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Outliers in clinical symptoms as preictal biomarkers

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1. Introduction

Previous findings have suggested that a preictal state might precede the epileptic seizure onset, which is the basis for seizure prediction attempts (Kuhlmann et al., 2018). Identification of specific preictal features remains one of the most challenging aspects in the field of epilepsy. Although most efforts to predict seizures relied on electroencephalographic (EEG) data, an increasing number of studies have focused on the concept of seizure self-prediction (Haut et al., 2007; DuBois et al., 2010; Schulze-Bonhage and Haut, 2011; Mackay et al., 2017; Haut et al., 2013; Privitera et al., 2019). Besides, some clinical symptoms have also been reported as possibly related to preictal states and may precede the seizure by several hours (Schulze-Bonhage et al., 2006). These preictal symptoms, also called premonitory or prodromal symptoms, consist of mood changes, cognitive disturbances, physical symptoms such as headache, tiredness, light/noise sensitivity, etc (Scaramelli et al., 2009; Haut et al., 2012; Besag and Vasey, 2018).

In a previous study, we highlighted the ability of machine learning models to identify high-risk states for upcoming seizures from clinical features (Cousyn et al., 2021). However, patients often experience a relatively few numbers of days with seizures in comparison with those without seizures. This lack of preictal observations is a major constraint for prediction algorithms, which require sufficient data from both classes (i.e., interictal and preictal) to be properly trained.

Here, we apprehend preictal states as outliers that clinically differ from an interictal baseline and assess the ability of several outlier detection methods – which only require interictal data to train the statistical models – to identify them.

2. Materials and Methods

2.1. Clinical evaluation score

We previously reported a daily self-assessment questionnaire with a four-point Likert scale (Cousyn et al., 2021), including 24 clinical features: i) a self-prediction score of seizure, ii) 22 prodromal symptoms, and iii) an anxiety level through the State-Trait Anxiety Inventory form Y-1.

2.2. Patients

Questionnaires were administered every morning to 24 inpatients who underwent continuous video-EEG during the preoperative evaluation of drug-resistant epilepsy (Cousyn et al., 2021). This study was authorized by the French CNIL committee (No. 2211991) and patients were informed about the use of their anonymized data.

Based on the analysis of video-EEG recordings, questionnaires were divided into: (i) “preictal” observations in case of a seizure occurring in the next 24 hours (n=58), or (ii) “interictal” observations for days without any seizure (n=190).

2.3. Outlier/anomaly detection methods

We used data from the interictal (“normal”) class to train the statistical models so that data from the preictal (“outlying”) class were mapped in a different and distant region of the space representation. We applied different outlier (or anomaly) detection methods (Figure 1 and Supplementary Material):

1. Mahalanobis Distance (MD): an outlier detector that relies on the mean and covariance matrix of the interictal class (Khan and Madden, 2014). The MD-based

anomaly score is basically the statistical distance between a test point and the distribution of normal (interictal) data;

2. Nearest Neighbor Data Description (NNDD): a non-parametric method that assumes the local structure of preictal prodromal symptoms (in the original space of representation) is different from that of interictal data (Khan and Madden, 2014). The anomaly score of a point is evaluated by computing the distance to its nearest neighbors in the normal class, normalized by the distances in this local neighborhood;
3. Support vector data description (SVDD): a very robust for modeling non-trivial data, without any prior assumption about the underlying distribution (Tax and Duin, 1999). SVDD uses a transformation (kernel) function to map the interictal data into a high-dimensional feature space where a boundary (a hypersphere covering the points) can be defined. The anomaly score is defined as the distance between a mapped data point and this hypersphere;
4. Support vector machine-one class (SVM-OC): a detector that defines a boundary achieving the maximum separation between the interictal points and the origin (Schölkopf et al., 2001). SVM-OC also applies a kernel transformation such that the decision boundary can enclose the majority of the projected data. For any test point, the anomaly score is defined as the distance to the boundary.

