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Original article

Effect of interictal epileptiform discharges on EEG coherence and phase lag in patients with focal epilepsy

Mostafa M. Elkholy [a]

[a] *Department of Clinical Neurophysiology (Neuro-Diagnostic and Research Center), Faculty of Medicine, Beni-Suef University, Egypt*

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Corresponding Author:

Mostafa Mahmoud Elkholy

mostafaelkholy@med.bsu.edu.eg

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Abstract:

Background and Aim:

Epilepsy is a network disease, and its pathological networks could be related to the interictal epileptiform discharges (IEDs). The aim is to explore the effect of IEDs on EEG functional connectivity metrics (coherence and phase lag degree) in patients with focal epilepsy. **Methods:** The study included 14 patients with focal epilepsy and 14 matched healthy controls. EEGs of the patients were segmented into two-second epochs: a. epochs containing IEDs, b. resting epochs with no IEDs. The selected epochs were analyzed using Fast Fourier Transform to yield four frequency bands: Delta, Theta, Alpha and Beta. Coherence and phase lag degree were computed between the EEG electrodes and were assessed at the intra-hemispheric (frontal-parietal and frontal-temporal) and inter-hemispheric (frontal, temporal and parietal) levels. The frequency of IEDs was calculated from a sixty-minute EEG recording session. **Results:** Patients had significant IED-related connectivity disruption in the form of higher phase lag degree at both intra-hemispheric and inter-hemispheric levels of the following frequencies: delta (P=0.022) and theta (P=0.041) at the left frontal-parietal, beta at the left frontal-temporal (P=0.009), theta at the inter-hemispheric frontal (P=0.003), delta (P=0.006), and beta (P=0.041) frequency bands at the inter-hemispheric temporal level. The frequency of IEDs correlated with phase lag degree of theta (P=0.004, r= 0.720) frequency over the right frontal-parietal level. **Conclusions:** Patients with focal epilepsy showed dynamic IED-related changes in EEG functional connectivity mainly demonstrated by increase of phase lag degree of delta and theta frequency over the frontal and temporal regions.

1. Introduction:

In the last ten years, there was an evolving shift in understanding of focal epilepsy as a network disease originating from dysfunction within a network of cortical and subcortical brain structures and not being due to a focal or regional cortical pathology. [1]

Electrophysiological tools such as electroencephalography (EEG) and magnetoencephalography (MEG) have the advantage of very high temporal resolution compared to other functional brain assessment tools and could measure dynamic changes in inter-regional connectivity. [1]

Previous studies have demonstrated different aspects of disrupted networks and connectivity in patients with focal epilepsy, however the relation between interictal epileptiform discharges and connectivity patterns was little explored. [2-4]

The aim of this study is to explore the effect of interictal epileptiform discharges on EEG functional connectivity metrics (coherence and phase lag degree) in patients with focal epilepsy.

2. Patients and Methods:

This cross-sectional case control study was performed on twenty-eight individuals (patients and controls of equal number). The study protocol was approved from the local ethical committee of faculty of Medicine, Beni-Suef University (Approval number: FMBSUREC/02102022) and in accordance with the principles of Helsinki Declaration and an informed consent was obtained for experimentation with human subjects.

1. Selection of patients:

Fourteen patients of focal epilepsy were retrospectively selected fulfilling the following inclusion criteria: a.age older than 16 years, b.patients have repeated seizure disorder with their EEG showing epileptiform discharges, c.EEG is technically suitable for selection of enough amount of epochs during awake state.

2. EEG recording and extraction:

Nineteen gold disc electrodes were placed on the subject's scalp according to the international 10/20 system of electrode placement, with additional ground electrode at the forehead and bilateral aural reference electrodes. The impedances of the electrodes were always less than 5 kohms.

Raw EEG signals were acquired using Natus, Neurowork EEG system (Nicolet EEG V32 amplifier) with a 1-70 Hz frequency band and 512 Hz sampling rate.

During the session of EEG recording, the subject was supine, relaxed, and awake in a silent environment. An EEG technician monitored the signal quality and instructed the patient to minimize any eye and muscle artifacts.

