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Brain network analysis of seizure evolution

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The human brain is one of the most complex biological systems. Neuroscientists seek to understand the brain function through detailed analysis of neuronal excitability and synaptic transmission. In this study, we propose a network analysis framework to study the evolution of epileptic seizures. We apply a signal processing approach, derived from information theory, to investigate the synchronization of neuronal activities, which can be captured by electroencephalogram (EEG) recordings. Two network-theoretic approaches are proposed to globally model the synchronization of the brain network. We observe some unique patterns related to the development of epileptic seizures, which can be used to illuminate the brain function governed by the epileptogenic process during the period before a seizure. The proposed framework can provide a global structural patterns in the brain network and may be used in the simulation study of dynamical systems (e.g. the brain) to predict oncoming events (e.g. seizures). To analyze long-term EEG recordings in the future, we discuss how the Markov-Chain Monte Carlo (MCMC) methodology can be applied to estimate the clique parameters. This MCMC framework fits very well with this work as the epileptic evolution can be considered to be a system with unobservable state variables and nonlinearities.

Introduction

Epilepsy can be defined as recurring seizures caused by sudden, brief and significant changes in the way the brain works (*see* www.epilepsyfoundation.org). Nearly 3 million people in the U.S. and over 40 million people worldwide (1% of the population) currently suffer from epilepsy, which is the second most common brain disorder after stroke (Cockerell *et al*. 1996, *see* also www.epilepsyfoundation.org).

Uncontrolled epilepsy poses a significant burden to society due to the associated healthcare costs. The diagnosis and treatment of epilepsy is complicated by the disabling aspect that seizures occur spontaneously and unpredictably due to the nature of the chaotic disorder. Part of understanding the mechanism of epilepsy and seizure development is understanding how seizures evolve and progress. Although visual inspection of electroencephalogram (EEG) recordings can be used to identify the seizure onset, the presei-

zure period, also known as seizure pre-cursor, is not detectable by EEG visualization (Lehnertz & Litt 2005). The seizure pre-cursor can be viewed as the abnormal brain activity preceding a seizure governed by the epileptogenesis.

It was previously shown in several studies that the pre-seizure period may be manifested by spatial and temporal changes in the dynamics of EEG recordings (Chaovalitwongse 2005, Chaovalitwongse *et al*. 2006, 2007, Sackellares *et al*. 2006). However, investigating both spatiotemporal properties of EEG signals remains a difficult task, as EEG data are large-scale and analyzing such data requires efficient and sophisticated techniques.

Although the brain may have originally emerged as an organ with functionally dedicated regions, recent evidence suggests that the brain evolved by preserving, extending, and recombining existing network components, rather than by generating complex structures *de novo* (Sporns & Kotter 2004, Anderson 2007). This is significant because it suggests that (1) the brain network is arranged so that the functional neural complexes supporting different cognitive functions share many low-level neural components, and (2) the specific connection topology of the brain network may play a significant role in seizure development.

One recent hypothesis in epilepsy research is that the temporal lobe seizure development may be initiated by specific connected structures in the brain's cortical network (Sackellares *et al*. 2006). This line of thinking is also supported by Sakata and Yamamori (2007) who demonstrated that specific connected structures are either significantly abundant or rare in cortical networks. If seizures evolve in this fashion, then we should be able to make some specific empirical hypotheses regarding the evolution of seizures that might be borne out by investigating the synchronization between the activities in different brain areas, as revealed by quantitative analyses of EEG recordings.

The goal of this study was to test the following two hypotheses: (1) The brain activity in the orbitofrontal areas is highly correlated, while the activities in the temporal lobe and subtemporal lobe areas are highly correlated with their own side (left only or right only) during the pre-seizure period. The high correlation can be viewed as a recruitment operation initiated by an epileptogenic area through a regular communication channel in the brain. Note that the connection of these brain areas has been a long-standing principle in normal brain functions and we believe that the same principle should hold in the case of epilepsy as well. (2) Some brain regions are consistently active, which is manifested by a higher degree of synchronization among EEG electrodes within the same region, during the pre-seizure state. We postulate that the active connection may be driven by seizure evolution, regulating abnormal communications in the epileptogenic brain areas or vulnerable areas in the brain network. To test these hypotheses, we herein propose network-theoretical methods through a multivariate statistical analysis of EEGs to study the seizure development by investigating the topological structure of the brain connectivity network.

Background

The development of seizures can be captured by an EEG, which records the voltage potentials reflecting changes in the electrical activities of neural assemblies. These changes are reflected by wriggling lines along the time axis in a typical EEG recording. For this reason, EEGs have been the main tool for neurologists and neuroscientists to study epileptogenetic processes and other neurological disorders. A typical electrode placement for intracranial EEG recordings used in our study is shown in Fig. 1a. An emerging view in recent epilepsy research suggests there are four stages in seizures: normal, pre-seizure, seizure onset and post-seizure (Litt & Echauz 2002, Iasemidis 2003, Lehnertz & Litt 2005; Fig. 1b).

