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Machine learning detects EEG microstate alterations in patients living with temporal lobe epilepsy

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ABSTRACT

Purpose: Quasi-stable electrical distribution in EEG called microstates could carry useful information on the dynamics of large scale brain networks. Using machine learning techniques we explored if abnormalities in microstates can identify patients with Temporal Lobe Epilepsy (TLE) in the absence of an interictal discharge (IED).

Method: 4 Classes of microstates were computed from 2 min artefact free EEG epochs in 42 subjects (21 TLE and 21 controls). The percentage of time coverage, frequency of occurrence and duration for each of these microstates were computed and redundancy reduced using feature selection methods. Subsequently, Fishers Linear Discriminant Analysis (FLDA) and logistic regression were used for classification.

Result: FLDA distinguished TLE with 76.1% accuracy (85.0% sensitivity, 66.6% specificity) considering frequency of occurrence and percentage of time coverage of microstate C as features.

Conclusion: Microstate alterations are present in patients with TLE. This feature might be useful in the diagnosis of epilepsy even in the absence of an IED.

1. Introduction

Diagnosis of epilepsy is dependent on accurate clinical history and/or identification of ictal or interictal discharges (IED) on EEG. Repeated scalp EEG having a sensitivity upto 90% is considered gold standard in the management of epilepsy owing to its wide availability and low cost [1]. However, the detection of interictal discharges is dependent on several factors including seizure frequency, sleep deprivation, type of epilepsy, medications, interobserver variability etc. making the sensitivity of scalp EEG in temporal lobe epilepsy (TLE) highly variable [2]. Temporal and spatial attributes of EEG such as Lyaponov exponent, wavelet based analysis, fractal dimensions, time-frequency analysis, etc. have been used as measures to enhance the detection of IED [3]. A significant method in evaluating these attributes is based on machine learning techniques. Machine learning is a "field of study that gives computers the ability to learn without being explicitly programmed" [4]. Gotman [5] first proposed possible applications of machine learning in epilepsy with minimal clinical manifestation and classified type of seizures by decomposing EEG signal into half waves. Support vector machine (SVM) using Independent Component Analysis (ICA), Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA) [6] and power spectrum [7] as feature extraction methods from EEG have been used with overall accuracy of 86.1% in predicting seizure. A major factor to be noted is that, all these attributes were

