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Classification of Epileptogenic networks in temporal lobe epilepsy patients in contrast to the healthy controls

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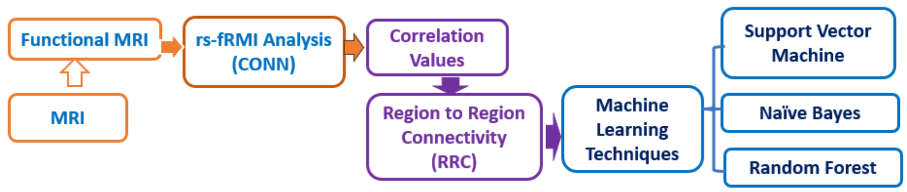
Article

ABSTRACT



This study aims to investigate the classification of individuals with Left Temporal Lobe Epilepsy (LTLE) and Right Temporal Lobe Epilepsy (RTLE) in comparison to Healthy Controls (HC) based on machine learning approaches. The dataset of patients and Healthy Cohorts of resting-state functional magnetic resonance imaging (rs-fMRI) is preprocessed using CONN software which works on MATLAB. Twelve Regions of Interest (ROIs) were selected in CONN. Supervised learning algorithms, particularly the Random Forest Algorithm, were employed for categorizing the connection matrices of the 12 ROIs. The Random Forest Algorithm achieved the highest accuracy during five cross-validation folds, with 83% accuracy in classifying Right Healthy Controls (RHC)-RTLE and 72.10% in classifying Left Healthy Controls (LHC)-LTLE. Feature importance plots generated by the Random Forest Algorithm were utilized to identify critical relationships influencing the categorization, demonstrating distinct connection patterns between individuals with RTLE and RHC and LTLE and LHC, suggesting potential implications for understanding temporal lobe epilepsy.

Keywords: rs-fMRI, functional MRI, Right Temporal Lobe Epilepsy (RTLE), Magnetic resonance imaging, Machine Learning, Random Forest.

INTRODUCTION

Advances in advanced magnetic resonance imaging (MRI), especially functional MRI (fMRI), SPECT, PET, and CT are revolutionizing how people with neurologic disorders are treated. One of fMRI's primary benefits over EEG and MEG is its higher spatial resolution. By acquiring detailed spatial maps of brain activity, fMRI allows researchers to pinpoint neural activity in specific brain regions[1] or structures. A relatively common diagnostic method for neurological disorders is resting-state functional magnetic resonance imaging (rs-fMRI)[2]. The basis of rs-fMRI is the blood oxygenated level dependency(BOLD) signal. It is predicated on the idea that variations in local blood flow and oxygenation align with variations in brain activity. Functional connectivity (FC) analysis is a crucial component of rs-fMRI, which examines the temporal relationships between various brain regions. Several techniques are frequently employed to investigate functional connectivity[3] such as independent component analysis (ICA), graph theory, and seed-based correlation analysis.

The brain is active at rest, and this activity measures changes or modifications that people with temporal lobe epilepsy (TLE) experience. To fully comprehend how complex epilepsy is, the primary goal of this investigation is to investigate the changes in FC during the resting state. Modifications in FC may facilitate the use of surgical methods to treat temporal lobe epilepsy in patients who are not responding to medication. Surgery is the most effective line of treatment[4] for about 20–30% of epileptic individuals whose seizures are not controlled by medication.[5] Approximately 60–70% of patients[6] achieve seizure independence after a thorough preoperative assessment.

A useful method for researching neurological disorders, such as epilepsy, is non-invasive brain imaging called resting-state functional magnetic resonance imaging, or rs-fMRI. rs-fMRI is the imaging methodology used in this work. Recording spontaneous brain activity while the patient is at rest, enables scientists and medical professionals to examine the brain's functional connectivity (i.e., not executing any activities). This approach sheds light on how communication between various brain regions—which might be

