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A systematic review of cross-patient approaches for EEG epileptic seizure prediction

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Abstract. Seizure prediction could greatly improve the quality of life of people suffering from epilepsy. Modern prediction systems leverage Artificial Intelligence (AI) techniques to automatically analyze neurophysiological data, most commonly the electroencephalogram (EEG), in order to anticipate upcoming epileptic events. However, the performance of these systems is normally assessed using randomized splitting methods, which can suffer from data leakage and thus result in an optimistic evaluation. In this review, we systematically surveyed the available scientific literature looking for research approaches that adopted more stringent assessment methods based on patient-independent testing. We queried three scientific databases (PubMed, Scopus, and Web of Science), focusing on AI techniques based on non-invasive EEG recorded from human subjects. We first summarize a standardized signal processing pipeline that could be deployed for the development and testing of cross-patient seizure prediction systems. We then analyze the research work that meets our selection criteria: 21 articles adopted patient-independent validation methods, constituting only 4% of the published work in the entire field of epileptic seizure prediction. Among eligible articles, the most common approach to deal with cross-patient scenarios was based on source domain adaptation techniques, which allow to fine-tune the predictive model on a limited set of data recorded from a set of independent target patients. Overall, our review indicates that epileptic seizure prediction remains an extremely challenging problem and significant research efforts are still needed to develop automated systems that can be deployed in realistic clinical settings. Our review protocol is based on the PRISMA 2020 guidelines for conducting systematic reviews, considering NHLBI and ROBIS tools to mitigate the risk of bias, and it was pre-registered in PROSPERO (registration number: CRD4202452317).

Keywords: seizure prediction · seizure forecasting · artificial intelligence · machine learning · deep learning · patient independent · domain adaptation · electroencephalography

1 Introduction

Epilepsy is a widespread neurological disorder affecting more than 50 million people worldwide [1]. This clinical condition is characterized by the presence of recurrent seizures [2, 3], resulting in behavioral and cognitive impairments [4, 5] that significantly affect quality of life [6] and can even lead to death [7, 8]. Although the presence of seizures can be controlled with antiseizure medications, about 30% of patients are characterized by drug-resistant conditions [9]. A reliable epileptic seizure prediction system would thus provide immense benefits, for example by granting enough time to take corrective actions to minimize the consequences of epileptic events in daily life, such as while driving a car or during work activities [10].

Forecasting ictal events requires continuous monitoring of neuronal activity. In this respect, electroencephalogram (EEG) recording represents not only the election tool for diagnosis, but also a cost-effective and portable system to continuously monitor brain activity [11, 12]. Indeed, the high temporal resolution of the EEG allows to capture fast changes in brain dynamics, which characterize epileptiform discharges [13] and could thus provide informative features for predictive models [14].

Since early investigations dating back to the 1970s [15], several frameworks have been proposed to build seizure forecasting systems, ranging from statistical approaches based on probabilistic modeling to recent approaches based on cycles analysis [16]. In the past decade, however, improvements in machine learning and deep learning algorithms have paved the way for the adoption of Artificial Intelligence (AI) techniques in automated clinical diagnosis [17, 18]. In the field of seizure *detection*, researchers proposed AI systems to automatically detect the beginning and end of seizures by focusing on high oscillations of brain signals or other features extracted by learning-based classifiers [19–21]. Epileptic seizure *prediction* turned out to be a much more challenging task, since it requires to reliably identify the period preceding an epileptic event [22–26]. Nevertheless, in the current literature there are hundreds of articles describing AI-based epileptic seizure prediction systems that achieve remarkable accuracy in standard benchmark datasets [27–32]. However, in many cases the model validation process has been based on randomized splitting procedures [33–35], which do not necessarily guarantee an appropriate evaluation of model performance. Indeed, randomized methods do not allow to test the capability of the model to generalize to data samples that were never seen during training (i.e., new independent patients), thus increasing the risk of overfitting and leading to optimistic evaluation scores [36].

A robust alternative, which more closely matches the real-life use of seizure prediction devices, would require the deployment of cross-patient evaluation methods, such as leave-one-patient-out validation schemes [37–39]. However, designing a forecasting system that can work “out of the box” with new patients is extremely challenging [40], due to the large intra- and inter-individual variability of EEG signals between patients and even between seizures in the same patient [41]. The most common approach to tackle this challenge consists in applying source domain adaptation techniques, which allow to fine-tune pre-trained models using a limited number of seizures from new patients [42, 43]. These approaches aim to learn a set of relevant features from the source data (e.g., a dataset containing recordings from a pool of training patients) that are subsequently adapted to the clinical data from the target patients. Although adaptation methods can lead to significant improvements in epileptic seizure prediction, they still rely on the acquisition of limited data from new patients.

