Resting-State Whole-Brain Functional Connectivity Networks for MCI Classification Using L2-Regularized Logistic Regression

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***Abstract*—Mild cognitive impairment (MCI) has been considered as a transition phase to Alzheimer's disease (AD), and the diagnosis of MCI may help patients to carry out appropriate treatments to delay or even prevent AD. Recent advanced network analysis techniques utilizing resting-state functional Magnetic Resonance Imaging (rs-fMRI) has been widely used to get more comprehensive understanding of neurological disorders at a whole-brain connectivity level. However, how to explore effective brain functional connectivity from fMRI data is still a challenge especially when the ultimate goal is to train classifiers for discriminating patients effectively. In our research, we studied the functional connectivity of the whole brain by calculating Pearson's correlation coefficients based on rs-fMRI data, and proposed a set of novel features by applying Two Sample T-Test on the correlation coefficients matrix to identify the most discriminative correlation coefficients. We trained a L2-regularized Logistic Regression classifier based on the five novel features for the first time and evaluated the classification performance via leave-one-out cross validation. We also iterated 10-fold cross validation ten times in order to evaluate the statistical significance of our method. The experiment result demonstrates that classification accuracy and the area under receiver operating characteristic (ROC) curve in our method are 87.5% and 0.929 respectively, and the statistical results prove that our method is statistically significant better than other three algorithms, which means our method could be meaningful to assist physicians efficiently in "real-world" diagnostic situations.**

***Index Terms*—Alzheimer dementia, functional connectivity network, logistic regression, mild cognitive impairment.**

I. Introduction

ALZHEIMER'S disease (AD) has been the most common form of dementia which affects elderly's health seriously and brings huge burden to the families and society. In order to relieve and even prevent this healthcare crisis, researchers around the world have made great efforts to develop effective pharmacological and behavioral methods for postponing AD.

Currently, mild cognitive impairment (MCI) has been considered as a transition phase between normal aging and dementia, especially AD. It means there are deficiencies in memory of individuals, but this impairment has not significantly influenced individuals' daily functioning, and not met clinical criteria of dementia. Previous studies have proved that people with MCI have a higher risk of conversion to AD: about $10\% \sim 15\%$ annually [1]–[3] comparing to normal elderly: about $1\% \sim 2\%$ annually [4]. Thus, earlier discrimination of MCI is crucial to warn potential patients and guide them through appropriate treatments for delaying or even preventing onset of AD. Generally, clinicians make diagnosis for MCI by judging whether individuals meet criteria of MCI. The diagnostic criteria for MCI, as formulated by the Mayo Alzheimer's Disease Research Center (ADRC), are as follows [5]:

1) Memory complaint by patient, family or physician.
2) Normal activities of daily living.
3) Normal global cognitive function.
4) Objective impairment in one area of cognitive function as evidenced by scores > 1.5 standard deviations (SD) below age-appropriate norms.
5) Clinical dementia rating score of 0.5.
6) Not demented.

As can be seen from the above, clinicians diagnose MCI mainly based on their observations, experience, and individuals' subjective reports. So there may be difficult to complete an accurate and objective diagnosis due to the very mild symptoms of cognitive impairment in MCI patients.

Recent researches about brain informatics have showed that AD and MCI patients exhibit differences in the brain structure or cognitive functions. Due to the inherent advantages, e.g., notably safety and high spatial-temporal resolution, functional magnetic resonance imaging (fMRI), which reflects the spontaneous blood oxygen level-dependent signal fluctuations, has been used to investigate the brain functional changes in AD and MCI widely [6], [7]. Especially, brain function can be evaluated by measuring functional connectivity (FC) between spatially distinct brain areas based on resting-state fMRI (rs-fMRI) [8], [9]. For example, during a episodic memory task in MCI patients, decreased connections were found between hippocampus and prefrontal gyrus, temporal gyrus and parietal gyrus [10]. Delbeuck *et al.* also revealed abnormal functional connectivity in several brain regions of MCI patients [11]. Reduced connection strength and efficiency were also observed in resting-state functional brain networks of MCI patients [12], [13]. Other researchers found

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there were discriminative network node attributes in prefrontal cortex, insula, and white matter connectivity in the parietal cortex between normal elderly and MCI patients [14]. In the previous study of our research team, we found that functional connectivity of MCI patients decreased in the regions of left dorsolateral superior frontal gyrus, the right orbital frontal gyrus and left inferior temporal gyrus [15]. Thus the functional connectivity has provided obvious evidences for the abnormal brain functional changes between normal elderly and MCI patients.

Concurrently, advanced statistical algorithms and pattern recognition techniques have been actively used to mine neurodegenerative patterns during the early stage of AD [16]–[18]. Due to the powerful statistical analysis and knowledge mining abilities, machine learning and pattern classification methods would be useful to assist clinicians effectively in finding the very mild symptoms of cognitive impairment and implementing "real-world" clinical diagnosis for MCI. For example, Wee *et al.* constructed functional connectivity networks from multi-frequency sub-bands and trained a SVM based classifier to diagnose MCI with classification accuracy of 86.5% [14]. Javier Escudero *et al.* investigated the classification of AD, MCI and control subjects based on MRI features with four techniques, and the accuracy rates for classification of controls from AD and MCI were 89.2% and 72.7% respectively [19]. In our previous research, we proposed an ontology driven decision support method with reasoning engine implemented using C4.5 algorithm for diagnosing MCI based on cortical thickness in MRI, and the performance was 80.2% sensitivity [20]. Therefore, it is crucial to develop machine learning based diagnosis and prognosis methods for MCI using identified subtle brain biomarkers from fMRI data, then early intervention may be applied to MCI patients in order to delay or even prevent the transition from MCI to AD or other dementias.

