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Research progress of functional connectivity analysis in diseases

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Abstract

Automatic classification of diseases based on neuroimaging data has received increasing attention. Resting-state functional magnetic resonance imaging is a non-invasive, high-resolution technique that can be used to extract disease features, these features can further be used to classify diseases with the help of machine learning methods. Two common fMRI analysis methods, including functional connectivity and functional connectivity density, bring a lot of evidence for disease classification and study differences between patients and healthy controls. In this paper, we introduce the concepts of functional connectivity and functional connectivity density, and provide an overview of some recent approaches to functional connectivity and functional connectivity density in disease classification and their progress.

Keywords

Rs-fMRI, Classification, Functional connectivity, Functional connectivity density.

1. Introduction

The brain contains many anatomically connected, functionally independent and mutually influencing brain regions[1]. It is a complex system that has been studied all the time. It is responsible for individual cognitive functions such as perception, movement, language, and learning, and is extremely important to the human body. Understanding how the brain processes information is an important topic.

The development of brain imaging technology provides imaging tools for us to observe the functional activities of the brain, which is of great significance for the diagnosis and efficacy evaluation of brain diseases in clinical practice. Compared with commonly used brain imaging techniques such as electroencephalography, magnetoencephalography, and positron emission tomography, magnetic resonance imaging (MRI) has the advantages of non-invasiveness and high spatial resolution, and is widely used in clinical examinations. Functional magnetic resonance imaging (fMRI) based on the principle of blood oxygenation level dependent contrast enhancement (BOLD)[2] is developed on the basis of traditional magnetic resonance imaging technology. Oxyhemoglobin in blood is a diamagnetic substance, and deoxyhemoglobin is a paramagnetic substance. Brain neurons consume a lot of oxygen and glucose when they are active. Local tissue oxyhemoglobin increases and deoxyhemoglobin decreases, resulting in a changed T2-weighted signal. Thus the enhancement of the FMRI signal, reflects changes in the metabolic levels in local brain regions caused by neuronal activities.

Early fMRI research was mainly based on task-state experiments to study which brain regions of the brain are activated or functional connections between brain regions under a certain experimental task. The diversity can also influence the experimental results. Resting-state functional magnetic resonance imaging (rs-fMRI) is a magnetic resonance scan performed without the subject doing any specific tasks. In the awake state with eyes closed and resting,

the oxygen consumption of the brain, which only accounts for 2% of the body weight, accounts for 20% of the oxygen consumption of the whole body[3]. A large number of studies have shown that the brain performs meaningful functional activities in the resting state[4, 5]. Resting-state fMRI studies have overcome the problems existing in the task state, and have been widely used in studying functional activities inside the brain, providing imaging data for the study of the physiological and pathological mechanisms of diseases.

This paper mainly summarizes the two aspects of functional connectivity (FC) and functional connectivity density (FCD), both of which are related to the research of resting-state fMRI.

2. Introduction of the Method

2.1. Functional Connectivity

The human brain is a very complex information processing system. Through the cooperation between multiple brain regions, information is processed to complete the functional activities of the brain. The traditional brain region network research is task-based, and different scholars study the network connection of brain regions under a specific task. Many studies have shown that in the resting state, the human brain also has a default functional network, which can obtain information from the external environment, process and store it, and each brain region achieves a dynamic balance in this activity. The research on the network connectivity of the human brain in the resting state has become an important topic in the study of the network connectivity of brain regions, and the use of fMRI to study the functional network connectivity of the brain regions is the general trend[6].

