Journal of Neurological Sciences [Turkish] **32:(2)**# 44; 361-371, 2015
http://www.jns.dergisi.org/text.php3?id=888

Research Article

Interhemispheric Correlation and Epileptic Seizures: Are They Related? A Preliminary Retrospective Study

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Summary

Objectives: For the purpose of predicting seizure activities in focal temporal lobe epilepsy we examined interhemispheric correlation coefficients in pre-ictal EEG data.
Materials and Methods: We used video-EEG data obtained from the İzmir Katip Çelebi University Atatürk Training and Research Hospital Neurology Department database to conduct preliminary retrospective analyses. 31 patients (mean age 32.3 ± 7.6; 17 female) diagnosed with focal temporal lobe epilepsy in 2010-2013 were randomly selected and a total of 52 seizures were analyzed. 20 sec pre-ictal EEG data were studied for each seizure. In order to observe the change in the correlation coefficients 20 sec pre-ictal EEG data were divided into 10 windows (each 2 sec). The furthest window to the seizure was labeled as 1st window, the closest window to the seizure was labeled as 10th window. Interhemispheric Pearson correlation coefficients were computed for each window in 9 electrode pairs. The variability of the correlation coefficients between windows was analyzed with Repeated Measures of ANOVA.
Results: Pearson correlation coefficients decreased significantly from the 1st window to the 10th window in the following electrode pairs: F7T1-F8T2; T1T3-T2T4; FP1F3- FP2F4; C3P3-C4P4 ($p<0.05$). Post hoc multiple comparison analysis revealed that the significant difference in correlation coefficients was mainly observed between the first two windows (0-4 seconds) before seizure onset and the last three windows (14-20 seconds) before seizure onset.
Conclusion: The results of the present study suggest that interhemispheric correlation may be applicable for the detection of epileptic seizures in EEG signals.

Key words: Focal Epilepsy; Electroencephalogram; Seizure prediction; Interhemispheric correlation

Interhemisferik Korelasyon ve Epileptik Nöbetler Arasında Bir İlişki Var mı? Retrospektif Ön Çalışma

Özet

Amaç: Fokal temporal lob epilepsisinde, nöbet aktivitesinin önceden kestirimini yapabilmek amacıyla nöbet öncesi EEG verisinde interhemisferik korelasyon katsayılarının incelenmesi amaçlanmıştır.
Gereç ve Yöntem: Bu retrospektif ön çalışmada İzmir Katip Çelebi Üniversitesi Tıp Fakültesi Atatürk Eğitim ve Araştırma Hastanesi Nöroloji Anabilim Dalı video-EEG veritabanından alınan veriler kullanılmıştır. 2010 -2013 yılları arasında fokal temporal lob epilepsi tanısı almış hastalardan 31 tanesi rastgele seçilmiş (ortalama yaş 32.3 ± 7.6; 17 kadın)

ve toplam 52 nöbet verisi analiz edilmiştir. Herbir nöbet için nöbet öncesi 20 s'lik EEG verisi analiz edilmiştir. Korelasyon katsayılarındaki değişimi gözlemek için nöbet öncesi 20 s'lik EEG verisi herbiri 2s olan 10 pencereye bölünerek incelenmiştir. Nöbete en uzak olan pencere "1. pencere", nöbete en yakın pencere ise "10. pencere" olarak işaretlenmiştir. Herbir pencere için, 9 elektot çiftinde interhemisferik Pearson korelasyon katsayıları hesaplanmıştır. Pencereler arasında korelasyon katsayılarının değişkenliği tekrarlayan ölçümlerde ANOVA yöntemi ile analiz edilmiştir.

Bulgular: F7T1-F8T2; T1T3-T2T4; FP1F3- FP2F4; C3P3-C4P4 elektrot çiftlerinde Pearson korelasyon katsayıları 1. pencereden 10. pencereye doğru anlamlı düşme göstermiştir ($p<0.05$). Post hoc çoklu karşılaştırmalarında korelasyon katsayıları arasındaki anlamlı farklılığın ilk iki pencere (0-4 s) ile son üç pencere (14-20 s) arasında olduğu görülmüştür.

Sonuç: Bu çalışmanın sonuçları interhemisferik korelasyon katsayılarının EEG sinyallerinde epileptik nöbetleri belirlemek için kullanılabileceğini göstermiştir.

