LETTER

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The potential scale-free network mechanism underlying the formation of focal epilepsy

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Abstract – Abnormal brain networks are likely to be the trigger of seizure generation of epilepsy. Clarifying the effects of abnormal structures on brain function is of great significance for brain diseases. Due to the complexity of brain networks, the relationship between structural and functional brain networks is not yet well-defined. In this letter, we apply a generative model depicting the interrelationship between structural and functional connectivity, to reproduce similar resting whole brain networks and focal epileptic networks through networks with different topologies. It is found that only the underlying network connected with scale-free structure can reproduce the properties of focal epilepsy network, while the resting network has a small probability of reproduction under both the small-world network and the scale-free network. In particular, this reproduction capacity is immune to the nodal distance modes of the underlying network. This suggests that there exists severe heterogeneity in the focal epilepsy network similar to the scale-free network, which may facilitate to the clinical structural inference of seizure location.

Introduction. – There is a generalized network structure in the brain [1], and network theory provides a perspective for exploring the complex neuronal activity within the brain. Current mainstream tools for brain network analysis consist of structural brain networks which reflect real connectivity within the brain and functional brain networks related to the cognition. Epilepsy is a common brain disorder, and with the development of modern imaging and neurophysiological techniques, epilepsy has been demonstrated to be a brain network disorder. Therefore, the pathological mechanisms of epilepsy can also be understood through a network perspective.

It is hypothesized that the foci of epilepsy affect not only the area where they are located, but also the remaining brain regions, and these epilepsy-related areas then form a persistent abnormal network that hampers the activity of normal brain networks [2,3]. Such abnormal networks are embedded in brain networks and may have their specific connectivity and presentation structurally or functionally, thus causing functional and cognitive barriers in patients, but the causal relationship between this specificity and brain disease remains to be explored. The structure of epileptic networks has important associations with the frequency and range of seizures, the more intense dynamical state switching existing in epileptic networks compared to normal individuals, and the more localized excitability abnormalities are observed in networks with highly heterogeneous connectivity [4,5]. Using graph theoretic analysis, it has been suggested that the clustering coefficients and mean path lengths of networks of epileptic patients increase most significantly in the α, θ, and δ frequency bands during and after seizures, with networks heading towards a more ordered direction. This network with small-worldness is thought to be more conducive to synchronization and potentially favorable to seizures [6]. In contrast, patients with focal epilepsy were found to shift their networks towards a more random network topology based on DTI data [7]. This indicates that there may be differences in network topology changes across epilepsy patients. Regardless of the direction of variation, the existence of such abnormal networks inevitably has a persistent and irreversible effect on the patients.

While brain functionality is explored on a large scale, structural networks are often used as assisting tools for the initial identification of epileptogenic networks. Some

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lesion areas can be directly observed by imaging tools, and we can visualize the presence of an abnormal structural network intuitively, this kind of obvious lesion is very helpful for pre-surgical evaluation. Even so, the relationship between this structural connection and its functional associations remains unclear, and we do not know the pattern of response to seizure in this abnormal structure. It can be said that clinically defined epileptogenic foci have not been clearly labelled and depicted both structurally and functionally [8]. Therefore, identification and localization of epileptogenic foci or epileptogenic networks is important both for drug selection and pre-surgical guidance.

The brain is constructed in a sophisticated and efficient manner, and these are associated with the special design of neuronal cells, neural circuitry coding, etc., within the brain [9]. These complicated wirings within the brain are often constructed with the aim of conserving the energy consumption of brain activity [10]. Usually, energy consumption is positively correlated with connection distance [11,12]. Therefore, functional connections are usually based on the principle of cost minimization in the evolution of neural activity and there exists a large number of short distance connections [11]. It is possible to relate structural and functional networks from an energy perspective. However, the known small-world properties of brain networks cannot deny the existence of long-distance connections, which requires a more sophisticated theory to describe the criteria for the formation of functional networks, which will allow for an accurate depiction of epileptic networks, both structurally and functionally.

