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Discriminant analysis of functional connectivity patterns on Grassmann manifold

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ABSTRACT

The functional brain networks, extracted from fMRI images using independent component analysis, have been demonstrated informative for distinguishing brain states of cognitive function and brain disorders. Rather than analyzing each network encoded by a spatial independent component separately, we propose a novel algorithm for discriminant analysis of functional brain networks jointly at an individual level. The functional brain networks of each individual are used as bases for a linear subspace, referred to as a functional connectivity pattern, which facilitates a comprehensive characterization of fMRI data. The functional connectivity patterns of different individuals are analyzed on the Grassmann manifold by adopting a principal angle based Riemannian distance. In conjunction with a support vector machine classifier, a forward component selection technique is proposed to select independent components for constructing the most discriminative functional connectivity pattern. The discriminant analysis method has been applied to an fMRI based schizophrenia study with 31 schizophrenia patients and 31 healthy individuals. The experimental results demonstrate that the proposed method not only achieves a promising classification performance for distinguishing schizophrenia patients from healthy controls, but also identifies discriminative functional brain networks that are informative for schizophrenia diagnosis.

Introduction

Functional magnetic resonance imaging (fMRI) is being increasingly used in studies of functional connectivity of the brain. The functional connectivity is typically investigated using regional correlation analysis approaches or independent component analysis (ICA) method (Calhoun et al., 2009a, 2009b). The regional correlation analysis approaches estimate the brain connectivity by computing correlation measures of functional temporal signals between regions of interest (ROIs) or correlating functional temporal signals of a seed region to those of other brain voxels. The selection of ROIs typically requires *a priori* knowledge about the problem under study. In contrast to the regional correlation analysis methods, the ICA approach is a data driven technique. For brain network analysis, the ICA, particularly spatial ICA, is used to discover spatially independent components, each of which encodes temporally coherent brain regions (Calhoun et al., 2009b). An independent component is often referred to as a functional brain network.

In fMRI data analysis, two approaches are available for applying the spatial ICA to a group of subjects. One approach is to perform the spatial ICA for each subject separately and establish correspondence among components of different individuals by sorting components somehow. The other approach is to apply the spatial ICA to concatenated group data formed by concatenating data from all subjects in the temporal dimension and obtain subject specific components by back reconstruction (Calhoun et al., 2009b). By analyzing the subject specific spatial components and/or associated time courses, one can make group inferences of interest. In fMRI studies of brain disorders, the inferences have been focusing on group difference of spatial components, especially the default mode component.

The ICA as a subspace analysis technique has also been widely applied to problems of image and signal classification in machine learning and pattern recognition community. For example, the ICA was used to represent face images in face recognition (Yuen and Lai, 2002). In this study, the ICA was used as a feature extraction and dimensionality reduction step to extract features by projecting individual images to the independent components. The features used in this face image classification study are equivalent to the component specific time courses computed in fMRI image analysis.

An increasing number of studies have suggested that schizophrenia is associated with aberrant brain connectivity patterns, including abnormal connections between prefrontal/frontal cortex to other cerebral sites and disrupted interregional connections within the cortico-cerebellar-thalamo-cortical circuit and between different lobes and subcortical areas (Chaddock et al., 2009; Erdi et al., 2008; Friston and Frith, 1995; Lawrie et al., 2002; Schlosser et al., 2005; Stephan et al., 2006, 2009; Welsh et al., 2010). Aberrant functional

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connectivity within the default mode network has also been observed in schizophrenia using ICA (Garrity et al., 2007) and correlation/coherence (Bluhm et al., 2007; Zhou et al., 2007) methods. It has also been shown that symptoms in antipsychotic-naive patients with first-episode schizophrenia were associated with both structural deficits and alterations in the functional brain networks of regions with gray matter volume reduction (Lui et al., 2009).

Since the functional brain networks have been demonstrated discriminative at the group level in many studies (Calhoun et al., 2009a; Garrity et al., 2007; Liang et al., 2006; Liu et al., 2008; Zhou et al., 2007), efforts have been made to achieve individual classification based on fMRI data by identifying abnormal brain regional correlations or coupling ICA and classification techniques (Calhoun et al., 2008; Demirci et al., 2008a, 2008b; Jafri et al., 2008; Shen et al., 2010). Specifically, most ICA based fMRI image classification studies have been focusing on the spatial independent components which encode temporally coherent brain regions. For example, a classification method was proposed to distinguish subjects with bipolar disorder, chronic schizophrenia, and healthy controls based on temporal lobe and default mode components (Calhoun et al., 2008). In another schizophrenia study, the researchers examined multiple independent components and their combinations for classification (Demirci et al., 2008a). This study demonstrated that different components had distinct classification performance. Among those components studied, temporal lobe and lateral frontal parietal mode components yielded better classification performance (Demirci et al., 2008a). Although these studies indicate that different independent components have distinct discriminative performance, the selection of independent components has been relying on *a priori* knowledge and no systematic component selection method is available for classification.

In this paper, we propose a novel discriminant analysis algorithm, capable of automatically identifying discriminative spatial components and combining them for classification. The key elements of the proposed method are as follows. 1) The independent components of each individual are represented as a linear subspace, which facilitates a comprehensive characterization of temporal signals of fMRI data. The linear subspace spanned by independent components is referred to as a functional connectivity pattern (FCP). 2) The FCPs of different individuals are analyzed on the Grassmann manifold (Harris, 1992), which facilitates direct comparison of FCPs by adopting a subspace distance metric. 3) A forward component selection technique is used to select independent components to construct the most discriminative FCP in conjunction of a support vector machine (SVM) classifier (Guyon and Elisseeff, 2003; Vapnik, 1998). 4) A bagging technique is adopted to achieve robust classification of individuals and to facilitate the optimization of classification parameters (Breiman, 1996; Fan et al., 2008b, 2008c).

We apply the proposed algorithm to a schizophrenia study with 31 schizophrenia patients and 31 healthy individuals based on resting-state fMRI data. We also compare the FCP representation with the component specific time courses for distinguishing schizophrenia patients from normal controls using the same feature selection and classification strategies. The experimental results demonstrate that the FCP representation has achieved superior classification performance than the traditional discriminant analysis techniques. We also demonstrate that the incorporation of prior knowledge can improve the classification performance in the present study. The preliminary results of this study have been presented in our recent studies (Fan et al., 2010a, 2010b). This study is the first to demonstrate the potential of pattern classification methods for automatically identifying discriminative functional brain networks and optimally combining them to achieve accurate diagnosis of schizophrenia.

