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Investigation of network brain dynamics from EEG measurements in patients with epilepsy using graph-theoretic approaches

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***Abstract*—'Small-world' neuronal networks are characterized by strong clustering in combination with short path length, and assist the progress of synchronization and conceivably seizure procreation. In this article we aim to investigate if the brain networks display 'small-world' features during seizures, by using graph-theoretic measures as well as scalp EEG recordings from patients with focal and generalized epilepsy.**

Specifically, we used linear cross-correlation to characterize patterns between nodes in scalp EEG recordings of 5 patients for 3 periods of interest: before, during and after seizure onset. For each period we reconstruct graphs from the linear cross-correlation calculations and use different network measures to characterize the graphs such as clustering coefficient, characteristic path length, betweenness centrality and network small-world-ness.

In three (out of five) patients, our results suggest that shortly after seizure onset and in the early postictal period the brain network changes towards a more small-world structure, in agreement with earlier graph-theoretic based results related to epilepsy. However, for one patient the opposite was observed: small-worldness decreased after seizure onset. Finally, for one patient we could observe no differences in the network properties before and after the onset. These preliminary results suggest the potential use of graph-theoretic measures to quantify brain dynamics before and during seizures after further refinements.

***Index Terms*—Epilepsy, EEG, complex networks, graph theory, small-world.**

I. Introduction

Epilepsy is one of the most common neurological disorders of the brain, characterized by sudden and unpredictable seizures. It is a condition that affects 0.6-0.8% of the world population, and in 25% of the epileptic patients seizures cannot be controlled by anti-epileptic drugs or surgery [1]. It is essential for a patient to have a warning that a seizure is about to occur in order to avoid potentially endangering situations. Moreover, reliable seizure prediction algorithms would enable the implementation of closed loop therapeutic strategies [2].

The scientific community has continuously performed research towards improvement and development of automated seizure detection and prediction algorithms based on electroencephalographic (EEG) measurements, in order to characterize the transition from the interictal to the ictal state (pre-ictal phase) in quantitative terms [3]. Most of these algorithms are based on linear and non-linear time series analysis techniques of pre-seizure changes in the dynamics of either intra-cranial or scalp EEG recordings [1], [4]–[6]. However, the reported results are not always reliable and/or reproducible, often due to the large number of false positives.

In the last decade, many researchers use 'complex network analysis' —a methodology based on graph theory, that describes important properties of complex systems— to investigate the brain, which in this context is considered as a complex network of dynamical systems [7] underlying functional interactions in closely related brain areas [8]. In order to understand the brain's function and dysfunction, it is important to evaluate the strength, as well as the temporal and spatial patterns of both anatomical and functional brain networks. Different types of networks, such as random, small-world and scale-free networks, might possibly support effective and fixed globally synchronized dynamics [9]–[11]. It is reported that there is a correlation between statistical network properties (such as degree and clustering coefficient) and network synchronization. Some studies which concentrate on the correlation between structural properties of networks and the dynamics of these networks demonstrate evidence that epileptic seizures are correlated with changes in functional network features [12]. Moreover, global and local changes in network topology have been reported during the preictal and interictal phases [13], indicating specific brain regions that may facilitate seizures and might be potential targets for focal therapies. During the seizure it was observed that these networks developed through an obvious topological progression [14], where the topology changed severely in organization but the overall synchronization changed only weakly.

In this paper we apply EEG-based graph theoretic approaches, which can assess the activation patterns of the brain

TABLE I
EPILEPTIC PATIENTS

Patient No.	No.of Seizures	Seizure Onset
1	1	Focal Onset
2	2	Focal Onset
3	2	Focal Onset
4	1	Generalized
5	1	Generalized

network during the pre-ictal and ictal phases. We use different graph theoretic measures (such as degree, clustering coefficient and path length) in order to investigate the characteristics of the brain network for each patient. We apply commonly used measures of local and global connectivity and provide the relation between network properties and dynamical processes in these networks. Finally, we determine the effect of EEG seizures on neural network properties and discuss the results in comparison with the literature.

Similar network measures have been used to study the brain activity recorded from intracranial EEG signals of epileptic patients. However, they have rarely been used for non-invasive scalp EEG measurements. Moreover, to the best of our knowledge, some of the network measures we examine here have not been applied before on epileptic brain networks.