Multivariate analysis on EEG signals

In any study of the brain connectivity network, signal processing and data mining techniques are required to extract useful information buried in the raw EEG data. We can categorize signal processing techniques into two types based on the number of sources, univariate and multivari-

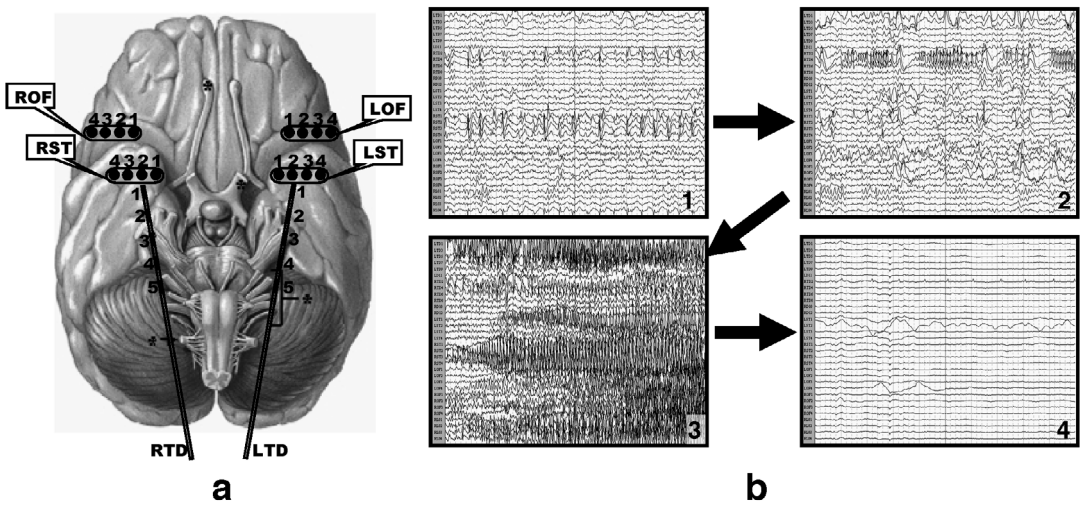

Fig. 1. — **a**: Inferior transverse views of the brain, illustrating approximate depth and subdural electrode placement for EEG recordings. Subdural electrode strips are placed over the left orbitofrontal (LOF), right orbitofrontal (ROF), left sub temporal (LST), and right sub temporal (RST) cortex. Depth electrodes are placed in the left temporal depth (LTD) and right temporal depth (RTD) to record hippocampus activity. — **b**: Twenty-second EEG recordings of (1) normal activity, (2) pre-seizure activity, (3) seizure onset activity, and (4) post-seizure activity from Patient 2 obtained from 32 electrodes. Each horizontal trace represents the voltage recorded from electrodes shown in **a**.

ate measures. Univariate measures process the information from a single data source, such as a single electrode. There are several signal properties one can extract using univariate measures such as power spectrum, autocorrelation, entropy, and divergent rates. Multivariate measures (also referred as spatiotemporal measures) allow one to determine the synchronization that commonly occurs among a group of sources. This is very important because multivariate measures can uniquely determine specific types of connection between two or more sources, and quantifying the synchronization between different brain areas (measured by different electrodes) is crucial to a greater understanding of the brain connectivity network. The synchronization may be attributable to the brain's anatomical, functional, or dynamical connectivity. In this study, the synchronization patterns are postulated to reflect the seizure evolution (epileptogenic process), and we shall use electrode synchronization as a similarity measure of EEG signals from different brain areas.

This is fine in theory; however there are a few complexity issues in calculation of multivariate measures. In spite of the theoretical capability of multivariate methods to find the common patterns from multiple sources, the complexity of the calculation increases exponentially with the number of sources. Therefore, we use multivariate measures for quantifying the synchronization from only 2 electrodes at a time. Specifically, a simple signal processing used to calculate the synchronization between electrode pairs is employed in this study. Then we apply a data mining technique based on network-theoretical methods to the multivariate analysis of EEG data.

Brain synchronization

In general, statistical similarity measures can be categorized into two groups: linear and nonlinear dependence measures. The linear measure is mainly used for measuring a linear relationship between two or more time series. For example, the most commonly used measure is cross-correlation function, which is a standard method of estimating the degree of correlation in time domain between two time series (Knapp & Carter 1976, Fel'dshtein 2000). The result of a cross correlation function can be calculated at different time lags of two time series to show the level of redundancy at different time points.

Frequency coherence is another linear similarity measure, which calculates the synchrony of activities at each frequency (Miltner *et al*. 1999). Although the information from cross-correlation function and frequency coherence has been shown to be identical (Olivier *et al*. 2004), the similarity between two EEG signals in different frequency bands such as delta, theta, beta, alpha and gamma, is still commonly used to investigate EEG similarity patterns (Lachaux *et al*. 1999, Miltner *et al*. 1999). For example, Bartolomei *et al*. (1999) used frequency coherence measures to investigate the interactions between medial limbic structures and the neocortex during ictal periods (seizure onsets). In another study by Towle *et al*. (1999), the coherence pattern of cortical areas from epileptic brain was investigated to identify a cortical epileptic system during interictal (normal) and ictal (seizure) periods.

