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Hierarchical organization in neuronal functional networks during working memory tasks

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***Abstract*—Existing studies have shown that neuronal functional networks (NFNs) exhibit small-world properties. However, the issue of whether NFNs have any other complex network topology properties remains unresolved. In this paper, we introduced a new hierarchical clustering-based method that can clearly indicate the hierarchical modular organization of NFNs. Based on the modularity function Q proposed by Newman, we can divide the NFNs into suitable sub-modules. We proposed a new measure function to calculate the correlations between pairs of spike trains without requiring binning of the spike trains through small time windows. This method can be used to analyze the level of synchronization between spike trains and functional connectivity relationships between neurons. We analyzed NFNs constructed from multi-electrode recordings in rat brain cerebral cortexes in vivo. These rats had been trained to perform different working memory cognitive tasks. The results show that NFNs exhibit a clear hierarchical modular organization in rat brains. These results provided evidence confirming that the brain networks are complex. This can also be used as a means of studying the relationship between neuronal functional organization and cognitive behavioral tasks.**

Keywords—neuronal functional networks; hierarchical clustering; modularity

I. INTRODUCTION

The brain has highly complex internal neuronal connections [1]. Over the past several years, complex network analysis has been applied to the brain. The study of brain functional networks has involved fMRI data, EEG, and multiple-electrode recordings at the micro-scale. The network nodes in brain functional networks can be individual voxels or anatomically defined ROIs, time series of multivariate EEG, and neurons using multiple-electrodes [2-4]. The edges are defined as the connections between the nodes, including structural connectivity, functional connectivity, and effective connectivity [5].

Understanding the processes within the brain that are involved in decision-making with respect to different tasks and conditions is an important part of neuroscience. The brain usually makes decisions based on the evaluation of the activity of large populations [6]. With the development of multiple-electrode recording techniques, signals from dozens of neurons can be recorded simultaneously [7]. Studying the inherent connectional structures between neurons is a key element in understanding the functions of the brain at the micro level.

Most of the studies of brain functional networks have been conducted in image datasets based on the human brain, including the resting-state or the task-related fMRI data. Complex network analysis based on graph theory has become the preferred method of analyzing these network topological characteristics. Small-world properties have been found in brain networks, indicating that the brain has the ability to transfer information rapidly under optimal conditions. The analysis of the topological properties of brain functional networks provides an effective means of understanding the development of human brain organization and disease diagnosis [8-9].

Hierarchical modular organization also is an important network topological property. Unlike community structures, hierarchical networks are composed of different layers, a network consisting of multiple sub-networks and sub-networks consisting of smaller sub-sub-networks. The study of community structures originated in the social network and a number of new methods have been applied to social networks [10]. In fMRI functional networks, methods of detecting community structures can be used to assess the functional modules of the brain. Methods based on selecting the maximum modular function values have been applied to studies of human brain fMRI networks and to animal models [11-13].

To date, non-human brain functional networks remain largely unexplored on the micro-scale, especially in animal models. These animals perform working memory cognitive tasks. In this study, we recorded the simultaneous activity of neurons in the anterior cingulate cortexes (ACC) and prefrontal cortexes (PFC) of several rats using multi-electrode recording. The rats performed two working memory tasks. Neuronal functional networks (NFNs) were constructed based on the calculation of correlations between pairs of neurons. Several studies have shown that NFNs exhibit small-world properties [14-15]. However there is still a dearth of studies of the modular structure of NFNs. In this paper, we introduced a new hierarchical clustering-based method to identify hierarchical modular organization of NFNs. The method does not require any prior knowledge of the level of hierarchy of the data set or

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the number of modules. This method clearly indicated the hierarchical modular organization of different NFNs.

II. MATERIALS AND METHODS

A. Behavioral tasks and electrophysiological recordings

We recorded the activities of populations of neurons from four adult male rats in vivo using multi-electrode recording. All experiments were performed in accordance with animal protocols approved by the United States National Institutes of Health (NIH). The rats were trained to perform two different working memory cognitive tasks (two rats for the first task and two for the second task). The first task was a do more and get more task (DM-GM). The rats were deprived of drinking water for some time. The longer the rats stayed in the top of the rectangular box, the more water they were given to drink when they returned to the bottom of the box. The rats were exposed to this apparatus until they understood how to pay more to get more reward. The second task was a Y-maze. The rats were trained to move from a waiting area to the left or right arm alternately of a Y-type box. When they moved to the correct arm, the rat received water for a reward.