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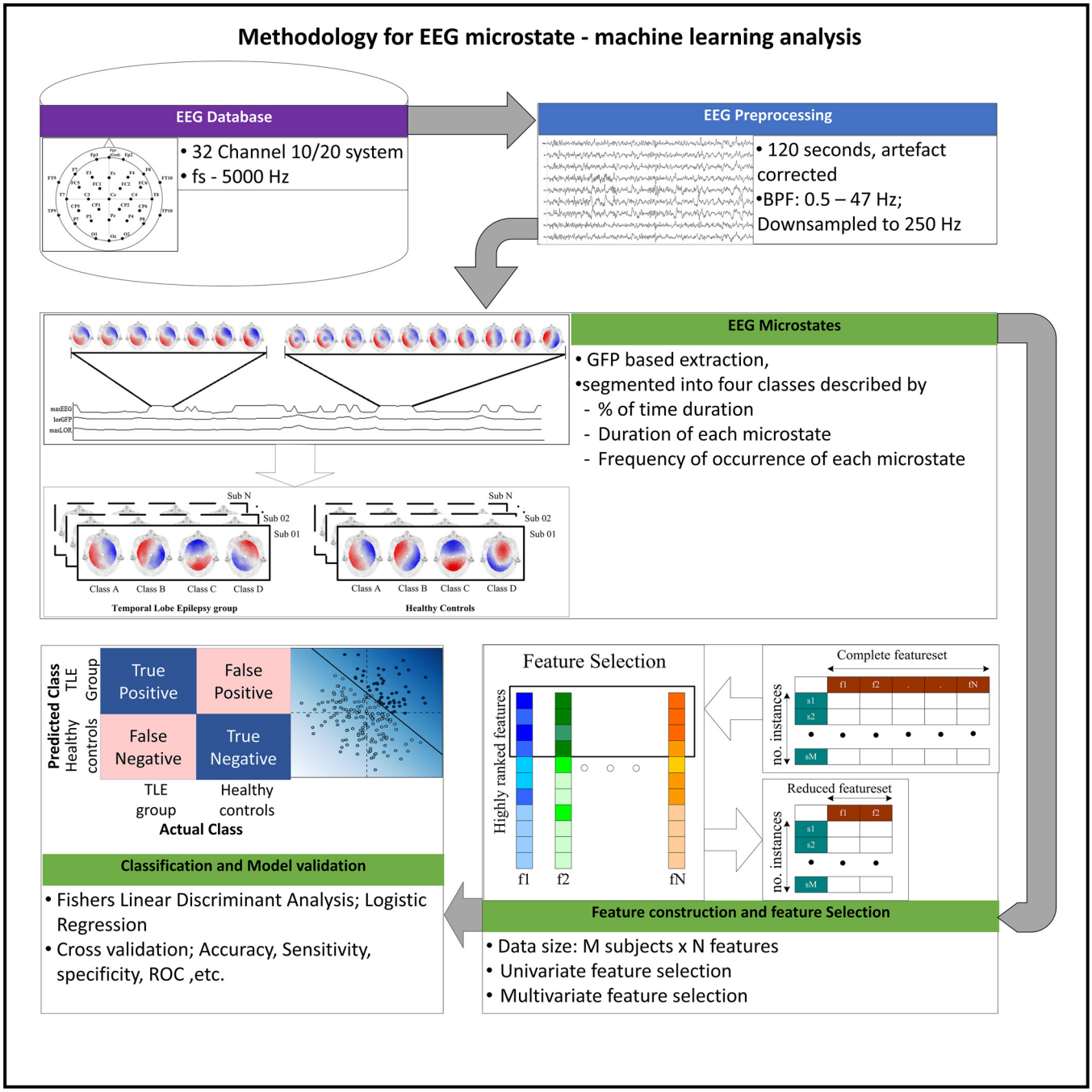

Fig. 1. Methodology for EEG microstate - machine learning analysis.
fs → sampling frequency; BPF → Band Pass Filter; GFP → Global Field Power; ROC → Receiver Operating Characteristics.

dependent on the presence of an ictus or IED and will underperform in identifying epilepsy in its absence. A notable exception in this regard is a recent study that used directed functional connectivity measures in 40 TLE patients without IED. An automated diagnosis using decision tree classification yielded an accuracy of 90.7% with 95.0% sensitivity and 85.7% specificity [8].

EEG microstates are quasi-stable brief patterns of coordinated electrical activity on the cortical surface indicating large scale neuronal networks [9]. They represent functional state variations in brain and are considered as building blocks of mentation on EEG [10–12]. There are four common topographical shapes of microstates namely A, B, C and D. Simultaneous EEG- fMRI has revealed correlations of these microstates with phonological (microstate A), visual (microstate B), salience network (microstate C) and frontoparietal network (microstate D) [13]. Despite the differences in the temporal resolution of microstates and fMRI networks, due to their structural similarity, together with evidence from simultaneous EEG-fMRI, more recent studies view these four microstates as temporally distinct electrophysiological components of default mode network (DMN) [13–16]. Quantitative measurements of microstate duration and frequency could hold important information [17] about epilepsy as it has found applications in understanding psychiatric disorders [18–20].

To understand microstate alterations in TLE, we undertook this exploratory study with a hypothesis that TLE also might have microstate alterations which could be useful in identifying it in the absence of IED or an ictus. We used IED negative EEG in 21 patients with TLE and compared them with 21 healthy controls. To ascertain the usefulness of microstates in predicting epilepsy at a single subject level, we used two