EEGs were reviewed by an Electroencephalogarpher who extracted high quality segments during awake eye closed state without any visually screened muscle or eye artifacts. Each patient had two segments of EEG a. resting EEG without any visible epileptiform discharges, b. EEG segment with multiple epochs of interictal epileptiform discharges (IEDs) including few seconds (1-3 sec) before and after IEDs. The total duration of these segments ranged between 4 and 8 minutes for resting segments and 1-3 minutes for segments with IEDs.

3. Frequency of inter-ictal epileptiform discharges (IEDs):

This was achieved by counting the number of IEDs (spikes or sharp waves) divided by the duration of the EEG recording in minutes.

4. EEG processing:

The extracted EEG segments of all patients were imported to NeuroGuide software program (NeuroGuide, Deluxe 3.2.1, Applied NeuroScience) in department of Clinical Neurophysiology, faculty of Medicine, Beni-Suef University. The records were re-referenced to linked ear reference, filtered at 1-30 Hz interval, and digitized at sampling rate of 256 Hz. Another manual selection procedure was conducted to obtain 2 second epochs with a total duration of 1 minute of either: a.resting EEG with no IEDs, or b.EEG showing IEDs within the selected epochs. To ensure high quality EEG selection, split-half reliability and test-retest reliability tests were conducted and only total records with values > 90 and 95 % respectively were accepted for subsequent spectral analysis. **(Thatcher et al., 2008)**

The total selected EEG segments were subjected to power spectral analysis using Fast Fourier Transform (FFT) with a 25% sliding window method of Kaiser and sterman [5] to eliminate the FFT windowing effects. This yields the average power spectral values for the different frequency bands at each of the 19 recording sites. The used frequency bands were as follows: Delta (1-3.5 Hz), Theta (4-7.5 Hz), Alpha (8-12Hz) and Beta (13-25 Hz).

5. Measures of brain connectivity (EEG coherence and phase lag degree):

Coherence is a measure of the consistency of phase differences over time interval and is equivalent to a squared correlation coefficient. It depends on the number of degrees of freedom used to estimate the consistency of the phase differences. It ranges from 1 (constant phase differences in successive epochs) to 0 (random phase differences). [6]

Phase lag is an analytical measure that can be computed for every instant of time between two channels. [7] Absolute phase lag ranges from 0 to 180° and has a (+/-) sign to indicate the directional relationship (lead/lag) between the two channels. However, previous reports stated that "In the absence of Directed Transfer Functions (DTF) using Multivariate Auto-Regression, a simple coherence and phase analysis cannot separate magnitude and direction". [8]

For that reason, the absolute value of phase difference was chosen to represent the magnitude of inter-relation ignoring its (+/-) sign.

EEG coherence and phase lag degree were calculated using the paired cross-spectrum comparing each single EEG channel to each of the remaining 18 channels yielding pairs of inter-electrode values of connectivity measures in the four specified frequency bands.

EEG coherence and phase lag were assessed at the intra and inter-hemispheric levels as follow: a.intra-hemispheric (fronto-parietal, F3-P3 and F4/-P4 and fronto-temporal, F3-T3 and F4-T4) b.inter-hemispheric (frontal, F3-F4, parietal, P3-P4, and temporal, T3-T4).

6. Data management and statistical analysis:

Data were analyzed using SPSS (statistical package for the social science software) Version 25.0. Quantitative variables were expressed by mean, standard deviation and 95% confidence interval or by median and interquartile range (IQR) (as appropriate) and the connectivity measures with and without IEDs were compared using paired t test or Wilcoxon sign test (as appropriate). Comparison of connectivity measures between patients and controls were conducted using independent t test or Mann-Whitney U test (as appropriate).

Qualitative variables were expressed by number and percent. Pearson correlation was used to correlate two continuous variables, otherwise Spearman correlation was used. In all tests, p-value was considered significant if less than 0.05.

