

Classification of temporal lobe epilepsy with and without hippocampal sclerosis via two-level feature selection

Xin Wang^{1,a}, Yan-shuang Ren^{2,b} and Wen-sheng Zhang^{1,c*}

¹ Institute of Automation, Chinese Academy of Sciences, Beijing, China

² Department of Radiology, Guang An Men Hospital of China Academy of Traditional Chinese Medicine, Beijing, China

^awangxin2012@ia.ac.cn, ^byanshr2006@163.com, ^cwszhang_casia@hotmail.com

*Corresponding author

Keywords: Classification, Temporal Lobe Epilepsy, Two-level Feature Selection.

Abstract. Hippocampal sclerosis (HS) is one of the most common histopathological abnormalities encountered in patients with temporal lobe epilepsy (TLE), which often serves as a diagnosis index of TLE. However, some patients with TLE have no pathologic characteristics of HS, which brings challenge to the diagnosis of TLE. Therefore, exploring effective methods to classify TLE patients with and without HS is meaningful to understanding the pathogenesis of TLE. In this paper, we propose a two-level feature selection method for classification. We select the categories of features as the first level and pick out the discriminating dimensions as the second level. Furthermore, we combine six regional brain characteristics as our features, including regional homogeneity (ReHo), amplitude of low-frequency fluctuation (ALFF), regional functional connectivity strength (RFCS) and three graph-based features. Results show that our method yields higher classification performance compared against the classifiers with single feature and without any level feature selection using functional magnetic resonance imaging (fMRI) data. Moreover, the discriminative brain regions selected by our method are consistent with previous studies. Thus, our method can accurately classify TLE patients with and without HS, which is interpretable from the perspective of physiology at the same time.

Introduction

Temporal lobe epilepsy (TLE) is the most common type of localization-related epilepsy which affects patients' normal lives. Approximately 60-70% of TLE patients have magnetic resonance imaging (MRI) signs of hippocampal sclerosis (HS). However, there exists a small group of TLE patients who have no HS or other abnormalities in MRI scans, the so called "imaging-negative" patients [1]. Detecting the differences between TLE with and without HS can conduce to the diagnosis and treatment of TLE.

Over the past decades, functional magnetic resonance imaging (fMRI), a non-invasive technology with high temporal and spatial resolution, has been largely used to study abnormalities of TLE patients. In addition, there are many features of fMRI data used to analyze the TLE patients. Zhang *et al.* [2] use amplitude of low-frequency fluctuation (ALFF) to analyze the differences

between left mesial temporal lobe epilepsy (mTLE) patients and right mTLE patients. In [3], Regional Homogeneity (ReHo) is used to identify abnormal areas of patients with mesial temporal lobe epilepsy and hippocampus sclerosis (mTLE-HS). Wei *et al.* [4] find alterations related to mTLE by studying functional connectivity and some topological properties in graph-theory analysis. In the large existing literature on analyzing abnormalities of TLE patients, there is a relative lack of studies that consider all the above features to study TLE patients.

Once the features are extracted from fMRI data, feature selection is necessary for removing redundant information and improving classification performance. T-test is one of the most commonly used methods to select features of fMRI data. Qiao *et al.* [5] apply t-test to pick out useful features to classify mild cognitive impairment and healthy controls. In addition, principal component analysis (PCA) is also used to project high dimensional features onto a lower dimensional space for classification of fMRI data [6]. However, these methods to pick out the most discriminative dimensions are independent with classification performance. Recursive feature elimination (RFE) is a method which selects features based on classification accuracy, which can achieve better performance [7]. Chanel *et al.* [8] use RFE to select features for classification of autistic patients and healthy controls. However, the category used in this paper is single. When some categories are considered at the same time, selecting the suitable categories of features is important to improve classification performance.

