Periodicity in functional brain networks: Application to scalp EEG from epilepsy patients*

Manolis Christodoulakis[1], Avgis Hadjipapas[2], Eleftherios S. Papathanasiou[3], Maria Anastasiadou[1], Savvas S. Papacostas[3] and Georgios D. Mitsis[4]

***Abstract*— Seizure detection and prediction studies using scalp- or intracranial-EEG measurements often focus on short-length recordings around the occurrence of the seizure, normally ranging between several seconds and up to a few minutes before and after the event. The underlying assumption in these studies is the presence of a relatively constant EEG activity in the interictal period, that is presumably interrupted by the occurrence of a seizure, at the time the seizure starts or slightly earlier. In this study, we put this assumption under test, by examining long-duration scalp EEG recordings, ranging between 22 and 72 hours, of five patients with epilepsy. For each patient, we construct functional brain networks, by calculating correlations between the scalp electrodes, and examine how these networks vary in time. The results suggest not only that the network varies over time, but it does so in a periodic fashion, with periods ranging between 11 and 25 hours.**

I. INTRODUCTION

Epilepsy is one of the most common neurological disorders of the brain affecting $0.6-0.8\%$ of the world population. It is characterized by sudden unpredictable seizures, caused by abnormal electrical activity in the brain. The scientific community has continuously performed research for the development of automated seizure detection and prediction algorithms based on electroencephalographic (EEG) measurements, in order to characterize the transition from the inter-ictal to the ictal state (see e.g. [4], [3], [7]). A key goal is to be able to detect significant deviations from the so-called inter-ictal state in signal properties. To this end, knowledge of the baseline (inter-ictal) state properties is vital.

In the current study, we examine the baseline properties of long-duration scalp EEG data in patients with epilepsy — continuous recordings spanning $22-72$ hours. Earlier studies on long-duration scalp and intracranial EEG data have also revealed the appearance of the circadian rhythm and its influence on measures characterizing the EEG. Kreuz et al. [5] observed that some channel combinations reflect the circadian rhythm resulting approximately in a 24-hour periodicity. Schad et al. [8] also observed the presence of the circadian rythm in features extracted from the EEG data. Navarro et al. [6] showed that different vigilance states have an influence on EEG measures. Schelter et al. [10] studied the distribution of false predictions with regards to the circadian rhythm and their relation to the sleep-wake cycle, and revealed that the majority of false predictions in non-REM sleep are associated with sleep stage II. More recently, Schelter et al. [9] presented a strategy to avoid false seizure predictions by taking into consideration the circadian rhythms and using adaptive thresholds.

Here, for each patient, we constructed one functional brain network every 5 seconds, where the nodes represent the areas on the scalp around each electrode and the node connections represent correlations between these brain areas. Subsequently, we use graph-theoretic measures to investigate properties of the resulting functional networks, including the average degree of the network, its global efficiency and its clustering coefficient. For all three measures, we observed clear periodic patterns, of duration between 11 and 25 hours, depending on the patient, that occurred regardless of the presence of seizures. In addition, since graphs with similar network measure values may have different structure, we compared this structure at different times using the graph edit distance. The results revealed the same patterns of periodicity observed for the aforementioned network measures.

To our best knowledge, this is the first time that properties of the functional brain networks in patients with epilepsy are examined using network-based measures over long time periods. The occurrence of periodic patterns in these networks is an important finding, highlighting the necessity for monitoring long-duration data when designing automated seizure detection or prediction algorithms in order to obtain more reliable results.

II. METHODS

A. EEG recordings

Long-term EEG recordings were collected at the Neurology Ward of the Cyprus Institute for Neurology and Genetics. Twenty-one electrodes were placed according to the $10-20$ international system with two additional anterotemporal electrodes. The data were recorded using the XLTEK system, at a sampling rate of 200Hz using a cephalic reference. A 50Hz Notch filter was applied to remove line noise and subsequently the signals were band-pass filtered between 1

*This work was partially supported by the European Regional Development Fund and the Republic of Cyprus through the Research Promotion Foundation (Project ΥΓΕΙΑ/ΔΥΓΕΙΑ/0609(ΒΕ)/11).