3. Results:

1. Demographic and clinical characteristics of the participants:

The patient group included 14 patients with focal epilepsy (8 males, their mean age was 28.6 ± 10.8 years). The control group included 14 participants matched with the patients in age and sex distribution (P = 0.455 and 0.430 respectively). Other clinical and EEG characteristics of the patients are demonstrated in **Tables 1 & 2**

Table1: Disease duration and frequency of epileptiform discharges of the patients

	Mean	SD	Median	IQR	95% CI for mean
Disease duration (years)	**6.6**	**6.1**	**4.2**	**9.5**	**3.1 / 10.1**
Frequency of IEDs	**1.8**	**2.2**	**1**	**1.4**	**0.5 / 3.1**

IEDs, inter-ictal epileptiform discharges; SD, standard deviation; IQR, inter-quartile ratio, CI, confidence interval.

Table2: Location of epileptiform discharges and AED intake of the patients

		Patients (n=30)	
		Frequency	Percentage
Side of IED	right	3	21.4%
	Left	10	71.4%
	Bilateral	1	7.2%
Location of IEDs	Temporal	11	78.6%
	Frontal	3	21.4%
AED intake	Yes	10	71.4%
	No	4	28.6%

IEDs, inter-ictal epileptiform discharges; AED, antiepileptic drugs

2. Effect of interictal epileptiform discharges on EEG coherence and phase lag:

There was no significant change of EEG coherence during IEDs compared to resting EEG without IEDs. On the other hand, EEGs during IEDs showed statistically significant higher phase lag degree of delta (P=0.022) and theta (P=0.041) frequency bands at the left frontal-parietal level, beta frequency at the left frontal-temporal level (P=0.009), theta frequency at the inter-hemispheric frontal level (P=0.003), delta (P=0.006), and beta (P=0.041) frequency bands at the inter-hemispheric temporal level. (figures 1-4).

To explore the effect of laterality of epileptic discharges, we repeated the previous comparison including only the 10 patients with left sided epileptiform discharges. Similar findings were observed with no significant coherence difference and significantly higher phase lag degree in the same connections (left frontal-parietal, left frontal-temporal, inter-hemispheric frontal, and temporal regions).

3. Comparison of IED-related EEGs of patients and healthy controls:

There were limited coherence differences with significantly lower alpha coherence at the inter-hemispheric parietal (P=0.027) and temporal (P=0.041) levels.

Epileptic patients had significantly higher phase lag degree in their IED-related EEGs compared to controls in the following regions: Delta (P=0.044) and theta (P=0.029) at left frontal-parietal connections, theta band at left frontal-temporal (P=0.039), delta band at inter-hemispheric frontal (P=0.032) and temporal (P=0.004) regions.

4. Correlation of disease duration and frequency of epileptiform discharges with connectivity measures:

The frequency of epileptic discharges showed significant correlation with phase lag degree of theta (P=0.004, r= 0.720) frequency over the right frontal-parietal level.

No significant correlation was found between age, disease duration and both connectivity measures.

4. Discussion:

This study was designed to explore the effect of interictal epileptiform discharges on EEG-based functional connectivity (coherence and phase lag degree) of focal epilepsy patients by comparison to IED-free segments of the patients and matched healthy controls.

The main finding of the current study was alteration of IED-related functional connectivity of the patients in the form of higher phase lag degree, more significant over the left hemisphere especially frontal and temporal regions. These connectivity alterations were predominant in the delta and theta frequency bands.

Study of connectivity and network disruption in focal epilepsy has gained its importance as it may help in better understanding of pathophysiology underlying disease initiation and propagation which could improve management of these patients especially those with drug-resistant intractable epilepsy. [9]

The relation between interictal epileptiform discharges, brain connectivity and network properties were demonstrated in previous reports using different approaches and functional measures. Azeez and colleagues found a higher degree of phase locking value of all frequency bands at epileptogenic zones during epileptiform discharges in children with rolandic epilepsy. Moreover, they demonstrated a shift of the brain network functional organization of delta, theta, and beta bands towards more functionally ordered networks (high clustering coefficient and long average path length). [10]

