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Original article

Sensitivity of Functional Connectivity Analysis in Diagnosis of Idiopathic Childhood Focal Epilepsies

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Abstract:

Background: Idiopathic childhood epilepsy causing an alteration in the brain functional connectivity including increased neuronal excitability, establishment of critical interconnections and perhaps causing complicated structural changes. **Aim:** to study the changes in EEG functional connectivity (coherence and phase lag) among children with different types of idiopathic epilepsy in comparison to normal controls**. Subjects and methods:** This case-control research conducted on fifteen subjects with newly diagnosed idiopathic childhood epilepsy and fifteen age & sex-matched healthy controls. Both groups were subjected to clinical history taking, routine EEG by using the international 10-20 system and the data analyzed using the quantitative electroencephalography (QEEG) to detect the impact of interictal epileptiform activity on the brain functional connectivity. **Results:** There is an interictal reduction in the brain functional connectivity, in specific frequency bands, in patients with idiopathic focal epilepsy. **Conclusion:** In idiopathic focal epilepsy, there is an alteration in the brain functional connectivity only in specific frequency bands.

1. Introduction:

Idiopathic epilepsy refers to a collection of epileptic illnesses that are thought to be primarily caused by hereditary factors. Individuals diagnosed with Idiopathic epilepsy generally exhibit normal cognitive functioning and do not display any physical irregularities in their brain structure. Idiopathic epilepsy typically presents itself throughout early childhood to puberty, although it may also be diagnosed at a later stage. The etiology of certain idiopathic epilepsy types is understood, although inheritance does not always adhere to a straightforward monogenic route [3].

The diagnosis of idiopathic epilepsy is mostly based on clinical evidence. However, clinical criteria alone may not provide enough information to determine the specific kind of epilepsy. Therefore, electroencephalogram (EEG) testing plays a crucial role in diagnosing individuals with idiopathic epilepsy [12].

Quantitative EEG is a modern method of analyzing electroencephalography by recording digital EEG data and subjecting them to complicated mathematical algorithms for processing, transformation, & analysis. QEEG has introduced novel methods for extracting features from EEG data, such as analyzing specific frequency bands, measuring signal complexity, & examining functional connectivity [6].

Functional connectivity study primarily captures a direct observational assessment of functional associations between two brain regions, which may be facilitated by intermediary structures transmitting information from the first region to the second. The synchronized brain activities represent the coherent oscillations or mass neuronal activity occurring between distinct regions of the brain [1].

Connectivity analysis in EEG typically involves investigating changes in coherence among sources and sensors. Coherence refers to the degree of covariation in amplitude and phase between two signals, and it quantifies the linear correlation among two time series. This correlation is expressed in the frequency domain [2].

Purpose of this work is to study the changes in EEG functional connectivity (coherence and phase lag) among children with idiopathic focal epilepsy by comparison to normal controls).

2. Patients And Methods:

This is a case-control study including fifteen subjects with newly diagnosed idiopathic focal epilepsy and fifteen age & sex-matched healthy controls. The cases were recruited from the Pediatrics Clinic. The neurophysiological studies were carried out in the Neurodiagnostic and Research Center, Beni-Suef University Hospital. (Ethical approval number: FMBSUREC/06112022/Ali).

a. Selection of patients: fifteen patients of idiopathic focal epilepsy were retrospectively selected fulfilling the following inclusion criteria: a- Age range between 6 - 14 years old. b- Newly diagnosed idiopathic focal epilepsy according to the last classification of epilepsy 2017. c- Untreated or on monotherapy for less than 3 months.

b. EEG recording and extraction: After thoroughly washing the subject's scalp, nineteen gold disc electrodes were positioned according to the international 10/20 standard of electrode placement. Additionally, a ground electrode was inserted on the forehead, and bilateral aural reference electrodes were used. The electrode impedances consistently remained below Five k ohms.

Raw EEG signals were recorded utilizing Nihon Khoden EEG device with a frequency band of 1-30 Hz. Throughout the twenty-minute EEG recording session, the individual remained in a supine position while being awake and relaxed in a quiet atmosphere. An EEG technician was monitoring the recording to check the signal quality, minimize any artifacts caused by eye and muscle movements, & confirm the wakeful condition.

