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Characterizing electrical signals evoked by acupuncture through complex network mapping: A new perspective on acupuncture

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ABSTRACT

The electrical signals are obtained in spinal dorsal root after different manipulations of acupuncture (MA) being taken at the 'Zusanli' point of the experiment rats. After combining the analysis of the data generated from neuronal network model and that evoked by acupuncture, it is found that features of neuronal chaotic rate time series induced by periodic stimuli can be characterized by complex network approach. The features of signals evoked by MA 'nb' 'nx' (twisting) and MA 'tb' 'tx' (lifting and thrusting) are shown to be different according to the topologies of the mapped networks. This study provides us a new perspective on the analysis of acupuncture and may give potential helps on clinical treatment.

1. Introduction

Acupuncture, as an essential part of traditional Chinese medicine (TCM), has been proved to be effective for the treatment of diseases [1–3], especially in the treatment of pain [4–6]. It has been demonstrated that the nervous system, neurotransmitters and endogenous substances respond to acupuncture [7–9]. The underlying molecular mechanisms of acupuncture effects have also been widely studied [10,11]. However, the underlying mechanisms of acupuncture are still unclear, and whether acupuncture information can be transmitted by electrical signals is also unknown.

Classical acupuncture literatures hold that manipulations of acupuncture (MA) with different types exerts different effects on body functions [12]. MA with different amplitudes and frequencies differentially modulate cerebral blood flow velocity, arterial blood pressure and heart rate in human subjects [13]. Clinically, types of MA can be differentiated by manipulations of the inserted acupuncture needle: (1) twisting; (2) lifting and thrusting; (3) a combination of the two methods mentioned above. These 3 types of MA have different effects on blood pressure in the anesthetized rat [14]. 'Zusanli' point is one of the most effective acupuncture points in medical treatment. Acupuncture on 'Zusanli' point could modulate visceral activity only through spinal reflexes [15]. Therefore the functions of acupuncture could be investigated after eliminating the effects of senior central nervous system. The afferent pathways of acupuncture signals and the central sites have been identified in the anterolateral tract in the spinal cord [16].

Since the reasons why different types of MA have different effects are still not clear, some investigators have studied this problem through characterizing neural electrical signals evoked by different types of MA by nonlinear data analysis

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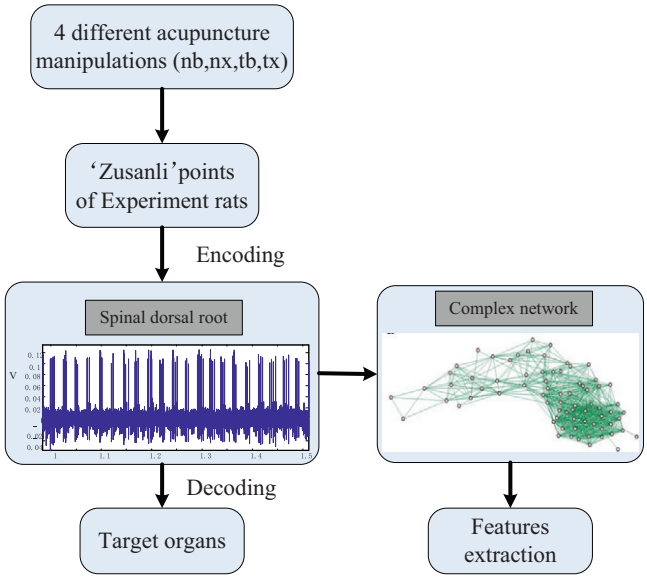

Fig. 1 – Process of extraction of the features in acupuncture signals by the complex network approach.

[17,18]. However, the differences between the results of different types of MA are not obvious based on nonlinear analysis. In addition, the methods to recognize the firing patterns of different MA efficiently have not been found. Complex network is an efficient framework for better understanding problems in engineering, social and biological fields [19,20]. Recently, a new method of characterizing pseudoperiodic time series by complex network approaches has been put forward [21–24]. After mapping the time series of signals from time domains to complex network domains, features of the time series can be extracted by studying the topological structures of the complex networks. It has been shown to be efficient in characterizing ECG signal [21]. Whether features in nonlinear neural systems can be extracted by mapping the detected time series to complex network domain has not been studied. Firing rate is one of the most essential features in neuronal activities, and chaotic firing rates widely exist in physiological recordings [25]. Information can be extracted from time dependent firing rates or spiking coherence, etc. [25]. As the transmission path of acupuncture signals can be seen as a highly chaotic system, we aim to investigate whether complex network mapping algorithms can be applied to characterize acupuncture signals.

