Study on Resting-State fMRI Data of Mild Traumatic Brain Injury Based on Machine Learning

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Abstract: ***This study aims to select abnormal function connections in the resting-state function connection network (FCN) of mild traumatic brain injury (mTBI) in the acute phase, then analyze the function connections changes among different brain networks and the corresponding pathophysiological mechanisms. Sixty-nine patients with mTBI and sixty healthy subjects with age, sex, and education level matched were recruited for the study. All subjects accepted resting-state fMRI scan, neuropsychological assessment, PSQI, and treadmill testing. This study adopted the elastic net to select subjects' abnormal function connections, which were input into a support vector machine for classification validation. Furthermore, we performed a correlation analysis between the mTBI group and abnormal functional connectivity and psychometric scores. The classifier achieved accuracy = 84.62%, recall = 85.27%, precision = 84.62%, and F1 score = 84.72%. The decreased function connections between networks include visual network (VN)-visual network (VN), visual network (VN)-frontoparietal network (FPN), somatomotor network (SMN)-ventral attention network (VAN). Furthermore, there are decreased function connections between the cerebellum network (CN) with ventral attention network (VAN), somatomotor network (SMN), default mode network (DMN), and frontoparietal network (FPN). Abnormal functional connections are widely distributed in various networks. The interaction of various networks may lead to motor, executive, cognitive and emotional dysfunction in patients with mTBI. Abnormal functional connections affect brain networks and functions through global distribution and local aggregation. The most affected network areas are cerebellum, visual, and somatomotor networks. The cerebellum network and other networks have extensive coordination and interaction.***

Keywords: Brain network, Elastic net, Mild traumatic brain injury, Resting-state fMRI, Support vector machine

1. Introduction

Traumatic brain injury (TBI) is one kind of nerve injury, which is not only a major cause of people death and disability but also a momentous public health problem all over the world [1]. According to the definition of the interdisciplinary special interest Subcommittee on the head injury of the American rehabilitation Congress, mild traumatic brain injury (mTBI) accounts for approximately 85% of TBI cases [2]. The main causes of mTBI include sports accidents, falls, attacks, active soldiers, domestic violence, etc [3]-[4]. The mTBI patients also suffered from various physical, emotional, or cognitive problems, such as sleeping disorders, anxiety, and depression [5]-[8]. A large number of studies have indicated that the cognitive and emotional defects of mTBI are caused by the damage to brain function connection [9]-[12], especially by the disconnection of important network centers [13]-[14].

So far, early diagnosis of patients with mTBI remains a major challenge. No obvious contusion or hemorrhage is diagnosed by conventional neuroimaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI). Detecting and locating the microstructure disorder of mTBI is significant to understanding the potential pathophysiology. Numerous studies applying functional magnetic resonance imaging (fMRI) identified that resting-state cortical networks are postulated to underlie sensory, motor, and cognitive function [15]-[17]. These experiments prove a crucial conclusion that the resting-state brain is not in a real resting state. On the contrary, coherent brain activity can be demonstrated in a limited spatial map without external interference. During the individual rest, the neural activities in the brain region fluctuate spontaneously, forming a resting-state tissue network [18]-[19]. Some studies have shown that resting-state fMRI based on spontaneous blood oxygen level-dependent (BOLD) response has the advantage of non-invasive neuroimaging, which can detect the disease-induced neurological dysfunction after mTBI and reveal the relevant neuropathological mechanism [20]-[21].

In addition, the field of the connectome is conducive to exploring the structural and functional connections of brain regions and revealing how these connections participate in specific behavioral, cognitive, and emotional processes [22]-[24]. At the same time, evaluating the functional connections between all brain regions not only contributes to the study of the correlation between brain attributes and outcome measurements (including demographic, clinical, and behavioral measurements), but also provides corresponding statistical capabilities. The connectome utilizes an N x N symmetric matrix to represent the functional connection matrix, whose principle is to divide the brain into discrete and non-overlapping brain regions and calculate the functional connection strength between paired brain regions. Studies have confirmed that when MRI-based diagnosis, features are usually generated by dividing the brain into different regions of interest (ROI), many of which may not be related to mTBI [25]. In summary, most mTBI patients perform brain network disorders and functional defects caused by abnormal brain functional connections. Therefore, this study takes the resting-state functional connectivity network (FCN) of subjects as the research object, aiming to simplify the FCN and search for the abnormal functional connectivity between mTBI and the healthy control group, which is advantageous for analyzing the relationship between abnormal functional connectivity and cognitive behavior of mTBI.

