Higher-order interactions in functional brain networks in major depressive disorder

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***Abstract*—Neuroscience explores the anatomy, function and development of the central and peripheral nervous system. Neuroscientists lately study functional brain networks to understand mental disorders like depression. Analysis of these networks can aid in diagnosing depression. Q-analysis, a higher-order interaction approach, may be more effective in identifying brain regions relevant to depression, compared to the standard paired approach. This study examined functional brain networks, by using higher-order interaction approach with Q-analysis method, in depressed patients and healthy subjects using fMRI data. Results indicated fewer and weaker higher-order interactions in depressed patients compared to controls. Modularity and clustering were also reduce in depression. These findings highlight the importance of studying higher-order interactions in functional brain networks for diagnosing and understanding depression.**

Keywords—neuroscience, functional brain networks, depression, diagnosis, higher-order interactions, Q-analysis, fMRI.

I. Introduction

In recent years, neuroscience has been actively exploring the functional networks of the brain [1]. One of the approaches in this study is to analyze the properties of these networks, including higher-order interactions between different brain regions. Depression, as a common mental disorder, significantly affects the quality of life of patients and their ability to function in society. Diagnosis of depression plays an important role in determining the presence of the disorder, its severity and the choice of the most effective treatment method.

Analysis of the functional networks of the brain can be of significant help in the diagnosis of depression. The studies available in this field indicate the presence of changes in the structure and functional activity in various areas of the brain in patients suffering from this mental disorder [2-7]. Analysis of the functional networks of the brain provides an opportunity to identify the above changes and determine which areas of the brain are associated with the development of depression.

II. Methods

A. Q-analysis

It is important to emphasize that when analyzing the functional networks of the brain at the level of paired interactions between individual areas, an incomplete understanding of the interaction between different areas may arise. Therefore, the use of higher-order interaction analysis methods is more effective. One of these approaches is Q-analysis, which allows one to identify strongly related groups of brain regions that play a significant role in the context of depression [8]. The Q-analysis method is widely used to study functional networks and identify the modular structure [9,10].

B. Basic definitions

Before continuing, it is necessary to define the basic concepts used in this paper.

An incidence matrix is a matrix in which each column corresponds to a clique (i.e., a complete subgraph) in a graph, and each row corresponds to a node in the graph. The values in each cell are set according to the rule: if the current node is associated with a click, then the current cell is assigned the value "1", otherwise "0". Thanks to this view, you can see which nodes belong to each click.

Before start calculating the matrix of common faces, first we should calculate the multiplication of the transposed incidence matrix by the original incidence matrix. After that, we should create a single matrix, the size of which will be equal to the size of the matrix obtained as a result of calculations at the last step. Next, the unit matrix should be subtracted from the resulting matrix, and the result will be a matrix of common faces. Mathematically, it will look like this:

$$Sfm = (Inm^{T} * Inm) - I_{clq,clq} \quad (1)$$

In this formula Sfm is the common face matrix, Inm^{T} is the transposed incidence matrix, Inm is the initial incidence matrix, and $I_{clq,clq}$ is the unit matrix the size of cliques count.

The matrix of common faces contains the following values: -1, 0, 1, n. The value "-1" in the matrix indicates that the corresponding cliques do not have common connections, the value "0" means that the cliques have a common connection through the node, and the value "1" indicates that the cliques are connected through a common edge. In turn, the value "n" means that the corresponding cliques are connected through a face of dimension n.

A simplicial complex is a connected structure and, therefore, there are "indirect" connections between all pairs of simplices included in it. These connections or q-connections, which are also called q-chains, exist in different dimensions, called q-levels. It is very important not to confuse q-connectivity and q-nearness, since a pair of simplices can be q-connected, but not q-nearness, although q-nearness implies q-connectivity. Q-connections are formally identified using the Q-analysis of the complex [8]. We used the following formulas to calculate three structure vectors to characterize the considered network.

First structure vector:

$$Q = \{Q_0, Q_1, \ldots, Q_{qmax-1}, Q_{max}\}, \quad (2)$$

where Q_q – the number of q-connected components in each q-level.

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Second structure vector:

$$N_S = \{n_0, n_1, \ldots, n_{qmax-1}, n_{qmax}\}, \quad (3)$$

where n_q is the number of simplices at q-level and above.