This paper is structured as follows. In Section 2, we introduce the experimental procedures of acupuncture and the signals evoked by acupuncture. In Section 3, whether complex network mapping is appropriate for analysis of time dependent firing rates generated by neuronal network model is investigated. Here, noisy Hindmarsh-Rose (HR) neuronal network driven by periodic stimulation is used for the verification. In Section 4, features in time series evoked by acupuncture manipulations are extracted by the method based on complex network mapping. Finally, the conclusion is given.

2. Experiment design and firing rate time series evoked by acupuncture

The flow chart of the experiment design and data analysis is illustrated in Fig. 1. Healthy Sprague–Dawley rats (190–210 g) anesthetized deeply by 20% ethyl carbamate (1.5 g/kg) are prepared for the experiments. After dissecting the rat to expose the lumbar nucleus, nerve tracts in L4 spinal dorsal root which is corresponding to transmission path of acupuncture signals are separated. Transmission properties of 4 basic types of MA ('nb', 'nx', 'tb', 'tx') are investigated. Here, 'nb' and

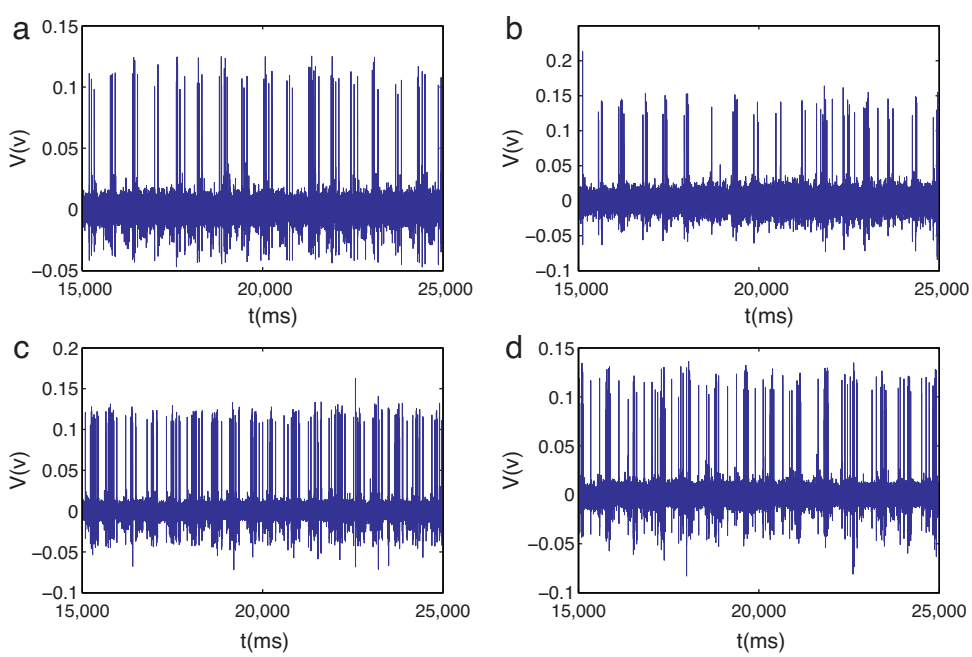

Fig. 2 – Original signals evoked by different acupuncture manipulations. V denotes the potential value of the detected signals. (a) 'nb', (b) 'nx', (c) 'tb', and (d) 'tx'.

'nx' manipulations belong to twisting type while 'tb' and 'tx' manipulations belong to lifting and thrusting type. Each type of manipulation is taken at 'Zusanli' point of one experimental rat for 90–100 times periodically within 2 min. Considering the adaption of neurons to the acupuncture stimulations, the data induced by the acupuncture of the first 10 times are eliminated. Manipulations are stopped taking for 5 min between different patterns of MA to eliminate the effects of the previous MA. To keep the precision of neural encoding, the acupuncture needle is kept in the skin of one rat for the whole process of the experiments. The data are detected by platinum electrodes and recorded by MP150 (BIOPAC), and the sampling frequency is 40 kHz. The data come from experiments on 7 rats, and all experiments on one rat are regarded as one session.