Only a few studies employed cross-patient evaluation methods to measure the performance of AI-based epileptic seizure prediction systems. As a result, existing reviews on this matter only focused on randomized splitting results [44, 45, 24], making it difficult to establish what could be the realistic prediction accuracy of such systems. The goal of this systematic review is to fill this gap. We screened thousands of scientific articles focused on EEG epileptic seizure prediction, in order to summarize a standardized signal processing pipeline based on the most common practices. We then aggregated all cross-patient results, providing a transparent way to evaluate the state of the art in the field and compare the underlying methodological approaches. We conclude our article by discussing the open challenges and the most promising future research directions.

2 Materials and Methods

We followed the PRISMA 2020 (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [46] and pre-registered our review protocol in PROSPERO (International Prospective Register of Systematic Reviews; registration number: CRD42024523172).

2.1 Search strategy

Three online scientific databases (PubMed, Scopus and Web of Science) were searched up to April 01, 2024, without starting timepoint or region restriction. Our search was limited to full-text English articles published in journals, conferences, or as preprints, which were filtered using a list of keywords combined through the following regular expression:

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((seizure prediction) OR (seizure forecasting) OR (seizure anticipation)) AND ((EEG)
OR (electroencephalography) OR (electroencephalogram) OR (electrophysiology) OR (electrophysiological))
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The PRISMA diagram describing our selection procedure is shown in Figure 1. According to our eligibility criteria, reviews and articles based on animal experiments or invasive EEG recordings were excluded. Our choice to focus on articles that used scalp EEG datasets is motivated by the fact that the invasiveness of neuro-technologies that do not directly provide treatment is difficult to accept from the patient side, thereby calling for the development of minimally invasive or noninvasive monitoring solutions [16]. Given that the diagnosis of epilepsy is usually carried out using scalp EEG monitoring devices, in most clinical settings it could be easier to deploy scalp-based predictive models, while stereo EEG is generally suggested in the

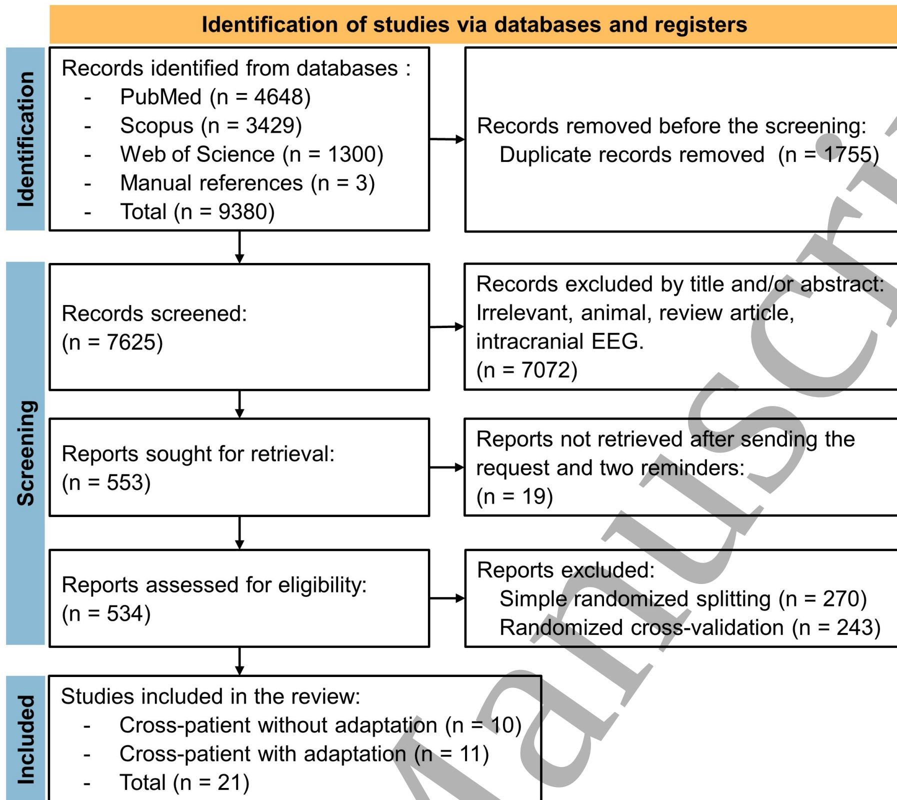

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) diagram depicting the article selection procedure and the filtering criteria applied at each step. At the identification level we report the number of articles per scientific database. At the screening level we report the number of articles excluded based on the study criteria. The final level reports the number of eligible articles included for review, divided according to validation method.

presurgical evaluation of focal epilepsy with MRI-negative condition, namely where the epileptogenic zone is not identifiable by non-invasive investigation [47]. Furthermore, although intracranial EEG systems are becoming increasingly popular, intracranial recording requires a delicate setup and sophisticated technological settings (e.g., implantation robots), making it only possible in very few hospitals worldwide by specially trained teams of clinicians and investigators [48].

Although our systematic review focuses on cross-patient settings, we included articles using randomized splitting during the initial screening phase, in order to quantify the proportion of studies based on cross-patient evaluation with respect to the total number of articles about epileptic seizure prediction (see screening section in Figure 1). To retrieve non-open access articles, we sent an email request directly to authors with two weekly follow-ups and also requested articles through the ResearchGate platform[5].