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disrupted in epilepsy—is affected. rs-fMRI reveals patterns of functional connectivity by tracking correlations in the activity of several brain areas across time. In individuals with epilepsy, networks implicated in the production and transmission of seizures (such as the epileptogenic zone) frequently exhibit aberrant connections. Many times, localized or broad failure in particular brain networks is linked to epilepsy. These networks can be mapped with the use of rs-fMRI, which might reveal regions that might be involved in seizure activity even in the absence of overt seizures. This is especially helpful when seizures are hard to pinpoint with conventional methods like structural MRI or electroencephalogram (EEG). While positron emission tomography (PET), task-based fMRI, and electroencephalography (EEG) are also utilized in the diagnosis of epilepsy, rs-fMRI has the benefit of not requiring the patient to actively participate. Patients who may have difficulty with task-based imaging, such as children or those with cognitive disabilities, will find this to be especially helpful. Epilepsy patients' rs-fMRI data is generated and compared to those of Healthy Cohorts(HC). Functional connectivity alterations were found in specific regions of the brain that are relevant to memory-related functional ability. These regions are used in this work for classification. Finding discrepancies between the functional connectivity patterns of TLE patients at rest and those of healthy controls may help during surgery. Understanding the differences in the regions of interest can help surgical assistance by determining which regions' connection patterns are most impacted when compared to the TLE and healthy groups.

Patients who are candidates for epilepsy surgery can have their aberrant brain networks and functional connections identified by rs-fMRI. It gives surgeons a better understanding of the regions that are essential for the beginning of seizures as well as regular brain activity. By observing changes in brain connection over time, rs-fMRI can help with not only the planning of surgery but also the diagnosis of epilepsy subtypes, tracking the progression of the condition, and assessing the efficacy of treatment.

History of Machine Learning in Neuro-Imaging

The most cutting-edge research concentrates on the diagnostic requirements for epileptic patients, a field in which EEG is currently being actively used in clinical practice. According to the present standards, highly skilled specialist epileptologists must laboriously manually annotate many hours of EEG recording to make diagnoses and provide treatments.[7] Machine learning techniques allow the automatic identification of epilepsy markers utilizing certain spectral, morphological, or network-based properties in interictal (non-seizure) data. While some feature-based methods try to mimic the expert's eye by employing features similar to those that epileptologists see, other end-to-end neural networks and deep learning models try to extract previously unidentified epilepsy markers directly from the raw data. Sorting regular EEG data into normal and abnormal categories is one example of this; abnormal is by definition heterogeneous.[8] Machine learning-based clinical decision support for epileptologists has enormous potential for diagnosing and localizing epileptic foci because it can uncover complex relationships among brain regions and actions that are difficult to see with the naked eye. Numerous deep-learning-based techniques have also been developed to lessen metal artifacts in CT imaging of various anatomies[9]. Patients who use deep brain stimulation (DBS) devices may benefit from improved brain CT imaging through the application of similar approaches. Figure 1 demonstrates the popularity of the utilization of rs-fMRI and machine learning approach and the articles published about them in recent years.

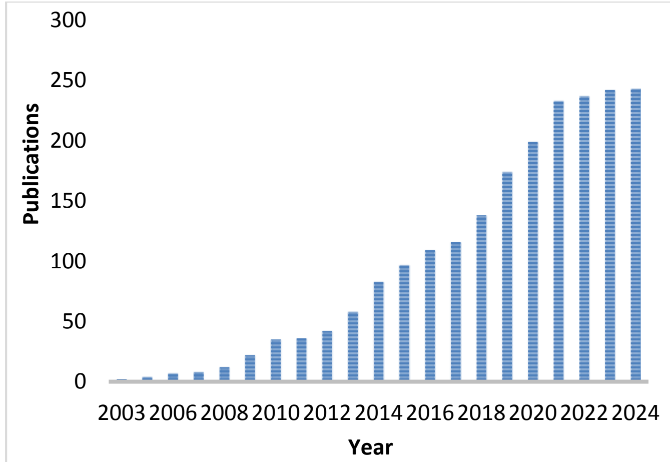

Figure 1. Publications obtained from Pub Med with the following Search query: "Resting-State Functional Magnetic Resonance Imaging" or "rs-fMRI" or "fMRI"

FMRI & rs-fMRI: Machine Learning Perspective

Until the 2000s, magnetic resonance imaging (MRI) served as the main neuroimaging technique used to investigate the roles played by various brain regions and how this combines to produce various cognitive images that are derived from neural processes. Numerous follow-up investigations and identifying associated impulsive variations in well-characterized cortical nets as suggested by Biswal et. al.[2] have made rs-fMRI a valuable tool for investigating the brain's functional architecture. Over the last decade, the number of studies using the resting-state paradigm has increased at a never-before-seen rate. Compared to other task-based experiments, these methods are far more straightforward and can nonetheless yield important information about the functional connectivity of the healthy brain and how it is disrupted in disease. Another appealing feature of the resting state is that it facilitates cross-site cooperation.