[1]M. Christodoulakis and M. Anastasiadou are with the Department of Electrical and Computer Engineering, University of Cyprus, Nicosia, Cyprus {manolisc,manast09}@ucy.ac.cy

[2]A. Hadjipapas is with St George's University of London Medical Programme at the University of Nicosia, Medical School, Nicosia, Cyprus and with St George's University of London, London, UK hadjipapas.a@unic.ac.cy

[3]E. S. Papathanasiou and S. S. Papacostas are with The Cyprus Institute for Neurology and Genetics, Nicosia, Cyprus {neurophy,savvas}@cing.ac.cy

[4]G. D. Mitsis is with the Department of Electrical and Computer Engineering, University of Cyprus, Nicosia, Cyprus and with the Department of Bioengineering, McGill University, Montreal QC, Canada gmitsis@ucy.ac.cy

978-1-4244-7929-0/14/$26.00 ©2014 IEEE

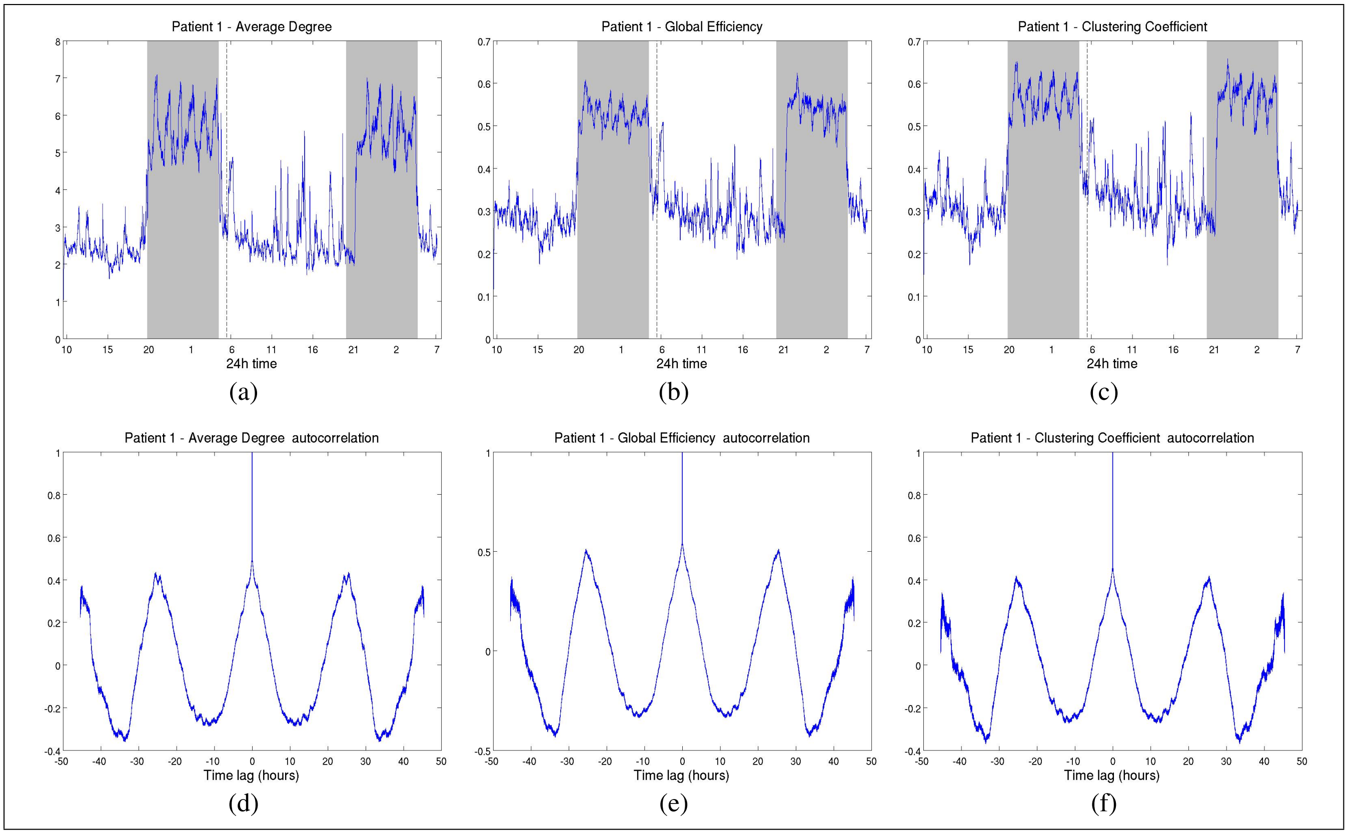


Fig. 1. Average degree (a), global efficiency (b), and clustering coefficient (c) of the functional brain network of Patient 1 as a function of time. For presentation purposes, the measures have been smoothed. The vertical dashed line indicates the seizure onset and the grey bars show sleep intervals. A clear pattern of repetition can be observed in all three measures, with duration approximately 25 hours. The autocorrelations of the three measures over the time lag (d–f) are also periodic with a period around 25 hours, confirming the aforementioned results in (a), (b), (c).

and 45Hz. Finally, the data was converted to the *bipolar* montage — where pairs of electrodes placed in nearby locations of the scalp are used to obtain the time-series by subtracting the corresponding measurements — as this representation seems to be more robust to volume conduction effects [1].