Although linear measures are very useful and commonly used, they are insensitive to nonlinear coupling between signals, and non-linearity in neural networks. To be able to investigate more of the interdependence between EEG electrodes, nonlinear measures should be applied. Nonlinear measures have been widely used to determine the interdependence among EEG signals from different brain areas. For example, Arnhold *et al*. (1999) and Quyen *et al*. (1999) studied the similarity between EEG signals using nonlinear dynamical system approaches. They applied a time-delay embedding technique to reconstruct a trajectory of EEG in phase space and used the idea of generalized synchronization proposed by Abarbanel *et al*. (1992) to calculate the interdependence and causal relationships of EEG signals.

We propose an approach to investigate and quantify the synchronization of the brain network, specifically tailored to study the propagation of epileptogenic processes. Mars *et al*. (1985) investigated this propagation, where the average amount of mutual information during the ictal period (seizure onset) was used to identify the focal site and study the spread of epileptic seizure activity. Subsequently, Palus *et al*. (1993) applied the information-theoretic approach to measure synchronization and identify causal relationships between areas in the brain to localize an epileptogenic region. Here, we apply an information-theoretic approach, called cross-mutual information, which can capture both linear and nonlinear dependences between EEG signals, to quantify the synchronization between nodes in the brain network. In order to globally model the brain network, we represent the brain synchronization network as a graph.

Graph/network representation

Modeling the brain network as a graph is not new. In the past decade, several studies attempted to use network-theoretic methods to study the brain network. For example, the topological relationships between brain networks and social networks were proposed by Sakata and Yamamori (2007). In an earlier study, Sporns and Kotter (2004) demonstrated that the brain evolved a highly efficient network architecture whose structural connectivity (or motif) is capable of generating a large repertoire of functional states. In another recent study, the brain network graph was investigated to verify that the re-use of existing neural components played a significant role in the evolutionary development of cognition (Anderson 2007).

Applying network/graph-theoretic methods to EEG signals, we can model the brain connectivity/synchronization network as a complete graph $G(V,E)$, where V is a set of vertices and E is a set of edges. Vertices (also called nodes) are represented by EEG electrodes (also referred as channels). Edges (also called arcs) are represented by the synchronization/similarity between two EEG electrodes whose degrees correspond to the edge weights. In short, a brain connectivity network can then be constructed as a graph whose vertices are EEG electrodes and the weighted edges are the coupling strength of electrode pairs. Every pair of vertices is connected by a weighted edge.

In this study, we focus on the structural changes in the brain connectivity network that may be related to the seizure evolution. The structural changes could be represented by connectivity fractions/partitions through aggregation and segregation of the brain network. In this study, we propose two network-theoretic approaches, spectral partitioning and maximum

clique, to identify independent/segregated and clustered brain areas.

Materials and methods

Data acquisition

The EEG recordings (Table 1) were obtained from bilaterally, surgically implanted macro electrodes in the hippocampus, temporal and frontal lobe cortexes of two patients who underwent presurgical clinical evaluation for possible surgical treatment of intractable temporal lobe epilepsy. The recordings were obtained using a Nicolet BMSI 4000 recording system with amplifiers of an input range of 0.6 mV, sampling rate of 200 Hz and filters with a frequency range of a 0.5–70 Hz. Each recording included a total of 26 to 32 intracranial electrodes (8 subdural and 6 hippocampus depth electrodes for each cerebral hemisphere, and a strip of 4 additional electrodes if deemed necessary by the neurologist). The recorded EEG signals were digitized and stored on magnetic media for subsequent on-line analysis.

Network modeling

When we analyze the synchronization and model the brain network, we have to divide long-term EEG recordings into non-overlapping EEG epochs. This is because EEG recordings are considered to be highly non-stationary, in which the EEG temporal properties lie on a very small scale. In other words, it is widely known that EEG patterns tend to appear very briefly (for less than 30 seconds). Examples include sharp wave transients, spikes, spike-wave complexes, and spindles. Thus a proper size of EEG epochs has to be used to correctly estimate the cross-mutual information (CMI) degrees, which can reflect on the level of similarity at a suitable time scale.

In this study, we choose an EEG window (epoch) size of 10 seconds to calculate the CMI, which is considered to be stationary period for EEG signals (Iasemidis *et al*. 2000, 2003). As mentioned in the previous section, we model the brain connectivity network as a graph, where vertices are represented by EEG electrodes and edges are represented by the synchronization between two EEG electrodes. To quantify the synchronization through the level of interdependence, cross mutual information is used to measure the flow of information between two electrodes. The cross-mutual information is commonly used to quantify the information conveyed from one site to another site. In other words, it demonstrates how much information from electrode x was presented by electrode y and *vice versa*. It also has the capability to detect both linear and nonlinear dependent patterns of two random variables since both linear and nonlinear rules can be defined by probabilistic relationship. The cross-mutual information between electrodes x and y is given by

$$\mathrm{CMI} = \iint p_{xy}(x,y) \log_2 \frac{p_{xy}(x,y)}{p_x(x)\, p_y(y)} dxdy.$$

If these two random variables are statically independent, $p_{xy}(x,y) = p_x(x)p_y(y)$, then CMI = 0, which implies that there is no correlation between electrodes x and y. An example shown in Fig. 2c represents a scatter plot of an electrode pair at the right mesial temporal lope, RTD2 *vs*. RTD4, showing uncorrelated patterns, which have a low CMI value (*see* Fig. 2b). On the other hand (*see* Fig. 2d), a linear relationship was discovered in the scatter plot of the other electrode pair, also at the right mesial temporal lobe, RTD4 *vs*. RTD6. This kind of linear dependent pattern yields a high CMI value (*see* Fig. 2b).

