



Research report

Functional connectivity among spike trains in neural assemblies during rat working memory task



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HIGHLIGHTS

- Multi-electrode neural recording in PFC of free-moving rats during a working memory task.
- Functional connectivity analysis in PFC spike networks via maximum likelihood estimation.
- A feature network was constructed by connections among active neurons in neural assembly.
- Connection strength and global efficiency in the PFC network increased in correct trials.
- Characteristics in PFC spike networks can be highlighted in the feature space.

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ABSTRACT

Working memory refers to a brain system that provides temporary storage to manipulate information for complex cognitive tasks. As the brain is a more complex, dynamic and interwoven network of connections and interactions, the questions raised here: how to investigate the mechanism of working memory from the view of functional connectivity in brain network? How to present most characteristic features of functional connectivity in a low-dimensional network? To address these questions, we recorded the spike trains in prefrontal cortex with multi-electrodes when rats performed a working memory task in Y-maze. The functional connectivity matrix among spike trains was calculated via maximum likelihood estimation (MLE). The average connectivity value C_c , mean of the matrix, was calculated and used to describe connectivity strength quantitatively. The spike network was constructed by the functional connectivity matrix. The information transfer efficiency E_{glob} was calculated and used to present the features of the network. In order to establish a low-dimensional spike network, the active neurons with higher firing rates than average rate were selected based on sparse coding. The results show that the connectivity C_c and the network transfer efficiency E_{glob} varied with time during the task. The maximum values of C_c and E_{glob} were prior to the working memory behavior reference point. Comparing with the results in the original network, the feature network could present more characteristic features of functional connectivity.

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1. Introduction

Working memory refers to a limited-capacity storage system, which provides temporary storage and manipulation of the

information in short periods of time and relates to many cognitive operations [1]. Ethology studies have shown that medial prefrontal cortex (mPFC) plays a critical role in working memory and lesions of rat mPFC impairs working memory performance [2,3].

Studying on neural activity has long been an important tool to study the spatiotemporal organization of information processing circuits in brain functions [4–9]. Recently, studies on the functional networks in brain have attracted increasingly widespread attention. By studying the dynamics functional networks thereby enabled, we may gain insight into the nature of brain as the embodiment of the mind and understand mechanism of cognitive function

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better. Furthermore, functional connectivity among neural signals has been an effective tool to unveil the mechanism of information processing in cognitive functions [10–12].

For the past few years, researchers primarily dedicated to study functional networks in working memory using macro-scale neural signals (EEG and fMRI etc.) [13–15]. The speedy development of multi-channel microelectrode recording enables researchers to record micro-scale neural signals (spikes and local field potentials (LFP)) for the deep understanding of working memory [16,17]. Spikes are the temporal sequence of action potentials generated by neurons and considered to be neural responses to external stimuli [18]. Since spikes have excellent spatial and temporal resolution [19], studies on functional networks based on the simultaneous spiking activity of neurons allow us to understand the neural mechanism in working memory better.

The functional connectivity among neural signals can be estimated via a great diversity of methods. Studies have shown that Granger causality is one of the most effective methods for estimating the functional connectivity among neural signals. However, Granger causality is applicable for continuous-valued signals (LFP, EEG etc.) [20–22], which it cannot be directly used in point-process time series (e.g., spikes) [18]. Considering the discrete characteristics of spikes, a method of maximum likelihood estimation (MLE) was provided based on the generalized linear model (GLM) and applied to deal with spikes recorded from primary motor cortex of monkey [23]. Afterwards, the MLE method was improved and used to deal with ensemble spikes recorded from primary motor cortex of cat [24]. Considering neurons as nodes and connection strengths as links, further approaches were used to quantitatively measure the functional connectivity characteristics in the networks [25–27]. These measures have been widely used to evaluate the function connectivity in cognitive task or range of neurological disorders [28–30], using neural signals different scales [31,32].

