Localizing Epileptogenic Zone from High Density EEG Data Using Machine Learning

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Sehresh Khan, Aunsia Khan (✉)
National University of Modern Languages, Rawalpindi, Pakistan
aunsia.khan@numl.edu.pk

Nazia Hameed
University of Nottingham, Nottingham, UK

Muhammad Aleem Taufiq
University of Applied Sciences, Fachhochschule Fulda, Germany

Saba Riaz
Shaheed Zulfikar Ali Bhutto Institute of Science and Technology, Karachi, Pakistan

Abstract—Drug-resistant focal epilepsy is the failure of antiepileptic drugs schedule to obtain epileptic free brain activities. In human brain cerebrum or cerebral hemispheres are the most commonly involved brain regions in epilepsy. In case of antiepileptic drugs failure, surgical treatment is the best cure possible for which correct localization of epileptogenic region is a challenging task for neurologists as well as for computer scientist for automatic localization. This research work's aim is to explore the functional activities of all brain regions in drug-resistant focal epileptic patients and achieve high accuracy for the classification of epileptogenic region (ER) with the high-density electroencephalographic (hdEEG) data. The proposed system includes frequency analysis for feature extractions followed by individual subject's registration of hdEEG signals with anatomical brain images for most precise localization of ER possible. The datasets attained from feature extraction process are then preprocessed for class imbalanced and then evaluated using different machine learning domains including the techniques under Bayesian networks, Lazy networks, Meta techniques, Rule based systems and Tree structured algorithms. Considering human brain both as stationary object as well as dynamic object, frequency-based and time frequency-based features are considered in 12 subjects respectively. Through this novel approach 99.70% accuracy is achieved to classify ER from healthy regions using KSTAR and IBK algorithm and 91.60% accuracy has been achieved to classify generator from propagator regions by applying IBK algorithm.

Keywords—Drug-resistant focal epilepsy, epileptogenic zone localization, computer-aided diagnosis, machine learning, epilepsy regions classification, high density EE

1 Introduction

Epilepsy is complicated brain disease, which causes unpredictable functional activities of brain. These interruptions of normal brain functions are known as epileptic seizures. Epileptic patients face multiple frequencies of seizures, which are unprovoked. In some cases, this disease is cured by medicines but in some cases antiepileptic drugs do not work. In case of antiepileptic drugs failure, the main problem in the domain of epilepsy treatment is the identification of epileptic zone in the brain for a correct analysis and treatment. For such analysis, Brain of the patients are observed through multiple imaging techniques including magnetic resonance imaging (MRI), Diffusion spectrum magnetic resonance imaging (DSI), Diffusion Tensor Imaging (DTI) and many more. Diseases such as Epilepsy damage the brain cells and effect patient's daily life. Unlike other structural damages of the brain, identification of the brain zones generating or propagating the unhealthy signals (causing epilepsy) is much difficult. The abnormal functional and effective connectivity between different regions of the brain can be analyzed through fMRI, EEG, MEG and many other functional imaging techniques. Moreover, surgical procedures are mostly followed which are costly and even more challenging [1]. Therefore, especially in the epileptic patients who are drug resistant, it is important to identify correct epileptic region, before proceeding towards surgical evaluation.

Detection of epileptogenic zone through conventional scalp EEG system does not provide promising results especially for the frontal lobe epilepsy patients because of the fast cortical spread and artefacts caused by muscle movements [2]-[4]. In case of negative-MRI, mostly patients recommended and went through by intracranial EEG (iEEG). To get succeeded in the iEEG process with optimal number of intracranial electrodes, the most challenging and vital part is the correct identification of the epileptogenic region [5], [6]. However, high-density EEG increases the vision of whole neural network by covering most of the scalp area [7]. To overcome the risks involved in iEEG, hd-EEG played an important role to understand the neural network and the effective connectivity, abnormal electrical activities, spikes, seizures and clinical manifestations in different cortical and sub-cortical brain regions [8], [9]. The visual study of hd-EEG in focal epilepsy patients can provide a good improvement in localization of epileptogenic zone [9] but the problem with visual analysis is the requirement of expert's review which is not optimal automated solution.