Anahtar Kelimeler: Fokal Epiliepsi; Elektroensefalogram; Nöbet kestirimi; Interhemisferik Korelasyon

INTRODUCTION

Epilepsy affects about 1% of the world's population. Approximately 30 % of the patients are resistant to anticonvulsive medication and about 50% of these patients are candidates for epilepsy surgery.[2,3,4,10] Mesial temporal lobe epilepsy (MTLE) is the most common and susceptive type for surgery among treatment-resistant partial epilepsy.[2] 60% ictal scalp EEG of MTLE may be normal or may not provide information about localization.[22]

The unpredictable feature of seizures and consequences of them have negative effect on the patients' life quality.[1,20,24,28] Besides, the detection of seizures is commonly based on visual analysis of EEG data by an epileptologist. The workload of this analysis is quite formidable and detecting the seizure onset is particularly subjective and an indefinite estimation.[9] Güldiken B. et al. stated that using epilepsy classifications, the diagnosis and treatment of some patients sometimes remains to be unsatisfactory.[9] Xue suggests that EEG analysis technology is promising for the study of early prediction of seizures.[29] Ramgopal et al. emphasized that collaboration among multidisciplines for the invention of new technologies will allow for a better approach towards prevention, detection and prediction of seizures[24]. Thus, there are a number of multidisciplinary studies seeking for reliable and robust methods or improving the current ones for the detection and prediction of seizures.[1,5,8,17-21,23-26] Such systems would not only improve the life quality of the patients but ease the work of specialists.[28,1,19,20]

In the present study we focused on whether objective features can be extracted from the close pre-ictal EEG that are predictive of a seizure which cannot be noticed by visual analysis. The main purpose of our research study is to test whether by the help of interhemispheric correlation of EEG data we could predict epileptic seizures in temporal lobe epilepsy.

MATERIAL AND METHODS

In the present preliminary retrospective study we used video-EEG data obtained from the database of the Department of Neurology, İzmir Katip Çelebi University Atatürk Training and Research Hospital.

Participants

31 patients (mean age 32.3 ± 7.6;17 female) diagnosed with focal temporal lobe epilepsy in 2010-2013 were randomly selected and totally 52 seizures were analyzed. According to the long term video –EEG monitorization reports of patients, that were prepared co-author neurology specialist, seizure onset was in the left

anterior temporal region in all seizures. Left hippocampal volume reduction was seen in cranial MRI of 14 patients. Seizure age of onset was 17.7 ± 7.5 years (min. 6 years- max. 32 years).

EEG Recordings

EEG recordings were performed by digital video EEG system (Neurofax EEG-1100K) with a sampling rate of 100 Hz from 18 channels. In the recordings bipolar electrode assembly was applied (Left hemisphere; Fp1F7, F7T1, T1T3, T3T5, T5O1, FP1F3, F3C3, C3P3, P3O1, Right hemisphere; Fp2F8, F8T2, T2T4, T4T6, T6O2, FP2F4, F4C4, C4P4, P4O2).

Analysis

Seizure detections were done by a neurology specialist (epileptologist) by using the video-EEG monitorization data and clinical semiologies of the patients. EEG/video monitoring allows the localization of interictal epileptiform discharges and localizing the seizure onset zone.[13,16] We analyzed 20 sec pre-ictal raw EEG data for each seizure. 20 sec pre-ictal EEG data were divided into 10 windows (each 2 sec)(Figure 1). The furthest window to the seizure was labeled as 1st window and the closest window was labeled as 10th window. As the sampling rate was 100 Hz, for each electrode pair and window 200 amplitude values were obtained. Eventually for each seizure a total of 2000 amplitude values were determined. Interhemispheric Pearson correlation coefficients were computed in each window for 9 electrode pairs; Fp1F7 - Fp2F8, F7T1 - F8T2, T1T3 - T2T4, T3T5 - T4T6, T5O1 - T6O2, Fp1F3 - Fp2F4, F3C3 - F4C4, C3P3 - C4P4, P3O1 - P4O2. The variability of correlation coefficients between windows was analyzed with Repeated Measures of ANOVA by using SPSS 15.