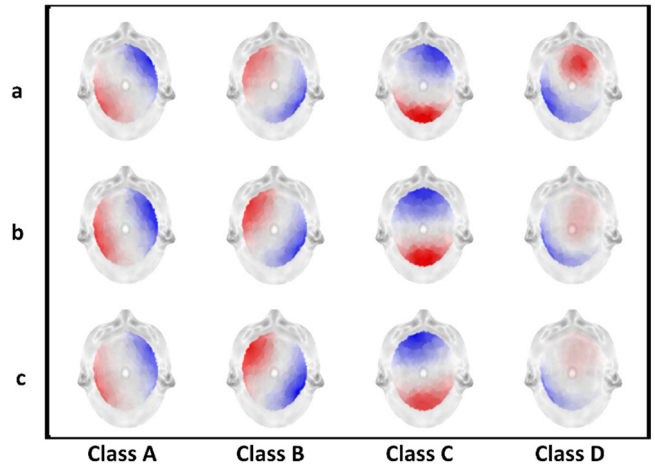

Fig. 2. Microstate scalp maps of EEG signals obtained using sLORETA. a. EEG microstate scalp maps of template data in 4 classes [24]; b. EEG microstate scalp maps of epilepsy group; c. EEG microstate scalp maps of healthy controls.

contemporary machine learning algorithms viz. logistic regression and Fishers Linear Discriminant Analysis (FLDA) owing to the exploratory nature of the study, its limited sample size and relatively small number of features. To the best of our knowledge, application of microstates in epilepsy and implementation of machine learning using microstates are novel components of this study.

2. Materials and methods

2.1. Participants

The study was conducted in a tertiary care neurological institute with the approval of institute ethics committee for humans after obtaining written informed consent form. The data was acquired as part of a larger study understanding hemodynamic correlates of IED in lesional epilepsy. Twenty one male patients (age 25.14 ± 6.08) with TLE (based on the Video EEG, MRI localization) having no interictal discharges were retrospectively selected. Six patients had right TLE, 12 left TLE and 3 bilateral TLE. The mean duration of illness was 13.43 ± 6.86 years, mean age at onset of disease was 12.0 ± 6.56 years, and the mean frequency of seizures per month was 9.24 (0.03–100) and mean number of antiepileptic drugs (AED's) were 2.66 ± 0.79. All patients were recruited in the interictal period with an average time of 38 days from the last ictus. The matched control group comprised 21 healthy subjects (age 28.1 ± 4.2) from the existing imaging data bank. There were no significant differences in age or sex between the two groups ($p = 0.075$). None of the subjects had prior history of trauma, and were not on medications for psychiatric illness. Scalp EEG was verified in all subjects (SS, SC) to rule out the presence of an IED.

2.2. Data acquisition

EEG data was recorded using a 32 channel (Brain Products GmbH, Germany) 10–20 acquisition system. Since, the data was acquired as part of a larger study understanding hemodynamic correlates of IED with simultaneous EEG-fMRI, (Skyra, Siemens, Erlangen, Germany) an initial sampling frequency of 5000 Hz was used. ECG electrode, FCz reference electrode, AFz ground electrode were part of the 32 channels. A minimum threshold of 10 k Ω and EEG recording was performed using brain recorder (version 1.03, Brain Products). All subjects were awake with eyes closed during the entire procedure.

2.3. Data analysis (Fig. 1)

2.3.1. EEG pre-processing

The acquired raw EEG was pre-processed offline using Brain Vision Analyzer (Brain Products GmbH, Gilching, Germany). Ballistocardiogram (BCG) artifacts were removed using average subtraction method considering R peaks as reference [21]. Segments containing sleep spindles and k complexes were visually removed. The corrected EEG data was then filtered using a band pass filter with minimum and maximum cut off frequency of 0.5 Hz and 47 Hz respectively. A notch filter of 50 Hz was applied to reduce the baseline artefact. The filtered data was then down sampled to 250 Hz sampling frequency. Ocular motion and other artefacts were corrected visually and using Independent Component Analysis. Similar to previous studies [22,11], the first 120 s artefact free EEG data of each subject were retained for microstate analyses, after applying a band pass filter (BPF) of 2–20 Hz, and re-computing against the average reference.