In new era of artificial intelligence and machine learning, promising results are observed in current literature to analyze neural networks. Many studies have been carried out for the application of Machine learning on seizure detection and epileptic localization, however, ignoring the challenges while working on the complex datasets of neurological disorder. The most common classifiers for instance SVM [10, 11, 12], K-NN [13, 14], CNN [15-17], DT [18] and DF [19] has been applied for seizure detection, and localization using limited databases [20, 21]. The classifiers like K-NN is one of oldest classifiers that uses a simple logic to determine the output on the basis of k-nearest neighbors from feature set [22]. However, the main problem with k-NN is the majority voting especially when the data is skewed resulting into biased results for most frequent data sample. However, SVM is a binary classifier that make binary

decisions. The problem with SVM is, it cannot make decision in case of nonlinear function without a kernel. The ADTree on the other hand creates a decision tree modified by boosting and is applied to two class problems. IB1, IBK and Kstar are simple instance-based learners that predicts the target class. RIDOR (Ripple down rule learner), on other hand, is a rule-based classifier that can classify data of various kind. In contrast, this research has been focused on using Bayes Network, Naïve Bayes [23], RBFNetwork [24], IB1, IBK, Kstar, Ridor, ADTree [25] classification techniques over High density complex EEG data. Due to the limitations and applicability of different classifiers, only these set of classifiers has been selected for the final experimentation purpose. To work with machine learning techniques the vital part is features selection. Features can be selected through channel based deep learning, image processing, signal processing or by using any statistical implications [26], [27]. For abnormal zone localization, EEG is analyzed per individual channels, with respect to individual frequency band. Moreover, classification techniques were used with all possible combinations and folds of EEG based plus relevant clinical features of the patients [28].

In this research work we presented a region-based analysis approach for the classification of epileptic brain regions from the healthy brain regions. For this purpose, high density EEG data is mainly considered to analyze the patients with focal epilepsy who were suggested for surgical treatment after the failure of antiepileptic drugs. For a better registration of EEG frequency signals on brain regions, each patient's personal anatomical images (MRI) are considered and registered with the Harvard-Oxford atlas (HOA) atlas. Considering the feature extraction, the most vital part of this approach, Fourier and Wavelet transform features are extracted for each brain region. As it is well known, frequency-based connectivity methods are based upon the spectral characteristics of the physiological signals and are able to differentiate causal interactions within specific frequency bands of interest [29],[30]. Instead, we hypothesize that the application of time-variant methods (e.g., ADTF) to EEG signals would allow capturing the dynamic evolution of the activity and characterizing the outgoing and ingoing information flow between different regions during an epileptic event.

This work is based on the estimation of functional connectivity in epilepsy allowing the identification of driving sources that are involved in inter-ictal activities as well as in the generation of seizure using EEG data. The region that is involved in the generation of the seizure is called generator while the propagator is the area which is normal healthy brain area without seizure. This study is divided into two groups of analysis, one to identify the epileptogenic regions from healthy regions and second the extraction of generator regions from propagators or healthy regions. Under both group of analysis, multiple experiments have been taken into account to cover all analytical aspects. The presented approach is implemented using different open-source software commonly available like MATLAB 2019, Brainstrom 3 and a comprehensive library of analysis tool known as FSL [31]. It is used for efficient analysis FMRI, MRI and DTI brain data.

The rest of the paper is organized as follows: The details of the proposed epileptogenic regions localization approach are explained in "Methodology" section.

The Analyzed results of all the experiments are presented and discussed under the "Results" head. The approach presented in this paper with its outcome is then concluded in "Conclusions" section.

2 Methodology

2.1 Sample selection

Participants selected for this study are 12 patients diagnosed with drug resistant focal epilepsy including five male and seven female patients aged between 20 to 68 years. Patients were suffering from this disease from past 2 to 48 years. The average seizure frequency was 3.2 per day ranging between 1 per day to 30 per day.

All the patients were recommended for surgery and were admitted for the pre-assessments. To identify seizure semiotics, neurophysiological investigations including video-EEG, hdEEG [256-channel], arterial spin labelling (ASL), and electrical source imaging (ESI) has been performed. With the neurophysiological investigation techniques different advanced neuroimaging modalities were also analyzed to accurately localize epileptogenic zone. All the findings including neurophysiological and neuroimaging are presented in detail in [32], [33]. The modalities considered for this research are hdEEG, MRI, ESI and ASL with the major focus on hdEEG with actual MRI based atlas registration.

2.2 Data acquisition

High-density EEG with 256 channels (Electrical Geodesic, Inc., Eugene, OR) was performed by following international 10/20 system to evenly place electrodes on scalp surface. The hdEEG data were recorded with respect to a reference electrode (Cs). The sampling rate selected for recording was 250 Hz. All the patients were guided to be in the rest position. The hdEEG recordings were further inspected and averaged with respect to peaks of spikes identified by expert neurophysiologist.