2.2 Assessment of risk of bias

The NHLBI[6] and ROBIS[7] tools were considered in the search and selection processes to mitigate the risk of bias. In the search process, the review question was formulated with respect to the PICO tool [49], and the eligibility criteria were clearly explained in a separate section. To limit the effect of publication bias [50], preprint and conference articles were also included. In the selection process, two independent reviewers (authors S.S. and M.P.) evaluated the articles in two rounds after removing duplicates. During the first

[5] https://www.researchgate.net/
[6] https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
[7] https://www.bristol.ac.uk/population-health-sciences/projects/robis/robis-tool/

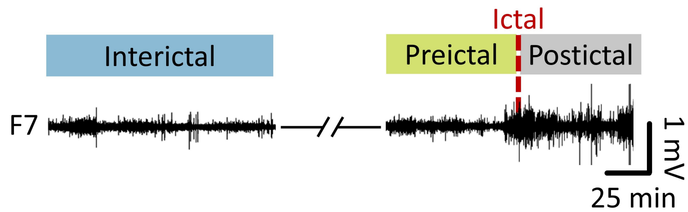

Fig. 2. A sample signal recorded from one scalp electroencephalogram (EEG) channel, labeled according to the four primary states related to a seizure event, including interictal (normal brain activity), preictal (the period before a seizure event), ictal (seizure event), and postictal (the period immediately after a seizure event).

round, articles were filtered according to the title and abstract. During the second round, the full text of the remaining articles was analyzed to determine whether each article contained relevant cross-patient results. In the end, all relevant references cited within each eligible article were also manually reviewed.

2.3 Definition of epileptic seizure prediction tasks

EEG recordings during the monitoring of epileptic patients can be categorized into four primary states: preictal, ictal, pos-tictal and interictal (Figure 2). These states correspond to brain activity during the time interval before a seizure event, seizure occurrence, the immediate period after the end of the seizure, and normal brain activity between seizures, respectively [51]. Identification of the ictal state is performed by clinicians leveraging on a convergence of electro-clinical signs of the seizure occurrence. In contrast, there is no consensus on the duration of the other states (pre-ictal, post-ictal, and interictal), which are characterized by a large temporal variability between studies ranging from a few minutes to a couple of hours [52].

In this review, we focus on AI-based methods, which usually frame epileptic seizure prediction as a discrete classification problem that requires discriminating between interictal and preictal states [26]. However, we should note that others have proposed to cast it as a regression problem that requires estimating the time before the next ictal state [16], and recent approaches further argue that considering the likelihood of a seizure is more realistic than simply detecting a preictal state [53]. These alternative approaches often aim to create seizure *forecasting* models, which could take into account the dynamic evolution of brain states to provide a probabilistic estimate of seizure occurrence over longer time horizons [16, 53].

2.4 AI-based seizure prediction pipeline

The most common pipeline for building AI-based epileptic seizure prediction systems is represented in Figure 3. It consists of several stages, which can be grouped into signal recording, signal pre-processing, and training/optimization. The details of each stage are explained below.

2.4.1 Signal recording Brain signals used to monitor patient conditions can be recorded from the scalp (EEG) or using intracranial electrodes (iEEG). In scalp recordings, electrodes are located on the patient's scalp following a standard positioning system, such as the international 10-20 EEG system [54]. In intracranial recordings, the electrodes are implanted inside different lobes to directly record brain activity [11, 55, 56]. Both methods could be used in clinical units during the diagnostic process: intracranial recordings have a higher temporal resolution [57], which allow to more accurately monitor specific brain circuits responsible for epileptic activity [58, 59], but scalp EEG represents a non-invasive, cost-effective, and portable alternative that also allows monitoring of whole brain activity to investigate large-scale brain dynamics [60, 61].

2.4.2 Signal pre-processing The most common pre-processing methods include bandpass and notch filtering, which eliminate unwanted frequencies and increase the quality of EEG signals [62, 63]. It is also common to remove physiological artifacts such as eye movements [64]. However, to reduce computational cost, some studies propose to avoid signal pre-processing [34]. A comprehensive comparison of the most popular pre-processing techniques can be found in [35]. Afterward, the EEG signals are normally divided

