qMTNet\(^{+}\), an Improved qMTNet with Residual Connection for Accelerated Quantitative Magnetization Transfer Imaging

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**Purpose:** To develop qMTNet\(^{+}\), an improved version of a recently proposed neural network called qMTNet, to accelerate quantitative magnetization transfer (qMT) imaging acquisition and processing.

**Materials and Methods:** Conventional and inter-slice qMT data were acquired with two flip angles at six offset frequencies from seven subjects for developing networks and from four young and four older subjects for testing its generalizability. qMTNet\(^{+}\) was designed to incorporate residual and multi-task learning to improve its performance. qMTNet\(^{+}\) is composed of multiple fully-connected layers. It can simultaneously generate missing MT-weighted images and qMT parameters from undersampled MT images. The network was trained and validated with 7-fold cross-validation. Additional testing with unseen data was performed to assess the generalizability of the network. Performance of qMTNet\(^{+}\) was compared with that of qMTNet\(-1\) and qMTNet-acq for fitting and MT images generation, respectively.

**Results:** qMTNet\(^{+}\) achieved quantitative results that were better than qMTNet across all metrics (peak signal-to-noise ratio, structural similarity index, normalized mean squared error) for both conventional and inter-slice MT data. Produced offset images were better quantitatively than those produced by qMTNet-acq.

**Conclusion:** qMTNet\(^{+}\) improves qMTNet, generating qMT parameters from undersampled MT data with higher agreement with ground truth values. Additionally, qMTNet\(^{+}\) can produce both qMT parameters and unsampled MT images with a single network in an end-to-end manner, obviating the need for separate networks required for qMTNet. qMTNet\(^{+}\) has the potential to accelerate qMT imaging for diagnostic and research purposes.

**Keywords:** Quantitative imaging; Magnetization transfer; Artificial neural network; Deep learning; Acceleration

**INTRODUCTION**

Quantitative magnetization transfer (qMT) imaging quantifies the MT contrast by fitting acquired MT images to a two-pool MT model (1). qMT parameters are magnetization exchange rate (\(k\)) and pool fraction ratio (\(F\)) that characterize the...
magnetization transfer dynamics between macromolecular-bound and free proton pools. Although qMT imaging has been used for some clinical studies (2–5), it has not found a widespread popularity. The major limitation of qMT is that scanning and processing time is quite long compared to standard sequences. qMT requires multiple acquisitions of MT images to fit the model, thus increasing the scan time proportionally. Data also need to be fitted to the model, which requires significant processing time (6). Some studies have attempted to expedite qMT imaging using approaches such as sparse acquisition (7), inversion recovery qMT (8–11), or inter-slice qMT (12–14) based on incidental MT effect in sequential multi-slice scanning (15–19). However, these methods only seek to reduce the acquisition time.

With an increasing popularity of deep learning and neural networks, a family of artificial neural networks (ANN) called qMTNet have been recently proposed to accelerate both data acquisition and fitting time for qMT imaging (20). Building blocks of qMTNet consist of qMTNet-acq, a convolutional neural network to produce unsampled MT images from acquired ones, and qMTNet-fit, a multilayer perceptron (MLP) to fit qMT parameters from fully-sampled MT data. From these subnetworks, qMTNet can produce qMT parameters from under-sampled MT data, achieving a 3-fold acceleration for acquisition and over 5000-fold acceleration for fitting. Fitted values produced by these networks are similar to reference values quantitatively and qualitatively.

Motivated by (20), in this study, we proposed qMTNet+ an improved version of qMTNet. Unlike qMTNet that separates the acceleration process into two subnetworks, qMTNet+ is a single network that is trained end-to-end to produce both qMT parameters and un-acquired MT offset images from under-sampled data. qMTNet+ utilizes residual connection and multi-task learning to improve the performance. The proposed network demonstrated improved fitting performance for both conventional presaturation MT and inter-slice MT.