Several decades ago, Hebb induced the classical neural assembly theory, suggesting that active neural assemblies specialized participates in information processing in the brain [33]. In the years followed, numerous evidences indicated that neural systems may be employing sparse approximations to represent cognitive information [34]. Experimental studies also demonstrated that neural activity in cortex is sparse and a small portion of responsive neurons primarily encode information rather than a large population of silent neurons [35,36]. These mean that, in many cases, not all the neurons recorded are ‘important’ for the underlying mechanism of brain function. Therefore, it is necessary to extract the feature information from original data and construct a feature data representation to enhance the characteristics in neural networks. To address this question, some methods were proposed for feature extraction, such as principal component analysis (PCA) and nonnegative matrix factorization (NMF) [37,38]. However, how to identify ‘important’ neurons from all the neurons recorded is a key for feature extraction. Sakurai et al. [39] introduced the coding by neural-assembly in PFC when animals were performing cognitive tasks and showed that some active neurons encode the primary information. The results indicated that these active neurons may be the ‘important’ neurons, which are more important components than the silent ones in cognitive function.

Therefore, in the present study, we extracted information from active neurons (fire at higher rates than average) and constructed feature datasets. The functional connectivity in both feature and original space were assessed via MLE. Furthermore, the connection strength and information transfer efficiency in spike network in feature space and original space were compared to show the dynamic changes in functional connectivity during the working memory task and investigate whether the characteristics in spike network can be effectively described in the feature space.

2. Materials and methods

All surgical and experimental procedures conformed to the Guide for the Care and Use of Laboratory Animals and were approved by the Tianjin Medical University Animal Care and Use Committee.

2.1. Delayed-alternation task in Y-maze

Male Sprague–Dawley rats (12 weeks, 300–350 g) were used for the experiments. Before training sessions, rats were raised in a climate and humidity controlled room on a 12-h light-dark cycle with free access to water and limit access to food to maintain body weights at 85% of normal body weight. After 2 days, rats were placed in Y-maze about 30 min per day to adapt to the environment over 2 consecutive days. After all above, rats were trained on a delayed-alternation task in Y-maze. As shown in Fig. 1A, A was assumed to be starting point while B and C were ending points. Food cups were placed at the point B and C. The rats were given two training sessions (10 trials per session) per day. Each trial consisted of a sample run and a choice run. On the sample run, the rats were allowed to go either left or right to get food reward. After consuming the reward, the rat voluntarily went back to the start point. After 5 s delay, the rats have a choice run. The rats were rewarded for choosing the previously unvisited arm. After a trial, the rats were allowed to return and start next trial. Once rats’ performances were stable at ~80% correct on 2 consecutive days, the electrophysiological recordings were initiated.

2.2. Electrophysiological recordings and data preprocessing

Once rats reached the acquisition criterion in the task, they will undergo a chronic implant surgery. 16-channel microelectrode arrays (nickel-chromium, <1 M Ω) were implanted into mPFC of rats when they were anesthetized by chloral hydrate (350 mg/kg). The coordinates for mPFC were determined according to the rat brain in stereotaxic coordinates (Fig. 1B; AP: 2.5–4.5 mm; ML: 0.2–1.0 mm; DL: 2.5–3.5 mm). After recovery, neural activity was recorded when rats performed the delayed-alternation task in Y-maze.

The wideband signals were recorded during the working memory task with Cerebus Data Acquisition System (Cyberkinetics, USA). Spikes (high-pass filter: 500–7500 Hz) exceeding a preset voltage threshold were sampled at 30 kHz and were stored with time stamps in the Neural Signal Processor. The spikes recorded were the simultaneous electrical activity of several neurons near the tip of the microelectrode, therefore spike-sorting was performed using offline sorter (Plexon, Texas, USA) to classify single-unit activity (Fig. 2A). Single neurons with a signal-to-noise of <3.0 and a very low baseline firing rate (<30 spikes/min) were discarded. Time stamps were recorded when rats arrived at the infrared sensor in Y-maze and defined as the ‘reference point’ (RP) in this study.

2.3. Data analysis and statistics

We recorded neural activity from rat mPFC when they performed the working memory task in Y-maze. In the present paper, we described 60 trials from four rats: 15 trials (19 neurons) from rat 1, 15 trials (23 neurons) from rat 2, 15 trials (25 neurons) from rat 3, and 15 trials (20 neurons) from rat 4. Data in the text and figures are expressed as means \pm SEM. Statistical differences were evaluated by using Student’s *t*-test/Welch–Satterthwaite *t*-test. *P*-value was considered statistically significant as follows: **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

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