Methods

The discriminant analysis algorithm for FCPs consists of two components. The first component is to discover functional brain networks for each subject from its 4D fMRI data using spatial ICA. The second component is for brain network selection and classification.

Discovery of spatial independent components from fMRI data

From each subject's fMRI data, the spatial ICA can be used to discover functional brain networks decoded by spatial independent components. Denoting the spatial temporal fMRI data by a $(n \times m)$ data matrix $X = [x_1, x_2, \cdots, x_n]'$, where x_i is a vector representation of a 3D fMRI image with m voxels at time point i, n is the number of time points, the ICA approach models the fMRI data as

$$X = M \cdot S, \tag{1}$$

where M is the $(n \times l)$ mixing coefficient matrix, and S is the $(l \times m)$ independent component matrix with l components. The number of independent components is a free parameter that can be estimated by information theoretic approaches (Li et al., 2007).

The ICA method can be applied to fMRI data of individual subjects separately. However, to make independent components of different individuals comparable, post-processing approaches have to be used to sort the independent components since there is no direct correspondence among independent components of different individuals. Therefore, we adopt a group ICA method which generates independent components with correspondence across different individuals (Calhoun et al., 2009b). However, other techniques, like tensor ICA (Beckmann and Smith, 2005), can be used here to discover the brain networks. In the group ICA method we used, fMRI data from all subjects are firstly temporally concatenated, forming a large 4D fMRI image; then one ICA is performed on the concatenated image, which yields group independent components. To get subject specific independent components, a back-reconstruction step is implemented by mapping aggregated group independent components to each individual subject (Calhoun et al., 2009b).

From each individual's fMRI data, the group ICA method typically yields dozens of independent components, i.e., functional brain networks, among which some are related to the problem under study while others simply encode noise or artifact. The selection of networks of interest and artifact removal has been relied on visual inspection and prior knowledge, which cannot lead to novel knowledge discovery for the problem under study. To mitigate this problem, we propose a data driven method to select discriminative functional brain networks and optimally combine them for classification.

Subspace representation of functional brain networks and discriminant analysis on the Grassmann manifold

A linear subspace representation of functional brain networks is adopted to represent fMRI data. In particular, an individual's independent components are manipulated as a linear subspace, which facilitates a comprehensive characterization of temporal signals of fMRI data and is referred to as a functional connectivity pattern (FCP). The FCPs of different individuals are analyzed on the Grassmann manifold (Harris, 1992), which facilitates direct comparison of FCPs by adopting a subspace distance metric. To construct the most discriminative FCP, a forward component selection technique is used to select independent components in conjunction of a support vector machine (SVM) classifier. To achieve robust classification and facilitate classification parameter optimization for small sample size problems, we adopt a bagging technique to build classifiers.

Subspace representation of functional brain networks and Riemannian distance between subspaces

From a multivariate data representation perspective, the independent components are basis functions which span a subspace for data representation. Different combinations of these basis functions can represent signals of distinct interests. For example, by removing noise components, we can improve the signal-noise ratio of fMRI data (Perlbarg et al., 2007; Thomas et al., 2002). Similarly, a subspace spanned by discriminative independent components can better characterize the brain state than the original fMRI image signals for classification. Therefore, we represent the independent components of each subject as a subspace, referred to as an FCP, which conveys richer information than the representation of independent components as spatial maps (Calhoun et al., 2008; Demirci et al., 2008a). Given an individual's functional brain networks, i.e., independent components $IC=\{ic_i|i=1,\cdots,k\}$, an FCP is a linear subspace spanned by a subset of IC,

$$FCP = \operatorname{span}\left(\overline{IC}\right), \overline{IC} \subseteq IC. \quad (2)$$

From a manifold viewpoint, FCPs are elements of a Grassmann manifold which is a space of k-dimensional subspaces in an n-dimensional vector space (Harris, 1992). On the Grassmann manifold, the distance between two FCPs can be measured by a Riemannian distance metric which is the length of the shortest geodesic connecting these two FCPs. There are several metrics available for measuring the Riemannian distance between elements of the Grassmann manifold. Among them, a computational efficient way to define a Riemannian distance is to utilize principal angles between two subspaces, which can be computed from the Singular Value Decomposition (SVD) of the dot multiplication of the two subspaces (Bjorck and Golub, 1973). Given two subspaces $A=\{a_1,a_2,\ldots,a_k\}$ and $B=\{b_1,b_2,\ldots,b_k\}$, where $\{a_1,a_2,\ldots,a_k\}$ and $\{b_1,b_2,\ldots,b_k\}$ are orthonormal basis vectors for subspaces A and B, respectively, the principal angles $0\leq\theta_1\leq\theta_2\ldots\leq\theta_k\leq\frac{\pi}{2}$ between two subspaces A and B are defined recursively by

$$cos\,\theta_i = \max_{a_i\in B}\max_{b_i\in B} a_i'b_i = \max_{a_i\in A}\max_{b_i\in B} b_i'a_i, \text{ subject to} \quad (3)$$
$$a_i'a_i = b_i'b_i = 1, a_i'a_j = b_j'b_j = 0, (j = 1,\ldots,i-1).$$

This procedure first finds the basis vector $a_1\in A$ and the basis vector $b_1\in B$ which minimize the angle between them and this angle is called the first principal angle θ_1. Then, the second principal angle is similarly computed by searching the orthogonal complement of a_1 in A and the orthogonal complement of b_1 in B. This procedure iterates to find all the principal angles. Numerically, the ordered singular values of $A'B$ are corresponding to cosine of principal angles (Bjorck and Golub, 1973). Since the independent components of FCPs are not necessarily orthonormal, an orthonormalization has to be implemented before using the SVD procedure to compute the principal angles.