In the early 1990s, brain functional connectivity was extended from electrophysiological research to functional imaging by Professor Friston and others from Welcom's laboratory in the United Kingdom, and divided it into FC and effective connectivity. FC refers to the temporal correlation of neurophysiological indices measured between different regions of the brain that are spatially separated[7]. The brain functional connectivity networks (FCNs) studies the inside of the brain from different scales, the micro-scale is neurons, the meso-scale is neuron clusters, and the large-scale is brain regions, to study the interaction or relationship between them, and see if there are significant differences between disease patients and healthy controls. To study the brain from a large scale of brain regions, functional connections can be divided into connections between brain regions and connections within brain regions. Connections between brain regions are mainly aimed at the research between different brain regions, occupying a main part of the brain region connection, the connections within the brain regions are mainly to measure activities of brain regions, such as the use of internal correlation-based algorithms to study the brain from inside.

When studying brain FCNs, graph theory in mathematics can well describe the properties of brain FCNs, can be used to examine the overall structure of the network, and has a high degree of spatial detail, and is widely used in social sciences, biological information and other fields. Many visualization tools can produce very beautiful functional connection diagrams, showing functional connections in brain regions or other scales. For example, we use the AAL90 template that comes with the Brainnet viewer tool to show functional connections[8], see Figure 1.

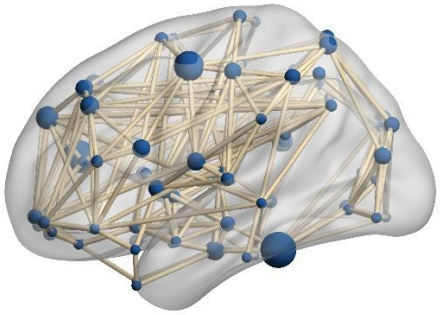

Figure 1: The connection between brain regions

Due to the inference limitation of directed networks, graph theory mostly designs brain FCNs as undirected graphs $g=(v,e)$, where v represents the set of nodes in brain regions, e represents the functional connectivities between these brain regions, see Figure 2. FC is calculated as the correlation between the time series of two brain regions, commonly known as Pearson's correlation coefficients.

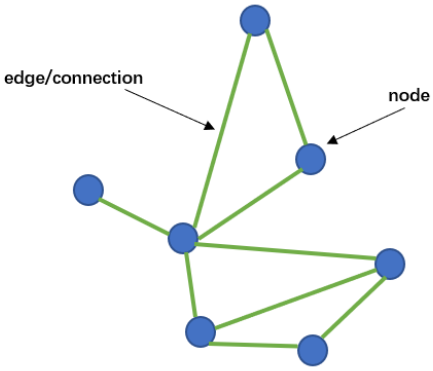

Figure 2: Undirected graphs

2.2. Functional Connectivity Density

The method of FCD was first proposed by Tomasi[9]. It measures the FCD of each voxel in the whole brain, the larger the density value, the more voxels that have FC with the voxel, and vice versa, the distribution of the brain functional connectivity hub area can be quickly determined by this method. As a purely data-driven approach, FCD allows us to analyze FC from a global and local perspective without setting any prior assumptions. FCD is developed from the perspective of FC. Tomasi et al. used a large amount of data in the functional connectome project to demonstrate the robustness of the method between different individuals and different datas.

3. Application in Disease

3.1. Application of functional connectivity in disease

Aiming at the problem of low accuracy of autism classification, a support vector machine recursive feature elimination (SVM-RFE) autism classification and control algorithm based on FC can find the optimal features on large sample data to help improve the classification accuracy, 35 regions of interest were selected to build FC matrix, and the most discriminative informative features were found through SVM-RFE and 4-fold cross-validation strategy, finally achieving an accuracy of 90.6%. The highest classification accuracy in leave-one-out cross-validation reaches 95%[10].

The most common tumors in the brain are metastases, which are often associated with high morbidity and mortality. Using independent component analysis (ICA) to analyze the resting-

state magnetic resonance functional data of patients with brain metastases, seven common resting state networks (RSNs) can be identified, and it is found that the RSNs of patients show significant spatial shifts. This finding suggests that multiple RSNs in patients can be localized prior to surgical resection of metastases and that spatial shifts of RSNs needs to be fully considered[11]. Brain metastases can affect whole brain functional and structural connectivity networks[12]. Using graph theory to calculate network properties, dividing the brain into 90 regions through Automated Anatomical Labeling (AAL) template, at the same time constructing a high-resolution network containing 1024 regions, it was ultimately found that compared with healthy controls, patients with brain metastases exhibited a more stochastic altered "small-world" network in both functional and structural network connectivity, the coupling between patients' functional and structural connectivity decreased. After removing these metastases-affected nodes, the performance of the brain network declined. These discoveries are beneficial for surgical planning and postoperative evaluation of metastases.