In the field of epilepsy research, functional magnetic resonance imaging (fMRI) and resting-state fMRI (rs-fMRI) have different properties and uses. In fMRI research, participants do particular activities to monitor brain activation associated with those tasks, offering insights into cognitive processes and task-specific brain activity. On the other hand, spontaneous oscillations in BOLD signals during rest are captured by rs-fMRI, which reveals intrinsic patterns of functional connectivity. Machine learning algorithms applied to rs-fMRI aim to uncover abnormalities in functional connectivity associated with neurological illnesses like epilepsy, differentiating between healthy and epileptic brains based on faulty resting-state connections.[10]

MATERIAL AND METHODS

CONN[11] neuroimaging software, based on MATLAB 2022b, is used to determine connection patterns between Temporal Lobe patients(TLE) and healthy controls. Functional Connectivity [12] could be between seeds and voxels, as well as between regions of interest (ROIs) and voxels. Within- and between-subject factors are also included in group-level analyses. A dataset of 16 Healthy Controls was generated for rs-fMRI, and a dataset of 16 Epilepsy patients was available(out of which 7 subjects are for Right TLE(RTLE) and 9 subjects are for Left TLE(LTLE)).

The statistical dependency or coordination between neural activity in various brain regions is called functional connectivity.[13] The primary indication of functional connectivity is the temporal correlations between signals originating from distinct brain areas. For example, if two regions show comparable patterns of activity over time, they are deemed functionally related. Functional connectivity studies often focus on large-scale brain networks, such as the default mode network (DMN).[14] These networks are collections of brain regions that regularly exhibit synchronized activity, indicating a cooperative role for these networks in particular cognitive activities. In this study, Region-Region Connectivity in CONN[11] is considered and their correlational analysis[15] is the basis used as a feature for the machine learning approach. In functional connectivity analysis (fMRI data analysis, for example), a first-level connectivity matrix is a matrix that measures the connection or correlations between various brain areas or voxels at the first level of analysis for a particular participant or session. Typically, it is a square matrix with a row and column for each brain region (such as a Region of interest (ROI) or voxel). Every matrix component symbolizes the relationship (correlation, for example) between two locations.

Database- The age group considered for the subjects has an average age of 28. It includes a few subjects with ages of 15-25 years and a few subjects with ages which ranged from 35-45 years. Subjects had a mixed gender of Male and Females suffering from RTLE and LTLE. The average age of healthy controls is around 24 years. So the experimentation done in this work and the accuracy results obtained are based on the varied range of age as well as gender.

The Regions of Interest (ROIs) selected for the said study are described in the given Tables.

Table 1. List of ROIs for Statistical Testing in RTLE and Right Regions of Healthy Controls (RHC)

ROI Name	Abbreviation
Medial Prefrontal Cortex	MPFC
Posterior Cingular Cortex	PCC
Cingulate Gyrus, anterior division	AC
Cingulate Gyrus, posterior division	PC
Planum Temporal Right	PT r
Temporal Pole Right	TP r
Insular Cortex Right	IC r
Parahippocampal Gyrus, anterior division Right	aPaHC r
Parahippocampal Gyrus, posterior division Right	pPaHC r
Hippocampus Left	Hippo l
HippocampusRight	Hippo r
Amygdala Right	Amygdala r

Table 2. List of ROIs for Statistical Testing in LTLE and left Regions Healthy Controls (LHC)

ROI Name	Abbreviation
Medial Prefrontal Cortex	MPFC
Posterior Cingulate Cortex	PCC
Cingulate Gyrus, Anterior division	AC
Cingulate Gyrus, posterior division	PC
Planum Temporal Left	PT l
Temporal Pole Left	TP l
Insular Cortex Left	IC l
Parahippocampal Gyrus, anterior division Left	aPaHCl
Parahippocampal Gyrus, posterior division Left	pPaHC l
Hippocampus Left	Hippo l
Hippocampus Right	Hippo r
Amygdala Left	Amygdala l

MACHINE LEARNING IN RS-FMRI

The popular machine learning algorithms for the rs-fMRI use unsupervised methods of learning. Modeling resting-state activity is more difficult than in task-driven investigations since these oscillations are not caused by controlled stimuli. Consequently, the methods of analysis[16 17 18] employed to describe the spatial-temporal patterns for the activity or task fMRI are frequently inappropriate for rs-fMRI.

To gain a better understanding of data in both the temporal and spatial domains, it is not surprising that early analytical techniques concentrated on subdivision or grouping tactics. Using techniques like ICA [19], aided in the identification of networks at rest. Following this, the main objective for rs-fMRI is brain parcellations or lateralization which will aid in surgical decisions[20 21].

