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MAJOR PAPER

Differentiating Alzheimer's Disease from Dementia with Lewy Bodies Using a Deep Learning Technique Based on Structural Brain Connectivity

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Purpose: Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are representative disorders of dementia of the elderly and the neuroimaging has contributed to early diagnosis by estimation of alterations of brain volume, blood flow and metabolism. A brain network analysis by MR imaging (MR connectome) is a recently developed technique and can estimate the dysfunction of the brain network in AD and DLB. A graph theory which is a major technique of network analysis is useful for a group study to extract the feature of disorders, but is not necessarily suitable for the disorder differentiation at the individual level. In this investigation, we propose a deep learning technique as an alternative method of the graph analysis for recognition and classification of AD and DLB at the individual subject level.

Materials and Methods: Forty-eight brain structural connectivity data of 18 AD, 8 DLB and 22 healthy controls were applied to the machine learning consisting of a six-layer convolution neural network (CNN) model. Estimation of the deep learning model to classify AD, DLB and non-AD/DLB was performed using the 4-fold cross-validation method.

Results: The accuracy, average precision and recall of our CNN model were 0.73, 0.78 and 0.73, and the specificity precision and recall were 0.68 and 0.79 in AD, 0.94 and 0.65 in DLB and 0.73 and 0.75 in non-AD/DLB. The triangular probability map of the MR connectome revealed the probability of AD, DLB and non-AD/DLB in each subject.

Conclusion: Our preliminary investigation revealed the adaptation of deep learning to the MR connectome and proposed its utility in the differentiation of dementia disorders at the individual subject level.

Keywords: *Alzheimer's disease, deep learning, dementia with Lewy bodies, structural brain connectivity*

Introduction

Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are representative disorders of dementia of the elderly. The prevalence of such senile dementia has been increasing globally and AD and DLB account for 70% of senile dementia and are the important social problems worldwide.[1,2]

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Neuroimaging in clinical medicine of dementia was previously mainly used to exclude other organic disorders, however now neuroimaging is one of the leading components of the early diagnosis of dementia disorders, because it can estimate the early structural and functional changes such as brain atrophy, hypoperfusion and hypometabolism in AD and DLB.[3–7]

The MR connectome is a recently developed neuroimaging technique for brain network analysis. Functional MR connectome with resting state functional MRI and a structural MR connectome based on diffusion tensor MR imaging have revealed the significant alteration of the brain network in various neurodegenerative disorders.[8–10]

In AD, several reports revealed that the disconnection and disability of "hub" areas in AD brain which integrating its cognitive symptoms.[11–14] Further, the alteration of the

brain network in AD, and DLB compared with healthy controls was also reported.[15,16] A graph analysis based group analysis is useful to reveal the alteration of the brain network in dementia disorders, but it is not easy to apply the results to estimate and classify disorders at the individual subject level. In this investigation, we proposed the adaption of machine learning as an alternative method of the graph theory to solve the disadvantage of brain network analysis.

Machine learning is one of the techniques that support artificial intelligence technology and the convolution neural network (CNN) is one of the major machine learning models that are suitable for image recognition and classification.[17] A multilayered neural network model including multiple convolution layers is called the "deep learning" machine learning model and has a high accuracy in image recognition and classification.

The network data handling in the graph analysis can be revealed as an adjacent matrix and its data type is similar to image data (Fig. 1). Therefore, the brain network can become a subject for machine learning and it may contribute to the recognition and classification of dementia disorders. The high accuracy of machine learning in image recognition and classification may be translocated to the network analysis by handling the adjacent matrix data of network as an image data. In this investigation, we try to adapt the machine learning to the structural MR connectome to distinguish and classify AD and DLB from healthy subjects.

