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Summary

A reliable identification of a high-risk state for upcoming seizures may allow for preemptive treatment and improve the quality of patients' life. We evaluate the ability of prodromal symptoms to predict preictal states using a machine learning (ML) approach.

Twenty-four patients with a drug-resistant epilepsy were admitted for a continuous video-EEG monitoring and filled out a daily four-point questionnaire on prodromal symptoms. Data were then classified into: i) a preictal group for questionnaires filled in a 24-hour period prior to at least one seizure (N_1=58), and ii) an interictal group for questionnaires filled in a 24-hour period without seizures (N_2=190). Our prediction model was based on a Support Vector Machine (SVM) classifier and compared to a linear Fisher's classifier.

The combination of all the prodromal symptoms yielded a good prediction performance (AUC=0.72 [0.61-0.81]). This performance was significantly enhanced by selecting a subset of the most relevant symptoms (AUC=0.80 [0.69-0.88]). In comparison, linear classifier systematically failed (AUCs<0.6).

Our findings indicate that the ML analysis of prodromal symptoms is a promising approach to identify preictal states prior to seizures. This could pave the way for development of clinical strategies in seizure prevention and even a non-invasive alarm system.

Keywords

Epilepsy; preictal state; prodromal symptoms; prodromes; seizure prediction; machine learning

1. Introduction

Epileptic seizures have long been considered as resulting from an abrupt and unpredictable transition in brain activity. However, recent studies on the underlying mechanisms of transition from an interictal state to seizure (i.e. ictogenesis) suggest some preictal changes.[1] A reliable identification of a high-risk state of seizure may therefore allow for preventive treatment and would improve the patients' quality of life. While EEG signals have been mainly investigated to characterize preictal states,[1] analysis of clinical symptoms are increasingly reported.[2]

Seizures can be preceded by subjective symptoms that are interpreted by the patients as precursors of an upcoming seizure. They can refer to focal aware seizures, formerly called 'auras', or to prodromal symptoms, which are not considered as part of the ictal event. Prodromal symptoms may appear up to 24h preceding the seizure onset and, as we previously reported,[3] do not share the classical cortical focus-related semiology.

Prodromal symptoms are poorly understood but may reflect changes related to the preictal period. Although not yet specific enough for clinical use, they could refine the pathophysiology of ictogenesis and the seizure prediction strategies. Further, some prospective studies (see *Supplementary table 1*) investigated their ability in seizure prediction and highlighted premonitory features but with rather low sensitivities.[4–9]

Although prediction performances of machine learning (ML) algorithms are well known in different clinical fields, they have never been applied to the analysis of prodromal symptoms.[10] In our study, we applied ML methods to evaluate the ability of prodromal symptoms scales to identify a preictal state.

2. Methods

Assessment of prodromal symptoms

We collected the 22 most frequently reported prodromal symptoms in the literature[2,3,6,7,11–15] and created a self-rated questionnaire, which also included a self-prediction of seizure. Each item was scored using a four-point Likert scale ranging from 'not at all' to 'very much so'.

Measuring anxiety level

We also used the validated Sate-Trait Anxiety Inventory (STAI) form Y-1 (state anxiety) for daily evaluation of anxiety level. It includes 20 questions with a four-point Likert scale and scores range from 20 (low) to 80 (high anxiety).

Study design and participants

Consecutive 29 patients with drug-resistant epilepsy admitted in the Epilepsy Unit of the Pitié-Salpêtrière University Hospital (Paris, France) for a continuous video-EEG monitoring were included from March 2019 to June 2020. They had to fill out these questionnaires every morning during their stay. Continuous video-EEG recordings were analyzed to identify seizures during the hospital stay. We excluded patients with a final diagnosis of psychogenic non-epileptic seizures (N=1) or with mistakes in filling out the questionnaires (N=4). The study was also discontinued in one patient because of inter-current event (severe head injury during a seizure). This study was conducted according to the French legislation and was authorized by the national committee for the protection of privacy and personal data (CNIL, No. 2211991). Patients were informed about the use of their anonymized data in this study.