Fig. 2 illustrates the original signals evoked by different acupuncture manipulations. The detected time series contain information of many neurons. We take the network as a whole to investigate the collective encoding properties. Firing rate is one of the most essential mechanisms for the encoding of the external stimuli [26]. To show the rate coding of acupuncture, time dependent firing rates of neuronal population are calculated in a sliding Gaussian window by the following algorithm [26]. The response function of the neurons are $\rho_i(t) = \sum_{j=1}^{n_i} \delta(t - t_{i,j})$, where i is the indice of neurons, j is the indice of spikes. n_i is the number of spikes in neuron i. $t_{i,j}$ denotes the time of spike j generated by neuron i. The time dependent firing rate of the neuronal population is defined as $r(t) = 1/N\sum_{i=1}^{N} \int_{-\infty}^{+\infty} d\tau\omega(\tau)\rho_i(t-\tau)$, where N is the number of neurons, $\omega(\tau)$ is the Gaussian windows function, which is used to make the curve smooth. $\omega(\tau) = 1/\sqrt{2\pi}\sigma \exp(-\tau^2/2\sigma^2)$, $\sigma = 80$ ms.

The time dependent firing rates induced by MA 'nb' and MA 'tb' calculated by this algorithm are shown in Fig. 3. The time series of time dependent firing rates induced by acupuncture are pseudoperiodic, because the intensities of acupuncture stimuli are periodic and the signal transmission path is noisy. Acupuncture information is created by both stimuli and network dynamics. The stimuli in each manual acupuncture manipulation are also not identical. Furthermore, these variations may also come from the signal transmission path which consists of neurons with chaotic properties. We aim to investigate the chaotic features of firing rates time series evoked by different MA. Owing to the pseudoperiodic properties of the time dependent firing rates, the complex network approach is suit for the analysis.

3. Complex network mapping analysis based on data generated by neuronal network model

Complex network approach is a new developed method for extracting features in pseudoperiodic time series. It can be used to distinguish the differences between the noisy periodic time series and chaotic time series, and it has also been applied to the analysis of biological signals [21,22]. Here, we illustrate this method and investigate whether it can be used to characterize the pseudoperiodic firing rate time series generated by chaotic neuronal populations exposed to periodic stimuli. Here we first apply neuronal network model to generate the firing rate time series and the chaotic properties in the network are altered by changing the noise intensities. The Hindmarsh-Rose (HR) neuronal model is aimed to study the spiking-bursting behavior of the membrane potential observed in experiments of a single neuron. The firing patterns of HR neuron tend to be chaotic when exposed to external stimuli. Therefore, we choose network consists of HR neuronal models to mimic the transmission path of the acupuncture signals.

The model of a single HR neuron is described as

$$\begin{aligned} \dot{x}_i &= y_i - ax_i^3 + bx_i^2 - z_i + I_i(t) \\ \dot{y}_i &= c - dx_i^2 - y_i \\ \dot{z}_i &= r[s(x_i - x_0) - z_i] \end{aligned} \tag{1}$$

where x_i is the membrane potential, y_i is associated with the fast current Na^+ or K^+ and z_i with the slow current. Here, $a = 1.0$, $b = 3.0$, $c = 1.0$, $d = 5.0$, $s = 4.0$, $r = 0.006$, and I_i is the external current input, which is used to mimic the acupuncture periodic stimuli. Here i is the index of the neuron, $i = 1, 2, 3 \ldots N$ with $N = 10$. The external stimuli are described as

$$I_i(t) = A \sin\left(\frac{2\pi}{T}t\right) + \xi_i(t) \tag{2}$$

where $A = 0.1$ and $T = 200$ ms. The variabilities of acupuncture stimuli are simulated by adding white noises to the input current. $\xi_i(t)$ indicates the neuron network being in stimuli of different noises, which are assumed to be Gaussian white noise with zero mean and correlation. D_N represents its intensity. $\langle \xi_i(t)\xi_i(t') \rangle = D_N\delta(t - t')$. We choose $D_N = 0.1$ and $D_N = 0.01$ to represent the cases that the neurons are in different conditions with high noise intensity and low noise intensity.