Rongli and colleagues showed IED-related decrease in functional connectivity within default mode network of rolandic epilepsy patients that was correlated with cognitive dysfunction in the information processing domain. [11] Galle Bettus and colleagues found higher functional connectivity of intracerebral EEG measured by cross correlation in regions affected by epileptiform abnormalities in patients with intractable temporal lobe epilepsy. [12] Moreover, Derek and colleagues demonstrated that interictal epileptiform discharges resulted in increased connectivity strength but no changes in network structure of infantile spasm patients. [13] On the other hand, Giannina and colleagues showed that functional connectivity maps were unchanged by removing IED effects. [9]

The altered functional connectivity in this study was predominant in the delta and theta frequency bands, consistent with the idea of frequency specific epileptic network disruption demonstrated in previous studies. [4, 14]

The significant correlation in the current study between frequency of IEDs and phase lag degree of theta waves are consistent with a similar finding of positive correlation between functional connectivity in rolandic area and number of IEDs in children with rolandic epilepsy highlighting epileptogenic network disruption during the active seizure period associated with excess IEDs. [11]

Dynamic changes and alteration of epileptic brain networks with epileptic discharges could be caused by dysregulation of neurotransmitters that lead to abnormal electrical activity. [10]

The disruption of resting interictal functional connectivity and brain networks in epileptic patients and its dynamic alteration in relation to epileptiform discharges indicates the combined role of transient and chronic seizure activity in functional network abnormalities. [11] It was hypothesized that epileptic networks are evolving from transient IED related effects to a more persistent connectivity changes caused by plasticity-related reorganization of epileptic brain networks. [9]

Dynamic changes of EEG-based functional connectivity networks with IEDs may reflect activation of pathological networks associated with seizures and could be related to cognitive dysfunction that was linked to the frequent interictal spikes. [13]

The pathological IED-related connectivity disruption highlights an important question about the clinical importance of treating frequent interictal spikes which may necessitate further research in different types of epilepsy syndromes.

In conclusion, patients with focal epilepsy showed dynamic IED-related changes in EEG functional connectivity mainly demonstrated by increase of phase lag degree of delta and theta frequency over the frontal and temporal regions.

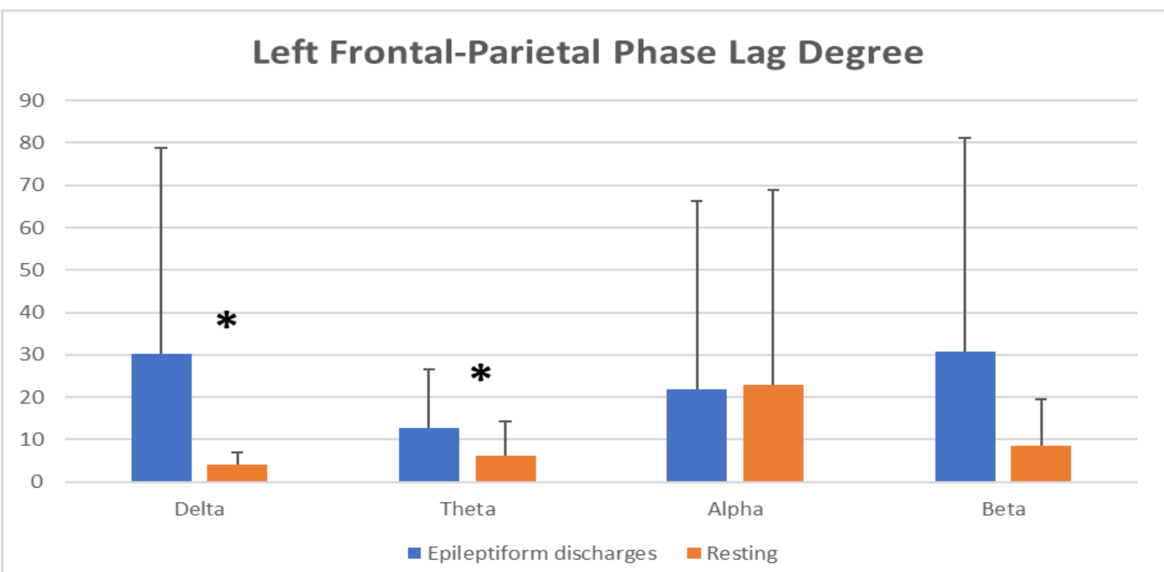

Figure1: Epileptiform discharges-related left frontal-parietal phase lag degree compared to resting EEG