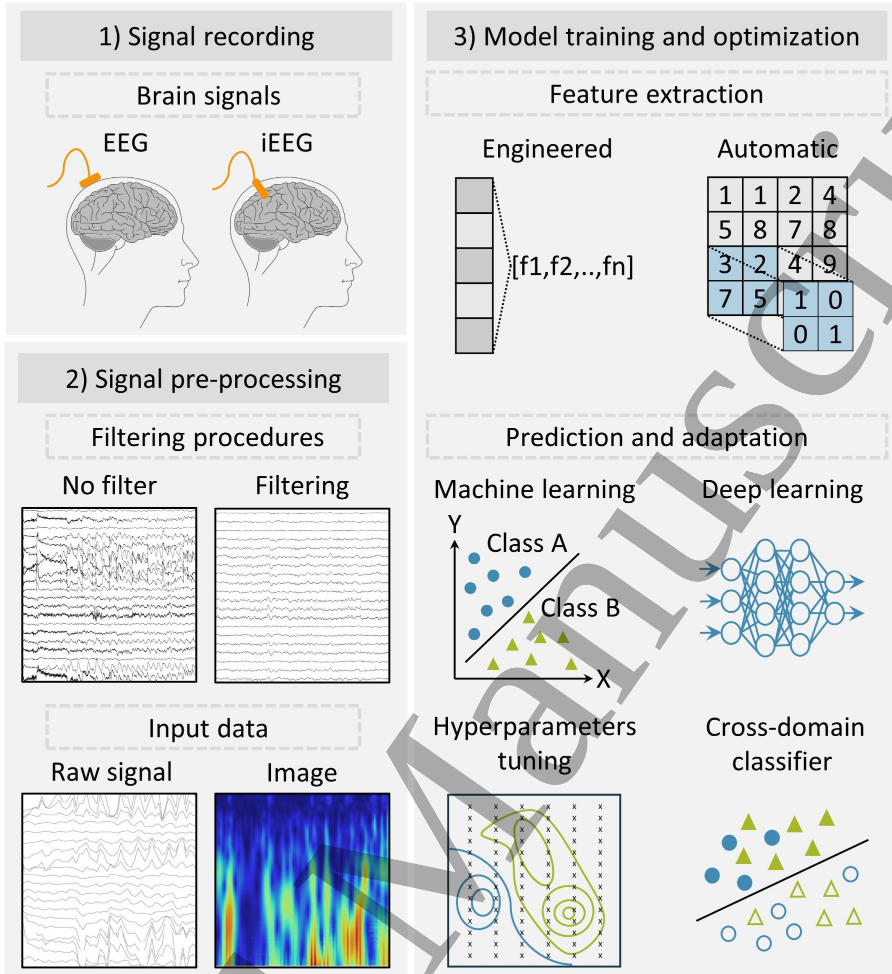

Fig. 3. The most common options for setting up a epileptic seizure prediction pipeline. Panel 1 refers to different methods for recording brain signals, including non-invasive (EEG) and invasive (iEEG) methods. Panel 2 illustrates the approaches for filtering and preparing the input data. Panel 3 addresses feature extraction methods, including manually engineered features and automatic extraction using machine learning models. Panel 3 also presents the variety of learning models and tuning techniques that can be deployed.

into windows, whose duration ranges between 1 and 60 seconds [33, 35]. Each windowed signal can then be directly given as input to the predictive model [65, 51] or converted into a spectrogram or scalogram image by means of Wavelet or Fourier analysis [66–68]. It should be noted that window size is a highly variable hyperparameter from seconds to minutes, which can significantly influence model performance depending on the specific application [69, 70].

2.4.3 Model training and optimization To train traditional machine learning algorithms, a set of standard features is usually extracted from the raw signal [71]. The most commonly used engineered features include both time and frequency components, which rely on the extraction of univariate or multivariate characteristics that could compactly represent the EEG information [72, 73]. Traditional machine learning approaches are normally based on decision trees, support vector machines (SVM), K-Nearest Neighbors, Naive Bayes, or regression models (for a review, see [26]). However, deep learning models are becoming increasingly popular due to their performance and flexibility [74, 75]. In this case, the raw EEG signals can be provided directly as input to the deep network, which automatically extracts the most relevant features for the task

[76–78]. During the training phase, the model hyperparameters are often tuned using trial and error, grid search, hierarchical optimization [79, 42, 78], or by relying on dedicated software such as Optuna [80, 36].

In addition to that, a promising approach to discover more informative features could be the development of channel selection techniques. Indeed, EEG signals are commonly collected from multiple electrodes placed on the scalp, each of which samples neuronal activity from a different area of the brain: each channel might thus provide a different contribution to the detection of seizure events [81, 82]. One could try to identify the most informative channels for seizure forecasting by applying advanced channel selection techniques, such as mutual information-based selection [83], recursive feature elimination [84], or other approaches based on machine learning [85, 34]. This can reduce the computational complexity of the forecasting system, as well as increase its accuracy by minimizing noise and irrelevant data. Furthermore, optimizing channel selection could be particularly beneficial for real-time applications where rapid processing and interpretation of EEG data is essential [86, 87].

After training is complete, there are generally two options for deploying the predictive models. The system can be directly applied to new recordings, which is considered a patient-independent setup, or it can be further fine-tuned using data from the new patients, which is considered a source domain adaptation setup [88–90, 43].

