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The Analysis of Nonlinear Invariants of Multi-Channel EEG Signal Using Graph-Theory Connectivity Approach in Patient with Depression

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Abstract: There is a need to analyze the patients who are suffering from the common disorder in the brain called depression is the most common and disabling mental health disorder which affects not only on the person who is suffering but also on their entire families, friends and the overall society. Current clinical diagnosis relies almost maximum on patient self-report and clinical opinion, leading to a number of subjective biases. Our aim is to develop an objective that supports clinicians in their diagnosis and monitoring of depression. In this study, the analysis is carried over with depression patients who are suffering with cognitive disabilities. By using graph-theory approach and statistical analysis we can analyze EEG and is useful for the analysis of the functional activity of the brain and a detailed assessment of this non-stationary waveform can provide crucial parameters indicative of the mental state of patients. The complex nature of EEG signals calls for automated analysis using various signal processing methods. This study attempts to classify the EEG signals of normal and depression patients using well-established signal processing techniques involving graph-theory concept The use of multichannel system is emphasized using brain connectivity analysis.

Key word: Disabilities, waveform, brain, signals, patients

INTRODUCTION

Depression is a common brain disorder but it is based severe mood disorder. Depression can reflect many symptoms which represent in the form of person falling, thinking and day-to-day activities. To dignose a person as depressive patients these symptoms should present more than fifteen days (Yesavage *et al*., 1983). Major depression is common occurring in 15% of the population which is also noted in higher society (Kessler *et al*., 1996). World Health Organization (WHO) indicated that depression is one of the biggest global burden of disease (Moussavi *et al*., 2007). Major depression is a recurrent disorder which affects from an adolescent, adult to older individual. The, however, neural mechanism which is underplaying the pathophysiology mechanism is still unclear. Recent studies have found the alteration in brain function network using Electro Encephalo Graphy (EEG) and functional MRI (fMRI) (Knott *et al*., 2001; Thibodeau *et al*., 2006; Anand *et al*., 2005; Harvey *et al*., 2005; Lee *et al*., 2015). Today's cognitive neuroscience is the major area of research in the analysis of the behavior of brain activity. There are many image and signal processing methodologies such as fMRI and EEG to acquire the brain dynamically and the complex nature of the brain can be analyzed very well with the multichannel EEG rather than any other modalities. Anand *et al*. (2005) studied brain connectivity network using functional MRI.

They found increased connectivity in limbic regions decrease connectivity anterior cingulated cortex and limbic regions which consistent with the hypothesis of activation in response to negative response and reduce executive and working memory processes (Anand *et al*., 2005). Another study by Harvey *et al*. (2005) carried out for cognitive control and brain resources in major depression using fMRI techniques. The found inferior frontal lobe, medial frontal lobe and anterior cingulated cortex enrolment in depressed. They suggest that the depression may impair the cognitive capacity and attention controls during working memory (Harvey *et al*., 2005;Peraza *et al*., 2012). EEG studies found depression patients have higher beta power and faster mean total spectrum frequency. As well intra-hemispheric theta power asymmetry reduction was noted in patients bilaterally at many regions intra-hemispheric beta power asymmetry was unilateral being restricted to the right hemisphere (Knott *et al*., 2001; Thibodeau *et al*., 2006). Still, the neural mechanism is unclear about

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depression disorder whose need further mathematical modelling to understand these processes. The mathematical concepts in graph theory concepts introduced by authors require a small-world analysis. The graph theory provides a powerful and versatile approach to understanding the function of human brain systems. In this study we hypotheses that the functional brain networks had the efficient small world the healthy subjects whereas these properties may be disrupted in the patients with depressive disorders.

MATERIALS AND METHODS

Ten patients who are suffering with depressive disorder were enrolled in this study. Healthy individual with the mean age group of 27 year (SD±6year) were taken for Electro Encephalo Graphy (EEG) recording. The patients were recruited from Neuro-Psychiatric Hospital. The patient does not reported any additional Neuro-Psychiatric symptoms (including epilepsy, schizophrenia, ADHD, OCD or mild traumatic disorder etc.). Neurological and physical examinations were performed by licensed medical doctors. Ten right hand healthy individual with the same age, education and gender were taken as control group for comparisons. The healthy individual's does not report any history of neuro-psychiatric disease and they were not taking any medication which may affect the study Fig. 1and 2.

