Computer Methods and Programs in Biomedicine 232 (2023) 107427

Contents lists available at ScienceDirect

Computer Methods and Programs in Biomedicine

journal homepage: www.elsevier.com/locate/cmpb

Discriminating and understanding brain states in children with epileptic spasms using deep learning and graph metrics analysis of brain connectivity

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A R T I C L E I N F O

Article history:
Received 1 September 2022
Revised 13 February 2023
Accepted 15 February 2023

Keywords:
Neurology
Epilepsy
Brain connectivity
EEG
Deep learning
Convolutional neural network
Graph Theory

A B S T R A C T

Background and objective: Epilepsy is a brain disorder consisting of abnormal electrical discharges of neurons resulting in epileptic seizures. The nature and spatial distribution of these electrical signals make epilepsy a field for the analysis of brain connectivity using artificial intelligence and network analysis techniques since their study requires large amounts of data over large spatial and temporal scales. For example, to discriminate states that would otherwise be indistinguishable from the human eye. This paper aims to identify the different brain states that appear concerning the intriguing seizure type of epileptic spasms. Once these states have been differentiated, an attempt is made to understand their corresponding brain activity.

Methods: The representation of brain connectivity can be done by graphing the topology and intensity of brain activations. Graph images from different instants within and outside the actual seizure are used as input to a deep learning model for classification purposes. This work uses convolutional neural networks to discriminate the different states of the epileptic brain based on the appearance of these graphs at different times. Next, we apply several graph metrics as an aid to interpret what happens in the brain regions during and around the seizure.

Results: Results show that the model consistently finds distinctive brain states in children with epilepsy with focal onset epileptic spasms that are indistinguishable under the expert visual inspection of EEG traces. Furthermore, differences are found in brain connectivity and network measures in each of the different states.

Conclusions: Computer-assisted discrimination using this model can detect subtle differences in the various brain states of children with epileptic spasms. The research reveals previously undisclosed information regarding brain connectivity and networks, allowing for a better understanding of the pathophysiology and evolving characteristics of this particular seizure type. From our data, we speculate that the prefrontal, premotor, and motor cortices could be more involved in a hypersynchronized state occurring in the few seconds immediately preceding the visually evident EEG and clinical ictal features of the first spasm in a cluster. On the other hand, a disconnection in centro-parietal areas seems a relevant feature in the predisposition and repetitive generation of epileptic spasms within clusters.

1. Introduction

Epilepsy is a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition, Fisher [20]. Epileptic seizures are produced by abnormal excessive and synchronous neural activity, often causing manifestations that include violent convulsions and loss of awareness. Epilepsy comprises a wide range of disorders of different causes and varying associated features. Similarly, epileptic seizures can have diverse expressions that constitute different seizure types, [7]. This disease could affect around 50 million people worldwide regardless of age and is one of the most common chronic neurolog-

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https://doi.org/10.1016/j.cmpb.2023.107427

ical disorders [10]. In terms of mortality, 8.18% of patients die at a median age of 34.5 years, which is more than the mortality of general population [6]. Concerning its economic impact, epilepsy generates 2.5 billion dollars through direct costs in the US,[1] but due to misdiagnosis, unemployment, or declines in labour productivity, the value of indirect costs is also high.

Since epilepsy consists of abnormal electrical discharges of neurons in the cerebral cortex, electroencephalograms (EEGs) appear to be the most widely used tests by clinicians and researchers to characterize and study the disease. This technique was first introduced by Hans Berger in the 1920s to measure electrical activity in the brain generated from its interneural communications [9]. It uses a set of electrodes placed around the scalp that registers electrical activity. Each electrode or channel represents a time series where an electrical potential represented on the Y-axis varies during different timestamps on the X-axis. The amount of data registered in each test is related to the number of electrodes, the sampling rate, and the recording duration used to collect the data. In the case of epilepsy, the abnormal activity in EEGs can be detected by comparing a regular background activity with changes that occur during seizures (ictal states) or with abnormal epileptiform activities that appear between seizures (interictal states) and also comparing ictal versus interictal states. Although the differences could be evident in some cases, this is a complex task even for trained epileptologists. Accurate identification of abnormalities heavily depends on experts with extensive clinical experience that usually have a nonlinear working method that is highly time-consuming and requires careful inspection, creativity, and problem-solving skills. However, even in the best of scenarios, some cases escape human perception and could be assisted and complemented by new technologies that efficiently circumvent difficulties humans may not be capable of solving.

Computational modelling, network theory, and artificial intelligence have proven to be necessary tools in the study of the human brain [2]. Network theory is a way to study brain connectivity, whose deviations can be considered the basis of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis or even epilepsy [16]. Regarding the analysis and interpretation of EEG signals, the large amount of data, the temporal complexity and the stochastic nature of the signal make it difficult to extract essential features by simple visual analysis or by purely statistical techniques. Regarding [3], the alternative has been the use of nonlinear dynamics analysis techniques applied to time series analysis or artificial intelligence approaches, especially deep learning methods, [1]. Deep learning was introduced by [13] as hierarchical models that can learn data representations with multiple levels of abstraction. The main idea behind these models is that we can replicate the behaviour of biological neurons with a minimal computational unit called artificial neuron. These neurons are then organized by sequentially connected layers, creating artificial neural networks. Neural networks with several stacked layers are called deep networks and their properties have been extensively studied in the field of brain disorders, [15].

The motivation of this work is focused on certainly the most mysterious seizure type, known as epileptic spasms of focal onset in children. One of its most intriguing features is that, unlike regular epileptic seizures, these usually appear in clusters, following a pseudo-periodic pattern, lasting several minutes, preferably upon awakening from sleep. This means that once a cluster begins, multiple spasms will follow at different intervals as if generated by some kind of repetitive loop in the brain, [18] and [19]. It is not well known what exactly is occurring between these spasms within a cluster, and EEG at the time is visually indistinguishable from the background EEG activity of the patient. In fact, several additional brain states can be associated with this type of seizure:

- *"Interspasms with"*. The moment between spasms within a cluster with epileptiform abnormalities. A cluster refers to an interval of time when a set of recurrent spasms occur.
- *"Interspasms without"*. The moment between spasms within a cluster, without epileptiform abnormalities.
- *"Wakefulness with"*. State in which the patient is awake, away from seizures, with visible epileptiform abnormalities.
- *"Wakefulness without"*. The moment of wakefulness, away from seizures, without visible epileptiform abnormalities.
- *"Prespasm"*. It marks the 1–2 s immediately preceding the first spasm in each cluster, with no identifiable EEG or clinical change from baseline, by human visual inspection only.