Table1. EEG dataset characteristics.

Patient	Gender	Age	Number of electrodes	Seizure onset zone	Duration of EEG recordings (days)	Number of seizures
1	Male	29	26	R hippocampus	6.07	19
2	Male	37	30	L/R hippocampus	9.88	11

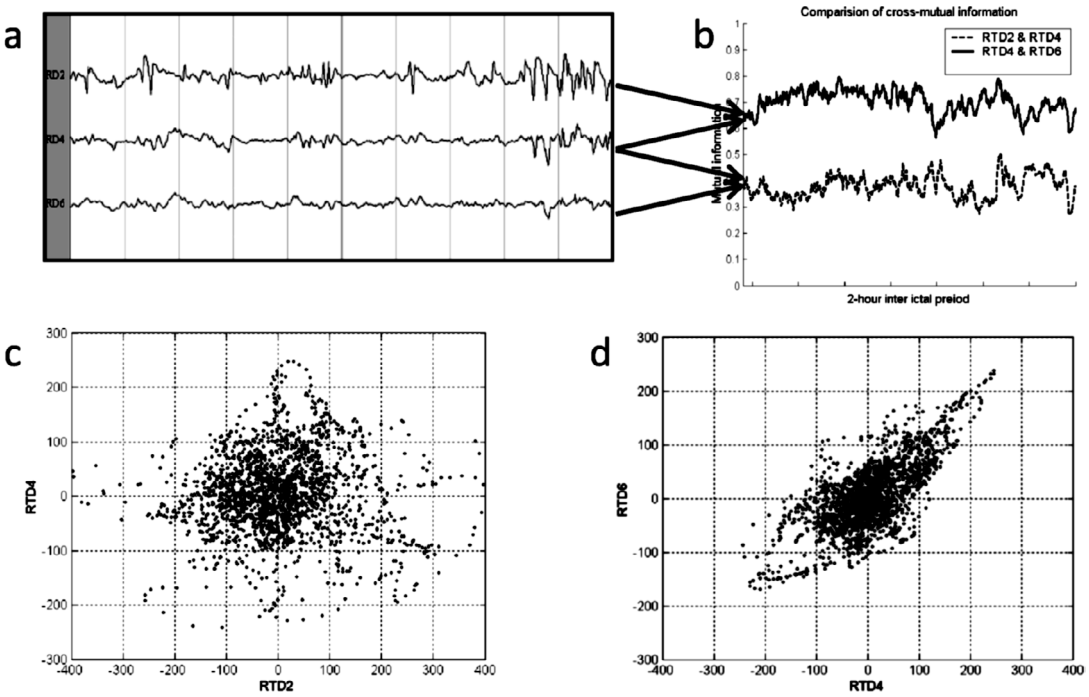

Fig. 2. — **a**: A 10-second segment of 3 EEG signals from the right temporal depth electrodes during normal period from Patient 1. — **b**: A comparison of cross-mutual information measured from RTD2 *vs.* RTD4 and RDT4 *vs.* RTD6. — **c**: A scatter plot of RTD2 *vs.* RTD4. — **d**: A scatter plot of RDT4 *vs.* RTD6.

Spectral partitioning

Spectral partitioning, first developed by Fiedler (1973, 1975), has been successfully applied in several applications for the past few decades. One of many applications is a parallel processing problem, which is to partition processors into two groups with the minimum cost of communication among processors. This problem can be trivially applied to our brain network problem, where we try to partition the brain network into two groups with the minimum cost (maximum synchronization) among the brain areas. Generally speaking, the spectral partitioning problem is used to find a cut or a group of edges which separate nodes into two groups and satisfy some specific conditions.

The problem can be formally defined as follows: Let the graph $G(V,E)$ contain a set of edges as a cut $E(A,B)$, whose end nodes are A and B. The cost of cut to separate a graph into group A and B is $\mathrm{cut}(A,B) = \sum_{i\in A, j\in B} \omega_{ij}$, where ω_{ij} is the communication cost between nodes i and j.

Suppose the condition of partition is to separate nodes in a graph into two groups with an equal number of nodes, i.e., $|A| = |B|$, we can formulate this problem as an integer programming problem to assign each node to one of two classes, –1 and +1, for groups A and B, respectively. To separate the graph into two balance groups with a minimum total cut value, we can formulate the problem as:

$$\begin{aligned} &\min \frac{1}{4}\omega_{ij}\left(x_i - x_j\right)^2 \\ &\text{s.t.} \sum_{i\in V} x_i = 0 \\ &x_i \in \{-1,+1\} \end{aligned} \quad .$$

This problem has been proven to be an NP-hard problem (Garey *et al.* 1976, Ding *et al.* 2001), which has been shown to be solvable in no less than non-deterministic polynomial time. In word, the complexity of this problem increases exponentially as the number of nodes increases. This problem can be reformulated as a continuous quadratic programming problem given by

$$\min \frac{x(\mathbf{D}-\mathbf{W})x}{2}$$
$$\text{s.t.} \sum_{i \in V} x_i = 0$$
$$-1 \le x_i \le +1$$

where $\mathbf{D}$ is an $n \times n$ diagonal matrix of total cost of connecting each node, and $\mathbf{W}$ is an $n \times n$ cost matrix between two adjacent nodes. The matrix $\mathbf{D} \times \mathbf{W}$ is known as a Laplacian matrix, which is positive semi-definite. From the above equation, the solution can be found by finding the eigenvector corresponding to the second smallest eigenvalue l_2. Therefore, this problem is equivalent to solving a linear equation: $(\mathbf{D} - \mathbf{W})x = lx$. Each element of the eigenvectors corresponds to each node and can be used to classify nodes into two different groups. For example, nodes with positive and negative eigenvalue belong to group A and B, respectively.