After several days of training, the 16-channel multi-electrode arrays were inserted into the different brain cortexes (ACC for DM-GM task and PFC for Y-maze task). The spike activities of populations of neurons and local field potential (LFP) were recorded. The spikes of a single neuron were sorted using an off line sorter (Plexon, Denton, TX, U.S.). More than one neuron was recorded per electrode. For each neuron, the spikes were sorted into spike trains of a single neuron. Multiple-neuronal spike trains were then analyzed per-trial.

All experimental and recording processes were controlled by computer and monitored by a high-speed video recording system.

B. Construction of NFNs

As in other methods of analyzing the functional networks of the brain, calculating the correlations between pairs of neurons is the first step in analyzing neuronal connectivity relationships. The Pearson correlation coefficient is commonly used to measure the similarity between two spike trains of neurons, but this method requires binning the spike trains into non-overlapping, short time windows (1 if spikes are present, 0 otherwise) [16-17]. The choice of the size of the time window is very arbitrary and has a direct impact on the results. Several other binless spike train measures have been proposed recently [18]. Neural coding is a neuroscience-related field concerned with characterizing the relationship between the stimulus and the neuronal responses. Rate coding and temporal coding are all related to inter-spike intervals (ISI) of neurons. ISI is one of the ways in which neural coding can be studied [19]. Thomas Kreuz proposed the ISI-distance to measure spike train synchrony [20]. In this paper, we proposed a multi-step interval ISI-distance and a new approach that extracts information from the different spike intervals and calculate the correlations between pair wise neurons.

The p-step interval ISI-distance of q^{th} neuron is defined as follows:

$$h_{qp} = \frac{\sqrt{\sum_{i=p+1}^{t(q)} (x_{qi} - x_{q(i-p)})^2}}{\sqrt{\sum_{i=1}^{t(q)} x_{qi}^{\;2}}} \tag{1}$$

Specifically, the element x_{qi} denotes the time of i^{th} spike of the q^{th} neuron, and t(q) is the number of spikes in q^{th} neuronal spike trains. According to Eq. 1, we obtain the 1-step interval ISI-distance of q^{th} neuron as follows:

$$h_{q1} = \frac{\sqrt{\sum_{i=2}^{t(q)} (x_{qi} - x_{q(i-1)})^2}}{\sqrt{\sum_{i=1}^{t(q)} x_{qi}^{\;2}}} . \tag{2}$$

Different higher-step interval ISI-distances are calculated in a similar manner.

Then n neuronal spike trains were converted to a new multi-dimensional matrix V through the conversion of multi-step interval ISI-distance.

$$V = \begin{bmatrix} h_{11}, \dots, h_{1p} \\ h_{21}, \dots, h_{2p} \\ . \\ . \\ h_{n1}, \dots, h_{np} \end{bmatrix} . \tag{3}$$

The new matrix V represents the original multi-neuronal spike train and the line of matrix V represents a single neuronal spike train. As in principal component analysis (PCA), this method produced a dimensionality reduction among the spike trains. Unlike in PCA, the number of spikes in each neuronal spike trains can differ.

The correlation coefficient between two neurons is given by the functional distance of two neuronal spike trains. Based on the matrix V, the correlation coefficient can be defined using a Gaussian kernel. This technique has been widely used in graph analysis methods.

$$s_{ij} = e^{-\|h_i - h_j\|^2 / 2\sigma^2} . \tag{4}$$

Where $\|h_i - h_j\| = \sqrt{\sum_{k=1}^{p} (h_{ik} - h_{jk})^2}$. This is the Euclidean distance between two vectors. σ is a scale parameter that controls the decay of the Gaussian kernel. Matrix S is called correlation matrix. The value of s_{ij} is between 0 and 1. The closer the value of s is to its maximum, 1, the stronger the synchrony.

