Deep neural network for water/fat separation: Supervised training, unsupervised training, and no training

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Purpose: To use a deep neural network (DNN) for solving the optimization problem of water/fat separation and to compare supervised and unsupervised training.

Methods: The current T2*-IDEAL algorithm for solving water/fat separation is dependent on initialization. Recently, DNN has been proposed to solve water/fat separation without the need for suitable initialization. However, this approach requires supervised training of DNN using the reference water/fat separation images. Here we propose 2 novel DNN water/fat separation methods: 1) unsupervised training of DNN (UTD) using the physical forward problem as the cost function during training, and 2) no training of DNN using physical cost and backpropagation to directly reconstruct a single dataset. The supervised training of DNN, unsupervised training of DNN, and no training of DNN methods were compared with the reference T2*-IDEAL.

Results: All DNN methods generated consistent water/fat separation results that agreed well with T2*-IDEAL under proper initialization.

Conclusion: The water/fat separation problem can be solved using unsupervised deep neural networks.

KEYWORDS
deep learning, label free, unsupervised, water/fat separation

INTRODUCTION

R2* corrected water/fat separation estimating water, fat, and inhomogeneous field from gradient-recalled echo (GRE) signal is a necessary step in quantitative susceptibility mapping to remove the associated chemical shift contribution to the field.1–5 Several algorithms, including hierarchical multiresolution separation, multi-step adaptive fitting, and T2*-IDEAL, have been proposed to decompose the water/fat separation problem into linear (water and fat) and nonlinear (field and R2*) subproblems and solve these problems iteratively.6–8 Water/fat separation is a nonlinear nonconvex problem that requires a suitable initial guess to converge to a global minimum. Multiple solutions including 2D and 3D graph cuts and inphase echo-based acquisition have been proposed to generate an initial guess.3,9–11 The performances of these methods are dependent on the assumptions inherent in these methods, including single species dominant voxels, field smoothness, or fixed echo spacing to generate a suitable initial guess and avoid water/fat swapping.12

[Correction after online publication 10 December 2020. The authors have updated Figure 2 to correct the rows for f (field offset) and R2*.

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Magn Reson Med. 2021;85:2263–2277. wileyonlinelibrary.com/journal/mrm | 2263
Recently, deep neural network (DNN) has been used to perform water/fat separation using conventional supervised training of DNN with reference data (STD).\textsuperscript{13,14} This STD water/fat separation method does not require an initial guess with the potential use of fewer echoes to shorten the scan time, or improve SNR with the same scan time, and lessen dependency on acquisition parameters compared to current standard approaches.\textsuperscript{13,14} However, the training of STD requires reference water/fat reconstructions (label), which can be challenging to calculate as discussed above.\textsuperscript{15}

In this work, we investigate an unsupervised training of DNN (UTD) method that uses the physical forward problem in $\mathbf{T}_2^*-$IDEAL as the cost function during conventional training without a need for reference water/fat reconstructions (label free). We further investigate a no-training DNN (NTD) method using a cost function similar to that used in unsupervised training to reconstruct water/fat images directly from a single dataset. We compare the results of the STD, UTD, and NTD methods with current $\mathbf{T}_2^*-$IDEAL method.

## METHODS

### 2.1 Water/fat separation $\mathbf{T}_2^*$-IDEAL

Water/fat separation and field estimation is a nonconvex problem of modeling multi-echo complex GRE signal ($S$) in terms of water content ($W$), fat content ($F$), field ($f$), and $R_2^*$ decay per voxel\textsuperscript{16}:

$$\begin{align*}
(W, F, f, R_2^*) &= \arg\min_{W, F, f, R_2^*} \sum_{j=1}^{N} ||S_j - e^{-R_2^* t_j} e^{-i2\pi v_F t_j} (W + Fe^{-i2\pi v_F t_j})||_2^2,
\end{align*}
$$

where $N$ refers to the number of echoes; $S_j$ is the GRE signal $S$ at echo time $t_j$ with $j = 1, \ldots, N$; and $v_F$ is the fat chemical shift in a single-peak model. $\mathbf{T}_2^*-$IDEAL solves Equation (1) by decomposing into linear ($W, F$) and nonlinear ($f, R_2^*$) subproblems. With an initial guess for $f$ and $R_2^*$, the linear subproblem for $W$ and $F$ can be solved. With updated $W, F$, the nonlinear subproblem for $f$ and $R_2^*$ is linearized through first-order Taylor expansion and solved using Gauss-Newton optimization.\textsuperscript{8} These steps are repeated until convergence is achieved. In this study, initial guesses for the field $f$ and $R_2^*$ decay were generated using in-phase echoes.\textsuperscript{3} The subsequent solutions to Equation (1) resulted in the reference reconstructions $\Psi_{\text{REF}}(S) = \{W, F, f, R_2^*\}$.