From the principal angles, several distance metrics can be derived, for example, projection metric, which is defined as (Hamm and Lee, 2008)

$$d_p = \left(\sum_{i=1}^{k} sin^2\theta_i\right)^{\frac{1}{2}} = \left(k-\sum_{i=1}^{k} cos^2\theta_i\right)^{\frac{1}{2}}. \quad (4)$$

Its corresponding similarity measure between two subspaces can be similarly defined as

$$S_p = \left(\frac{1}{k}\sum_{i=1}^{k} cos^2\theta_i\right)^{\frac{1}{2}}. \quad (5)$$

Classification of functional connectivity patterns and step-wise forward component selection using SVMs

Support vector machines are a set of supervised binary classification algorithms and have been extended for regression and multiclass classification (Vapnik, 1998, 1999). One attractive feature of the SVM algorithm is its inherent sample selection mechanism, i.e., only support vectors affect the decision function, which may help us find subtle difference between groups. The SVM algorithm constructs a maximal margin linear classifier in a high (often infinite) dimensional feature space, by mapping the original features via a kernel function. Therefore, it is needed to define a kernel function for applying the SVM algorithm to the classification of FCPs. Plugging the similarity measures of subspaces in the commonly used kernel functions, we can define kernel functions for FCPs (Wolf and Shashua, 2003). Particularly, we define a Sigmoid kernel function as

$$K(A,B) = \tanh(\gamma S(A,B)), \quad (6)$$

where A and B are two FCPs, $S(A,B)$ is a similarity measure between A and B, as defined in Eq. (5) , γ is the kennel parameter. Other kernels can be similarly defined. With the kernel function, we can build SVM classifiers for FCPs (Chang and Lin, 2001).

As demonstrated in previous studies (Calhoun et al., 2008; Demirci et al., 2008a), the independent components have different discriminative power. Therefore, the discriminative performance of an FCP varies with its basis functions, i.e., the independent components. To achieve effective and efficient classification and to find the most discriminative FCP, we propose a step-wise forward component selection method, similar to the forward feature selection algorithm (Guyon and Elisseeff, 2003). In particular, starting with a subset of the independent components, we iteratively add more components into the subset one by one. At each iteration, the incorporated component makes the new subset, i.e., the new FCP, more discriminative than others. The flowchart of the forward component selection algorithm is shown in Fig. 1 and the algorithm is summarized as:

Input: A starting FCP, F_0, which could be a void set of functional brain networks, candidate functional brain networks $IC=\{ic_i|i=1,\ldots,k\}$, training data $IC^j=\{ic_i^j, i=1,\ldots,k\}, j=1,\ldots,n$, which are functional brain networks corresponding to n training samples, as well as class labels of the training samples, $l^j=+1\ or -1, j=1,\ldots,n$.
Output: A set of FCPs, $F_i, i=1,\ldots,k$, with an incremental number of functional brain networks and their associated classifiers.

Begin:

For $i=1,\ldots,k$
- For each functional brain network $ic_i\in IC$
  - Build a SVM classifier with $F_{i-1}+ic_i$ based on the training data and evaluate its performance.
- End for
- Find ic_* with which F_{i-1} constitutes the best FCP, update $IC=IC\backslash ic_*$ and $F_i=F_{i-1}+ic_*$.

End for
Output $F_i, i=1,\ldots,k$, and their associated SVM classifiers.
End

The FCP's discriminative performance can be estimated by performing a cross-validation on training data. In order to achieve robust classification as well as to facilitate the optimization of classification parameters for small sample size problems, we adopt a bagging technique (Breiman, 1996; Fan et al., 2008b, 2008c). In particular, a leave-one-out sampling strategy is used to sample the training data. For a training dataset with n individuals, n samples are generated, each consisting of *n-1* individuals as a training set and the remaining one individual as a testing set. Classifiers are built for each training dataset and tested with its corresponding testing individual. The classification performance can be estimated by averaging the classifiers' performance for all testing individuals. Comparing the classification performance of FCPs with different numbers of functional brain networks, we can find the most discriminative one. Instead of rebuild a classifier with the most discriminative FCP based

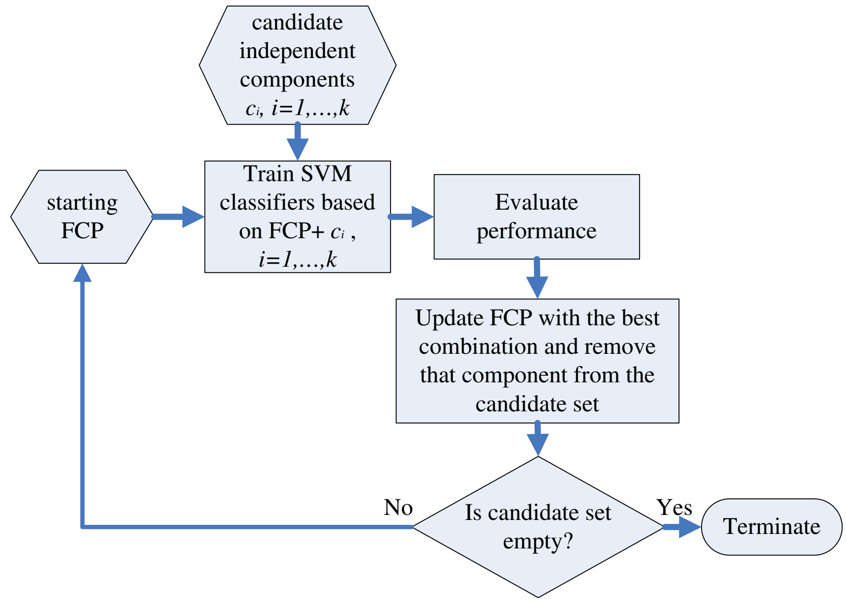

Fig. 1. Flowchart of the forward component selection algorithm.

on the training data, we construct an ensemble classifier whose base classifiers are those built with the most discriminative FCP on n samples' training sets. The ensemble classifier's output is the average value of classification scores of n base classifiers. The construction of an ensemble classifier is illustrated in Fig. 2.

Experimental results

The proposed method was applied to the classification of schizophrenia patients based on their resting-state fMRI data. Since previous fMRI studies of schizophrenia indicated that both default mode and temporal lobe components were informative for diagnosis of schizophrenia (Calhoun et al., 2008; Garrity et al., 2007; Zhou et al., 2007), we sought the most discriminative FCP for distinguishing schizophrenia patients from normal controls by initializing the forward component selection algorithm with default mode and temporal lobe components, besides searching for the most discriminative FCP in a fully data driven way.