Data acquisition process and EEG recording: The EEG was recorded with 30 electrodes using Ag-AgCL electrode as per 10-20 system international electrode placement. The signals were taken for the following electrodes: Fp1, Fp2, F8, F4, F7, F3, P4, P3, O2, O1, A2, A1, Fz, Cz, Pz, T4, T3, C4, C3, T6, T5 and two additional electrode dedicated to the vertical Electrooculogram (EOG). The reference electrode was placed between the FCz and Cz and the ground electrode was placed at Iz as per 10-20 international system. The sampling rate is 1000 Hz and the impedance between the electrode and scalp was maintained below 5 kΩ. The data was recorded in a close room at comfort sit stage for 10 min. The recording room was maintained with minimal electronic gadget and proper grounding. The EEG was down sampled to 250 Hz for further post processing analysis. The data were partitioned into two-second non-overlapping segments. Sixty, two-seconds EEG segments were randomly selected from 10 min data for each patient and healthy control. Followed by the EEG data were decomposed by frequency band such as delta: 0.5-3.5 Hz, theta: 4-8 Hz, alpha: 8-12 Hz and beta: 12-30Hz frequency bands. For each subject and each frequency band, an average functional connectivity matrix was calculated over the EEG segments and was used to compute graph metrics. Followed by the graph theory measures were calculated.

Computation of functional connectivity: We compute functional connectivity between 30 EEG electrodes to investigate the structure of brain networks in the delta, theta and alpha frequency bands. Functional connectivity between every pair of electrode by pairs was calculated using the Phase Lag Index (PLI). PLI is a consider as the measure of asymmetry of phase differences between the pair of signals (Stam *et al*., 2007). The instantaneous phase of two signals was consider to compute phase synchronization which was accomplished by using the analytical signal based on Hilbert transformation (Stam *et al*., 2007). Followed by the PLI was measured from the time series of phase differences $\Delta\phi$ (tk), k=1…. N by means of.

$$\text{PLI} = \left|\langle \text{Sign}[\Delta\Phi\ (t_k)]\rangle\right| \tag{1}$$

in Eq. 1 $\Delta\Phi$ is for the phase difference and t_k represents average over time t. The PLI can be measure by at least or with the synchronization likelihood (Montez *et al*., 2006) or phase coherence (Stam *et al*., 2007) to compute true changes in synchronization but it may minimally affected with the active reference electrodes and/or the influence of common sources and/or (Peraza *et al*., 2012). This may cause due to zero lag synchronization is removed from the analyses and the PLI only quantifies the relative phase distribution's asymmetry which may also refers to the likelihood that the phase difference $\Delta\phi$ in interval $-\pi < \Delta\phi < 0$ is different from the likelihood that it is in the interval $0 < \Delta\ \phi <-\pi$. PLI values basically vary between the range between 0 and 1. The zero PLI value zero indicates either no coupling or coupling with a phase difference. In other hands one indicates perfect phase locking at a value of $\Delta\phi$ different from 0. Higher nonzero phase locking indicates the larger is the PLI.

Graph theory analysis: In The EEG signal, the electrodes are consider as vertices or nodes in the graph and the strength of the synchronization of electrodes between EEG time series can be taken as a measure of association between the vertices. we measure the graph theory parameters by converging the N X N synchronization matrix into a binary graph. A binary graph is a network