To study the dynamics of multiple brain regions, Harvard-Oxford atlas has been used. HOA divides the brain into 112 cortical and subcortical regions of interests (ROIs). To maintain every patient's individual peculiarities, HOA was registered on individual anatomical space perceived through each patient's T1-weighted MRI images as shown in figure 1(c). A source waveform for each ROI was calculated by averaging all the time series within the region represented in figure 1(e). The hdEEG data localization, registration of atlas with the patient's anatomical space and then finding of average time series for each ROI was evaluated by Brainstorm software [34]. Full process of Data acquisition through hdEEG including MRI brain registration, HOA atlas, Atlas registration, spike average calculated for each ROI and separate EEG spike of each region extracted of subject 1, are represented in figure 1(a-e) respectively.

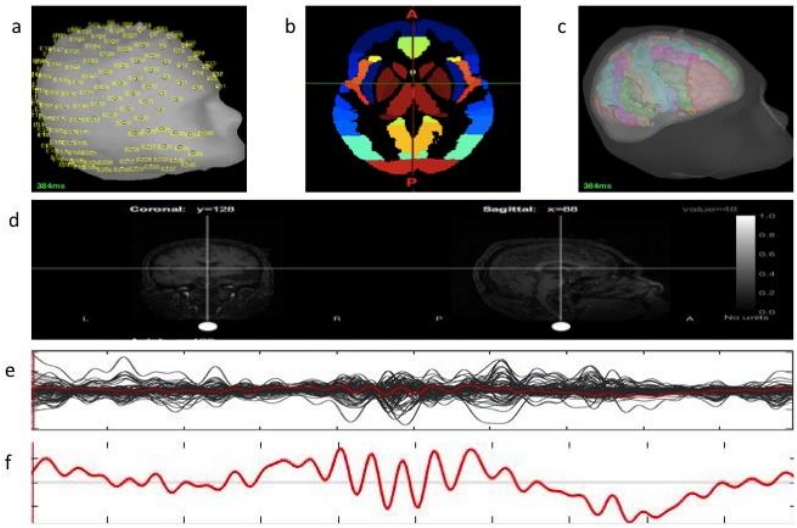

Fig. 1. Hd-EEG data mapping on subjects.01 individual anatomical image. a) Hd-EEG cap registration on subject's scalp surface. b) Harvard-Oxford atlas. c) HOA registered MRI based individual head surfaces. d) 3T anatomical MRI used for the registration of individual brain anatomy with the atlas regions and associated electrode spikes. e) Average oscillation of all brain regions. f) Average spike of one ROI.

2.3 Region of interests

This study is divided into two groups of analysis as shown in Fig. 2; Group-I) Full brain analysis for the classification of healthy region (HR) and epileptogenic region (ER), Group-II) Brain's functionally active zone analysis for the prediction of Generator region (GR) among the Propagator Regions (PR).

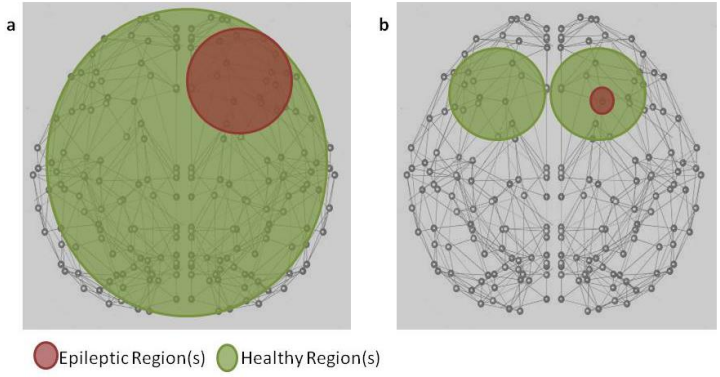

Fig. 2. Two groups of Analysis. a) Full Brain Analysis. b) Brain's functionally active zone analysis

For first group of analysis common 104 regions of all patients are selected based on HOA. For all ROI hdEEG average time series data is considered as shown in figure 1(e, f). For the analysis of second category, Five ROI based on the semeiotics from HOA of both Hemispheres for each patient is taken into consideration. These regions selection was based on previous research done by [8] which has shown the contribution of these regions independently as well as their effect in the form of a network. For each ROI, their Mean values of blood flow (CBF) and current density (CD) are also considered which were calculated previously for the research done by [32] and [33]. The most common brain regions involved in the functionally active zone analysis are listed in table 1.