Every daily questionnaire was then classified into one of the two following groups (Figure 1): i) preictal group when patients experienced at least one electro-clinical seizure in the next 24

hours after filling out the questionnaire (N_1=58) and, ii) interictal group for days without any seizure (N_2=190). In order to avoid confusion with symptoms from focal aware seizures, questionnaires had to be filled at least 10 minutes before the seizure onset.

Univariate between-group comparisons

We applied nonparametric permutation tests ($\alpha = 0.05$, two-tailed, 10000 permutations, FDR corrected for multiple comparisons) to compare each prodromal symptom between interictal and preictal groups.

Prediction models

In order to study predictive values of prodromal symptoms, we evaluated their power to discriminate between interictal and preictal groups. There were two stages in building the prediction model (Figure 1): i) a training phase, in which a binary classifier (interictal or preictal group) used 70% of the labelled days to learn the model; and then ii) a testing phase, in which the remaining labeled days were used to evaluate its prediction performance. A cross-validation procedure was used with 10000 folds.

Classification was performed using self-reported scales of prodromal symptoms and the Support Vector Machine (SVM) classifier.[16] SVM classifiers were chosen because of their robustness for modelling complex data, without any prior assumption about the underlying distribution. In addition, they can use a transformation (kernel) function to project the data into a higher dimensional space: input data that cannot be distinguished in the original space may become separable after transformation into the new high dimensional feature space (Figure 1). More versatile and powerful than linear or polynomial kernel functions, we used here SVM models with a Gaussian kernel.[17] The kernel width parameter γ was set to be the median pairwise distances among training points.[16]

Classification performance using class-imbalanced data may be biased in favour of the majority class.[18] To prevent this type of bias, we applied the Synthetic Minority Over-sampling TEchnique (SMOTE) that oversamples points of the minority class based on the similarities between the existing data.[18] To avoid biased models and overoptimistic predictions, the oversampling was applied within each fold of cross-validation.[19] We also controlled the classifiers' performance by using permutation tests.[20] For all prediction parameters considered in this study, the randomization of groups labels yielded very low p-values <0.001 (not shown in Table 1). For completeness, we also compared the results from the SVM classifier with those obtained from a standard linear model (a Fisher's classifier).

Unlike other items, STAY-Y1 scores are discrete variables that range from 20 to 80. In order to have comparable scales for each item in the prediction models, we converted them into ordinal variables using the same four-point scale as prodromal symptoms: 0 [20-35], 1 [36-50], 2 [51-65] and 3 [66-80].

Classification performance was measured by different attributes (all metrics were computed by applying a cross-validation, excluding the learning period in the classification):

1. *Area under the curve* (AUC) of the receiver operating characteristic (ROC), from 0.5 (random classification) to 1 (perfect classification);

2. *Sensitivity* evaluates the proportion of true positives that are correctly predicted. It suggests how good the test is at predicting preictal states;

3. *Specificity* evaluates the proportion of true negatives that are correctly predicted. It suggests how good the test is at identifying interictal states;

4. *Accuracy* is the proportion of true results, either true positive or true negative, in our data. It measures the degree of veracity for each prediction. As it may be biased towards the majority class, we also considered the precision – also called positive predictive value –, which is the fraction of relevant instances among the detected instances.[19]

Selection of the most relevant prodromal symptoms

The SVM classifier was first evaluated with the whole set of prodromal symptoms (N=24). Then, 'irrelevant' symptoms were removed one by one by a pruning procedure: i) AUC values were estimated by cross-validation, after removal of each symptom; ii) the symptom without which the model has the highest AUC was removed from the subset of symptoms; iii) the procedure was repeated with the remaining symptoms. We could identify a set of 11 symptoms that improved the classification performances after their removal (Table 1). If the removal procedure continued, the classification performances considerably decreased.