The ultimate aim of this study is to design a classification method for discriminating and classifying MCI individuals from normal control subjects using rs-fMRI data. In our research, we studied the functional connectivity of the whole brain by calculating Pearson's correlation coefficients based on rs-fMRI data, and proposed a set of novel features by applying Two Sample T-Test on the correlation coefficients matrix to identify the most discriminative correlation coefficients. We trained a L2-regularized Logistic Regression classifier based on the five novel features for the first time and evaluated the classification performance via leave-one-out cross validation. We also iterated 10-fold cross validation 10 times in order to evaluate the statistical significance of our method. The experimental result demonstrates that classification accuracy in our method is 87.5%, which is better than other popular classification algorithms (including K-nearest neighbors, neural network, classification tree, random forest, and support vector machine). Specifically, the area under receiver operating characteristic (ROC) curve (AUC), which is generally considered as a metric to measure diagnostic power and make cost-versus-benefit decisions, is 0.929 in our method, indicating relatively good diagnostic capability. The statistical results of classification accuracy and AUC also demonstrate that L2-regularized Logistic Regression is statistically significant better than K-nearest neighbors, classification tree, and support vector machine.

This paper is organized as follows: the following section describes the procedures about data pre-processing, feature extraction from FC and classification. Section III shows the comparison of several classifiers' performance metrics. Section IV discusses abnormal FC, performance comparison, and limitations of our framework, followed by the conclusion in Section V. Besides, there are many technical terms in this paper, and we list these technical terms and their abbreviations in Table I to improve the readability.

TABLE I
TECHNICAL TERMS AND ABBREVIATIONS

Technical Terms	Abbreviations
mild cognitive impairment	MCI
Alzheimer's disease	AD
magnetic resonance imaging	MRI
functional magnetic resonance imaging	fMRI
positron emission tomography	PET
resting-state fMRI	rs-fMRI
Digital Imaging and Communications in Medicine	DICOM
functional connectivity	FC
Alzheimer's disease Neuroimaging Initiative	ADNI
subjects with MCI	MCIs
normal control subjects	NCs
Statistical Parametric Mapping software	SPM
Resting-State fMRI Data Analysis Toolkit	REST
Waikato Environment for Knowledge Analysis	WEKA
Montreal Neurological Institute space	MNI
automated anatomical labeled template	AAL
regions of interest	ROI
left dorsolateral superior frontal gyrus	SFGdor.L
right orbital middle frontal gyrus	ORBmid.R
left middle frontal gyrus	MFG.L
left lingual gyrus	LING.L
left temporal pole	TPOsup.L
left median cingulate and paracingulate gyri	DCG.L
right supramarginal gyrus	SMG.R
left supramarginal gyrus	SMG.L
left middle temporal gyrus	MTG.L
Vapnik-Chervonenkis dimension	VC dimension
receiver operating characteristic curve	ROC
area under ROC curve	AUC

II. MATERIALS AND METHODOLOGY

A. Subjects

All of the subjects used in this research were selected from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu/). The ADNI project was

launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations [21]. The primary goal of ADNI is to determine whether serial MRI, fMRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to assess the brain's structure and function and then track the progression of AD.

This research included 36 subjects with MCI (MCIs) and 24 normal control subjects (NCs). All subjects gave written informed consent at the time of enrollment for imaging and genetic sample collection and completed questionnaires approved by each participating site's Institutional Review Board (IRB). By analyzing preprocessed results, we excluded 20 subjects either for the excessive head motion (more than 2.0 mm of maximal translation and 2.0° of maximal rotation) or due to the normalized error. Finally, 22 MCIs and 18 NCs were retained for further study. The NCs' ages ranged from 65.2 to 94.7($\mathrm{M} = 77.30$, $\mathrm{SD} = 7.33$, male/female $= 10/8$), and the MCIs' ages ranged from 66.3 to 87.4($\mathrm{M} = 74.91$, $\mathrm{SD} = 5.88$, male/female $= 11/11$). There were no significant differences between two subject groups in age ($\mathrm{p} = 0.26$) and gender distribution ($\mathrm{p} = 0.79$).

B. FMRI Data Acquisition and Preprocessing

All the fMRI data were downloaded in original DICOM format from the ADNI website. The fMRI data were acquired using a 3.0 Tesla Philips Medical Systems during the task-free scans. The acquisition parameters for the resting state fMRI were depicted as follows: Flip angle $= 80°$; repetition time (TR) $= 3000$ ms; echo time (TE) $= 30$ ms; pixel size $= 3.3 \times 3.3$; slice thickness $= 3.3$ mm; matrix size $= 64 \times 64$. Detailed acquisition parameters could be referred at the ADNI website (http://www.adni-info.org/).

In this study, we preprocessed the original fMRI data with Statistical Parametric Mapping software (SPM8) running under Matlab 7.0 on Ubuntu. Firstly we removed the first 10 image volumes of functional time series manually to stabilize the MR signal, and retained 130 volumes for each subject. Then we implemented following preprocessing steps including slice timing, realignment, normalization to the Montreal Neurological Institute (MNI) space (resampling voxel size $= 3$ mm $\times$ 3 mm $\times$ 3 mm) and smoothing using a Gaussian kernel of $4 \times 4 \times 4$ mm^3 full-width at half maximum (FWHW). Finally, all the data were filtered with a low frequency range (0.01–0.08Hz) to remove effects of very low frequency drift and high frequency noise using the REST Toolkit (http://pub.restfmri.net/) [22]. The automated anatomical labeled (AAL) template was used to define the brain regions of interest (ROI) [23]. This template divides the whole cerebra into 90 ROIs with 45 for each hemisphere. The time series of each ROI was obtained by averaging the fMRI time series over all voxels in the corresponding region.