In this letter, we first analyzed the network properties of epileptic and normal networks driven by empirical data, and then reproduced epileptic functional and normal networks with specific properties in networks with different topologies by using the evolutionary model of functional networks. We hope that in the process of reproduction, the structural properties associated with the disease can be reflected in these changing network structures, providing an in-depth understanding of the structure-function connection relationship, and thus providing new perspectives on the localization of the lesion and on the understanding of the functional disorders caused by the disease. In addition, a clear description of the lesion structure can also improve the preparations for brain dynamics modeling and provide a theoretical basis for understanding the working mechanism of the brain and the mechanism of brain disease formation and propagation.

Materials and methods. –

Data acquisition. In this letter, we use seven groups of patient data and 20 groups of normal human data as the empirical data, which were used as the fitting criteria for generative networks. Patient SEEG data were recorded from more than 100 channels of seven patients who had been admitted to the hospital with refractory focal epilepsy at Sanbo Brain Hospital of Capital Medical University in Beijing. Normal human data were obtained from `https://physionet.org/content/eegmmidb/1.0.0/`. We selected 20 of these groups of closed-eye resting-state data as control groups for the patients. The functional networks derived by both sets of data were obtained by calculating the Pearson correlation coefficient between the two signals and sparsifying the network at a certain density.

Network structure. Brain network is a large heterogeneous network, and this heterogeneity can be understood by using network science. There are some unique and important properties in structural brain networks and some of the most basic network structures can be used to explain how these properties emerge and evolve.

Random structure. The same species exhibits anatomically consistent structural connectivity [13], but brain structure can be affected by innate or acquired influences that are not independent of each other, and thus there are still differences between individuals [14]. Such subtle differences can be characterized using random connections, mostly known as ER random model, in which pairs of nodes in this model are randomly connected with a defined probability. A major feature of random networks is the normal distribution of degrees.

Small-world connectivity. Small-world networks have higher clustering coefficients and shorter average path lengths compared to random networks. Duncan Watts and Steven Strogatz [15] developed a classical small-world model. It starts from a regular connection, each edge of the original network is then reconnected randomly with probability p. Small-world model are the networks that arise in the transition from regular to random networks, and this competition for highly clustered short paths is thought to be the mechanism that promotes the separation and integration of information within the brain.

Scale-free connectivity. The connectivity between nodes in scale-free networks exhibits severe heterogeneity [16,17]. In the classical scale-free model of BA [18], network generation follows the law of growth and meritocratic connectivity, resulting in a pivotal structure, also called the core regions, that act as bridges to promote the integration of brain information. This can be observed in brain network which, hence, is believed to have the scale-free properties.

Grid connectivity. Grid connectivity is a regular planar connectivity defined by us, in which all nodes except the boundary ones have four neighboring nodes. Although this regular structure cannot explain the physiological mechanisms in real situations, it can help us to visualize the connectivity of the network and to specify the abstract connections within the network.

Economical clustering generative model. The brain can be interpreted as a large complex network, and graph theory has provided several approaches to characterize brain networks. A wealth of research associating functional brain network properties with neurophysiological

activity enriches the understanding of the working mechanisms of the brain. However, the underlying mechanism of how to drive the formation of functional network is currently unknown. The distance is an important element in determining whether a connection is generated between nodes. Usually, the long-distance connections require greater energy consumption compared to short ones, so the connection probability is generally negatively correlated with the distance between two nodes. In 2012, Vertes indicated that the probability of node connection by distance function alone seems to be insufficient to demonstrate the real topology of brain functional networks. He then proposed the economic clustering generative model (probabilistic model) based on both the anatomical distance and network topology to simulate brain functional networks, which can be modelled as [19]

$$P_{i,j} \propto (k_{i,j})^{\gamma}(d_{i,j})^{-\eta}, \tag{1}$$

where $P_{i,j}$ denotes the connection probability between node i and node j, $k_{i,j}$ is the number of nearest neighbors in common between nodes i and j, and