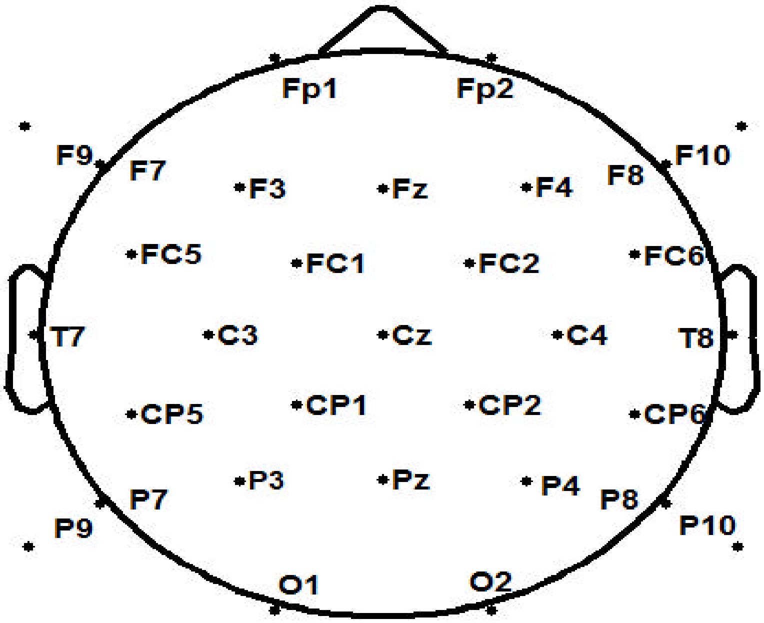

Fig. 1: (10-20) Electrode international standard system

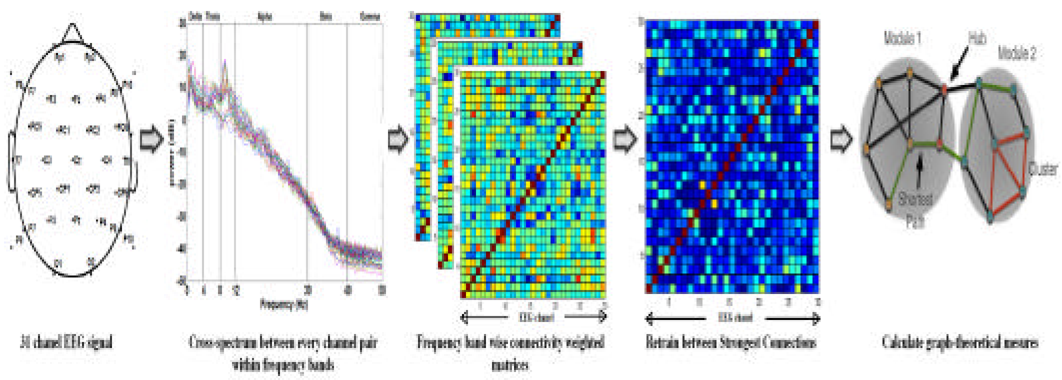

Fig. 2: The pipeline diagram for signal processing

that consists of elements called ‘‘vertices’’ and the undirected connections between elements called as edges. For binary matrix edges between vertices either will be exist (i.e., one value) or do not exist (i.e., zero value); they do not have the waited values (i.e between zero to one). The subject-wise PLI matrices for each EEG frequency band applied threshold with 20-60% of the strongest PLI values in each matrix. Followed by we calculated the graph theory paramiters of Cluster Coefficient ‘C’, Path Length ‘L’ and Local Efficiency ‘LE’ were calculated.

Cluster coefficient ‘C’: The clustering coefficient of a network computes the micro-scale efficiency of a network. To compute the cluster coefficient of the network we determined which other vertices is directly connected with the other vertices (1 edge away) for a node which is called neighbour’s of that node. Simplifying, the clustering coefficient is the ratio between all existing edges between the neighbors’ and the maximum possible number of edges between the neighbour’s. This is the ranges between 0 and 1. This cluster coefficient is measured for all vertices and then averaged for the graph. For calculating coefficient, the method as described by Stam *et al.* (2009) was used which states that the weights between node i and other nodes j should be symmetrical (wij = wji) and that $0 < wij < 1$

(Stam *et al*., 2009). Both conditions are met when using the PLI as weight definition for the clustering coefficient (i.e., wij = PLI). The weighted clustering coefficient of node i is defined as:

$$C_i^W = \frac{\sum_{K\neq 1}\sum_{1\neq k}^{1\neq i} W_{ik}\, w_{i1} w_{kl}}{\sum_{K\neq 1}\sum_{1\neq k}^{1\neq i} W_{ik}\, w_{i1}} \tag{2}$$