2. Materials and Methods

2.1 Subjects

The IRB of Xiangya Third Hospital of Central South University approved this study, and all subjects signed informed consent. This study is also in line with the relevant Measures for Ethical Review of Biomedical Research Involving Humans (China, 2016). From April 2014 to February 2021, we recruited 69 patients with mTBI and 60 healthy subjects matched by gender, age, and education level in the emergency department of Xiangya Third Hospital, Central South University. The inclusion and exclusion criteria were consistent with our previous studies [26].

2.2 Data Preprocessing

The preprocesses of this study utilized the Statistical Parametric Mapping (SPM12) toolkit and MATLAB 2013a software. The data scanned at different time points are transformed into data at the same time point through slice timing. Realignment can exclude rotation greater than 3 degrees or move more than 3 mm. Then the data is spatially smoothed and filtered by a bandpass filter (0.01-0.1hz). Next, all functional images are registered to normalize on the Montreal Neurological Institute (MNI) template. Finally, the structural image is divided into gray matter, white matter, and cerebrospinal fluid.

2.3 Feature Extraction

We take the resting-state FCN as the object of research, the FCN of each subject was obtained by utilizing rest and IBASPM toolkit. Since the functional connection matrix is symmetrical about the diagonal, we only need to extract the functional connection of the upper right half angle. In this study, we operated on the upper right half-angle features, sorted from left to right and from top to bottom. Each subject had a total of 6670 functional connection features. Finally, the features of each subject were standardized.

2.4 Feature Selection

In this study, the number of features far exceeds the number of samples. To avoid over-fitting, feature selection helps reduce the prediction error and improve the interpretability of the model. We adopt the elastic net [27] to extract the abnormal functional connections. The elastic net is a regularized linear regression model including L1 and L2 regularization terms, which combines the advantages of ridge regression and lasso. The elastic net contains a mixed parameter ρ, which works together with λ. The elastic net can simultaneously perform variable selection and continuous contraction, generating a sparse weight vector for feature selection. It is particularly useful for multi-feature small sample problems. As shown in equation (1), the elastic net is composed of mean square loss and two regularization terms. The y is the class label (patient or control group), x is the feature of functional connection, and w is the weight of the features. Parameters of the penalty term include λ and ρ. According to multiple tests and evaluations, parameter λ is selected as 0.14, and parameter ρ is adjusted to 0.8.

$$w = \arg_w \min\left\{\sum_{i=1}^{N}(y_i - w^T x_i)^2 + \lambda\rho||w||_1 + \frac{\lambda(1-\rho)}{2} + ||w||_2^2\right\} \quad (1)$$

2.5 Classification

The support vector machine (SVM) is a classifier model which is widely applied in fMRI research. Its basic principle is to maximize the interval between different data points by constructing a hyperplane and finally transform it into the solution of a convex quadratic programming problem. SVM is preponderant in solving small sample, nonlinear and binary classification problems. Compared with other multivariable pattern analysis (MVPA) methods, SVM can provide higher prediction accuracy and lower sensitivity to noise. We directly import the SVM from sklearn, set the parameter "kernel" to linear, the regularization parameter "C" to 1, and other parameters remain the default.