3. Results

Study patients

Questionnaires of twenty-four patients were analyzed. Their mean age was 35.0 years (min. 22, max. 54) and 13 patients were women (54.2%). The mean duration of video-EEG monitoring was 10.3 days (min. 2 days, max. 21 days). Patients had mainly temporal focal epilepsy (N=14, 58.3%) and a mean number of seizures of 3.8 during the stay (min. 0, max. 9). Only one patient had a generalized epilepsy.

A 'classical' statistical approach (Table 1)

A linear statistical comparison of groups revealed that the self-prediction of seizure was strongly associated with the preictal group ($p<0.001$). Sensory symptoms such as hypersensitivity to noise and hearing impairment also tended to be more frequently reported during the preictal period (respectively $p=0.03$ and $p=0.07$).

Nevertheless, prediction models based on the linear Fisher's classifier failed in most cases (AUCs<0.60) when each symptom was individually analyzed. Predictions also failed when using a combination of the 24 symptoms (AUC=0.55 [0.40-0.69]) and no improvements were obtained by the feature removal procedure (AUC=0.59 [0.44-0.73]).

SVM classifier's contributions (Table 1)

SVM-based predictions using individual symptoms failed in most cases (AUCs<0.60). However, the combination of all the symptoms provided a good prediction performance (AUC=0.72 [0.61-0.81]), which was considerably improved using the most relevant symptoms (AUC=0.80 [0.69-0.88]). Refined analyses suggested that the time to seizure (< or ≥ 6 hours after filling the questionnaire) and the daily number of seizures (1 or more)) have no effect on the prediction of preictal states. The impact of seizure clusters (i.e. ≥ 3 seizures within a 24h period[21]) could not be assessed as only 7 days from 6 patients were concerned.

Among the 58 days with seizures identified on video-EEG, 45 (77.6%) were reported by patients. In order to assess prediction performances based on these seizures, the algorithm was trained to detect preictal states using only the reported seizures. Then, we tested its performances to distinguish between interictal and preictal phases, including reported and unreported seizures. Although prediction performances decreased, they remained good using the most relevant symptoms (AUC=0.74 [0.64-0.82]).

4. Discussion

Our study highlights the ability of SVM classifiers to identify a preictal state from prodromal symptoms. This new strategy allows capturing complex distribution of data, whether linear or

not, which is usually not the case with traditional statistical models. Indeed, we obtained good prediction performances considering combinations of all the symptoms and of the most relevant ones. In contrast, the prediction model based on linear analyses failed in most cases (AUCs<0.6) and thus cannot be considered for a clinical use. This confirms the low performances – especially the sensitivity – of standard analyses, as previously reported.[4,7–9,15] In addition, unlike previous studies that used binary variables (yes/no), we applied four-point scales to assess prodromal symptoms, which allowed a more complex distribution of data to be taken into account.

The contrast between the good predictions from symptom combinations and the failure of individual analysis is not surprising. We did not expect to obtain robust predictions based on a single symptom, given difficulties reported in the previous studies. The preictal state seems to be a much more complex condition that may only be captured by combinations of various symptoms.

Only one patient had a generalized epilepsy. Indeed, we included patients with drug-resistant epilepsy, regardless of the type of epilepsy. However, drug-resistance is more frequent in focal epilepsies and most patients underwent continuous video-EEG as part of the presurgical evaluation.