Materials and Methods

Subjects

The Institutional Review Board approved this study and written informed consent was obtained from all subjects. Brain connectivity data from 48 subjects (18 AD; 7 males and 11 females average age 73.4 y.o., 8 DLB; 2 males and 6 females, 72.8 y.o. and 22 HC; healthy control subjects; 10 males and 12 females, 72.0 y.o.) were used. The diagnosis of AD was based on the criteria of DSM-4 and that of DLB was based on the clinical diagnostic criteria of DLB.[1,18]

MR imaging and structural network analysis

All MR studies were performed on a 3T MR unit (Achieva; Philips Medical Systems, Best, The Netherlands) with an 8-channel head coil. The structural connectivity data were constructed by a connectome mapper (http://www.connectomics.org/mapper/) based on deterministic tractography with 32 axis diffusion tensor MR images (TR/TE = 5452/70 ms, resolution = 1.75 × 1.75 mm, slice thickness (TH) = 3.0 mm, FOV = 224 × 224 mm, matrix = 128 × 128, number of excitations (NEX) = 2, *b* value = 0, 1000 s/mm, motion probing gradient (MPG) directions = 32, Δ/δ = 39.0/28.0 ms) and high-resolution 3D T_1-weighted images (MPRAGE; TR/TE/inversion time (TI) = 15/3.54/1100 ms, resolution = 0.81 × 0.81 mm, TH = 0.86 mm, FOV = 260 × 260 mm, matrix = 320 × 320 mm).[19]