In the late 2000s, machine learning discovered another, potentially more therapeutically useful application. These neuroimaging-based indicators can be used to create prognostic or diagnostic tools through the application of machine learning. These neuroimaging-based indicators can be used to create prognostic or diagnostic tools through the application of machine learning. Together with statistical evaluation, visualization and understanding of these models can offer new perspectives on the degree of abnormal resting-state patterns in brain diseases[22 23] The majority of these techniques[24] concentrate on obtaining connectome features for single-subject predictions.

UNSUPERVISED MACHINE LEARNING

Understanding the dynamics and functional architecture of the healthy brain is the primary objective of unsupervised learning approaches in rs-fMRI. Techniques such as matrix splitting and grouping, for instance, can disclose the underlying structure of dynamic functional connectivity in the brain.

K-Means

The objective of clustering, given a set of data points $\{X_1,..., Xn\}$, is to divide the data into distinct groups $\{C_1,..., C_k\}$. The clustering objective of many clustering algorithms varies, to optimize within-cluster similarity or between-cluster dissimilarity-means. Currently, the most often used learning algorithm for data partitioning is K-means clustering. The within-cluster variance is what the algorithm seeks to minimize.

Formally, this translates to the subsequent clustering goal:

Initialize cluster centroids $\mu 1, \mu 2, , \mu k$ randomly or based on some heuristic

Repeat until convergence: Assign each data point xi to the nearest cluster centroid:

$$c^{(i)} = \text{argmin}_j \|x^{(i)} - \mu_j\|^2 \quad (1)$$

Update cluster centroids to be the mean of the data points assigned to them:

$$\mu_j = \frac{1}{|C_j|} \sum_{x_i \in C_j} x_i \quad (2)$$

where C_j is the set of data points assigned to cluster j.

SUPERVISED MACHINE LEARNING

Detailed characterizations of rs-fMRI are made possible by machine learning techniques. Much work has gone into applying rs-fMRI to guide treatment decisions and predict illness prognosis, as well as to classify patients against controls. From creating individual-level forecasts to mapping functional networks.

Support Vector Machine

Support vector machines or SVMs[25] for tasks like regression and classification, a support vector machine builds a hyper-plane or set of hyper-planes in an infinite or high-dimensional space.

Gaussian Naive Bayes

Naive Bayes[26] is a set of supervised learning algorithms based on applying Bayes' theorem with the "naive" assumption that every pair of features, given the value of the class variable, is conditionally independent. In Gaussian Naive Bayes, the likelihood of features is assumed to be Gaussian.

Given a dataset X = $\{x_1,x_2,...,x_n\}$ with features $x_i = (x_{i1},x_{i2},...,xi)$ and corresponding class labels $y = (y_1,y_2,...,in)$. Let C_k represent the kth class, where k = 1,2,..., K, with prior probability $P(C_k)$ or each feature xij, assume it follows Gaussian distribution within the class Ck.

$$(x_{ij}|C_k) = \frac{1}{\sqrt{2\pi\sigma_{jk}^2}} exp\left(-\frac{(x_{ij} - \mu_{jk})^2}{2\sigma_{jk}^2}\right) \quad (3)$$

is the mean of feature j in class k.

σ_{jk}^2 is the variance of feature j in class k.

To predict the class label for a new instance x^*, calculate the posterior probability for each class C_k using Bayes' theorem:

$$P(C_k|x^*) = \frac{P(C_k)\prod_{j=1}^{d} P(x_j^*|C_k)}{\sum_{i=1}^{K} P(C_i)\prod_{j=1}^{d} P(x_j^*|C_i)} \quad (4)$$

Assign the class label for x^* as:

$$\hat{y} = \text{argmax}_k P(Ck|x*) \quad (5)$$

Random Forest

Random forest[27,28] is a machine-learning algorithm that combines the outputs of multiple decision trees to produce a single result. In this section the comparison is done for the Regions of Interest for the RTLE versus RHC and on similar lines it is done for LTLE versus LHC.