$$d_{i,j} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2} \tag{2}$$

is the Euclidean distance denoting the anatomical distance between node pairs of i and j, described by coordinate points (x_i, y_i) and (x_j, y_j), respectively. In this letter, we consider two types of distance distributions, *i.e.*, regular (Re) and random (Ra) distributions,

$$d_{i,j}^{Re} = \sqrt{(x_i^{Re} - x_j^{Re})^2 + (y_i^{Re} - y_j^{Re})^2}; \quad x_{i,j},\ y_{i,j} = i, j, \tag{3}$$

$$d_{i,j}^{Ra} = \sqrt{(x_i^{Ra} - x_j^{Ra})^2 + (y_i^{Ra} - y_j^{Ra})^2};$$
$$x_{i,j},\ y_{i,j} = \mathrm{Rand}(0, 1), \tag{4}$$

η and γ are the parameters of distance penalization and preferential attachment (the exponent of a power law), respectively.

Controlling metabolic costs is an important principle of the brain's physiological activity, and longer connection distances usually mean higher energy consumption, so promoting energy minimization contributes to connection formation. Most connections in the brain tend to be short-distance connections, but the unique small-world properties of brain suggest the existence of long-distance connections, so node distance is not the only factor in the mechanism of brain network formation. The inclusion of a network topology term in this generative model allows for the formation of additional connections between nodes that already share neighbors in common and can better fit the properties of the real brain. This suggests that brain network is a unique and complex system determined by one or more balances factors [20]. The two-parameter economic clustering generative model proposed by Vertes [19] can yield more accurate simulated experimental data in terms of fitting not only the empirical normal data but also the pathological brain networks by accurately capturing subtle or strong topological changes within brain network.

Network properties. The brain as a complex dynamic system can be analyzed using complex network theory. Conducting the study of complex networks begins by considering the properties between large-scale nodes and their connections in the network from a statistical perspective.

Clustering coefficient (CC) is the ratio of the number of real connections between the neighbors of a node (E_i) to the number of all possible connections ($k_i(k_i - 1)/2$), representing the degree of connectedness around this node and expressing the secondary attractiveness of this node. The average clustering coefficient is the calculated average of all nodes in the network, *i.e.*,

$$CC = \frac{E_i}{k_i(k_i - 1)/2}. \tag{5}$$

The higher the clustering coefficient of the system, the higher the stability [21,22].

Network efficiency (EFF) refers to the average of the inverse of the shortest path lengths between node pairs (d_{ij}) in a network with N nodes, reflecting the information transfer in the network, and is a global characteristic, calculated as

$$\mathrm{EFF} = \frac{1}{\frac{1}{2}N(N+1)} \sum_{i>j} \frac{1}{d_{ij}}. \tag{6}$$

Modularity (MOD) shows the degree of community division in the brain network and can reflect the functional separation (MOD↓) and integration (MOD↑) of the brain, which can be described as

$$\mathrm{MOD} = \sum_{i=1}^{n} (e_{ii} - a_i^2) = \mathrm{Tr}e - \parallel e^2 \parallel, \tag{7}$$

where n is the total number of community, e_{ij} is the ratio of the connections between communities i and j to the total connections of the whole network, $\mathrm{Tr}e = \sum_i e_{ii}, a_i = \sum_i e_{ij}$.

The fit of the generative model to the empirical data-driven brain network is measured by using these important network properties. The connection probability between two points in the generative model depends on two aspects, one is the number of common neighbors of the two nodes and the second is the distance between them, controlled by exponential parameters η and γ in eq. (1), respectively. In this letter, under a pair of parameters (η, γ), we will build the 0-1 functional network using the generative model [15] by setting 0.5 as the threshold of the connection probability. Then, we will compare the network properties of the generated network with the mean value of data-driven network properties, where the Euclidean distance between the two sets of network properties is used as a measure of their numerical similarity. The smaller

Euclidean distance the more the network properties of the generated network match the data network. We refer to the parameter space with smallest Euclidean distance as the best-fit parameter space (BFPS).