Although epileptic spasms have been a well-recognized entity for more than 150 years, their pathophysiology and the anatomical brain structures involved in their genesis are still not fully clarified. Little is known about their origin, their unusual EEG correlation, and their peculiar response to medication. They do not respond to common anti-seizure medication and are many times refractory (as is the case for our population) but some respond to Adrenocorticotropic Hormone (ACTH), steroids, or vigabatrin, [8]. The main objective of this paper is to consistently discriminate distinctive brain states in and around epileptic spasms that are indistinguishable under the expert visual inspection of EEG traces and by analyzing brain connectivity and network measures at each of the different states, we aim at disclosing novel information for gaining insight into the pathophysiology and evolving features of this particular seizure type. This may subsequently contribute to the understanding of general epileptogenicity itself and could be applied to many epilepsies and seizure types. Therefore, two interesting case studies are presented from a medical point of view.

Considering that the *Prespam state* can be regarded as a key class since this is the moment immediately preceding the seizures, the most obvious case study will try to discriminate between both *Wakefulness* states (as this is a resting state, representing the regular background activity) and *Prespasm*. The unpredictability of seizures is undoubtedly one of the most severe problems for patients with epilepsy. Detecting them could allow for devising ways to warn patients and caregivers for timely interventions that could prevent injuries and even control or mitigate seizures. By discriminating and characterizing connectivity in the *Prespasm* state we intend to reveal information as a step forward in paving the way for future studies in the field of epileptic spasms and other seizure types.

The second case study will work with the *Interspams* states and *Prespasm.* Although the *Interspams* state is visually indistinguishable from *Wakefulness*, epileptologists consider that the brain is not in a resting state. The tendency to generate one spasm after another, in the form of clusters, with apparently regular EEG activity in between such spasms, does not seem entirely logical. Many have hypothesized that an ongoing abnormal encephalographic activity persists throughout the cluster that characterizes the enduring predisposition to generate epileptic spasms within that cluster [19]. This scalp EEG activity must be very subtle and complex, at least at the scalp level and for human analysis, since it remains invisible to expert inspection and assessment. It is currently unclear whether this activity exists and how or where it is generated. Uncovering this EEG information allows for a better understanding of the pathophysiological mechanisms involved in epilepsy and different types of epileptic seizures. This improved knowledge creates, in turn, opportunities for clinical planning and management.

Since both use cases cannot be solved by human visual perception, we propose the use of images of graphs-based representa-

[1] https://www.ajmc.com/view/examining-the-economic-impact-and-implications-of-epilepsy

tion of brain connectivity and deep learning models to discriminate between states of both use cases. In particular, we use Convolutional Neural Networks (CNNs), the best deep model for processing images [12] trained with EEGs previously transformed into a set of graphs representing the topology and intensity of brain activations at a given time of the seizure covering all the states described above. The nodes correspond to the electrode positions and the edges to the electrical activity between them. Representing brain states in this way contributes to the performance of the models and to a better understanding of brain functioning during the states. The results are complemented by applying graph theory. The metrics obtained will allow a better understanding of the epileptic states.

The rest of the paper is structured as follows. Section 2 compiles a set of related works. Section 3 describes the sources used in the research and defines applied methods. Section 4 shows the results obtained. Section 5 discusses the results of the previous section. Finally, Section 6 gives some conclusions and proposes future works in this research line.

2. Related works

In this work, the graph images obtained from the electroencephalograms were processed with deep learning models to discriminate epileptic states. Then, these states are analyzed using network analysis techniques. This section enumerates some related works describing the state of the art of this research.

Brain connectivity has been widely studied with classical techniques, as seen in Lang [21], where different works are compiled depending on three different forms: anatomical, functional, and practical connectivity. For example, [17] uses metrics such as small world, hierarchical modularity, or hubs to obtain study brain networks in several diseases. Also, [5] provides a review of network analysis to study patients with epilepsy. In De Asis-Cruz, [22], statistical correlation is used over preprocessed Magnetic Resonance Imaging (MRI) Scanners of pregnant women to find an association between maternal distress and fetal brain functional activity. Signal processing methods like Short-Time Fourier Transformation (STFT) over EEGs are applied in Ren [23] to confirm that elderly adults increased their functional connectivity when performing tasks with hand-held audiovisual tools. Then, Balconi and Fronda [24] study the relationship between inter-brain and intra-brain connectivity using the Hyperscanning algorithm and ANOVA over EEGs. A graph model with MRIs from schizophrenic patients and healthy individuals to check brain connectivity, Kim and Levina [25]. (Zandbagleh et al. 2022) develops a Support Vector Machine (SVM) to classify high and low schizotypy EEGs. All these works are based on brain connectivity but are not applied to epilepsy or use deep learning models as in our work.

As far as epilepsy is concerned, some papers using classical methods are worth mentioning. Filipcik [26] uses a technique that comprises Independent Component Analysis, Matching Pursuit Algorithm, and Granger Causality to detect the Seizure Onset Zone before performing surgery on epileptic patients. Graph theory is used by Carboni [27] with EEGs and MRIs to measure the connectivity in patients with focal epilepsy. Another interesting work is Leitgeb [28], where complex network models from graph theory are used to find changes in EEGs from pediatric patients. Also, Mitsis [29] benefit from brain connectivity by using measures like coherence and applying graph theory to detect and predict epileptic seizures. In Hao [30], Functional Magnetic Resonance Imaging (rs-fMRI) was transformed into directed graphs, and an SVM was used to classify controls from patients with temporal lobe epilepsy. Zhang [31] also, use graph theory to study the use of ultrasound over the brain of epileptic rats as a treatment. Finally, Li and Jung [32] create embeddings based on graph entropy to cluster EEGs for seizure detection. Even though the previous researchers worked with epileptic patients or animals, none of them applied to the case of epileptic spasms or used deep learning models apart from working with graphs.

Regarding the use of deep learning models, the following works are available. In Riaz [33], a convolutional model called FCNet is used to classify MRIs of patients with Attention Deficit Hyperactivity Disorder. Brain connectivity is studied by Azevedo [34] using Geometric Deep Learning over a large dataset of fMRI. In the particular case of epilepsy, MohanBabu, Anupallavi, and Ashokkumar [35] apply an optimized deep learning network model with a long short-term memory to predict seizures in EEGs. Another work is Gleichgerrcht [36], where deep learning models are used in the case of temporal lobe epilepsy to classify between seizure-free or disabling seizures. Another work Hekmati [37] uses a Multilayer Perceptron (MLP) to localize epileptic seizures based on fMRI. fMRIs are used alongside EEGs to Multilayer brain networks and deep learning models Dang [38] to perform EEG-based epilepsy detection. Some connectivity and graph measures in the form of a vector are extracted from EEGs of epileptic patients to predict seizures with LSTMs, Tsiouris [39]. In Ouichka, Echtioui, and Hamam [40] evaluate different convolutional models to predict epileptic seizures in intracranial EEGs. Also Partamian [41] uses some connectivity measures modelled as matrices that are fed into CNNs to detect seizures. Rijnders [42] obtain some connectivity metrics from EEGs, which are used to train a CNN model that can diagnose epilepsy. Then, the convolutional filters are obtained and used as biomarkers. Finally, Raeisi [43] use Graph Convolutional Neural Networks for the detection of seizures in neonatal EEGs.