2.3.2. Microstates segmentation

EEG epochs were transformed into maps of momentary distributions of scalp potentials [22,23] following standard steps in microstate segmentation using sLORETA (KEY Institute for Brain Mind Research, Zurich). The overall potential variance across the electrodes were quantified by measuring the *global field power* (GFP). The momentary peaks which were obtained by the GFP were extracted and further clustered into four microstate classes using k-means based clustering method as in previous study [24]. Group model maps were computed based on individual model maps. The resulting class-labeled group model maps were compared with templates to assign model maps of each participant to four microstate classes (also known as back-fitting procedure). Across topographies these four microstates explained 63.34 ± 0.06 of the total variance of GFP. Three parameters based on temporal attributes of EEG data were derived from the 4 classes of microstates. They were mean duration (ms) indicating the stability of underlying neuronal structure, frequency of occurrence (/s) indicating the tendency of a underlying neuronal generators to become activated and the percentage of time coverage (%) representing the time of coverage of each microstate compared to others. The microstate scalp maps derived from epilepsy group, control group and the template are represented in Fig. 2.

2.3.3. Feature selection

The data from the microstate parameters had a binary class continuous variable distribution with 42 instances (21 TLE and 21 Healthy Controls) and 12 microstate attributes (4 classes x 3 parameters). Since the microstate attributes had different units, the data was normalized to [0,1] scale. An information based univariate feature evaluation method was implemented which computes the gain of individual feature to its class (Waikato Environment of Knowledge Analysis, version 3.8.2). A ranking based search method was based on

$$G(x, y) = H(x) - H(x|y)$$

Where, $x \rightarrow$ dependent variable (group); $y \rightarrow$ independent variable (feature attributes).

On performing a Leave One Out Cross Validation (LOOCV), the frequency of occurrence, duration and percentage of time coverage of microstate class C resulted in higher average merit. To observe how these individual characteristics of microstate C contribute as a set of attributes in distinguishing TLE from healthy controls, a subset based evaluation method with a Best First search method was implemented. On performing LOOCV, the frequency of occurrence and percentage of time duration of microstate C occurred in all folds.

Therefore, from the above methods it was concluded that these two microstate parameters of class C were significantly different between the groups. Hence, only % of time duration and frequency of occurrence of class C were considered for classification.

2.3.4. Classification

After feature selection, the dataset consisted of 2 independent variables (feature attributes) and 42 instance labeled pairs. Considering the developed feature set as multivariate in nature, FLDA was implemented to determine the discriminating capability of microstate C parameters to differentiate the two groups. FLDA transforms multivariate to univariate observations such that the observations derived from each of these population are maximally separated. The significance in using FLDA is its robustness to near normality and variation in covariance matrices as compared to conventional methods of discriminant analysis [25]. Further, multinomial logistic regression was used to determine the predictive capability of these microstate parameters in distinguishing the two groups, following the steps as elaborated in previous studies [26–28].

Though both the methods develop similar classifier models, the discriminative and the predictive capabilities of microstate parameters were evaluated considering measures pertaining to accuracy, sensitivity, specificity, receiver operating characteristics (ROC) and F1 measure [29].

3. Results

3.1. Classifier performance

Considering the LOOCV based evaluation, FLDA resulted in an overall accuracy of 73.80 with 81.0% sensitivity and 66.7% specificity. This resulted in 31 correctly classified subjects among 42 subjects with 17 true positive instances (TPI) and 14 true negative instances (TNI). Logistic regression had an overall accuracy of 66.7% with 71.4% sensitivity and 61.9% specificity resulting in 28 correctly classified instances from an overall of 42 instances (TPI = 15; TNI = 13).

To further evaluate the classifier performance using ROC (Fig. 3), a 10 fold stratified cross validation was performed for both the classifier methods resulting in 37 training and 5 test instances. The measures from the 10 fold cross validation also showed similar performance characteristics as observed in LOOCV based evaluation. An optimal threshold value of 0.49 was selected resulting in highest TPR of 0.85 and lowest FPR of 0.38 as observed in Table 1. Considering the multinomial logistic regression classifier, an optimal threshold of 0.49 was selected which resulted in highest TPR of 0.80 and lowest FPR of 0.42.

3.2. Clinical correlation

Frequency of occurrence and percentage of time coverage of microstate C was correlated with the age at onset of epilepsy, frequency of seizures, duration of epilepsy and number of antiepileptic drugs using Pearson's linear correlation. There were no significant correlation of microstate C with these clinical variables (Supplementary Table 1).