MACHINE LEARNING IN EPILEPSY

Presently, neuroimaging helps epileptic patients when a specific treatment may be targeted based on the identification of an underlying lesion. Vergun et al.'s study[29] suggests that using rs-fMRI and machine learning techniques can help identify areas of the eloquent cortex, and provide the surgeon with safer maximum resection boundaries. Several rs-fMRI imaging metrics were employed along with an SVM classifier. Yang et al.[30] found that they could predict the lateralization of temporal lobe epilepsy in a group of 12 individuals with 83% accuracy. Chiang and colleagues[15,31] were able to lateralize temporal lobe epilepsy in a group of 24 patients with 95.8% accuracy by employing rs-fMRI imaging features in conjunction with a machine learning technique called computer-automated diagnosis using fMRI interictal graph theory. The use of machine learning techniques on rs-fMRI data from patients, aged 4 to 19, was examined by Paldino and colleagues.[32,33]

CLASSIFICATION OF NETWORK CONNECTIONS

Supervised machine learning algorithms including Support Vector Classifier (SVC), Gaussian Naive Bayes (NB), and Random Forest were employed to classify individual network connections derived from the connectivity matrix of the study cohort. Classification tasks were conducted separately for Right Temporal Lobe Epilepsy (RTLE) and Right Healthy Controls (RHCs), as well as for Left Temporal Lobe Epilepsy (LTLE) and Left Healthy Controls (LHCs). Cross-validation using 5 folds was implemented to assess the mean accuracy of the machine learning models in classifying the groups (TLE and HCs). A feature importance plot was used to visualize the regions utilized for the classification of the healthy and the patient groups.

RESULTS AND DISCUSSION

RTLE v/s RHC

The classification model was implemented using multiple supervised learning algorithms, Support Vector Machine, Naive Bayes, and Random Forest. A comparison of performance metrics of different machine learning models. Table 3 indicates that Random Forest gave the highest mean cross-validation accuracy of 83% in classifying the networks of HC and RTLE patients. Furthermore, it is analyzed for the Feature Importance[34 35] of the random forest model to get the Top k significant features as shown in Figure 2.

Table 3. Performance Metrics for classification of network connections in RTLE v/s RHC

Algorithm	Mean Cross-Validation Accuracy
Support Vector Classifier	70 %
Gaussian Naive Bayes	72.1%
Random Forrest Classifier	83.1%

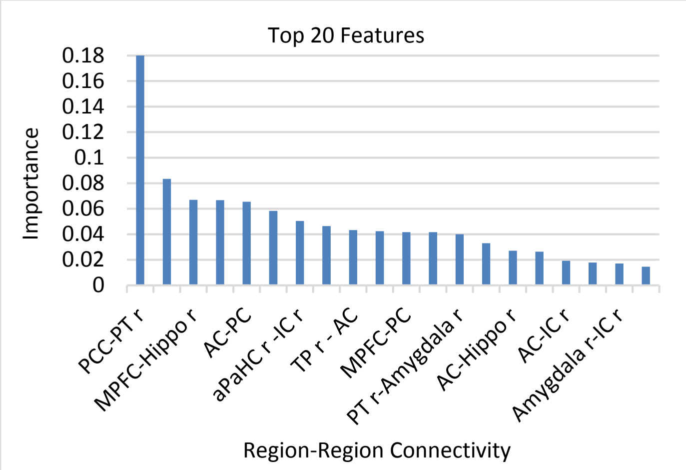

Figure 2. Feature Importance plot of significant networks in the classification of RTLE and RHC subjects

LTLE v/s LHC

A similar process was repeated for the classification of networks between HC and LTLE using the same algorithms (SVM, Naive Bayes, Random Forest). The comparison of performance metrics in HC and LTLE network classification (Table 4) showed similar results, with Random Forest achieving the highest mean cross-validation accuracy of 72%. (Figure 3 shows the top k significant network connections which were derived from the Feature Importance plot from the random forest.

Table 4. Performance Metrics for classification of network connections in LTLE v/s LHC

Algorithm	Mean Cross-Validation Accuracy
Support Vector Classifier	56.6 %
Gaussian Naive Bayes	72%
Random Forrest Classifier	72.1%

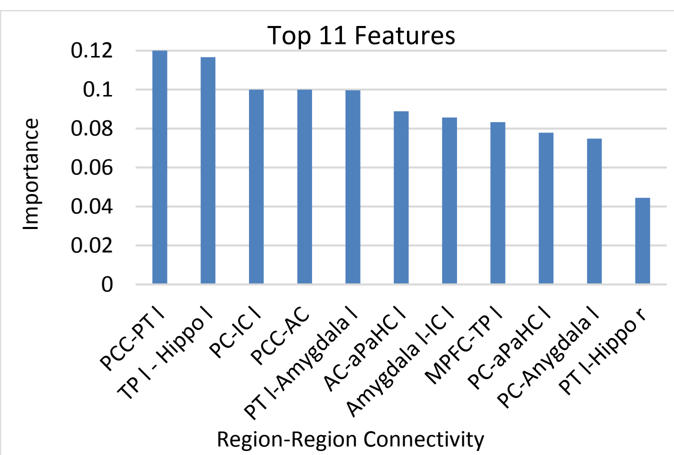

Figure 3. Feature Importance plot of significant networks in the classification of LTLE and LHC subjects