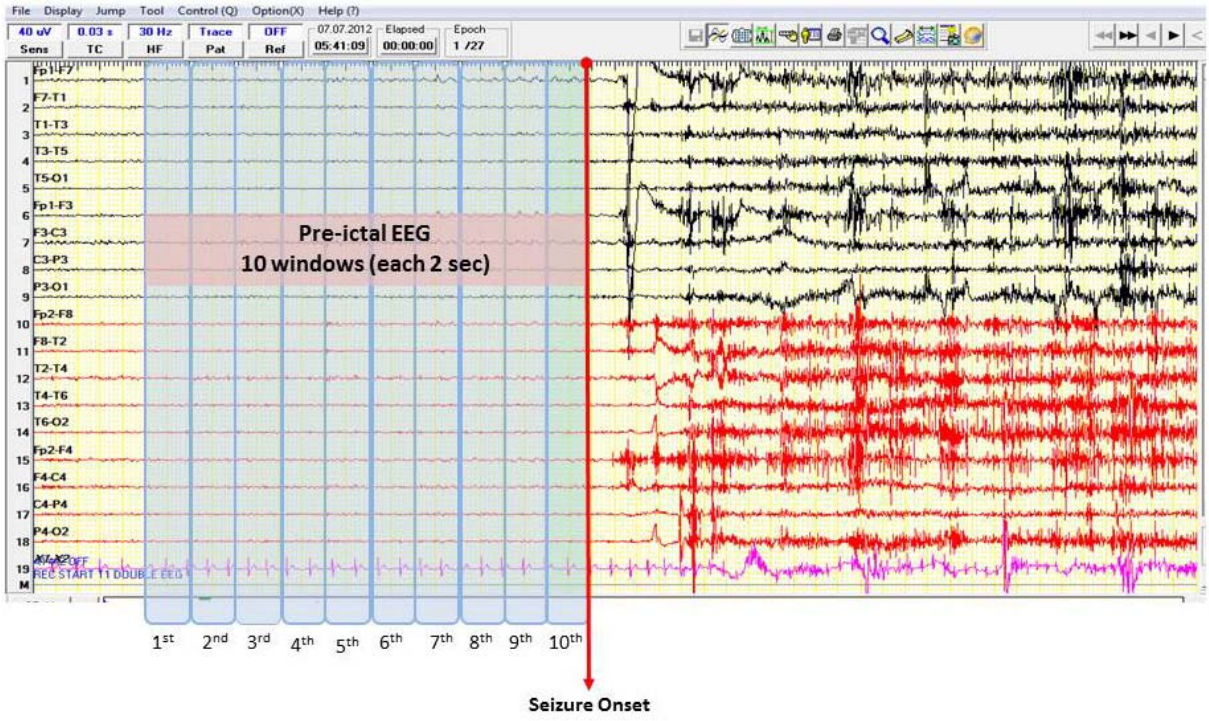

Figure 1: *EEG data of a seizure onset. 60 sec EEG data is represented. From top to down 18 EEG channels are listed. Left hemisphere electrodes are drawn in black (upper part), right hemisphere electrodes are in red (lower part). The red arrow in the middle shows the onset of epilepsy seizure. Ten pre-ictal EEG windows are labeled with blue bars (each 2 sec). The closest window to the seizure is labeled as 10th, the furthest window as 1st.*

RESULTS

The findings of the present study demonstrate that the correlation coefficients decreased from the furthest (1st) window to the closest (10th) window (Table 1). Pre-ictal 10 windows are listed in the leftmost column in Table 1. The duration of each window is 2 sec. In the first column windows are listed getting closer to the seizure from top to down. The mean and std error values of Pearson correlation coefficients are displayed for 9 interhemispheric electrode pairs in Table 1. It is clearly seen that from the 1st window to the 10th window there is a gradual decrease in the correlation coefficients in all electrode pairs except "Fp1F7 - Fp2F8".

The highest correlation values were in the P3O1-P4O2 electrode pair (Table 1). The highest mean value was 0.74 in the 2nd window and the lowest mean value was 0.60 in the 9th window in this electrode pair. The second and third highest correlation values were in the C3P3-C4P4 and F3C3-F4C4 electrode pairs respectively (Table 1). The lowest correlation values were in the F7T1-F8T2 electrode pair. The highest correlation value in the F7T1-F8T2 electrode pair was 0.44 and the lowest correlation value was 0.27 (Table 1).

Pearson correlation coefficient relationships and distribution across the pre-ictal 10 windows are displayed in Figures 2- 6. The markers in the figures indicate the mean values of correlation coefficients in each window. The decline of markers across the axis shows the trend of "closer the window, lower the correlation coefficient". According to Repeated Measures of ANOVA, there was no significant difference between pre-ictal windows in the following electrode pairs: Fp1F7-Fp2F8, T3T5-T4T6, T5O1-T6O2, F3C3-F4C4. The difference between the windows in electrode F7T1-F8T2 failed to reach statistical significance according to multivariate test, but an increasing trend is observed (Wilks' Lambda =.69, $F(9,36)=1.77$, $p=.108$, multivariate partial eta squared=.31). However a significant difference may be observed ($p<0.05$) between the 2nd and 9th windows in the Bonferroni post-hoc test (Figure 2).