Results. – We use the laws embedded in the generative model to simulate and generate a simulated functional network with the properties of the real brain functional network. In the generative network, the connection probabilities between nodes are mutually constrained based on two physiological factors, their connection distance and shared similar inputs. During the process of simulation generation, we have tried the connection structures of regular network connection (fig. 1(A)), random network connection (fig. 1(B)), small-world network connection (fig. 1(C)), scale-free network connection (fig. 1(D)) and self-defined planar grid connection (fig. 1(E)). These five underlying connection networks have the same scale and similar average degree as the reference network, in order to exclude other factors other than the network structure that affect the network properties. The distance matrix contains both regular and random arrangements (fig. 2).

As shown in fig. 3, for each network structure, the difference between the generated network and the reference network is minimal in the BFPS. The difference between the reproducibility of the scale-free network and other networks can be seen in this minimal difference. We present a comparison of the properties between the generative network and reference network obtained from the parameters in the BFPS for different network structures and network distances. The smaller the Euclidean distance, the more consistent the network properties of the generated network and reference network under the set of parameters.

When the node distance distributions are the same and taking the scale-free network connectivity during the simulation of the empirical data network, the network can well generate an epilepsy-like functional network that is composed of a comprehensive network feature including the average clustering coefficient (CC), network efficiency (EFF) and modularity (MOD). In particular, it can reproduce the three states of the patient to the greatest extent (fig. 3(A)). In fact, the generated function network is a probabilistic representation based on the evolutionary laws of the structural network, and is just a phenomenological statistical network lacking the physiological properties embedded in the real network. However, if the generative network and empirical network are consistent in various network properties at the same time, the similarity between them can be illustrated to a certain extent. Unfortunately, except for the scale-free network, the simulated network characteristics of the other remaining network models under the best parameters are not in good agreement with the empirical network (fig. 3(B)), indicating a failure of the fit. This result reflects the greater potential of scale-free networks to evolve epilepsy-like focal networks compared to other network structures in these underlying complex network models. The same procedure

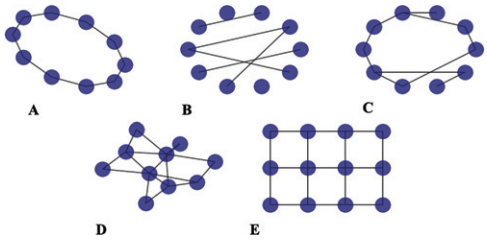

Fig. 1: Five different models of complex networks: (A) rule-based network, *i.e.*, a homogeneous network with a simple connection structure that is easy to observe and analyze; (B) random networks, *i.e.*, the nodes are connected to each other with a certain probability; (C) small-world networks, *i.e.*, with high clustering and short paths, consistent with most real network properties; (D) scale-free networks, *i.e.*, networks with highly concentrated nodes and the rest of nodes sparsely connected; (E) grid networks, *i.e.*, the nodes are connected on a plane in the form of a grid.

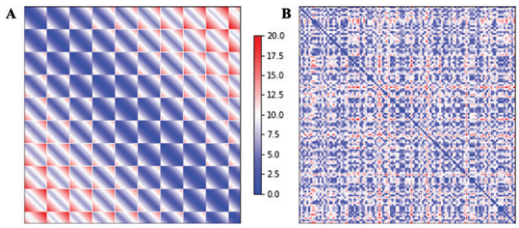

Fig. 2: Two different distance distribution matrices. (A) Regular distribution, *i.e.*, the coordinates of nodes are distributed according to a specific arrangement rule, and the distances between neighboring nodes are consistent; (B) random distribution, *i.e.*, the coordinates of all nodes are taken randomly to get a random distance matrix.

was applied to normal subjects, with a slight change in the situation. Among the 20 sets of empirical data, only 4 sets of data-driven functional network properties were well matched by either the small-world generative model or the scale-free generative model. The differences in the network models used in the fitting process between patients and normal individuals reflect the uniformity of epileptic network properties between patients, which may be instructive for the way epileptic networks are structurally connected.