To address the above issues, we propose an effective classification method, named two-level feature selection method, for fMRI classification of TLE patients with and without HS. What's more, we take ReHo, ALFF, regional functional connectivity strength (RFCS) and three graph-based features as our features. In particular, we first select three kinds of features from the six features by t-test as the first level feature selection, and pick out the most discriminative dimensions in the three selected features by RFE as the second level. Then, we build three MLDA classifiers and combine their results for TLE classification. Furthermore, the most discriminative brain regions selected through the weight of the corresponding features can reveal the abnormalities of TLE patients. In general, the classification performance can be improved by using the two-level feature selection method which picks out the most valuable information.

Materials and Methods

Subjects, Data Acquisition and Data Preprocessing

Twenty TLE patients with HS (average age 35.3 years old, 10 females) and twenty TLE patients without HS (average age 34.4 years old, 10 females) were analyzed in this study. The subjects were recruited from Department of Radiology, Guang An Men Hospital of China Academy of Traditional Chinese Medicine, Beijing, China. Experiments were performed on a GE signa 1.5T echo speed superconducting MRI scanner. Subjects were asked to relax themselves but not to fall asleep. Functional images were acquired using an echo-planar imaging sequence with whole-brain coverage (TR=2000ms, TE=30ms, flip angle=90°, field of view (FOV)=24cm, matrix=64×64, thickness=5mm, slices=33). Statistical Parametric Mapping (SPM8) and Data Processing Assistant for Resting-State fMRI (DPARSF) were used for fMRI data preprocessing. The first 10 time points were discarded for subject's adaptation to the scanning and the scanner calibration. Further preprocessing procedures included slice timing, realignment, spatial normalization to the

standard Montreal Neurological Institute EPI template and resampling to a voxel size of $3 \times 3 \times 3$ mm³, followed by removing the linear trend and temporal band-pass filtering (0.01 Hz–0.08 Hz).

Feature Extraction

In this study, six regional brain characteristics were used as our features. Every subject had six kinds of features, and the dimensions of each feature were 116 which was the number of brain regions divided by Automated Anatomical Labeling (AAL) atlas.

The ReHo analysis and ALFF analysis were done by Resting-State fMRI Data Analysis Toolkit (REST) software [9]. The map of each subject was divided into 116 regions of interest (ROIs) using the AAL atlas. The Regional functional correlation strength (RFCS) [10] of one ROI was the average of the functional connectivity between it and all the other ROIs.

Graph-based features. Before computing the graph-based features, we constructed a network of brain. First of all, we used the AAL atlas to partition the brain into 116 ROIs as nodes of the brain network. Edges were defined as functional connectivity of all pairs of the 116 regions using the Pearson's correlation coefficient. We obtained a matrix that measured the network. After removing all self-connections and negative connections, we set the threshold at 15% which was optimal for our study. Finally, we obtained the binary adjacency matrices.

Once the network was constructed, we calculated three graph-based features from the aspect of centrality, functional segregation and network resilience. They are degree, clustering coefficient and average neighbor degree [11]. The three graph-based features were computed at each of the 116 nodes.

Feature Selection

As some features are redundant, employing a feature selection algorithm can not only discover useful information but also improve classification performance. We used two-level feature selection in this study.

First level feature selection. As described in the previous section, we extracted six kinds of features. Although each of the six features measured the brain's network from different perspectives, some of them didn't fit our data. We utilized t-test to select the three most discriminating kinds of features from all the six features. To be specific, t-test was used to calculate the number of dimensionality of significant difference of each feature. The larger the number of the feature's dimensionality of significant difference was, the more discriminating the feature was.

Second level feature selection. After that, we used RFE to select feature's dimensionality. RFE is an iterative feature selection algorithm, which consists of iteratively removing features with lowest score and selecting the feature subset according to the prediction accuracy [12]. Whether to select a voxel (a dimension of feature) in the current feature set or not was determined by the weight value of a voxel resulting from training a classifier.

