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Convolutional Neural Network-Based Automatic Segmentation of Substantia Nigra on Nigrosome and Neuromelanin Sensitive MR Images

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Original Article

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Recently, neuromelanin and nigrosome imaging techniques have been developed to evaluate the substantia nigra in Parkinson's disease. Previous studies have shown potential benefits of quantitative analysis of neuromelanin and nigrosome images in the substantia nigra, although visual assessments have been performed to evaluate structures in most studies. In this study, we investigate the potential of using deep learning based automatic region segmentation techniques for quantitative analysis of the substantia nigra. The deep convolutional neural network was trained to automatically segment substantia nigra regions on 3D nigrosome and neuromelanin sensitive MR images obtained from 30 subjects. With a 5-fold cross-validation, the mean calculated dice similarity coefficient between manual and deep learning was 0.70 ± 0.11. Although calculated dice similarity coefficients were relatively low due to empirically drawn margins, selected slices were overlapped for more than two slices of all subjects. Our results demonstrate that deep convolutional neural network-based method could provide reliable localization of substantia nigra regions on neuromelanin and nigrosome sensitive MR images.

Keywords: Parkinson's disease; Substantia nigra; Deep learning; Image segmentation; Nigrosome, neuromelanin

INTRODUCTION

Parkinson's disease is the second most common neuro-degenerative disease (1). The cause of Parkinson's disease is known as degeneration of dopaminergic neuron in the substantia nigra pars compacta (SNpc) (2). Recently, neuromelanin and nigrosome imaging techniques (3, 4) have been developed as indirect monitoring tools for determining dopamine activities in the substantia nigra (5). Neuromelanin imaging is obtained using strong T1-weighting and magnetization transfer (MT) preparation. Nigrosome imaging is obtained using paramagnetic susceptibility weighting. Although

visual assessments have been mainly performed to evaluate their structures, recent studies have shown that quantitative analysis of neuromelanin and nigrosome in the substantia nigra (6) could be helpful in various clinical applications.

However, manual delineation of the substantia nigra regions is difficult and time-consuming due to the substantia nigra's tiny size on MR images. In addition, simple approaches such as intensity-based thresholding are not appropriate due to inhomogeneous bias fields of MR images and the relatively low signal-to-noise ratio of substantia nigra imaging. In this context, automatic segmentation tools could provide efficient and objective quantitative analysis for substantia nigra regions. Recently, deep learning methods have been developed and validated for medical image segmentation (7-9). These methods have shown superior performances to other methods.

The objective of this study was to investigate the potential of convolutional neural network-based automatic region segmentation techniques for quantitative analysis of the substantia nigra. For training and validation, neuromelanin-sensitive and nigrosome-sensitive MR images were used. These images were generated from 3D multi-echo gradient echo acquisition.

MATERIALS AND METHODS

MR Image Acquisition

A recently proposed imaging technique (10) that could simultaneously obtain both neuromelanin and nigrosome contrasts for the substantia nigra was utilized in this study. To obtain these contrasts, MT pulses and flow saturation pulses were added to multi-echo 3D gradient sequence. Institutional review board approved 30 subjects were scanned* on a clinical 3T MRI with following multi-echo 3D gradient echo protocol: MT pulse (off-resonance = 860 Hz), regional saturation pulse (inferior to the imaging slab), TR = 80 ms, number of echoes = 5, TE = 4.9, 13.5, 22.2, 30.9, 39.6 ms, flip angle = 20, voxel size = 0.75 × 0.75 × 1.5 mm^3, bandwidth = 144 Hz/px, number of slices = 32, acceleration factor = 2, and total scan time = 5 min. From obtained five echo complex data (Fig. 1a), neuromelanin-sensitive image, nigrosome-sensitive image, and quantitative susceptibility map were reconstructed (Fig. 1b, 1c).