MATERIALS AND METHODS

Data Acquisition

All experiments were approved by the local institutional review board. Written consent was obtained from each participant. To acquire data for training networks, seven healthy subjects (5 males, 24–29 years) were scanned with a Siemens 3T Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany). Additional data for generalizability testing were acquired from four healthy young subjects (3 males, 25–27 years) and 4 healthy older subjects (3 males, 61–76 years) with a Siemens Verio 3T scanner. The scanning protocol followed previous works (12, 20). It is briefly described here for the sake of completeness. Each subject was scanned with four sequences in the same session, consisting of a conventional presaturation MT (1), an inter-slice MT, an inversion recovery T1 mapping, and a multi-echo spin-echo T2 mapping. Balanced steady state free precession readout was used for both MT sequences with TR = 4.55 ms, TE = 2.275 ms, matrix size = 128 × 128, and FOV = 220 × 220 mm². Twenty five slices (whole brain) were acquired for inter-slice MT owing to its rapid acquisition time. One central slice was acquired for conventional MT for comparison purpose. Seven central slices were acquired for T1 and T2 mappings due to their long acquisition time.

Data Processing

For qMT fitting, MT data acquisition was performed at 12 different scan conditions with two flip angles (30° and 75°) and six off-resonance frequencies (2 kHz, 3 kHz, 5 kHz, 9 kHz, 15 kHz, and 25 kHz) (21). To reduce intensity variation due to acquisition, all MT images were normalized by the image at 25 kHz off-resonance excitation as the MT effect at this frequency was negligible. Ground truth qMT parameters for training and validating the network were produced with a dictionary-driven fitting method (12). A dictionary of MR signal intensities was first constructed with Bloch equation simulation using a two-pool MT model obtained from tissue properties (T1, T2 values of the free pool, qMT parameters) and scanning parameters (flip angle, off-resonance frequency). After the dictionary was established, multiple linear interpolations between entries in the dictionary were used to fit qMT parameters. qMT parameters obtained from this dictionary fitting method were considered as ground truth values for training and evaluating neural networks.

Development and Validation of qMTNet+

The overall scheme of qMTNet+ compared to qMTNet is shown in Figure 1. qMTNet+ is similar to qMTNet in structure, composing of multiple layer perceptrons. Distinct from qMTNet, qMTNet+ can produce both qMT parameters and un-acquired 8 MT images from acquired four MT images with a single network trained in an end-to-end manner. All experiments and training were conducted with
Python 3.5.2, Tensorflow (22) 1.15.0, Keras 2.2.4 with an Intel i7 7700 CPU. A GPU was not used as we found that training and inference time were satisfactory. Details of qMTNet+ are shown below.

1) qMTNet+ with residual connection

The detailed structure of qMTNet+ is shown in Figure 2. qMTNet+ processes an input vector of length 6, consisting of T1 value, T2 value, and four acquired MT data of the pixel. qMTNet+ consists of a shared path with four fully connected hidden layers with 100 neurons each (denoted in blue). Two branches were then added on top of this. Both branches contained 3 additional fully-connected hidden layers and one output layers with two and eight neurons for qMT parameters' residual (green branch) and MT offsets (yellow branch), respectively. The generated offset was then concatenated with the input, going through three more fully-connected hidden layers to produce estimates of qMT parameters (red branch). These qMT parameters were then added with the residual from the residual branch to produce final qMT parameters, which were compared with reference values during training. This design motivates the network to combine information that can be learned from the four acquired MT images as well as the generated 8

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**Fig. 1.** Overview of qMTNet and qMTNet+ approach. (a) qMTNet comprises of two separate sub-networks: qMTNet-acq to produce missing MT images and qMTNet-fit to fit MT data and produce qMT parameters; (b) qMTNet+ consists of a single network that can produce both values of interest.
MT images. Unless specified otherwise, we used rectified linear unit (ReLU) as activation for immediate MLP layers, sigmoid as activation for the output (out1, out2), and linear activation for the residual. Residual connection ensures the flow of gradient to avoid a gradient vanishing problem (23). Dropout (24) with drop probability of 20% was added to outputs of each branch (out1, out2, and residual qMT) to prevent overfitting.