Classification

In this study, we used maximum uncertainty LDA-based approach (MLDA) [13] as base classifier and built a multi-classifier based on the three MLDA classifiers corresponding to three selected features. We combined the three base classifiers through weighted voting and the weights was obtained by computing the classification accuracy using leave-one-out cross validation. At the same time, we used the coefficients of the feature in the classifier to evaluate the importance of this

feature (ROIs). The weight of the ROIs in a classifier was the absolute value of coefficients of the feature, multiplied by the base classifier's accuracy. The final ROI's weight of the multi-classifier was the sum of all the three base classifiers. The framework of our algorithm was shown in Fig. 1.

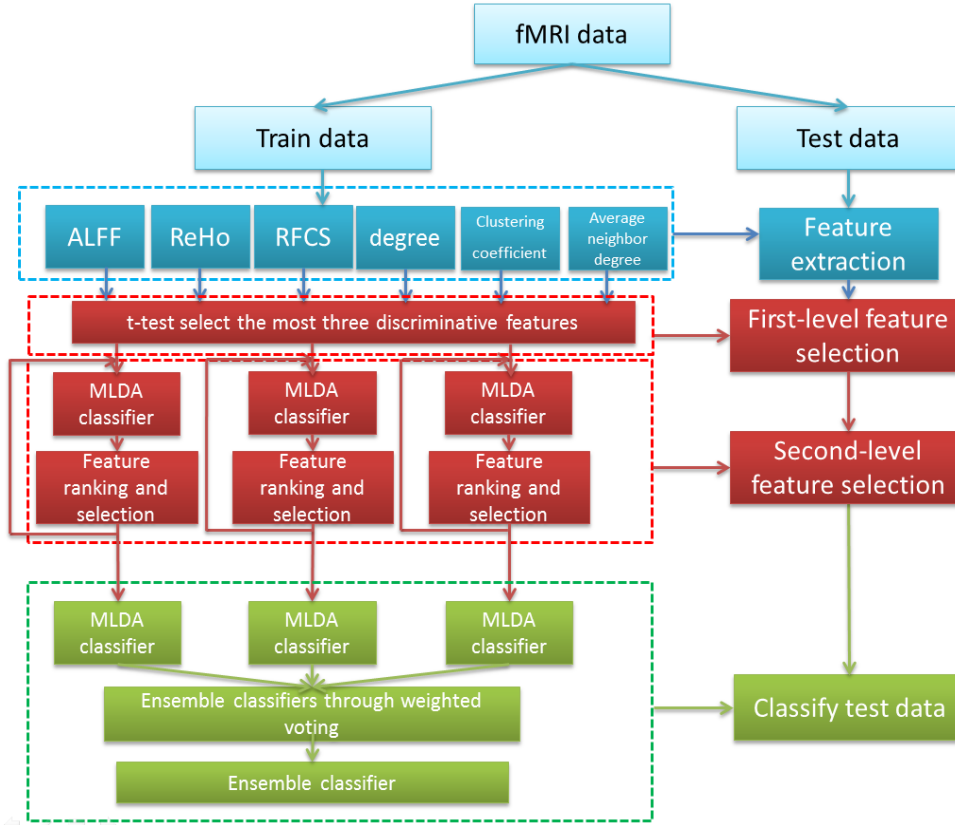


Fig. 1. A flowchart of classification with two-level feature selection

Evaluation

Due to the limited number of data, we used leave-one-out cross validation to estimate the performance of our algorithm. Each of the samples was treated as testing data in turn; the rest of the samples were treated as training data. Accuracy, sensitivity and specificity were used to test the performance of our algorithm.

Results

Our classification algorithm achieved 92.5% classification accuracy (95% sensitivity and 90% specificity). The results of our algorithm were better than the values obtained using the single feature or all the features without the first-level feature selection. To validate the efficacy of RFE as the second-level feature selection, we also designed classifier without second-level feature selection. The classification performance was listed in Table 1.