II. METHODS

A. Data acquisition

Long-term EEG recordings were collected in the Neurology Ward of the Cyprus Institute of Neurology and Genetics. The recordings were obtained using the Neuroworks XLTEK system, at a sampling rate of 200Hz and filtered between 0.5–50 Hz. Brain activity was recorded using a bipolar electrode montage of twenty one electrodes which were placed according to the 10-20 international system with two additional anterotemporal electrodes. Also, another four electrodes were used to record the electrooculogram (EOG) and electrodardiographic (ECG) signals, respectively. We obtained data from 5 patients, as shown in Table I. All seizures have been identified visually and marked by specialized neurologists.

B. Functional network construction

The nodes in our network represent the scalp electrodes that monitor the brain activity of each patient. Two nodes are connected with an edge if the correlation between the time series recorded at the two electrodes is sufficiently high. Common measures for estimating the correlation between pairs of time series include cross-correlation, coherence, synchronization likelihood, and Granger causality among others (see e.g. [15] for a review). In this work, the correlation measure of choice is the simple linear cross-correlation, one of the most commonly used measures for estimating EEG signal correlation.

For each patient, we examine a fraction of the recorded data 15 minutes before and 15 minutes after the seizure onset. We process the data in 10-second non-overlapping windows and construct one functional network for each such window. Edges are calculated following a process similar to that in [13]: the 10-sec window is split into 20 segments, each of duration 1 sec and overlapping with the previous by 0.5 sec. Within each 1-sec subwindow the cross-correlation of each pair of electrodes is calculated, allowing time-shifts of length at most 250ms. Subsequently, we consider the maximum absolute cross-correlation among all subwindows as a representative of the correlation between the particular pair of electrodes. If this value exceeds the threshold of 0.75, the pair of electrodes (nodes) is regarded to be connected, otherwise it is not. We experimented with thresholds between 0.6 and 0.9 obtaining similar results overall. Note that the networks we construct are binary and undirected.

C. Network Measures

We examined the patients' brain state at various times before, during and after the seizure, by analysing the functional networks constructed as described above, using the measures explained in the current section. In the definitions below, let N denote the set of all nodes of the network and n the number of such nodes.

1) Average degree: the degree, k_i, of a node i is defined as the number of other nodes in the network to which node i is connected (equivalently, the number of edges adjacent to i). The average degree among all nodes in the network gives a picture of how well connected the graph is.

$$K = \frac{1}{n} \sum_{i \in N} k_i$$

2) Characteristic (or, average) path length: the shortest (or *geodesic*) path length, $d_{i,j}$ between a pair of nodes, i and j, is the minimum number of edges that have to be traversed to get from node i to j. Then the *characteristic path length* is defined as the average shortest path length over all pairs of nodes in the network. This measure too provides an indication of how well integrated the graph is.

$$L = \frac{1}{n(n-1)} \sum_{i,j \in N, i \neq j} d_{i,j}$$

3) Global Efficiency: The efficiency of a path between two vertices is defined as the inverse of the shortest distance between the vertices. When such a path does not exist, the efficiency is zero. *Global efficiency* [16] is the average efficiency over all pairs of nodes.

$$E = \frac{1}{n(n-1)} \sum_{i,j \in N, i \neq j} \frac{1}{d_{i,j}}$$

It is inversely related to the characteristic path length.

4) Clustering coefficient: it indicates how 'clustered' the network is, that is, it identifies groups of nodes that are largely connected with other nodes in the same group, but have a much smaller number of connections to nodes outside their group. Formally, the *clustering coefficient* [17] of a node i is

$$C_i = \frac{2t_i}{k_i(k_i - 1)}$$

where k_i is the degree of node i, and t_i denotes the number of edges between neighbours of i. Then the global clustering coefficient, C, of the network is defined as the mean clustering coefficient among all nodes.

$$C = \frac{1}{n} \sum_{i \in N} C_i$$

5) Betweenness centralization: the measure of *betweenness centrality* [18], b_i, of a node i measures how many geodesic paths between any pair of nodes pass through i. It is a measure of the 'importance' of a node; the higher the betweenness centrality the more shortest paths will need to be re-routed in case of damage to that node. Formally,

$$b_i = \sum_{j,k \in N, j \neq k} \frac{n_{j,k}(i)}{n_{j,k}}$$

where $n_{j,k}$ is the number of shortest paths between j and k, and $n_{j,k}(i)$ is the number of such paths that pass through node i. Then, *betweenness centralization* [19] is a measure that summarizes the variation in betweenness centrality in the network. It is defined as the ratio of the variation in betweenness centrality among all nodes in the network to the maximum such variation in any network of the same size.