The firing rate curve is obtained by calculating the spikes of all HR neurons in the Gaussian sliding windows similar to that in Section 2. Here $\sigma = 40$ ms, because the time scales of the acupuncture signal and the signal generated by the model are not identical. So a pseudoperiodic time series is obtained. In order to map this time series from time domain to complex network domain, this time series is divided into individual cycles by local extremes. The phase space distance between cycle C_i and cycle C_j is defined as

$$D_{ij} = \min_{l=0,1,\ldots,\left|l_j - l_i\right|} \frac{1}{\min(l_i, l_j)} \sum_{k=1}^{\min(l_i,l_j)} \left\| X_k - Y_{k+l} \right\| \tag{3}$$

X_k and Y_k are the kth points in C_i and C_j, whose lengths are l_i and l_j, respectively. D_{ij} is the weight of the edge which connects node i with node j. A weighted network is constructed by this algorithm. Then, this network is transformed into a binary network by choosing a threshold d. The threshold d is selected according to the peak value of the distribution of D_{ij} [21]. If the weights of the weighted network is smaller than d, the corresponding weights in the binary network are 1. Then the features of the time series can be characterized by studying the topological structure of the complex binary network.

Assortativity is an important feature of topological structure in complex network. It is a preference for a network's

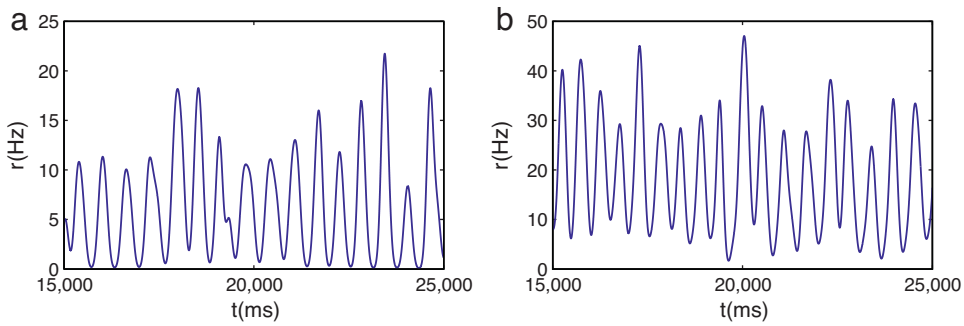

Fig. 3 – Time dependent firing rates *r* evoked by different acupuncture manipulations in Gaussian sliding windows. (a) 'nb' and (b) 'tb'.

nodes to attach to others that are similar or different. Complex network can be characterized to be assortative or dis-assortative. When the nodes which have relative high degrees tend to connect with the nodes with high degrees, the network is assortative. When the nodes with higher degrees tend to connect with the nodes with lower degrees, the network is dis-assortative. Assortativity can be studied by calculating the average degree of neighbors of nodes with degree k in complex network, which is defined as

$$k_{nn} = \sum_{k'} k' P(k'|k) \tag{4}$$

where $P(k'|k)$ denotes the conditional probability when a node with degree k links to a node with degree k'. If k_{nn} value increases with k value, the complex network is assortative.

Time dependent firing rates of HR neuronal network with different external inputs are shown in Fig. 4(a) and (b). The difference between them are not obvious even in their power spectrum as shown in Fig. 4(e). However, the properties underlying the irregular time series can be observed after mapping them to complex network domain. It is shown that the k_{nn} values have a basically linear relationship with the k values in Fig. 4(c) with $D = 0.01$. Therefore, the complex network constructed by the system with lower noisy inputs tend to be assortative. In Fig. 4(d), k_{nn} values become saturated when $k > 50$. So the complex network constructed by the system with higher noisy input is not assortative. Here, the differences in the complex networks can be reflected based on the analysis of assortativity.

To investigate the assortativity of the constructed binary networks more quantitatively, assortativity coefficient is introduced. It is defined as

$$R = \frac{M^{-1}\sum_i j_i k_i - [M^{-1}\sum_i \frac{1}{2}(j_i + k_i)]^2}{M^{-1}\sum_i \frac{1}{2}({j_i}^2 + {k_i}^2) - [M^{-1}\sum_i \frac{1}{2}(j_i + k_i)]^2} \tag{5}$$

where j_i and k_i represent the degrees of two nodes of one edge, $i = 1, \ldots, M$, and M is the number of edges. The value of R ranges from -1 to 1. When $R = 1$, the network is completely assortative. When $R = -1$, the network is completely disassortative. For the network with $D_N = 0.01$, the corresponding assortativity coefficient $R = 0.51$, and for the network with $D_N = 0.1$, $R = 0.08$. These results are in accordance with the studies shown in Fig. 4(c) and (d).

