A small-world of neuronal functional network from multi-electrode recordings during a working memory task

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Abstract—Graph theory is a very useful tool in the study of functional and anatomical network in the brain. It had been widely used in the functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) signals. Only very few studies analyzed the neuronal connections composed of individually recorded neurons. Particularly applying in the case of neuronal functional networks of animal behavior-dependent was rare. Scientists have found the small-world network properties in the functional network derived from fMRI and EEG signals. Whether there are existing small-world properties in the neuronal networks of multi-electrode recording? We use graph theory techniques to construct and analyze the neuronal networks. In the functional networks of a simultaneously recorded population of neurons in prefrontal cortex of the rat, in a Y-maze working memory task, we find that the neuronal connection density is highly relevant to rat behavior. We find there is a small-world effect in the neuronal functional network compared to a random graph with the same size and average connection density. We also find that small-world properties have a great relationship to correlation coefficient threshold selection. These findings indicate that neuronal functional networks of multi-electrode recordings are also small-world networks. Network connection topology and connection density are related to the working memory tasks in the rat.

Keywords—graph theory; functional network; small-world network; Y-maze; multi-electrode recording

I. INTRODUCTION

Functional specialization and functional integration are two basic criteria in the brain’s information processing [1]. Studies have found that the brain is an extremely complex and dynamic network of a highly efficient small-world properties. A variety of information can be quickly transmitted and processed within the whole brain or local brain areas. Functional specialization means that neighboring neurons have a high probability of connection to other neurons to form an independent functional unit. The clustering coefficient of complex network can be used to represent this characteristic. Functional integration means that long axonal projection need more energy to connect other neurons. The short path length of complex network can reflect this characteristic.

Graph theoretical approach provides a powerful way to quantitatively describe the organizational principles of brain networks [2,3]. Since Watts and Strogatz [4] proposed small-world network model in 1998, there have found existing the small-world properties in many areas of real complex networks with large clustering coefficient and average shortest path length. Small-world properties can also be found in the research of brain functional networks. But the studies of brain functional network were mainly use functional magnetic resonance imaging (fMRI) techniques [5,6,7,8], others used the EEG[9] and MEG[10] signals. Stam et al.[11] reported that small-world architecture in functional networks in the brain was disrupted in AD from EEG data. These methods can only analyze the macroscopic level of structure of the brain functional connectivity, typically used to analyze large-scale brain functional connectivity between brain regions. Only few studies have attempted to look at the microscopic level of connectivity, such as the functional networks consisting of individual cortical neurons.

In recent years, development of multi-electrode recording has allowed to record the larger numbers of cortical neurons simultaneously. How to analyze interactions between neurons of multi-electrode recordings is a big challenge [12,13]. Understanding what makes neurons fire is a central question in neuroscience. Some constructed the neuronal functional network of multi-electrode recordings using graph theory which regarded individual neuron as a graph node and pairwise correlations between the neuronal spike trains as graph connected edge. Bettencourt [14] have attempted to quantify small-world properties with micro-electrode arrays to estimate the connectivity of neuronal assemblies, but these recorded neurons grown in vitro. Yu et al. [15] found that the networks had small-world properties of cortical neurons recording in visual cortex of anesthetized cats. While the neuronal functional networks of animals performing working memory task had not been studied, it is not clear whether these networks are relevant to the animal task and whether small-world properties can be found in these networks.

In this study, we analyze multi-neuronal activity of multi-electrode recordings in the prefrontal cortex (PFC) of the rat during a Y-maze working memory task. Using graph theory we calculate the pair-wise cross-correlation coefficient between
the neuronal spike trains and construct the neuronal functional networks. By calculating the correlation connection density, we find connection density is dependent on the Y-maze task, that is, different functional networks corresponding to the animal’s different direction choices in this task. Compared with random networks (with the same nodes and the same density), we find these neuronal functional networks also show small-world networks properties (high clustering coefficient and small the shortest path length). Finally, we compare the “small-world-ness” under different correlation coefficient threshold and find this value is highly related to correlation coefficient, that is, the larger the correlation coefficient, the stronger small-world properties.