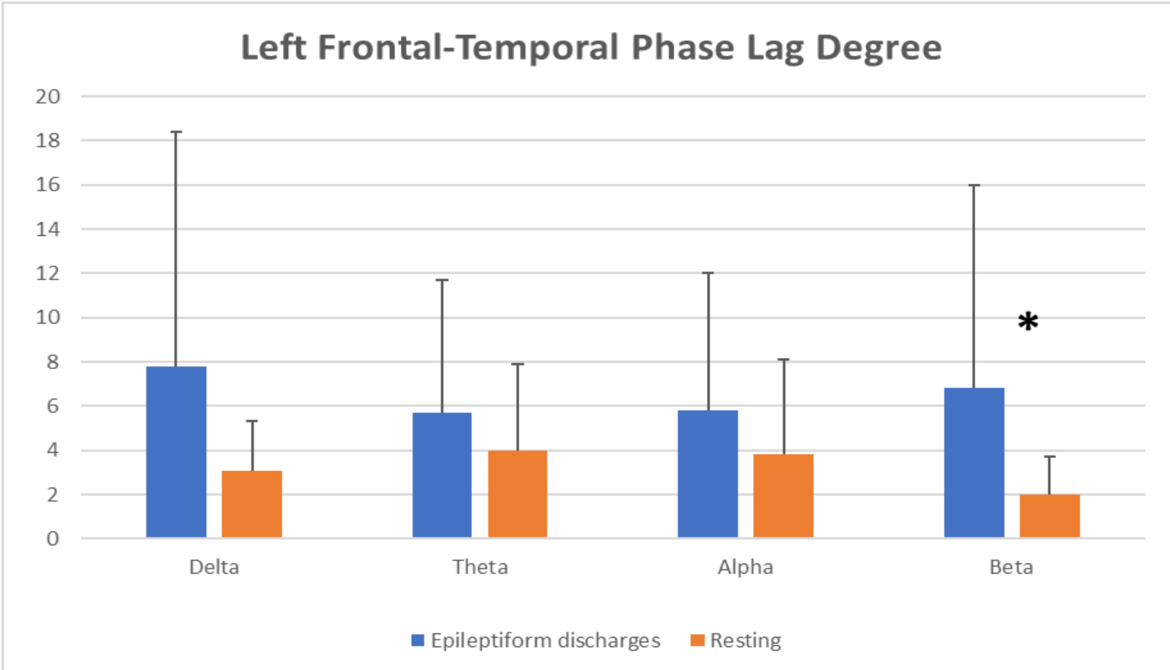

Figure 2: Epileptiform discharges-related left frontal-temporal phase lag degree compared to resting EEG