The properties of nonlinear biological systems with periodic and noisy inputs can be reflected by mapping their firing rate time series to complex networks. Then, we try to extract the nonlinear characteristics of acupuncture based on this framework.

4. Analysis of acupuncture signals by complex network approach

Similar to the analysis of signals generated by neuronal network model, signals evoked by acupuncture are also investigated by the network mapping approach. Firstly, transform the spikes time series into firing rate time series as described in Section 2. Then calculate weights of the complex network D_{ij} by the algorithm in Eq. (3). Distributions of weights in the complex network constructed based on two types of MA are different as shown in Fig. 5. Choose the weight value corresponding to the peak of the distributions as the thresholds for the generation of the binary networks. The corresponding binary network is constructed according to the algorithm similar to Section 3. The constructed networks are shown in Fig. 6 with 75 nodes in each one. The binary networks are drawn by 'Pajek' software according to KK algorithm. KK algorithm is a method of drawing general undirected graphs for human understanding. The graph theoretic distance between nodes in a graph is related to the geometric distance between them in the drawing.

Shapes of the constructed network based on two different MA are obviously different. Nodes in the network constructed based on MA 'nb' are distributed on a low dimensional manifold, which is similar to the case when the intensity of the external noise is relatively low in Section 3.

Then average degree of neighbors of nodes k_{nn} with degree k is applied to characterize the network features as shown in Fig. 7. In network constructed from MA 'nb', it is found that k_{nn} value increases with k value. That means the nodes which have relative high degrees tend to connect with the nodes with high degrees. So this network is assortative. In network constructed from MA 'tb', k_{nn} values saturate when k is larger than 15. So this network is not assortative.