### 2.2 STD water/fat separation

In this work, we adapted the approaches in recent works\textsuperscript{13,14} and made $W, F, f,$ and $R_2^*$ the target output of the network. A U-net type network $\Psi(S'; \theta)$ with network weights $\theta$ is trained on $M$ training pairs $\{S', \Psi_{\text{REF}}(S')\}$, where $S'$ and $\Psi_{\text{REF}}(S') = \{W, F, f, R_2^*\}$ are the input complex GRE signal and the corresponding reference $\mathbf{T}_2^*-$IDEAL reconstruction (reference), respectively. The cost function is given by:

$$E_{\text{STD}} = \frac{1}{2} \sum_{i=1}^{M} ||\Psi_{\text{REF}}(S') - \Psi(S'; \theta)||_2^2.$$  \hspace{1cm} (2)

### 2.3 UTD water/fat separation

In the proposed method, termed unsupervised, we seek to use deep learning framework to calculate $W, F, f,$ and $R_2^*$ without access to reference reconstructions (labels). This is done by using the physical forward problem in Equation (1) as the cost function during training. This cost function is given by:

$$E_{\text{UTD}} = \frac{1}{2} \sum_{i=1}^{M} \sum_{j=1}^{N} ||S_j - \tilde{S}_j(\Psi(S'; \theta))||_2^2.$$  \hspace{1cm} (3)

with $\tilde{S}_j(\Psi) = e^{-R_2^* t_j} e^{-i2\pi v_F t_j} (W + Fe^{-i2\pi v_F t_j})$ for $\Psi = \{W, F, f, R_2^*\}$.

### 2.4 NTD water/fat separation

Recently, a single test data is used to update DNN weights in deep image prior\textsuperscript{16} and fidelity-imposed network edit.\textsuperscript{17} This inspires the idea that DNN weights $\theta^*$ initialized randomly may be updated on a single GRE dataset $S$ to minimize the cost function in Equation (3) in a single dataset $S$.

$$E_{\text{NTD}} = \frac{1}{2} \sum_{j=1}^{N} ||S_j - \tilde{S}_j(\Psi(S_j; \theta^*))||_2^2.$$  \hspace{1cm} (4)

The resulting network weights are specific to the data $S$, and the resulting output $\Psi(S_j; \theta^*)$ can be taken as the water/fat separation reconstruction of $S$. In contrast to the above STD and UTD that involve conventional training data, no training is required here; the cost function is the same as that in the unsupervised training. Therefore, this method is referred to as no-training DNN (NTD).

### 2.5 Network architecture

The network $\Psi(S; \theta)$ consisted of 2 fully 2D convolutional neural subnetworks $\Psi_M$ and $\Psi_p$, with identical structure and encoding and decoding paths (Figure 1A):

$$\begin{align*}
\Psi(S; \theta) &= \begin{bmatrix}
\Psi_M([S]; \theta_M) \\
\Psi_p(\phi(S); \theta_p)
\end{bmatrix} = \begin{bmatrix}
|W| \\
|F| \\
R_2^* \\
\phi(W) \\
f
\end{bmatrix},
\end{align*}
$$  \hspace{1cm} (5)
Here, \(|S|\) and \(\phi(S)\) are the magnitude and the phase of the complex GRE signal \(S\), respectively, each containing \(N\) channels, 1 for each echo. \(|W|\) and \(\phi(W)\) are the magnitude and the phase of the water map. \(|F|\) and \(\phi(F)\) are the magnitude and the phase of the fat map. \(\theta = \begin{bmatrix} \theta_M \\ \theta_P \end{bmatrix}\), with \(\theta_M\) and \(\theta_P\) the network weights for the 2 subnetworks. The encoding paths included repeated blocks (\(n = 5\)), each consisting of convolution \((2 \times 2)\), activation function (Sigmoid), batch normalization, and max pooling \((2 \times 2)\). The decoding paths with repeated blocks \((n = 5)\) had similar architecture to the encoding path, except max pooling was replaced with deconvolution and upsampling, along with