An electroencephalographer examined the EEGs and extracted high-quality segments while the subject was awake with the eyes closed, ensuring that no muscle or ocular artifacts were visually detected. Each patient had EEG segment with multiple epochs of interictal epileptiform discharges (IEDs) including few seconds (1-3 sec) before and after IEDs. Segments containing IEDs exhibited an overall duration varying from one to three minutes.

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

This was accomplished by dividing the count of IEDs (spikes or abrupt waveforms) by the EEG recording duration in minutes.

d. EEG processing:

For the analysis of EEG functional connectivity, EEG data devoid of artifacts is necessary. Epochs exhibiting indications of drowsiness, eye movements, blinking, or muscle activity were meticulously eliminated through visual inspection. The resulting Montage was subsequently connected to the aural Montage.

The investigation of functional connectivity was conducted using fast Fourier transformation (FFT) on various frequency bands. The frequency spectra were then averaged over all chosen epochs at each recording site to get the coherence & phase lag values.

The designated frequency regions were as follows: beta (13-30 Hz), theta (4-8 Hz), & alpha (8-13 Hz). The following electrodes were chosen: (F3 and F4) are frontal, (P3 and P4) are parietal, & (T5 and T6) are temporal.

Interhemispheric coherence and phase lag were assessed by measuring the connectivity between frontal (F3-F4), parietal (P3-P4), and temporal (T5-T6) electrodes in both the right & left hemispheres.

Intrahemispheric coherence and phase lag were measured between frontal (F4-F8), parietal & temporal (P4-T6) electrodes in right hemisphere and between frontal (F3-F7), parietal and temporal (P3-T5) electrodes in the left hemisphere.

e. Measures of brain connectivity (EEG coherence & phase lag degree):

Equipped with the square of the correlation coefficient, coherence quantifies the consistency of phase differences across time intervals. Ascertaining the consistency of the phase differences requires a specific quantity of degrees of freedom. The value of the parameter varies between 1 (representing constant phase differences between consecutive epochs) and 0 (representing arbitrary phase differences) [5].

Phase lag is a quantitative statistic that may be calculated for any given moment in time between two channels [4]. The absolute phase lag spans from 0 to 180° and is denoted by a (+/-) symbol to show the direction (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" [11].

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

EEG coherence & phase lag degree were estimated through a paired cross-spectrum analysis, which involved comparing each individual EEG channel with the remaining 18 channels. This analysis resulted in pairs of inter-electrode values representing connection measurements in the four required frequency bands.

EEG coherence and phase lag were evaluated at both the intra & inter-hemispheric levels as follow:

a- inter-hemispheric frontal (F3-F4), parietal (P3-P4) & temporal (T5-T6) electrodes between the right and left hemispheres.

b- intra-hemispheric frontal (F4-F8), parietal & temporal (P4-T6) electrodes in right hemisphere and between frontal (F3-F7), parietal and temporal (P3-T5) electrodes in the left hemisphere.

f. Data management and statistical analysis:

The collected and coded data were input twice into Microsoft Access to facilitate data manipulation. The Statistical Package for Social Science (SPSS) software version 22 in Windows 7 was utilized for data analysis (SPSS Inc., Chicago, IL, USA). Simple descriptive analysis of quantitative parametric data in the form of percentages and numbers for qualitative data, and arithmetic means for measuring central tendency and standard deviations for assessing dispersion.

The inclusion of quantitative data in the investigation was initially assessed for normality in each study group using the One-Sample Kolmogorov-Smirnov test. Subsequently, inferential statistics were chosen.

For quantitative parametric data: Utilize the one-way ANOVA test to compare quantitative measures across multiple independent groups of quantitative data, while the Benferroni post-HOC test is employed to determine the significance level among both groups. Utilizing a paired t-test to compare two dependent quantitative variables.

For quantitative nonparametric data: To compare more than 2 independent groups, the Kruskal Wallis test was applied. Two sets of dependent data are compared utilizing Wilcoxon tests.

For qualitative data: Utilizes the chi-square test to compare two or more qualitative categories).