C. Feature Extraction From Functional Connectivity

The framework of our MCI classification method is depicted graphically in Fig. 1. FC which examines inter-ROI correlations in neuronal variability [24] is usually measured using a pairwise

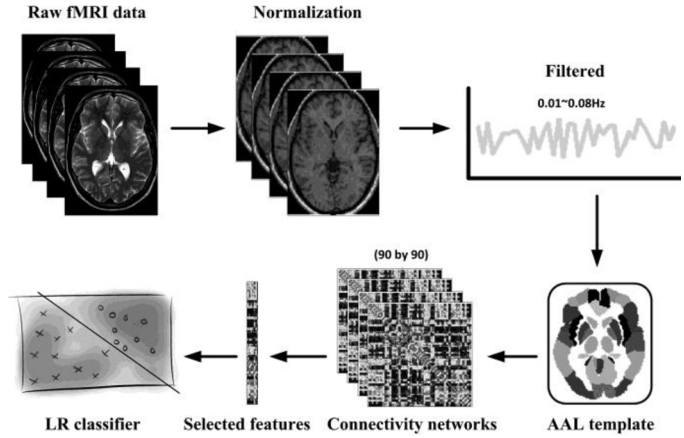


Fig. 1. Schematic diagram illustrating the proposed classification method.

Pearson's correlation coefficients between a given pair of brain ROIs. Following data preprocessing, the Pearson's correlation coefficients were calculated between time series of each pair of regions and then a correlation coefficients matrix ($\mathrm{M}_{(90\times90)}$) was obtained for each subject. Since the matrix is symmetric, only the elements above the diagonal were used for the further study. The element $\mathrm{M}_{(\mathrm{i,j})}$ of the matrix represented the correlation coefficient between region i and region j.

In order to detect the significant differences among the FC between two subject groups, a Two Sample T-Test ($\mathrm{p} < 0.001$) was used to investigate the differences of every possible connectivity between MCIs and NCs. Compared with NCs, five pairs of connectivity were significantly different in MCIs (see Table II and Fig. 2). The three decreased connectivity in MCIs were between left dorsolateral superior frontal gyrus (SFGdor.L) and right orbital middle frontal gyrus (ORBmid.R), left middle frontal gyrus (MFG.L) and right orbital middle frontal gyrus (ORBmid.R), left lingual gyrus (LING.L) and left temporal pole (TPOsup.L); the two increased connectivity in MCIs were between left median cingulate and paracingulate gyri (DCG.L) and right supramarginal gyrus (SMG.R), left supramarginal gyrus (SMG.L) and left middle temporal gyrus (MTG.L). Finally, we selected these five discriminative correlation coefficients as a set of novel features and input them to the following classification framework.

D. Classification Using Logistic Regression

As can be seen from the above, we have proposed five novel features after Two Sample T-Test. The FC of MCI and NC groups showed significant difference on each feature, this also implied that the distributions of two groups' correlation coefficients on these features were nearly linearly separable (see Fig. 3). Thus, we adopted the high-efficiency linear Logistic Regression classifier in the proposed method.

Logistic Regression has been widely used in many fields like social science and medical field. It is a type of probabilistic statistical classification model and measures the relationship between a categorical dependent variable and one or more independent variables by using probability scores as the predicted values of the dependent variable. In our method, we used Logistic Regression to explore the best fitting model to describe the relationship between MCI individuals and the set of novel

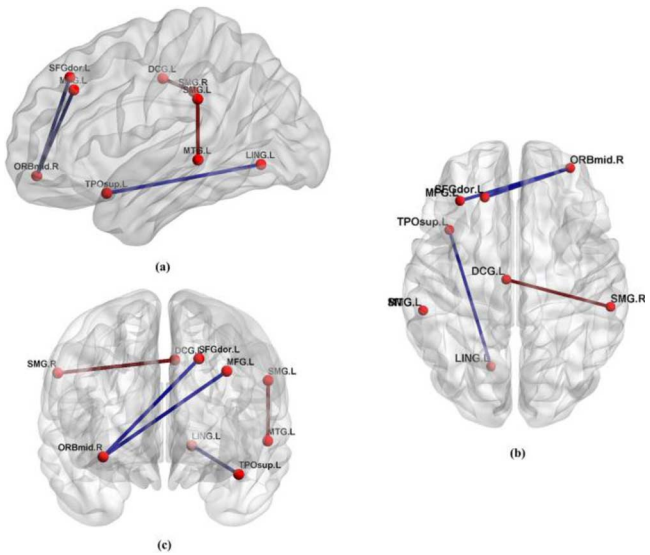


Fig. 2. Abnormal functional connectivity in the MCI group. (a) Sagittal direction. (b) Axial direction. (c) Coronal direction. The red dots represent those AAL regions with significantly abnormal connectivity. The red lines indicate significantly increased connectivity in MCI group while the blue lines indicate significantly decreased connectivity in MCI group.