In this work, we analyzed long-duration data from five patients with epilepsy. Table I summarizes the duration of the recordings, as well as the number and type of seizures of each patient. Seizures were identified and marked by expert neurophysiologists (coauthors ESP and SSP).

TABLE I
EEG RECORDINGS

Patient	Length of Recording	Number of Seizures	Type of Epilepsy
1	47 h	1	Focal
2	22 h	2	Focal
3	68 h	2	Focal
4	94 h	1	Generalized
5	66 h	1	Generalized

B. Functional Network Construction

The data has been processed in 5-second non-overlapping windows. Within each window, the normalized cross-correlation was calculated pairwise, between each pair of the bipolar time series, and whenever the correlation exceeded a pre-specified threshold the corresponding pair was considered as being connected. This process results in the construction of one functional brain network per 5-sec window. Subsequently, we examined the evolution of this network over time, specifically looking for long-term (several hours) periodicities. We experimented with window sizes ranging between 5 and 20 sec. and with thresholds between 0.4 and 0.9 obtaining similar results overall.

Network evolution was monitored firstly by observing three global network properties: the average degree (average number of connections per node), the global efficiency (average inverse distance between pairs of nodes) and the clustering coefficient (average per node connectivity between the node's neighbours). The periodicity of each of the observed network properties was further quantified by computing the normalized autocorrelation of the respective network measures' time series.

In addition to examining the network properties, we also investigated whether periodicities exist in the structure of the networks themselves. The measure of graph edit distance