3. Results:

1. Demographic & clinical characteristics of the participants:

The patient group involved 15 cases with idiopathic focal epilepsy (7 male & 8 female, their mean age was 9.6 ± 2.2 years). The control group involved 15 participants matched with the cases in age & gender distribution (with P-value > 0.05). Other clinical and EEG characteristics of the cases are illustrated in **Tables 1 & 2.**

Table (1): Demographic data in different study groups.

Variables	**Focal** (N=15)	**Control** (N=15)	**P-value**	**Sig.**
Mean age /SD	9.6 ±2.2	9.9 ±2.1	0.9	NS
Male	7 (46.7%)	7 (56.7%)	0.8	NS
Female	8 (53.3%)	8 (43.3%)		

Table (2): Clinical history of patient groups.

Variables	**Focal** (N=15)
	No. (%)
Consanguinity	
Negative	7(46.7%)
Positive	8(53.3%)
Family history of epilepsy	
Negative	8(53.3%)
Positive	7(46.7%)
History of status epilepticus	
No	15(100%)
Yes	0(0%)
History of febrile convulsion	
No	15(100%)
Yes	0(0%)
History of chronic illness	
No	15(100%)
Yes	0(0%)
History of AEDs	
No	15(100%)
Yes	0(0%)
MRI brain	
Normal	15(100%)

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

The focal group EEG coherence compared to EEG in normal control group, shows a statistically significant lower coherence degree of frontal delta (P value=0.02), frequency band and lower coherence of parietal alpha (P value=0.002) at the inter-hemispheric level (**Figure 1 &2**).

But among patients, shows no statistically significant variance among the right & left hemispheres with p-value more than 0.05 (**Table 3**).

Figure (1): FFT coherence inter-hemispheric (Alpha) in study groups.

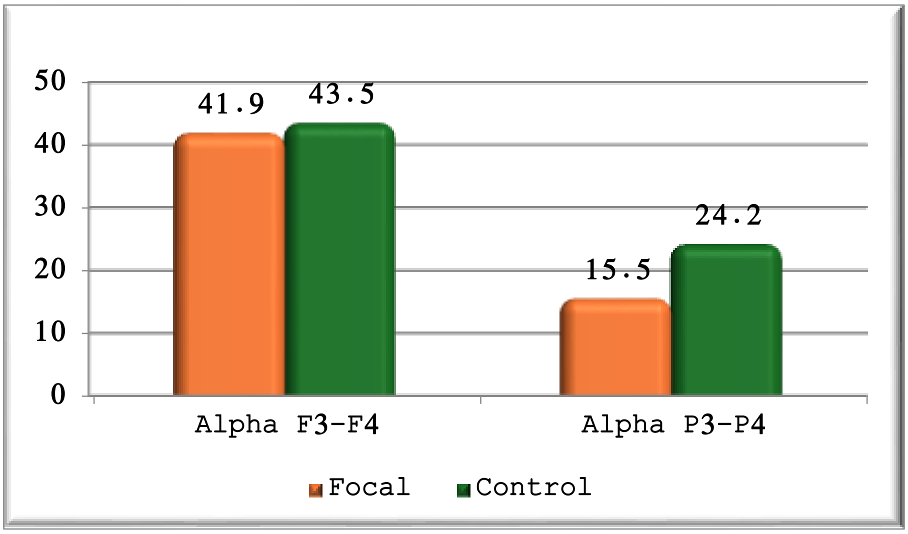

Figure (2): FFT coherence inter-hemispheric (Delta) in study groups.