II. MATERIALS AND METHODS

A. Neurophysiological data

The experimental multiple spike trains take from the research group of brain sciences, Fudan University. The rat performs a Y-maze task. In the Y-maze task, rat need to remember the last spatial position choice (left or right arm of the Y-maze) and the next time choose the opposite position (right or left arm). For example, in this trial, rat choose the right arm of the Y-maze (R-choice trial), then in the next trial, rat must choose the left arm of the Y-maze (L-choice trial). Multi-electrode recordings are used to simultaneously record neurons. The number of electrodes used in experiments is 16 electrodes. Electrodes are inserted into the rat prefrontal cortex (Fig.1.A).

![Figure 1. (A) With the use of a multiple electrodes technique, the red areas (interaural 13.20mm and bregma 4.20mm) are recorded. (B) Spikes are detected from multi-electrode array. Features of the spike shapes are extracted and the spikes are sorted accordingly.](image)

Single spikes are isolated by plexon's off-line spike-sorting program. In total, there are 20 individual neurons identified. We use the period between 58 and 592s (534s of data in all) in which all spike trains are present.

B. Construction of neuronal functional network

Current researches on the brain network are divided into three different types of connectivity: neuroanatomical, functional and effective [16]. The functional connectivity is often defined as the temporal correlation between spatially distant neurophysiological events. At a macroscopic level, these networks had been evaluated using fMRI, EEG and MEG. Major problems of these methods were difficult to define the node and functional connectivity. We use the graph theory to construct the neuronal functional network in which a single neuron is regarded as a node and temporal coherence (measured by cross-correlation tests) of spike trains is regarded as the connection between nodes, so the calculation of the cross-correlation between spike trains is the first step.

Currently, there are many correlation calculation methods of spike trains. Papers [17,18] compared and assessed a variety of classical and recently proposed spiking synchrony measures. In this study the cross-correlation metric is used. To quantify spike trains correlation between two neurons, we first divided each spike train into discrete bins of width $\delta_t$ seconds. 1 indicated that the spike occurred within the time window and 0 indicated that within time window neuron didn’t fire, resulted in binary vectors. For each pair of binary vectors, cross-correlation function was calculated:

$$R_y(k) = \sum_{t=0}^{N_k-1} x_t y_{t+k}$$  (1)

Where $x_t$ and $y_t$ are vectors of each spike train. In general, the correlation function requires normalization to produce an accurate cross-correlation coefficient. Cross-correlation coefficient measures the overall degree of synchrony between different spike trains, the value ranging between 0 for independent and 1 for fully correlated spike trains [19,20]. The correlation matrix is then computed by calculating all the correlation between spike trains. It is a symmetric matrix. We applied a threshold $\gamma$ determined to generate a binary matrix $R$. when the correlation coefficient is greater than $\gamma$, $R_{xy} = R_{yx} = 1$ indicated that exists functional connectivity between two neurons, otherwise $R_{xy} = R_{yx} = 0$. Undirected graph of the functional connectivity network is constructed according to the binary matrix, if $R_{xy} = R_{yx} = 1$ then an edge is drawn between node $i$ and node $j$.

C. Functional network metrics

Graph theory is a valuable framework to study the topology of complex network. Networks can be represented by graphs, which are sets of vertices and corresponding sets of edges. Graph structure can be represented by the adjacency matrix. Here, the network of neuronal functional connectivity is symmetric binary matrix, corresponding to the graph of no direction and no weight.

Recent studies have presented evidence that the prefrontal cortex plays a crucial role in every aspect of the cognitive
Figure 2. Schematic overview of network creation. (A) raster plot of the original spike trains of a trial, containing a total of 20 neurons. (B) Plot the pair-wise cross-correlation coefficient of the first four neurons. (C) The correlation matrix of 20 neurons. (D) By thresholding, a binary matrix is obtained where only retained elements which greater than the threshold. (E) This graph can then be constructed.

processes necessary for behavioral planning [21]. Fujisawa [22] found that the functional efficacy of apparent monosynaptic interactions varied dynamically and predictably in the task. In a working memory task, the connections between neurons may be different and can we use the analysis of functional networks to distinguish these differences in the behavior of rats? We first calculate the average connection density to compare the different functional network connection properties of rat between right-choice and left-choice trials in the Y-maze.