For the electrode pair T1T3-T2T4 there was a significant effect for window [Wilks' Lambda=.61, $F(9, 36)=2.54$, $p<.05$, multivariate partial eta squared=.39]. Post hoc multiple comparison analysis revealed that between the 1st window and the 8th, 9th and 10th windows (the dashed lines in Figure 3) there were significant differences ($p<0.05$). Furthermore there were significant differences between the 2nd window and 8th, 9th windows (long dash and two dots in Figure 3) and between the 3rd window and 9th window (dash and dot in figure 3) ($p<0.05$).

Another significant difference among pre-ictal windows was for the electrode pair FP1F3-FP2F4 [Wilks' Lambda= 0.55, $F(9,36)= 3.22$, $p<.001$, multivariate partial eta squared= .45]. According to the pairwise comparisons the difference was between the 1st and the 9th windows ($p<0.05$) (Figure 4).

As for the electrode pair C3P3-C4P4 there was a significant effect for window [Wilks' Lambda= 0.59, $F(9,36)= 2.76$, $p<.05$, multivariate partial eta squared= .41]. According to the pairwise comparisons the differences were between the 2nd window and the 9th and 10th windows and between the 3rd window and the 10th window ($p<0.05$) (Figure 5).

Furthermore, the difference between the pre-ictal windows in P3O1-P4O2 electrode pair fell only marginally short of significance [Wilks' Lambda= 0.67, $F(9,36)= 1.94$, $p=.078$, multivariate partial eta squared= .33]. According to the post hoc comparisons significant difference is calculated between the 2nd and the 9th window ($p<0.005$) (Figure 6).

Table 1: Pearson correlation coefficients of pre-ictal windows for each interhemispheric electrode pairs. Mean and standard error values for all seizures (n = 52) from 31 subjects are provided.

	Electrode Pairs								
Windows	**Fp1F7 - Fp2F8**	**F7T1 - F8T2**	**T1T3 - T2T4**	**T3T5 - T4T6**	**T5O1 - T6O2**	**Fp1F3 - Fp2F4**	**F3C3- F4C4**	**C3P3 - C4P4**	**P3O1 - P4O2**
1th	0.42 (0.05)	0.40 (0.05)	0.50 (0.04)	0.43 (0.04)	0.40 (0.04)	0.56 (0.04)	0.60 (0.03)	0.65 (0.03)	0.70 (0.03)
2nd	0.49 (0.03)	0.44 (0.04)	0.50 (0.03)	0.44 (0.04)	0.41 (0.04)	0.58 (0.03)	0.58 (0.03)	0.65 (0.03)	0.74 (0.02)
3rd	0.50 (0.03)	0.40 (0.03)	0.49 (0.03)	0.45 (0.04)	0.39 (0.04)	0.57 (0.03)	0.57 (0.03)	0.65 (0.02)	0.68 (0.03)
4th	0.37 (0.04)	0.35 (0.05)	0.46 (0.03)	0.45 (0.03)	0.39 (0.04)	0.53 (0.04)	0.56 (0.03)	0.61 (0.03)	0.69 (0.02)
5th	0.41 (0.05)	0.32 (0.05)	0.42 (0.04)	0.44 (0.03)	0.38 (0.03)	0.52 (0.04)	0.55 (0.03)	0.61 (0.03)	0.70 (0.03)
6th	0.45 (0.04)	0.33 (0.05)	0.43 (0.04)	0.43 (0.03)	0.37 (0.04)	0.52 (0.04)	0.56 (0.04)	0.61 (0.03)	0.68 (0.03)
7th	0.44 (0.04)	0.31 (0.05)	0.44 (0.04)	0.44 (0.03)	0.36 (0.03)	0.49 (0.04)	0.56 (0.03)	0.65 (0.02)	0.69 (0.03)
8th	0.40 (0.05)	0.31 (0.05)	0.36 (0.03)	0.39 (0.03)	0.33 (0.03)	0.45 (0.05)	0.56 (0.03)	0.61 (0.02)	0.65 (0.03)
9th	0.47 (0.04)	0.27 (0.05)	0.33 (0.04)	0.37 (0.03)	0,30 (0.04)	0.44 (0.04)	0.49 (0.03)	0.54 (0.03)	0.60 (0.03)
10th	0.55 (0.03)	0.32 (0.04)	0.35 (0.04)	0.36 (0.03)	0.28 (0.04)	0.52 (0.04)	0.48 (0.04)	0.56 (0.03)	0.64 (0.03)

Mean and standard error values for all seizures (*n = 52*) from 31 subjects are provided.