As can be seen, there are few papers where deep learning models have been used in epilepsy but none for discriminating the states in the particular case of epileptic spasms raised in this work. This means that we can discriminate between different epileptic states that are indistinguishable by the human eye. Furthermore, to our knowledge, no studies take advantage of transforming EEGs into image representations of graphs to be classified by a deep learning model. Apart from obtaining an accurate classifier that demonstrates the differences between the different states, we have studied their connectivity with graph metrics, helping to understand some of the mechanisms underlying these seizure states.

3. Methods

3.1. A training dataset of graphs representing EEGs

3.1.1. Collecting the EEGs

This study has been performed with a set of retrospectively collected scalp EEG samples obtained from a group of pediatric patients with epilepsy. In particular, an epileptic seizure type known as epileptic spasms of focal onset had been successfully recorded and classified during video-EEG monitoring (synchronized video and EEG recordings) at Hospital Universitario La Paz in Madrid, Spain. The hospital is officially categorized as a tertiary referral centre by the National Healthcare System, with the highest level of epilepsy care. The present research has followed strict recommendations by the hospital Ethics Committee.

For each patient, a set of 25 electrodes was placed on the exact scalp locations according to the standardized international 10–10 and 10–20 systems for electrode placement. An EEG tracing is formed by several records called channels that represent the potential difference between two electrodes in a particular instant of time. EEGs can, therefore, be studied as time series, considering that it is a data sequence that has been measured in different time intervals in chronological order. Data has been collected and processed for these cases using a Nicolet video-EEG machine and associated software, with a 512 Hz sampling rate (512 values are col-

Table 1
Summary of information in patients' EEGs.

	Length	Epileptic spams	Clusters
Patient 1	119 horas	75	14
Patient 2	101 horas	170	7
Patient 3	125 horas	331	16
Patient 4	7 horas	40	7
Patient 5	3 horas	115	3

lected every second). Data has been collected and processed with a software called Nicolet EEG Software.[2]

The dataset is created from the data of five pediatric patients (ages 5–11 years), anonymized using identification numbers from 1 to 5, with video-EEG recorded focal onset epileptic spasms. Complete long-term video-EEG recordings had been previously analyzed and interpreted by the same specialized clinical neurophysiologist (one of the authors), creating a medical report according to regular clinical practice. The reports were later reviewed and confirmed by a second physician. The patients were monitored during different periods in which multiple epileptic spasms grouped in clusters occurred. This information is collected in Table 1.

For this study, recordings were again examined, and for each patient, specific segments from different states were carefully selected and manually cut and labelled. Only the parts with the fewest artefacts were selected through expert visual inspection, and passive patient behaviours were sought within those segments (as confirmed through given instructions, patient feedback, and/or concurrent video analysis). Generally, it is crucial to verify that optimal technical standards are met for any EEG recording and that no segments with excess artefacts or atypical conditions undergo computer analysis. The EEG technician himself should guarantee this. Each of the five patients has a set of 98–118 EEG segments categorized according to the different states defined. Segment duration varied slightly from 3 to 6 s because even the same state categories may have different durations (for example, spasms or epileptiform abnormalities). They were hand-selected by an epileptologist to include homogenous information.

Finally, we need to transform the EEGs into a format that can be managed with Python. In this case, we have used a tool called BrainStorm[3] that converts .e files into .edf (European Data Format). BrainStorm works with 64 channels, while ours are 25-channel EEGs.

3.1.2. Modelling the EEGs as graphs

In a graph-transformed EEG, nodes represent the electrodes and their positions on the scalp while edges obtain their values depending on a given connectivity measure. In this way, depending on the metric it extracts the information of a single node/channel or describes the relation between a pair of nodes/channels.

As no tools could do the transformation we needed, we have developed a Python open-source library called EEGraph[4] that could model the EEGs as images representing the connectivity between brain regions, [14]. The library receives an EEG file, and by setting a window size and the connectivity measure to be used (either in time or frequency domains), it returns both a set of adjacency matrices and images of the graphs. Fig. 1 shows the workflow followed by the library.

We implemented 12 of the most studied connectivity measures for the potential difference between electrodes. In our case, we have transformed the whole dataset into images with labels describing different brain states concerning the spasms. The nodes use a tag with the name of the electrode, and the edges use different colour scales and widths depending on the type of connectivity measures used. Before obtaining the images, we checked that there are no empty graphs nor repeated instances that could introduce noise or a bias in the dataset. Then, if the connectivity measure belongs to the time domain, the signal can be represented with only one value. In this case, the edges vary from grey to black alongside its width (the highest values have wider edges in black). For each connectivity measure, there is a default threshold that avoids the creation of edges without relevance. Fig. 2 shows an example of the image output using a time-frequency connectivity measure.

If the connectivity is in the frequency domain, the signal must be decomposed into three frequency bands: theta, alpha, and beta. We have decided to focus only on these bands for several reasons. Firstly, the main focus of our study is not the actual ictal/seizure state (*Spasms state*) but rather the states preceding or possibly predisposing to this particular type of seizure (*Wakefulness, Interspasms,* and *Prespasms* states). These states look more like background activity and interictal states than seizure activity. Most background activity at this age range (5–11 years) is above delta frequency, unlike at younger ages where slower frequencies are more relevant, [11]. Secondly, we have tried to concentrate on the usual real-world clinical setting where sampling frequencies are usually set at around 256 Hz or less, not allowing for a good analysis of high-frequency oscillations, [4]. It is also very difficult to examine gamma frequencies in the scalp EEG setting due to the filtering effect by interposed tissues such as the skull and the meninges, as well as due to contamination by artefacts (such as muscle-derived). We believe the analysis of slower and higher frequency bands is more suited for intracranial recordings, although we do not disregard their potential implication in any setting. In this case, we obtain a graph, following the structure of the previous one, for each band that is then combined, generating a coloured graph. Fig. 3 shows an example of an image output using a frequency domain connectivity measure.

During the research, we worked with all the metrics provided by EEGraph, but only 5 of them gave good results. Following, we describe and formally define each of them.

Pearson correlation (C), which describes the correlation between two-time series, is defined in Eq. (1).

$$C_{x,y} = \frac{\sigma_{xy}}{\sigma_x \sigma_y} \tag{1}$$

In the Equation, x and y are both time series, σ_{xy} is the covariance for the time series, $\sigma_x$and σ_y are their respective standard deviations. The value ranges from −1 to 1, where 1 means a perfect correlation, −1 is a perfect inverse correlation, and 0 is no correlation.