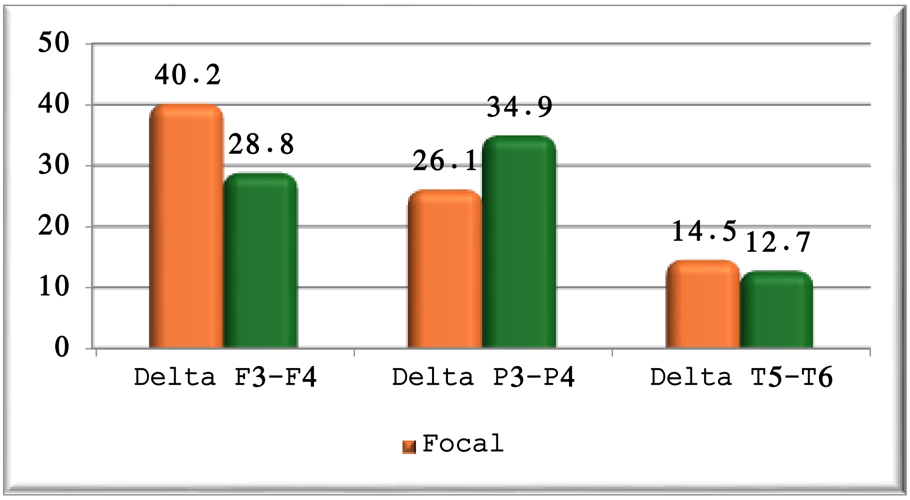

Table (3): FFT coherence (Right & Left) in focal group.

FFT coherence		Left	Right	P-value	Sig.
		Mean± SD	Mean± SD		
Alpha	F	56.7±20.1	51.9±23.2	0.57	NS
	P	54.2±14.6	51.3±22.1	0.67	NS
Beta	F	58.2±8.7	50.03±14.7	0.11	NS
	P	49.5±21.2	49.1±20.7	0.96	NS
Delta	F	41.1±11.3	51.4±19.1	0.07	NS
	P	47.7±16.4	48.8±15.7	0.8	NS
Theta	F	55.1±9.4	55.6±10.8	0.87	NS
	P	45.7±17.2	54.8±19.4	0.17	NS

The focal group EEG phase lag during IEDs compared to EEG without IEDs in normal controls, show a statistically significant greater phase lag degree of temporal alpha frequency band, at inter-hemispheric level (P value=0.01). (**Table 5**).

But among patients, shows no statistically significant variance in all measures among the right & left hemispheres with p-value >0.05.

Table (5): inter-hemispheric Phase lag in study groups.

Phase lag Inter-hemispheric	Focal (N=15) Median/range	Control (N=15) Median/range	P-value	Sig.
Alpha				
F3-F4	-3.3(-31.2/9.4)	-0.8(-3.4/63)	0.3	NS
P3-P4	1 (-167/180)	-0.71 (-27.9/6.7)	0.8	NS
T5-T6	-1.8 (-173/165.7)	-26.5 (-175.4/91.9)	**0.01**	**S**
Beta				
F3-F4	0.70 (-11.5/24.4)	1.5 (-1.3/3.3)	0.2	NS
P3-P4	0.6 (-163/180)	1.5 (-17.3/14.2)	0.9	NS
T5-T6	-3.6 (-169/176)	-25.2 (-176.2/171.1)	0.8	NS
Delta				
F3-F4	0.5 (-20.4/19.7)	-0.98 (-3.9/5.4)	0.1	NS
P3-P4	2.8 (-18.5/180)	1.1 (-2.5/3.2)	0.6	NS
T5-T6	2.5 (-39/162)	2.6 (-11.8/27.2)	0.3	NS
Theta				
F3-F4	-3.1 (-19.7/3.3)	-0.38 (-10.2/5.8)	0.7	NS
P3-P4	-3.6 (-137/180)	-0.44 (-13.7/4.06)	0.8	NS
T5-T6	-9.6 (-168/172)	-0.9 (-174.9/168.2)	0.3	NS

3. Correlation of (frequency of epileptiform discharges) with connectivity measures:

No significant correlation was found between frequency of epileptiform discharges and both connectivity measures (coherence & phase lag).

4. Discussion:

In our study we aimed to sightsee the effect of interictal epileptiform activity on brain functional connectivity using coherence and phase lag degree, as quantitative EEG parameters, in patients with idiopathic focal epilepsy that newly diagnosed and not receiving any antiepileptic medications with age range from 6 to 14 years old by comparison to free segments of the matched healthy controls.

Study of connectivity and network disruption in idiopathic focal epilepsies, 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.

The main finding of the current study was alteration of IED-related functional connectivity of the patients with idiopathic focal epilepsy in the form of reduction in coherence degree mainly in the delta & alpha frequency bands which prove the idea of frequency specific epileptic network disruption in the previous studies.