2) Training procedure

Seven-fold cross-validation was used to train and verify the performance of the network. Separate models were developed for conventional and inter-slice qMT data. qMTNet\* was trained with Adam optimizer (25) to minimize summation of mean squared errors (MSEs) for qMT parameters and MT offset images:

$$L(T1,T2,MT_{\text{acq}}) = \lambda_{\text{MT}} \frac{1}{N} \sum (\text{Out1-}MT_{\text{unacq}})^2 + \lambda_{\text{qMT}} \frac{1}{N} \sum (\text{Out2-}qMT_{\text{dict}})^2$$

where $MT_{\text{acq}}$ denoted acquired MT images, $MT_{\text{unacq}}$ denoted unacquired MT images, $qMT_{\text{dict}}$ denoted fitted qMT parameters produced by the dictionary method, Out1 and Out2 were outputs of the network as specified in Figure 2, N was the number of training pixels per batch, $\lambda_{\text{MT}}$ and $\lambda_{\text{qMT}}$ were weights that balanced the contribution from each loss term. They were both set to be 1 in all experiments.

We adopted the training procedure that was used for qMTNet-fit for all subsequent experiments. qMT parameters $k_r$ and $F$ were normalized by their respective maximum values of $11.2 \text{s}^{-1}$ and $20.1\%$, respectively. A batch of 128 samples was randomly selected from the training data to
update the network’s parameters for each training step. The initial learning rate was 0.001. It was reduced by a factor of 5 if the monitored validation loss was not improved for 25 epochs. Early stopping was used to prevent overfitting if the validation loss plateaued for 50 epochs.

3) Evaluation

All post-processing and quantitative analysis were done using MATLAB 2019a (Mathworks, Natick, MA, USA). For quantitative assessment, peak signal-to-noise ratio (PSNR), structural similarity index measure (SSIM), and normalized root mean square error (NRMSE) were used to compare values generated by networks and ground truth reference values. To verify the improvement of qMTNet+1, we compared it to two networks developed (20): qMTNet-acq and qMTNet-1. qMTNet-acq utilized a series of convolutional layers to generate unacquired MT images from acquired ones. qMTNet-1 produced qMT parameters from T1 value, T2 value, and under-sampled acquisition through seven feedforward MLP layers.

Generated MT offset images from qMTNet+ were compared with data acquired during imaging experiments as well as images generated from qMTNet-acq. Generated qMT parameters from qMTNet+ were compared with reference values produced by the dictionary-fitting method as well as to values produced by qMTNet-1 which also operated on under-sampled MT data. Generalizability of networks was assessed by applying them to an unseen test dataset and resulting qMT maps were compared to those from the dictionary fitting method.

RESULTS

Table 1 shows PSNR values of MT images generated by qMTNet+ and qMTNet-acq after cross-validation. MT-weighted images produced by qMTNet+ showed an improvement over qMTNet-acq for both types of MT data acquisition. Dictionary fitting with generated MT images also showed an increase in PSNR value for qMTNet+, confirming the accuracy and applicability of generated MT values for conventional fitting methods.

Figures 3 and 4 show fitted qMT parameter maps from four ANN-based methods in a representative slice for conventional and inter-slice MT data, respectively. These four methods were composed of dictionary fitting on MT weighted images produced by qMTNet-acq and qMTNet+ and direct fitting of under-sampled MT data with qMTNet-1 and qMTNet+. All four methods operated on under-sampled data for a fair comparison. All fitted qMT parameters maps were visually similar to ground truth values from dictionary fitting methods for both k, and F. There were little visual differences between qMT parameter maps generated from these four methods. However, five times magnified error plot and PSNR values showed that qMTNet+ achieved an improvement over previous networks. Table 2 summarizes three quantitative metrics from cross-validation for qMTNet-1 and qMTNet+, supporting the lower visual error map of qMTNet+ compared to other networks. The performance of qMTNet+ was comparable to or better than that of qMTNet-1 regardless of data acquisition scheme (conventional or inter-slice) or type of qMT parameters (k, or F). Even with a larger network, qMTNet+ still showed relatively fast run time of 0.35s per 128 × 128 slice on average compared to 0.23s for qMTNet-1 on an Intel i7-7700 CPU. For reference, the conventional dictionary fitting method took 1392s (23.2 minutes) per slice on average.

Peak signal to noise ratios of qMTNet+ and qMTNet-fit for unseen data are shown in Table 3. These two networks showed good performances for both young and old subject groups whose data were acquired from a scanner (Siemens Verio), different from training data (Siemens Tim Trio). qMTNet+ showed comparable or better quantitative values over qMTNet-fit for most data combinations, qMT parameters, and subject groups except for Conventional-F map–old subjects group combination. Table 4 compares statistics of inter-slice qMT parameters in white matter and gray matter region-of-interest for qMTNet-1, qMTNet-fit, and the reference dictionary fitting. Reference values and values generated showed no significant difference either ANN (P < 0.01, Wilcoxon signed rank test [26]).