Normalized Cross-Correlation (CC) uses the lag of one time series concerning the other to measure their similarity.

$$CC_{x,y}(m) = \frac{R_{xy}}{\sqrt{R_{xy}(0)R_{yy}(0)}} \tag{2}$$

In this equation, R_{xy} is the cross-correlation between the two signals x and y. Then, $R_{xx}$and R_{yy} are the autocorrelations of the signals.

Corrected Cross-Correlation (CCC) measures how symmetric the cross-correlation between two time series concerning the second time series' lag with the first one. Eq. (2) defines it.

$$CCC_{x,y}(m) = CC_{x,y}(m) - CC_{x,y}(-m) \tag{3}$$

Here, x and y are again time series, CC is their cross-correlation, and m is the lag.

Squared Coherence (SC) measures the spectrum relationship between two-time series, considering leading, lagged, and smoothed

[2] https://neuro.natus.com/neuro-support
[3] https://neuroimage.usc.edu/brainstorm/
[4] https://github.com/ufvceiec/EEGRAPH

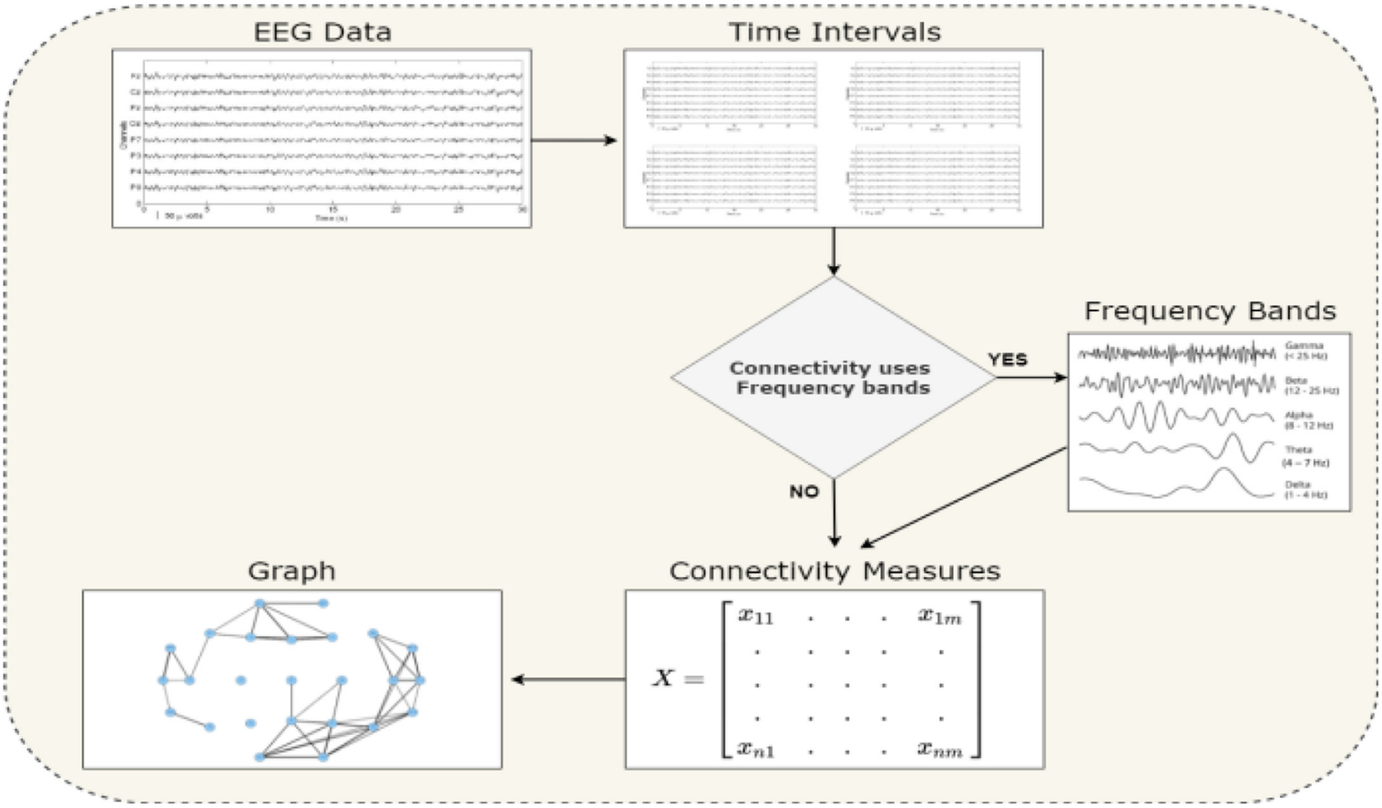

Fig. 1. Workflow followed by EEGraph.