TABLE II
SIGNIFICANT DIFFERENCE OF CONNECTIVITY BETWEEN MCIS AND NCS

AAL region	AAL region	MCI	NC	P value
Decreased connectivity in MCI				
SFGdor.L	ORBmid.R	-0.035320	0.305652	0.000015
MFG.L	ORBmid.R	0.004579	0.342187	0.000063
LING.L	TPOsup.L	-0.148602	0.095847	0.000283
Increased connectivity in MCI				
DCG.L	SMG.R	0.395715	0.203558	0.000843
SMG.L	MTG.L	0.057768	-0.245769	0.000467

- The AAL region columns show the pairs of regions that have significant difference of connectivity.
- The MCI column represents the mean correlation coefficients of these pairs of regions in MCI group while the NC column represents the mean correlations coefficients in NC group.
- P is the P value of Two Sample T-Test between two groups.

features. Logistic Regression generated the coefficients of features, which could be used to assess features' significance levels, and formed a formula to predict a logit transformation of the probability of MCI:

$$\text{logit}(p) = \beta_0 + \beta_1 x_1 + \cdots + \beta_5 x_5 \tag{1}$$

where p is the probability of presence of MCI. The logit transformation is defined as the logged odds:

$$\text{odds} = \frac{p}{(1-p)} = \frac{(\text{probability of presence of MCI})}{(\text{probability of absence of MCI})} \tag{2}$$

and

$$p = \exp \frac{(\beta_0 + \beta_1 x_1 + \cdots + \beta_5 x_5)}{(1 - \exp(\beta_0 + \beta_1 x_1 + \cdots + \beta_5 x_5))} \tag{3}$$

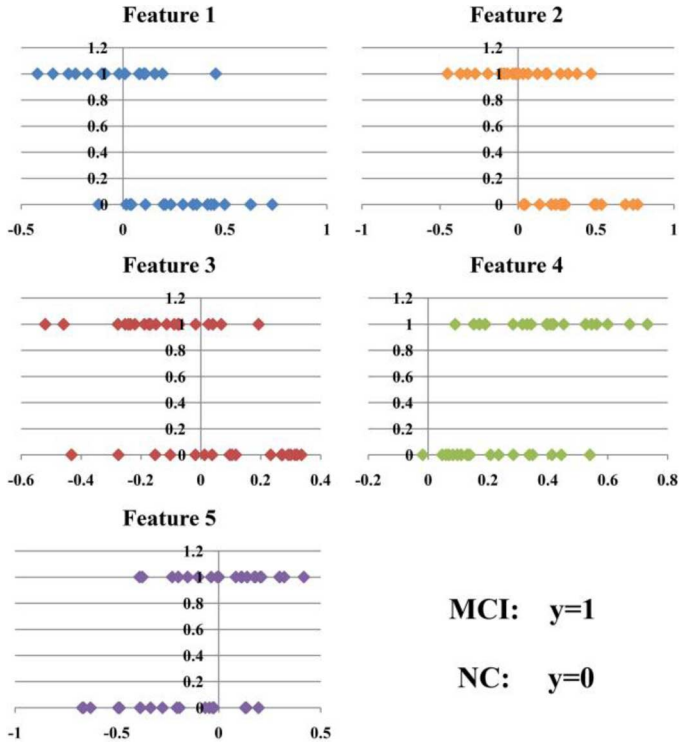


Fig. 3. Distributions of two groups' correlation coefficients on five features.

$$\frac{p}{(1-p)} = \exp(\beta_0 + \beta_1 x_1 + \cdots + \beta_5 x_5) \tag{4}$$

$$\text{logit}(p) = \text{In}(\frac{p}{1-p}). \tag{5}$$

Unlike the ordinary linear regression, we chose parameters by maximizing the likelihood of observing the sample values rather than minimizing the sum of squared errors.

Further, considering the limited data instances in our experiment, we used L2 regularization in Logistic Regression to improve the performance of the classification model. Because L2 regularization has a close relationship with minimization of the Vapnik-Chervonenkis dimension (VC dimension) [25] of the learned classifier, it would tune and generalize the model and solve the problem of bias-variance trade off.

We implemented L2-regularized Logistic Regression using LIBLINEAR [26] and evaluated classification performance in an integrated Data Mining toolkit named WEKA (Waikato Environment for Knowledge Analysis, version 3.7.9) [27]. Considering the limited data instances in this research, we used leave-one-out cross validation strategy to ensure a relatively unbiased estimate of the generalization power of the classifiers to new subjects. In this strategy, L2-regularized Logistic Regression classifier was trained using 39 instances and the remaining one was used to test the performance. This process was repeated 40 times to ensure that each instance has been tested. At the end, the recorded performance measures of the 40 tests were averaged. Simultaneously, we trained other five popular classification algorithms (including K-nearest neighbors, neural network, classification tree, random forest, and support vector machine) using the same novel feature set in WEKA to compare the performance of our method. Learning parameters of these algorithms were listed in Table III.