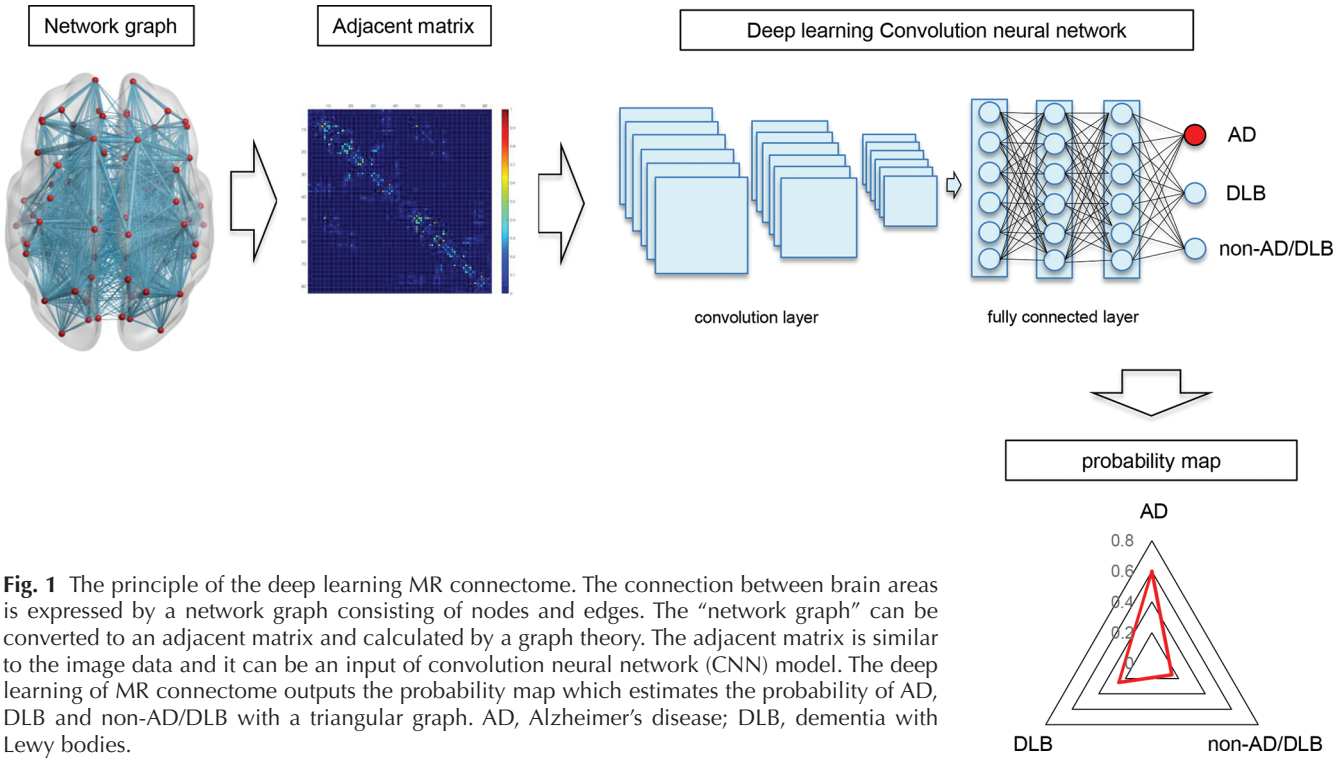

Fig. 1 The principle of the deep learning MR connectome. The connection between brain areas is expressed by a network graph consisting of nodes and edges. The "network graph" can be converted to an adjacent matrix and calculated by a graph theory. The adjacent matrix is similar to the image data and it can be an input of convolution neural network (CNN) model. The deep learning of MR connectome outputs the probability map which estimates the probability of AD, DLB and non-AD/DLB with a triangular graph. AD, Alzheimer's disease; DLB, dementia with Lewy bodies.

Machine learning and estimation

For the construction and modification of the machine learning model, Windows PC with Intel Core i5 2GHz 16GB and Neural Network Console version 1.10 (https://dl.sony.com/) was used as a deep learning integrated development environment. As a learning model, a six layer CNN model including three convolution layers and three fully connected layers was adapted (Fig. 2). The parameters of each layer are described in Fig. 2. Adam was applied as a parameter update method. The 4-fold cross-validation method was used for the training and estimation of the learning model (Fig. 3). In the 4-fold cross-validation method the data set was established with all data were divided into four groups. Three groups were used as the training data including five cases for validation and the other group was used as the test data.

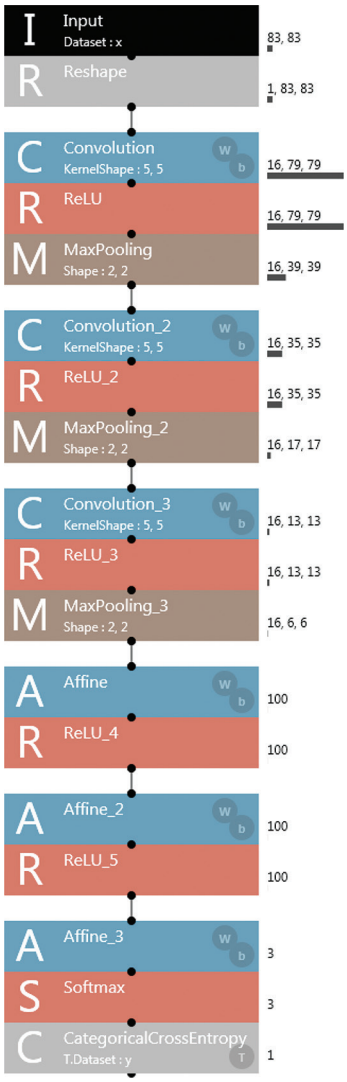

Fig. 2 A convolution neural network (CNN) machine learning model adapted to the MR connectome. As a machine learning model, a six-layer CNN model with three convolution layers (each consisting of convolution, ReLU; Rectified Linear Unit and MaxPooling) and three fully connected layers (Affine with ReLU) was adapted. The specific elements of the layer were described on the right side of each layer.

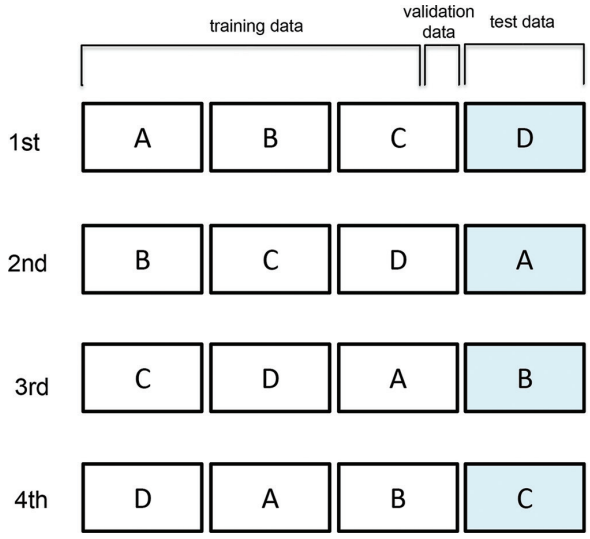

Fig. 3 The 4-fold cross-validation method. In the 4-fold cross-validation method, all sample data were split into four groups. One group was set as the test data and the remaining three groups were set as the training and validation data. An average of four times of investigations was estimated as the performance of the machine learning model.