2.5 Model Evaluation

2.5.1 Performance metrics Several metrics can be used to measure the performance of seizure prediction systems. The most common metrics for classification tasks are accuracy (ACC), sensitivity (SEN, also known as Recall), specificity (SPE), false positive rate (FPR) per hour, and the area under the curve (AUC), which is normally derived from the receiver operating characteristic (ROC) curve. In presence of unbalanced datasets (which is often the case in clinical diagnosis), it is also common to report Precision (often referred to as Positive Predictive Value) and F1 score, as well as the Area Under the Precision-Recall Curve. In addition, the seizure prediction horizon (SPH) could be considered to indicate the intervention time before a seizure occurs, and thus quantify the time spent under alarm or false alarm. Most of these metrics can be computed by first measuring the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) rates:

$$\text{ACC} = \frac{TP + TN}{TP + TN + FN + FP} \tag{1}$$

$$\text{SEN} = \frac{TP}{TP + FN} \tag{2}$$

$$\text{SPE} = \frac{TN}{TN + FP} \tag{3}$$

$$\text{FPR} = \frac{FP}{FP + TN} \tag{4}$$

$$\text{Precision} = \frac{TP}{TP + FP} \tag{5}$$

$$\text{F1-Score} = 2 \cdot \frac{\text{Precision} \cdot \text{Recall}}{\text{Precision} + \text{Recall}} \tag{6}$$

For regression problems the output is a real number, which could represent the probability of the onset of a seizure or the time until the upcoming seizure [91]. The most commonly used metrics in this context are mean absolute error (MAE), mean squared error (MSE), root mean squared error (RMSE), coefficient of determination (R^2 score), and mean absolute percentage error (MAPE). These metrics can be calculated with the following formulas, where y, $\hat{y}$, and n represent the true value of an observation, the predicted value of an observation, and the number of observations, respectively:

$$\text{MAE} = \frac{1}{n} \sum_{i=1}^{n} |y_i - \hat{y}_i| \tag{7}$$

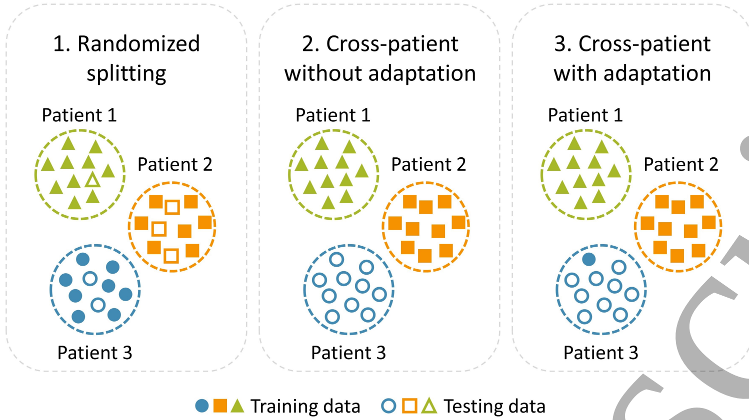

Fig. 4. Schematic representation of possible evaluation methods that are commonly used to assess the performance of epileptic seizure prediction systems. Panel 1 depicts the most commonly used randomized splitting of the data. Panel 2 depicts a leave-one-patient-out validation method without adaptation, while Panel 3 illustrates leave-one-patient out validation with domain adaptation.

$$\mathrm{MSE} = \frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2 \tag{8}$$

$$\mathrm{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2} \tag{9}$$

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2} \tag{10}$$

$$\mathrm{MAPE} = \frac{100\%}{n}\sum_{i=1}^{n}\left|\frac{y_i - \hat{y}_i}{y_i}\right| \tag{11}$$

2.5.2 Validation methods The most common approaches to evaluate model performance are based on a randomized split of training and testing patterns or the implementation of randomized cross-validation methods, where data from all patients are randomly divided into separate folds that are iteratively used to monitor the prediction accuracy (panel 1 in Figure 4). One critical issue with these methods is that the model is trained using data from all patients, thus increasing the risk of information leakage [36]. A more robust alternative is to implement cross-patient testing, where the model is tested using a completely separate set of data recorded from left-out (independent) patients. In this case, the most challenging scenario is to directly evaluate the model using the set of new patients, without further tuning (panel 2 in Figure 4). A reasonable trade-off is to use source domain adaptation techniques to fine-tune the model using a few samples (e.g., one or two seizures) recorded from the new patients (panel 3 in Figure 4). Although adaptation approaches require the recording of at least one epileptic event from the target patients, they allow to significantly improve prediction accuracy [90, 92].

The present review focuses on cross-patient approaches, but we still included articles that used randomized approaches during the initial screening stage (see the PRISMA diagram in Figure 1) in order to quantify the ratio of articles using cross-patient settings with respect to the entire literature focused on epileptic seizure prediction. Furthermore, it should be noted that we use the terms randomized splitting and cross-patient validation in this review, but in the literature these conditions may be identified under different names. Randomized splitting is often referred to as patient-dependent, patient-specific, or subject-specific evaluation. Cross-patient approaches without adaptation are often referred to as patient-independent, cross-subject, inter-subject or leave-one-patient-out, while cross-patient approaches that incorporate source domain adaptation are often called incremental adaptation or calibration methods.