This study makes a comparison between the memory-related regions for the right side of the controls with the RTLE group and similarly the memory-related regions for the left side of the controls and the left-sided TLE group. The literature reviewed for carrying out this research had compared RTLE and LTLE groups with controls and not particularly for left and right regions of controls. The current study lays the groundwork for further advancements in understanding network classification among Healthy Controls (HC) and Temporal Lobe Epilepsy (TLE) patients using resting-state functional magnetic resonance imaging (rs-fMRI). To enhance the robustness and generalizability of our findings, expanding the dataset by including a larger and more diverse sample of subjects is imperative. This will not only contribute to the reliability of the identified network changes but also allow for the exploration of potential subgroups within the TLE population.

Because fMRI data is high-dimensional, the number of features can increase rapidly when there are numerous ROIs. To prevent overfitting, appropriate feature selection or dimensionality reduction strategies are crucial. Supervised machine learning techniques are essential for identifying or predicting outcomes based on patterns of brain connection in resting-state fMRI (rs-fMRI) research. The capacity of these algorithms to assess feature importance is a major benefit as it facilitates the identification of the most important brain areas and their connections that influence the model's predictive performance. These findings are helpful in figuring out which areas of the brain or linkages between functions are critical in identifying distinct cognitive states or illnesses. Changes in connection are seen in temporal lobe epilepsy (TLE), such as decreased connectivity in areas of the hippocampus and amygdala implicated in memory-related functions. Additionally, TLE patients have extensive network connectivity issues, such as in the default mode network (DMN).

rs-fMRI provides a non-invasive method that helps map the functional connectivity of brain areas during rest, enabling deeper insights into how epilepsy affects network organization in the brain. Disturbances in the functional connectivity between various brain regions are common signs of the abnormal brain activity that characterizes epilepsy. Researchers can map resting-state networks (RSNs), which may be altered in epileptic patients, by using rs-fMRI to record the spontaneous variations in brain activity while a patient is not executing any specific task. Looking ahead, the application of more sophisticated machine learning techniques, particularly Deep Neural Networks (DNNs), holds great promise for unveiling nuanced connectivity patterns. Integrating DNNs can unveil intricate relationships within the data, capturing subtle distinctions that traditional algorithms may overlook. This approach can provide a more comprehensive and detailed characterization of network alterations in TLE patients compared to HC, ultimately offering a clearer and more refined understanding of the neurobiological underpinnings of this condition. Furthermore, future research could delve into longitudinal studies to investigate dynamic changes in network connectivity over time, providing insights into the evolution of TLE-related alterations. Additionally, exploring the potential correlation between clinical outcomes and network changes may open avenues for personalized therapeutic interventions.

Conclusion

This study presents an exploration of connectivity differences between HCs and TLE subjects. The identified 12 ROIs are used as a base for comparison of the Right HC-RTLE and on similar lines for comparison between the Left HC-LTLE group. Alterations in connection are seen in the hippocampus and amygdala regions that are important in memory-related functions of temporal lobe epilepsy (TLE) patients, and these abnormalities are commonly reported in patients with temporal lobe epilepsy (TLE). In networks such as the default mode network (DMN), patients with TLE also exhibit widespread connection abnormalities. The application of ML specifically the Random Forest Algorithm, proved effective in classifying connectivity matrices, achieving high accuracy rates of 83% for RHC-RTLE and 72.10% for LHC-LTLE. Feature importance plots facilitated the identification of critical connections influencing the classification. The unique connection characteristics linked to temporal lobe epilepsy are better understood as a result of these discoveries, with particular emphasis on the right hemisphere. These insights pave the way for further investigations into personalized treatment ap- approaches and the development of diagnostic tools for temporal lobe epilepsy.

Declaration- Every individual participant participating in the study gave informed consent. Every procedure followed the guidelines set out by the Helsinki Declaration of 1975.

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Conflict of Interest

There is no conflict of interest for this research work.

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