The advantages of this method are that it does not need to bin the spike trains into short time windows and that it is easy to implement.

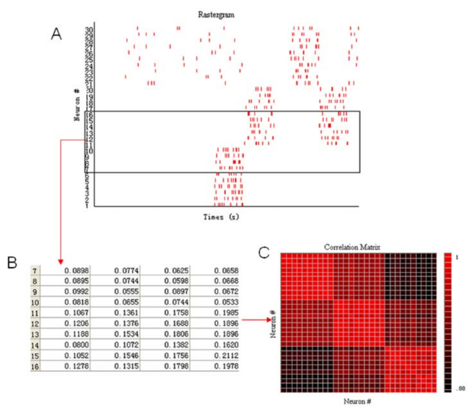

Fig. 1. Original method overview. (A) Raster plot of a surrogate data set of neuronal spike trains composed of 30 neurons. Each row represents a neuron. Every ten neurons form a community, and there is a high level synchronization between neurons in the same community. (B) Four multi-step interval ISI-distances were calculated from ten neuronal spike trains. (C) As shown, the correlation matrixes between 30 neurons exhibited even more obvious hierarchy.

Figure.1 shows the process of calculating a surrogate neuronal data set. The resulting matrix S is a weighted matrix. In fMRI functional networks, the weighted matrix must usually be converted into a binary matrix by a threshold. However, choosing the threshold is very difficult. Schwarz retained the strongest 2% of the all edges in the fully weighted networks, but this technique is very subjective. In this paper, we directly analyze the network in the weighted matrix.

C. Hierarchical clustering

To identify the hierarchical modular organization between neurons, we used a hierarchical clustering algorithm to determine the hierarchy of NFNs. Using the linkage and dendrogram functions in Matlab toolbox (Matlab 2009), the distance between nodes used in linkage function was found to be d_{ij}=1-s_{ij}. The smaller the distance d_{ij} between two nodes, the more likely that those two nodes would be placed in the same group. This hierarchical clustering algorithm has been widely used in analysis of fMRI functional networks [21-22].

Each level of the hierarchy obtained by dendrogram function was taken to represent a special kind of community structure. To assess the best division of the hierarchical organization and partition the NFNs into subgroups, we used a widely used modularity function Q, which was proposed by Newman [23]. The modularity Q for a given partition of a weighted network is defined as follows:

$$Q = \frac{1}{l}\sum_{i,j\in N}\left[w_{ij} - \frac{k_i k_j}{l}\right]\delta_{i,j} \tag{5}$$

where l is the total weight of all connections in the network, w_{ij} = s_{ij}, and k_i and k_j are the degrees of each node. δ_{ij} is the Kronecker delta symbol and $\delta_{i,j} = 1$, if nodes i and j are in the same community and 0 otherwise.

Given a partition of the network, modularity Q measures an actual partition relative to a randomly connected network. If a NFN is not a random network, then NFN can be partitioned into different community structures by maximizing the value of Q. The process involves two steps; the first step is to obtain the results of a division using the cluster function in the Matlab toolbox. The second step is to calculate the corresponding Q value. We increased the number of communities to implement the above process until the maximum value of Q appeared and the corresponding divides were observed.

D. Parameter selection

The method proposed in this paper attempts to reduce the number of parameters, but it is also controlled by two parameters, the number of multi-step interval ISI-distances, p, and the Gaussian kernel function parameter, σ. The selection of values for p and σ may affect the results of the experiments. To analyze these two parameters, we proposed the evaluation coefficient ω.

$$\omega = \frac{\sum_{i=1}^{n}\sum_{j=1}^{n} s_{ij}\delta_{ij}}{\sum_{i=1}^{n}\sum_{j=1}^{n} s_{ij}(1-\delta_{ij})}. \tag{6}$$

s_{ij} is the correlation coefficient between two neuronal spike trains, δ_{ij} is the Kronecker delta function and δ_{ij} = 1 if nodes i and j are in the same community and 0 otherwise. The coefficient ω represents the proportion of sum of similarity in the communities and sum of similarity outside the communities. The value of ω is between 0 and 1. The smaller the value of ω, the more obvious the community structure and the better the experimental results.

