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A Prediction Model for Cognitive Performance in Health Ageing Using Diffusion Tensor Imaging with Graph Theory

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***Abstract*—In this study, we employed diffusion tensor imaging (DTI) to construct brain structural network and then derive the connection matrices from 96 healthy elderly subjects. The correlation analysis between these topological properties of network based on graph theory and the Cognitive Abilities Screening Instrument (CASI) index were processed to extract the significant network characteristics. These characteristics were then integrated to estimate the models by various machine-learning algorithms to predict user's cognitive performance. From the results, linear regression model and Gaussian processes model showed presented better abilities with lower mean absolute errors of 5.8120 and 6.25 to predict the cognitive performance respectively. Moreover, these extracted topological properties of brain structural network derived from DTI also could be regarded as the bio-signatures for further evaluation of brain degeneration in healthy aged and early diagnosis of mild cognitive impairment (MCI).**

Keywords: Diffusion tensor imaging (DTI), graph theory, cognitive abilities screening instrument (CASI), linear regression model, Gaussian processes model, mild cognitive impairment (MCI)

I. Introduction

Alzheimer's disease (AD) is the most common form of dementia, that comprising 50-70% of all dementia cases[1]. Currently, 35.6 millions of people suffer from AD globally and the number is predicted to rise to 115.4 million by 2050[2]. By the time patients begin to suffer from the symptoms of dementia, it causes memory loss and other cognitive deficits.

Mild Cognitive Impairment (MCI) is a cognitive decline that cannot be simply explained by an individual's age and education, but does not notably intervene with the individual's activities of daily living. The risk of conversion to AD is higher in MCI than in the general aged population, as up to 50% of these patients develop the disease within 2 years [3]. In a four- year prospective cohort study, 41% of patients with MCI progressed to dementia by the end of the study. A systemic review found that most types of dementia are preceded by a recognizable phase of mild cognitive decline. The prevalence of MCI for people age 65 and older ranged from 3% to 19% which means that currently around 71,000 to 447,000 persons in Taiwan have MCI and this number will increase to 170,000 to 1,080,000 in year 2031. Thus, early detection and diagnosis for people with MCI has been an inevitable health issue in Taiwan.

Recently, non-invasive neuroimaging and neurophysiological techniques, such as structural magnetic resonance imaging (MRI), diffusion MRI, functional MRI, and EEG/MEG have provided a new perspective on structural and functional connectivity patterns of the human brain. And the combination of neuropsychological techniques and neuroimaging data is one proposed way to increase diagnostic power for dementia, since preclinical AD has been associated with both cognitive and imaging changes [4, 5]. Moreover, some researches also employed the machine learning and pattern recognition methods to not only classify AD, MCI and normal controls from individual MRI datasets, but also predict clinical score of cognitive performance [6-9].

In this study, we aim to demonstrate an objective method to predict individual cognitive performance based on the topological properties of brain structural network and machine learning approaches. We assume that these features of network characteristics derived from brain structural network could be regarded as the imaging-based bio-signatures to benefit our understanding in aging and neurodegenerative diseases. These complex features will be integrated as the bio-signatures for not only further early detection and diagnosis, but also a useful tool for evaluating the efficacy of intervention in patients with MCI and AD.

II. Materials and Methods

A. Participants

96 elderly Han Chinese male subjects with mean age of 80.6±5.6 years (range, 65-92 years) recruited from the community and a public veterans home in northern Taiwan. All participants were undergone neuropsychological assessments. The neuropsychological assessments include the following two batteries: (1) Mini-Mental-State Examination (MMSE); (2) Dementia severity will be assessed by the clinical dementia rating (CDR) score.

B. Cognitive Performance

All participants also had sufficient visual and auditory acuity to undergo cognitive testing. There were administrated the Cognitive Abilities Screening Instrument, Chinese version (CASI C-2.0) The CASI test, which is a 100-point

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cognitive test and provides quantitative assessment in nine domains of cognitive function (long-term memory, short-term memory, attention, concentration/mental, language, visual construction, and list-generating fluency), was designed for cross-cultural studies.

The exclusion criteria included the following: (1) presence of any diagnosis on Axis I of DSM-IV, such as mood disorder or psychotic disorder; (2) neurobiological disorder, such as dementia, head injury, stroke, or Parkinson's disease; (3) severe medical illness, such as malignancy, heat failure, and renal failure; (4) illiteracy; (5) subjects with CDR score of great than 0.5, or a score of 50 or less on CASI [14]; and (6) having ferromagnetic foreign bodies or implants anywhere in the body that are electrically, magnetically, or mechanically activated. Based on these criteria, a group of non-demented elderly subjects have been recruited for this study.