The discriminative performance of the proposed method was evaluated using a leave-one-out cross-validation. In each leave-one-out validation experiment, one subject was first selected as a testing subject, and the remaining subjects were used for selecting components and constructing a SVM classifier. Then, the trained SVM classifier was used to classify the testing subject. The classification result was compared with the ground-truth class label for evaluating the classification performance. By repeatedly leaving each subject out as a testing subject, we obtained the average classification rate from all of these leave-one-out experiments. Classification rates corresponding to different numbers of components in FCPs were obtained to evaluate the performance of the FCPs with different numbers of functional brain networks. Using this procedure, we performed two experiments: starting component selection with and without prior knowledge.

We also compared the FCP representation with the component specific time courses for distinguishing schizophrenia patients from normal controls, in conjunction with the same feature selection and classification strategies. In particular, the time courses corresponding to each component were averaged for each subject as a component specific time course feature, therefore each component was associated with one time course feature. Each feature was normalized across subjects to have a standard normal distribution before classification. A similar forward

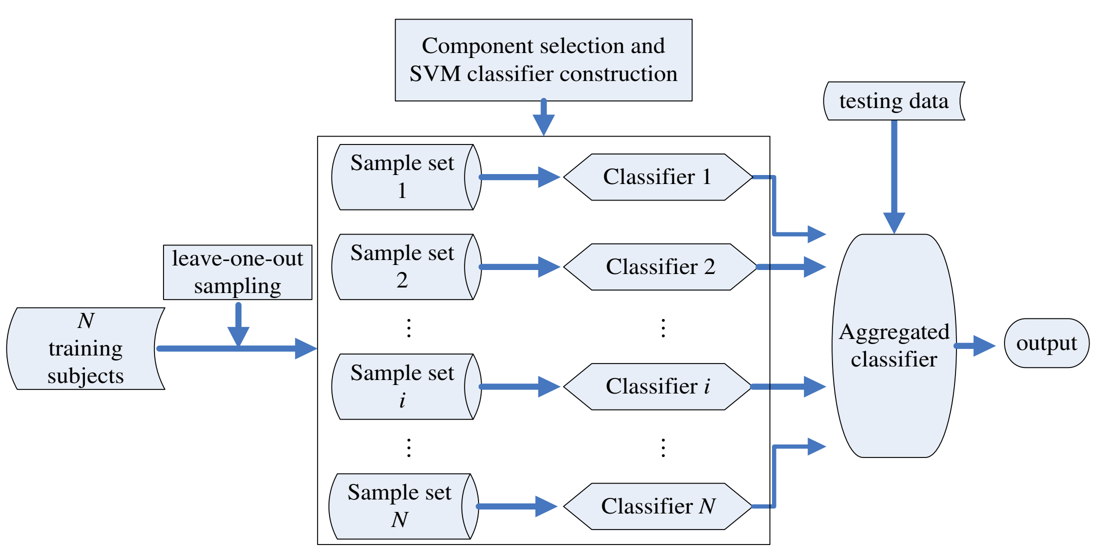

Fig. 2. Flowchart of the ensemble classifier construction.

Table 1
Demographic and clinical details of the subjects.

	Controls (n = 31)	Schizophrenia (n = 31)	p value
Gender (male)	16	17	0.8[a]
Age (years)	26 ± 4	24 ± 6	0.20[b]
Duration of illness (months)	–	27 ± 24	–
Medication dose (mg)	–	442 ± 208[c]	–
PANSS	–	83 ± 20	–
PANSS_P	–	20 ± 7	–
PANSS_N	–	20 ± 6	–
PANSS_G	–	40 ± 10	–
PANSS_S	–	8 ± 3	–

[a] The P value was obtained by Pearson Chi-square.
[b] The P value was obtained by two-sample two-tailed *t*-test.
[c] Chlorpromazine equivalent excluding 10 non-medications.

feature selection method was used to select the most discriminative feature set in conjunction with a linear SVM classifier, as well as two nonlinear SVM classifiers with Gaussian kernel and Sigmoid kernel using LIBSVM (Chang and Lin, 2001). The default kernel parameters were used as implemented in LIBSVM. For classification of FCPs, the Sigmoid kernel defined by Eq. (6) was used with $\gamma = 1$. For all SVM classification, the trade-off parameter C was optimized in the set of {0.1, 1, 10, 100, and 1000}.

Finally, we evaluated the diagnosis performance of the ensemble classifier built on the most discriminative FCP using a different leave-one-out cross-validation. Similar to the leave-one-out cross-validation used in the evaluation of the proposed method's discriminative performance, in each leave-one-out classification experiment, one subject was first selected as a testing subject, and the remaining subjects were used for training an ensemble SVM classifier. Then, the constructed ensemble classifier was used to classify the testing subject and the classification result was compared with the ground-truth class label for evaluating the classification performance. By repeatedly leaving each subject out as a testing subject, we obtained the average classification rate from all of these leave-one-out experiments. It is worth noting that another cross-validation was implemented in the training stage of each leave-one-out cross-validation for identifying the optimal FCP and constructing an ensemble classifier.

Demographic information, imaging data, and image processing

The study includes 31 schizophrenia patients recruited from the Institute of Mental Health, Second Xiangya Hospital, China and 31 age and gender-matched healthy subjects. This dataset has been used in a previous study of brain network analysis (Liu et al., 2008). To make the study self-contained, we provide the demographic and clinical details again for the study participants, as summarized in Table 1. Confirmation of the diagnosis for all patients was made by clinical psychiatrists, using the Structured Clinical Interview for DSM-IV. During the time of the data collection, experienced psychiatrists assessed the symptoms of these patients using the Positive and Negative Syndrome Scale (PANSS). All subjects were right-handed. The exclusion criteria were as follows: no history of neurological or significant physical disorders, no history of alcohol or drug dependence and no history of receiving electroconvulsive therapy. All the healthy subjects had no history of psychiatric illness. All subjects gave voluntary and informed consent according to the standards set by the Ethics Committee of the Second Xiangya Hospital, Central South University.

Imaging was performed on a 1.5 Tesla GE scanner in the Second Xiangya Hospital. Blood oxygenation level dependent (BOLD) images of the whole brain using an echo planar imaging (EPI) sequence were acquired in 20 axial slices (TR = 2000 ms, TE = 40 ms, flip angle = 90°, FOV = 24 cm; 5 mm thickness and 1 mm gap). The fMRI scanning was done in darkness. All the subjects were instructed to keep their eyes closed and not to think about anything in particular. For each subject, the fMRI scanning lasted 6 min.