In Eq. 2, I = k, I = l and k = l are not included. For isolated vertices, the clustering coefficient is defined as Ci = 0. The mean weighted clustering coefficient of network is defined as:

$$C_{mean}^{w} = \frac{1}{N}\sum_{i=1}^{N} C_i^W \tag{3}$$

Characteristic path length 'L': The path length L measure the no of nodes crossed to reached another node between from any source node among the N no of nodes. The characteristic path length 'L' is denotes the average shortest path connecting between any two nodes of the network. The path length provide the information of who well the elements (i.e., nodes) are inter connected to each other in a network. Inverse of path length represent the efficiency of the system. The shortest path algorithm compute the lowest cost path called shortest path length between a given node to and every other node. The weighted path length calculates the distance between two vertices of the weighted networks and is calculated following the approach of Latora and Marchiori who represent the length of an edge as the inverse of the weight. The average shortest path length for a node i to all other nodes is represent as:

$$L_i^W = \frac{1}{N}\sum_{i\neq j}^{N} \min\left\{L_{ij}^W\right\} \\ -1 \tag{4}$$

In Eq. 4 min {Lijw} is the weighted shortest path length Lij between node i and j and N represents the number of vertices.

Local Efficiency 'LE': Brain functional networks have reasonable small-world properties which represents the efficient transfer of parallel information at relatively low cost. Wattz and Strogatz 1st proposed the small-world network (i.e clustering coefficient and characteristic path length) parameters in neuroscience research. This study employed a single network efficiency measure to quantify the functional connectivity network. For a graph (network) G with N nodes and K edges, the global efficiency of G was calculated as:

$$E_{loc}(G) = \frac{1}{N}\sum_{i\in G} E_{glob}(Gi) \tag{5}$$

In Eq. 5 G is the shortest path length between node i and j. The local efficiency of G was calculated as:

$$E_{glob}(G) = \frac{1}{N(N-1)}\sum_{i\neq j\in G}\frac{1}{d_{ij}} \tag{6}$$

Statistical analysis: All statistical analyses were carried out using MATLAB. Between group difference were measured for clustering coefficient, path length and local efficiency parameters using two-tailed t-tests for independent samples by "ttest2" MATLAB function with 95% of significance confidence interval.

RESULTS AND DISCUSSION

In this study we analyse graph theory measurements in patients with depressive disorders and compared with age gender matched healthy control. We observed in patients with depressive disorders, significant differences ($p>0.05$, FDR) in clustering coefficient, path length and local efficiency.

Findings of clustering coefficient: We found the clustering coefficient significantly ($p>0.05$, FDR) decreased in patients with depressive disorders compare to healthy control in beta frequency Fig. 3 and 4.

Findings of path length: We noted Path Length significantly ($p>0.05$, FDR) increase in patients with depressive disorders compare to healthy control in beta frequency. The increase path length indicates power information flow Fig. 5 and 6.

Findings of path local efficiency: We found the local efficiency significantly ($p>0.05$, FDR) reduced in patients with depressive disorders compare to healthy control in beta frequency Fig. 7 and Table 1. Figure 6 Box car representation of clustering coefficient for patients with depressive disorders (red color) and healthy control color) for delta, theta, alpha and beta frequency band. Compare to healthy control, patients with depressive disorders shown reduced local efficiency in beta frequency band.

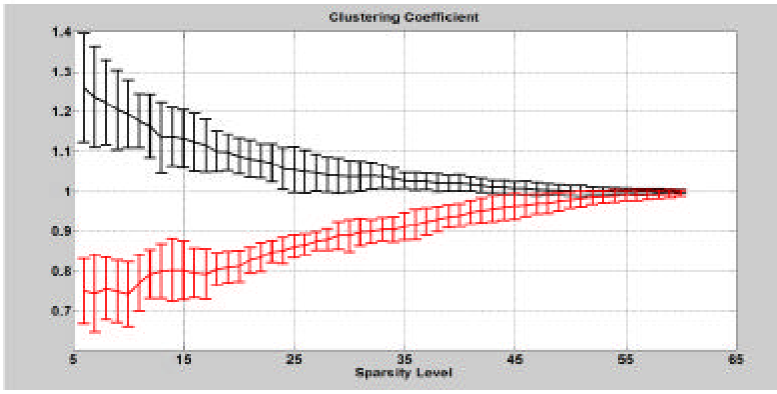

Fig. 3: Graphical representation of clustering coefficient for patients with depressive disorders (red color) and healthy control (black color) for beta frequency band. Compare to healthy control, patients with depressive disorders shown reduced clustering coefficient