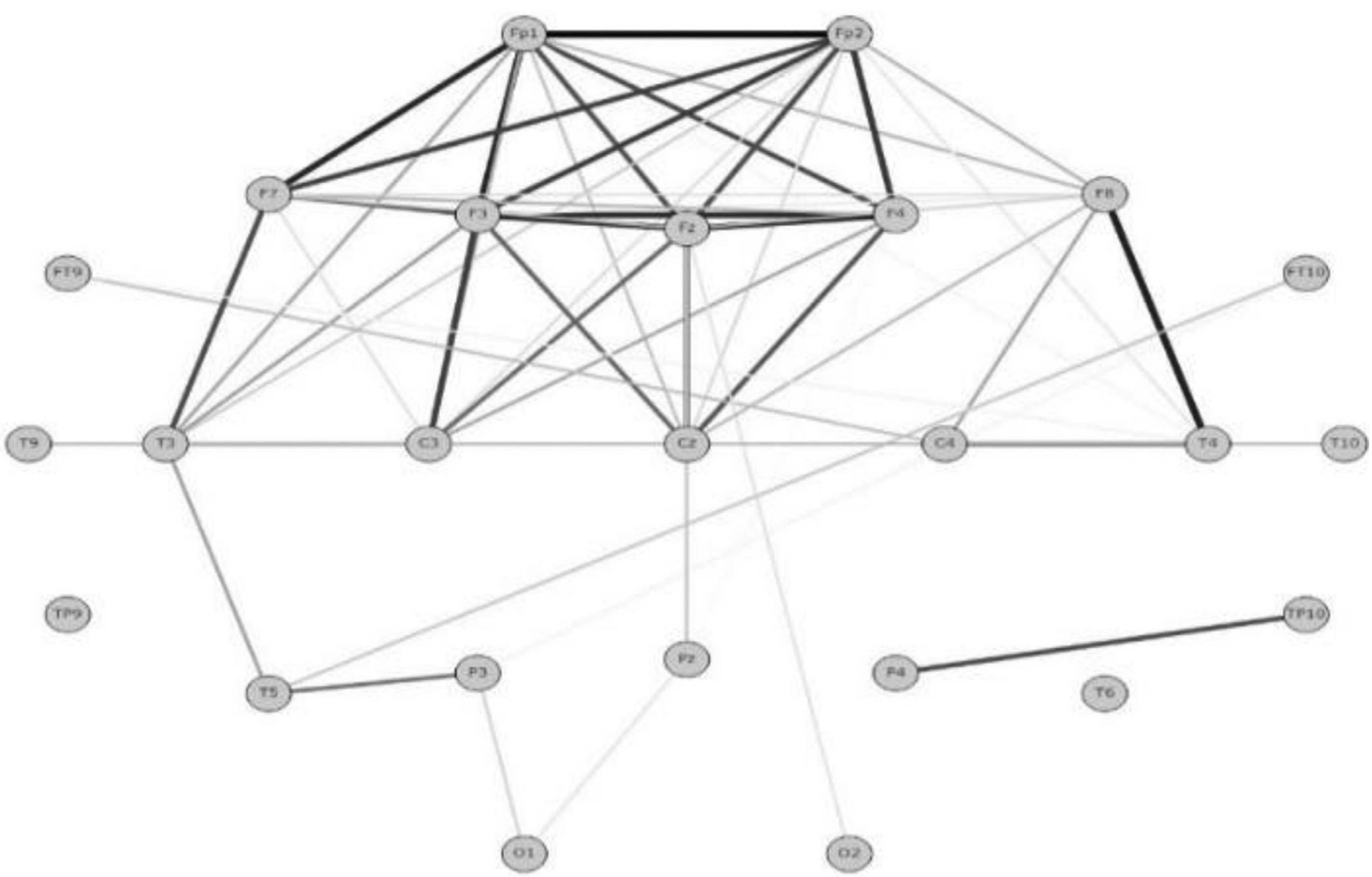

Fig. 2. An EEG timestamp representation as a graph using EEGraph with a time-domain connectivity measure.

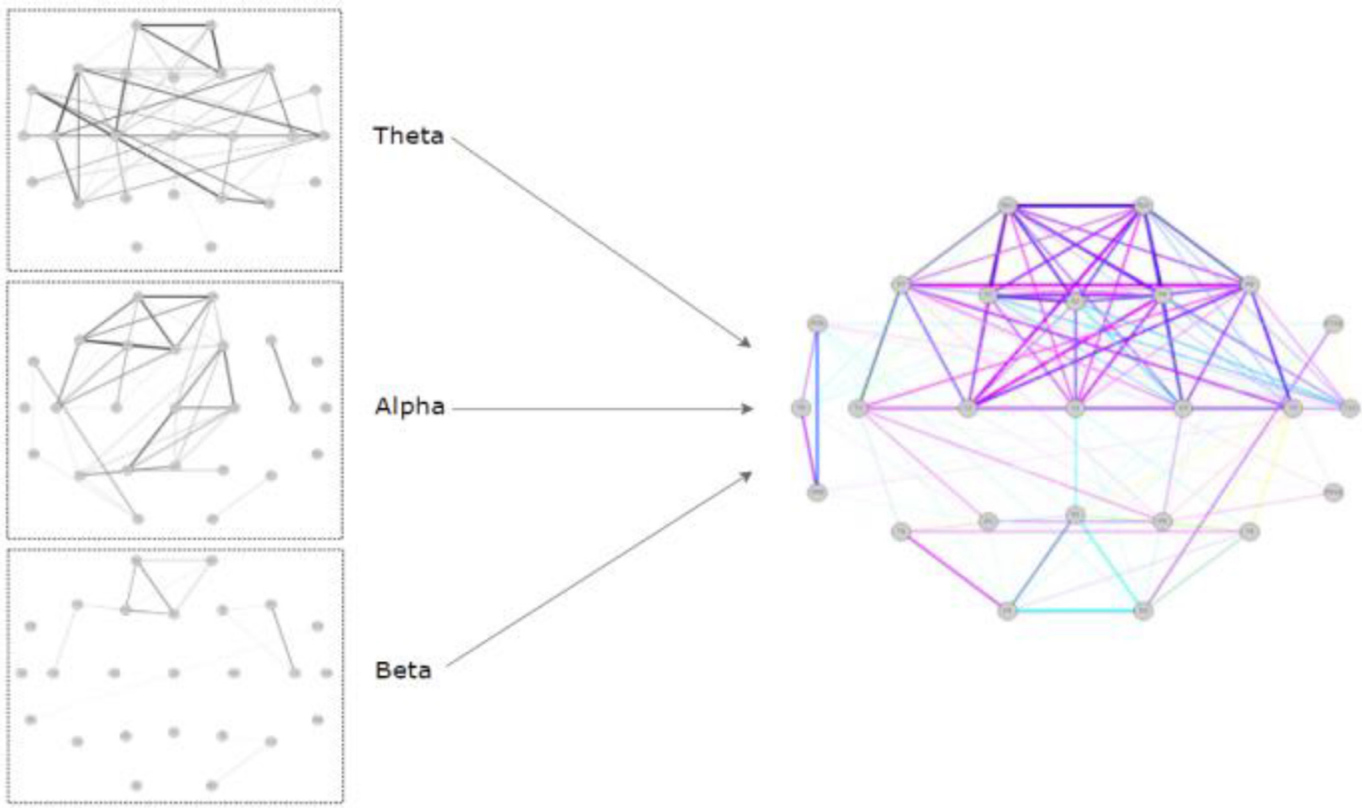

Fig. 3. An EEG timestamp representation as a graph using EEGraph with a frequency domain connectivity measure.

relationships. Eq. (4) provides a formal definition.

$$SC_{x,y}(f) = \frac{|G_{x,y}(f)|^2}{G_{x,x}(f)G_{y,y}(f)} \tag{4}$$

In the Equation above, G_{xy} denotes the cross-spectral density between time series x and y, G_{xx} and G_{yy} their power spectral densities. SC provides a value between 0 and 1, where 0 means no correlation and 1 perfect correlation in the frequency spectrum.

Imaginary Coherence (IC) is similar to squared coherence as it measures the relationship between the spectrum of two-time series but is less sensitive to external effects. The following Equation describes it.

$$IC_{x,y}(f) = \frac{Imag(G_{xy}(f))}{\sqrt{G_{xx}(f)G_{yy}(f)}} \tag{5}$$

In this Equation, G_{xy} denotes the cross-spectral density between time series and G_{xx}, $G_{yy}$the power spectral density for both time series.