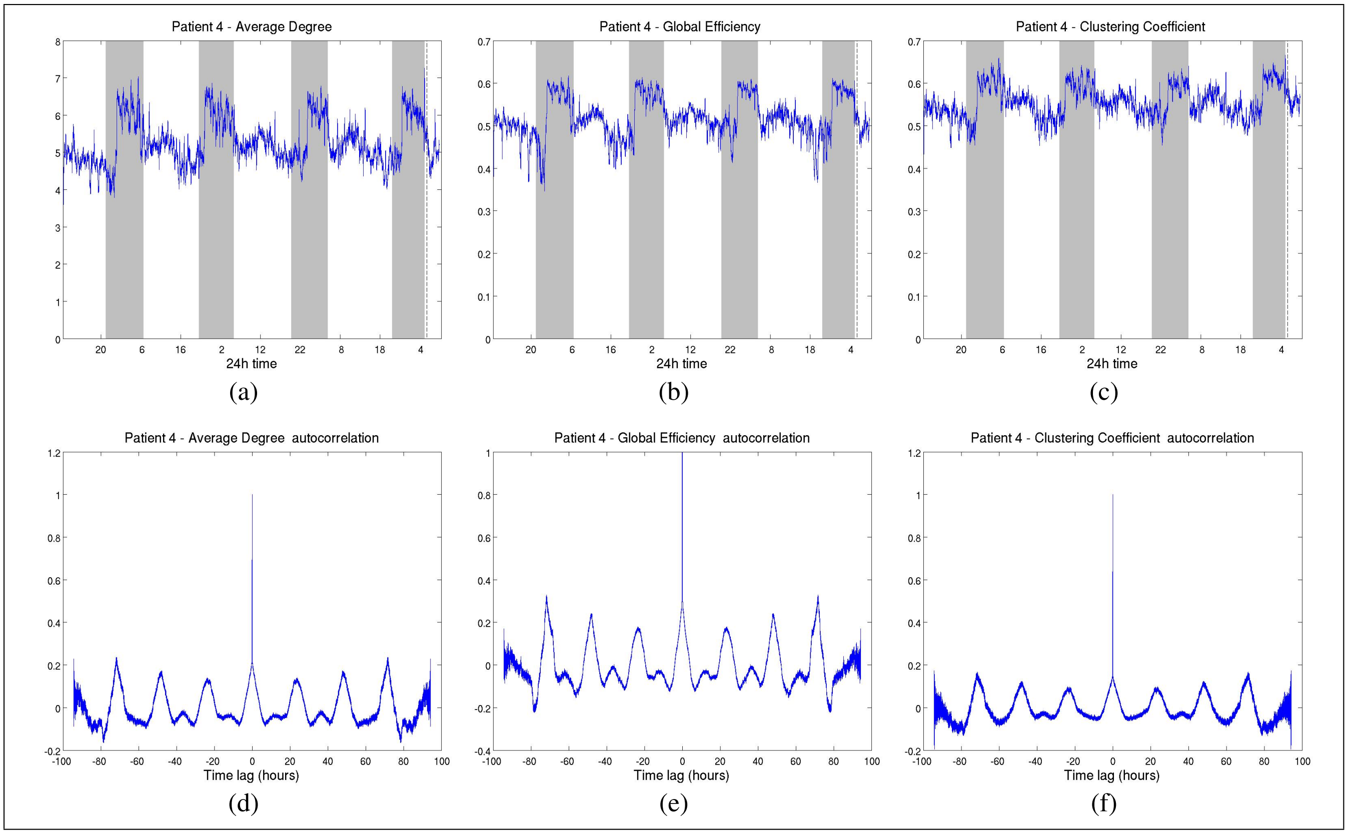


Fig. 2. Average degree, global efficiency, and clustering coefficient (a–c) of the functional brain network of Patient 4 and their corresponding autocorrelation sequences (d-f). A period of approximately 24 hours can be observed.

[2] was used to estimate graph similarity (or dissimilarity in this case), whereby the distance between two graphs that consist of the same set of nodes, is defined as the minimum number of edge insertions and deletions that must take place to convert one graph into the other. The periodicity in the network structure was quantified by computing the average (dis-)similarity (in terms of graph edit distance) of the sequence of networks with time-lagged copies of these networks.