**FIGURE 1** (A) The deep convolutional network used in this study consists of 2 subnetworks, \(\Psi_M(|S|; \theta_M)\) and \(\Psi_P(\phi(S); \theta_P)\), with identical structure. The inputs of the subnetworks are the magnitude of the complex gradient echo images \(|S|\) and phase images \(\phi(S)\), respectively. The outputs are the magnitude-related components (magnitude of water \(|W|\) and fat \(|F|\), and \(R_2^*\)) and the phase-related components (phase of water \(\phi(W)\) and fat \(\phi(F)\), and field \(f\)), respectively. (B) Depiction of the subnetwork illustrating the output of intermediate layers.
concatenation of corresponding feature maps with the encoding path. The last block consists of convolution with linear activation function. Figure 1B shows the subnetwork architecture: representative input and output images for a test set in UTD method, along with outputs of intermediate layers. These show how learned features at different levels transform the input data into the final output images. Yellow arrows indicate concatenation of encoder and decoder layer outputs with the same feature maps. Training was performed using the Adam optimizer.

### 2.6 Data acquisition

Data were acquired in healthy volunteers (n = 12) and patients (n = 19), including thalassemia major (n = 11), polycystic kidney disease (n = 7), and suspected iron overload (n = 1). Two 1.5T GE scanners (Signa HDxt, GE Healthcare, Waukesha, WI) with 8-channel cardiac coil were used to acquire data. The healthy subjects were imaged on both scanners using identical protocols (24 scans). Patients were scanned on 1 scanner, selected at random, using the same protocol (19 scans). This protocol contained a multi-echo 3D GRE sequence with the following imaging parameters: number of echoes = 6, unipolar readout gradients, flip angle = 5°, ΔTE = 2.3 ms, TR = 14.6 ms, acquired voxel size = 1.56 × 1.56 × 5 mm³, bandwidth = 488 Hz/pixel, reconstruction matrix = 256 × 256 × (28-36), ASSET acceleration factor = 1.25, and acquisition time of 20 to 27 seconds.

Additional data were acquired for 1 experiment in 6 subjects (3 healthy volunteers, 3 iron-overload patients) scanned once at a 1.5T Siemens scanner (Magnetom Aera, Siemens Healthcare, Erlangen, Germany) with an 18-channel body coil. The GRE imaging parameters for these 6 subjects were: number of echoes = 6; unipolar readout gradients; flip angle = 5°; TE1 = 1.7 ms; ΔTE = 2.3 ms; TR = 15 ms; acquired voxel size = 2.2 × 1.56 × 8 mm³; bandwidth = 1500 Hz/pixel, acquisition matrix = 256 × 192 × (28-36); slice and phase Fourier encoding = 7/8; GRAPPA acceleration factor = 2; and acquisition time of 20 to 25 seconds.

The study was approved by the institutional review board, and written informed consent was obtained from each participant.

### 2.7 Experiments and quantitative analysis

Multiple experiments were performed to assess the performance of DNN in water/fat separation and how supervised (STD), unsupervised (UTD), and no-training (NTD) compare against the T₂*-IDEAL reference method. The network architecture for Ψ(S; θ) was identical between the 3 DNN methods. Parameters in STD and UTD include number of epochs 2000, batch size 2, learning rate 0.001 for STD, and 0.0006 for UTD. The learning rates were experimentally found to produce optimal results. In NTD, parameters include number of epochs 10 000, batch size 2, and learning rate 0.0006.