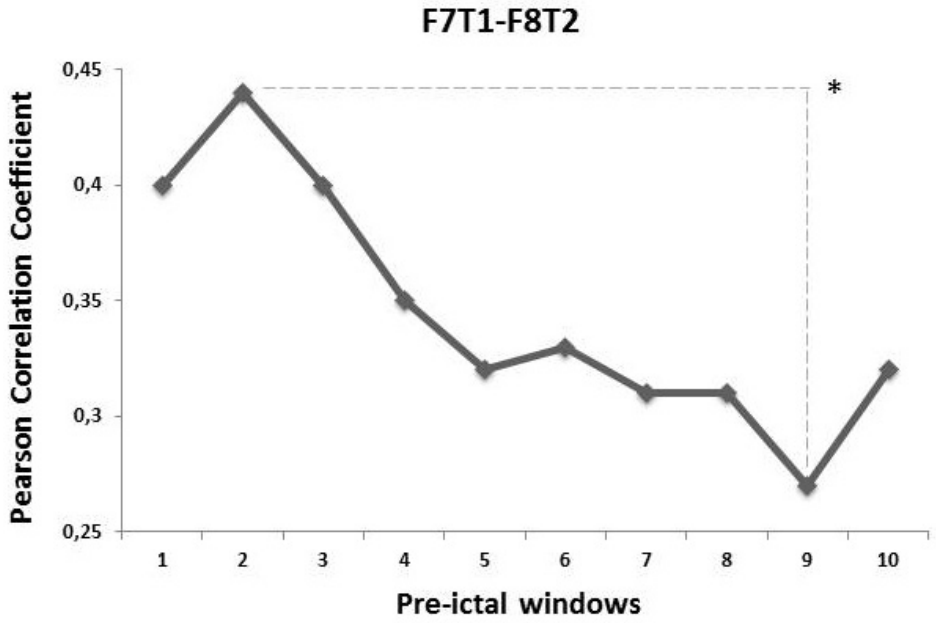

Figure 2: *Plot of Pearson correlation coefficient in pre-ictal windows for F7T1-F8T2 electrode pair. The y-axis shows the Pearson correlation coefficient scale and the x-axis is divided into ten pre-ictal windows. The markers indicate the mean values of correlation coefficients for F7T1-F8T2 electrode in ten pre-ictal windows. The * sign denote for p<0.05 according to pairwise comparisons.*

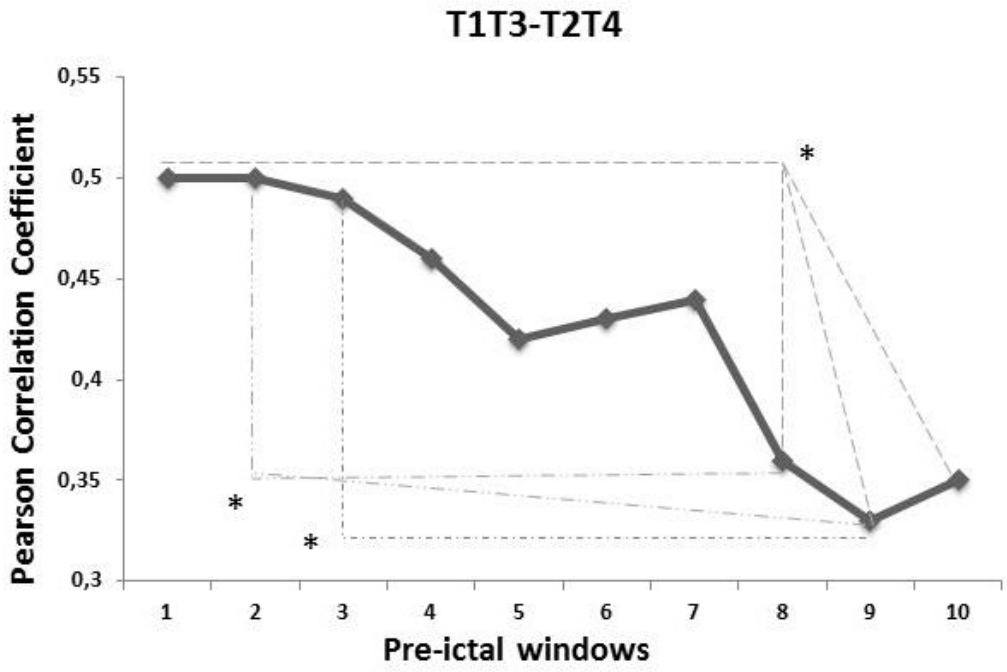

Figure 3: *Plot of Pearson correlation coefficient in pre-ictal windows for T1T3-T2T4 electrode pair. The y-axis shows the Pearson correlation coefficient scale and the x-axis is divided into ten pre-ictal windows. The markers indicate the mean values of correlation coefficients for T1T3-T2T4 electrode in ten pre-ictal windows. The * sign denote for p<0.05 according to pairwise comparisons.*