III. RESULTS

A. Surrogate data

There is no ground truth for real multi-electrode recording data sets and we cannot know the hierarchy of NFNs in advance. To illustrate the performance of the proposed method, we first obtained the experimental results of the surrogate data shown in Fig. 1. Two parameters were set the p = 4 and σ = 4.

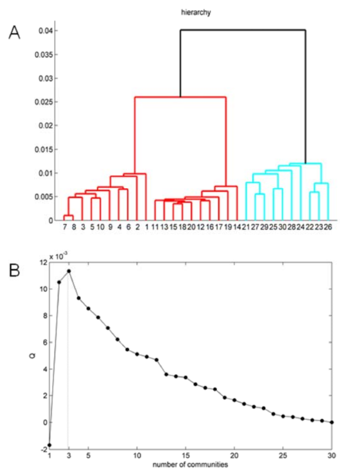

Fig. 2. (A) Hierarchical tree of surrogate data set in Fig. 1. (B) Modularity Q. The dashed line denotes the maximum value of Q.

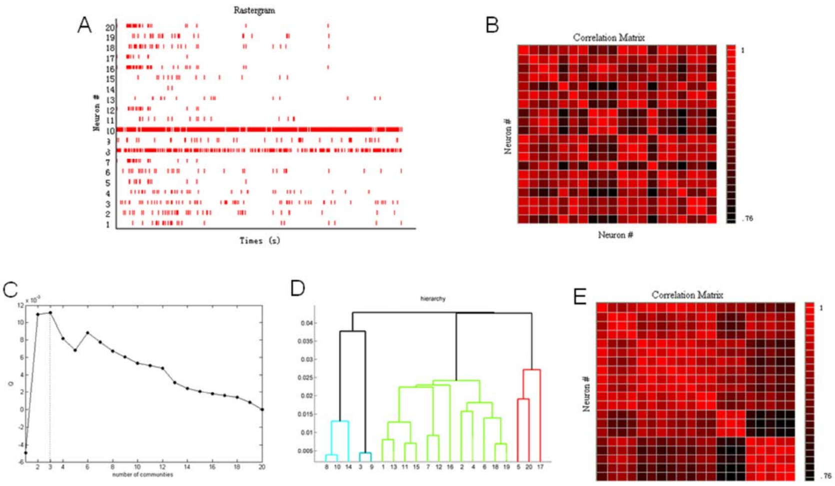

Fig. 3. The results of spike trains from Y-maze cognitive task. (A) Raster plot of neuronal spike trains of 20 neurons. (B) Correlation matrix. (C) Modularity Q. The dashed line denotes the maximum value of Q. (D) hierarchical tree. (E) Correlation matrix corresponding to three communities.

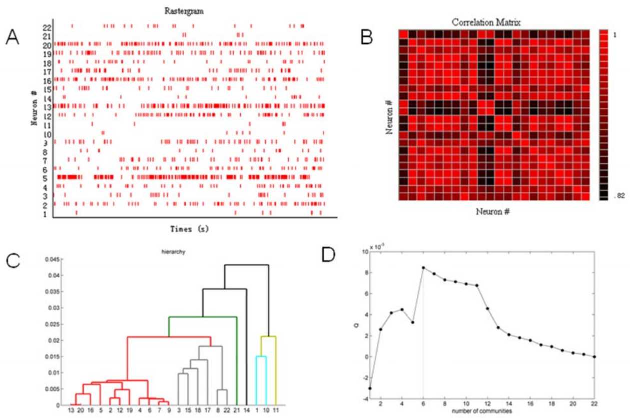

Fig. 4. Results of spike trains from DM-GM cognitive task. (A) Raster plot of neuronal spike trains of 22 neurons. (B) Correlation matrix (C) Hierarchical tree. (D) Modularity Q.

We ran the hierarchical clustering based on the correlation matrix in Fig. 1C. Fig. 2A shows the hierarchical structure of 30 neurons. As shown in Fig. 2B, the maximum modularity value of Q was obtained when the number of communities equals 3, which is marked by a dashed line. The optimal number of communities in the surrogate data is three, which is consistent with the initial data set, as shown in Fig. 1A.