This figure comes in agree with the study performed with **Li and his colleagues [8]** who also demonstrated that there was interictal epileptiform discharges-related decrease in functional connectivity within default mode network of Rolandic epilepsy patients.

However, in patients with idiopathic focal epilepsy, no significant difference in functional connectivity between the right and left hemispheres and that means no effect of the interictal epileptiform discharges on the local functional connectivity in those patients.

Iannotti's study [7] also showed that functional connectivity maps were unchanged by removing Interictal epileptiform discharges effects in patients with idiopathic focal epilepsy.

The results of our study also reveal that the interhemispheric phase lag index increased in alpha band in patients with idiopathic focal epilepsy and this could be a marker for seizure frequency in those patients, despites of the epileptiform discharges frequency reported in their routine EEG recording.

Lin and his colleagues [9] also reported in their study that reduction of seizures frequency by transcranial direct current stimulation was related with a reduction in the phase lag index in the alpha band but not in the number of epileptiform discharges.

Our results reveal no significant changes in phase lag index in frontal or temporal theta band in idiopathic focal childhood epilepsy which reveals that idiopathic focal epilepsy is a begnin form of epilepsies. As the increase in the fronto-temporal phase lag index in the theta band was positively related with the seizure severity as reported in 2022 by **Mao and his colleagues [10].**

5. Conclusion:

there was interictal epileptiform activity related alteration in the brain functional connectivity in idiopathic focal epilepsies in only specific frequency bands.

6. References:

1. **Babaeeghazvini, P., Rueda-Delgado, L. M., Gooijers, J., Swinnen, S. P., & Daffertshofer, A. (2021)**. Brain structural and functional connectivity: A review of combined works of diffusion magnetic resonance imaging and electro-encephalography. Frontiers in Human Neuroscience, 15, 721206.
2. **Bowyer, S. M. (2016).** Coherence is a measure of the brain networks: past and present. Neuropsychiatric Electrophysiology, 2, 1-12.
3. **Krey, I., Platzer, K., Esterhuizen, A., Berkovic, S. F., Helbig, I., Hildebrand, M. S., ... & Lemke, J. R. (2022).** Current practice in diagnostic genetic testing of the epilepsies. Epileptic Disorders, 24(5), 765-786.
4. **Oppenheim AV, Schafer RW. (2004).** From frequency to quefrency: A history of the cepstrum. IEEE Signal Process Mag.;21(5):95-106.
5. **Otnes RK, Enochson L. (1972).** Digital Time Series Analysis John Wiley and Sons. New York.
6. **Thatcher, R. W., & Lubar, J. F. (2009).** History of the scientific standards of QEEG normative databases. Introduction to quantitative EEG and neurofeedback: Advanced theory and applications, 2, 29-59.
7. **Iannotti GR, Grouiller F, Centeno M, Carmichael DW, Abela E, Wiest R, et al (2016).** Epileptic networks are strongly connected with and without the effects of interictal discharges. Epilepsia.;57(7):1086-96.
8. **Li R, Ji G-J, Yu Y, Yu Y, Ding M-P, Tang Y-L, et al (2017).** Epileptic discharge related functional connectivity within and between networks in benign epilepsy with centrotemporal spikes. Int J Neural Syst.;27(07):1750018.
9. **Lin, L. C., Ouyang, C. S., Chiang, C. T., Yang, R. C., Wu, R. C., & Wu, H. C. (2018).** Cumulative effect of transcranial direct current stimulation in patients with partial refractory epilepsy and its association with phase lag index-A preliminary study. Epilepsy & Behavior, 84, 142-147.).
10. **Mao, L., Zheng, G., Cai, Y., Luo, W., Zhang, Q., Peng, W., ... & Wang, X. (2022).** Frontotemporal phase lag index correlates with seizure severity in patients with temporal lobe epilepsy. Frontiers in Neurology, 13, 855842.

11. **Kaminski MJ, Blinowska KJ. (1991).** A new method of the description of the information flow in the brain structures. Biol Cybern.;65(3):203-10.
12. **Karoly, P. J., Rao, V. R., Gregg, N. M., Worrell, G. A., Bernard, C., Cook, M. J., & Baud, M. O. (2021).** Cycles in epilepsy. Nature Reviews Neurology, 17(5), 267-284.