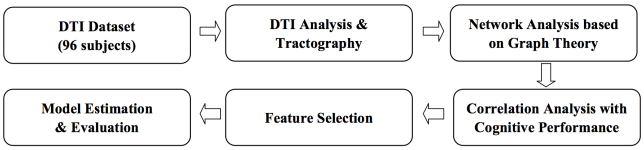

Figure 1 The diagram of workflow for structural connectivity analysis and the estimation of prediction model

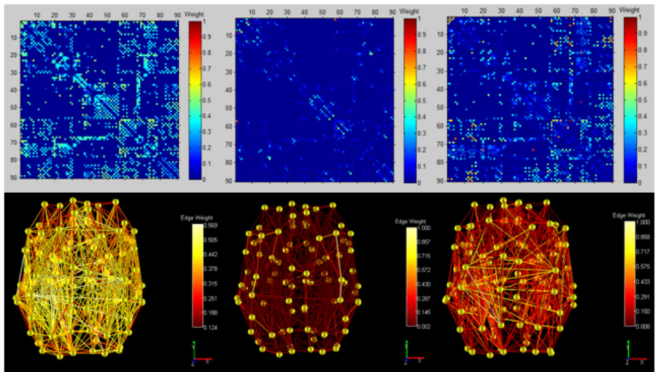

Figure 2 The visualization of the weighted connection matrices and brain networks of FA, FN, and Length matrix

The top left shows white matter connection matrix of FA value between any two nodes; the bottom left shows visual connection between the nodes. In the same way, the middle and the right shows whiter matter connection matrix and visual brain network based on fiber number and fiber length, respectively. And FN value and Length value were normalized with range of 0-1. The data was only normalized for visualization, not for all analyses in this study.

C. MRI acquisition

All healthy subjects and patients were received an MRI scan within 1 month after their cognitive assessments. Images have been acquired on a 3.0T Siemens MRI scanner (Siemens Magnetom Tim Trio, Erlangen, Germany) with 12-channels head coil in National Yang-Ming University in Taiwan. All the images were acquired parallel to the anterior commissure-posterior commissure line with the same FOV of 256 mm. DTI was performed using single-shot echo-planar imaging (EPI) sequence (TR/TE=10000/83 ms, diffusion encoding in 30 directions, b = 0, 1000 s/mm^2, matrix size = 128 × 128, number of average = 4).

D. Construction of Brain Structural Connection Matrix

Diffusion tensor imaging (DTI)), a non-invasive technique that can explore human WM microstructure, provide mounting evidence that features of WM microstructure are closely coupled with cognitive functions [15-17].

Figure 1 showed the diagram of workflow for structural connectivity analysis and the estimation of prediction model. The detail will be described in the following parts of D, E , F and G.

96 datasets will be processed by using PANDA (a Pipeline for Analyzing braiN Diffusion images, http://www.nitrc.org/projects/panda/) for DTI reconstruction, deterministic tractography and network construction. To determine the nodes of brain networks, we used the automated anatomical labeling (AAL) template to segment the whole cerebral cortex into 90 areas (45 regions in each hemisphere)[18]. Finally, we could extract three kinds of brain network connection matrices, fractional anisotropy (FA) matrix, fiber number (FN) matrix and fiber length (FL) matrix, to describe the edge between nodes within each subject shown in Fig. 2. The weighted values of FA matrix indicate the degree of myelination within each structural connection. From the FN structural connectivity, weights indicate the number of joint fibers connected between anatomical nodes. And from FL matrix, the weighted values indicate the length of fiber that reached from one node to another.

E. Topological Properties of Structural Brain Networks

First, the weight of edges in these three brain network matrices should be preprocessed to reduce the noise effect induced by data acquisition, reconstruction and tractography algorithm. For FN matrix, we kept the weight of edge when it is greater than 3, else setup as zero [13]. For FA matrix and FL matrix, when the weight of edge of FN matrix is greater than 3, the weight of edge is retained in both matrices, otherwise would be defined as zero. Moreover, these three weighted matrices could be also binarized based on that value is zero or not. One more rule for FA matrix is based on the FA value. If FA value is bigger than 0.2, the value of binary FA matrix would be 1, else would be zero.