The connection density is the number of edges in a graph comprising N nodes divided by the maximum number of possible edges. \( \rho = \frac{R}{R_G} \) (2)

The connection density is the number of edges in a graph comprising N nodes divided by the maximum number of possible edges. \( R = \sum_{i<j} r_{ij} \), \( r_{ij} = \begin{cases} 1 & r > \gamma \\ 0 & r \leq \gamma \end{cases} \). \( R_G \) indicate maximum number of possible edges of n nodes , \( R_G = C^2_n = \frac{n(n-1)}{2} \).

Graph properties can be characterized by various measures. How to evaluate a network is small-world network. The two most commonly used measures are the clustering coefficient which denotes the likelihood that neighbors of a node will also be connected to each other and average shortest path length which denotes the average number of edges of the shortest path between pairs of nodes.

The clustering coefficient of a node i is the ratio of the number of existing connections \( e_i \) to the number of all possible connections \( \frac{k_i (k_i - 1)}{2} \) in the subgraph \( G_i \):

\[
C_i = \frac{2e_i}{k_i(k_i-1)} = \frac{\sum_{j=1}^{n} a_{ij}a_{ji}}{k_i(k_i-1)}
\]

Clustering coefficient ranges from 0 to 1, the clustering coefficient of a network is the average clustering coefficient of all nodes:

\[
C = \frac{1}{N} \sum_{i} C_i
\]

Another important measurement is the shortest path length. The shortest path \( l_{ij} \) is the shortest absolute path length between the i\textsuperscript{th} node and the j\textsuperscript{th} node. Note that the absence of a path between \( i \) and \( j \) implies \( l_{ij} = +\infty \). The mean shortest absolute path length of a network is the average of the shortest absolute path lengths between the nodes:

\[
L = \frac{1}{N(N-1)} \sum_{i,j} l_{ij}
\]

Shortest path length is a measure of the transfer speed of parallel information in the brain, whereas clustering coefficient is a measure of the information exchange of each subgraph. Small-world properties are very popular in many real networks such as biological, social and technological networks. To evaluate small-world properties, functional networks often require comparison with a null model network that has similar statistical properties. Well established network models which have been extensively used as null models are the Erdös-Rényi random graph with the same number of nodes and the average density. In other words, small-world networks should have larger clustering coefficient and a shorter length of the shortest path. That is \( \frac{C_{\text{real}}}{C_{\text{random}}} \gg 1 \) and \( \frac{L_{\text{real}}}{L_{\text{random}}} = 1 \). Mark D.
Humphries [23] proposed to measure “small-world-ness” in a single measurement \(sw\):

\[
SW = \frac{C_{\text{real}}}{C_{\text{random}}} \div \frac{L_{\text{real}}}{L_{\text{random}}}
\]

A network is said to be “small-world” when \(sw > 1\).

III. RESULTS

In this study, 20 neuronal spike trains in the prefrontal cortex were recorded. The time lasted in each trial was not same. In order to obtain the same dimensions vectors, we will fix the time of each trial for 15s. We select 15s after spatial position (left or right arm of Y-maze) of the reward (water) as a trial time. During the time between 58 and 592s, there are 18 trials (including 9 L-choice trials and 9 R-choice trials). Each trial needs to construct a neuronal functional network.

A. Connection density comparisons between L-choice and R-choice

We first compare the connection density between R-choice trials and L-choice trials of the rat. According to the (2), we calculate the connection density of 18 trials respectively, for a given correlation coefficient threshold \(\gamma (\gamma = 0.7)\), of course, other threshold can be chosen to compare different results as there is no natural threshold to use.

We find that connection density when rats perform R-choice task are generally greater than L-choice task.

B. Efficient small-world properties

To assess the extent of small-world properties present in the multi-electrode recordings in a working memory task, we need to construct correlation coefficient matrix based on spike trains for each trial. We then examine graph metrics obtained for the neuronal functional networks constructed by thresholding. To ensure the network is a connected graph, threshold is not fixed for every network (threshold values ranged from 0.55 to 0.7).

If the degree of a node is zero in the network, it can not calculate the shortest path length. We remove the node which degree is 0, so the actual nodes in each network are less than the number of neurons (N=20). Therefore, every networks obtained from all trials are different. How to compare different sizes of networks is very difficult using graph theory to analyze brain network. In this study we are interested in the network metrics of functional networks compared to random networks. If a network is small-world network, L should be close to that of a random network, whereas C should be much higher than that of a random network.