Table 1. Classification performance between TLE patients with and without HS

feature \ performance	Accuracy (%)	Sensitivity (%)	Specificity (%)
ReHo	75.0	85.0	65.0
ALFF	77.5	80.0	75.0
RFCS	82.5	90.0	75.0
Degree	80.0	75.0	85.0
Clustering coefficient	77.5	70.0	85.0
Average neighbor degree	85.0	90.0	80.0
no 1st-level FS	82.5	85.0	80.0
no 2nd-level FS	87.5	90.0	85.0
our algorithm	92.5	95.0	90.0

The most discriminative brain regions were selected and the ROIs were drawn in Fig. 2. The discriminative ROIs included cerebellum, posterior cingulate gyrus, fusiform gyrus, parahippocampal gyrus, middle frontal gyrus and superior frontal gyrus.

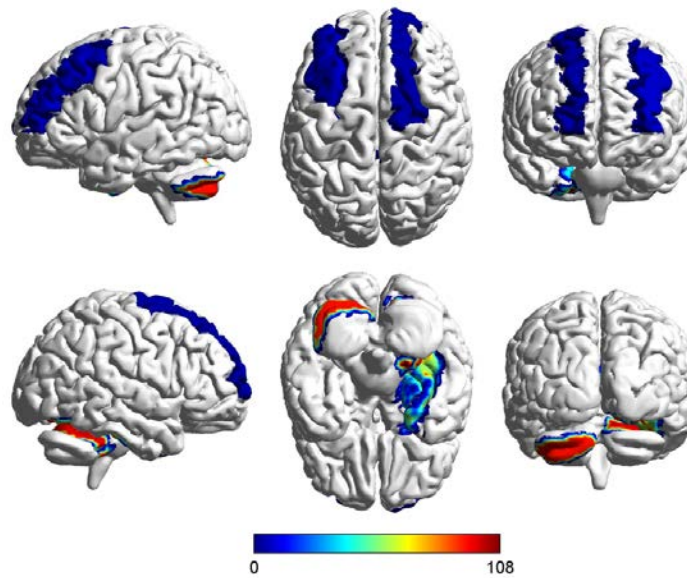


Fig. 2. The most discriminative brain regions between TLE patients with and without HS. The color bar indicates the index of displayed brain regions.

Discussion

The goal of the current study was to seek a general method to distinguish the TLE patients with HS from TLE patients without HS by high classification performance, and to increase our understanding of the different pathogenesis of TLE patients with and without HS.

Results showed that using single feature can't always achieve good classification performance as not all of the features fit for the dataset. If we simply combined all the features without the first-level feature selection, the results were not superior to some signal feature. What's more, using RFE to select the dimensions of feature as the second-level feature selection improved the classification performance. In general, our algorithm took different features into consideration and used two-level feature selection, which could achieve promising performance.

An important purpose of this study was to find the different pathogenesis of TLE patients with and without HS by selecting the most discriminative brain regions. Our results were consistent with previous studies. We found that the ROIs which could distinguish TLE patients with HS from TLE patients without HS mainly located at parahippocampal gyrus, frontal gyrus and posterior cingulate gyrus, which was consistent with the findings of previous studies [14, 15]. In addition, cerebellum is a key brain area to distinguish TLE patients with and without HS, which had been found in the previous studies [16, 17].

Conclusions

In this study, we developed a two-level feature selection method to classify TLE patients with and without HS. The initial features were six regional brain characteristics, including ReHo, ALFF, RFCS, degree, clustering coefficient and average neighbor degree. In order to pick out the most discriminative features, we performed a two-level feature selection. The first-level used t-test to select three kinds of features and the second-level picked out the discriminative dimensions as the final features using RFE. Finally, we combined three MLDA classifiers based on the final features to predict the group of the subjects. At the same time, we found the different pathogenesis of TLE patients with and without HS by selecting the most discriminative brain regions. The classification results showed that our method could get stronger classification power after considering different kinds of features and selecting the most valuable features. In conclusion, we hope that our method could provide useful information to the diagnosis of temporal lobe epilepsy.

Acknowledgement

This work was supported by the National Natural Science Foundation of China under Grants 61305018, 61432008, U1636220 and 61532006.