Our study has several limits. First, it is important to note that, so far, there is no evidence of a direct causality between prodromal symptoms and seizures. Besides, some studies considered prodromal symptoms as not specific enough for common practice and questioned their validity in seizure prediction.[3,8,15] Nevertheless, our results support the hypothesis that prodromal symptoms are associated with preictal states.[4–7,9] A study of the relationship between prodromal symptoms and interictal epileptiform discharges would also be interesting, in particular to better understand the underlying pathophysiological mechanisms. Second, we could not assess patient-specific predictions because of the limited number of seizures per patient. As the SVM

classifier required sufficient preictal data to ensure accurate predictions, an individual patient-specific approach was not achievable. A long-term patient follow-up would enable us to collect data over a longer time period and evaluate patient-specific predictions. Third, antiepileptic drug dosage was often reduced (in 19 out of 24 patients) to favor seizures. The self-prediction of seizure could have been influenced by these changes, as generally known to the patients. In addition, although only very progressive reduction was applied, the possibility of withdrawal – and not prodromal – symptoms cannot be entirely ruled out. Therefore, future studies could monitor patients without changes in medications, which would replicate the natural course of their epilepsy. Finally, as focal to bilateral and generalized onset tonic-clonic seizures were infrequent compared to focal seizures (10.3% versus 89.7%), the predictability of these seizure types could not be compared. In addition, awareness during seizures was not always assessed, especially during nocturnal seizures.

Our work provides a useful method that can be highly operable in clinical environments. Further, an effective translation of our approach to a suitable device for a long-term monitoring of patients could warn them of the high risk of seizure in order to take precautionary measures. In summary, our findings suggest that the daily collection of rated prodromal symptoms analyzed through machine learning algorithms is a promising approach to identify preictal states prior to seizures. A mobile device would allow for long-term monitoring of patients and evaluation of individual seizure prediction.

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Disclosure of Conflicts of Interest

V. Navarro reports fees from Boards with UCB Pharma, EISAI, Liva Nova, GW Pharma. The remaining authors have no conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table1. Predictive values of prodromal symptoms.

Univariate analyses							
Prodromal symptoms		T-values	p-values	Prodromal symptoms		T-values	p-values
1	Self-prediction of seizure	**3.56**	**0.0008**	13	Irritability	0.78	NS
2	Trouble concentrating	0.89	NS	14	Anxiety (STAI-Y1)	1.02	NS
3	Trouble understanding	0.69	NS	15	Clumsiness	0.38	NS
4	Trouble speaking	0.35	NS	16	Tremor	0.64	NS
5	Trouble reading	0.64	NS	17	Urge to urinate	0.97	NS
6	Trouble writing	1.32	NS	18	Spinning head	0.18	NS
7	Blurred vision	0.74	NS	19	Nausea	0.24	NS
8	Light sensitivity	1.29	NS	20	Headache	0.21	NS
9	Noise sensitivity	**2.37**	**0.03**	21	Thirst	0.52	NS
10	Tinnitus	1.51	NS	22	Hunger	0.23	NS
11	Hearing impairment	1.97	0.07	23	Funny feeling	1.01	NS
12	Bad mood	0.24	NS	24	Fatigue	1.31	NS

Prediction models	**Fisher's linear classifier**					**SVM classifier**				
	AUC	Specificity	Sensitivity	Accuracy	Precision	AUC	Specificity	Sensitivity	Accuracy	Precision
All symptoms	0.55 [0.40-0.69]	0.67 [0.42-0.86]	0.51 [0.32-0.72]	0.59 [0.48-0.69]	0.60 [0.47-0.76]	**0.72 [0.61-0.81]**	**0.68 [0.54-0.81]**	**0.72 [0.58-0.86]**	**0.70 [0.61-0.78]**	**0.70 [0.61-0.79]**
Most relevant symptoms*	0.59 [0.44-0.73]	0.70 [0.49-0.86]	0.54 [0.35-0.74]	0.62 [0.51-0.74]	0.64 [0.51-0.79]	**0.80 [0.69-0.88]**	**0.75 [0.63-0.86]**	**0.77 [0.63-0.89]**	**0.76 [0.68-0.84]**	**0.76 [0.68-0.85]**

Table 1 legend: Each cell contains the average value across all the folds of permutation and cross-validation tests [95% confidence interval is indicated]. AUC: area under the curve, NS: not significant. *The most relevant symptoms exclude symptoms 5, 6, 8, 10, 12, 14, 15, 19 and 21-23.