Manual Segmentation of the Substantia Nigra

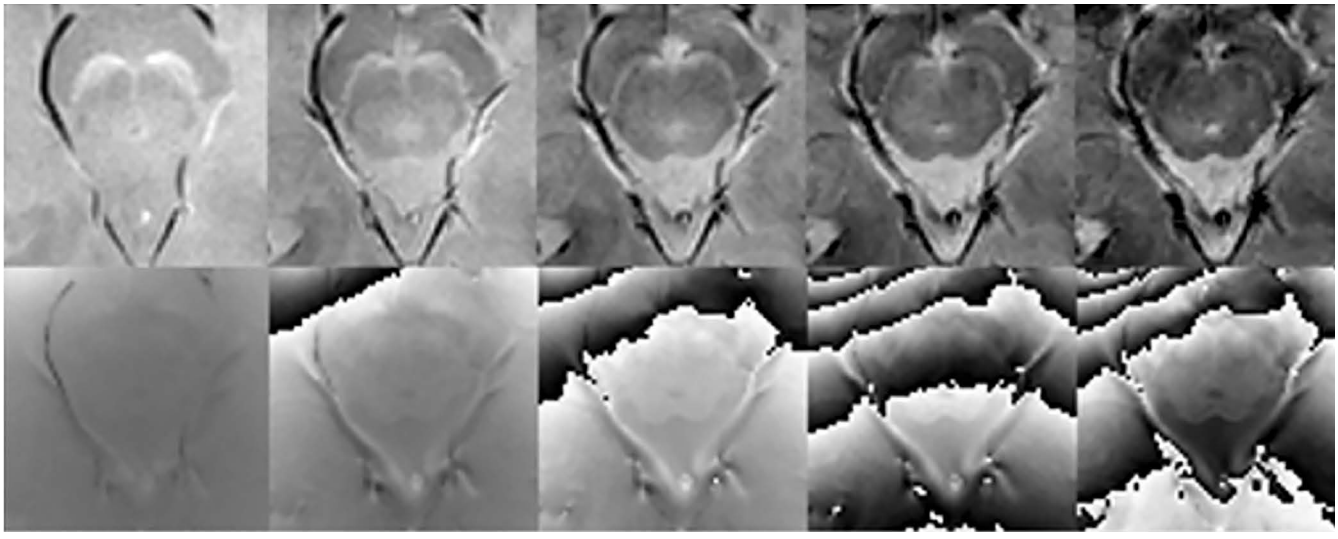
Ground truth regions for the substantia nigra were manually drawn by a neuroradiologist to train a deep learning based segmentation model. A previous study has suggested that three consecutive slices below the red nucleus are a good indication for diagnosing Parkinson's disease (11). Therefore, three consecutive slices inferior to the red nucleus were chosen for manual segmentations. In this step, a margin was drawn to sufficiently cover substantia nigra structures as shown in Figure 2a.

Automatic Segmentation Model

Our input data for the deep learning model were the first three echo magnitude 3D images obtained from each subject. Label data for substantia nigra regions were manually drawn by a neuroradiologist. Using these 3D input and label data, we trained the V-Net (12) architecture based on a fully convolutional neural network with 3D kernels. In this study, the depth of V-Net was 4 and 3 × 3 × 3 3D convolution kernels were used for all convolutional layers. The whole process of the automatic segmentation model is shown in Figure 3. Dice loss coefficient is effective for the classification of imbalanced class (13). Thus, we used dice loss coefficient as a loss function in this study. Note that the volume of the substantia nigra regions is very small compared to the volume of the entire image. Due to limited number of subjects, we performed various data augmentation processes such as cropping randomly, flipping left and right side over, and generating random noises to reduce the probability of over-fitting. As an output of the deep learning model, we generated a binary mask for substantia nigra regions. For the output of the automatic segmentation model, we added two refinement steps. First, we calculated the center of mass based on results to split left and right sides (Fig. 4b). Second, to eliminate remaining false-positive regions, we labeled connected components by 26-neighborhood and removed isolated small regions (Fig. 4a). These refinement steps were also implemented to be automatically performed. The model was configured to train our input data with batch size 2 over 128 epochs. It was trained and validated using PyTorch on a system equipped with a single graphical processing unit (NVIDIA K80).