An end-to-end deep learning framework[13] uses the time series signals preprocessed by fMRI as input, and calculates FC between 90 brain regions of the AAL template as the functional connectivity network(FCN), which is used as the basis for classification and combined with the content of deep learning, and finally achieves classification accuracy of 73.1% in distinguishing Attention Deficit Hyperactivity Disorder (ADHD) from healthy controls, the specificity is as high as 91.6%, and the sensitivity is 65.5%. The classification performance of this method is better, while finding the frontal lobe to be the most discriminative in differentiating between ADHD and healthy controls. FC plays a large role in improving classification accuracy and providing interpretable results.

The traditional FCN usually uses a kind of FCN to extract features, which are then used for disease classification. Some studies have gradually explored the fusion of multiple functional connection networks to extract features that are conducive to assisting disease diagnosis, and have made good progress.

A new network-based framework is a useful tool to aid in the diagnosis of schizophrenia. It first uses extended maximal information coefficient (eMIC) obtained from the rs-fMRI time series in four frequency bands to construct FCNs within the same and across frequency. Then, these FC networks are nonlinearly combined into a unified network using network fusion, and features are extracted from this unified network for classification. The experimental results show that on the public schizophrenia dataset COBRE, this method of using FC networks generated in different frequency bands for network fusion to extract features for classification has achieved the best performance. Using leave-one-out cross-validation, the classification accuracy of this method is 81.54% (permutation test $p<0.001$, performed 1000 times), the classification accuracy of the entire low frequency band is 71.54%, the classification effect of FC features combining four frequency bands is 76.15%, and the classification effect of combining the networks constructed with Pearson's correlation coefficient is only 69.23%[14].

Exploiting a multi-graph fusion functional connection network (FCN) framework to explore the common and complementary information between two FCNs, one is a fully connected FCN and the other is a 1 nearest neighbor(1NN) FCN obtained by adopting a most sparse FCN. The two FCNs are fused. Finally, the most basic L1SVM method is used to select features and diagnosis the disease[15]. When classifying three neurological disorders, Fronto-Temporal Dementia (FTD), Obsessive-Compulsive Disorder (OCD), and Alzheimer's Disease (AD), this framework is compatible with multiple state-of-the-art FCN analysis methods such as High-Order Functional Connectivity (HOFC), Sparse Connectivity Pattern (SCP), Sparse Connectivity Pattern (SCP), etc. And it is proved to be the best. When classifying ANDI, the classification accuracy of this framework is 88.84%±3.22, the sensitivity is 89.55%±1.85, and the specificity is 88.25%±2.49. By selecting reasonable brain regions for classification tasks, the framework achieves the best diagnostic performance for the several diseases mentioned above.

The above-mentioned applications of FC to classify diseases and identify the parts of the brain that have changed in patients provide imaging features for the study of these diseases, and the classification effects are also good.

3.2. Application of functional connectivity density in disease

Hu et al.[16]first found differences between idiopathic short stature and growth hormone-deficient subjects by FCD, the GH-deficient group had significantly lower FCD values in the left postcentral gyrus, right precentral gyrus, and left cerebellar lobes 7b and 6. Subsequently, these regions were used as seed points to compare the differences in FC, and it was found that the FC in these regions was correspondingly reduced in the growth hormone-deficient group. Growth hormone deficiency mainly has effect on the somatosensory, somatic motor and cerebellum network.