For each outlier detector, a two-step analysis was performed: i) all the 24 clinical features were first used to train/test the statistical model, and then ii) we selected the best features through a pruning procedure to optimize the model (Cousyn et al., 2021) and re-evaluated its performances.

2.4. Prediction performances

We evaluated outlier detectors' performances by developing a cross-validation strategy: for each fold, we first trained detectors on 80 % of interictal observations from all patients (n=152). The prediction model was then evaluated using the remaining 20 % interictal observations (n=38) and all the preictal observations (n=58). This procedure was repeated 1000 times.

Statistical parameters calculated for each fold of cross-validation were: i) the area under the curve (AUC), which summarizes the overall ability of a classifier to discriminate between the two classes and ranges from 0.5 (random) to 1 (perfect classification); ii) the sensitivity, which reflects its ability to identify preictal observations; iii) the specificity, which reflects its ability to identify interictal observations; iv) the positive predictive value (PPV) or precision, which reflects the proportion of correct preictal detections; v) the false positive rate (FPR) that corresponds to the probability of false alarms; and vi) the F1 score that quantifies the trade-off between the PPV and sensitivity.

3. Results

Our cohort was gender-balanced (13 [54.2%] females) with a mean age of 35 years (range 22-54 years). Mean seizure frequency was 3.8 seizures (range 0-9) per patient during the hospitalization (mean 10.3 days, range 2-21). Temporal lobe epilepsy was predominant (58.3% of patients).

All models yielded poor prediction performances when all the 24 clinical features were used (AUCs \leq 0.6; Table 1). Performances were, however, clearly improved by selecting the best variables; in particular, the SVM-OC detector reached good prediction levels (AUC = 0.71,

95% CI = [0.63 – 0.79]; PPV = 0.77, 95% CI = [0.70 – 0.84]; FPR = 0.31, 95% CI = [0.21 – 0.44]); and F1 score = 0.74, 95% CI = [0.64 – 0.81]).

Considering only preictal observations close to seizures (less than 6 hours) or associated with more than one seizure per day did not yield better performances.

4. Discussion

In this study, we found preictal states could be associated with clinical changes that differ from a baseline, i.e. the interictal state. Outlying clinical features were suggestive of a preictal state, which could be identified by outlier detection methods. Although machine learning models trained on both preictal and interictal data provided very good predictions (Cousyn et al., 2021), this approach is highly suitable when preictal observations are less frequent than interictal ones, which is quite a common situation. Our findings suggest that SVM-OC could be the most efficient detector compared to the other algorithms. Nevertheless, other detectors displayed quite similar performances and NNDD also provided faster computations (CPU times were 3 to 5 times shorter than those in SVM-OC).

It is important to note that our different outlier detectors reached only moderate sensitivities (i.e., preictal state detection) – around 70%. First, robust identification of outlying clinical states should rely on a large amount of data (Kuhlmann et al., 2018) – which was not achievable in this study. A daily home-based collection of clinical features over a longer period could help increase prediction performances. Second, the selection of the best features was performed through a post-hoc pruning procedure. A prospective study with a larger dataset for parameter optimization would be of interest to reduce the bias of the models. Finally, additional physiological parameters could refine the characterization of preictal-

related changes. Autonomic modifications such as heart rate or electrodermal activity could be easily recorded – even at home – using a dedicated wearable device (Kuhlmann et al., 2018; Vieluf et al., 2019). Besides, seizure-precipitating factors (sleep deprivation, menstrual cycles) and circadian rhythms should also be taken into account (Karoly et al., 2017; Baud et al., 2018; Privitera et al., 2019).

A suitable mobile device (e.g., tablet or smartphone) could allow for a long-term and prospective collection of data with real-time analysis. Besides, statistical algorithms could operate on a remote server or directly on the device and be continuously updated with new observations. Another advantage of these prediction algorithms is their easy implementation on any device with an appropriate operating system – including iOS or Android. In addition, one-class classification algorithms require a shorter training – as only interictal observations supply the training database – and can therefore be operational without waiting for a sufficient number of seizures. This could yield a time window for a broad range of therapeutic possibilities, from preventive measures, such as avoiding potentially risky activities, to designing behavioral and/or neurostimulation paradigms that could stop the seizure.