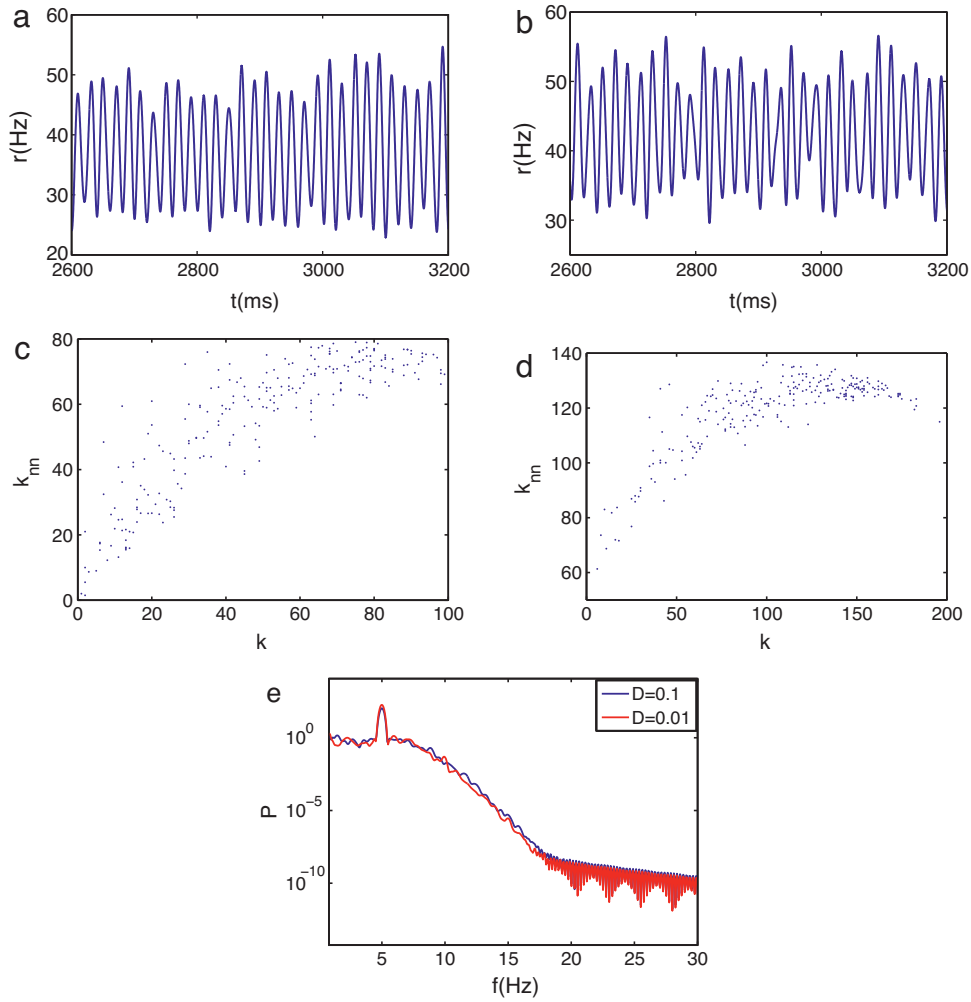

Fig. 4 – Characterizing signals of HR neuronal network through complex network approach. (a) Firing rate *r* of HR neuronal network, D_N=0.01; (b) firing rate *r* of HR neuronal network, D_N=0.1; (c) average degree of neighbors of nodes k_{nn} versus degree *k*,D_N=0.01; (d) average degree of neighbors of nodes k_{nn} versus degree *k*,D_N=0.1; (e) power spectrum of the firing rate time series with P denoting the power of signal in a given frequency *f*.

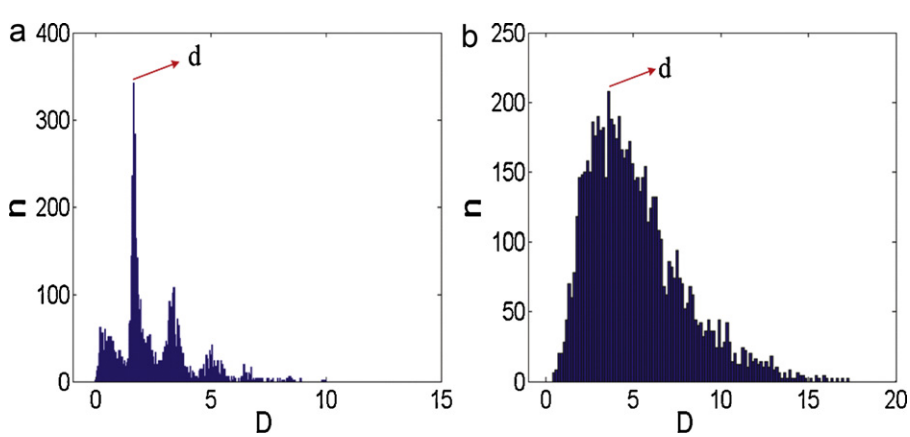

Fig. 5 – Distributions of weights in the complex network constructed from acupuncture signals. *n* denotes the number of $D_{i,j}$ values distributed in the corresponding bins, and *D* denotes the weights of the complex network. (a) MA 'nb', threshold *d* = 1.6 and (b) MA 'tb', threshold *d* = 3.6.

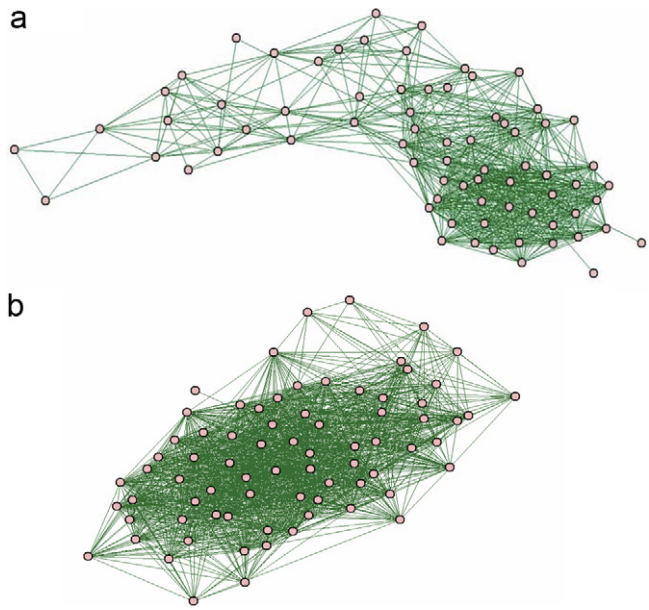

Fig. 6 – Topologies of network mapped from the time series of different MA. (a) MA 'nb' and (b) MA 'tb'.

To quantify this feature, assortativity coefficients R of these networks are calculated according to Eq. (5). R for MA 'nb' is 0.6015, and R for MA 'tb' is 0.1825. Then R values of 4 MA in all 7 sessions of experiments are calculated and shown in Fig. 8. It is found that R values of MA 'nb' and 'nx' are higher than MA 'tb' and 'tx'.

