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Schizophrenic patient identification using graph-theoretic features of resting-state fMRI data

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ABSTRACT

Resting-state functional magnetic resonance imaging (Rs-fMRI) is a promising imaging modality to study the changes of functional brain networks in schizophrenic patients. Several representations have been proposed to capture the essential features of these networks. In particular, graph-theoretic representations can be effectively used to discriminate healthy subjects from schizophrenic patients. In this paper, we propose a machine-learning system based on a graph-theoretic approach to investigate and differentiate the brain network alterations. The fMRI data samples are first preprocessed to reduce noise and normalize the images. The automated anatomical labeling (AAL) atlas is then used to parcellate the brain into 90 regions and construct a region connectivity matrix. A weighted undirected graph is hence constructed and graph measures are computed for each subject. These graph measures include betweenness centrality, characteristic path length, degree, clustering coefficient, local efficiency, global efficiency, participation coefficient and small-worldness. After that, feature selection algorithms are used to choose the most discriminant features. Finally, a SVM classifier is trained and tested on discriminant graph features. Experiments were performed on a large Rs-fMRI dataset formed of 70 schizophrenic patients and 70 healthy subjects. The performance was evaluated using nested-loop 10-fold cross-validation. The best detection results were found using the feature selection methods of Welch's *t*-test (82.85%), l_0-norm (91.43%), and feature selection via concave minimization (FSV) (95.00%). Our results outperform those of recent state-of-the-art graph-theoretic methods.

1. Introduction

Early diagnosis of mental disorders is still a challenging problem. Schizophrenia is a common psychiatric brain disorder affecting about 1% of the worldwide population [2–5]. This disorder affects many brain functions, and is characterized by hallucinations, disorganized thinking, delusions and disintegration in perception of reality [6].

Today, functional magnetic resonance imaging (fMRI) has become very popular for studies related to brain activity. Machine learning and pattern classification techniques were employed as key modules in fMRI-based decision support systems [7]. In particular, several studies have shown that machine learning and pattern classification techniques are useful for finding potential biomarkers for schizophrenia based on the type of the used discriminating features: structural features [8–19], functional features [20–26] or combination of functional and structural features [14,27].

Structural studies revealed anatomical changes within the brain such as the expansion of the lateral ventricles, in particular the temporal horns of the lateral ventricles [28], the shrinkage of the medial temporal structures such as the amygdala, the parahippocampal gyrus, and the hippocampus [29–31], the prefrontal cortex [32,33], the superior temporal gyrus [30], and the inferior parietal lobule [34,35]. Furthermore, some abnormal enlargements in the left hemisphere compared to the right hemisphere in male patients with schizophrenia were used as biomarkers [36,37]. Other studies have found that there are correlations between the temporal lobe and the prefrontal brain volumes [38,39], in addition to some disturbances of functional brain connectivity between temporal and frontal lobes in schizophrenia, which confirm the disconnectivity hypothesis [40,41]. These findings assert the widespread problems of the functional connectivity in schizophrenia.

Resting-state fMRI (Rs-fMRI) explores the brain function while the subject is not doing a specific task. Rs-fMRI is based on the

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spontaneous low-frequency fluctuations (0.01–0.1 Hz) in the blood oxygen level-dependent (BOLD) signal [42]. In recent years, automatic diagnosis techniques of brain mental disease using Rs-fMRI have been investigated by several studies [43–47]. Using this imaging modality, some brain regions were found to be continuously and dynamically "active" even when the brain is "at rest". Examples of these regions are: medial pre-frontal cortex (MPFC), medial, lateral, and inferior parietal cortex and posterior cingulate cortex/precuneus (PCC/PCu), which form the "default-mode network" (DMN) [48].

Slow activity fluctuations, measured by the BOLD signal in Rs-fMRI, enable the construction of the resting-state networks and the detection of the correlated activities between the various regions of the brain. Complex network analysis (CNA) is a powerful approach to measure the functional connectivity features such as functional integration, segregation, centrality, and resilience [49]. Functional connectivity matrices are represented topologically by CNA on graphs. The functional connectivity can be derived from the cross-correlation in different frequency bands, mutual information, or spectral coherence [50–54]. Normally, after graph representations are obtained, thresholding is performed to retain only the strongest connections.