3. Results

3.1 *Abnormal function connection and classification results*

The elastic net selected 12 pairs of abnormal function connections, as shown in Figure 1. These function connections were widely distributed in the visual network (VN), somatomotor network (SMN), ventral attention network (VAN), limbic network (LN), frontoparietal network (FPN), default mode network (DMN), and cerebellum network (CN). To locate the brain regions involved in these abnormal functional connections specifically, we applied the BrainNet toolbox to visualize localization, as shown in Figure 2. We found that the CN, VN, and SMN were the areas with the most concentrated distribution of abnormal functional connections. The results also showed that the CN, VN, and SMN were the key abnormal centers of mTBI.We adopted accuracy, recall, precision, and F1 score to assess the classification effect of the SVM, with accuracy = 84.62%, the recall = 85.27%, the precision = 84.62%, and the F1 score = 84.72%.

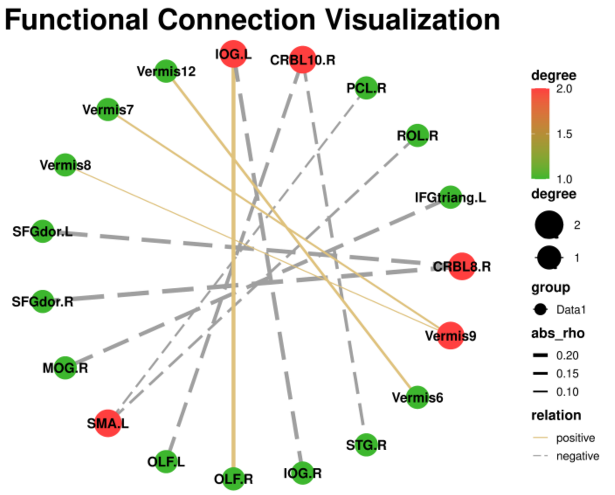

Figure 1: Functional connection visualization

3.2 *Correlation analysis of abnormal functional connection and Stroop-color response time*

This study performed the correlation analysis of 12 pairs of abnormal functional connections and Stroop-color response time. We found that there was a negative correlation between Stroop-color with the functional connection of the right middle occipital gyrus (MOG.R) and the left triangular inferior frontal gyrus (IFGtriang.L) (r=-0.0302, p=0.033), as shown in Figure 3.

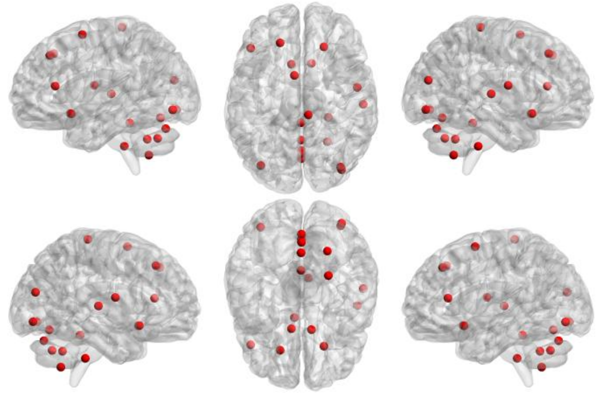

Figure 2: Visualization of brain nodes related to abnormal functional connections

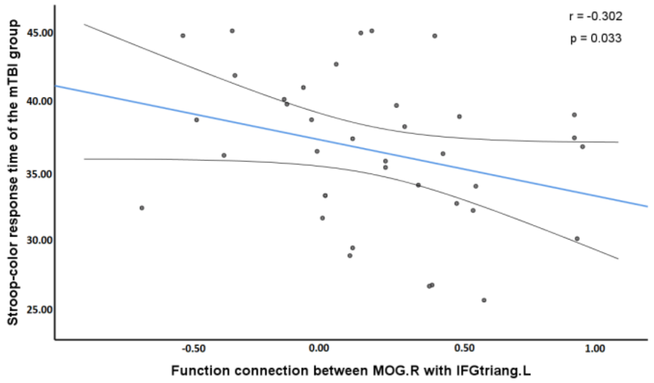

Figure 3: Correlation between Stroop-color response time of the mTBI group and functional connectivity of MOG.R with IFGtriang.L