4. Discussion

The study of EEG microstates using machine learning techniques suggests significant alterations in the frequency of neural generators of microstate C in patients living with epilepsy. Alterations in microstate C was 76.1% accurate in distinguishing epilepsy from healthy controls, even in the absence of a visible IED on EEG. These findings, provide first hand evidence for the use of EEG microstates in patients living with TLE.

Microstate C has a midline topography with a frontal to occipital alignment and is found most prominent at rest [12,30] and is predominated by a task inhibitory alpha activity [30]. Task inhibitory alpha activity is one of the most basic cognitive processes and is known to play a key role in coalescing brain activity at different frequencies [30]. Inappropriate activation of a task inhibitory alpha state could interfere with the normal syntax of the microstates [31]. It is possible that the alterations in microstate C observed in our study could be representative of the changes in alpha rhythm seen in patients with epilepsy. Abnormalities of alpha rhythm was known to be associated in patients with epilepsy [32] and a recent study on EEG has reported alpha rhythm abnormalities to be more specific for the diagnosis of epilepsy and less dependent on the number of AED's [33]. In the current study, it needs to be noted that both frequency of occurrence and percentage of time duration of microstate C were used as features for classification, since these had the highest ranking during feature

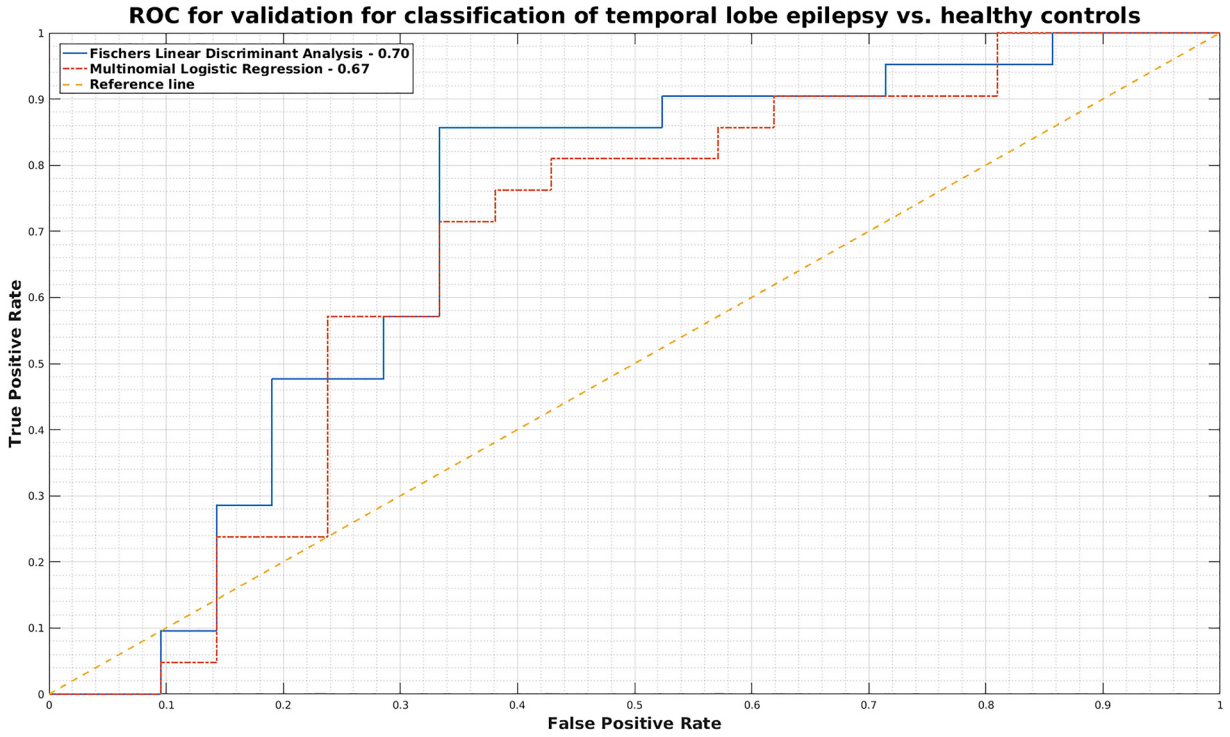

Fig. 3. ROC analysis of classification methods.