Note the above spectral partitioning problem only considers the cost to divide nodes in a graph into two groups. However, in our case, natural clusters need to be investigated to understand coupling activities or synchronization in the brain network. In order to make this model applicable to our investigation, we need to incorporate both inter-group (separation) and intra group (association factor within group) costs. This can be done by modifying the objective function. This approach, initially proposed by Shi and Malik (2000), is called the normalized cut (Ncut). The Ncut combines the inter-group and intra-group costs as cost ratios of two partitions, given by

$$\min \text{Ncut}(A,B) = \frac{\mathbf{W}(A,B)}{\mathbf{W}(A,A')} + \frac{\mathbf{W}(A,B)}{\mathbf{W}(A,B')},$$

where $\mathbf{W}(A,B)$ is the cut cost between group A and B, $\mathbf{W}(A,A')$ and $\mathbf{W}(B,B')$ are the association costs within groups A and B, respectively. The solution to this problem can be obtained by solving the following linear equation:

$$(\mathbf{D}-\mathbf{W})x = \lambda \mathbf{D}x \Rightarrow \mathbf{D}^{-\frac{1}{2}}(\mathbf{D}-\mathbf{W})\mathbf{D}^{-\frac{1}{2}}z = \lambda z.$$

Maximum clique

The partitioning of the brain network, described in the previous section, may give us some insights into how the brain activities are segregated. In this section, we hypothesize that the seizure evolution is initiated by one or a few brain areas (also known as epileptogenesis or focus), which try to recruit other brain areas to participate in the epileptogenetic process. This procedure should, therefore, involve repertoire of functional interactions as large as possible. The interactions among the recruited and focus areas that initiate seizure episodes can be viewed as the functional motifs of the seizure evolution. Therefore, we herein try to investigate the maximum number of brain areas presumably involved in the seizure functional motifs. The idea is similar to those of cortical networks, e.g., high complexity, short wiring, and small-world attributes (Sporns & Kotter 2004). We postulate that these motifs are in a form of the largest connected components (brain areas) preceding seizures. These components are in fact represented by the largest clique in the brain network.

We can model this problem as a maximum clique problem, where a group of brain areas (electrodes) participating in the seizure evolution can be discovered by searching the maximum number of nodes that are strongly coupled together into a complete subgraph of $G_0(V,E)$. The maximum clique problem has also been long known as a NP-hard problem (Pardalos & Xue 1992). We note that the brain network constructed from the CMI matrix forms a complete graph, in which each node has a link to every node. In order to determine if one node is synchronized with the other node, a threshold value is used to remove an edge with the CMI value lower than the threshold value. The removed edges are considered to represent an insignificant degree of synchronization (or no correlation).

The maximum clique problem can be formally defined as follows. Let $G(V,E)$ be an undirected graph where $V = \{1, \ldots, n\}$ is the set of vertices (nodes), and E denotes the set of edges. Assume that there are no parallel edges (i.e., more than 2 direct edges connecting the same pair of vertices) in G. Denote an edge joining vertex i and j by (i,j). We define a clique of G as a subset C of vertices with the property that every pair of vertices in C is connected by an edge; that is, C is a clique if the subgraph $G(C)$

induced by C is complete. Then, the maximum clique problem is the problem of finding a clique set C of maximal cardinality (size) $|C|$. The maximum clique problem can be represented in many equivalent formulations (e.g., an integer programming problem, a continuous global optimization problem, and an indefinite quadratic programming). Here, we represent it in a simple integer programming form given by

$$\max x_i$$
$$\text{s.t. } x_i + x_j \leq 1, \text{ where } (i,j) \notin E',$$
$$x_i \in \{0,1\}$$

where x_i is a binary variable indicating if electrode i is a member of the maximum clique. In order to find the maximum clique in the brain network, we apply an exact algorithm proposed by Carraghan and Pardalos (1990). This method works well in our case because the number of nodes (electrodes) in our study is modest.

Results

The spectral partitioning approach was applied to Patient 1, who had the epileptogenic area on the right mesial temporal lobe. We investigated structural patterns of the brain synchronization through local (partitioned) activity in each brain area during the period preceding a seizure. The maximum clique approach was applied to Patient 2, who also had bifocal epileptogenic areas on both left and right mesial temporal lobes. We investigated the clique structure of long-term (3 hours) periods of EEG recordings before and after a seizure.

Spectral partitioning

In the spectral partitioning procedure, we applied the normalized cut to partition graph into two natural partitions (clusters), in which two groups of electrodes can be separated into two highly synchronized groups. For visualization purposes, a 10-second segment of the similarity matrix (W) can be represented by a two-dimensional bitmap (*see* Fig. 3a and b). Note that this matrix is symmetric because the mutual information measure has no coupling direction. In each row and column of this bitmap, the color represents the synchronization level. Note that we will ignore the diagonal of the matrix because we can always find a very high level of self synchronization.