Table 1. Comparison of Peak Signal-to-Noise Ratio (PSNR) of Generated MT Offsets and Dictionary Fitted qMT Parameters from qMTNet-acq and qMTNet+

|          | qMTNet-acq | qMTNet+ |
|----------|------------|---------|
| MT images |            |         |
| Conv. qMT | 44.21 ± 2.11 | 45.18 ± 2.44 |
| Inter. qMT| 39.59 ± 2.13 | 39.90 ± 2.22 |
| k maps   |            |         |
| Conv. qMT | 31.64 ± 1.87 | 31.77 ± 1.35 |
| Inter. qMT| 30.61 ± 0.97 | 30.66 ± 0.96 |
| F maps   |            |         |
| Conv. qMT | 34.37 ± 1.27 | 34.61 ± 1.41 |
| Inter. qMT| 33.27 ± 1.04 | 33.71 ± 1.11 |

Conv. qMT = conventional presaturation qMT; Inter. qMT = inter-slice qMT qMTNet+ showed better metrics for all values.
DISCUSSION

In this study, we developed an artificial neural network called qMTNet+ to improve the performance of the recently proposed qMTNet (20) for accelerating data acquisition and fitting of qMT imaging. Our approach combined a multiple layer perceptron with residual connection and multi-task learning (27) to infer both un-acquired eight MT offset images and qMT parameters from acquired four MT offset images. Compared to qMTNet, the main contribution of
qMTNet\textsuperscript{+} is that both MT offset images and qMT parameters can be produced from a single network. Even with a more complicated structure and two types of output, qMTNet\textsuperscript{+} still has very fast computation time (on CPU) similar to that of qMTNet, which is negligible compared to the actual acquisition time. Quantitative and qualitative results showed that MT offset images and qMT parameters produced by qMTNet\textsuperscript{+} were comparable to or better than those from qMTNet.

qMTNet\textsuperscript{+} followed recent trends of using ANN to reduce...
the prolonged fitting time of conventional MR processing pipelines for applications such as MR fingerprinting (28), quantitative susceptibility mapping (29), myelin water imaging (30), and multi-phase-cycled bSSFP quantitative mapping (31). Similar to these studies, qMTNet+ employs network structures with multiple branches and residual connection to improve its performance. Residual connection has been shown to improve performance for various computer vision tasks (23, 32-34) as well as for MR processing (35, 36). Multi-task learning that optimizes multiple objectives is essential for learning problems with many networks or outputs such as generative adversarial network (37). qMTNet+ combines these two methods to improve upon qMTNet. The same feedforward MLP, qMTNet+ employs network structures with multiple branches and residual connection to improve its performance. Residual connection has been shown to improve performance for various computer vision tasks (23, 32-34) as well as for MR processing (35, 36). Multi-task learning that optimizes multiple objectives is essential for learning problems with many networks or outputs such as generative adversarial network (37). qMTNet+ combines these two methods to improve upon qMTNet. The same

Table 2. Quantitative Analysis of qMT Parameters from Two Acceleration Methods (qMTNet-1 and qMTNet+) with Cross-Validation over Seven Subjects

| Method      | Data type | PSNR (dB)  | SSIM x 100 | NRMSE (%) | Acceleration |
|-------------|-----------|------------|------------|-----------|--------------|
|             |           | $k_f$ F    | $k_f$ F    | $k_f$ F   | Acq Fit      |
| qMTNet-1    | Conv qMT  | $33.04 \pm 1.17$ | $35.09 \pm 1.93$ | $98.04 \pm 0.33$ | $98.48 \pm 0.39$ | $1.76 \pm 0.16$ | $1.23 \pm 0.19$ | 3 | 6052 |
|             | Inter qMT | $32.24 \pm 1.00$ | $35.22 \pm 1.13$ | $97.95 \pm 0.4$ | $98.67 \pm 0.34$ | $2.23 \pm 0.31$ | $1.44 \pm 0.15$ |
| qMTNet+     | Conv qMT  | $33.13 \pm 1.25$ | $35.85 \pm 1.35$ | $98.17 \pm 0.33$ | $98.68 \pm 0.33$ | $1.75 \pm 0.21$ | $1.11 \pm 0.06$ | 3 | 3977 |
|             | Inter qMT | $32.28 \pm 0.96$ | $35.26 \pm 1.15$ | $98.97 \pm 0.41$ | $98.67 \pm 0.34$ | $2.22 \pm 0.31$ | $1.43 \pm 0.15$ |

NRMSE = normalized root mean squared error; PSNR = peak signal-to-noise ratio; SSIM = structural-similarity index

Results are compared to ground truth values (dictionary fitted qMT parameters from 12 offset images). Metrics are shown as mean ± standard deviation.