Phase Locking Value (PLV) measures the fluctuations in the difference of phase in two-time series. Eq. (6) describes this measure.

$$PLV = |E[\exp(i\Delta\phi_{rel}(t))]| \tag{6}$$

In the Equation above the phase difference is denoted by $\Delta\phi_{rel}(t)$ of x and y at time t, belonging to an interval from 0 to 2π and E is a function that average the value in times.

Phase Lag Index (PLI) is similar to the previous one but considers the changes in the sign of the phase. The description of this measure is in Eq. (7)

$$PLI = |E[sign(\Delta\phi_{rel}(t))]| \tag{7}$$

The symbols of the equation are the same as Eq. (6) but the phase difference is in an interval [-π, π.

The Weighted Phase Lag Index (WPLI) is similar to PLI but is less sensitive to external effects. Eq. (8) denotes it.

$$WPLI = \frac{|\mathrm{E}[|\mathrm{Imag}(\mathrm{G_{xy}(f)})| * sign(\mathrm{Imag}(\mathrm{G_{xy}(f)}))]|}{\mathrm{E}[|\mathrm{Imag}(\mathrm{G_{xy}(f)})|]} \tag{8}$$

This Equation is similar to the previous one but uses the cross-spectral density between signals denoted as G_{xy}.

Directed Transfer Function (DTF) describes the random influence of channel j on channel i for each frequency using Eq. (9).

$$DTF^2_{j\to i}(f) = \frac{\left|H_{i,j}(f)\right|^2}{\sum_{m=1}^{k}\left|H_{i,j}(f)\right|^2} \tag{9}$$

H(f) is a transfer matrix of an MVAR (multivariate autoregressive model) where different elements are chosen. The Equation constitutes a normalized version of DTF ranging from 0 to 1. It indicates the inflow ratio from channel j to channel i for all inflows to channel i.

Power Spectrum (PS) is only applied to one time series describing its distribution in the frequency domain. Eq. (10) is used to calculate it.

$$PS(f) = |\mathrm{X(f)}| \tag{10}$$

In the Equation, Fourier Transformation is applied using *X(f)*.

The Shannon Entropy (H) measures the average amount of information that a time series contains.

$$H(x) = -\sum_i p(x_i)\log(p(x_i)) \tag{11}$$

In the Equation, the natural logarithm is calculated to p(xi) which is the unnormalized probability of the event x_i.

Table 2
Graph images in training set for use case 1.

	Connectivity measures in the time domain	Connectivity measures in the frequency domain
Greyscale images	302: Class 1 (148), Class 2 (154)	906: Class 1 (462), Class 2 (444)
Colour scale images	-	302: Class 1 (148), Class 2 (154)

Table 3
Graph images in training set for use case 2.

	Connectivity measures in the time domain	Connectivity measures in the frequency domain
Greyscale images	313: Class 1 (154), Class 2 (159)	939: Class 1 (462), Class 2 (477)
Colour scale images	–	313: Class 1 (154), Class 2 (159)

Spectral Entropy (SE) is similar to H but for the frequency domain. Eq. (12) describes it.

$$SE(X) = \frac{\sum_{f=0}^{f^{S}/2} p(f) log_2(p(\text{f}))}{\log_2(\text{psd.size})} \quad (12)$$

The Equation uses base 2 logarithm, f_s as the sampling frequency, p(f) as the normalized power spectrum density using the Welch method and psd.size is the size of the power spectral density.

Modelling the EEGs as graphs has two main benefits. First, the user can obtain a representation of the different brain areas with a connectivity network obtained with the desired parameters. Second, the implemented connectivity measures allow a spectral analysis (typical when working with EEGs) and an analysis of the brain states through time by obtaining different timestamps. In our case, we set the window size in 1 s for both use cases and have used the connectivity measures provided by EEGraph. Tables 2 and 3 show the number of graph images we obtained for both use cases and their classes (data always has a balance). It should be highlighted that we have created one training set for each of the 12 connectivity measures provided by EEGraph.

Output images have a size of 170 × 1,165 × 1 pixels in the case of black and white images and 170 × 1,165 × 3 in the case of colour ones. Images have been normalized, ranging from 0 to 1, by dividing the values by 255 to speed up the training time.

3.1.3. Convolutional neural networks

As we are working with images of graphs representations of brain connectivity, it makes sense to work with CNNs. A CNN uses the convolutional operator to extract the main features of an image regardless of its location Krizhevsky, Sutskever, and Hinton [44].

CNN models are composed of an input layer, a set of convolutional blocks, and a classification multilayer perceptron. The convolutional blocks comprise a convolutional layer and a pooling layer. These blocks are stacked to extract the main features of the image and, at the same time, reduce the dimensionality to a minimum piece of data with the extracted characteristics. Convolutional layers are composed of neurons and their weights, where each neuron is a matrix of numbers called a filter or kernel. The kernel goes through all the input images calculating an element-wise product which is finally summed up to obtain the output value, as is described in Eq. (13).

$$Y_k = f(W_k * X) \quad (13)$$

In the Equation above, X is the input image, W_k is the filter with the k_{th} feature map, which uses the convolutional operator element by element denoted by * (multiplying pixels in this case).

The output of a kernel corresponds to a feature of the image. After passing through the whole image, it obtains an activation map output matrix. One of the hyperparameters set during the training stage is the number of kernels and their size. Then, the pooling operation is applied, allowing for the reduction of dimensionality. There are two types of pooling layers: maximum and mean. The former obtains the maximum value in the activation map. The latter calculates the average of the values.

3.1.4. Classifying images of EEGs modelled as graphs

The proposed solution has to manage the output images from the EEGraph library. These represent different timestamps from EEGs. The images contain a graph describing brain connectivity at a particular moment. As we have said before, CNNs are the best deep learning model fitting with these data types.

As this work comprises two use cases, we have developed two different CNNs. In both cases, we used grid search to obtain the architecture's hyperparameters that perform best by combining different values Bergstra and Bengio [45]. The first use case starts with an input layer of 170 × 1165 (the size of the images plus a depth of 3 in the case of colours), followed by two convolutional blocks that process the image and a multilayer perceptron for the final classification. The first block has a convolutional layer with 16 filters of 3 × 3 size and ReLU as an activation function, followed by a MaxPooling layer. The second block is similar to the first but uses 32 filters and has a GlobalMaxPooling layer. After the convolutional stage, we use a dropout of 25%, meaning that this percentage of the neurons will be randomly disconnected to avoid overfitting. At this point of the architecture, the data classification starts with a multilayer perceptron of one hidden layer with 64 neurons and ReLU as an activation function, finished with an output layer of one neuron with a sigmoid activation function.

3.1.5. Training the models

We have used the following hyperparameters in this stage. Binary cross-entropy is the loss function whose prediction target is binary: 0 or 1, Ruby and Yendapalli [46]. The step size in the loss function is a learning rate of 0.00001 Plagianakos, Magoulas, and Vrahatis [47]. Finally, Adam, as an optimizer for both models, is defined as "an algorithm for first-order gradient-based optimization of stochastic objective functions, based on adaptive estimates of lower-order moments" Kingma and Ba [48]. The number of epochs has varied, with 1000 for the first use case and 200 for the second.