6) Network Small-worldness: a network is called *small-world* when it is highly clustered (large C) while at the same time it has a small characteristic path length (L) [17]. The *network small-worldness* [20] measures how close to being small-world a network is. Formally, it is defined as

$$S = \frac{C/C_{rand}}{L/L_{rand}}$$

where C and L are the clustering coefficient and the characteristic path length of the network, while C_{rand} and L_{rand} are those of a random network of the same size, respectively. Values $S \gg 1$ indicate that the network is small-world.

A more detailed discussion on these measures can be found in [21]. In Matlab, the Brain Connectivity Toolbox (BCT) [22] implements a number of these measures, while we created our own implementations for those measures not found in BCT.

III. Results

Among the 5 patients and 7 seizures that we applied our methods to, patients 2, 4 and 5 (4 seizures in total) yielded similar results. In this section we present the results corresponding to the second seizure of Patient 2, which is representative of this group of patients. On the other hand, Patient 1 yielded different results, as we will explain later in this section, while Patient's 3 brain network exhibited similar characteristics during the preictal, ictal and postictal periods.

A. Patients 2, 4 and 5

Figure 1 presents Patient's 2 brain network at various stages before, during and after the second seizure. By eye inspection alone, one can see that at seizure onset the network has a similar structure as before the seizure, but a few seconds later

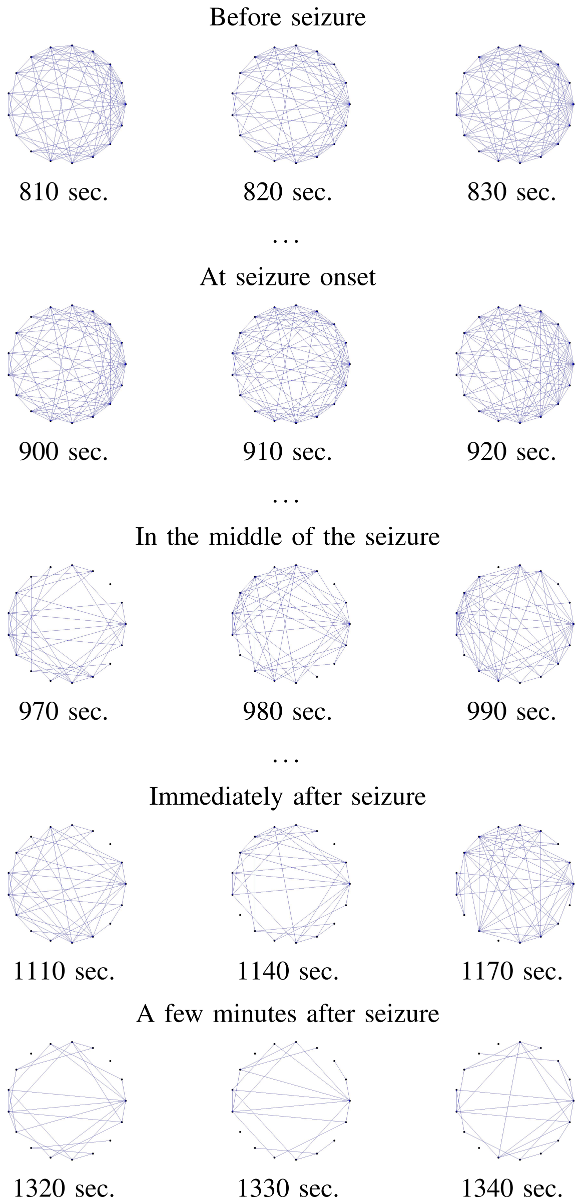

Fig. 1. Some indicative networks from the preictal, ictal and postical regions of the seizure. In this work, we examine 15 min. before and 15 min. after the seizure onset; hence, in the graphs above, the seizure occurs at 900 sec. (15 min.)

and while the seizure is still in progress, the connectivity is reduced significantly, while at the same time the characteristic path length remains low suggesting a small-world network. This process of connectivity reduction continues several minutes after the seizure ends and the network demonstrates a peak in its small-worldness several minutes later.