The fMRI images were preprocessed using statistical parametric mapping software (SPM2, http://www.fil.ion.ucl.ac.uk/spm). To allow for magnetization equilibrium, the first 10 images were discarded. The remaining 170 images were first corrected for the acquisition time delay among different slices, and then the images were realigned to the first volume for head-motion correction. The fMRI images were further spatially normalized to the Montreal Neurological Institute (MNI) EPI template and resampled to have 3 mm cubic voxels. Finally, temporal band-pass filtering ($0.01 < f < 0.08$ Hz) was performed in order to reduce the effects of low-frequency drift and high-frequency noise (Liu et al., 2008). From the preprocessed fMRI data, independent components were computed using GIFT software (http://icatb.sourceforge.net) and the number of components was automatically determined to be 19 (Li et al., 2007).

Discriminative performance without prior knowledge

In this experiment, we investigated the performance of the propose algorithm for identifying the most discriminative FCPs without utilizing any prior knowledge of schizophrenia studies, i.e., starting the forward component selection with a FCP with a void set of functional brain networks. The discriminative performance of FCPs with different number of components is shown in Fig. 3, demonstrating that the proposed method can achieve a correct classification rate up to 85.5% when the FCP was spanned by 7 discriminative independent components. Compared with the performance of time course features, the proposed method achieved 5% improvement for classification accuracy. The best classification rates for all the methods, along with their associated sensitivity and specificity, are summarized in Table 2.

The most discriminative FCP consisted of 7 independent components, as shown in Fig. 4, including temporal lobe component and brain regions belonging to default mode component, which were

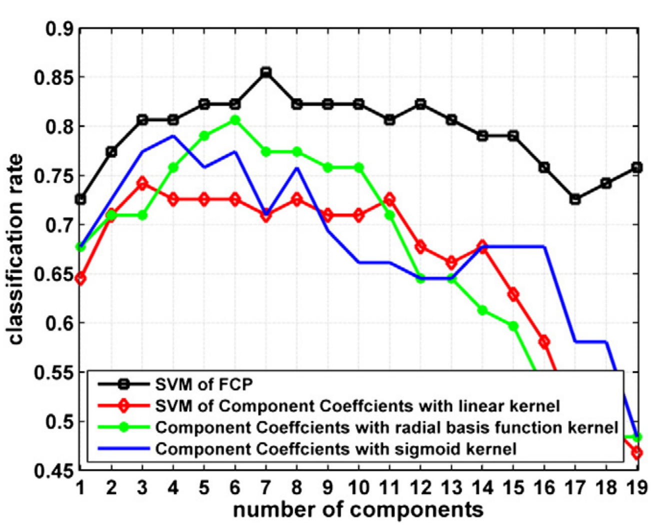

Fig. 3. Classification rates as a function of the number of components selected in classification without utilizing prior knowledge.

Table 2
Performance of time course features and functional connectivity patterns for classification of schizophrenia without utilizing prior knowledge.

Methods	Classification rate (%)	Sensitivity (%)	Specificity (%)
Our method	85.5	83.9	87.1
Component coefficients (linear)	74.2	83.9	64.5
Component coefficients (RBF)	80.7	83.9	77.4
Component coefficients (Sigmoid)	79.0	87.1	71.0

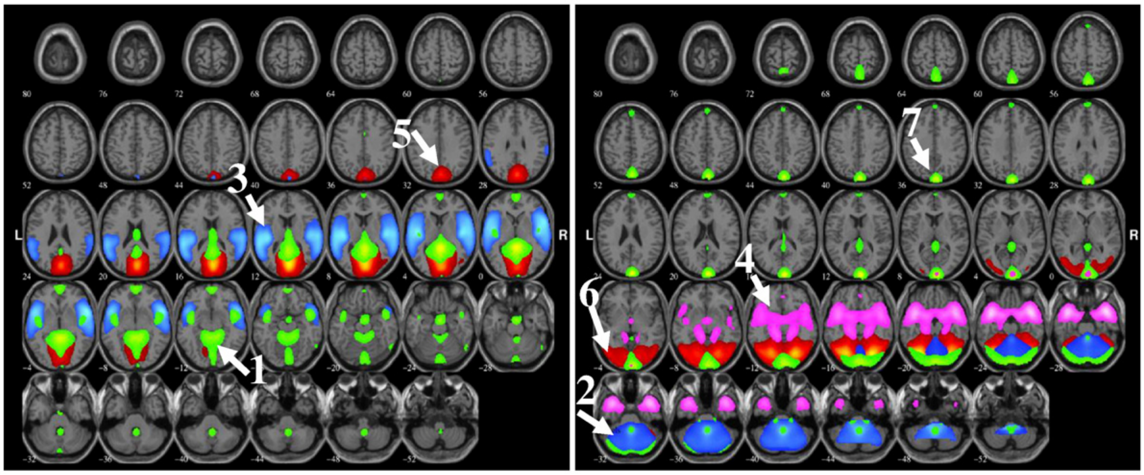

Fig. 4. The functional connectivity pattern that yields the best discrimination performance for distinguishing schizophrenia patients from normal controls. Functionally discrete networks are displayed in different colors and shown in the left and right panels. The numbers shown in the figures indicate the order of components that were selected in the forward component selection process.

demonstrated discriminative in previous schizophrenia studies (Calhoun et al., 2008; Demirci et al., 2008a). Other components are cerebellum, bilateral cuneus, bilateral precuneus, superior frontal lobe and part of occipital lobe and thalamus region, which were found significantly different between schizophrenia patients and healthy controls in previous studies (Honey et al., 2005; Liang et al., 2006). The order of brain networks selected by the forward component selection is also shown in Fig. 4. The most discriminative component evaluated individually, i.e., the first selected component to construct a FCP, covers parts of occipital lobe, cerebellum, superior frontal gyrus, and superior temporal gyrus, which were reported to have aberrant brain response to working memory (Kindermann et al., 2004). As indicated by the classification performance curve of FCPs shown in Fig. 2, the FCP's discriminative power gradually increased when other functional brain networks joined the first network one by one.