In the second step, the structural networks were analyzed by using graph theoretical methods and six topological properties of structural brain network were then calculated by the Brain Connectivity Toolbox (BCT, http://www.brain-connectivity-toolbox.net): (1)Degree: node degree is the number of links connected to the node. (2)Strength: node strength is the sum of weights of links connected to the node. (3) Local Efficiency: The local efficiency is the global efficiency computed on the neighborhood of the node. (4)Local Clustering Coefficient: the clustering coefficient of a node is the number of existing connections between the node's neighbors divided by all their possible connections. (5) Shortest Path Length: shortest path length is the minimum number of edges that must be traversed to go from one node to another. (6) Node Betweenness Centrality: node betweenness centrality is the

fraction of all shortest paths in the network that contain a given node [15].

F. Correlation Analysis

The bivariate correlation analysis and partial correlation analysis with co-variables of age and geriatric depression scale (GDS) factors were performed using SPSS software between the CASI scores and the topological properties derived from the binary and the weighted anatomical brain networks respectively in all 96 subjects. Then we extracted 26 features based on the criteria of correlation coefficient in two methods of correlation analysis

TABLE 1 Twenty-six network characteristics with correlation coefficient both greater 0.3 and p<0.01 with co-variables of age and GDS factors

Index of Feature	Region	Connection Matrix	Network Measure
1	ACG.L	binary FA (FN>3&FA≧0.2)	Eloc
2	ACG.L	weighted FA (FN>3&FA≧0.2)	Eloc
3	SPG.L	weighted Length(FN>3)	C
4	ANG.L	weighted FA (FN>3)	Eloc
5	ANG.L	weighted FA (FN>3&FA≧0.2)	Eloc
6	PCUN.L	weighted FA (FN>3)	Strength
7	PCUN.L	weighted FA (FN>3&FA≧0.2)	Strength
8	PCUN.L	weighted FA (FN>3)	Eloc
9	PCUN.L	weighted FA (FN>3&FA≧0.2)	Eloc
10	PCL.L	weighted FA (FN>3)	Strength
11	PCL.L	weighted FA (FN>3&FA≧0.2)	Strength
12	PCL.L	weighted Length (FN>3)	Strength
13	PCL.R	binary FA/FN/Length (FN>3)	L
14	PCL.R	binary FA (FN>3&FA≧0.2)	L
15	PCL.R	weighted FA (FN>3)	Strength
16	PCL.R	weighted FA (FN>3&FA≧0.2)	Strength
17	PCL.R	weighted Length (FN>3)	Strength
18	PCL.R	weighted Length (FN>3)	C
19	THA.L	weighted FA (FN>3)	Eloc
20	STG.L	binary FA/FN/Length (FN>3)	Degree
21	STG.L	binary FA (FN>3&FA≧0.2)	Degree
22	STG.L	binary FA/FN/Length (FN>3)	L
23	STG.L	binary FA (FN>3&FA≧0.2)	L
24	STG.L	weighted FA (FN>3)	Strength
25	STG.L	weighted FA (FN>3&FA≧0.2)	Strength
26	STG.L	weighted Length(FN>3)	Strength

ACG.L: Anterior Cingulate Gyrus in the left hemisphere; SPG.L: Superior Parietal Gyrus in the left hemisphere; ANG.L: Angular Gyrus in the left hemisphere; PCUN.L: Precuneus in the left hemisphere; PCL.L: Paracentral Lobule in the left hemisphere; PCL.R: Paracentral Lobule in the right hemisphere; THA.L: Thalamus in the left hemisphere ; STG.L: Superior Temporal Gyrus in the left hemisphere. Eloc: Local efficiency; C: Clustering coefficient; L: Shortest path Length.

TABLE 2 The performances of the estimated prediction models based on four algorithms and the leave-one-out cross-validation

Leave- one-out cross-validation					
Algorithm		Training data			validation data
		Correlation coefficient	*Mean absolute error*	*Root mean squared error*	*Mean absolute error*
Linear Regression Model	Average ± Std	0.7024 ± 0.0215	5.0954 ± 0.1907	6.6462 ± 0.1930	5.8120 ± 5.2935
	Median	0.7052	5.0620	6.6380	4.0961
PLS Classifier	Average ± Std	0.7981 ± 0.6403	4.8448 ± 0.0613	6.3443 ± 0.1711	6.8488 ± 5.6973
	Median	0.7316	4.8632	6.3908	5.2786
Gaussian Processes	Average ± Std	0.8542 ± 0.0030	4.1594 ± 0.0492	5.3826 ±0.1363	6.2543 ± 5.1784
	Median	0.8533	4.1754	5.4193	5.0663
Multilayer Perception	Average ± Std	0.9623 ± 0.0157	2.7315 ± 0.9845	3.3833 ± 1.1129	10.1988 ± 8.1555
	Median	0.9656	2.5734	3.1192	7.4496