Furthermore, the constructed complex networks based on MA 'tb' and 'tx' are similar to that evoked by noises with higher intensity in the network model. So the variabilities between different MA may be related to different fluctuations the acupuncture induces.

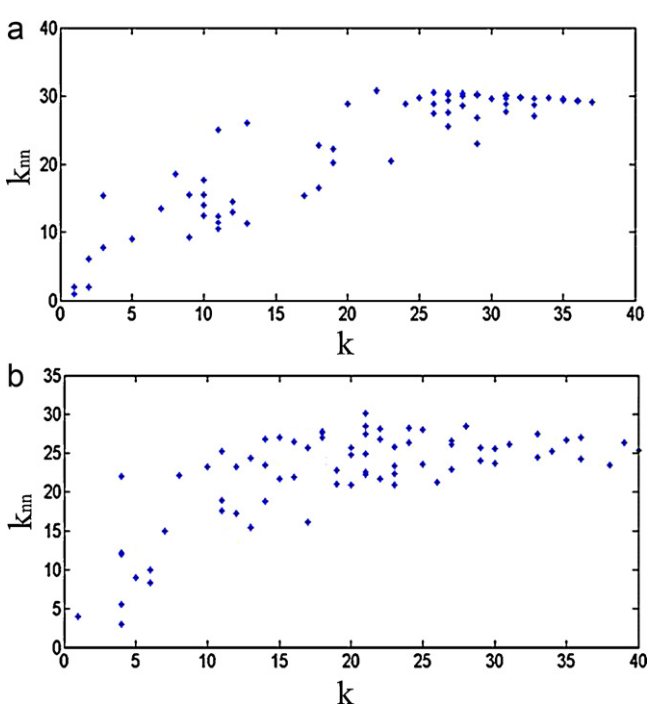

Fig. 7 – Average degree of neighbors of nodes k_{nn} with degree k in complex network which is constructed by acupuncture signals. (a) MA 'nb' and (b) MA 'tb'.

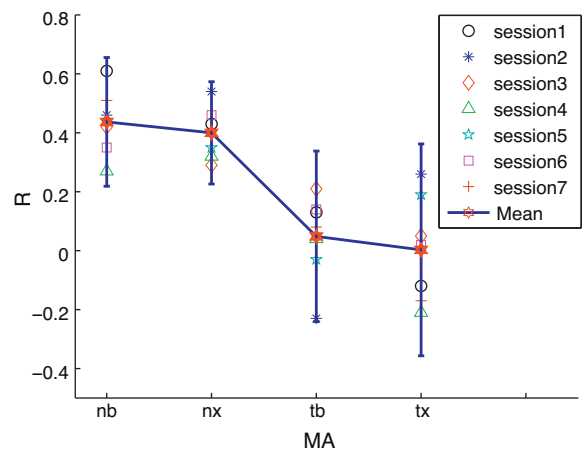

Fig. 8 – Assortativity coefficients R of all MA in 7 sessions. Error bar shows 95% confidence interval.

5. Conclusion

We introduce complex network method to the studies of acupuncture signals. After combining the analysis of the data generated from neuronal network model and that evoked by acupuncture, it is found that features of neuronal chaotic rate time series induced by periodic stimuli can be characterized by complex network approach. Some mechanisms of the differences between different manipulations of acupuncture are also revealed to some extent. Complex network of MA 'nb' and 'nx' are similar to that evoked by periodic stimuli and noises with lower intensity in the network model, and MA 'tb' and 'tx' are similar to periodic stimuli and noises of higher intensity. Furthermore, features of signals can be quantified by assortativity coefficients R of corresponding complex networks. It is shown that features of time series induced by MA 'nb' and 'nx' are different from those of MA 'tb' and 'tx' with statistic significance based on R values.

Some investigators have studied acupuncture signals though nonlinear analysis based on the time series of membrane potential or inter-spike intervals (ISI) of single neuron [17,18]. This study is based on the time dependent firing rates, which can be easily detected and calculated robustly and has more biological meaning. Moreover, the results we have obtained are in accordance with Refs. [17,18].

Therefore, based on the new perspective of complex network mapping, we could further understand the acupuncture and differentiate features of different MA. The quantitative analysis of acupuncture signals can also be used to make manual acupuncture more standardized. The complex network method may also be used as an interface between humans and neural systems. These results may provide potential helps in clinical treatment of acupuncture.

Conflict of interest

No conflict of interest statement for all authors.

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