After applying the normalized cut, we calculated an eigenvector corresponding to the second smallest eigenvalue. Subsequently, we separated electrodes into two groups with the minimum cut or separation with minimum cost by applying the threshold value at 0. Using the eigenvector (*see* Fig. 3c), electrodes were separated into two clusters (*see* the boxes in Fig. 3a). In Fig. 3, it is easy to observe a clear separation of these two clusters through the value of the eigenvector, in which a sharp transient from R(S)T4 to L(O)T1 is used as a separating point. The first group of synchronized electrodes is from L(S)T, L(T)D, R(S)T and R(T)D areas. The second group is from L(O)F and R(O)F areas. After the first iteration, it is clear that the synchronization in the LD-LT-RD-RT cluster is not uniform throughout all electrodes in the cluster. Therefore, we consequently performed another iteration of spectral partitioning on the LD-LT-RD-RT cluster to find highly synchronized groups of electrodes within the cluster. This procedure can be viewed as a hierarchical clustering. After rearranging the electrodes based on the synchronization level, we found two sub-clusters of electrodes in the bitmap (*see* Fig. 3b). The value of the eigenvector indicates that by applying the threshold of 0 there are two sub-clusters within the LD-LT-RD-RT cluster (Fig. 3d). The LD-LT-RD-RT cluster was separated into two sub-clusters: LD-LT and RD-RT. This observation suggests that there exists a highly synchronized pattern in the same side of temporal lobe as well as in the entire orbitofrontal area. This finding can be considered as a proof of concept that the seizure evolution also follows a regular communication pattern in the brain network.

Maximum clique

As mentioned earlier, the idea of applying the maximum clique technique is different from the one using the spectral partitioning approach as

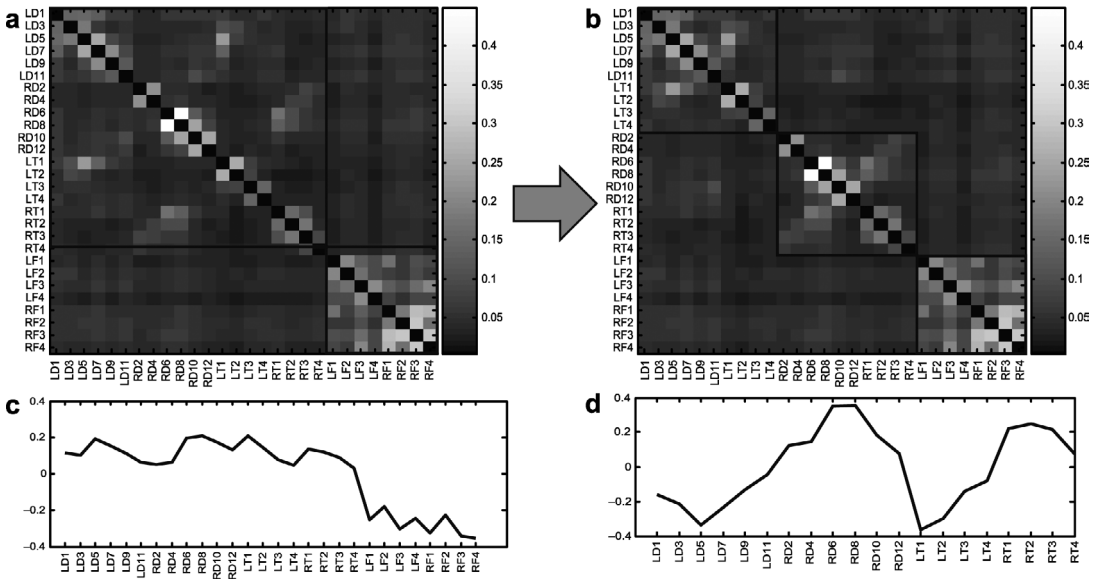

Fig. 3. — **a**: Similarity matrices after the first iteration of the spectral partitioning procedure. — **b**: Similarity matrices after the second iteration of the spectral partitioning procedure. — **c**: Eigenvector corresponding to the second smallest eigenvalue calculated when applying the spectral partitioning procedure to separate the brain network into 2 partitions (clusters). — **d**: Eigenvector corresponding to the second smallest eigenvalue calculated when applying the spectral partitioning procedure to separate the brain network into 3 partitions (clusters). Note that there are 3 partitions (clusters) in the brain network: LD-LT, RD-RT, and LF-RF. This confirms that the seizure evolution also utilizes the same network of other brain functions.