#### 2.7.1 Experiment 1

To compare the supervised (STD), unsupervised (UTD), and no-training (NTD) methods with the reference T₂*-IDEAL, training was performed on the combined sets of healthy subjects (2 scans each) and patients. This complex data of n = 43 scans (256 × 256 × 1582 × 6) were split at subject level into testing (2 subjects, 256 × 256 × 60 × 6, number of slices (60) vary depending on the selected subject) and training (256 × 256 × 1522 × 6). Next, in the healthy subject selected for testing, the corresponding images from the same subject (256 × 256 × 30 × 6) at the other scanner were removed from the training data. The remaining training data, randomly shuffled in slice direction, were further split (80%-20%) into training (256 × 256 × 1193 × 6) and the rest for validation (256 × 256 × 299 × 6). The weights corresponding to the lowest validation loss during training was selected as the optimal weights to be used during testing. Training time in each epoch was ~80 seconds. The testing data comprised of a pair of subjects (1 healthy volunteer, 1 patient). Regions of interest (ROIs) were drawn on the reference T₂*-IDEAL water and proton density fat fraction maps PDFF = \[ \frac{F_W + F_F}{F_W + F_F} \] (to select regions with moderate and high fat content). Several ROIs were drawn, including liver, adipose and visceral fat, aorta, spleen, kidney, and vertebrae. The ROIs were copied on DNN images, and measurements for each DNN method were compared with those on the reference T₂*-IDEAL maps using correlation and Bland-Altman analysis. This experiment was repeated 3 times; each time, 1 pair of subjects (1 healthy subject, 1 patient) was randomly selected, and the rest of data was used for training/validation as discussed earlier. An additional experiment was carried out in the first pair of subjects, where the input format of the complex data was changed from magnitude/phase to real/imaginary to compare performance of STD, UTD, and NTD methods.

#### 2.7.2 Experiment 2

This experiment tested the generalizability of the DNN methods and their dependence on acquisition parameters. For STD and UTD, n = 43 scans (1.5T GE) were used for training, and n = 6 scans (1.5T Siemens) were used for testing. NTD was performed in these 6 (1.5T Siemens) subjects as well. The same ROI analysis as in the first experiment was carried out. Results from the 6 subjects were compared with the
reference $T_2^*$-IDEAL images using correlation and Bland-Altman analysis.

### 2.7.3  Experiment 3

This experiment was designed to test the robustness of the NTD method. NTD, which required no training, was performed in all $n = 43$ scans. The same ROI analysis as in the first experiment was carried out. Results from these subjects were compared with the reference $T_2^*$-IDEAL output using correlation and Bland-Altman analysis. In 1 subject, NTD method results per epoch was compared with the $T_2^*$-IDEAL cost function per iteration when field was initialized with in-phase echoes\(^3\) and conventional 2D graph cut method from ISMRM Fat-Water Toolbox.\(^9,19\)

For all experiments, the $T_2^*$-IDEAL reference reconstruction was performed on CPU (Intel, i7-5820 k, 3.3 GHz, 64 GB) using MatLab (R2019a, MathWorks, Natick, MA); all DNN algorithms were developed using Keras (2.2.4)/TensorFlow (R1.13); and trainings were performed on GPU (Nvidia, Titan XP GP102, 1405 MHz, 12 GB).

### 3  |  RESULTS

#### 3.1  |  Experiment 1

Figure 2 compares the network output results in 1 healthy subject. Shown are the reference $T_2^*$-IDEAL (Figure 2A), STD (Figure 2B), UTD (Figure 2C), and NTD (Figure 2D) reconstructions. Whereas there is very good qualitative agreement among all methods, an artifact (yellow arrow) seen in the fat in the reference $T_2^*$-IDEAL and STD methods has been removed in UTD and NTD methods. The correlation and Bland-Altman analysis in Figure 3 comparing proton density fat fraction (PDFF) (Figure 3A), field (Figure 3B), and $R^*_2$ (Figure 3C) with the reference show excellent agreement. Corresponding test results for healthy volunteers in the second and third pair are shown in Supporting Information Figures S2 and S4. Among the 3 subjects (Figures 2 and 3) (Supporting Information Figures S2 and S4) and all 3 methods, correlation analysis (average slope = 0.98, average $R^2 = 0.99$) over all parameters and Bland-Altman analysis (average mean difference, average $+1.96$ SD, average $-1.96$ SD) in PDFF (3.19, 0.26, −2.68) in %, field (3.93, 0.52, −2.85) in Hz, and $R^*_2$...
FIGURE 3: ROI measurement correlation and Bland-Altman analysis comparing proton density fat fraction (A), field (B), and $R^*$ (C) reference images with the corresponding results for STD, UTD, and NTD methods in a healthy volunteer. Corresponding images are shown in Figure 2. ROI, region of interest.
(2.39, −0.62, −3.65) in Hz showed very good agreement between DNN and the reference $T_2^*$-IDEAL. Supporting Information Figure S1 shows the corresponding result when, instead of magnitude and phase, the real and imaginary components of the GRE signal are used as input for the network. Whereas in this case water and fat images agree well with reference, field and $R_2^*$ shows poor qualitative (Supporting Information Figure S1B-D) and quantitative (Supporting Information Figure S1E-G) agreement with the reference. This suggests that whereas both formats (real/imaginary or magnitude/phase) have identical information content, spatial and temporal distribution of information differ from one format to another, which makes the learning task easier in the latter case for the given network architecture.