Table 3. Quantitative Analysis (PSNR) of qMT Parameters from Two Acceleration Methods (qMTNet-1 and qMTNet+) with Unseen Subjects

| Method      | Data type | Young | Old | Reference |
|-------------|-----------|-------|-----|-----------|
|             |           | $k_f$ F | $k_f$ F | $k_f$ F |
| qMTNet-1    | Conv qMT  | $34.30 \pm 1.51$ | $36.47 \pm 1.08$ | $32.04 \pm 2.32$ | $33.78 \pm 2.17$ | $35.09 \pm 1.93$ |
|             | Inter qMT | $32.29 \pm 0.79$ | $34.87 \pm 0.94$ | $32.89 \pm 1.70$ | $34.65 \pm 1.39$ | $35.22 \pm 1.13$ |
| qMTNet+     | Conv qMT  | $34.29 \pm 1.46$ | $36.58 \pm 1.04$ | $32.35 \pm 2.38$ | $33.44 \pm 2.50$ | $35.85 \pm 1.35$ |
|             | Inter qMT | $32.32 \pm 0.76$ | $34.89 \pm 0.92$ | $32.87 \pm 1.61$ | $34.74 \pm 1.49$ | $35.26 \pm 1.15$ |

PSNR = peak signal-to-noise ratio (decibel).

Reference refers to cross-validated values. Young refers to the young subject group and old refers to the old subject group. Results from five cases are compared to ground truth values (dictionary fitted qMT parameters from 12 offset images). Metrics are shown as mean ± standard deviation.

Table 4. ROI Analysis for Inter-Slice qMT Parameters in Gray Matter and White Matter

| Tissue      | Fitting method | Young | Old |
|-------------|----------------|-------|-----|
|             | $k_f$ (s$^{-1}$) | F (%) | $k_f$ (s$^{-1}$) | F (%) |
| Gray Matter | Dictionary     | $1.36 \pm 0.36$ | $4.52 \pm 1.35$ | $1.48 \pm 0.73$ | $4.68 \pm 2.10$ |
|             | qMTNet-1       | $1.34 \pm 0.36$ | $4.55 \pm 1.30$ | $1.48 \pm 0.74$ | $4.75 \pm 2.11$ |
|             | qMTNet+        | $1.36 \pm 0.36$ | $4.56 \pm 1.32$ | $1.52 \pm 0.74$ | $4.72 \pm 2.13$ |
| White Matter| Dictionary     | $5.01 \pm 1.17$ | $10.28 \pm 1.01$ | $32.04 \pm 2.32$ | $33.78 \pm 2.17$ | $35.09 \pm 1.93$ |
|             | qMTNet-1       | $4.95 \pm 0.95$ | $10.14 \pm 0.87$ | $4.29 \pm 1.43$ | $9.89 \pm 1.57$ |
|             | qMTNet+        | $4.95 \pm 0.96$ | $10.15 \pm 0.88$ | $4.27 \pm 1.43$ | $9.92 \pm 1.60$ |

Values are collected from unseen subjects and presented as mean ± standard deviation. qMT parameters are compared among qMTNet+, qMTNet-1, and dictionary fitting (ground truth) on inter-slice MT data. No significant difference was observed between dictionary-fitting and either ANN (P < 0.01, Wilcoxon signed rank test).
approach can potentially be extended for aforementioned MLPs to produce more accurate fitting or processing of interested MR signals.