Supplementary table 1. Previous prospective studies on prodromal symptoms

Reference	Study design	Number of patients	Prodromal symptoms	Statistical analysis	Results
1	Daily questionnaire, VEEG monitoring	83	Seizure self-prediction in the next 24 hours (yes/no/do not know)	Generalized mixed-effects model	Twofold increase in seizures following a positive prediction
2	Diary, outpatient	71	Seizure self-prediction in the next 24 hours using a four-point Likert scale	OR and Chi square test	Positive prediction was associated with a twofold increased risk of seizure (OR 2.25); Sp =0.87; Se= 0.21
3	Diary, outpatient	71	▪ Same as reference 2 ▪ Hours of sleep ▪ 0-10 scales for anxiety and stress	OR and logit normal multiple logistic regression model	- One-unit increments of stress and anxiety were associated with an increased risk of seizure the following day - Increased hours of sleep were associated with a reduced risk of seizures - Self-prediction (OR 3.7) and hours of sleep for the night prior to the seizure remained significant in multiple logistic regression model
4	e-diary, outpatient	19	▪ 0-100 visual analog scales: happy, sad, relaxed, nervous, lively, bored ▪ 0-10 scale: stress ▪ Premonitory features: 18 items (yes/no) ▪ Hours of sleep	OR and multivariate logistic regression model	- Several mood items and 10 premonitory features associated with increased odds of seizure - In multivariate models, a 10-point improvement in total mood decreased seizure risk by 25% while each additional significant premonitory feature increased seizure risk by nearly 25%
5	e-diary, outpatient	19	▪ Seizure self-prediction in the next 24 hours using a five-point Likert scale ▪ 0-100 visual analog scales: happy, sad, relaxed, nervous, lively, bored ▪ 0-10 scale : stress ▪ Premonitory features: 18 items (yes/no)	OR and multivariate logistic regression model	- OR for prediction choices within 6 h was as high as 9.31 for “almost certain” - For 9 best predictors, median sensitivity of self-prediction was 0.5 and median specificity 0.95

			▪ Hours of sleep		- In multivariate models, self-prediction, favorable change in mood and number of premonitory symptoms were significant
6	PDA, outpatient	9	Entries of present prodromal symptoms (not specified in the paper)	Se, Sp	No significant result
7	e-diary questionnaires, outpatient	64	▪ Seizure self-prediction using a five-point Likert scale ▪ 0-100 visual analog scales of 4 mood valences ▪ Premonitory symptoms: 11 items (yes/no) ▪ Hours of sleep	Se, Sp, PPV, NPV	Participant self-prediction was associated with seizure occurrence at 6, 12, and 24 hours For the 12-hour prediction window, median specificity for seizure prediction was 0.94 and median sensitivity was 0.10

Supplementary table 1 legend: NA: not available; NPV: negative predictive value; OR: odds ratio; PDA: personal digital assistant; PPV: positive predictive value; Se: sensitivity; Sp: specificity