TABLE III
THE LEARNING PARAMETERS OF ALGORITHMS SETTING IN WEKA

Logistic Regression
▪ Training error cost (C): 6.0
▪ Regularization type: L2 (squared weights)
▪ Normalization: True
▪ ProbabilityEstimates: True
▪ Implementation: LIBLINEAR
K-Nearest Neighbours
▪ Number of neighbours: 1
▪ DistanceWeighting: No distance weighting
▪ DistanceFunction: EuclideanDistance
▪ WindowSize: 0
▪ Implementation: IBk
Neural Network
▪ HiddenLayers: a
▪ LearningRate: 0.3
▪ Momentum: 0.2
▪ NormalizeAttributes: True
▪ Seed: 0
▪ TrainingTime: 500
▪ ValidationSetSize: 0
▪ Implementation: MultilayerPerceptron
Classification Tree
▪ ConfidenceFactor: 0.25
▪ MinNumObj: 2
▪ NumFolds: 3
▪ ReducedErrorPruning: False
▪ Seed: 1
▪ SubtreeRaising: True
▪ Unpruned: False
▪ UseMDLcorrection: True
▪ Implementation: J48
Random Forest
▪ MaxDepth: 0
▪ NumExecutionSlots: 1
▪ NumFeatures: 0
▪ NumTrees: 10
▪ Seed: 1
▪ Implementation: RandomForest
Support Vector Machine
▪ KernelType: RBF, $e^{-0.0000*(x-y).(x-y)}$
▪ Cost (C): 1.0
▪ eps: 0.001
▪ Loss: 0.1
▪ Estimate class probabilities: False
▪ Normalize data: False
▪ Seed: 1
▪ Implementation: LIBSVM

III. EXPERIMENT RESULT

We have compared L2-regularized Logistic Regression algorithm with other five classification algorithms, and the weighted average of classification accuracy (averaged using weights proportional to class frequencies in the dataset) for each algorithm is synthesized in Table IV. To evaluate the performance of each algorithm for MCI diagnosis, we also computed the number of true positives *TP* (i.e., the number of MCIs which were correctly identified by the classifier), the number of true negatives *TN* (i.e., the number of NCs which were correctly identified by the classifier), the number of false positives *FP* (i.e., the number of NCs which were falsely identified as MCIs by the classifier), the number of false negatives *FN* (i.e., the number of MCIs which were not identified by the classifier). To comprehend these metrics visually, please see Table V.

TABLE IV
THE CLASSIFICATION ACCURACY AND AUC OF SEVERAL ALGORITHMS

Algorithm	Classification accuracy (Weighted Avg.)	AUC
Logistic Regression	87.50%	0.929
K-Nearest Neighbours	75%	0.737
Neural Network	82.5%	0.874
Classification Tree	75%	0.729
Random Forest	75%	0.850
Support Vector Machine	80%	0.788

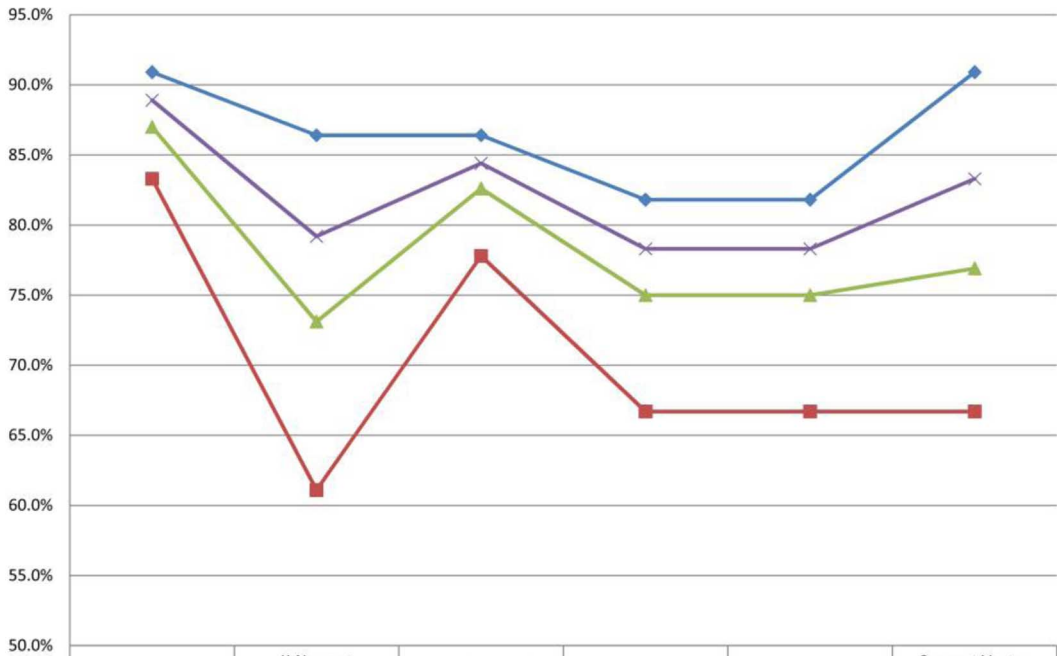
TABLE V
A CONFUSION MATRIX FOR MCI CLASSIFICATION

		Predicted Class		
		MCI	**NC**	**Total**
Actual Class	**MCI**	TP(true positives)	FN(false negatives)	m1
	NC	FP(false positives)	TN(true negatives)	m0
	Total	n1	n0	n

We then calculated the following statistical metrics to evaluate and compare the diagnostic power of different classification algorithms:

- The true positive rate (TPR) or sensitivity is defined as: $TP/(TP+FN)$.
- The true negative rate (TNR) or specificity is defined as: $TN/(FP+TN)$.
- Precision is defined as: $TP/(TP+FP)$.
- Recall is defined as: $TP/(TP+FN)$ whose calculating method is same to TPR.
- F-Measure is the weighted harmonic mean of precision and recall.
- The Kappa statistic is defined as: $(p_0 - p_e)/(1 - p_e)$, where $p_0 = (TP+TN)/n$, $p_e = [(n_1/n)^*(m_1/n)] + [(n_0/n)^*(m_0/n)]$.