Third structure vector:

$$\hat{Q}_q \equiv 1 - Q_q \div n_q \quad (4)$$

In this study, higher-order interactions in functional brain networks reconstructed based on functional magnetic resonance imaging (fMRI) data were studied in patients suffering from depression, as well as in healthy subject.

C. Data preparation

For calculations, data from 169 observed patients were used, 72 of whom were diagnosed with depressive disorder. Subjects having a previous history of comorbid psychiatric conditions, autoimmune diseases, neurological diseases, history of head trauma, or any metal implants in-compatible with the MRI were excluded. The normalized functional MRI volumes extracted were parcellated into 166 regions according to the automated anatomical labeling atlas AAL3. Connectivity matrix calculation from the averaged activity time-series was performed with the help of Pearson correlation coefficient estimation in Matlab ("corrcoef" function). Thus, we obtained for each subject a 166×166 symmetric connectivity matrix. Each cell of the connectivity matrix represents the strength of the connection (or edge) between two parcels [3]. To identify the statistical significance of the data, a random permutation of the data was performed 100 times, after which the consensus-networks were built. Consensus-network is formed according to the following principle: if 95% of the subjects from the group have a connection, then we leave it, otherwise – no.

D. Calculations

In this paper, we are interested in the structure of the whole complex, not individual components, so we will talk about the global structure and describe it by calculating number of components at each q-level. We represent this information in the form of the structure vectors.

III. Results

As a result of the calculations described above and visual analysis of the graphs, it was noticed that the data are clearly separable and the established error of 5% is acceptable. Next, cliques and structural vectors for the consensus-networks were calculated, and entropy and topology were calculated using common methods.

As a result of visual analysis of first structure vector (Fig. 1), it was noticed that the number of q-connected components in healthy subjects was higher than in patients' group. However, at q=13, the number of q-connected components was higher in patients' group.

According to the results of calculations, it was found that patients with depression have fewer higher-order interactions between regions of the brain, and these connections are weaker compared to the control group (Fig. 1). These conclusions are confimerd by previous studies that indicate impaired connections in functional networks in patients with depressions [5,6,11,12].

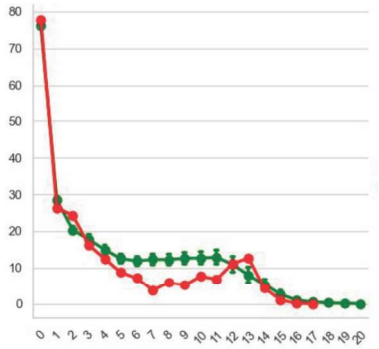

Fig. 1. First structure vector. Red – patient subjects, green – healthy subjects. Horizontally – the number of q-level, vertically – number of q-connected components.

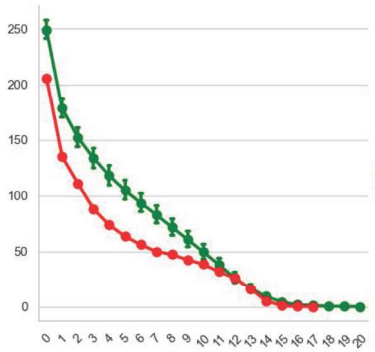

Fig. 2. Second structure vector. Red – patient subjects, green – healthy subjects. Horizontally – the number of q-level, vertically – number of simplices.

It was found that higher-order interactions between brain regions in healthy subjects have a higher number of simplices at q-levels from 0 to 7 than in patients with depressive disorder, as can be seen from the Fig. 2. In patients with depression, modularity is less pronounced. It is worth noting that healthy subjects have a confidence interval in more than half of the initial orders, unlike patients with depressive disorder, in whom the confidence interval is extremely small. The statement raises interesting observations, but it does not provide enough information to make definitive conclusions. It could indicate a potential avenue for further research and investigation into the differences between healthy subjects and patients with depressive disorder, with a focus on the parameters being measured and their significance.

IV. Conclusion

The present study highlights the need for in-depth study of higher-order interactions in the functional networks of the brain, especially when considering pathological conditions, including depression.

The results obtained indicate disturbances in interregional interactions in patients suffering from depression. Future research can complement current work by including other pathological conditions and applying other methods of analysis, such as machine learning, in order to increase the accuracy of the developed classifiers for the diagnosis of pathological conditions. There are also great prospects for applying this approach based on the evaluation of high-order interaction metrics in functional brain networks to the

diagnosis of other neural diseases, including Alzheimer's disease [13,14] and autism [15].

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