4. Discussion

In this study, the abnormal functional connection of mTBI is selected to reveal the corresponding neuropsychological results through machine learning. We found that abnormal functional connections were widely distributed in various brain networks. The most affected brain networks include the cerebellum network (CN), visual network (VN), and sensorimotor network (SMN). The functional connections of the VN-VN and VN-FPN are decreased. The VN is a significant network observed in this study, which many previous studies have also reported. Li's study found different patterns of network interaction between mTBI and healthy control groups, including salience network (SN) - cerebellum network (CN), visual network (VN) - sensorimotor network (SMN), and executive control network (ECN) - default mode network (DMN) connections [28]. Wang also found that compared with female patients with TBI, male patients showed increased intrinsic functional connectivity in the motor network, ventral stream network, executive function network, cerebellum network, and decreased connectivity in the visual network [29]. Amir observed the decreased connectivity of mTBI in the visual network through group comparison [30]. As the Frontoparietal network plays a key role in visual-spatial attention, we speculate that the decreasing functional connection of VN - VN, and VN - FPN may be one of the factors of visual perception impairment in patients with acute mTBI.

In this study, we found that the functional connection between the somatomotor network (SMN) with the ventral attention network (VAN) decreased in patients with mTBI. The SMN has always had an important impact on major diseases. Wang's study presented that the hubs of mTBI patients were distributed in a wider network, including default mode network (DMN), ventral attention network (VAN), frontoparietal network (FPN), somatomotor network (SMN), and visual network (VN) [31]. Miguel's study found that in terms of inter-state transition, schizophrenic patients have an increased probability of switching to limbic, somatomotor, and visual networks and a reduced probability of maintaining a state related to the default mode network orbital frontal network and global synchronization state [32]. The ventral attention network (VAN) is responsible for non-spatial attention and participates in stimulus-driven top-down attention selection, including awareness of significant events, attention reorientation, and alert state. We speculate that the abnormal functional connection between the somatomotor network (SMN) and the ventral attention network (VAN) may be an important factor leading to inattention in patients with mTBI.

In the mTBI group, we found there are decreased function connections between the cerebellum network with ventral attention network (VAN), somatomotor network (SMN), default mode network (DMN), and frontoparietal network (FPN). Many previous studies have confirmed that the cerebellum is related to motor function and cognitive function. Wang's study found that changes in cerebellar fractional anisotropy with acute mTBI were limited to specific regions and statistically correlated with cognitive deficits detected in neurocognitive tests [33]. Nathan found evidence supporting increased adaptive connectivity after mTBI, especially in the frontoparietal, cerebellum, and default mode networks [34]. We assume that there is extensive coordination and interaction between the cerebellum network and other networks. Qasim et al. adopted a dynamic causal model to find that there are unified interactions in all networks of healthy young people from the cerebellum to the cerebral cortex [35], which supports the universal cerebellar transformation and our hypothesis.

5. Conclusion

This study utilized the elastic network to rarefy the resting-state FCN and select the abnormal functional connection of mTBI. The results showed that the abnormal functional connections of mTBI patients were mainly distributed in the visual network (VN), somatomotor network (SMN), ventral attention network (VAN), limbic network (LN), frontoparietal network (FPN), default mode network (DMN) and cerebellum network (CN). Among these abnormal FCNs, the most seriously damaged FCNs are located in the cerebellum network (CN), visual network (VN), and somatomotor network (SMN). These results support that mTBI affects brain network connection and function in both global distribution and local aggregation, which leads to motor function, executive function, and cognitive and emotional disorder in mTBI patients. Meanwhile, we also found extensive coordination and interaction between the cerebellum network (CN) and other brain networks, which indicated the cerebellum network (CN) should be underlined in the follow-up of the mTBI further treatment.

We acknowledge that this research also has limitations. We only analyzed mTBI in the acute phase and did not study mTBI in the subacute phase. However, secondary injury and compensatory effects might occur in the sub-acute stage of mTBI. Therefore, we will conduct follow-up scanning to better understand the changes in brain networks in both the acute stage and sub-acute stage of mTBI.

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