we are only interested in the most highly synchronized group of electrodes in the brain network. We analyzed 3 epochs of 3-hour EEG recordings, 2 hours before and 1 hour after a seizure, from Patient 2 who had the epileptogenic areas on both right and left mesial temporal lobes (Figs. 4 and 5). During the period before the seizure onset, a pattern where all the LD electrodes were consistently selected to be in the maximum clique was visible (Figs. 4 and 5). During the seizure onset, the size of the maximum clique increases drastically. This is very intuitive because, in temporal lobe epilepsy, all of the brain areas are highly synchronized. We visually inspected the raw EEG recordings before and during the seizure onsets and found a similar semiological pattern of the seizure onset electrodes from the L(T)D areas initiated a highly organized rhythmic patterns and the patterns started to propagate throughout all the brain areas. We initially speculated that the epileptogenic areas could be the ones that are highly synchronized long before a seizure onset. In the previous case, we observed that the L(T)D electrodes are the ones that started the seizure evolution. However, in a further investigation of EEG recordings from the same patient, we found some contrasting results. The electrode selection pattern of the maximum clique demonstrated a very highly synchronized group of electrodes in both left and right orbitofrontal areas during the 2-hour period preceding the seizure (Fig. 6). After visual inspection on the raw EEG recordings, this seizure was initiated by the R(T)D area. Generally, it is known that the orbitofrontal areas communicate with each other more than other parts of the brain. This has led us to the conclusion that the brain areas that are selected to be in the maximum clique are the vulnerable brain areas, rather than the epileptogenic areas. In other words, the brain area(s) that are highly synchronized could be governed or manipulated by the epileptogenic areas so that they continuously show strong neuronal communication through the synchronization of EEG signals (measured by cross-mutual information).

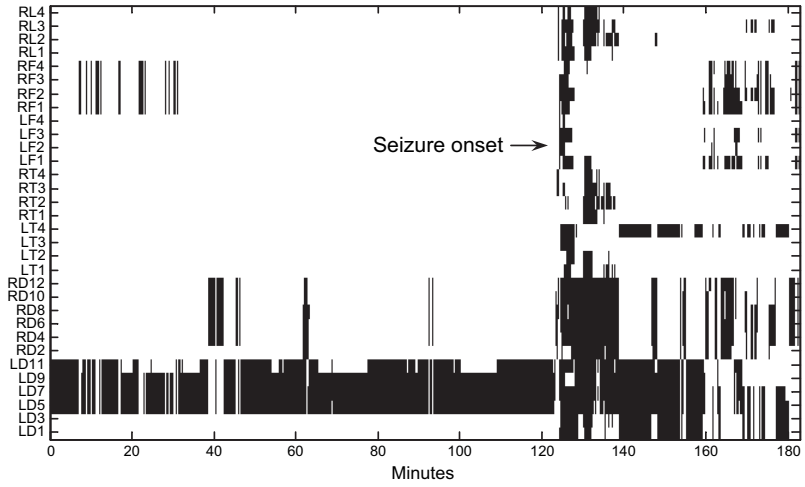

Fig. 4. Electrode selection of the maximum clique in the brain network over a 3-hour period (2 hours before and 1 hour after a seizure). The black area represents the selected electrodes in the maximum clique set. Note that the LD area tends to be very active during the 2-hour period before the seizure.

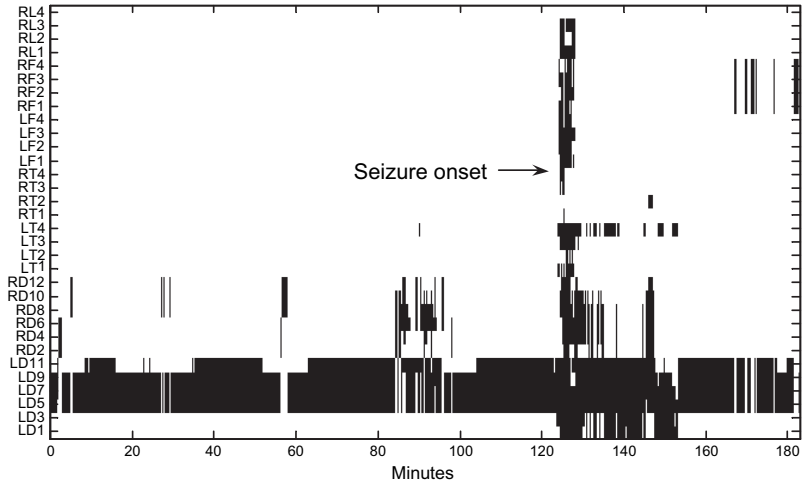

Fig. 5. Electrode selection of the maximum clique in the brain network over a 3-hour period (2 hours before and 1 hour after a subsequent seizure after the seizure shown in Fig. 4). The black area represents the selected electrodes in the maximum clique set. Note that the activity pattern in the brain network is similar to that in Fig. 4. The brain also manifested a very high connectivity in the LD area preceding the seizure.

Implications of the results

In normal brain functions, the orbitofrontal areas (both left and right) of the brain are highly synchronized active most of the time as it is considered to be the brain's executive function, and the temporal lobe areas are separated into left and right cortical hemispheres that work independently from each other. We hypothesized that this operation in the brain should be applied to the epileptic brains, even in the pre-seizure period. As we predicted, from the spectral partitioning results, both left and right orbitofrontal areas were also highly synchronized and active as well as right and left temporal lobe areas during the pre-seizure state. This suggests that the epileptogenetic processes slowly develop themselves through a regular communication channel in the brain network, rather than abruptly disrupt, collapse, or change the way brains communicate. From this observation, we postulate that this phenomenon may be a reflection of neuronal recruitment in seizure evolution. This observation confirms our first hypothesis. In addition, we found that nodes in the brain network are clustered during the seizure evolution.