Among these metrics, we expect higher values of sensitivity, specificity, precision, F-measure, and Kappa statistic which indicate better classification performance. The Kappa statistic which measures the agreement of prediction with the true class is expected to have a value close to 1.0 (1.0 signifies complete agreement). The experiment result is shown in Fig. 4 and supports the conclusion that L2-regularized Logistic Regression



	Logistic Regression	K-Nearest Neighbours	Neural Network	Classification Tree	Random Forest	Support Vector Machine
Sensitivity/Recall(%)	90.9%	86.4%	86.4%	81.8%	81.8%	90.9%
Specificity(%)	83.3%	61.1%	77.8%	66.7%	66.7%	66.7%
Precision(%)	87.0%	73.1%	82.6%	75.0%	75.0%	76.9%
F-Measure(%)	88.9%	79.2%	84.4%	78.3%	78.3%	83.3%

Fig. 4. The comparison of six classifiers' metrics for classifying MCI (sensitivity, specificity, precision, F-measure).

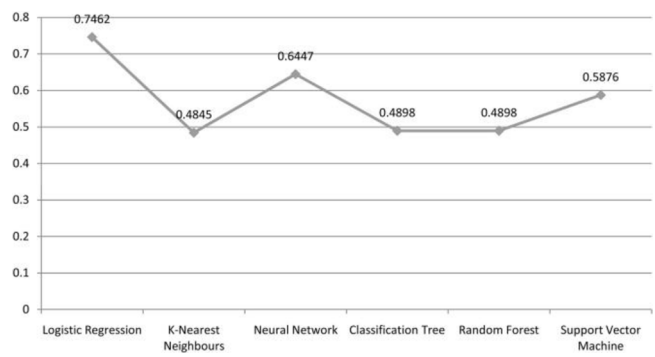


Fig. 5. The comparison of six classifiers' Kappa statistics.

algorithm used in our method gets a higher sensitivity, specificity, precision, and F-measure than other five classification algorithms. The value of Kappa statistic when using Logistic Regression is 0.7462 which is the most close to 1.0 (see Fig. 5).

Meanwhile, we used ROC curve and the area under the ROC curve (AUC) as shown in Table IV and Fig. 6. to measure classification imbalances of these classifiers. The ROC of L2-regularized Logistic Regression is the most upper left one among these algorithms, and the highest AUC of 0.929 obtained in our method means that it has a high true positive rate for a low false positive rate.

In order to evaluate if L2-regularized Logistic Regression is statistically better than other algorithms, we conducted a standard experiment in WEKA that ran these six machine learning algorithms on our dataset and then statistically analyzed the results. In this experiment, we adopted 10-fold cross validation strategy in which our dataset was randomly divided into 10 disjoint blocks of instances, then these data mining algorithms was trained using 9 blocks and the remaining block was used to test the performance of algorithms; this process was repeated 10 times to ensure the tests of each block and the recorded performance measures were averaged at the end. Additionally, in order to obtain statistically meaningful results, the number of iterations of 10-fold cross validation was set to 10. Therefore, this experiment consisted of 100 runs, for 6 algorithms, for 1 dataset, for a total of 600 results.

We chose L2-regularized Logistic Regression as the baseline algorithm and used corrected resampled T-Test with 95% confidence interval to make a comparison with other five algorithms. The statistical results of classification accuracy and AUC were listed in Tables VI and VII respectively. The annotation "v" or "*" in the second row indicate that a test result is statistically better or worse than the baseline algorithm at the significance level of 0.05. At the bottom of each column after the first column is a count (x/y/z) of the number of times that the corresponding algorithm is better than (x), the same as (y), or worse than (z) the baseline algorithm on our dataset [27]. According to the statistical results, K-nearest neighbors, classification tree, and support vector machine are statistically significant worse than the baseline algorithm (0/0/1) both in classification accuracy and AUC, and there are no statistical differences between L2-regularized Logistic Regression and neural network or random forest