Figure 4 compares the DNN results in 1 patient with moderate iron overload. Shown are the reference $T_2^*$-IDEAL (Figure 4A), STD (Figure 4B), UTD (Figure 4C), and NTD (Figure 4D) reconstructions. Very good qualitative agreement in both contrast and details is observed among these outputs. Correlation and Bland-Altman analysis in Figure 5 comparing PDFF (Figure 5A), field (Figure 5B) and $R_2^*$ (Figure 5C) with the reference show good agreement. The results for another patient with iron overload and for a patient with polycystic kidney disease are shown in Supporting Information Figures S3 and S5. Among the 3 subjects (Figures 3 and 4) (Supporting Information Figures S3 and S5) and all 3 methods, correlation analysis (average slope = 0.98, average $R^2 = 0.99$) over all parameters and Bland-Altman analysis (average mean difference, average +1.96SD, average −1.96SD) in PDFF (2.1, −0.63, −3.34) in %, field (5.94, 0.68, −4.63) in Hz, and $R_2^*$ (4.06, −0.19, −4.49) in Hz showed very good agreement between DNN and the reference $T_2^*$-IDEAL.

Figure 6 shows the normalized (with respect to epoch = 1 training loss) training and validations losses for the STD and UTD methods. Whereas validation loss for the STD method is initially (epoch < 250) lower than the training loss, it becomes larger at later epochs. The validation loss remains consistently larger than the training loss for UTD. The total training time for both methods was similar (~40 hours each).

### 3.2 Experiment 2

Figure 7 compares the DNN output for a healthy subject. Shown are the $T_2^*$-IDEAL (Figure 7A), STD (Figure 7B), UTD (Figure 7C), and NTD (Figure 7D) reconstructions. Very good qualitative and quantitative agreement between NTD and the reference $T_2^*$-IDEAL images are seen. In UTD and STD methods, whereas anatomical details agree well with the reference $T_2^*$-IDEAL, there is a lower agreement in contrast, partially due to difference in acquisitions parameters, including TEs between the training (GE, 1.5T) and testing (Siemens, 1.5T). The correlation and Bland-Altman plots in Figure 8 comparing reference
FIGURE 5  ROI measurement correlation and Bland-Altman analysis comparing proton density fat fraction (A), field (B), and R$^*_2$ (C) reference images with the corresponding results for STD, UTD, and NTD methods in an iron-overload patient. Corresponding images are shown in Figure 4.
**FIGURE 6** Normalized training and validation loss results for STD and UTD training methods

**FIGURE 7** Water, fat, field, and $R_2^*$ reference images are shown (A) in a healthy subject. (B-D) Show corresponding results for STD, UTD, and NTD methods when training (1.5T GE scanner; GE Healthcare, Waukesha, WI) and testing (Siemens 1.5T scanner; Siemens Healthcare, Erlangen, Germany) scanner and acquisition parameters were different.
FIGURE 8  ROI measurement correlation and Bland-Altman analysis comparing proton density fat fraction (A), field (B), and $R^*_2$ (C) reference images with the corresponding results for STD, UTD, and NTD methods in a healthy subject when training (1.5T GE scanner; GE Healthcare, Waukesha, WI) and testing (Siemens 1.5T scanner; Siemens Healthcare, Erlangen, Germany) scanner and acquisition parameters were different. Corresponding images are shown in Figure 7
FIGURE 9  ROI measurement correlation and Bland-Altman analysis comparing NTD method with the reference T2* IDEAL for proton density fat fraction (A), field (B), and R2 (C) in 31 subjects (12 healthy volunteers, 19 patients)


**FIGURE 10** Water/fat separation results comparing current T_2*-IDEAL with conventional initialization (1) and IP-based (2) initialization, with the proposed NTD method (3) results for field (A), water (B), R_2* (C), and fat (D). No initial guess was used for water and fat maps. Corresponding loss curves (E) are shown for T_2*-IDEAL versus iteration and NTD versus epoch. IP, in-phase.