Table 1. Common brain regions involved in the second category of analysis

Sr.	Label	Name	No. of Voxels in left hemisphere	No. of Voxels in Right hemisphere
1	IFGo	Inferior frontal gyrus, pars opercularis	236	200
2	IFGT	Inferior frontal gyrus, pars triangularis	189	164
3	STGP	Superior temporal gyrus, posterior division	119	118
4	MTGP	Middle temporal gyrus, posterior division	403	390
5	MTGTo	Middle temporal gyrus, temporo-occipital part	252	348
6	TP	Temporal pole	707	691
7	STGa	Superior temporal gyrus, anterior division	84	83
8	ITGa	Inferior temporal gyrus, anterior division	103	103
9	FOrC	Frontal orbital cortex	496	437
10	H	Hippocampus	224	210
11	ITGto	Inferior temporal gyrus, temporo-occipital part	211	237
12	MTGa	Middle temporal gyrus, anterior division	128	126
13	ITGp	Inferior temporal gyrus, posterior division	296	172
14	FP	Frontal pole	2045	2377
15	FMC	Frontal medial cortex	116	123
16	FOpC	Frontal operculum cortex	102	91
17	TFCa	Temporal Fusiform Cortex, anterior division	98	86
18	CoC	Central opercolar cortex	278	267
19	PP	Planum temporale	163	140

2.4 Feature extraction

For machine-learning data is the key to success however, the most difficult challenge is to apply it on medical images. Majority of medical imaging modalities are costly, time consuming and hectic especially for patients. For this study we tried to identify most optimal feature set using the above ROIs. We considered all possible features attained from any modality of all the subjects including demographic features as well as clinical. Some features are based on patients' demographic information like age, gender, epilepsy frequency etc and majority is with respect to each ROI obtained from functional imaging modalities. From hdEEG time series data, features are extracted with respect to different frequency bands as follows: Uper delta band (2-4 Hz), theta band (4-8 Hz), alpha band (8-12 Hz), beta band (12-30 Hz), and gamma

band (30-50 Hz). For each frequency band of each ROI, Fast Fourier Transform (FFT) and Continuous Wavelet Transform (CWT) is calculated. The FFT is a feature to represent the average frequency response in each band of each ROI. Equation (1) represents the delta band average frequency response (similar to all other selected frequency bands) is calculated as follows:

$$\Delta i = \frac{\sum_{k=fs\Delta i}^{fn\Delta i} |A_k|}{fn\Delta i - fs\Delta i} \quad (1)$$

where the starting frequency and maximum frequency in delta band is $fs\Delta i$ and $fn\Delta i$ respectively in a ROI i. A is the Fourier coefficient for the input delta time series. Same method is applied for all band frequency responses calculation for all regions. After considering human brain as stationary system by calculating FFT feature considering brain as non-stationary dynamic system Continuous Wavelet Transform (CWT) features have been calculated. Continuous Wavelet Transform for Delta band (CWTΔ) calculation is represented in equation (2) as follows:

$$\Delta i = \frac{\sum_{l=ts\Delta i}^{tn\Delta i} \sum_{k=fs\Delta i}^{fn\Delta i} |X_{l,k}|}{(tn\Delta - ts\Delta)(fn\Delta i - fs\Delta i)} \quad (2)$$

Where for the ith ROI, the starting frequency and maximum frequency in delta band is $fs\Delta i$ and $fn\Delta i$ respectively where as $ts\Delta$ and $tn\Delta$ is the starting and ending time of the delta time series. The Current Density (CD) and Cerebral Blood Flow (CBF) are also considered as clinical feature for brain active zone analysis. Current Density is calculated from ESI modality, whereas CBF is calculated from ASL modality by performing the equation (3) defined by [32] in detail.

$$CBF = \frac{\Delta M}{2\alpha M_{ob} TI_1 e^{\frac{-(TI_2+(n-1)slice_{time})}{T_{1b}}}} \quad (3)$$

where ΔM is the difference signal, M_{ob} is the equilibrium magnetization of blood estimated from the calibration scan, TI_1 and TI_2 are the sequence time parameters, n is the number of a given slice, $slice_{time}$ is the time taken to acquire each slice (~40 ms), T_{1b} is the longitudinal relaxation time of blood (1664 ms at 3T), and α is the inversion efficiency (0.95 for pulsed ASL) [32]. As a demographic feature, age, years since beginning of the epilepsy, sex and seizure frequency per day of all the patients are considered in features set. All the ROI are then carefully labelled as HR or ER, to apply machine-learning techniques. In total 16 features were gathered for each participation.