Figure 2 depicts the changes in the network measures in the 30 min. interval of interest. The average node degree at seizure onset is the same as before the seizure, then it starts decreasing several seconds after the onset and continues decreasing until a few minutes after the onset, where it gets its minimum value; finally, it increases again but not to its values before

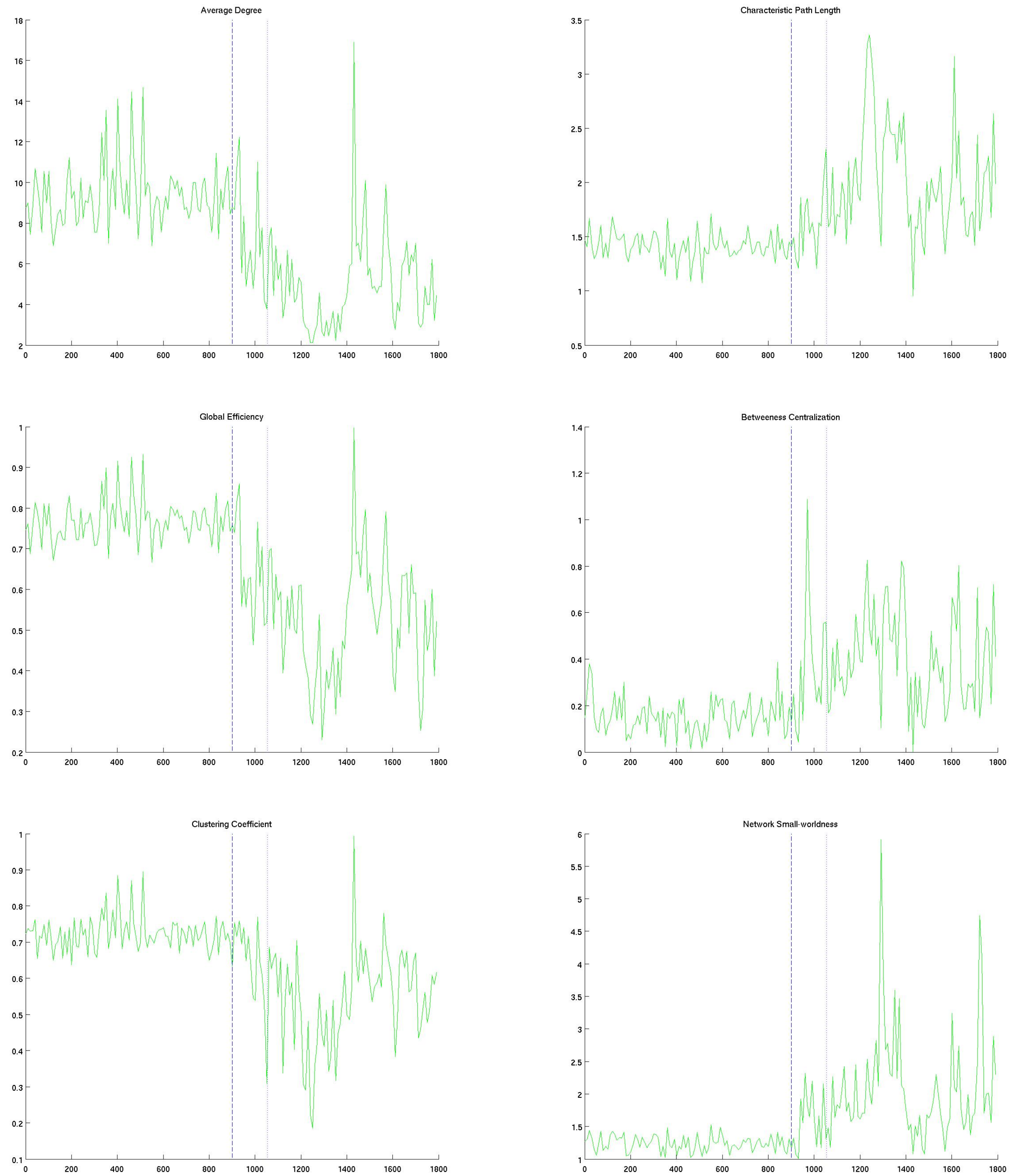

Fig. 2. Network measures for the whole of the observed period (15 minutes before and 15 minutes after the seizure onset). The dashed line indicates the seizure onset while the dotted line denotes its end.