T_2*-IDEAL with NTD in PDFF (Figure 8A), field (Figure 8B), and R_2* (Figure 8C) show very good agreement between the 2 as well as moderate agreement in STD and UTD methods. Supporting Information Figure S6 shows ROI analysis correlation and Bland-Altman plots from all 6 subjects combined in PDFF (Supporting Information Figure S6A), field (Supporting Information Figure S6B), and R_2* (Supporting Information Figure S6C). NTD shows very good agreement, whereas there is moderate agreement in UTD and STD. This experiment shows that NTD is generalizable, whereas STD and UTD underperform due to difference in scanner and acquisition parameters between testing and training data.

### 3.3 Experiment 3

Figure 9 shows the ROI-based correlation and Bland-Altman analysis in all 43 scans comparing NTD with T_2*-IDEAL.
in PDFF (shown in Figure 9A), field (Figure 9B), and $R_2^*$ (Figure 9C), demonstrating excellent agreement. Average slope and average $R^2$ were 0.99 over all parameters. Bland-Altman analysis (average mean difference, average $+1.96$ SD, average $-1.96$SD) in PDFF ($-0.72$, $1.5$, $-2.9$) in %, field ($0.61$, $4.8$, $-3.5$) in Hz, and $R_2^*$ ($-1.3$, $4.8$, $-7.4$) in Hz showed very good agreement between NTD and the reference $T_2^*$-IDEAL.

Figure 10 shows a comparison of NTD with $T_2^*$-IDEAL in a healthy volunteer. The $T_2^*$-IDEAL cost function per iteration is shown in the same graph as the NTD reconstruction cost per epoch. In the first row, $T_2^*$-IDEAL results of field (Figure 10A), water (Figure 10B), $R_2^*$ (Figure 10C), and fat (Figure 10D) show the results when the field was initialized with conventional 2D graph cut method from the ISMRM Fat-Water Toolbox.9,19 In the second row, the corresponding images show the result when in-phase-based initialization was used (the field and $R_2^*$ obtained from the in-phase echoes in this case). The third row shows the proposed NTD results. The generated maps when using 10 000 epochs are close the successful $T_2^*$-IDEAL result (1st and 2nd row) without a need for an initial guess. The corresponding $T_2^*$-IDEAL costs and NTD reconstruction loss are shown in Figure 10E. With conventional and in-phase-based field initialization, $T_2^*$-IDEAL requires ~100 iterations to converge. The proposed NTD method requires 10 000 epochs for convergence. Computation time for each iteration and each epoch was similar (~1.3 seconds).

4 | DISCUSSION

Our results demonstrate the feasibility of an unsupervised DNN framework both with training and without training to solve the water/fat separation problem. The proposed UTD method does not require reference images as in STD, allowing the use of DNNs for training data that are unlabeled but for which physical model is known. The NTD method further allows using DNN reconstruction of a single dataset (subject) for which a physical model is known.

For the nonlinear nonconvex water/fat separation problem, the reference $T_2^*$-IDEAL method uses traditional gradient descent optimization and is dependent on the initial guess. This problem may be alleviated using deep learning as long as the labeled training data is sufficiently large to capture test data characteristics. Labeled data may be difficult to obtain as in water/fat separation problems. Unlabeled data are easier to obtain; however, it still is difficult to ensure that training data do not lack test data characteristics. Accordingly, reconstruction directly from a test data without training is desirable, as in the reference $T_2^*$-IDEAL but without its dependence on initialization. This can be achieved using the proposed NTD.

The NTD method can overcome the initialization dependence in traditional gradient descent-based nonconvex optimization begs some intuitive explanation or interpretation, although rigorous explanation is currently not available. The cost function in DNN is minimized by adjusting network weights through backpropagation, which is achieved through iterative stochastic gradient descent. Perhaps stochastic gradient descent, along with nonlinear functions in the network, allow escaping local traps encountered in traditional gradient descent, and the intensive computation in updating network weights facilitates some exhaustive search for a consistent minimum. The network weights updating on a single test data may converge, as demonstrated in fidelity-imposed network edit17 and in deep image prior.15,20 Our data suggest that NTD can converge to a consistent minimum without initialization dependence for the nonlinear nonconvex water/fat separation problem.