Discriminative performance with prior knowledge

Previous fMRI studies of schizophrenia indicated that both default mode and temporal lobe components are informative for diagnosis of schizophrenia (Calhoun et al., 2008; Garrity et al., 2007; Zhou et al., 2007). To test their performance in the FCP based framework, we sought the most discriminative FCP by initializing the stepwise forward component selection algorithm with default mode component, temporal lobe component, and their combination. The correction classification rates as functions of the number of components included in FCPs are shown in Figs. 5–7, for starting the forward component selection with default mode network, temporal lobe network, and their combination, respectively. As shown in these figures, the combination of default mode and temporal lobe components is not necessarily the optimal solution, neither any of them individually. However, the discriminative performance of FCPs spanned by these two components and components selected by the propose algorithm can be improved.

As shown in Figs. 5–7, the best classification rate achieved was 87.1% by the proposed method initialized by the combination of default mode and temporal lobe components, indicating that the prior knowledge can improve the classification performance of FCPs and highlighting the importance of prior knowledge in clinical studies. Similar to the findings in the previous experiment, the discriminative performance of FCPs was superior to the combinations of time course features. The best classification rates for all the methods, along with their associated sensitivity and specificity, are summarized in Table 3.

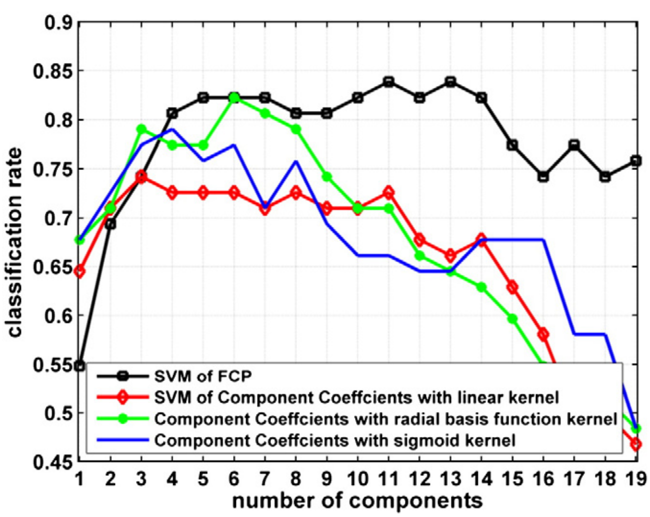

Fig. 5. Classification rates as a function of the number of components used in classification. The forward component selection is initialized with the default mode component.

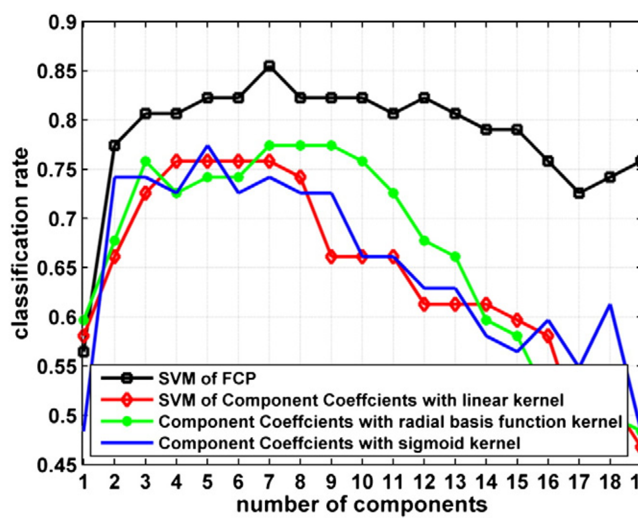

Fig. 6. Classification rates as a function of the number of components used in classification. The forward component selection is initialized with the temporal lobe component.

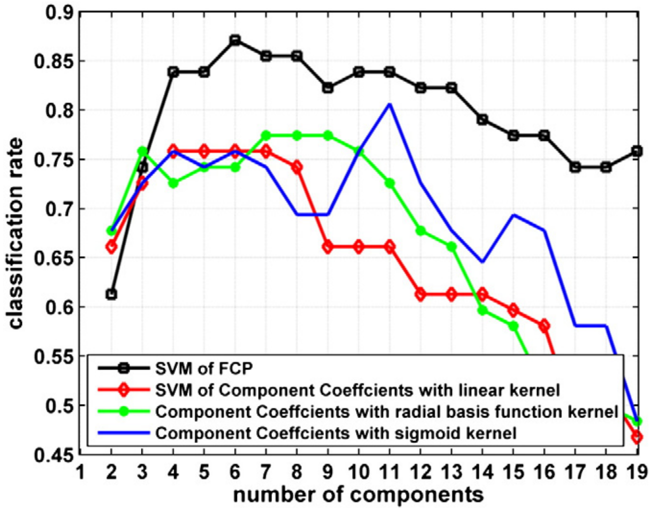

Fig. 7. Classification rates as a function of the number of components used in classification. The forward component selection is initialized with default mode and temporal lobe independent components.

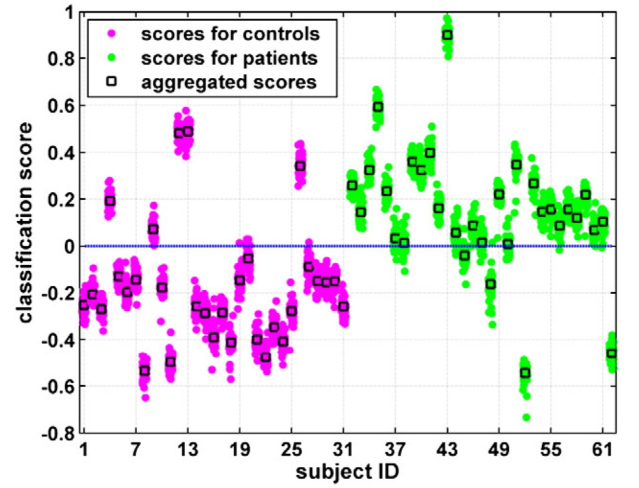

Fig. 9. The classification scores of testing subjects, including those yielded from the base classifiers and the aggregated classifiers.

Table 3
Performance of time course features and functional connectivity patterns for classification of schizophrenia with prior knowledge. The classification rates yielded by starting the component selection with default mode, temporal lobe, and their combination are listed from left to right, respectively.