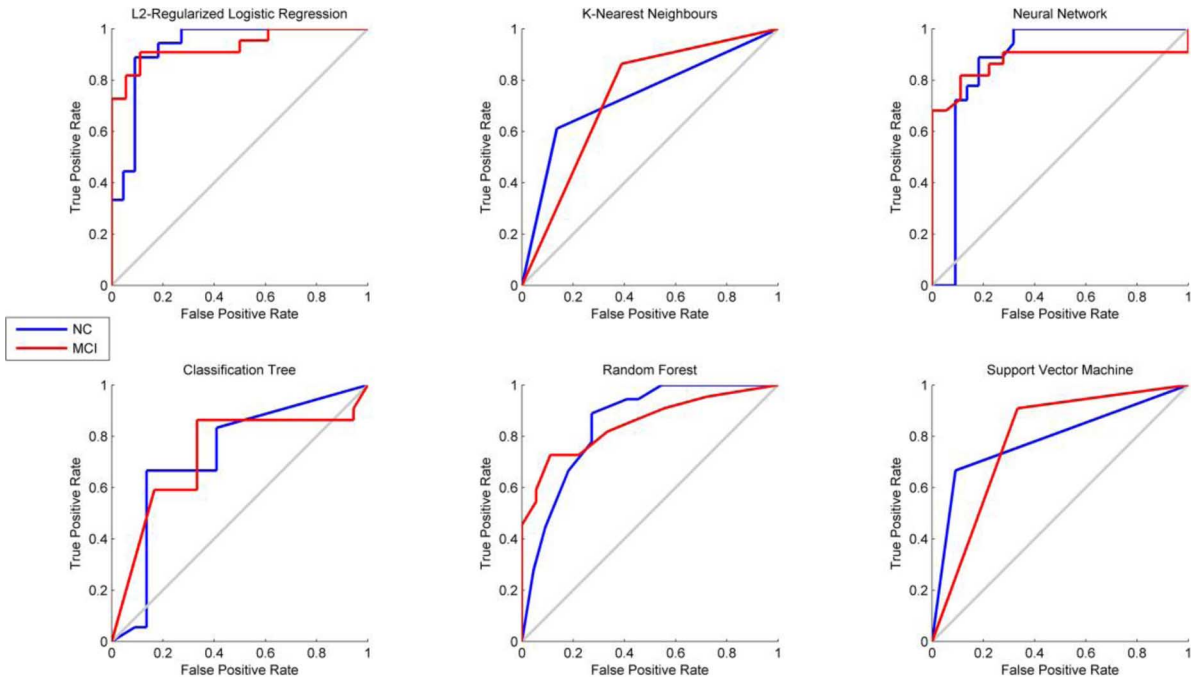


Fig. 6. ROC curves for classification of MCIs and NCs using the rs-fMRI.

TABLE VI
THE STATISTICAL RESULTS OF CLASSIFICATION ACCURACY

Logistic Regression	K-Nearest Neighbours	Neural Network	Classification Tree	Random Forest	Support Vector Machine
88.25	75.50 *	82.25	73.50 *	79.00	78.75 *
(v/ /*)	(0/0/1)	(0/1/0)	(0/0/1)	(0/1/0)	(0/0/1)

TABLE VII
THE STATISTICAL RESULTS OF AUC

Logistic Regression	K-Nearest Neighbours	Neural Network	Classification Tree	Random Forest	Support Vector Machine
0.92	0.74 *	0.90	0.72 *	0.86	0.77 *
(v/ /*)	(0/0/1)	(0/1/0)	(0/0/1)	(0/1/0)	(0/0/1)

(0/1/0). This proves that our method has relatively higher accuracy and reliability in discriminating and classifying MCI.

IV. DISCUSSION

This study explored the diagnostic power of functional connectivity networks which derived from rs-fMRI, for the automatic classification and recognition of MCI individuals from NCs. In the proposed classification method, we employed five effective functional connectivity features and trained a L2-Regularized Logistic Regression classifier for accurate discrimination of MCI individuals. This method could reach a weighted average classification accuracy of 87.5% by using leave-one-out cross validation strategy.

A. Abnormal Functional Connectivity in MCIs

In Fig. 2, we found that the functional connectivity between left dorsolateral superior frontal gyrus (SFGdor.L) and right orbital middle frontal gyrus (ORBmid.R), left middle frontal gyrus (MFG.L) and right orbital middle frontal gyrus (ORBmid.R) reduced in MCIs compared with NCs. These results indicated that the right orbital frontal gyrus was a pivotal region. In previous studies, dysfunction of the orbital frontal gyrus in AD has been reported many times[28], [29]. In the study about neurofibrillary tangle (NFT) pathology, researchers found that the posterior and medial orbital frontal gyrus in AD were destroyed seriously, and this damage could also be seen in autopsy inspection of the brain [30]. The orbital frontal gyrus

has been deemed to be closely related to olfaction, which is also one of the clinical manifestations of AD [28]. The orbital frontal gyrus was also considered to be one of the vulnerable regions in AD pathology, because it had strong connections with the temporal gyrus and the limbic regions that atrophied in the early stages of AD [29]. Moreover, decrease in the connectivity of dorsolateral frontal gyrus was also found in some researches, which brain region was deemed to be correlated with episodic memory [31].

In our results, reduced connectivity was also observed between left lingual gyrus (LING.L) and left temporal pole (TPOsup.L). The lingual gyrus is a brain structure that has been thought to have close relationship with vision and letter processing, and also play an important role in analysis of logical conditions and encoding visual memories. An significant differences between EMCI and LMC patients and between LMCI and AD patients was observed in brain regions including lingual gyrus [32]. The discriminative regions include lingual gyrus were also found in another Mild Cognitive Impairment classification [33]. The ventral default mode network of patients with Alzheimer's disease showed significantly decreases in the lingual gyrus and/or precuneus cortex [34]. In addition, Bokde *et al.* also reported that the connectivity associated with lingual gyrus, precentral gyrus and the middle frontal gyrus decreased [35]. Some studies have implicated that the cortices located in the left temporal pole have association with naming unique persons from faces, and progressive atrophy of the left temporal pole was usually conspicuous at the time of diagnosis for "semantic dementia," manifested by anomia and semantic memory loss [36]. In a study about principal component analysis of FDG PET, researchers found that the principal component containing left temporal pole was the hallmark of MCI/MCI patients [37]. In other studies about recognition of MCI patients using structural and functional connectivity networks, researchers found that the most discriminant regions for classification were mainly located in prefrontal cortex areas and temporal poles [14], [38].