Performance Evaluation

To demonstrate the utility of segmented regions of neuromelanin and nigrosome, quantitative values were calculated and compared using two region of interests of the left and right substantia nigra shown in Figure 2b. Neuromelanin volume ratios were calculated from neuromelanin sensitive image. Mean susceptibility values were calculated from quantitative susceptibility mapping



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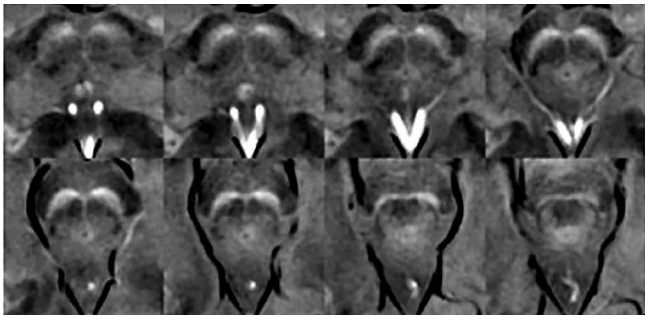

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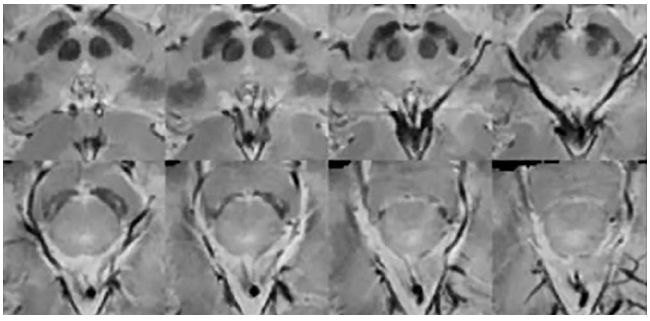


c

Fig. 1. Representative MR images of our protocol. (a) Acquired five-echo magnitude and phase. Reconstructed neuromelanin (b) and nigrosome (c) images.

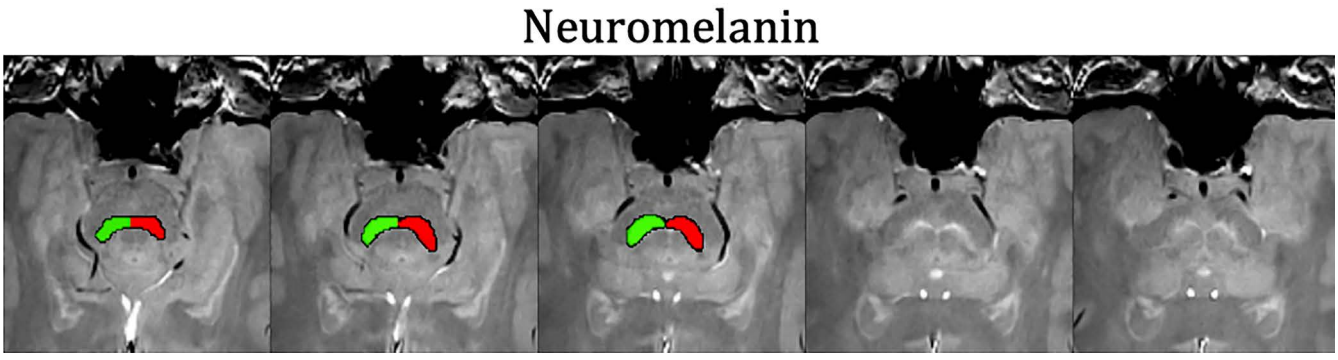
(Fig. 4c, 4d). Due to an insufficient number of included subjects in this study, a 5-fold cross-validation was performed. For each model, 24 subjects were used for training and 6 subjects were used for validation. The dice similarity coefficient can be used to evaluate the accuracy of segmentation. It describes the degree of similarity by measuring the overlap of two contour lines. For validation sets from the 5-fold cross-validation, dice similarity coefficients were calculated from segmentation results. Using manual segmentation and deep learning results, neuromelanin volume ratios were also calculated from the first echo magnitude. The ratio was calculated with the following equation:

$$\text{Neuromelanin Volume Ratio} = \left(\frac{\text{Pixels}>\text{mean}+3\text{SD}}{\text{Pixels}>\text{mean}+1\text{SD}} \right) \quad [1]$$