The learning model was trained by 100 epochs learning with the training data and the estimation was executed 10 times for the test data and the average value was recorded as an output of the data set. The average values of accuracy, precision, recall (sensitivity) and F-measure in four estimations with four data sets were recorded as the final outputs. The accuracy, precision, recall and F-measure were calculated by the following numerical formulas:

$$Accuracy = \frac{True\ positive + True\ negative}{True\ positive + False\ positive + False\ negative + True\ negative}$$

$$Precision = \frac{True\ positive}{True\ positive + False\ positive}$$

$$Recall = \frac{True\ positive}{True\ positive + False\ negative}$$

$$F\text{-}measure = \frac{2 \times Precision \times Recall}{Precision + Recall}$$

Results

The accuracy of CNN learning model for classification of AD, DLB and HC was 0.73 and the average precision and recall were 0.78 and 0.73 in the 4-fold cross validation method (Table 1). In the confusion matrix, the specificity precision and recall were 0.68 and 0.79 in AD, 0.94 and 0.65 in DLB and 0.73 and 0.75 in non-AD/DLB. The probability map of CNN learning model in classification AD, DLB and non-AD/DLB was revealed by a radar chart. The probability map was

provided by the softmax function at the output part of the deep CNN model and revealed the possibility of AD, DLB and non-AD/DLB in each subject ranging from 0.0 to 1.0 (Fig. 4).

Discussion

The human brain consists of over 10 billion neurons with a complex brain network of various sized connections from micro- to macro-level connections.[20] It is difficult to recognize and estimate the micro-level brain network technically, but the macro-level scale brain network can be estimated by the structural and functional MR connectome using diffusion tensor MR tractography and function MRI.[21,22]

By using a graph theory, complex network can be visualized by a "graph" consisting of nodes and edges. In structural MR connectivity of the brain, the node is a brain area and the edge is the number of streams in the MR tractography between two nodes.[23] The complex geometric structure of the graph can be converted to a simple adjacent matrix, and analyzed mathematically with various metrics reflecting the features of the network, such as centricity, clustering coefficients, small-worldness, global or local efficiency and characteristic path length.[24–26] Group studies using the functional and structural MR connectome revealed the alteration of brain network about various brain degenerative diseases.[23,27–30] Group analysis is a useful method for the estimation of brain disorders, but it is not easy to adapt its results to classify each individual subject. To classify each subject as AD, DLB or non-AD/DLB, we must extract the characteristics of AD, DLB and non-AD/DLB from many network metrics and establish a rule and equation to differentiate these conditions.

For extraction of the characteristics of the brain network, a machine learning model of image recognition and classification can be employed that may contribute to the assignment of differentiation and classification of the individual brain network. This consideration was based on the similarity of the type of network and image data and which suggested that machine learning, and especially the CNN model, was suitable for the estimation of the individual brain network.[31,32] The high accuracy of the CNN model in image recognition and classification is based on three features; the convolution layer, multilayered neural network classifier part and a optimization by a back propagation method.[33,34] The convolution layer extracts the features of matrix data by multiple filters and the multilayer (deep) convolution can extract the high dimensional features and its output is transmitted to following multiple layer neural network.[17] Further, the back propagation is an optimization algorithm to improve the accuracy of the current deep learning machine learning model which name comes from "backward propagation of errors". The back propagation tunes up the calculation parameters in each layer of multiple layer neural network to minimize the error between the final output and expected result.[34]