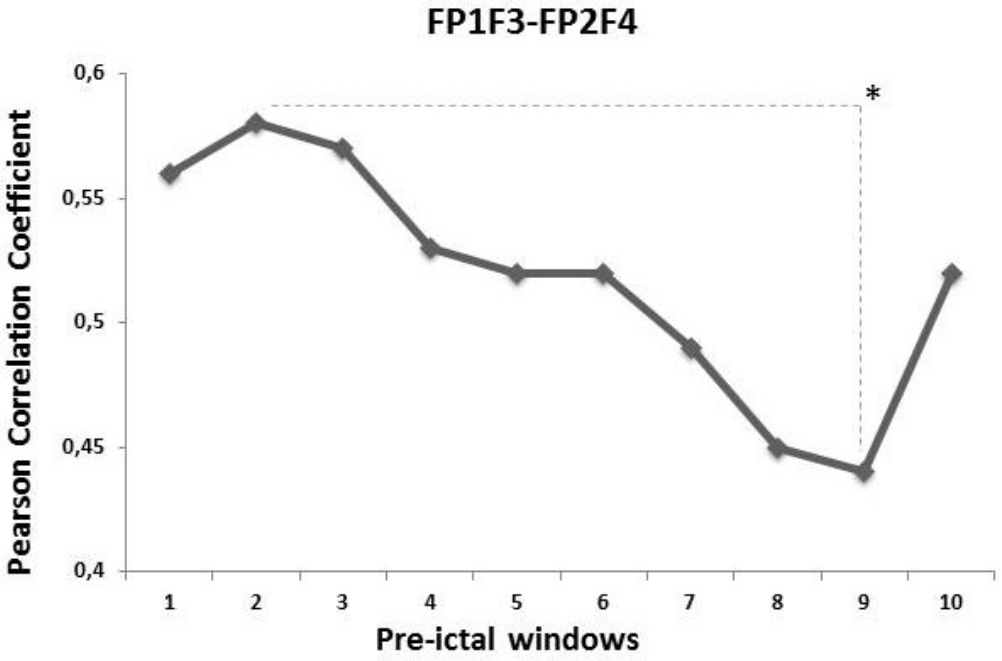

Figure 4: *Plot of Pearson correlation coefficient in pre-ictal windows for FP1F3-FP2F4 electrode pair. The y-axis shows the Pearson correlation coefficient scale and the x-axis is divided into ten pre-ictal windows. The markers indicate the mean values of correlation coefficients for FP1F3-FP2F4 electrode in ten pre-ictal windows. The * sign denote for p<0.05 according to pairwise comparisons.*