Mean susceptibility values were also calculated from the reconstructed quantitative susceptibility map.

RESULTS

The training was performed on a single graphical processing unit. The training time was approximately 2.2 hours for five different model training. For the 5-fold cross-validation, the calculated dice similarity coefficient value between manual and deep learning segmentations was 0.70 ± 0.11. Figure 5 visualizes segmentation results of manual and deep learning. Dice similarity coefficients were relatively low due to empirically drawn margins. However, selected slices were overlapped for more than two slices of all subjects. Figure 6a and 6b are representative examples of relatively low dice coefficient cases.



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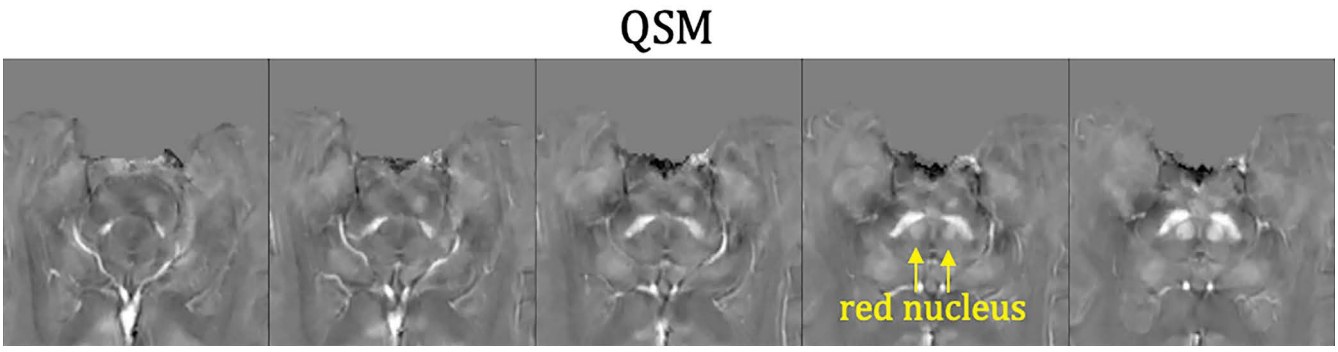


b

Fig. 2. Three slices below inferior parts of the red nucleus were chosen and regions including the substantia nigra with sufficient margins were manually drawn (a). Green and red areas represent right and left sides of the substantia nigra, respectively. Inferior parts of red nucleus (yellow arrows) were described on QSM images (b).