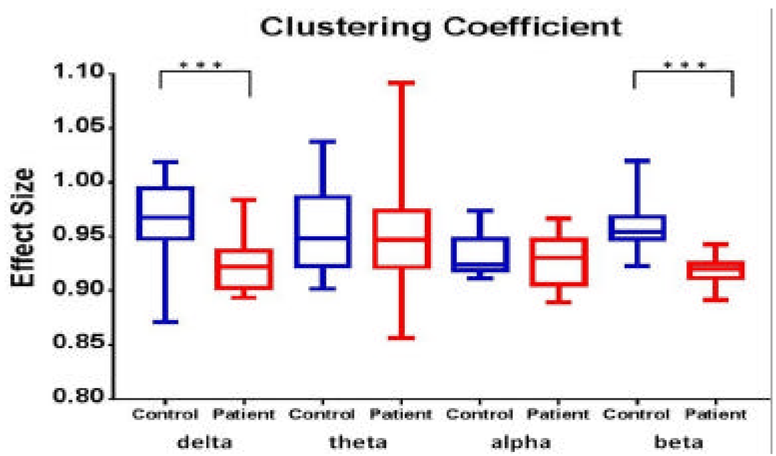

Fig. 4: Box car representation of clustering coefficient for patients with depressive disorders (red color) and healthy control (blue color) for delta, theta, alpha and beta frequency band. Compare to healthy control, patients with depressive disorders shown reduced clustering coefficient in beta and delta frequency band. *** indicates the significant ($p<0.05$ FDR) between the patients and control

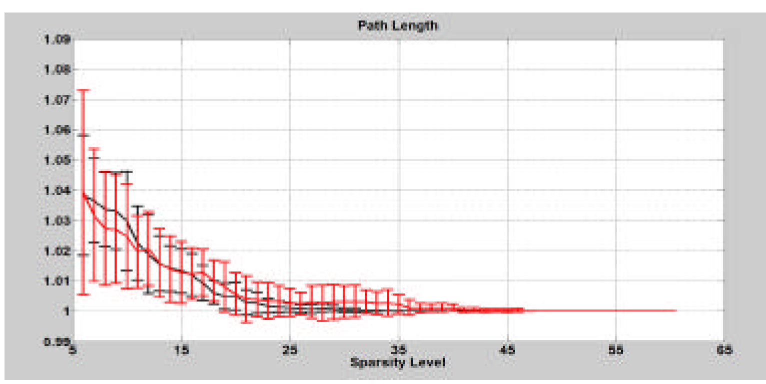

Fig. 5: Graphical representation of path length for patients with depressive disorders (red color) and healthy control (black color) for beta frequency band. Compare to healthy control, patients with depressive disorders shown increase path length