References

- [1] S.P.C. Bower, S.J. Vognin, K. Morris, Amygdala volumetry in "imaging-negative" temporal lobe epilepsy, *Journal of Neurology, Neurosurgery & Psychiatry*, 2003, pp. 1245-1249.
- [2] Z. Zhang, G. Lu, Y. Zhong, fMRI study of mesial temporal lobe epilepsy using amplitude of low - frequency fluctuation analysis, *Human brain mapping*, 2010, pp. 1851-1861.
- [3] H. Zeng, R. Pizarro, V.A. Nair, Alterations in regional homogeneity of resting - state brain activity in mesial temporal lobe epilepsy, *Epilepsia*, 2013, pp. 658-666.
- [4] W. Liao, Z. Zhang, Z. Pan, Altered functional connectivity and small-world in mesial temporal lobe epilepsy, *PloS one*, 2010, pp. e8525.

- [5] L. Qiao, H. Zhang H, M. Kim, S. Teng, L. Zhang, D. Shen, Estimating functional brain networks by incorporating a modularity prior, *NeuroImage*, 2016, pp. 399-407.
- [6] J. Ford, L. Shen, F. Makedon, L.A. Flashman, A.J. Saykin, A combined structural-functional classification of schizophrenia using hippocampal volume plus fMRI activation, *Engineering in Medicine and Biology*, 2002, pp. 48-49.
- [7] F. Zhang, J. P. Wang, J. Kim, T. Parrish, P.C. Wong, Decoding Multiple Sound Categories in the Human Temporal Cortex Using High Resolution fMRI, *PloS one*, 2015, pp. e0117303.
- [8] G. Chanel, S. Pichon, L. Conty, S. Berthoz, C. Chevallier, J. Grèzes, Classification of autistic individuals and controls using cross-task characterization of fMRI activity, *NeuroImage: Clinical*, 2016, pp. 78-88.
- [9] X.W. Song, Z.Y. Dong, X.Y. Long, REST: a toolkit for resting-state functional magnetic resonance imaging data processing, *PloS one*, 2011, pp. e25031.
- [10] Y. He, A. Dagher, Z. Chen, Impaired small-world efficiency in structural cortical networks in multiple sclerosis associated with white matter lesion load, *Brain*, 2009, pp. 3366-3379.
- [11] M. Rubinov, O. Sporns, Complex network measures of brain connectivity: uses and interpretations, *Neuroimage*, 2010, pp. 1059-1069.
- [12] F. De Martino, G. Valente, N. Staeren, Combining multivariate voxel selection and support vector machines for mapping and classification of fMRI spatial patterns, *Neuroimage*, 2008, pp. 44-58.
- [13] C.E. Thomaz, J.P. Boardman, D.L.G Hill, Whole brain voxel-based analysis using registration and multivariate statistics, *Proc. of the 8th Medical Image Understanding and Analysis MIUA*, 2004, pp. 73-76.
- [14] S.S. Keller, N. Roberts, Voxel - based morphometry of temporal lobe epilepsy: An introduction and review of the literature, *Epilepsia*, 2008, pp. 741-757.
- [15] L. Concha, C. Beaulieu, D.L. Collins, D.W. Gross, White-matter diffusion abnormalities in temporal-lobe epilepsy with and without mesial temporal sclerosis, *Journal of Neurology, Neurosurgery & Psychiatry*, 2009, pp. 312-319.
- [16] B.P. Hermann, K. Bayless, R. Hansen, J. Parrish, M. Seidenberg, Cerebellar atrophy in temporal lobe epilepsy, *Epilepsy & Behavior*, 2005, pp. 279-287.
- [17] J.D. Riley, D.L. Franklin, V. Choi, R.C. Kim, D.K. Binder, S.C. Cramer, J.J. Lin, Altered white matter integrity in temporal lobe epilepsy: association with cognitive and clinical profiles, *Epilepsia*, 2010, pp. 536-545.