2.5 Classification analysis

After finalizing all the calculations of feature data set, different type of analysis has been made to assess the role of these features to localize the epileptogenic zone.

Full brain analysis (Group-I): For localizing the epileptogenic region, using machine-learning techniques, representations of both classes are equally important therefore all 104 healthy and unhealthy ROIs are considered to train the model. For

each ROI all 14 features including FFT and CWT features are considered. Under this group of analysis three types of experiments has taken place. 1) Considering only 1 region as epileptogenic ROI (ER) whereas all other are considered as healthy regions, 2) Considering most active 10 regions from both hemispheres as unhealthy participation in brain activity while others as healthy ROI and 3) Considering most active 5 regions belong to only one of the hemisphere identified as the epileptic hemisphere, as ER. The types of experiment under Group-I are presented in Fig.3. These all experiments are defined to assess the effectiveness of this research method for the most accurate localization possible using hdEEG and demographic data.

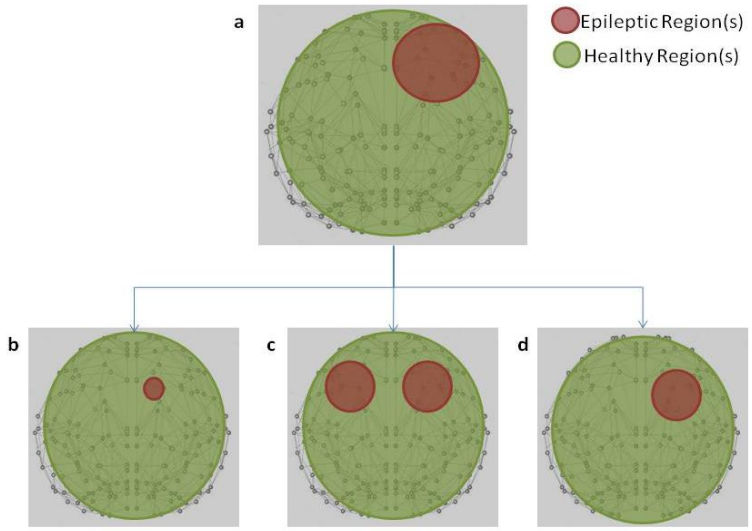

Fig. 3. a) Experiments under Full Brain Analysis. b) Exp-1: 1 ER. c) Exp-2: 5 ER of both hemispheres. d) Exp-3: 5 ER of one hemisphere.

Functionally active brain zone analysis (Group-II): Epileptic region localizing problem is not only localization of brain zone but also the exact region localization under the effected zone to further proceed for the surgical treatment. From all the subjects 10 regions are considered which were actively participating in brain functionality while performing hdEEG in both hemispheres. Only 1 ROI is consider as ER and the rest of 9 ROIs are considered as HR. Along with hdEEG features, ESI and ASL features are also considered to more precisely classify generator and propagator regions among the functionally active brain zone. These regions selection and labeling is based on earlier findings in [8, 32, 33].

For this group of analysis, 16 features of all ROI of each subject including FFT, CWT, CBF and CD are considered. To analyze the contribution of CBF and CD features in correct classification of generator as ER and propagators as HR two types of experiment has taken place under this group of analysis. 1) With CD and CBF features, 2) Without CD and CBF features.

Classification methods: After the construction of three full brain analysis and two active brain analysis datasets, different classification techniques with 10-fold cross-validation have been applied. These experiments are done by Weka version 3.8.3 [35]. For finding the most suitable classifier for the considered domain and under the complexity of features set, more than 25 classifiers from different classification domains like bayes, Lazy networks, Meta, Rule based and Tree structured were considered. Among them 9 classifiers i.e. Bayes Network, NaiveBayes [24], RBFNetwork [25], IB1, IBK, Kstar, Ridor, ADTree [26] and Ordinal CC are considered for comparative analysis because of their outperformance than others.