In this investigation, MR connectome in combination with a six-layer deep CNN model provided 0.71 accuracy in identification and classification of AD, DLB and non-AD/DLB. The 0.71 accuracy of our investigation was not beyond that of previous studies, which found 0.88 accuracy using CT, 0.97 using brain volumetry and fluorodeoxyglucose-positron emission tomography (FDG-PET), 0.95 using Cerebrospinal fluid (CSF) data and 0.76 using electroencephalogram.[35–39] However, our preliminary study revealed a new possibility of the MR connectome in the estimation of dementia disorders. The MR connectome together with a deep learning technique provides the probability of dementia disorders in an

Table 1 Results of the estimation of the deep learning MR connectome in the classification of AD, DLB and HC

			AD	DLB	HC
Accuracy	0.73				
Avg. precision	0.78	Precision	0.68	0.94	0.73
Avg. recall	0.73	Recall	0.79	0.65	0.75
Avg. F-measure	0.74	F-measure	0.72	0.76	0.73

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; HC, healthy control.

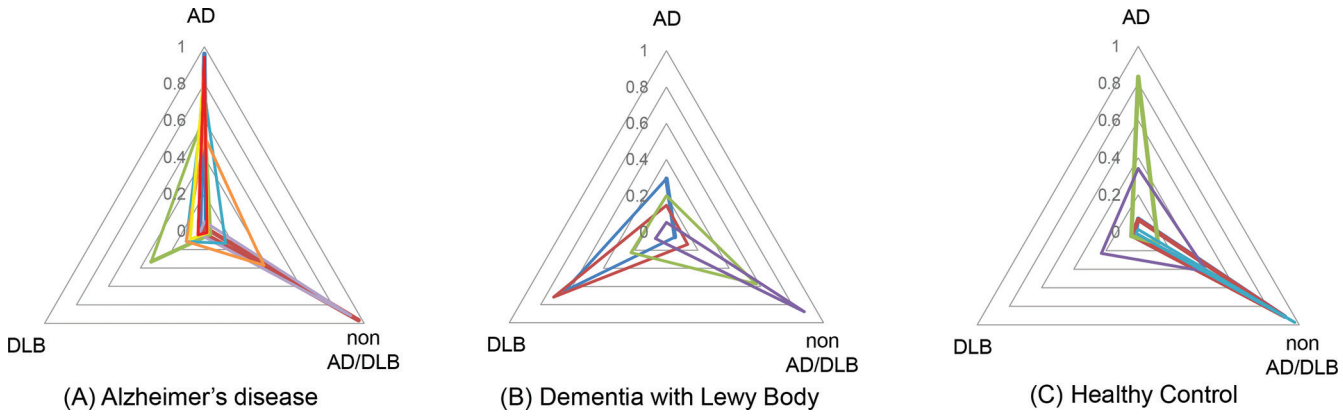

Fig. 4 Probability map provided by the deep learning MR connectome of AD (**A**), DLB (**B**) and HC (**C**). The triangular radar graph reveals the probability of AD, DLB and non-AD/DLB in each subject ranging from 0.0 to 1.0. AD, Alzheimer's disease; DLB, dementia with Lewy bodies; HC, healthy control.

individual subject. If the probability map of deep learning MR connectome is introduced into clinical practice of dementia, it may support the clinician in decision making and treatment of dementia disorders.

Our investigation has some limitations. The number of subjects is insufficient; especially the relative insufficiency of DLB subjects is a problem that should not be ignored. The relatively low accuracy of DLB classification might be induced by the small number of subjects in addition to the variety of DLB pathologies. In the construction of the structural MR connectome, the fiber tracking method was a deterministic method, not the latest probabilistic method. The adoption of the latest two-shell probabilistic method is ideally desirable.[40] The accuracy of our machine learning model in the classification of dementia may be improved by solving these problems.

Conclusion

Deep CNN machine learning technique could be adapted to structural brain network analysis and a MR connectome in combination with deep learning would contribute to the differentiation of dementia disorders in individual subjects.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of interest associated with this manuscript.

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