The scale-free network is highly concentrated due to its preferential attachment, and the degree distribution is power-law distributed, which means that there are a few tightly connected nodes as the bridge to the whole network, and most of the nodes are sparsely connected to each other. The epilepsy-like network generated by the scale-free network also exhibits a scale-free property in the degree distribution (fig. 4). This scale-free epilepsy-like network already matches the empirical network well in terms of comprehensive network properties. Although the power law of the degree distribution is not significant in the three states of the empirical network, it can still be found that some of the nodes are highly concentrated and the peaks of the distribution at small degrees also

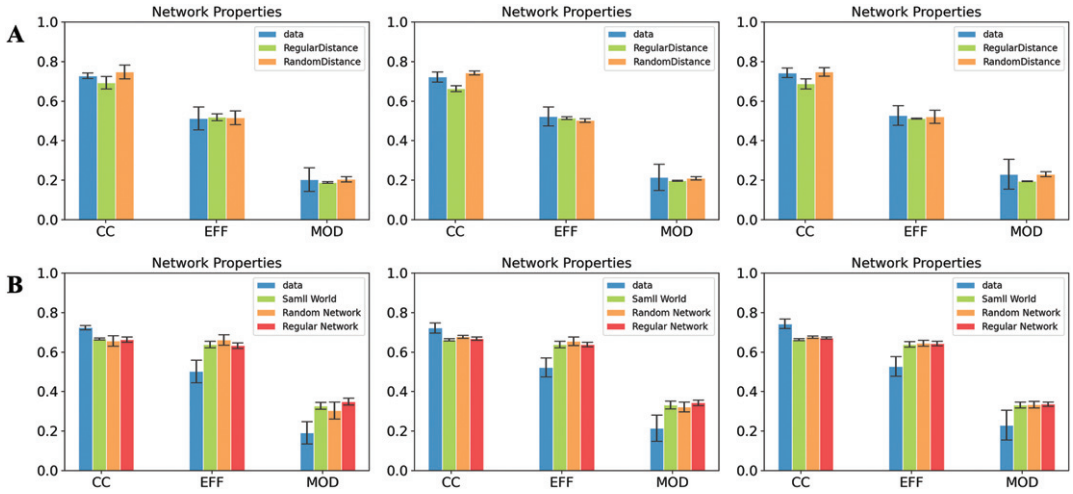

Fig. 3: Comparison between the network properties (clustering coefficient CC, network efficiency EFF, modularity MOD) of the generated epilepsy-like functional network and the empirical data-driven functional network in different network structures, for the interictal (left), ictal (middle) and post-ictal (right) periods. (A) The three network properties of the simulated epilepsy functional network evolved from the scale-free network with regular and random distributions of node distances in the optimal parameter space are similar to those of empirical data. (B) The differences between the simulated functional networks evolved from regular, random and small-world networks in the optimal parameter space and empirical data are larger than those in (A).

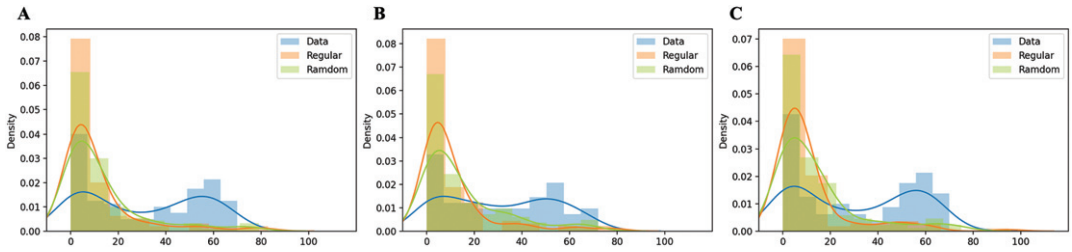

Fig. 4: The degree distribution of the generative and empirical networks. The data-driven empirical networks show a similar situation in the (A) interictal, (B) ictal and (C) post-ictal periods. The degree distribution of the generative networks with good fitting (orange, green) shows significant power-law characteristics.