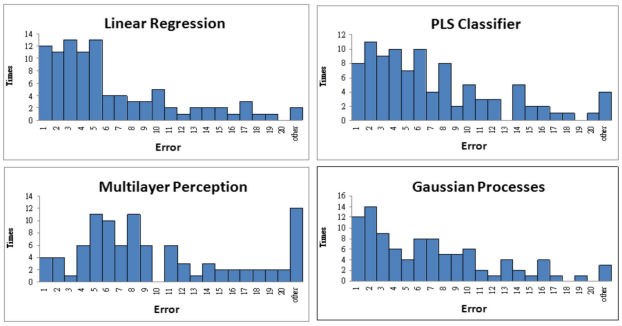

Figure 3 The histograms of the estimated error based on four selected algorithms and leave-one-out cross-validation

both greater than 0.3 and p value less than 0.01 shown in Table 1.

G. Estimation of Prediction Model

The model for predicting the cognitive performance using the above 26 topological properties of brain structural network was established by an opensource machine learning software - Weka (http://www.cs.waikato.ac.nz/ml/weka). Four algorithms for model estimation were selected for this study including linear regression model, PLS classifier, Gaussian processes, and multilayer perception. In order to realize the ability of prediction in each model, the leave-one-out cross-validation was employed here. 96 repetitions by 95 subjects as training data and 1 subject as testing data were analyzed to obtain the averaged/median correlation coefficient, mean absolute error and root mean squared error in training data and the mean absolute error in testing data. Table 2 shows the analyzed results based on four algorithms.

III. RESULTS

Table 1 shows the significant features extracted from the topological measurements of brain network characteristics. The correlation coefficient between these features and CASI score was higher than 0.3 and p<0.01. According to the results, we obtained twenty-six features and applied these features into further estimation of prediction model for cognitive performance in healthy aging subjects.

Table 2 shows the averaged/median correlation coefficient, mean absolute error, and root mean squared error

of training data and the mean absolute error of testing data by four algorithms with leave one out cross validation. From Table 2, the linear regression model shows the smallest mean absolute error of 5.81 with standard deviation of 5.29. The result of Gaussian processes was relatively better. The correlation coefficient in the training set was up to 0.85 and the error is about 6.25. The multilayer perception shows the highest correlation coefficient of 0.96, but poor ability of prediction with the highest mean absolute error of 10.2.

IV. Discussions

In this study, we successfully constructed binary and weighted brain anatomical networks from 96 normal elderly subjects using DTI. Network topological properties were analyzed based on graph theory, and twenty six features were extracted with high association according to the correlation analysis with CASI scores. Four kinds of machine learning algorithm, linear regression model, PLS classifier, Gaussian processes model, and multilayer perception, were then used for the estimation of prediction model for cognitive performance in healthy ageing. The leave-one-out cross-validation was employed for the evaluation of these models.

For the results, the linear regression model shows the lower mean absolute error for validation data and the Gaussian processes presents the higher correlation coefficient in training data. Moreover, we also analyzed the histogram of mean absolute error to identify the ability of models for predicating cognitive performance score. Figure 3 shows the histogram of error distribution of four algorithms. The error in multilayer perception algorithm appeared many times in the range of greater than 10. The errors of other three algorithms are mainly less than 10. That is the reason we could obtain the smaller median value of prediction error of 4.09 and 5.06 in linear regression model and Gaussian processes model respectively shown in Table 2.

Moreover, we will integrate with other imaging modalities, such as T1 and resting-state functional MRI for extracting more significant features. Based on T1 image, we could employ T1-based voxel-based morphology and T1-based anatomical network analysis. Based on resting-state functional MRI, the frequency information map of regional homogeneity, amplitude of low-frequency fluctuation and functional connectivity could also be analyzed for extracting the imaging-based bio-signatures. These features will provide different viewpoints from structural compositions, anatomical connectivity, and functional connectivity based on various MRI images. A prediction model for cognitive performance in healthy ageing with higher accuracy and lower estimated error will be estimated with these features in the future.

V. Conclusion

In this study, we purposed an approach using diffusion tensor imaging and graph theory to extract the features from three kinds of brain network matrices and various network characteristics. Using four machine learning algorithms, we estimated the prediction models based on the features and evaluated the efficiency of prediction models by leave-one-out cross-validation. The results showed that this concept is workable but the estimated error is still not good enough. We will integrate with other MRI modalities and extract more significant features to implement the prediction model with higher accuracy and lower error. Also, we will apply this approach for the MCI and AD dataset and look forward to evaluating the degree of cognitive performance after treatment and the efficiency of intervention in patient with dementia.

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