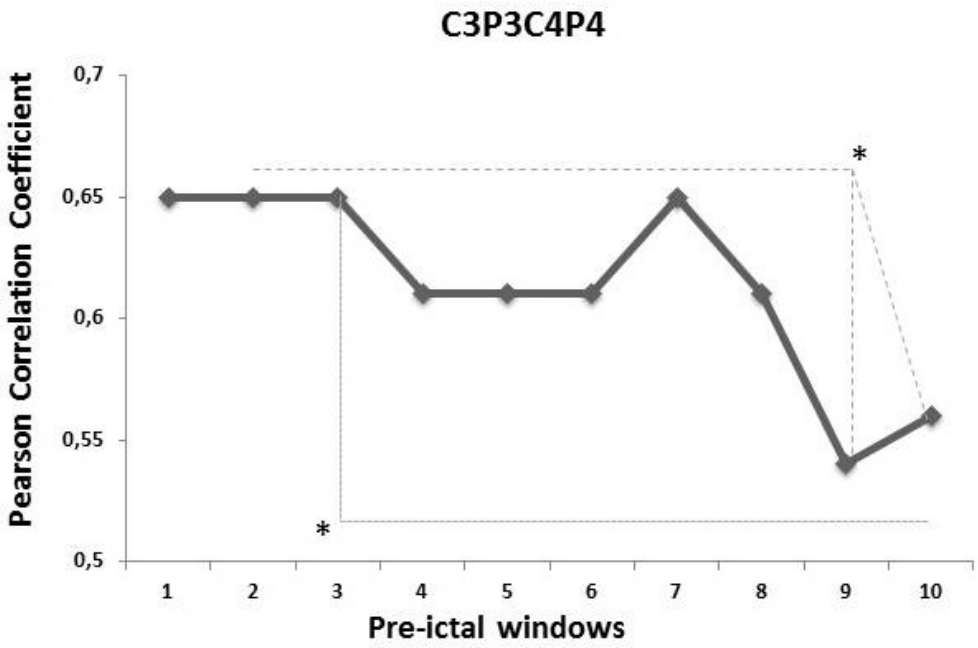

Figure 5: *Plot of Pearson correlation coefficient in pre-ictal windows for C3P3-C4P4 electrode pair. The y-axis shows the Pearson correlation coefficient scale and the x-axis is divided into ten pre-ictal windows. The markers indicate the mean values of correlation coefficients for C3P3-C4P4 electrode in ten pre-ictal windows. The * sign denote for p<0.05 according to pairwise comparisons.*

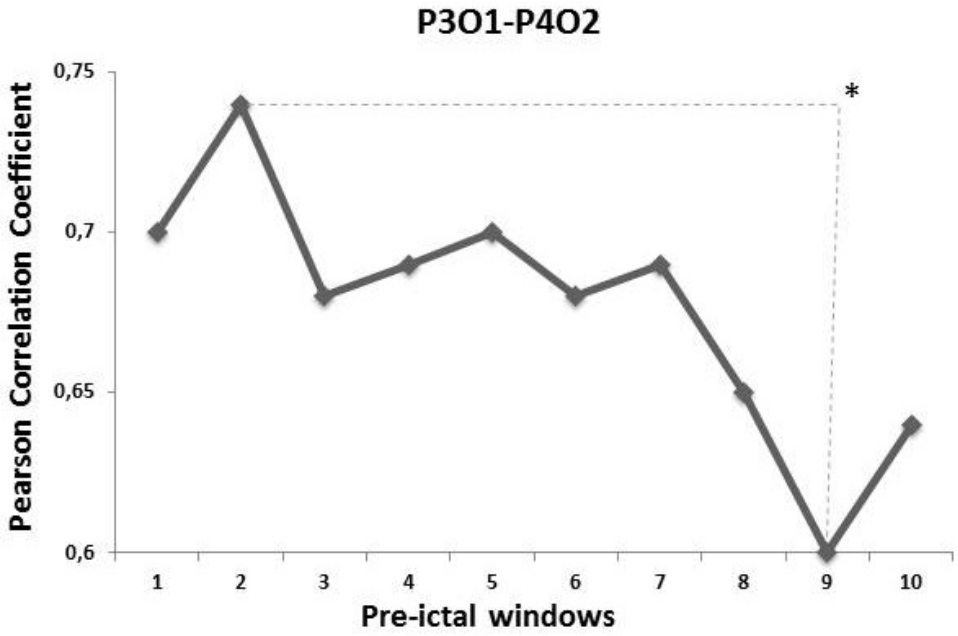

Figure 6: *Plot of Pearson correlation coefficient in pre-ictal windows for P3O1-P4O2 electrode pair. The y-axis shows the Pearson correlation coefficient scale and the x-axis is divided into ten pre-ictal windows. The markers indicate the mean values of correlation coefficients for P3O1-P4O2 electrode in ten pre-ictal windows. The * sign denote for $p<0.05$ according to pairwise comparisons.*

DISCUSSION

The present study represents the correlative results of left and right hemisphere pre-ictal EEG data in temporal lobe epilepsy. As far as we know, this is the first study that investigates the interhemispheric correlation of EEG data in epilepsy. Furthermore, in order to find the changes in brain dynamics that indicate an impending seizure we evaluated the time course of correlations in each electrode pair.

Research in the field of seizure prediction has implemented analysis techniques as correlation density[14,17,18] synchronization[26,27], similarity measures[11] etc. which detects spatial or temporal changes in EEG data. An investigation conducted by McSharry et al. showed that linear statistic (variance) method seems to perform just as well as the nonlinear technique.[18] Litt et al. reported that changes in the energy of signal are of predictive value.[15] Mormann et al. pointed that nearly all of these studies used univariate measures which means that they are related to only a single recording site.[19] But on the other hand the seizure activity is commonly accepted to be closely associated with synchronous neuronal activity in the brain.[7,8] The functional activity of the brain occurs as a result of mutual interaction between stimulation and inhibition processes. Synchronization in the neuronal network is believed to depend on the synaptic activity that is developed by a balance between excitation and inhibition. Any potential effect that changes the balance of excitation-inhibition is defined as epileptogenic mechanism. Synaptic, extracellular and intracellular mechanisms, that are required to trigger, propagate and terminate the seizures arise from excessive neuronal stimulation, are known to be associated with each other.[12] Returning to the analysis techniques, univariate measures fall short of mirroring