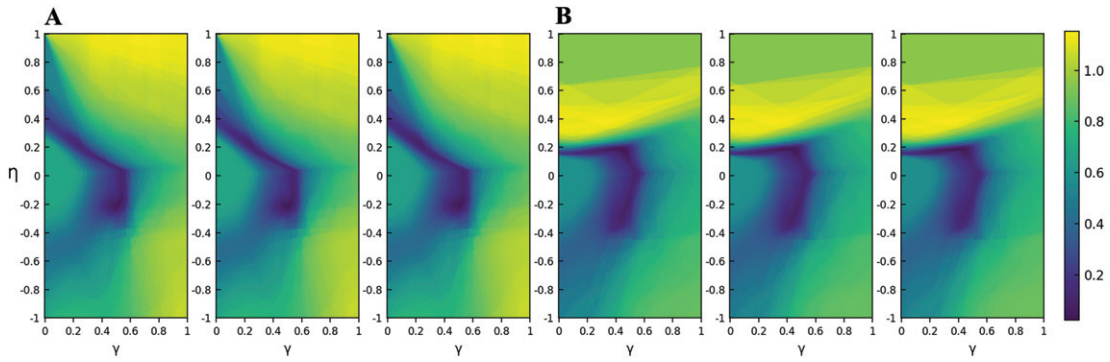

Fig. 5: Euclidean distances of the network properties between the generated network based on scale-free mechanism and the reference network in interictal (left), ictal (middle) and post-ictal (right) periods, under regular (A) and random (B) distance distributions, respectively. The different distance matrices result in different BFPS (dark section), and the parameter-generating networks in the BFPS are highly fitted to the properties of the reference network.

reflect the sparse connectivity of most nodes as in the scale-free network, unlike the near-average degree distribution in normal humans. This in the real epilepsy case may suggest the existence of a lesion.

Two influential factors are included in the generated models, the network topology and the distance of node connections. We used regular distance distribution and random distance distribution (fig. 2) in each network

model separately to observe the effect of distance penalty. We found that among the two networks with different distance distributions, only the scale-free network still shows the best ability to reproduce the epilepsy function network, and that the different distance matrices can slightly affect the range of the best-fit parameters regions, as shown in fig. 5. The generated networks evolving with different parameters still have similar properties. This means that even if distance parameters other than topological properties are introduced in the construction rules, they do not affect the evolutionary potential of the underlying network.

Discussion. – We can hopefully get a glimpse into the connectivity properties that form such structural networks with specific functionalities in already known functional networks. In this letter, we use a functional network formation law to explore the ability of different complex structural network models to evolve with real epileptic properties. Results show that epileptic network exhibits both structural and functional scale-free properties, which suggests that the presence of such core regions may be associated with lesions and may inspire the design of network structure and the localization of lesions in the pre-model building stage. The scale-free property is a non-negligible feature in epileptogenic networks, both from the perspective of the model and from the perspective of functional network generation laws. The formation pattern of functional networks can be used to infer the connection relationships of their underlying networks in reverse. The non-significance of the rest of network models in the generative fitting process does not completely deny their existence in brain connectivity, and the diversity of brain connectivity may require more consideration.

However, in this letter, we have considered only a few classical network properties, and although the morphology of the network can be roughly inferred to exhibit similar properties, the simulated real connectivity of the network is still in error with the empirical network, and thus enriching the criterion of the fit is also a direction for future improvement. In addition, the non-homogeneity of network scale cannot be avoided during data collection. The empirical epilepsy network is driven by invasive SEEG data which is usually a localized network of the brain in clinical evaluation, while the experienced network for healthy individuals is driven by whole brain EEG data. The use of functional networks in this study to infer their underlying structural connectivity is not influenced by network scale, but errors caused by network scale should still be taken into account when comparing network differences from different populations.

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