Training starts by randomly dividing the dataset into two parts. The larger (80% of the dataset) is used for training and the smaller (20% of the data) is used for testing (instances that will be used to check the performance of the model once trained). To ensure the generalization of the results and avoid overtraining we applied the cross-validation (CV) method to the training dataset. CV is a technique used to evaluate the results of statistical analysis and ensure that they are independent of the partition between training and test data. We used k-fold CV, a variant in which a partitioning of the training dataset into k subsets of data is performed and k training processes are carried out. In each of these processes a subset of data is selected to validate the results and the remaining k-1 are used for the training itself. In each repetition, the subset

Table 4
Accuracies for different connectivity measures in case 1.

	Train	Validation	Test
Squared coherence	**93.6%**	**88.2%**	**87.2%**
Pearson correlation	82.4%	80.4%	76.6%
Directed transfer function	81.9%	80.4%	76.6%
Corrected cross-correlation	79.4%	74.5%	70.2%

Table 5
Accuracies for different connectivity measures in case 2.

	Train	Validation	Test
Pearson correlation	**91.9%**	**86.8%**	**81.3%**
Corrected cross-correlation	75.5%	73.6%	71.9%

Table 6
Metrics for squared coherence in case 1.

	Train	Validation	Test
Specificity	94.0%	88.0%	91.3%
Sensitivity	94.1%	88.5%	90.9%
Precision	93.2%	88.5%	83.3%

of data used for validation is changed until the complete dataset is run through. In each run, the values of the implemented metrics are obtained and then averaged over the k runs to obtain the mean and the corresponding standard deviation. Our training set has been divided into 5 subsets (5-fold), so that in each iteration training is carried out with 80% of the training set and validation with the remaining 20%. Finally, the experiments have been repeated 10 times to ensure that the metrics obtained are valid and not the result of chance.

3.1.6. Graph theory to analyze the EEGs

As models have been trained with graph representations of the EEGs, we are obtaining some graph theory metrics to have an in-depth explanation of how the different brain regions behave in particular states. The most exciting metrics are degree strength and graph density, defined in the following.

Degree strength measures the sum of the weights (w_{ij}) for each node's edge (Si). Eq. (14) defines it.

$$S_i = \sum_{i=1}^{N} w_{ij} \tag{14}$$

The density of a graph is the number of edges in the network compared to the number of potential edges, Goldberg [49]. This metric indicates how the nodes are connected between them. It can measure brain connectivity as a whole and discern whether the brain is in a hyperconnectivity state or not.

4. Results

This work provides deep learning models for predicting two use cases in the field of epilepsy. For each use case, we have trained the models with the 12 possible connectivity measures provided by EEGraph. We have trained two models (one for each use case) and obtained the accuracy to measure their performances. Accuracy is the ratio between correct and performed predictions and is an excellent initial result to calculate the model performance. Tables 4 and 5 show the accuracy for use cases 1 and 2, respectively. They compile the different connectivity measures that have surpassed 70% with the test set.

These metrics for use case 1 and squared coherence connectivity can be seen in Table 6.

The same metrics for use case 2 and Pearson correlation are in Table 7.

Table 7
Metrics for Pearson correlation in case 2.

	Train	Validation	Test
Specificity	90.7%	88.9%	83.3%
Sensitivity	93.3%	84.6%	79.2%
Precision	93.2%	88.5%	83.3%

Table 8
Top 10 electrodes' degree strength for use case 1.

Class 1 (Prespasm)		Class 2(Wakefulness)	
Node	Value	Node	Value
Fp1	8.2(±3.71)	Fp1	5.7(±3.38)
Fp2	8.0(±3.89)	Fz	5.5(±3.27)
F8	7.8(±3.84)	F3	5.4(±3.35)
F7	7.7(±3.75)	Fp2	5.3(±3.46)
Fz	7.7(±3.65)	F7	5.3(±3.44)
F3	7.6(±3.72)	F4	5.2(±3.40)
F4	7.5(±3.99)	F8	5.2(±3.44)
T3	7.2(±3.98)	T3	4.9(±3.40)

Table 9
Top 10 electrodes' degree strength for use case 2.

Class 1(Interspasm)		Class 2(Prespasm)	
Node	Value	Node	Value
Cz	11.6(±4.13)	Cz	14.4(±3.0)
Pz	11.6(±4.26)	Pz	14.4(±2.92)
P4	11.4(±4.43)	P4	14.2(±3.11)
C4	11.2(±4.38)	C4	13.9(±3.26)
F4	11.1(±4.47)	Fz	13.6(±3.68)
T6	11.0(±4.29)	F4	13.4(±3.93)
Fz	11.0(±4.62)	F3	13.1(±3.95)
Fp1	10.9(±4.26)	C3	13.1(±3.42)
O1	10.9(±4.38)	P3	13.1(±3.42)
Fp2	10.8(±4.26)	O1	13.0(±3.17)

Table 10
Graph density for both cases.

	Class 1	Class 2
Use case 1	0.3268(±0.1538)	0.2477(±0.1238)
Use case 2	0.7679(±0.1491)	0.8230(±0.1506)

Once we have checked that deep learning models are good at classifying the states in both use cases, we are using graph theory to study the instances of the whole dataset. In this case, we have obtained two metrics: degree strength and graph density.

The values of the strength degree are in Table 8, showing the top 10 electrodes for each class in use case 1. Values indicate the average between all instances plus its standard deviation.

The same values but for use case 2 have been compiled in Table 9.

Finally, we have obtained the graph density for the classes in both use cases. This information corresponds to Table 10.

5. Discussion

All the results from Tables 3 and 4 seem to correspond to good models that do not overfit or underfit. This fact can be checked by accomplishing the bias-variance trade-off Belkin [50]. Bias is good as the differentiation between the proposed states cannot be made by humans, Fisher [20]. In the absence of a gold standard to verify the reliability of the identification of background activity states, interictal epileptiform discharges, or even ictal patterns by EEG, the interrater reliability of the diagnosis using EEG recordings is usually sought to assess this situation, Jing [51] and Benbadis [52].

In terms of variance, none of the models seems to overfit. Accuracy is an excellent metric to intuit how the model is performing.