Most brain areas seem to be communicating with their physiological neighbors during the process. The key process of seizure evolution could be the step where the epileptogenic area(s) govern or manipulate the other vulnerable or easily synchronized brain areas to communicate

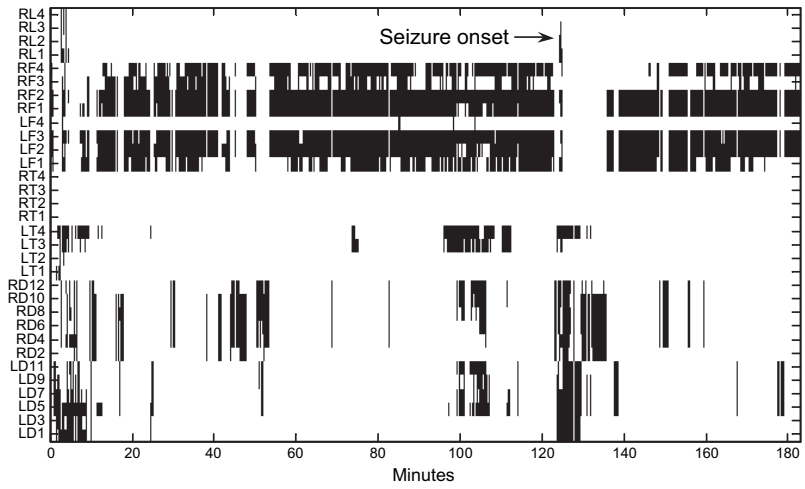

Fig. 6. Electrode selection of the maximum clique in the brain network over a 3-hour period (2 hours before and 1 hour after another seizure far away from the ones shown in Figs. 4 and 5). The black area represents the selected electrodes in the maximum clique set. Note that the activity pattern in the brain network is very different; a high degree of connectivity in the orbitofrontal areas (both left and right) preceding the seizure is apparent.

with their neighbors. This can be viewed as a recruitment of other brain areas done by the epileptogenic area(s). In most cases, the recruitment of seizure development should start with a weaker group, which in our case is represented by a vulnerable brain area. After enough neurons have been recruited, the disorders of epileptic brains spread out abnormal functions from than localized areas of cortex or other vulnerable areas throughout the cortical networks and the entire brain network. This phenomenon was shown by the results of our maximum clique approach, which confirms our second hypothesis. In addition, a different type of maximum clique patterns may be useful in the identification of incoming seizures. This study suggests that, in the future, this framework may be used as a tool to provide practical seizure interventions. For example, one can locate and stimulate the brain areas that seem to be vulnerable to the seizure evolution by electrical pulses through the monitoring process of the maximum clique. This will drastically reduce the risk of seizure to epilepsy patients.

Discussion and future work

We attempted to study seizure evolution by investigating some neuronal interactions among different brain areas. Analyzing multidimensional time series data like multichannel EEG recordings is a very complex process. The study of the brain network needs to involve the neuronal activities from not only a single source or a small group of sources, but also the entire brain network. Here we applied the cross-mutual information technique, a measure widely used in the information theory, to capture the neuronal interactions through the brain's synchronization patterns. Then we modeled the global interactions using network/graph-theoretic approaches, spectral partitioning and maximum clique. These approaches are used to generalize the brain network investigation to capture synchronization patterns among different sources (brain areas). The idea of analyzing EEG recordings from several sources (multiple electrodes) is very crucial since the knowledge from local information (i.e., single electrode) is very limited. In our future study, we plan to incorporate the knowledge of general brain communication in the brain network. For example, Anderson (2007) demonstrated the evolution of cognitive function through quantitative analyses of fMRI data.

The proposed framework can provide global structural patterns in the brain network and may be used in the simulation study of dynamical systems (like the brain) to predict oncoming events (like seizures). For example, an ON/OFF pattern of electrode selection in the maximum clique over one period of time can be modeled as a binary observation in a discrete state in a Markov model, which can be used to simulate the seizure evolution in the brain. In addition, the number of electrodes in the maximum clique

can be used to estimate the minimum number of features and explain dynamical models or the parameters in time series regression. Note that the proposed network model represents an epileptic brain as a graph, where there exist several efficient algorithms (e.g., maximum clique, shortest path) for finding special structure of the graph. This idea has enabled us, computationally and empirically, to study the evolution of the brain as a whole. The Monte-Carlo Markov Chain (MCMC) framework may be applicable in our future study on long term EEG analysis. The MCMC framework has been shown very effective in data mining research (Andrieu *et al*. 2003). It can be used to estimate the graph or clique parameters in epileptic processes from EEG recordings. Since long term EEG recordings are very massive, most simulation techniques are not scalable enough to investigate large-scale multivariate time series like EEGs. The use of MCMC makes it possible to approximate the brain structure parameters over time. More importantly, the MCMC framework can also be extended to the analysis of multi-channel EEGs by generating new EEG data points while exploring the data sequences using a Markov chain mechanism. In addition, we can integrate the MCMC framework with a Bayesian approach. This can be implemented in on-line simulation-based brain clique estimation scheme, which employs sequential sampling, electrode selection (maximum clique), and MCMC moves. Although the implementation of this MCMC framework remains to be further investigated, we expect that this framework will be very fast and efficient.

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