Table 1
Performance evaluation of classifier methods.

Sl.no	Classification method	ACC	SEN	SPC	TP	FN	FP	TN	FPR	TPR	Pres.	REC	F Measure	threshold
1	FLDA	76.1	85.7	66.6	18	3	8	13	0.38	0.85	0.69	0.85	0.76	0.4998
2	MLR	69.0	80.9	57.1	17	4	9	12	0.42	0.80	0.65	0.80	0.72	0.4968

ACC → Accuracy; SEN → Sensitivity; SPC → Specificity; TP → True Positive; FN → False Negative; FP → False Positive; TN → True Negative; FPR → False Positive Rate; TPR → True Positive Rate; Pres. → Precision; REC → Recall.

selection. Previous studies using microstates have reported decreased frequency of microstate C in patients with panic disorder [19] and increased frequency in schizophrenia [11,34,18], and syndrome of 22q11 deletion [35]. Drug induced [34,36] and memory deficit [37] induced alterations in microstate C also have been reported. Though we did not get significant correlations of selected microstate C features with number of AED and duration of disease, it is possible that the alterations in microstate C is not specific to epilepsy. It could reflect the combined effect of drug, disease and cognitive deficits that a patient living with epilepsy could harbour. Further studies will be required to understand these changes further.

A recent study using machine learning and directed connectivity measures in IED negative TLE patients [8] revealed an accuracy of 90.7% using a decision tree classifier. Other studies have reported accuracies ranging from 76 to 93% in the diagnosis of TLE using MRI [38,39]. Though the clinical relevance of 93% accuracy in automated diagnosis of TLE in patients with MRI evidence of hippocampal sclerosis might be peripheral, such methods could provide value addition in difficult to diagnose TLE. Towards this end, our study and Verhoeven et al. study [8] gains higher clinical momentum than MRI features because of the choice of IED negative EEG as inputs in these studies. Though the accuracy using microstates in our study is lesser, it is important to note that the Verhoeven et al. [8] classification was based on pre-identified 14 regions of interest, while our study input was completely data driven. Another point is that Verhoeven et al. [8] used IED negative segments in EEG whereas in our study we have excluded patients with IED in the total duration of EEG as it was possible that an IED could continue to alter the connectivity for several seconds before and after its onset [40]. While directed connectivity is an indicator of local connectivity, microstates are indicators of large scale connectivity. The choice of classifiers were also different using random forest and FLDA algorithms respectively. While all these factors could have played independent and important roles while determining accuracy, it is important to note that these automated methods have sensitivity comparable to an ictus in the diagnosis of epilepsy even without the presence of an IED.

Inclusion of patients with refractory epilepsy as in the study by Verhoeven et al. [8] could be a major limitation of our study together with limited sample size. Replicability in large number of patients with recent onset seizures might be required to assess the real validity of this tool. As we did not have the neuropsychological scores we cannot be certain that the microstate alterations are independent of the cognitive deficits. Another factor is that only temporal characteristics of EEG data was considered in this study. It remains to be seen whether adding other features based on spatial characteristics and time-frequency analysis, along with clinical variables could improve the performance measures of classifiers. Despite these limitations, the findings of the current study have advanced literature as it has reported microstate alterations in patients with epilepsy with 76.1% accuracy in predicting epilepsy even in the absence of an IED.

5. Conclusion

Large scale EEG microstate network alterations can provide subject specific measures of disease and can be used to identify temporal lobe epilepsy even when the interictal discharges are absent.

Author's contribution

Concept and Design: RDB, KRV, SSR, PSC, SS.
Analysis: KRV, SSR, SB, RP, VRR, GC, KKM, KT.
Draft: RDB, KRV, SSR, SB, KR, RCM.
Final approval: RDB, KRV, SSR, SB, RP, VRR, GC, KR, RCM, KT, KKM, PSC, SS.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2018.07.007.

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