III. RESULTS

A. Periodicities in network properties

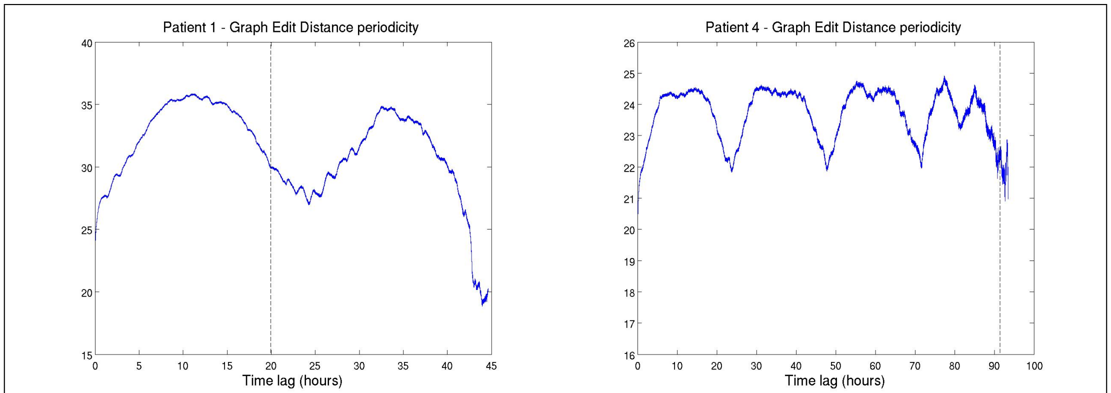
Fig. 1 illustrates the evolution of the average degree, the global efficiency, and the clustering coefficient for the functional brain network of Patient 1 over time, together with their respective autocorrelation sequences. Directly from the course of the three measures, a clear periodic pattern is visible: observe, for instance, an increase in the measures at approximately 8 p.m. followed by a decrease at 4 a.m. when the patient wakes up, and the pattern is repeated at about 9 p.m. the following day. The existence and exact duration of the periodic pattern is further demonstrated by computing the unbiased estimate of the autocorrelation function of each of the three network measures. In the corresponding figures (Fig. 1, d-f), the period can be clearly observed at approximately 25 hours, confirming our initial observations from the evolution of the three network measures.

For Patients 2, 3, and 4 similar patterns of periodicity were observed as in the case of Patient 1. Fig. 2 illustrates the three network measures and their corresponding autocorrelations for Patient 4. Again the repeating pattern is very clear, with a period of approximately 24 hours. Similarly, for Patient 2 the fundamental period was 11 hours, while for Patient 3 it was 23 hours. For Patient 5 no periodic pattern was observed, neither by eye inspection nor by the autocorrelations of the measures. It is possible that weaker and perhaps nonlinear correlations are present in this patient's EEG, which cannot be captured by a simple autocorrelation.

B. Periodicities in graph structure

Each of the network measures we examined in the previous section summarizes one important aspect of the network. When viewed independently, the measures do not give the entire picture; consider for instance a network with average degree 5: does each node have degree 5, or do most nodes have low degree and a few "hubs" possess a large number of connections, increasing the average to 5? However, in combination, the three measures describe the network in a much more informative way. Consequently, the fact that all three measures demonstrated the exact same periodicity in each patient, strongly suggests that the networks themselves may have had a very similar structure.

To demonstrate this fact, we performed direct comparisons of the networks, in addition to the indirect, through their



(a) (b)

Fig. 3. The periodicity in the network structure, as a function of the time lag, in terms of the graph edit distance of Patients 1 (a), and 4 (b).

properties, comparison. The measure of graph edit distance was used to compare pairs of graphs. We identified periodicities in the network structure by performing a form of "autocorrelation" on the vector of the consecutive, over time, graphs: a copy of the vector was shifted and aligned against itself and the average graph edit distance was calculated for all pairs of graphs of the particular alignment.

Fig. 3 shows the periodicities of the functional brain networks of Patients 1 and 4, in terms of their structure as computed by the graph edit distance. Note, that similarity is now indicated by local *minima*. The periods identified by this measure were similar to those calculated by the network measures, for all four patients that had periodicities, confirming our initial findings.

IV. CONCLUSIONS

In this paper, we have demonstrated that periodic patterns occur in the functional brain networks obtained from scalp EEG recordings of patients with epilepsy. First, we applied graph-theoretic measures, such as the average degree, the global efficiency and the clustering coefficient, and discovered that these network properties evolved in a periodic manner. These results suggest that the functional brain network itself has similar structure over periods of time, however they do not form a direct proof of the fact. For this reason, in addition to examining the network properties, we compared the networks in terms of their structure by means of the graph edit distance. Again, the same patterns of periodicity were observed confirming the initial results suggested by the network properties.