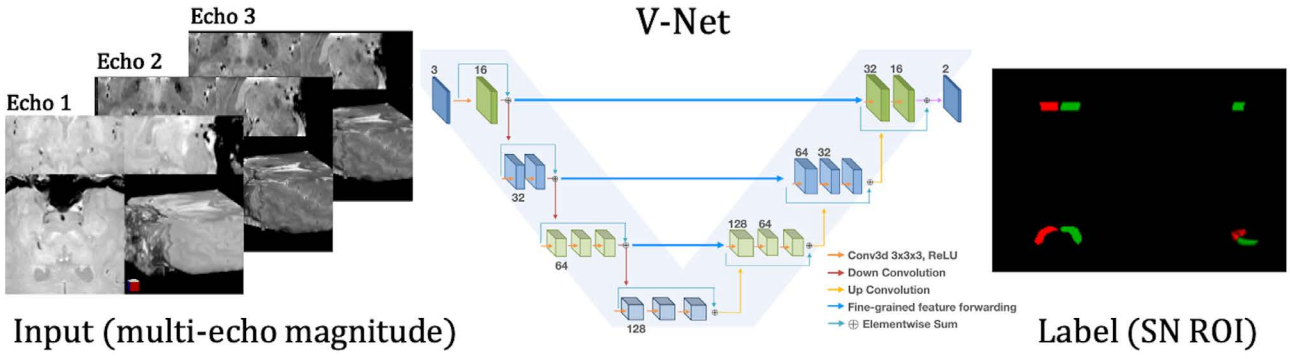


Fig. 3. Input and output of a 3D convolutional neural network-based automatic segmentation model.

Figure 7a and 7b show calculated quantitative values from manual segmentations and deep-learning based segmentations. For both neuromelanin and nigrosome analysis, these two measurements were highly correlated. For the estimated neuromelanin volume ratio, the calculated correlation coefficient between the two segmentations was 0.75 (Fig. 7a). For mean susceptibility values, the correlation coefficient between the two segmentations was 0.94 (Fig. 7b).

DISCUSSION

In this study, we trained a convolutional neural network to automatically segment substantia nigra regions on neuromelanin and nigrosome sensitive MR images. To