In summary, preictal states may be apprehended as an outlying condition that differs from an interictal baseline and displays clinical changes. Outlier detection methods can highlight these state changes using rated clinical features. Increasing the duration of data collection and the model complexity with additional clinical – and even multimodal – parameters could identify more subtle physiological modifications, which should improve prediction performances.

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Disclosure of Conflicts of Interest

V. N. reports fees from Boards with UCB Pharma, Eisai, GW Pharma. The remaining authors have no conflicts of interest.

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Figure 1: Overview of the detection of outlying clinical features.

Figure 1 legend:

a) Clinical scores are self-reported by patients in daily questionnaires. b) Observations are labelled as those reported the days without seizures (interictal or 'normal' class) and during days with seizures (preictal class). c) For all methods, only interictal observations are used to define the boundary of this normal class. Any point located or mapped outside these boundaries is detected as a preictal outlier.

Abbreviations: k-NN, k-nearest neighbors; SVDD, support vector data description; SVM, support vector machine

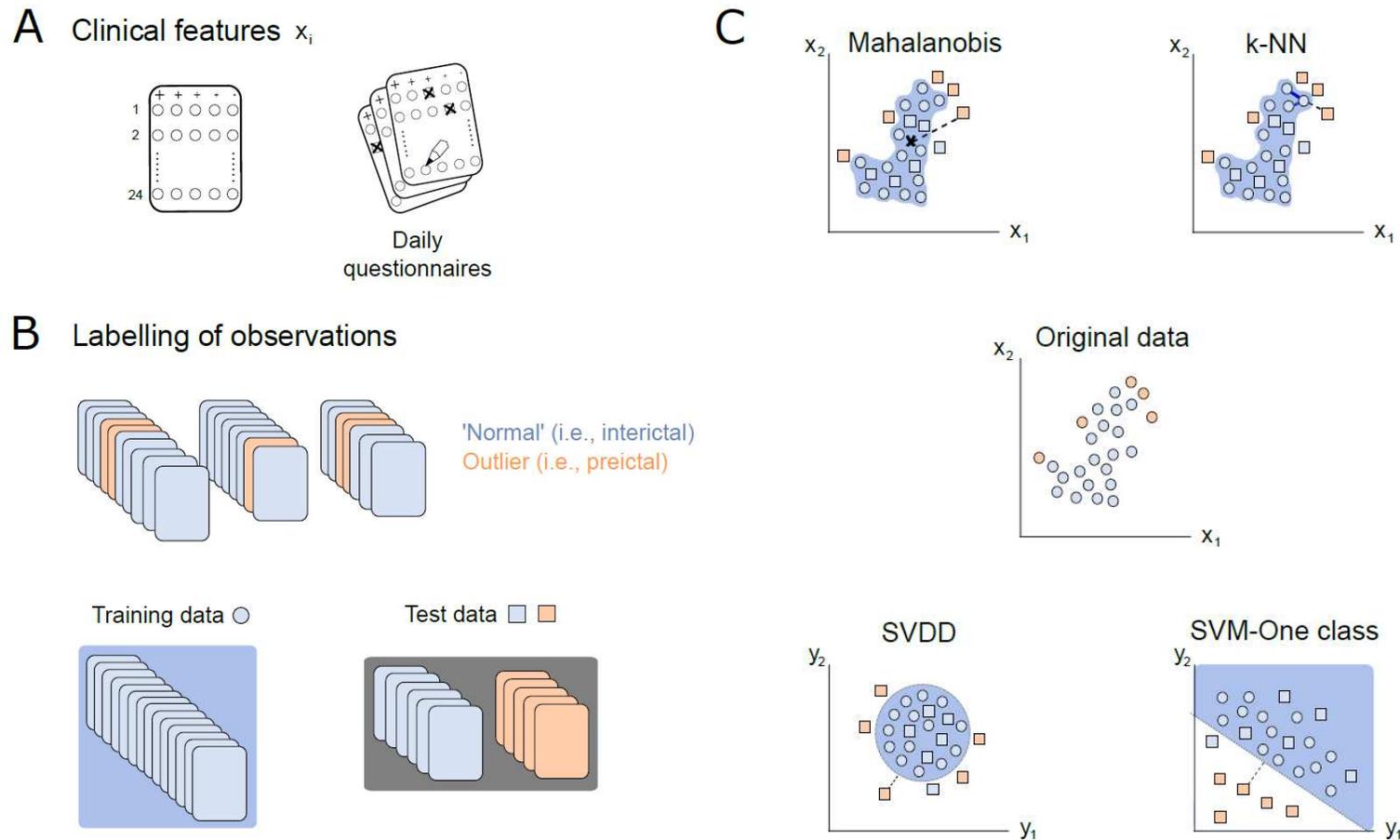


Table 1: Predictive values of outlying clinical features (median values and 95% [confidence intervals])

Table 1 legend:

Abbreviations: AUC, area under the curve; NNDD, Nearest Neighbor Data Description; SVDD, Support vector data description; SVM-OC, Support vector machine-one class; PPV, positive predictive value; FPR, false positive rate. The most relevant features for the SVM-OC model are: 1, 3, 7, 9, 13, 16 and 24;

Clinical features												
1. Self-prediction of seizure	7. Blurred vision	13. Irritability	19. Nausea									
2. Trouble concentrating	8. Light sensitivity	14 Anxiety (STAI-Y1)	20. Headache									
3. Trouble understanding	9. Noise sensitivity	15. Clumsiness	21. Thirst									
4. Trouble speaking	10. Tinnitus	16. Tremor	22. Hunger									
5. Trouble reading	11. Hearing impairment	17. Urge to urinate	23. Funny feeling									
6. Trouble writing	12. Bad mood	18. Spinning head	24. Fatigue									
Prediction models	Mahalanobis distance						NNDD					
	AUC	Specificity	Sensitivity	PPV	FPR	F1	AUC	Specificity	Sensitivity	PPV	FPR	F1
All features	.58	.58	.62	.69	.42	.66	.58	.58	.6	.68	.42	.64
	[.5-.67]	[.44-.73]	[.50-.72]	[.62-.77]	[.26-.57]	[.56-.72]	[.50-.67]	[.39-.76]	[.41-.81]	[.62-.76]	[.26-.57]	[.51-.75]
Most relevant features	.68	.65	.69	.76	.34	.73	.68	.65	.70	.75	.31	.71
	[.60-.76]	[.54-.70]	[.58-.75]	[.70-.83]	[.21-.45]	[.64-.77]	[.61-.76]	[.52-.81]	[.55-.75]	[.69-.83]	[.18-.47]	[.62-.77]
Prediction models	SVDD						SVM-OC					
	AUC	Specificity	Sensitivity	PPV	FPR	F1	AUC	Specificity	Sensitivity	PPV	FPR	F1
All features	.6	.55	.69	.68	.44	.68	.60	.55	.65	.69	.44	.67
	[.51-.68]	[.39-.76]	[.43-.82]	[.63-.75]	[.25-.60]	[.52-.76]	[.50-.67]	[.39-.71]	[.46-.79]	[.63-.76]	[.26-.58]	[.54-.74]
Most relevant features	.69	.65	.70	.76	.31	.73	.71	.72	.65	.76	.34	.74
	[.60-.76]	[.52-.79]	[.58-.79]	.68	.44	[.65-.78]	[.63-.79]	[.55-.84]	[.52-.79]	[.70-.83]	[.25-.47]	[.64-.81]