Methods	Classification rate (%)	Sensitivity (%)	Specificity (%)
Our method	83.9, 85.5, 87.1	83.9, 83.9, 90.3	83.9, 87.1, 83.9
Component coefficients (linear)	74.2, 75.8, 75.8	83.9, 80.7, 80.7	64.5,71.0, 71.0
Component coefficients (RBF)	82.3, 77.4, 77.4	77.4, 77.4, 77.4	87.1,77.4, 77.4
Component coefficients (Sigmoid)	79.0, 77.4, 80.7	87.1, 71.0, 74.2	71.0, 83.9, 87.1

Along with default mode and temporal lobe components, as shown in Fig. 8, are the components that have the best discriminative power when combined with the former two, including cerebellum, bilateral superior frontal region, bilateral superior frontal medial region, and bilateral anterior cingulate cortex. These components were also found significantly different between schizophrenia patients and healthy controls in previous studies (Liang et al., 2006; Liu et al., 2008; Ragland et al., 2009; Zhou et al., 2007).

Diagnosis performance of the bagging classifiers

In the above discriminative analysis experiments, the classification label information of leave-one-out testing subjects was utilized in the parameter selection stage, therefore it can be seen as the training stage of an ensemble classifier. To evaluate the diagnosis value of the propose method, in particular, the forward component selection initialized with the combination of default mode and temporal lobe functional brain networks, which demonstrated to have the most discriminative power in the previous experiments, a leave-one-out cross-validation was implemented to test the generalization ability of the ensemble classifiers. The classification rate on testing subjects obtained via the bagging procedure was 85.5%, with specificity of 83.9% and sensitivity of 87.1%. The classification scores of testing subjects yielded from the base classifiers and the aggregated classifiers are shown in Fig. 9. The average training accuracy of the leave-one-out experiments, including 61*62 tests, was 86.4% with standard deviation of 1.7%.

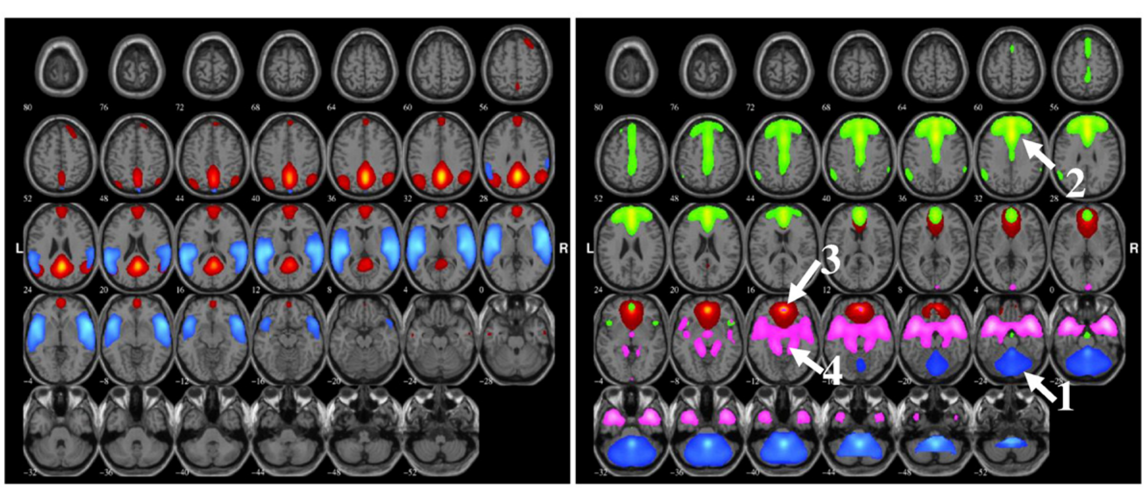

Fig. 8. The left panel shows default mode and temporal lobe components, and the right panel shows the independent components that yield the best discrimination performance when used in conjunction with default mode and temporal lobe components in classification of schizophrenia. Functionally discrete networks are displayed in different colors. The numbers shown in the figures indicate the order of components that were selected in the forward component selection process.

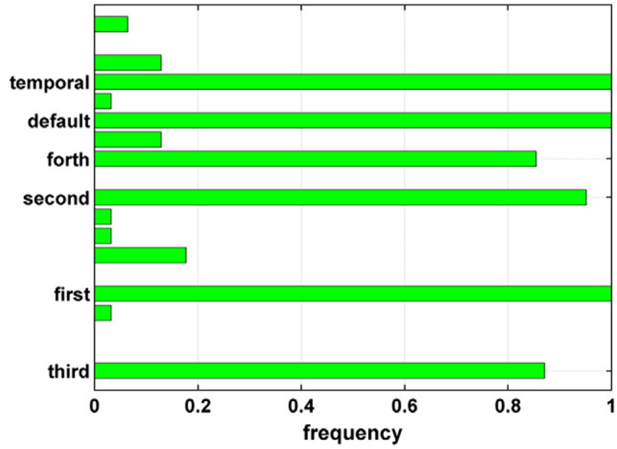

Fig. 10. The frequency of functional brain network selected in the leave-one-out cross-validation experiment. Besides the default mode and temporal lobe components, networks selected with the highest frequencies (>0.8) are those constituting the most discriminative FCP in the discriminative study, corresponding to its first to forth networks.

Although different components might be selected in the leave-one-out experiments, the components selected with high frequency to constitute the optimal FCP in conjunction with default mode and temporal lobe components were consistent with those selected in the discriminative analysis experiments. It is worth nothing that the frequency of components selected by the algorithm was correlated with the order of components selected in the discriminative study, i.e., the component consistently selected in different leave-one-out validation with frequency greater than 0.8 were the components selected in the discriminative analysis experiments and their order is consistent with their frequency, as shown in Fig. 10. These results indirectly indicated that the proposed method can achieve a stable component selection performance.