Evaluation and visualization: Using the above methodology, we have taken the five different experimental datasets including 3 from Group-I and 2 from Group-II as explained above. Initially, the data is having less numbers of effected regions in comparison to unaffected regions hence, creating class imbalance. It leads to the biased results as the classifier always focus on the majority class and produce high accuracies for it while producing the poor results for minority class. Therefore, class imbalance issue is being solved in this research using SMOTE [36].

For evaluating the classification result, 10-fold cross-validation has been used. To evaluate the performance of the classification models following measures have been calculated

1. Accuracy
2. Recall
3. F-Measure

3 Results

While comparing different type of classification methodologies and techniques, time complexity measurement and space complexity measurement are two key factors to be analyzed.

The classification results for each experiment under both groups of analysis can be seen in Table 2 and Table 3. It is noticeable that, for all experiments of both categories, the classification algorithms produce high classification accuracy with high percentage of recall and F-measure. However, it can be noted that the highest classification accuracy is achieved by the Kstar Classifier i.e. 99.79% accuracy with 99.6% Recall and 99.8% F-Measure in experiment 1 of Group-I where the affected area as ER is localized to only one region.

Table 2. Results; Classifiers Accuracy, Recall and F-measure percentage achieved in all experiments.

ML. Algorithms	Group-I: Full Brain Analysis								
	Exp1			*Exp2*			*Exp3*		
	Accuracy	*Recall*	*F-Measure*	*Accuracy*	*Recall*	*F-Measure*	*Accuracy*	*Recall*	*F-Measure*
BayesNet	99.3	99.6	99.3	92.2	96.7	92.6	95.4	98.3	95.5
NaiveBayes	99.3	99.7	99.3	91.9	96.7	92.3	95.4	98.3	95.5
RBFNetwork	99.4	99.7	99.4	84.4	97.2	86.2	79.3	98.5	82.6
IB1	99.5	99.6	99.6	77.3	96.4	81	84.4	98.1	86.3
IBK	99.7	99.6	99.7	83.5	95.3	85.2	80.6	98.1	83.5
Kstar	99.7	99.6	99.8	81.1	95.8	83.6	80.3	98.2	83.3
Ridor	99.5	99.2	99.5	95.6	91.2	95.4	97.4	95.2	97.4
ADTree	99.5	99.5	99.5	86.7	76.1	85.2	97.4	95.4	97.4

Table 3. Results; Classifiers Accuracy, Recall and F-measure percentage achieved in all experiments.

ML. Algorithms	Group-II: Active Brain Analysis					
	Exp1			*Exp2*		
	Accuracy	*Recall*	*F-Measure*	*Accuracy*	*Recall*	*F-Measure*
BayesNet	75.4	76.9	75.8	51.8	31.5	39.5
NaiveBayes	70.8	83.3	74.1	-	-	-
RBFNetwork	73.1	78.7	74.6	54.1	65.7	58.9
IB1	76.4	74.1	75.8	87	83.3	86.5
IBK	76.4	66.7	73.8	91.6	83.3	90.9
Kstar	79.1	75.9	78.5	82.8	65.7	79.3
Ridor	77.7	78.7	78	84.7	73.1	82.7
ADTree	81.4	82.4	81.7	89.8	80.6	88.8

For the cross validation of the proposed system of epileptic region localization using machine learning the average outcomes are also analyzed. The average accuracy in all experiments lied between the ranges of 69.34% to 99.54% as represented in table 4. By considering all the measures i.e. Accuracy, Recall and F-Measure, by considering average of all the classifiers, experiment 1 of Group-I outperformed all other experiments in both groups.

Table 4. Average Accuracy, Recall and F-measure percentage in all experiments.

Average Measures	Group-I			Group-II	
	Exp.1	*Exp.2*	*Exp.3*	*Exp.1*	*Exp.2*
Accuracy	99.52	86.62	89.49	76.39	69.34
Recall	99.50	93.19	97.41	77.48	60.79
F-Measure	99.51	87.66	90.72	76.67	67.18

However, with Fourier and Wavelet transform features, density of current flow and blood flow are also considered for the classification of generator from propagators within epileptic brain zone which reflected decline of accuracy from 76.39% to

69.34% on average among multiple classifiers. There is no significance of CD and CBF features is observed because the majority of the areas considered were already identified by increasing CD and decreasing CBF values trend as compared to healthy controls by [16]. There is no such distinguishing factor of these values among the considered regions to classify genrator verses propgators in Experiment 2 of active brain analysis (Group-II). These features can be of massive participation if would be used for full brain analysis (Group-I) experiments to classify ER(s) from HR(s) which is not easily applicable because of clinical limitations.