As observed for qMTNet, qMTNet+ can be generalized to unseen data with characteristics (scanner type, subject age) different from the training data. A potential shortcoming of the study design was that all subjects were normal, having no neurological pathologies or disorders. Levesque et al. (3) have shown that qMT parameters are reduced in patients with relapsing-remitting multiple sclerosis (MS). Significant changes in distribution of qMT parameters in patients might cause the network to under- or over-estimate actual qMT parameters, which is an observed problem when applying neural networks to other quantitative domains such as quantitative susceptibility mapping (38). In order to verify the robustness of the network, additional data from patient population should be acquired and compared with those of healthy cohorts.

The network structure of qMTNet+ was decided heuristically during the course of this study. Table 5 summarizes quantitative metrics for some experimentations with the network’s architecture or training procedure. A version of qMTNet+ without a residual connection (denoted qMTNet+ no res in the table) performed worse than qMTNet+ reported above with a residual connection. We also experimented with data augmentation in the form of adding Gaussian noise with zero-mean and 1% standard deviation as done in a previous study (28). However, this did not improve the performance of the network in our case. Performance did not show increase either with the addition of mean absolute error as extra loss function beside mean squared error.

In conclusion, in this study, we developed qMTNet+, an improved version of qMTNet, to accelerate qMT imaging data acquisition and fitting. qMTNet+ combines residual connection and multi-task learning in a single network to predict both qMT parameters and un-acquired MT offsets from a limited number of acquired MT images. qMTNet+ demonstrated improved performance over qMTNet while maintaining a short processing time and a generalization capability. qMTNet+ provides promising results for fast acquisition and processing of qMT imaging. Further studies are needed to verify its clinical applicability.

**Acknowledgments**

This work was supported by grants (NRF-2020R1A4A1018714 and NRF-2020R1A2C2008949) of the National Research Foundation (NRF) of Korea and Korea Health Technology R&D Projects (HI16C1111 and HI19C0149) through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare of South Korea.

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**Table 5. Quantitative Analysis of qMT Parameters from Four Variants of qMTNet**

| Method         | Data type | PSNR (dB)  | SSIM x 100 | NRMSE (%) |
|----------------|-----------|------------|------------|-----------|
|                |           | $k_f$      | $F$        | $k_f$     | $F$       |
| qMTNet+ Conv qMT | 33.13 ± 1.25 | 35.85 ± 1.35 | 98.17 ± 0.33 | 98.68 ± 0.33 | 1.75 ± 0.21 | 1.11 ± 0.06 |
| Inter qMT      | 32.28 ± 0.96 | 35.26 ± 1.15 | 98.97 ± 0.41 | 98.67 ± 0.34 | 2.22 ± 0.31 | 1.43 ± 0.15 |
| qMTNet+ Conv qMT | 32.45 ± 0.89 | 35.42 ± 1.08 | 97.86 ± 0.40 | 98.54 ± 0.31 | 1.89 ± 0.18 | 1.17 ± 0.09 |
| no res Inter qMT | 32.09 ± 0.99 | 34.98 ± 1.04 | 97.88 ± 0.42 | 98.62 ± 0.33 | 2.27 ± 0.35 | 1.48 ± 0.20 |
| qMTNet+ Conv qMT | 32.26 ± 0.88 | 35.16 ± 1.13 | 97.81 ± 0.26 | 98.45 ± 0.33 | 1.93 ± 0.16 | 1.21 ± 0.08 |
| Gaussian Inter qMT | 31.96 ± 0.99 | 34.93 ± 1.13 | 97.83 ± 0.44 | 98.56 ± 0.35 | 2.30 ± 0.33 | 1.49 ± 0.17 |
| qMTNet+ Conv qMT | 31.39 ± 4.04 | 34.96 ± 2.21 | 97.92 ± 0.50 | 98.51 ± 0.59 | 2.43 ± 1.72 | 1.25 ± 0.19 |
| mae+mse Inter qMT | 32.13 ± 0.92 | 35.00 ± 1.13 | 97.94 ± 0.38 | 98.62 ± 0.34 | 2.25 ± 0.31 | 1.48 ± 0.16 |

NRMSE = normalized root mean squared error; PSNR = peak signal-to-noise ratio (decibel); SSIM = structural-similarity index. qMTNet+ no res: qMTNet+ structure without residual connection; qMTNet+ Gaussian: qMTNet+ trained with added Gaussian noise; qMTNet+ mae+mse: qMTNet+ trained with combination of mean absolute error and mean squared error.

Metrics are shown as mean ± standard deviation.
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