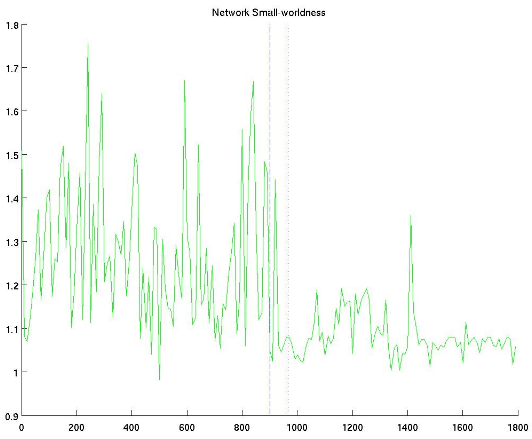

Fig. 3. Network small-worldness of Patient 1.

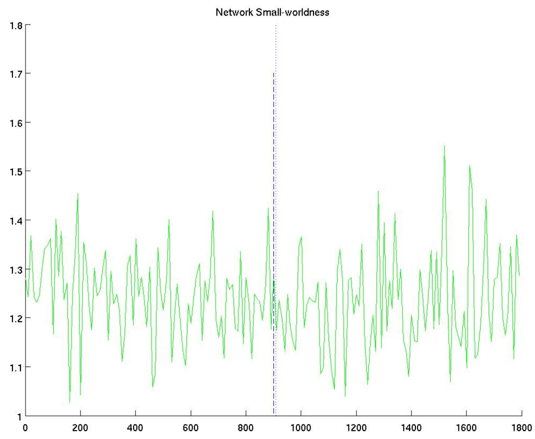

Fig. 4. Network small-worldness of Patient 3.

the seizure onset. Global efficiency follows the same trend as the average degree, while the characteristic path length exhibits the opposite trend. Both of these results are what one would expect: a lower node degree implies longer paths between pairs of nodes and hence reduced global efficiency. Global clustering also follows a decreasing trajectory after the seizure, while betweenness centralization and network small-worldness both increase.

Our results are in agreement with earlier research on epilepsy using graph-theoretic measures, despite having used a different setting. Kramer et al. [13] used intractranial EEG recordings and examined preictal and ictal networks; they too observed a decrease in the average node degree and an increase in the average path length, the betweenness centralization and the network small-worldness at the ictal interval. Ponten et al. [12] used the synchronization likelihood [23] for estimating the functional connectivity of the EEG and they too discovered an increase in network small-worldness at the late ictal and postictal states.

B. Patient 1

For Patient 1, all measures we computed for the brain networks exhibited the exact opposite trend to that of Patients 2, 4 and 5. In particular, the average degree, the global efficiency and the clustering coefficient all increased, while the characteristic path length, the betweenness centralization and the small-worldness decreased. In Figure 3, for example, we show the network small-worldness of Patient 1.

C. Patient 3

The brain networks of Patient 3 showed no obvious changes at any time before or after the seizure onset. As in Figure 4, where the network small-worldness is shown, all the network measures we examined for this patient remained relatively constant throughout the 30 min. period.

IV. Discussion & Conclusion

We constructed functional brain networks of seven seizures from five patients and investigated the characteristics of these networks using the average degree, the characteristic path length, the global efficiency, the cluestering coefficient, the betweenness centralization and the network small-worldness. In three patients, our results agree with earlier graph-theoretic research on epileptic patients.

On the other hand, for two patients (3 seizures) we observed different patterns in the network analysis. In particular, for Patient 1 we obtained opposite trends in all measures in comparison to Patients 2, 4 and 5. This difference can be attributed to the fact that Patient 1 had a complex partial seizure with secondary generalization as opposed to focal (Patient 2) and generalized (Patients 4 and 5). On the other hand, the structure of the brain network of Patient 3 did not change throughout the experiment. This can be explained by the fact that the epileptic event occurred during sleep; ictal changes took place only in the left temporal area and the doctors could clearly spot that neuron recruitment was taking place, but it involved only a small part of the brain.

In conclusion, although clear trends are visible in some patients, our results are not homogeneous among all patients. Further research is required on different types of functional networks and/or measures, such as using other linear and non-linear correlation functions, experimenting with larger correlation windows, and exploring weighted (rather than binary) networks, among others. Moreover, the identification of particular nodes that change during epilepsy is of significant interest, however, more patients are needed to validate the presence of such nodes. We intend to carry out this research on a larger number of patients for more conclusive results.

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