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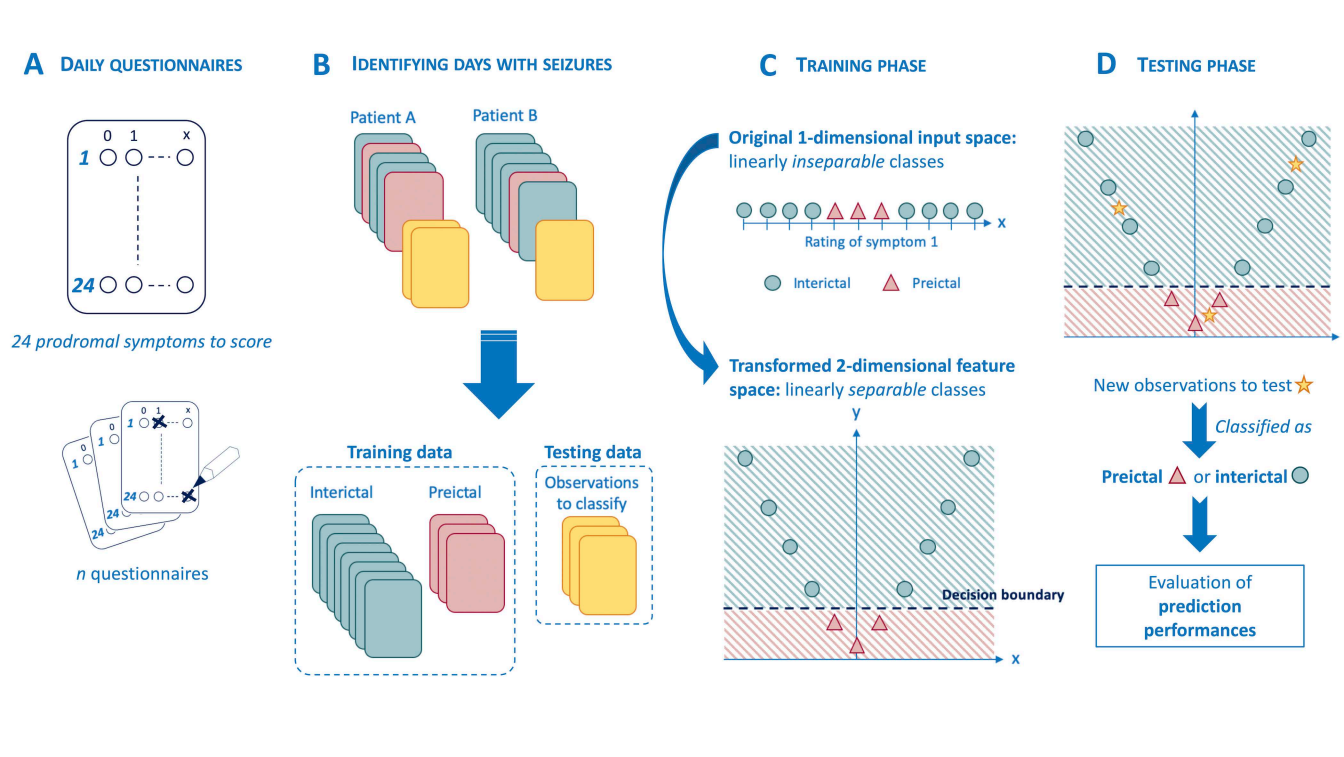
Figure 1. General scheme of the prediction method

Figure 1 legend: A) Daily questionnaires including 24 prodromal symptoms are filled out during *n* days. Each symptom is scored from 0 to x (in our study, x=3). B) Collection of daily questionnaires are grouped into interictal or preictal classes. Some of the data will be used to train the algorithm; the remaining data (indicated in yellow) will be used during the testing phase. C) Nonlinear transformation of non-separable data in the original input space: data are mapped into a higher dimensional feature space (from 1 to 2-dimensional space in this example) where data become separable. The model can be trained and a decision boundary can be fit to separate the two different classes (i.e. interictal and preictal groups). D) New data (represented here by the yellow star symbols) will be classified into one or another class in accordance to the decision boundary set during the training phase. Prediction performances are finally computed only on testing data.


A DAILY QUESTIONNAIRES
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n questionnaires
B IDENTIFYING DAYS WITH SEIZURES
Patient A
Patient B
Training data
Interictal
Preictal
Testing data
Observations to classify
C TRAINING PHASE
Original 1-dimensional input space: linearly inseparable classes
Rating of symptom 1
x
Interictal
Preictal
Transformed 2-dimensional feature space: linearly separable classes
y
Decision boundary
x
D TESTING PHASE
New observations to test
Classified as
Preictal or interictal
Evaluation of prediction performances