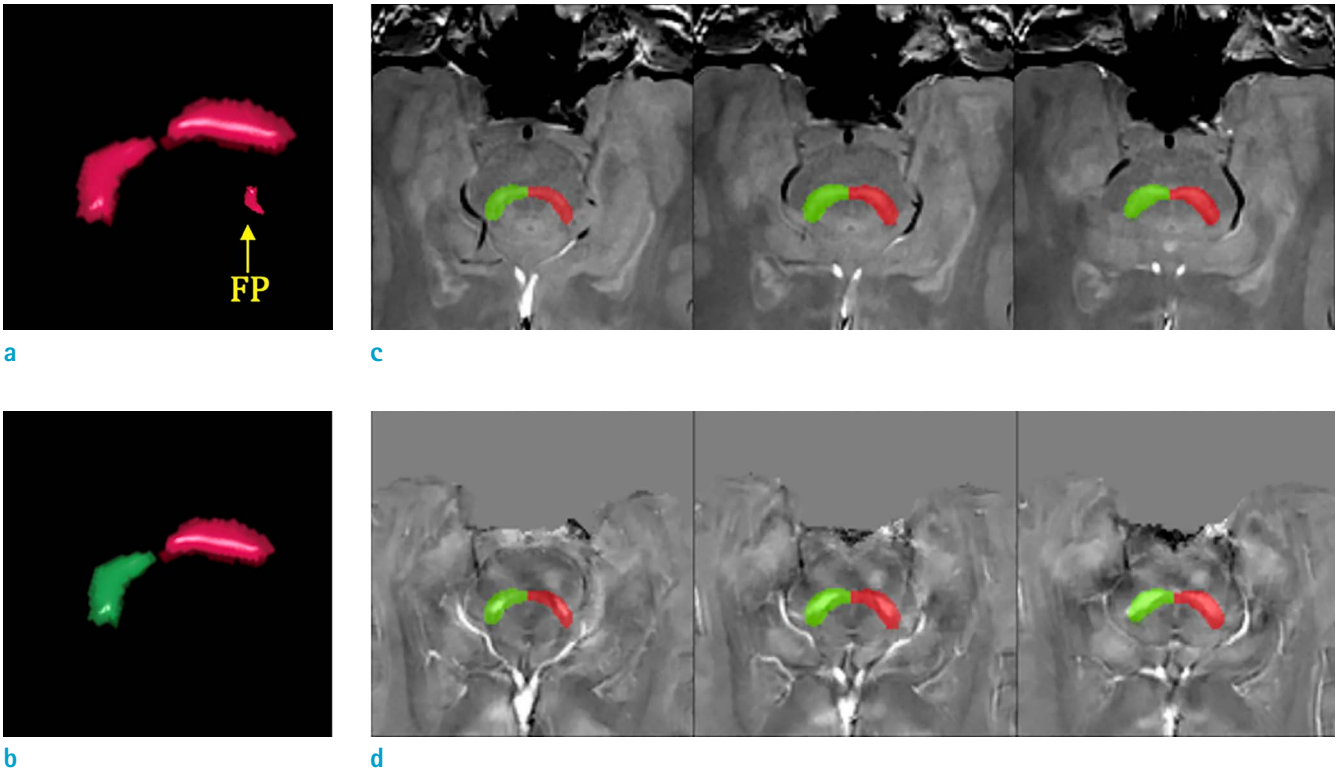


Fig. 4. Refinement steps for the network output (Step 1: False positive voxels were removed; Step 2: Left and right sides were divided). Representative segmentation results (a) before and (b) after refinement steps. (c) and (d) are overlapping results on neuromelanin sensitive image and quantitative susceptibility map, respectively.

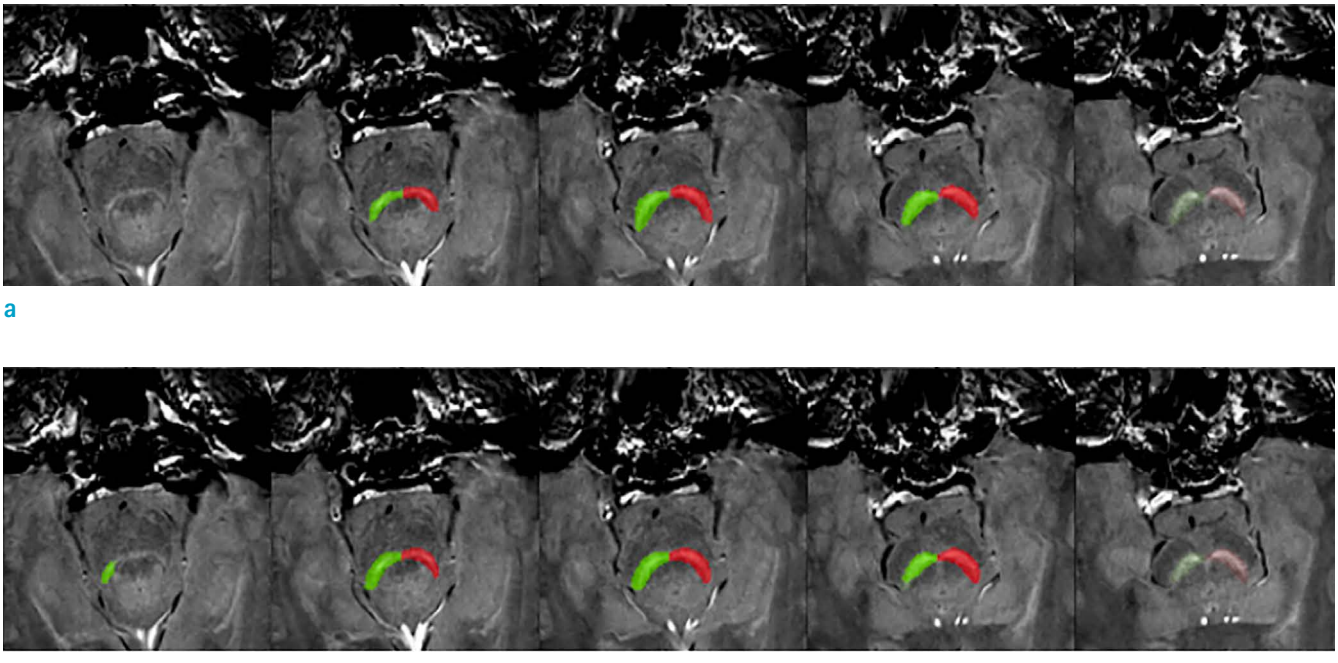
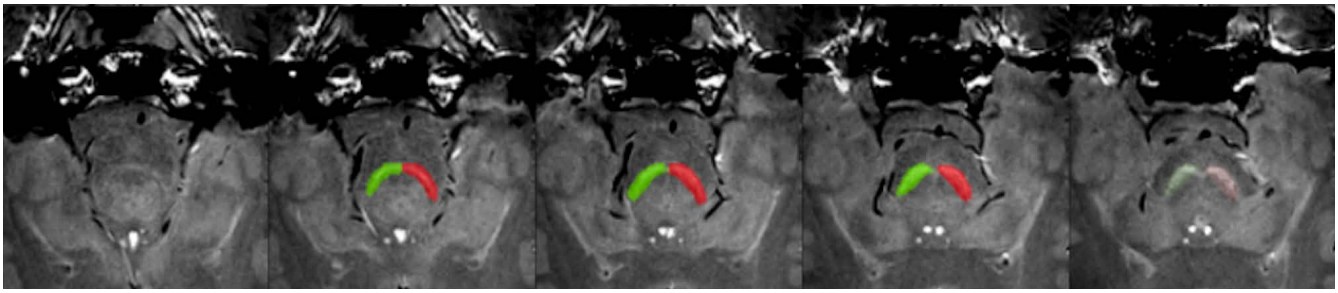