In recent years, many researchers have been exploring topics related to FCD, studying the differences in FCD between patients with different diseases and healthy controls, and identifying disease-related brain regions, providing support for further research on diseases. The pathological mechanisms of schizophrenia patients and siblings were first revealed by using FCD to study their FC hub regions and core FCD regions[17]. Cluster analysis found that the brain regions with increased FCD were mainly distributed in the superior frontal gyrus, middle frontal gyrus, limbic lobe, and middle occipital gyrus; the brain regions with decreased FCD were mainly distributed in the superior temporal gyrus, precentral gyrus, and posterior central gyrus. Based on the results of FCD, three Regions of Interest (ROI) were extracted as seed regions to explore the differences in whole brain FC, and it was concluded that FC of the patient group in the three seed regions significantly weakened. Guo[18] first found abnormal short-range FCD areas and long-range FCD areas in post-stroke aphasia (PSA) compared with healthy controls, and she also found that long-range FCD in the left superior temporal gyrus decreased. There was a positive correlation with the speech scores of the Chinese Aphasia Examination Scale (CAES), suggesting that abnormal hub centers can lead to impaired speech performance and speech fluency. The changes in FC of patients with chronic low back pain caused by lumbar disc herniation (LDH) in the resting state were exploited. The FCD values of LDH patients changed in multiple brain regions of visual network, the FC of the visual dorsal pathway and ventral pathway in LDH patients were enhanced, and the FCD value of the left lingual gyrus was positively correlated with the visual analogue scale (VAS) score.These indicate that the functional changes of visual network may be imaging biomarkers for LDH patients[19].

To compare the global functional connectivity density (gFCD) of 110 major depressive disorder (MDD) patients with comorbid insomnia and 30 healthy controls, MDD are divided into two groups, higher level insomnia (MDD-HI) and lower level insomnia (MDD-LI). FCD values differ across groups in the same brain region[20]. For example, in the bilateral parahippocampal/hippocampal gyri (PHG/HIP), the gFCD is higher in the two MDD than in the HC group, and it is higher in the MDD-LI than in the MDD-HI group . Additionally, the alteration of visual system is associated with insomnia symptoms in patients with MDD.

Wang et al.[21] measured the local and long-range FCD in white matter (WM) of 39 adolescents with schizophrenia (AOS) and 31 healthy controls, and obtained the functional centers of WM by comparing between groups. At the same time, they performed Spearman rank correlation analysis on the altered FCD regions and clinical PANSS scores. They found that abnormal FCD in dorsal raphe nuclei is correlated with the clinical symptoms. This also provides evidence for the existence of FC abnormalities in the WM of patients with schizophrenia.

After calculating FCD of the whole brain for patients with Parkinson's disease (PD) and normal control (NC), abnormal FCD values are extracted, then, the ROC curve was used to compare the performance of the FCD value of each abnormal brain area and the combined FCD value of each

abnormal brain area to diagnose PD. The brain regions with decreased FCD in PD patients were mainly located in the right lingual gyrus, bilateral insula and left superior temporal gyrus, while the increased FCD was mainly located in the left middle frontal gyrus. The area under the curve (AUC) of combining the FCD values of each abnormal brain region to diagnose PD is 0.955, and AUC of using the FCD value of each other abnormal brain region for diagnosing PD is also above 0.8[22]. The FCD values of abnormal brain regions have important reference significance in the diagnosis of PD.

FCD is gradually being applied to a large number of psychiatric diseases. These are shown in more details at the voxel level in order to study the changes in FC within the brain. In the future, more research studies can start from this.

4. Conclusion

The non-invasive nature of resting-state fMRI enables the application of automatic disease classification based on neuroimaging data in a variety of diseases. The applications of the two methods of functional connectivity and functional connectivity density to resting-state fMRI data can extract important features of diseases, have potential application value in disease classification, and provide imaging basis for disease diagnosis. In the future, more research will focus on using multimodal imaging information to improve the accuracy of disease classification.

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