Discussion and conclusion

This study proposed a pattern classification method and investigated the diagnostic value of functional brain networks, discovered from resting state fMRI data using ICA, for distinguishing schizophrenia patients from healthy individuals. The functional connectivity pattern identified by the proposed pattern classification method in a fully data driven way demonstrated a correction separation rate of 85.5% for distinguishing schizophrenia patients from healthy controls. The discriminative performance could be further improved to 87.1% when prior knowledge, i.e., the default mode and temporal lobe networks, was utilized in the algorithm to construct the functional connectivity pattern. The functional connectivity pattern for schizophrenia, discovered by the proposed method by incorporating the default mode and temporal lobe networks, achieved a correct classification rate of 85.5%, estimated with all classification parameters automatically optimized using the training data. The group-ICA was implemented on the entire dataset to get stable independent components and to facilitate straightforward interpretation of components selected in the cross-validation experiment. In each leave-one-out cross-validation, only diagnostic information of the training data was used to select the most discriminative FCP and build the classifier. Therefore, no bias was introduced in the cross-validation (Kriegeskorte et al., 2009). These validation results indicate that the proposed method can achieve a promising classification performance for diagnosis of schizophrenia using resting state fMRI data.

The proposed method performed pattern classification based on functional brain networks encoded by spatial independent components (Calhoun et al., 2009b). As a data driven technique, ICA can be applied to tasking data, which made the proposed method directly generalizable to more applications. The functional brain networks were embedded onto a Grassmann manifold (Harris, 1992) via a subspace representation of independent components, referred to as a FCP. A Riemannian similarity/distance measure based on principal angles between FCPs of different individuals was computed in the Grassmann manifold, which facilitated an easy manipulation of independent components. When the FCP just consists of one independent component, this measurement is equivalent to a correlation measure. Different from treating independent components as voxel-wise feature maps (Calhoun et al., 2008; Demirci et al., 2008a, 2008b), this Riemannian measure does not require any normalization step, like conversion of independent components to Z values (Beckmann and Smith, 2005), nor any dimensionality reduction step, like principal component analysis based feature transformation (Demirci et al., 2008a). In the present study, we chose the number of components based on the minimum description length (MDL) criterion with independent sampling (Li et al., 2007). Recent studies have demonstrated that a refined functional segmentation of the brain may be obtained when independent components were extracted using a high ICA model order (Abou-Elseoud et al., 2010; Kiviniemi et al., 2009; Smith et al., 2009; Ystad et al., 2010). Such refined functional segmentation of the brain may help identify more discriminative components for specific problems.

The functional connectivity pattern is a subspace representation of fMRI data with independent components as its bases. Such a data representation not only facilitates a comprehensive and compressive characterization of the original data, but also makes the identification of discriminative independent components relatively easier due to the small search space, equal to the number of independent components of interest. Since a typical ICA based fMRI study computes around 20 independent components (Calhoun et al., 2009b), the search space to construct a discriminative FCP is much smaller than the number of voxel-wise features of the voxel-wise feature map representation of independent components. In this study, we proposed a forward component selection method which can incorporate *a prior* knowledge about the discriminative performance of functional brain networks and is computationally efficient, therefore applicable to problems with a large number of independent components. Other component selection strategies, like backward selection (Guyon and Elisseeff, 2003), can be adopted too, and a full search of the component search space is even also feasible due to the relatively small search space. If the component selection method is powerful enough, the prior information might be not necessary. Furthermore, the performance of the proposed method might be improved if it is used in conjunction with functional brain network discovery techniques capable of identifying discriminative brain networks (Sui et al., 2010).

The functional connectivity pattern was utilized in conjunction with a support vector machine classification method to achieve the classification of individual subjects (Vapnik, 1998, 1999). The SVM classifier construction involves several parameters, including type of kernel and kernel parameters. In the present study, the classification based on a Sigmoid kernel achieved a promising classification performance without tuning kernel parameters. Optimizing the kernel parameters and kernel types might lead to better performance, however extensively tuning parameters might also lead to over-fitted classification models in small sample size problems.

In the present study, we found that the most discriminative FCP consisted of 6 independent components, including temporal lobe component and brain regions belonging to default mode component, which were demonstrated discriminative in previous schizophrenia studies (Calhoun et al., 2008; Demirci et al., 2008a; Garrity et al., 2007). Other components cover brain regions including cerebellum, bilateral cuneus, bilateral precuneus, superior frontal lobe and part of occipital lobe and thalamus region. These findings are consistent with previous studies in which abnormal functional connectivity among a number of brain regions have been reported (Chaddock et al., 2009; Erdi et al., 2008; Friston and Frith, 1995; Lawrie et al., 2002; Schlosser et al., 2005; Stephan et al., 2006, 2009; Welsh et al., 2010). Some previous meta-analytic of MRI studies of schizophrenia have reported that schizophrenia is associated with abnormal gray matter density increases in basal ganglia, and decreases in bilateral frontal, cingulate, temporal, and insular cortex, and thalamus (Ellison-Wright et al., 2008; Glahn et al., 2008), which might induce the abnormal functional connectivity in these regions. Such evidence has been accumulating; for instance, abnormal frontotemporal functional connectivity in schizophrenia (Lawrie et al., 2002; Liang et al., 2006; Liu et al., 2008; Zhou et al., 2007) and aberrant brain integration between the medial superior frontal gyrus and both the anterior cingulate and the cerebellum in schizophrenia (Honey et al., 2005; Liang et al., 2006). For a long time the cerebellum has been viewed as a brain region primarily dedicated to coordination and control of voluntary movement. However, increasing evidence indicates that cerebellar function is impaired in schizophrenia (Andreasen and Pierson, 2008; Liang et al., 2006; Picard et al., 2008). All these findings indicate that the identified components have their disease related significance. Furthermore, the potential association between aberrant functional connectivity and brain atrophy pattern also implies that better discriminant performance might be achievable if the brain anatomy atrophy pattern is studied using structural MRI data classification techniques (Fan et al., 2007b) in conjunction of the examination of the brain functional connectivity pattern, or both of them are exanimate simultaneously (Fan et al., 2007a, 2008c).

In summary, this study presented a novel pattern classification method, capable of automatically identifying discriminative functional connectivity patterns for distinguishing brain disorders from healthy controls. The experimental results demonstrated that the proposed method not only achieved a promising classification performance for distinguishing schizophrenia patients from healthy controls, but also identified discriminative functional brain networks that are informative for schizophrenia diagnosis. Ongoing work is devoted to the validation of the proposed method by applying it to other problems, such as analysis of family members of schizophrenia patients and early diagnosis of mild cognitive impairment (Fan and Browndyke, 2010; Fan et al., 2008a).

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