Fig. 5. Comparison of manual and deep learning results (Case of high DSC): (a) manual delineations, and (b) deep learning segmentations.



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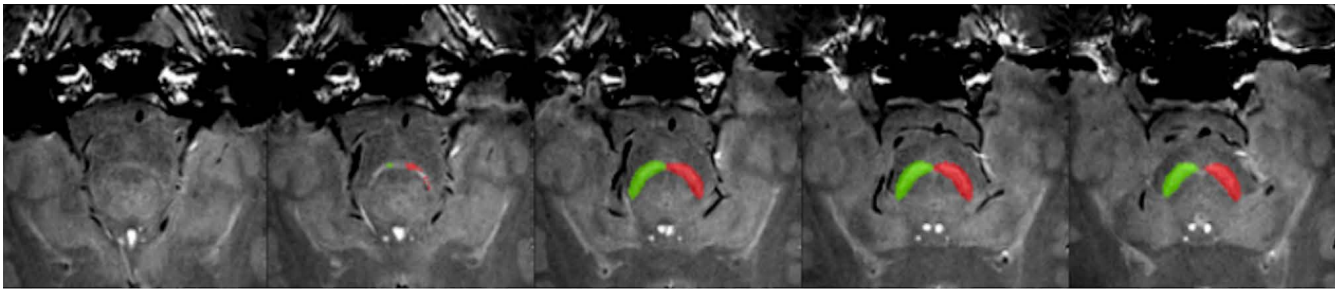

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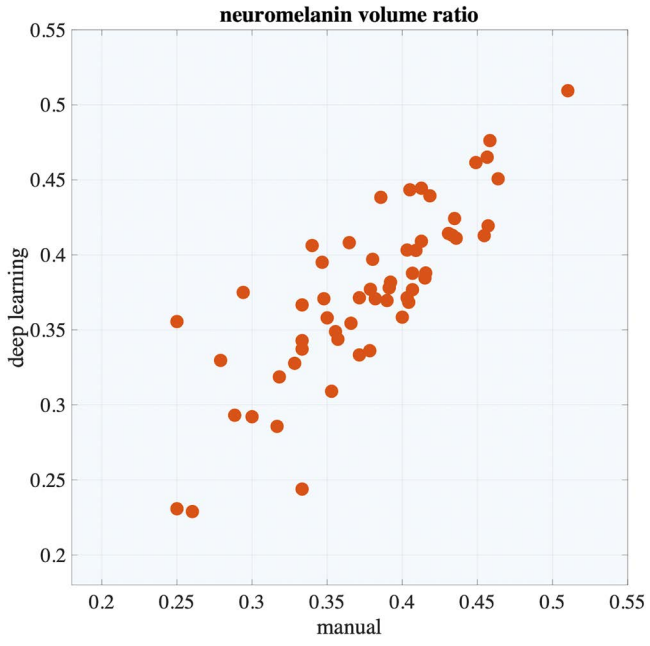
Fig. 6. Comparison of manual and deep learning results (Case of relatively low DSC): (a) manual delineations, and (b) deep learning results.