3 Results

3.1 Eligible papers

The initial identification step resulted in 9380 potential articles, which became 7625 after removal of duplicate records. The reviewers then excluded 7072 articles based on their title and abstract (since we expected cross-patient studies to be rare, we preferred to use a more generic query and manually discard irrelevant results). The full texts of the remaining 534 articles were individually examined, resulting in 21 eligible articles based on cross-patient settings (10 without adaptation, 11 with source domain adaptation). A detailed summary of all eligible articles is provided in the following.

3.2 Cross-patient without adaptation

Table 1 summarizes the results achieved by the studies that explored the cross-patient setting without adaptation. All articles framed epileptic seizure prediction as a classification task between interictal and preictal states. They explored datasets of different sizes, ranging from 7 to 24 subjects. The input data was created either by exploiting engineered signal features or by directly feeding the model with raw signal windows. The duration of the preictal and interictal states differed widely between studies, for example, the preictal period ranged between 10 and 30 minutes before a seizure, and the interictal period ranged between 4 to 12 hours away from a seizure. Also the length of the signal windows varied significantly between studies, from 1 to 20 seconds. These design choices could be problematic and misleading: for example, one study obtained better results using a small window [93], while another achieved higher accuracy with a longer window [94]. Note that in one case [95] we calculated the mean SEN and SPE from the tabular data reported in the article, since the authors did not provide an aggregated performance measure.

Most of the studies relied on neural network models of different types, from classical multi-layer perceptrons to convolutional neural networks (CNN) or even Transformer architectures. However, as expected, all studies reported poorer performance in cross-patient settings compared to easier (patient-dependent) settings [96, 95, 37, 38, 36, 94]. This suggests that none of the proposed methods is able to find general features, shared between subjects, that can be used to reliably predict seizures in unseen patients. Only one study reported an exceptionally high prediction accuracy (approaching 100%) [97]; however, the article lacks many methodological details and the evaluation setting is described in an unclear way, suggesting that the validation was in fact conducted using randomized procedures rather than patient-independent settings.

In addition to common trends between studies, some authors reported specific insights. One work compared classical machine learning and deep learning models [96], concluding that they were similar in terms of predicting in unseen patients. Another work [37] exploited interpretability techniques such as Shapley values to characterize the contribution of each channel to inform the classification. The idea of selecting only the most relevant channels was further pursued in another study [93], although the proposed method might lead to the selection of different channels for each patient. More recent work [94] investigated the potential of brain connectivity networks (i.e., a 2D representation of structural, functional and effective connectivity between brain regions) to predict upcoming seizures, reporting promising results.

3.3 Cross-patient with adaptation

Table 2 summarizes the results from cross-patient settings featuring source domain adaptation. Also in this case, all articles framed epileptic seizure prediction as a classification task between interictal and preictal states. The duration of the preictal state ranged between 15 and 60 minutes (but was set mainly at 30 minutes), while the duration of the interictal state ranged between 1 and 4 hours. The length of the signal window varied between 1 and 30 seconds. In some cases, the authors undersampled the number of interictal states to balance the classes, while in other cases they introduced overlapping windows to create more data points associated with the preictal state. Also in this case, the most common approaches were based on neural networks.

Notably, all studies report improved performance compared to the same methods implemented without adaptation. In one case [92] the authors showed that calibrating a pre-trained model with one or two seizures from the target patient can improve the performance of traditional machine learning algorithms, such as XGBoost classifiers, although the improvement was more marked for deep learning models. Some studies

Table 1. Summary of epileptic seizure prediction articles adopting a cross-patient setup without adaptation. Each row corresponds to one eligible article, reporting the most common performance metrics including percentage of accuracy (ACC), sensitivity (SEN), specificity (SPE) and F1-score, false positive rate (FPR) per hour, and the minutes of seizure prediction horizon (SPH). None of these articles reported the area under the curve (AUC). Articles using more than one dataset are reported sequentially.

Authors	Year	Dataset	Input type	Classifier	ACC	SEN	SPE	F1	FPR	SPH
Tsiouris et al.[96]	2017	CHB-MIT	Engineered features	Neural Network	-	68	67	-	-	-
Buyukcakir et al.[95]	2020	CHB-MIT	Engineered features	Neural Network	-	20	59	-	-	4
Dissanayake et al.[37]	2021	CHB-MIT	Raw signal	CNN	59	-	-	-	-	60
Jemal et al.[38]	2022	CHB-MIT	Raw signal	CNN	-	67	-	66	0.6	-
Hussein et al.[97]	2022	CHB-MIT	Scalograms	Transformer	100	100	100	-	0.004	-
Choi et al.[93]	2022	Private	Raw signal	CNN+GRU+Attention	83	80	86	-	-	-
Shaik Gadda et al.[98]	2023	CHB-MIT	Engineered features	XGBoost	61	67	63	59	-	10
Shafiezadeh et al.[36]	2023	CHB-MIT	Engineered features	XGBoost	50	56	44	-	-	-
		Private	Engineered features	XGBoost	51	49	55	-	-	-
Sarvi Zargar et al.[39]	2023	EPILEPSIAE	Engineered features	Transformer	-	98	-	-	0.03	-
Tian et al.[94]	2023	CHB-MIT	Raw signal	CNN	86	85	87	-	-	-