To quantitatively analyze the global and local network properties derived from functional and structural brain imaging, graph theoretical methods have been applied to the brain [55–59]. Local network properties include betweenness centrality, degree, local efficiency, and participation coefficient. Examples of global network properties are average clustering coefficient, average path length, global efficiency, and small-worldness. The graph theoretical methods represent a good way for describing the distinctive possible network alterations in schizophrenia. Functional and structural network disruptions due to schizophrenia have been revealed by brain network analyses [60,61]. Examples of these disruptions include reduced presence of high-degree hubs, and decreased clustering and small-worldness. Besides, local differences of reduced clustering and degree were found in right orbitofrontal cortical nodes, medial parietal, premotor and cingulate regions [56]. In another study, significantly lower small-worldness and lower clustering coefficient were also found in brain networks of schizophrenia patients [62]. Methodologically, from Rs-fMRI data, the functional connectivity matrices or their equivalent functional networks have been usually derived. In these networks, the correlation of time courses between brain regions describe the strength of functional connections [42].

Functional connectivity has been used to compare between patients and control subjects [56,63]. Supervised machine learning techniques typically achieve better classification accuracy than conventional statistical methods. Several studies have applied automatic machine learning approaches to discriminate healthy subjects from schizophrenic patients. For example, based on resting-state functional connectivity, a Support Vector Machine (SVM) classifier distinguished between older and younger adults [64]. Fekete et al. [1] achieved 100% accuracy with 18 healthy and schizophrenic subjects. Arbabshirani et al. [65] achieved an accuracy of 96% with 28 healthy and 28 schizophrenic patients. A major drawback of previous studies is the relatively small datasets. Cheng et al. [66] presented an accuracy of 79% with 48 healthy and schizophrenic subjects. Drawbacks of this study include using a small dataset, limited investigation of suitable features for computer-aided schizophrenia diagnosis, and low accuracy. Anderson et al. [62] achieved 65% accuracy with 146 healthy and schizophrenic subjects. While this study enjoys a large dataset, the resulting accuracy is relatively low. In this paper, we focus on feature selection optimization and large-scale robustness in computer-aided schizophrenia detection. In particular, we conduct a thorough investigation of suitable graph-theoretic features (derived from functional connectivity matrices) and the selection of the most discriminative features for schizophrenia classification. The exploited graph features are: betweenness centrality, characteristic path length, degree, clustering coefficient, local efficiency, global efficiency, participation coefficient and small-worldness. These measures were employed to explore regional activity of the brain regions in schizophrenia patients at rest. Moreover, we conducted our experiments on the large-scale schizophrenia dataset provided by the Center for Biomedical Research Excellence in Mental Illness and Brain Function (COBRE). In addition, we propose a classification scheme with combined graph measures and optimized feature selection and report an accuracy of 95%. The classification framework consists of six modules, namely preprocessing, anatomical parcellation, graph construction, feature extraction, feature selection and classification with a SVM classifier. Fig. 1 shows a block diagram of the proposed classification system.

The rest of this paper is organized as follows: Section 2 describes the used dataset, and explains the modules of data preprocessing, anatomical parcellation, brain network analysis, computation of graph metrics, feature selection and SVM classification. Section 3 reports and discusses the results. Section 4 concludes the paper.

Table 1
Participant demographics in COBRE.

	Patients	Controls
No. of subjects	70	70
Age	37.9 (18–65)	35.8 (18–65)
Gender (M/F)	56/14	48/22
Handedness (R/L)	59/11	67/3

2. Materials and methods

2.1. Dataset description

The COBRE dataset,[1], formed of functional and anatomical MR data samples for 70 healthy subjects and 70 patients with schizophrenia, was employed. A multi-echo MPRAGE (MEMPR) sequence was used for anatomical imaging with the following parameters: TR/TE/TI = 2530/[1.64, 3.5, 5.36, 7.22, 9.08]/900 ms, flip angle = 7°, slab thickness = 176 mm, FOV = 256×256 mm, data matrix = $256 \times 256 \times 176$, number of echoes = 5, voxel size = $1 \times 1 \times 1$ mm, pixel bandwidth = 650 Hz, total scan time = 6 min. With 5 echoes, the TR, TI and time to encode partitions for the MEMPR are similar to that of a conventional MPRAGE, resulting in similar GM/WM/CSF contrast. Data for Rs-fMRI was collected with single-shot full k-space echo-planar imaging (EPI) with ramp sampling correction using the intercommissural line (AC-PC) as a reference (TR: 2 s, TE: 29 ms, matrix size: 64×64, 32 slices, voxel size: $3 \times 3 \times 4$ mm^3). Rs-fMRI, anatomical MRI, and phenotypic data including: age, handedness, gender and diagnostic information, were recorded for every subject. A brief summary of the demographic data included in COBRE is shown in Table 1.

2.2. Data preprocessing

All the preprocessing steps were executed in MATLAB (MathWorks) using the Data Processing & Analysis for Brain Imaging (DPABI) software tool [67]. For each participant, the following steps have been performed: slice time correction for interleaved acquisition, head motion correction based on Friston's 24-parameter motion model [68] and co-registration of structural and functional

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[1] http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html.