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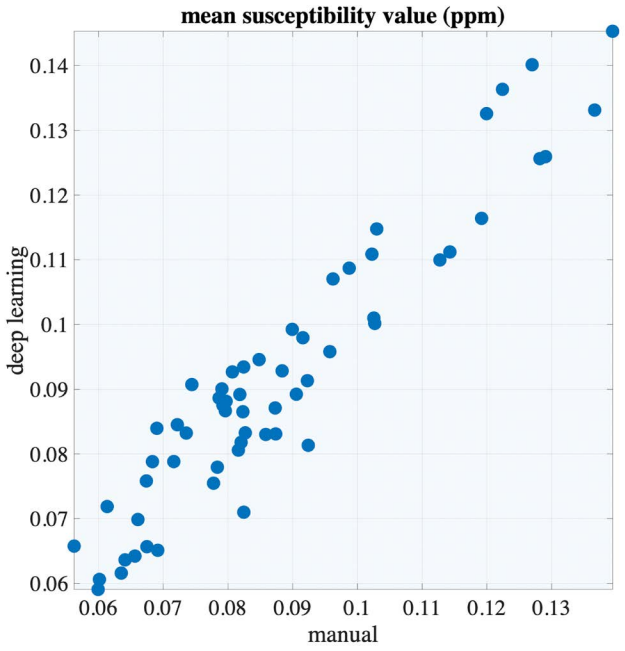

b

Fig. 7. Calculated quantitative values from manual segmentations and deep-learning based segmentations for (a) neuromelanin volume ratio (calculated correlation: 0.75) and (b) mean susceptibility value (calculated correlation: 0.94).

do this, we utilized a fully convolutional neural network architecture (V-Net) with 3D convolutional kernels. Cropped multi-contrast 3D images were used as input data and manually drawn masks were used as output data. Results demonstrated that the trained model could provide reliable localizations of substantia nigra regions on 3D MR images in validation data. Quantitative analysis of neuromelanin volume ratios and susceptibility values using segmented results demonstrated potential benefits of the trained model.

Calculated dice similarity coefficients between manual segmentation and network outputs seemed to be relatively low compared to those of other medical image segmentation studies. This is related to the fact that the substantia nigra is a very tiny structure and the boundary of the structure on the MR image is not well-delineated due to limited imaging resolution and signal-to-noise ratio. In this study, we used 0.5 as the thresholding value for the substantia region as the network output. However, by adjusting the thresholding value, we can easily reduce or increase the margin of segmented results. Considering that it is difficult to obtain a consistent delineation even if a manual drawing is performed by a radiologist, reliable localization is meaningful for applications of nigrosome-sensitive and neuromelanin-sensitive MRI.

Segmentation results provided reliable quantitative analysis results for both neuromelanin volume ratios on neuromelanin-sensitive images and susceptibility values on quantitative susceptibility maps. This showed the potential of automated quantitative analysis for Parkinson's disease patients in clinical practice. It can also reduce processing time to test data using a network model. Additionally, the pipeline of our quantitative analysis process does not need manual interventions. Although we demonstrated that relatively low dice similarity coefficients dit not significantly affect results of quantitative analysis, improved and consistent segmentation results should be demonstrated for actual distributions of clinical data. Therefore, to utilize this method in clinical practice, further investigations with more data are necessary.

In conclusion, this study demonstrated the potential of convolutional neural network-based automatic region segmentation techniques for quantitative analysis of the substantia nigra on neuromelanin and nigrosome images.

Acknowledgments

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