Table 2. Summary of epileptic seizure prediction articles adopting a cross-patient setup with source domain adaptation. Each row corresponds to one eligible article, reporting the most common performance metrics including percentage of accuracy (ACC), sensitivity (SEN), specificity (SPE) and F1-score, area under the curve (AUC), false positive rate (FPR) per hour, and the minutes of seizure prediction horizon (SPH). Articles using more than one dataset are reported sequentially.

Authors	Year	Dataset	Input type	Classifier	ACC	SEN	SPE	AUC	F1	FPR	SPH
Peng et al.[90]	2021	CHB-MIT	Image	Autoencoder	-	73	-	-	-	0.24	-
Peng et al.[42]	2022	CHB-MIT	Image	Autoencoder	84	82	-	0.84	-	0.13	-
Wu et al.[99]	2022	CHB-MIT	Raw signal/Image	CNN	93	95	-	-	-	0.14	-
Liang et al.[102]	2023	CHB-MIT	Image	CNN	-	89	-	0.86	-	0.18	5
Liang et al.[89]	2023	CHB-MIT	Image	CNN	-	89	-	0.85	-	0.18	5
Jemal et al.[101]	2024	CHB-MIT	Raw signal	CNN	71	-	-	0.75	66	-	-
	2024	SIENA	Raw signal	CNN	52	-	-	0.52	52	-	-
Deng et al.[43]	2024	CHB-MIT	Raw signal	CNN	83	75	-	0.9	-	-	1
Zhao et al.[88]	2024	CHB-MIT	Raw signal	Gaussian mixture	-	71	-	0.68	-	0.38	-
Zhang et al.[100]	2024	CHB-MIT	Image	Transformer	-	80	-	0.81	-	0.26	5
Mao et al.[79]	2024	CHB-MIT	Image	CNN	65	54	66	0.65	-	-	-
Shafiezadeh et al.[92]	2024	CHB-MIT	Raw signal	CNN	69	70	70	0.85	-	-	-
		CHB-MIT	Engineered features	XGBoost	61	58	67	-	-	-	-
		Private	Raw signal	CNN	71	75	71	0.87	-	-	-
		Private	Engineered features	XGBoost	63	74	71	-	-	-	-

used a large portion of the data from unseen patients to adapt the models (e.g., all but one target seizure) [89, 88], which results in improved performance but might not be considered a realistic scenario in clinical settings. In another study [99], the authors first trained a generic predictive model by pooling seizure data from all available patients, except the target one. The patient-specific model is then obtained by training a new model with the same architecture using the data from the target patient, at the same time distilling knowledge from the generic model by imposing constraints on the model parameters. Also in this case, however, training the patient-specific model requires the use of a lot of data from the target patient, which may not be realistic in clinical settings.

A few studies [42, 100, 101] applied adversarial learning techniques to map the high-dimensional EEG data into a domain-invariant subspace, showing that adversarial models could reduce the impact of noise in the data and facilitate the extraction of complex relations between the source and target domains. Other studies highlighted that the application of appropriate tuning procedures could play a crucial role in improving the performance of the adapted models [102, 88, 92].

4 Discussion

Our survey of the existing literature on seizure prediction algorithms allowed us to identify the most promising approaches that can work in cross-patient prediction settings. We first provided an overview of the most common design choices that should be made to set up an AI-based seizure prediction pipeline, including the choice of the brain signals to be recorded, the signal pre-processing stages and the most popular model training and optimization techniques. We then aggregated the results of 21 eligible articles that implemented predictive models in cross-patient settings using human scalp EEG recordings.

Overall, our analysis suggests that cross-patient seizure prediction from scalp EEG remains a very challenging task, and there is no consensus about the machine learning methods that should be deployed to solve it. Several studies relied on traditional machine learning classifiers and the use of engineered signal features to perform the prediction; however, the recent trend is moving toward the use of deep learning models that are directly fed with raw EEG signals and/or images representing the signals in the time-frequency domains. Moreover, there is an increasing number of studies proposing to exploit source domain adaptation methods to fine-tune generic predictive models using a few data points sampled from new target patients. Such approaches normally achieve higher prediction accuracy compared to patient-agnostic methods, but still require recording at least one seizure event from each patient and might thus have limited applicability in realistic clinical scenarios.