On average the recall percentage lied between the ranges of 60.79% to 99.50% whereas the average F-measure lied between the ranges of 67.18% to 99.51%. The highest rate of accuracy, recall and f-measure is achieved in experiment 1 as listed in table 3. For experiment 2 and 3 of Group-I analysis and experiment 1 of Group-II analysis, more recall percentage is achieved as compared to accuracy and F-measure whereas in experiment 1 of Group-I, same results are achieved for accuracy, recall and f-measure and in experiment 2 of Group-II, high accuracy is achieved as compared to recall and F-measure.

Fig. 4 represents all the measures calculated in all experiments for this research work as a spiral graph. As shown in the figure 3, experiment 1 of Group-I outperformed in all the measures and touched the upper bound near 100% achievement.

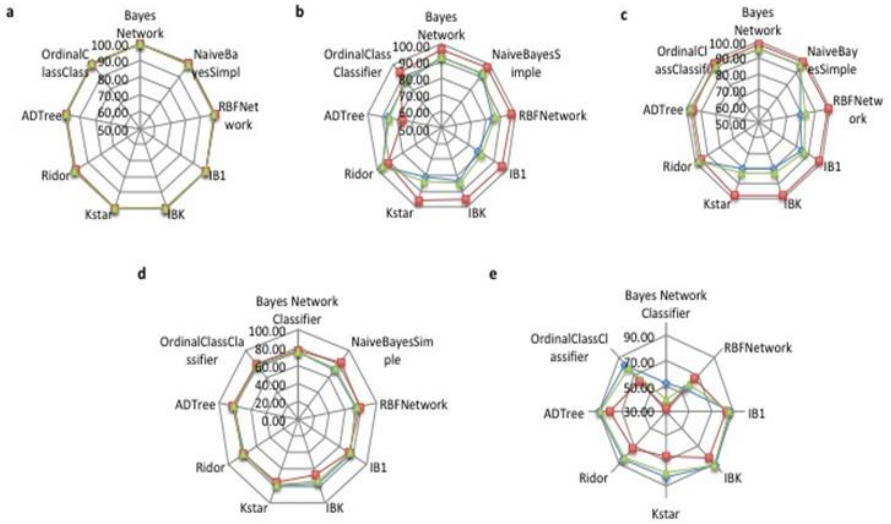

Fig. 4. Accuracy, Recall and F-measure comparison for different classifiers. a) Full brain analysis considering one ER. b) Full brain analysis considering ten ER(s) across both hemispheres. c) Full brain analysis considering five ER(s) of one hemisphere. d) Active brain analysis including CD and CBF measures. e) Active brain analysis without CD and CBF measures

4 Conclusion

A novel approach for the localization of epileptic region is presented in this research to classify epileptogenic brain regions from healthy brain regions based on high density EEG data using different open source softwares like MATLAB 2019, Brainstrom 3 and FSL. This approach is based on rich features extracted through signal processing and classification using several machine learning algorithms. This research is majorly divided into two categories; 1) classification of epileptic region from healthy brain regions, 2) classification of generator region from the propagator regions of epileptic brain zone. The results of this research validated both approaches by achieving the classification accuracy up to 99.5% in first category by only considering features based on hdEEG epochs of 1 second each. Whereas the results of this research also validated the contribution of features like blood flow (CBF) and current density (CD) are extracted from other modalities such as ESI and ASL to classify generator regions from the propagator regions with the classification accuracy of 91.6%.

To conclude, the approach adopted in this research for the localization problem of the drug resistant focal epileptic patients, high accuracy has been achieved using multiple machine learning algorithms. Fourier transform features and wavelet transform features are the major contribution in feature set for full brain classification into ER and HR. This research can be further explored for the more accurate classification of generator from the propagator regions by considering multiclass classifiers and features from other clinical biomarkers.

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6 Authors

Sehresh Khan and **Aunsia Khan** works at National University of Modern Languages, Rawalpindi, Pakistan. Available on mail at aunsia.khan@numl.edu.pk

Nazia Hameed is with School of Computer Science, University of Nottingham, UK

Muhammad Aleem Taufiq works at University of Applied Sciences, Hochschule Fulda, Germany

Saba Riaz is with Shaheed Zulfikar Ali Bhutto Institute of Science and Technology, Islamabad, Pakistan

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