Figure 4. Small-world properties of networks for R-choice trial. (A) The original binary connection matrix and functional network from multi-electrode recordings. (B) The random network of the same size and connection density as the original network. (C) Path length and clustering coefficient of two networks for 9 right trials. (D) "small-world-ness" \(sw\) for 9 right trials.

Since the number of neurons (between 14 and 19) is limited by thresholding in this study, “small-world-ness” \(sw\) are generally small, including a trial of \(sw = 0.955\), that is, in this trial, neuronal function network is a random network. The small-world properties \(sw\) varies between 0.955 and 1.848 with a mean of \(sw = 1.343\) during the R-choice trials. In the other hand, The small-world properties \(sw\) varies between 1.151 and 1.739 with a mean of \(sw = 1.417\) during the L-choice trials. The results have showed that small-world properties have a relationship to the size of networks [8]. The small-world metrics are larger when the number of nodes is larger from previously published results on small-world characterization of functional brain network constructed using EEG, MEG and fMRI data.
C. Relationship between small-world properties and cross-correlation threshold

Importantly, we find that "small-world-ness" of functional networks is correlated with correlation coefficient threshold.

Regarding first R-choice trial as example, we compared networks for cross-correlation coefficient threshold values from 0.5 to 0.7 with an increment of 0.05. When $\gamma < 0.5$, the density of connections between neurons is very large and close to random networks. When $\gamma > 0.7$, the constructed neuronal functional network is no longer a connected graph and we do not compare it.

We find that as the correlation coefficient threshold increases, the "small-world-ness" is larger and connection density is smaller. In addition, the negative correlation between the "small-world-ness" and the connection density may indicate that community structure and modularity may exist within the brain functional networks [24,25].

IV. DISCUSSION

The structure of brain is a complex network in which information is continuously processed and transported between neuronal synapses. In this paper, we propose to use graph theory to analyze the neuronal functional networks. Early studies have provided substantial evidence show the existence of small-world network (a high degree of clustering and short path lengths). These studies focused on the fMRI or rs-fMRI, constructing these functional networks needed to regard areas of cortex as a node, the correlation between the regions as the connection edge. A recent research of complex brain networks has emphasized the linking network topology with cognitive and behavioral functions. Topological changes in these networks were investigated under different conditions of a classical N-back paradigm working memory task. These functional networks were also constructed from blood oxygen level dependent (BOLD) signal.

Our primary purpose is to employ graph-theoretical methods to analyze the neuronal functional networks from multi-electrode recordings. The first finding is that functional connection density varied dynamically during R-choice task and L-choice task of Y-maze. we can predict behavioral choice of rat by comparing connection density $\gamma$. The small-world attributes satisfy the opposing demands of local and global processing. To evaluate the small-world property, we have discussed three different topological measures. Our results on the small-world characterization of neuronal functional networks are also largely consistent with other types of functional brain network. Therefore, in this study, from the microscopic level, we demonstrated that exist small-world properties in the networks composed of individually recorded neurons.

In our study, only part of cortical neurons in the prefrontal cortex was recorded. We have reason to believe that the same small-world network structure will appear in the other cortex. Although the number of electrodes is limited, it is reasonable to foresee that similar small world topology will be found in other brain cortical regions. Progress in neural recording techniques has allowed recording large-scale neurons in a wide area through functional multi neuron calcium imaging (fMCI)[26,27].

Currently some networks with small-world network of neuron assemblies by simulating the network structure are modeled. Now we find the small-world structure in the real cortex will help researchers to build a more realistic network model to simulate the firing patterns of neurons.

As the number of recorded neurons is not too much, we did not analyze whether the functional network structure is a scale-free network. With the increase of the number of simultaneously recorded neurons, scale-free structure and community structure will be found in the neuronal functional networks.

V. CONCLUSION

To our knowledge, this is the first study of neuronal functional network during a working memory task. Our
findings show that neuronal connection densities are significantly different during the working memory task. The small-world attribute is evident in the neuronal functional networks: $sw$ is significantly greater than 1, indicating that functional connections between neurons are optimized, rather than the previously estimated that the functional connections between neurons are random.

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