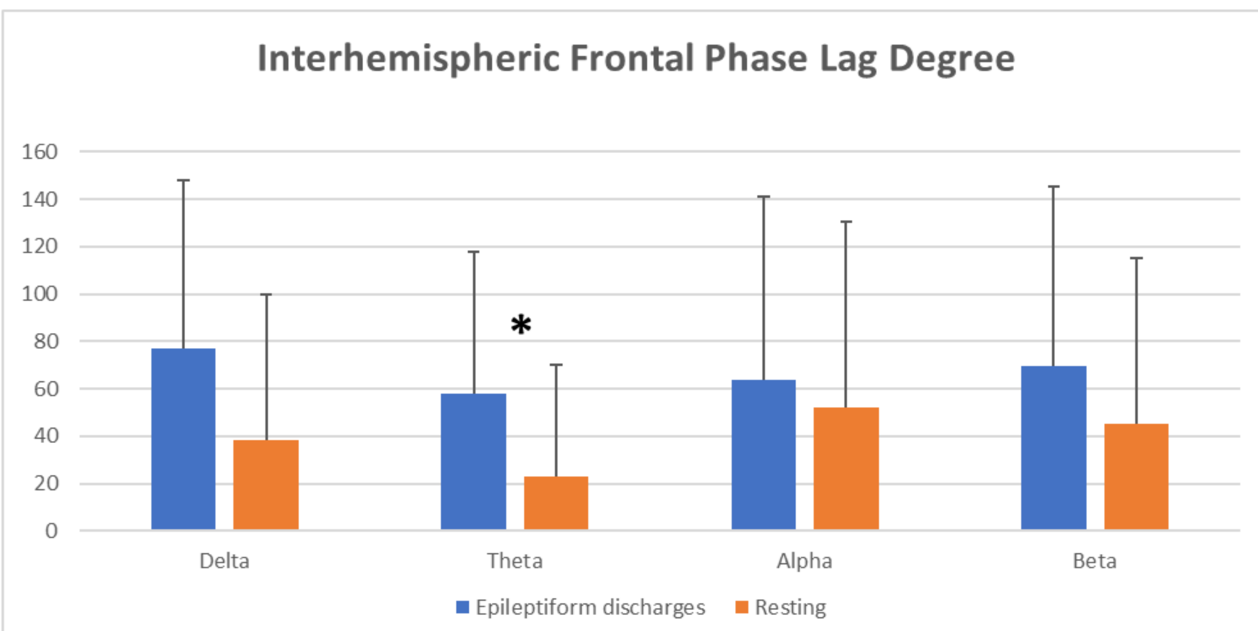

Figure 3: Epileptiform discharges-related inter-hemispheric frontal phase lag degree compared to resting EEG

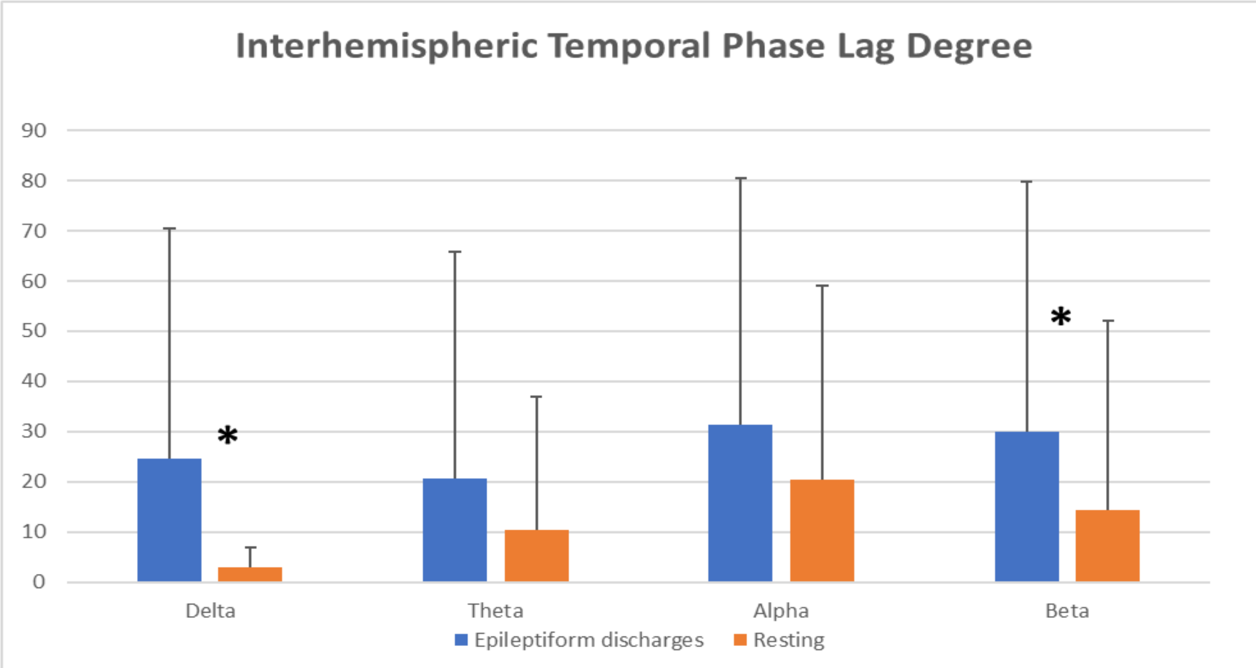

Figure 4: Epileptiform discharges-related inter-hemispheric temporal phase lag degree compared to resting EEG

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