\pm$ 7.4	124.5 $\pm$ 8.3
	$b = 1000$	91.5 $\pm$ 22.3	101.1 $\pm$ 10.2	89.8 $\pm$ 5.7	75.8 $\pm$ 5.3	29.4 $\pm$ 7.4
	$b = 1500$	63.8 $\pm$ 17.3	73.6 $\pm$ 9.2	65.8 $\pm$ 5.0	57.9 $\pm$ 5.2	7.5 $\pm$ 4.6
	$b = 2000$	47.7 $\pm$ 12.9	56.0 $\pm$ 7.1	50.7 $\pm$ 7.5	43.7 $\pm$ 6.3	7.9 $\pm$ 5.2
	$b = 0\sim 2000$: 6points	0.85 $\pm$ 0.23	0.66 $\pm$ 0.064	0.64 $\pm$ 0.07	0.66 $\pm$ 0.06	1.17 $\pm$ 0.58
MD with LSQ fitting (x10 ⁻³ mm ² /s)	$b = 0\sim 1000$: 4points	1.05 $\pm$ 0.44	0.83 $\pm$ 0.18	0.68 $\pm$ 0.09	0.76 $\pm$ 0.07	3.08 $\pm$ 0.03
	$b = 1000\sim 2000$: 3points	0.61 $\pm$ 0.19	0.58 $\pm$ 0.10	0.58 $\pm$ 0.28	0.56 $\pm$ 0.12	1.78 $\pm$ 1.83
MD with 2-point (x10 ⁻³ mm ² /s)	$b = 0, 1500$	0.96 $\pm$ 0.34	0.78 $\pm$ 0.16	0.67 $\pm$ 0.07	0.69 $\pm$ 0.05	3.10 $\pm$ 0.05
	$b = 500, 1500$	0.78 $\pm$ 0.19	0.68 $\pm$ 0.12	0.65 $\pm$ 0.08	0.63 $\pm$ 0.09	2.97 $\pm$ 0.08
(b) T2wsup-DWI						
Subject	Imaging parameters	CSF + tissue		Tissue: GM	Tissue: WM	CSF 100%
		Temporal	Cerebellum	Putamen	Frontal WM	Ventricle
T2 (ms)	TE = (25, 80) (ms)	69 $\pm$ 88	66 $\pm$ 6	53 $\pm$ 3	57 $\pm$ 2	NA
DWI S.I. (a.u.)	$b = 0$ (s/mm ²)	199.5 $\pm$ 40.2	199.8 $\pm$ 21.4	179.4 $\pm$ 14.8	162.9 $\pm$ 12.0	74.6 $\pm$ 47.5
	$b = 250$	151.0 $\pm$ 45.7	160.5 $\pm$ 17.0	147.5 $\pm$ 5.1	132.1 $\pm$ 8.6	12.6 $\pm$ 29.0
	$b = 500$	121.2 $\pm$ 40.6	136.7 $\pm$ 14.1	125.5 $\pm$ 6.6	108.2 $\pm$ 7.4	3.4 $\pm$ 17.5
	$b = 1000$	88.5 $\pm$ 25.3	99.3 $\pm$ 11.1	89.8 $\pm$ 5.7	75.8 $\pm$ 5.3	2.4 $\pm$ 9.9
	$b = 1500$	63.1 $\pm$ 17.9	73.3 $\pm$ 9.5	65.8 $\pm$ 5.0	57.9 $\pm$ 5.2	1.5 $\pm$ 4.9
	$b = 2000$	47.7 $\pm$ 13.0	56.0 $\pm$ 7.1	50.7 $\pm$ 7.5	43.7 $\pm$ 6.3	6.8 $\pm$ 5.2
	$b = 0\sim 2000$: 6points	0.85 $\pm$ 0.23	0.71 $\pm$ 0.11	0.64 $\pm$ 0.07	0.66 $\pm$ 0.06	NA
MD with LSQ fitting (x10 ⁻³ mm ² /s)	$b = 0\sim 1000$: 4points	0.77 $\pm$ 0.42	0.74 $\pm$ 0.10	0.68 $\pm$ 0.09	0.76 $\pm$ 0.07	NA
	$b = 1000\sim 2000$: 3points	0.60 $\pm$ 0.22	0.58 $\pm$ 1.02	0.58 $\pm$ 0.28	0.56 $\pm$ 0.12	NA
MD with 2-point (x10 ⁻³ mm ² /s)	$b = 0, 1500$	0.75 $\pm$ 0.19	0.71 $\pm$ 0.09	0.67 $\pm$ 0.07	0.69 $\pm$ 0.05	NA
	$b = 500, 1500$	0.62 $\pm$ 0.18	0.65 $\pm$ 0.09	0.65 $\pm$ 0.08	0.63 $\pm$ 0.09	NA

These ROIs were the same as in Fig. 7. The ADC at pure CSF in the Standard was close to the literature free-water value of 3×10^{-3} mm²/s. Note that the ADC values at the CSF-PVE portions (cerebellum, temporal lobe) for the Standard including $b = 0$ were greater than the pure tissue (putamen, frontal WM) values ($0.6\sim 0.7 \times 10^{-3}$ mm²/s), but those for T2wsup became close to the pure tissue values. LSQ fitting: least-square fitting using denoted number of b-value range data, 2-point: obtained with two different b-value data. ADC, apparent diffusion coefficient; b , b-value; CSF, cerebral spinal fluid; DWI, diffusion-weighted imaging; PVE, partial volume effect; SD, standard deviation; SIs, signal intensities; Std, standard; T2wsup, T2-based water suppression; WM, white matter.

diffusion. Here, perfusion is capillary flow, and diffusion includes stationary water and tissue when considering CSF-PVE (i.e., three compartments in a single voxel). Pure tissue is further divided into two components: fast and slow.⁴¹ A recently proposed model of neurite

orientation dispersion and density imaging (NODDI)⁴² assumed three compartments, including isotropic water. Separating residual components is expected to be easier and more precise compared with the current approach if the free-water component can be separated in those

models by combining it with the currently proposed technique.

Conclusion

A new diffusion MRI technique called the T2wsup-dMRI was proposed and assessed for suppressing water signals based on T2 differences to more easily solve the problem of CSF-PVE artifacts in the current dMRI technique. This technique has higher SNR compared with other already proposed wsup techniques with FLAIR or NBZ. The currently proposed T2wsup-dMRI could be useful in clinical settings, although further optimization of the pulse sequence and processing techniques and clinical assessments, particularly for long T2 lesions, are required.

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Conflicts of Interest

The authors declare no conflicts of interest.

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