In this study, the two increased connectivity were between left median cingulate and paracingulate gyri (DCG.L) and right supramarginal gyrus (SMG.R), left supramarginal gyrus (SMG.L), and left middle temporal gyrus (MTG.L). Recent studies have investigated an important network named Somatomotor Network (SMN), which has been deemed to be involved in several neurological or psychiatric conditions (AD, schizophrenia, or depression) [39]. Roberto Esposito *et al.* found that the MCI group, when compared to HC, showed significant increased connectivity in the right Supramarginal Gyrus (rSG), and the MCI-AD converted group showed increased connectivity in the rSG compared to either MCI or HC groups. The increased intrinsic SMN connectivity that they observed in the MCI and MCI AD-converted groups may be interpreted as a compensatory mechanism set in motion in the attempt to counteract cognitive decline [40]. Il Han Choo *et al.* found that compared to cognitively normal elderly, amnestic MCI showed significantly increased PIB binding uptake in the bilateral median cingulate and paracingulate gyrus [41], which was deemed to be correlated with memory [42]. Meanwhile, cognitive impairment in MCI and AD patients was found to be associated with different degrees of damage in several brain regions, including the temporal lobe (right transverse temporal gyrus, left middle temporal gyrus, and right superior temporal gyrus) [32]. The exact function of middle temporal gyrus is still unknown, but it has been associated with processes including contemplating distance, recognition of known faces, and accessing word meaning while reading [43]. Y. Sakurai *et al.* indicated that lesions of the posterior region of the left middle temporal gyrus may result in alexia and agraphia for kanji characters (characters of Chinese origin used in Japanese writing) [44]. In other studies about working memory tasks, researchers demonstrated increased activity in frontal and parietal regions, including the middle temporal gyri in MCI patients [45], [46]. Bo Zhou *et al.* also found that AD patients showed increased functional connectivity between the bilateral thalamus and brain regions including the middle temporal gyrus when compared to NC subjects [47]. In a study about brain functional activity in the default mode network (DMN), Zhigang Qi *et al.* found that the aMCI patients exhibited increased activity in the left middle temporal gyrus comparing to the healthy elderly [48].

In summary, the five pairs of abnormal functional connectivities found in this study is consistent with the previous findings, and they could be used as effective features for classification and discrimination of MCI.

B. Comparison of Classification Performance

The classification performance of the proposed method has been compared with other five classifiers in this study (see Table IV, Table VI, Table VII, and Figs. 4–6. Specifically, for classifying MCIs from NCs, the L2-regularized Logistic Regression classification method had the highest classification performance and achieved a sensitivity of 90.9%, a specificity of 83.3%, a precision of 87%, a F-Measure of 88.9%, and a Kappa statistic of 0.7462. The AUC value of the proposed method was 0.929, indicating relatively higher diagnostic power, especially in condition of small sample size of MCI and NC. The statistical results of classification accuracy and AUC also demonstrated that L2-regularized Logistic Regression was statistically significant better than K-nearest neighbors, classification tree, and support vector machine. We believed that the reason why logisitic regression classifier had the highest performance was that we did feature extraction and selection using Two Sample T-Test. After Two Sample T-Test, we selected the five most discriminant correlation coefficients as features, and the distributions of these features were nearly linearly separable as depicted in Fig. 3. Logistic Regression classifier was a high-efficiency classifier especially suitable for linear classification and found the best fitting model to describe the relationship between MCI and the five linearly separable features.

We also compared the classification performance of the proposed method with other previous studies about classification of AD or MCI based on functional connectivity networks. Greicius *et al.* could discriminate AD patients at a sensitivity of 85% and a specificity of 77% by applying a goodness-of-fit analysis to the default mode network between AD patients and normal controls [49]. Wang, Jiang *et al.* proposed a discriminative approach to

distinguish AD patients from normal subjects using the correlation/anti-correlation coefficients between all pairs of regions as features, and the average correct prediction ratio was 83% [50]. Wee *et al.* utilized a multi-spectrum strategy to construct multiple FC networks for each subject, and then extracted local clustering coefficients as features for MCI classification using a support vector machine (SVM) based classifier, the classification accuracy obtained by the their method was 86.5% [14]. Luping Zhou *et al.* proposed a learning framework based on sparse inverse covariance estimation (SICE) and applied it to analyzing the brain metabolic covariant networks built upon FDG-PET images for the prediction of the Alzheimer's disease, and achieved an accuracy of 81.6% for predication of MCI [51].

To summarize, we demonstrate that FC changes could be used to classify and discriminate MCI individuals. Our proposed method achieves a relatively high accuracy and has potential to assist clinicians in the recognition and diagnosis of MCI.

C. Limitations

This study also has some limitations. First, we only extracted and selected five pairs of abnormal functional connectivity (Pearson linear correlation coefficients) as features; however, there are many other functional connectivity properties may be used as biomarkers in the prediction of MCI, such as clustering coefficient, frequent subnetwork patterns, etc. [14], [52]. We will explore other effective features to improve the accuracy and reliability of the prediction. Beside, other imaging modalities can be used to provide complementary information for AD/MCI diagnosis [38], [53], [54]. Second, we only used default learning parameters in these classification algorithms, the optimization of parameters may influence the classification performance [55], [56]. We will investigate the problem about parameter optimization and explore more efficient algorithms. Finally, in view of the small sample size of MCI and NC in this study, probabilistic statistical results need further investigations. We need to evaluate our proposed method with larger sample sizes in the future.

V. Conclusion

This study explored the diagnostic power of functional connectivity networks which derived from rs-fMRI, for the automatic classification and discrimination of MCIs from NCs. In this method, abnormal functional connectivity was selected via statistical analysis, and Logistic Regression classifier was trained using L2 regularization. This method achieves relatively high classification performance and proves that it is feasible to explore brain disease pathology using machine learning algorithms based on FC derived from rs-fMRI. The promising experiment result indicates relatively good diagnostic power and demonstrates that our method has the potential to assist clinicians in MCI assessment and could be potentially usable in "real-world" diagnostic situations.

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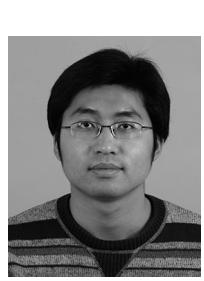

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