Whereas some image details in STD, UTD, and NTD methods were different from the reference images, quantitative measurements in the liver include ROI measurements of several voxels and regions, which are less dependent on image details.21,22 Our results showed whereas STD and UTD methods fail when acquisition parameters in training and testing data are different, NTD method is free from this limitation and can be generalized. The network architecture can be further optimized for this problem. For instance, we found changing activation function (ReLU to Sigmoid) significantly improved field and $R_2^*$ results in unsupervised training, whereas not much change was observed in water and fat maps. Because field and $R_2^*$ have a nonlinear relationship with respect to input complex signal, whereas that of water and fat is linear, designing task-specific networks for $\Psi_M (|S| : \theta_M)$ and $\Psi_P (\phi (S) : \theta_P)$ may yield further improvement and potentially decrease the number of learned weights.

This study has a number of limitations. Although the input data are complex, the networks only accept real values, and 2 separate input channels were used instead. This potentially can change the noise properties and suboptimal network performance, which can be addressed by including complex networks for this purpose.23 Generation of reference images requires solving the $T_2^*$-IDEAL problem, which can be challenging to calculate depending on acquisition protocol. The advantage of the proposed unsupervised methods is that they only require complex input signal for training. Whereas the NTD method requires a large number of epochs to converge, which is computationally expensive, one could use a previously trained network (trained on data with the same imaging parameters) and update the weights for the new dataset.17 Only 2 scanner manufacturers and models were used for this study; variety in manufacturer, model, and field strengths would help further generalize. There were limited
number of cases used for training in STD and UTD methods in this study; including more cases would strengthen network performance and reliability.

5 CONCLUSION

In summary, we demonstrated the feasibility of using unsupervised DNN to solve the water/fat problem with very good agreement compared to reference images.

DATA AVAILABILITY STATEMENT

The code and data that support the findings of this study are openly available in DL-MRI-Water-Fat-Separation at https://github.com/RaminJafari/DL-MRI-Water-Fat-Separation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

FIGURE S1 Water, fat, field and R2* reference images are shown (A) in a healthy volunteer. B-D, Show corresponding results for supervised (STD), unsupervised (UTD), and no-training (NTD) methods. ROI measurement correlation and
Bland-Altman analysis shows excellent agreement between each DNN method and the reference $T_2^*$-IDEAL reconstruction for proton density fat fraction (E), field (F), and $R_2^*$ (G)

**FIGURE S3** Water, fat, field and $R_2^*$ reference images are shown (A) in a moderate iron-overload patient. B-D, Show corresponding results for supervised (STD), unsupervised (UTD), and no-training (NTD) methods. ROI measurement correlation and Bland-Altman analysis shows very good agreement between each DNN method and the reference $T_2^*$-IDEAL reconstruction for proton density fat fraction (E), field (F), and $R_2^*$ (G)

**FIGURE S4** Water, fat, field and $R_2^*$ reference images are shown (A) in a healthy volunteer. B-D, Show corresponding results for supervised (STD), unsupervised (UTD), and no-training (NTD) methods. ROI measurement correlation and Bland-Altman analysis shows excellent agreement between each DNN method and the reference $T_2^*$-IDEAL reconstruction for proton density fat fraction (E), field (F), and $R_2^*$ (G)

**FIGURE S5** Water, fat, field and $R_2^*$ reference images are shown (A) in a polycystic kidney disease patient. B-D, Show corresponding results for supervised (STD), unsupervised (UTD), and no-training (NTD) methods. ROI measurement correlation and Bland-Altman analysis shows excellent agreement between each DNN method and the reference $T_2^*$-IDEAL reconstruction for proton density fat fraction (E), field (F), and $R_2^*$ (G)

**FIGURE S6** ROI measurement correlation and Bland-Altman analysis comparing supervised (STD), unsupervised (UTD), and no-training (NTD) methods with the reference $T_2^*$-IDEAL for proton density fat fraction (A), field (B), and $R_2^*$ (C) in n = 6 subjects (3 healthy volunteers, 3 iron-overload patients)

How to cite this article: Jafari R, Spincemaille P, Zhang J, et al. Deep neural network for water/fat separation: Supervised training, unsupervised training, and no training. *Magn Reson Med*. 2021;85:2263–2277. [https://doi.org/10.1002/mrm.28546](https://doi.org/10.1002/mrm.28546)