B. Spike train data

We used the spike train method to the spike trains recorded using multi-electrode in vivo. Fig. 3 shows the experimental results of spike trains of the Y-maze task. The trial lasted 50 s and covered 20 neurons. The maximum value of Q appeared when the number of communities equals 3, indicating that the 20 neurons can be divided into three groups.

Fig. 4 shows the results of a set of spike trains for a DM-GM task. The trial lasted 22 s and covered 22 neurons. As shown in Fig. 4D, the maximum modularity value of Q appeared when the number of communities equals 6, indicating that the 22 neurons can be divided into six groups. The neurons contained in each group are shown in Fig. 4C. Experimental results showed more obvious hierarchical module structures in neuronal functional connections recorded for different cognitive tasks.

C. Parameter selection

In the present experiment, we constructed a number of networks using the different values of parameters p and σ. Because we do not know the true division of the real spike trains. We can only evaluate the performance in the surrogate data set using different parameters.

Fig. 5B shows that the value of σ does not affect the performance of the proposed method, usually setting σ=4 in the graph analysis method. However, the value of p was found to play an important role. As shown in Fig. 5A, when the value of p remained relatively small, the evaluation coefficient ω remained large. Therefore, the value of p was made as large as possible ($p \geq 4$).

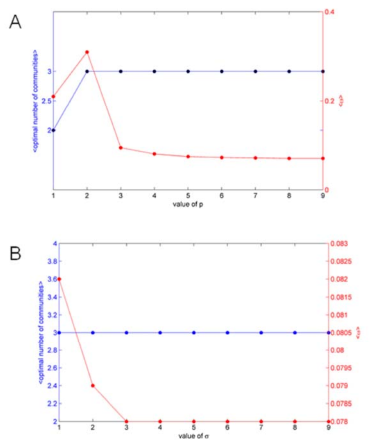

Fig. 5. (A) The number of identified communities and the value evaluation coefficient ω for different values of parameter p. (B) The number of identifying communities and the value evaluation coefficient ω for different values of parameter σ.

IV. DISCUSSION AND CONCLUSION

In this paper, we introduce a new method of hierarchical clustering analysis that can assess the hierarchical modular organization of NFNs. The results in different spike train data sets showed obvious modular organization in neuronal connectivity structures in rat brains. These structures were attributed to the performance of different cognitive tasks, indicating that the functional connections between neurons are not random. These results provide new evidence that the functional network of the brain are complex and have small-world properties.

Using the weighted network modularity Q proposed by Newman, the proposed method can be used to identify the optimal divisions of NFNs, which are regarded as community structures. Currently, the neural mechanism of community structure is still unknown. It is still not clear how these different community structures form in the rat brain.

Finding the functional structures between neurons is a key element in neuroscience research [24]. Different hierarchical structures may be found using different types of analysis. Due to the lack of standard data sets for known structures, there is a dearth of studies evaluating these methods. In addition, the connections between the neurons are not static and can change dynamically over time through various synaptic plasticity principles. Analyzing the neuronal signal data superior to the fMRI data involves addressing its high time resolution. This renders the analysis of NFNs more difficult.

This method also has limitations. Modularity function Q has a resolution limit problem and does not recognize smaller modules. Some evaluation functions have been proposed to overcome this problem. Lu proposed a partitioning criterion of community coefficient C to determine the optimal number of communities and solve the resolution limit problem [25]. In addition, hierarchical clustering does not recognize the overlapping nodes and modules. This will be the subject of our next study.

In conclusion, this clustering-based method clearly identifies the organizational structures of NFNs and can partition the NFNs into different community structures in the study of rat brains according to modularity function Q, which performs different cognitive tasks. The method can potentially detect the spatial-temporal patterns in neuronal population coding, analyze neural circuits, and predict individual animal behavioral outcome. The connection structures between neurons may correspond to different types of animal behavior. We hope to use hierarchical structures in spike trains of different trials to predict the behavioral outcomes of single trials.

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