These periodicities may be possibly related to the well known circadian rhythm of approximately 24 hours, or, in some cases, the circasemedian rhythm of approximately 12 hours. Although the existence of both notions of circadian and circasemedian rhythms are well established, it is an important finding that these rhythms are reflected on scalp EEG measurements —and subsequently on the functional brain networks obtained from them. It appears that long-term variability may be much larger than short-term variability, including seizure-related modulations, and hence is likely to affect the performance of seizure detection and prediction algorithms. We believe that such algorithms will benefit by taking into consideration the expected underlying activity when looking for abnormalities in the EEG.

In future work, we aim exploring the effect of the seizure occurrence in the underlying repeating rhythm in more detail. To this end, we intend to perform similar analysis on EEG data from patients with psychogenic seizures, for whom there is no abnormal electrical activity in the brain during seizures, and compare them to patients with epilepsy.

REFERENCES

[1] M. Christodoulakis, A. Hadjipapas, E. S. Papathanasiou, M. Anastasiadou, S. S. Papacostas, and G. D. Mitsis. Graph-theoretic analysis of scalp EEG brain networks in epilepsy – the influence of montage and volume conduction. In *Proc. 13th BIBE*, 2013.

[2] P. J. Dickinson, H. Bunke, A. Dadej, and M. Kraetzl. On graphs with unique node labels. In Edwin Hancock and Mario Vento, editors, *Graph Based Representations in Pattern Recognition*, volume 2726 of *LNCS*, pages 13–23. Springer Berlin Heidelberg, 2003.

[3] M. A. Kramer, U. T. Eden, K. Q. Lepage, E. D. Kolaczyk, M. T. Bianchi, and S. S. Cash. Emergence of persistent networks in long-term intracranial EEG recordings. *The Journal of Neuroscience*, 31(44):15757–15767, 2011.

[4] M. A. Kramer, E. D. Kolaczyk, and H. E. Kirsch. Emergent network topology at seizure onset in humans. *Epilepsy Res.*, 79(2–3):173–86, 2008.

[5] T. Kreuz, R. Andrzejak, F. Mormann, A. Kraskov, H. Stögbauer, C. E. Elger, K. Lehnertz, and P. Grassberger. Measure profile surrogates: A method to validate the performance of epileptic seizure prediction algorithms. *Physical Review E*, 69(6):061915, 2004.

[6] V. Navarro, J. Martinerie, M. Le Van Quyen, M. Baulac, F. Dubeau, and J. Gotman. Seizure anticipation: Do mathematical measures correlate with video-EEGevaluation? *Epilepsia*, 46(3):385–396, 2005.

[7] S. C. Ponten, F. Bartolomei, and C. J. Stam. Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. *Clin. Neurophysiol.*, 118(4):918–27, 2007.

[8] A. Schad, K. Schindler, B. Schelter, T. Maiwald, A. Brandt, J. Timmer, and A. Schulze-Bonhage. Application of a multivariate seizure detection and prediction method to non-invasive and intracranial long-term EEG recordings. *Clin. Neurophysiol.*, 119(1):197–211, 2008.

[9] B. Schelter, H. Feldwisch-Drentrup, M. Ihle, A. Schulze-Bonhage, and J. Timmer. Seizure prediction in epilepsy: From circadian concepts via probabilistic forecasting to statistical evaluation. In *IEEE Engineering in Medicine and Biology Society*, pages 1624–1627, 2011.

[10] B. Schelter, M. Winterhalder, T. Maiwald, A. Brandt, A. Schad, J. Timmer, and A. Schulze-Bonhage. Do false predictions of seizures depend on the state of vigilance? A report from two seizure-prediction methods and proposed remedies. *Epilepsia*, 47(12):2058–2070, 2006.