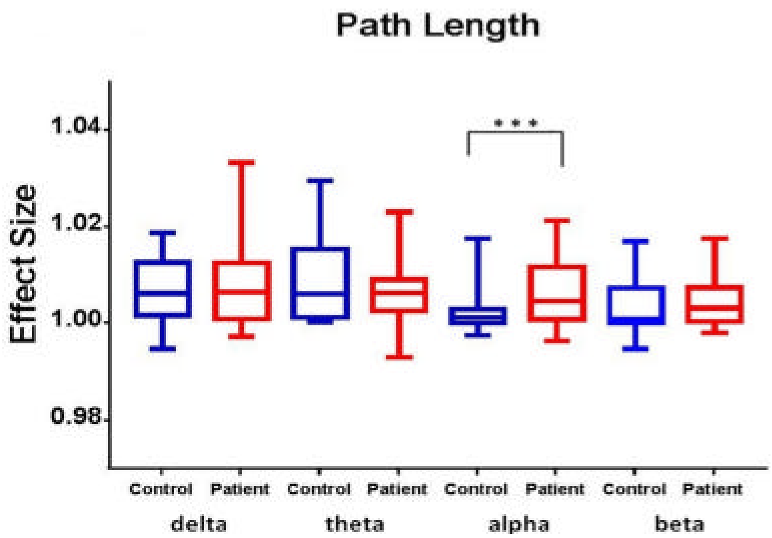

Fig. 6: Box car representation of path length for patients with depressive disorders (red color) and healthy control (blue color) for delta, theta, alpha and beta frequency band. Compare to healthy control, patients with depressive disorders shown increase clustering coefficient in alpha and beta frequency band

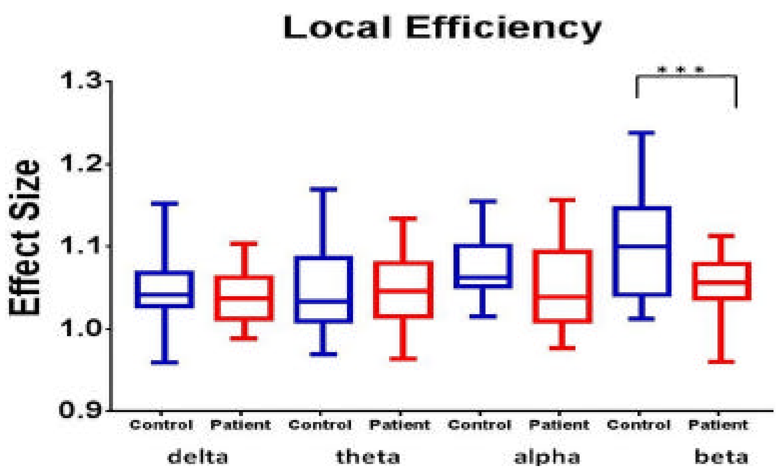

Fig. 7: Graphical representation of local efficiency for patients with depressive disorders (red color) and healthy control (blue color) for beta frequency band. Compare to healthy control, patients with depressive disorders shown reduced local efficiency

Table 1: Clustering coefficient (C), Path length (P) and Local Efficiency (LE) for patients with depressive disorders and healthy control for Delta, Theta, Alpha and Beta frequency band. Compare to healthy control, patients with depressive disorders shown reduced Clustering coefficient and local efficiency and Path Length in beta frequency band significantly ($p<0.05$, FDR)

Variable	Delta		Theta		Alpha		Beta	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C								
Control	0.96	0.037	0.95	0.039	0.93	0.017	0.95	0.020
Patient	0.92	0.027	0.95	0.057	0.92	0.023	0.91	0.012
P								
Control	1.007	0.0065	1.008	0.0082	1.003	0.0054	1.003	0.0058
Patient	1.007	0.0088	1.006	0.0073	1.006	0.0069	1.004	0.0057
LE								
Control	1.048	0.048	1.045	0.053	1.071	0.036	1.097	0.062
Patient	1.037	0.030	1.050	0.044	1.05	0.052	1.055	0.037

CONCLUSION

Brain functional connectivity abnormalities have been hypothesized to be a neurological biomarker. Here we investigated graph theory measurement of functional brain connectivity using a resting-state EEG in patients with depression and age-gender-matched healthy controls. A key finding of our study is alter graph theory measurements in patients with depression in beta frequency band, that the previously reported augmentation in this band alter temporal oscillation and frequency fluctuation which suggests for decline of higher cognitive functions. Altered brain functional connectivity using fMRI were reported. These altered neuronal oscillatory dynamics could be indicative of aberrant neuronal maturation, an interpretation that is in line with neurobiological studies showing decline of higher cognitive functions and mental processes. It is an highly advanced method in comparison with already existing methods such as spectral and Fourier methods, the spatio temporal analysis is very well analyzed using this connectivity network. It is applicable for further study of diseases such as Alzhemiers, Dementia, ADHD, meditation related data for better analysis in cognitive neuro science.

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