Notably, our review highlighted that almost all research in this area is focused on the CHB-MIT dataset [19]. On the one hand, this allows for a more objective comparison between different methods; on the other hand, however, focusing on a single dataset might not guarantee the generalizability of results to different conditions, such as recording devices or patient populations. Indeed, the adoption of small publicly available datasets increases the risk of overfitting the data, since researchers could design and develop machine learning models with the goal of optimizing the performance on the type of epileptic patterns contained in a specific set of recordings. This could limit the generalizability and reproducibility of the results and also influence the choice of AI-based techniques and pre-processing steps (for a recent review of the most common EEG datasets for seizure detection and prediction, see [57]).

Furthermore, researchers should be aware of the importance of implementing a proper statistical evaluation of seizure prediction algorithms, which is crucial to guarantee an adequate understanding of the reliability of the reported prediction performance. One possibility is to compare the performance of a prediction algorithm with that of a random predictor, which can be established by means of Monte Carlo simulations [103] or by using other approaches of surrogate analysis [104], possibly also considering the multivariate nature of EEG time series [105] or implementing alarm times surrogates under controlled conditions [106]. Comparison with a simple random predictor is computationally the most efficient form of statistical evaluation for the performance of a prediction algorithm; however, more sophisticated surrogate-based approaches could offer greater confidence in determining whether or not an algorithm performs better than chance [107]. It is also crucial to develop methods that can quantify the uncertainty around each prediction, in order to provide an estimate of the confidence at which the forecast is performed. Ideally, it would be advantageous to predict upcoming seizures with a precise temporal resolution, at best a long time interval in advance of the seizure in order to grant enough time for intervention [108]. Nevertheless, only a few approaches have tried to quantify the uncertainty of deep learning models applied to EEG signals, using fairly simple methods based on the measure of the entropy of the neural network outputs [109, 110].

Although our review has focused on predictive approaches based on non-invasive EEG recordings, we should also note that the use of intracranial EEG signals might enable the deployment of alternative methods that can exploit finer-grained electrophysiological signatures of upcoming seizure events [111, 58, 112]. In this respect, a promising advance in the last few years has been the realization of the existence of cycles of epileptic brain activity that unfold over different timescales: daily (circadian), multi-day (multidien) and yearly (circannual) [113]. This discovery could make it possible to develop forecasting models operating over days, rather than hours or minutes, thanks to the analysis of periodic cycles of epileptic brain activity over long time courses, or even to model seizure cycles using patient-reported seizure calendars [16]. Nevertheless, we should point out that forecasting methods based on cycles analysis not only rely on invasive EEG recordings, but also require the collection of patient-specific information, such as self-reported diaries [114, 115], and therefore cannot work “out of the box” in a cross-patient setup [116–118]. Moreover, although recent studies have shown that mobile and wearable devices have the potential to track informative signals related to these cyclical patterns [119, 120], scalp EEG can be found in almost every clinical center and therefore still represents a promising and cost-effective tool to support the creation of cross-patient predictive models.

5 Conclusions

The scientific community is investing a lot of effort to make epileptic seizure prediction become a reality [121]. Building effective seizure prediction systems would be a game changer for patients suffering from such a debilitating condition, but unfortunately our systematic review suggests that achieving robust results is still extremely challenging. Predicting the occurrence of seizures remains difficult especially due to the high variation between seizure events, within the same patient but even more among different individuals [44, 23]. This implies that finding universal features of brain signals that could predict upcoming seizures is non-trivial [122] and would likely require a synergy between mechanisms, models, data, devices and algorithms [25].

One key limitation in this endeavor is the lack of large-scale annotated datasets that could be used to train more robust machine learning algorithms. The collection of clinical data in this field is costly and arduous because seizure events are rare in most patients [52], calling for international collaboration between multiple research units. An analogous effort has already led to significant improvements in the development of automated seizure classification systems [123], suggesting that such an investment could pay off in the long term. Besides the creation of high-quality datasets, we argue that scientists must focus on the creation of a standardized workflow that should be used to validate seizure prediction systems. Indeed, the use of randomized cross-validation methods has led to an overestimation of prediction performance, therefore researchers should adopt cross-patient validation approaches to ensure the generalizability of their findings. More transparent and standardized protocols would also allow us to better understand the impact of design choices and model parameters on system performance [41], at the same time improving the reproducibility of scientific findings.

Last but not least, we believe that future research should strive to improve the interpretability of the machine learning algorithms used to build seizure prediction devices. Indeed, in medical settings robustness and interpretability of decisions could be more important than system accuracy, since clinicians should always have a detailed and explicit understanding of the characteristics that drive automated classifications [124]. Unfortunately, many state-of-the-art methods for seizure prediction from EEG signals are based on black-box machine learning models, weakening the trust of clinicians in them for high-risk decisions [125]. Collaboration between bioengineers, data scientists and clinicians will therefore be crucial to bridge this gap and develop more transparent and reliable models.

In conclusion, we believe that the development of hybrid approaches, backed up by interdisciplinary research efforts, will not only increase clinician trust in the adoption of seizure prediction systems, but will also pave the way for advancements in personalized patient care through more interpretable predictive tools.

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