interactions between different brain regions. Bivariate measures (related to two different recording sites) for the analysis of synchronization in the EEG have the advantage of examining the spatiotemporal dynamics of seizures.[19,20,5] Therefore, the interhemispheric correlation coefficient which we used to detect the change in the relation between two hemispheres can also be regarded as a valuable approach for the investigation of seizure dynamics.

The study group in the present research was comprised of temporal lobe epilepsy patients. As the seizure onset is unilateral (focal temporal seizure) in these subjects, it is hypothesized that the correlation coefficient between hemispheres will be affected from this unilateral generation, especially in the close pre-ictal EEG data. As a result, the Pearson correlation values were higher in the furthest window to the seizure while the correlation values decreased approaching the seizure. In other words, by the help of interhemispheric correlation coefficient decrease we have been able to predict an impending seizure at least 6 sec before the seizure onset which is determined by an epileptologist. Accordingly, Mormann et al. have observed that pre-ictal periods are characterized by a decreased level of synchronization.[20] Thus it is concluded that, synchronization level in neural signals from different regions may serve as a secure guide in predicting and detecting seizures.[20,21] As the correlation reflects the dependence of two variables, the change in the dependence level between two hemispheres may also be a valuable indicator for seizures.

Another interesting result of the present study is that the significant correlation decrease approaching the seizure was between the anterior and posterior regions of the brain. Pearson correlation coefficients computed between the electrode pairs T1T3 - T2T4, Fp1F3 - Fp2F4, C3P3 - C4P4 significantly decreased from the furthest window to the closest window to the seizure. Whereas the correlation change between the windows was not significant in other electrode pairs. Furthermore, the highest correlation values were in P3O1-P4O1 and C3P3-C4P4 electrode pairs. In the remaining electrode pairs the correlation values were lower. The lowest correlation values were in F7T1-F8T2 electrode pair. When the pair of electrodes having the highest correlation values is examined (Fp1F3-Fp2F4, F3C3-F4C4, C3P3-C4P4, P3O1-P4O2) it is clearly seen that they are in the midline of the scalp (Table 1). Besides, electrode pairs having lower correlation values in Table 1 appear to be farther away from each other. Thus the low correlation coefficient between the electrode pair F7T1-F8T2 is possibly because of the distance between them. Furthermore, the lower level of correlation values in the first window of pre-ictal EEG gives the impression that there may be a decline some time before these EEG recordings. We have been unable to obtain such long duration records. In this respect an insufficient aspect of the present study is that the duration of the EEG data in pre-ictal state was 20 sec. Long durations of pre-ictal EEG data must be analyzed to observe the correlation change.

In the light of the results of the present study and the other existing studies which used bivariate measures to analyze epilepsy EEG, we suggest that unilateral onset epileptic seizures can be preceded by interhemispheric correlation changes. We presume that the pre-ictal changes in interhemispheric correlation in focal epilepsy may start long before the onset of seizures which may be the inherent feature of seizures. From this point of view we conclude that analyses of different interhemispheric dependence measures might help to gather more information about epileptic seizures.

The findings of the present preliminary study may contribute to the detection of seizures in temporal lobe epilepsy. In

future, with further analysis –including the reliability and validity studies- interhemispheric dependence measures as correlation may became applicable to develop software for the prediction and detection of the seizures.

Future plans:

• In order to verify whether the interhemispheric correlation method can be used in a clinical setting we will analyze longer duration of pre-ictal, and even seizure free interictal EEG data.

• Determining the lateralization of seizures, and guiding patients to epilepsy surgery is clinically valuable. Therefore, advanced signal processing methods such as signal energy and entropy will be planned to be used.

ACKNOWLEDGMENT

The authors are thankful to Veysel Uçgun and Hayal Tunç, (Izmir Atatürk Education and Research Hospital, Sleep and EEG Lab.), Nur Evirgen for their supports. The study was partially presented at the 24th National Biophysics Congress, September 25 - 28, 2012 Marmara University, Istanbul.

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Received by: 31 October 2014
Revised by: 25 December 2014
Accepted: 05 May 2015

The Online Journal of Neurological Sciences (Turkish) 1984-2015
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
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Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

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