Nevertheless, other metrics like specificity, sensitivity, and precision should be studied in fields like medicine. Specificity gives the ratio between the number of true negatives (*Prespasm* states classified as *Prespasm*) and the total of those predicted as true negatives and false positives (resting states classified as *Prespasms*). This situation could be a problem in the case of developing a device as it will notify the patient of an incoming spasm or even perform an intervention when that is not occurring. Precision measures the ratio between the number of true positives (*Prespasm* states correctly classified) and the total of those predicted as true positives and false positives, which is interesting in terms of erroneously identifying false spasms as spasms. Sensitivity is the same as precision but taking into account false negatives (*Prespasm* states classified as another state) instead of false positives, very useful to avoid notifying the patient of a spasm when this is not happening.

Essential features of epilepsy emerge on a network level, and therefore it benefits significantly from using network analysis tools such as the ones implemented in our work, Tables 7 to 9. They can objectively characterize underlying pathological brain activity associated with epilepsy.

As a starting point, we observe that degree strength in all electrodes and graph density overall are significantly higher in the *Prespasm* (immediate preictal) state than the *Wakefulness* (resting regular background activity) or the *Interspasms* state. Here, increased brain connectivity seems to occur in a phase of immediate preparation for the seizure cluster. When comparing *Prespasm* with *Wakefulness*, it is a frequency domain connectivity measure that shows the most accuracy; we could interpret the degree of synchronization between different frequency bands across the brain that differentiates these two states more clearly. On the other hand, when comparing *Prespasm* with *Interspasms*, as it is time-domain connectivity, the measure that provides the best performance, it suggests that what marks the difference with the *Interspasms* state is more related to the similarity between signals from different brain areas. Consistent evidence shows that local and dispersed assemblies of synchronized neural activity across the epileptic brain can change in the background or interictal state and regularly throughout seizure initiation and progression. Those changes may mark times of increased seizure generation. Also, multiple studies have reported that the epileptic brain is characterized by increased neuronal synchrony except possibly before seizure onset, when synchrony may decrease locally. Regions of reduced synchrony can be the bridging connections between the seizure onset zones and the surrounding brain. There is reduced functional connectivity between the epileptic neuronal assembly, generating focal seizures and surrounding brain regions. In effect, the seizure onset zone is at some point disconnected from surrounding brain regions, Litt [53]; Warren [54].

Furthermore, these connectivity measures allow us to locate the regions with higher metrics in each state. In the immediate preictal state, areas of maximal degree strength seem to point towards electrodes in more anterior brain regions, perhaps prefrontal and premotor, when considering frequency synchronization. However, when comparisons are made with the Interspasms state, the significant changes seem to correlate with medial centro-parietal regions.

The underlying pathogenesis of epileptic spasms is complex and not fully understood. The condition is proposed to be a widespread derangement of a network at a particular stage of development. Many hypothesize that epileptic spasms could be triggered by an interaction between the cortical grey and subcortical structures. Once activated, the subcortical, the brainstem, or both could become generators of epileptic spasms, [19]. Epileptic spasms seem to be a final common manifestation of processes that start on a cortical level in varying sites. The disruption in the resting state networks of the brain by chaotic brain activity could be responsible [18]. Direct or delayed involvement of prefrontal, premotor/motor, and centro-parietal cortices has explicitly been implicated in determining ictal changes, de la Vaissière [55]; Nariai [56].

Looking at the results in Tables 5 and 6, the model for use case 1 still performs very well, with values around 88% in the validation stage. So, this model performs the same with false negatives and true negatives. In the case of the model for use case 2, it seems that the models have good values with worse results in terms of sensitivity. These results mean that the model categorized some *Prespasm* states as *Interspasms*. This situation makes sense from a pathophysiological point of view since the two states compared in use case 2 are supposed to be more similar than those in use case 1. From a clinical point of view, the consequences of this slightly lower sensitivity may not be as relevant as in the previous case because the states in use case 2 imply an increased probability of a seizure coming either immediately or sometime soon.

The study has some limitations related to the number of patients and the variability in their age. Although the number of patients seems small, several papers use deep learning techniques with EEGs of epileptic patients like Fraiwan and Alkhodari [57]; Ilakiyaselvan, Khan, and Shahina [58]; Srinath and Gayathri [59]; Yao [60]. We also should highlight that the population itself is rare. To begin with, epileptic spasms are not very common themselves, let alone of focal onset and at the age range of our population. The age range (5–11 years) of patients was carefully selected. This kind of seizure is more typical of the first year of life (so-called infantile spasms), which is where most of the literature has concentrated. The fact that epileptic spasms may occur later in life is enigmatic and unraveling these somehow peculiar brain mechanisms and how they persist beyond the usual age may yield clinically relevant clues. Although the brain undergoes many maturational changes throughout life, particularly during childhood but also during adulthood, some periods seem more stable than others. In the pediatric population, major comparative EEG changes clearly occur in the neonatal and early infancy periods. EEG characteristics remain however very much stable within the age range of our population, which is consistent with maturational status and processes more typical of that period. Our population selection also avoids the more turbulent adolescent period. All of this justifies the smaller number of patients included, [11].

6. Conclusions and future works

In this work, we have used deep learning models and network analysis to reliably identify, quantify and try to understand relevant characteristics of brain function that cannot be visually assessed, and which are particularly valuable in the clinical setting of patients with epileptic spasms.

In the first case, the model seems accurate according to all metrics, with values above 88%. In the second case, the second model has a low sensitivity value, but it does not seem to be a critical problem for this use case. As for the connectivity study, we show evidence that the epileptic cortex in children with focal epileptic spasms is temporally functionally disconnected in the period between spasms within a cluster and becomes hyperconnected again in the immediate seconds preceding the spasms themselves. We speculate that this dissociation observed mainly in centro-parietal areas during interspasm states suggests an involvement of these regions in the early predisposition to seizure onset, playing a role in the generation of focal epileptic spasms, particularly within clusters. According to our results, other areas such as the prefrontal, premotor, and motor cortexes might be more involved in the hypersynchronized state that occurs in the few seconds immediately preceding the visually evident EEG and ictal clinical features of the first spasm of a cluster. By discriminating the *Prespasm* and *Interspasms* states and depicting some of their characteristics, we also provide information that may be helpful in the steps leading to prediction of epileptic spasms and perhaps other seizure types. To our knowledge, this is the first time such findings have been described.

Nevertheless, a significant challenge remains in distilling biological mechanisms from network phenotypes of disease processes Stacey [61]. These results may constitute a clinically useful electrophysiological signature for different aspects of the management of these patients, including spatial mapping of the seizure onset zone for epilepsy surgery. Much remains to be learned in epilepsy, and these instruments could provide new insights for understanding the mechanisms of other seizure types and epilepsies.

It remains for future work to perform further analysis using hybrid models that could segment the EEGs. For example, separating the EEGs by channels feeding different recurrent neural networks (RNN) and combining the outputs using an evolutionary algorithm could help in the final accuracy of the model. We also plan to corroborate the results obtained in this study using graphical convolutional neural networks (GCNN), a type of CNN especially oriented to the analysis of graphs.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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