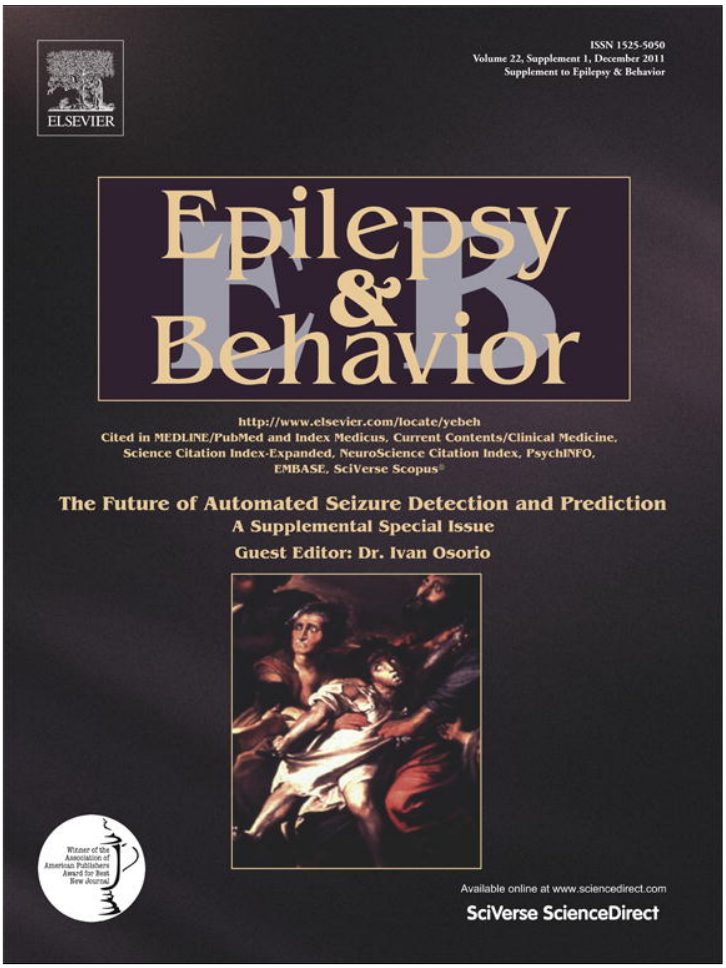

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Anticipating the unobserved: Prediction of subclinical seizures

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ABSTRACT

Subclinical seizures (SCS) have rarely been considered in the diagnosis and therapy of epilepsy and have not been systematically analyzed in studies on seizure prediction. Here, we investigate whether predictions of subclinical seizures are feasible and how their occurrence may affect the performance of prediction algorithms. Using the European database of long-term recordings of surface and invasive electroencephalography data, we analyzed the data from 21 patients with SCS, including in total 413 clinically manifest seizures (CS) and 3341 SCS. Based on the mean phase coherence we investigated the predictive performance of CS and SCS. The two types of seizures had similar prediction sensitivities. Significant performance was found considerably more often for SCS than for CS, especially for patients with invasive recordings. When analyzing false alarms triggered by predicting CS, a significant number of these false predictions were followed by SCS for 9 of 21 patients. Although currently observed prediction performance may not be deemed sufficient for clinical applications for the majority of the patients, it can be concluded that the prediction of SCS is feasible on a similar level as for CS and allows a prediction of more of the seizures impairing patients, possibly also reducing the number of false alarms that were in fact correct predictions of CS.

This article is part of a Supplemental Special Issue entitled The Future of Automated Seizure Detection and Prediction.

1. Introduction

In clinical epileptology, subclinical seizures (SCS) have been treated like a second-class citizen for a long time [1,2]. SCS are lacking subjective or objective clinical features by definition. However, it may be questioned whether the influence of SCS can indeed be disregarded in clinical practice. Cognitive impairment and problems with memory consolidation have been ascertained even for transient interictal discharges [3–5]. It has been observed that cognitive deterioration can be stopped and even dramatically improved when therapy eliminates seizures or reduces seizure frequency [5]. Similar to these forms of interictal epileptiform abnormalities, SCS have been reported to be accompanied by unnoticed cognitive disturbances, namely, memory deficits [6], or by longer-lasting BOLD changes [7]. SCS have been found to be of considerable clinical relevance and of prognostic significance with respect to epilepsy surgery outcome [1,2,8]. Additionally, SCS can induce permanent neuronal changes, leading to long-lasting cognitive defects [1]. For these reasons, several authors have concluded that substantial advantages could be gained by considering SCS similarly to CS for the management of epilepsy [1,2,6,8,9]. Given this evidence of the impact of SCS on patients and their importance for diagnostic and therapeutic purposes, we analyze in the following whether inclusion of SCS is also of benefit in seizure prediction.

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In general, fundamentally new therapeutic options like closed-loop electrical stimulation [10–15] and automatic local administration of antiepileptic medication [14,16] would be facilitated if sufficient prediction performance could be achieved (for overviews see [17–19]). This would be of considerable interest especially for patients with pharmacoresistant epilepsies [20,21]. Up to now the focus has been on clinically manifest seizures (CS), and SCS have not been studied explicitly for seizure prediction, as suggested in previous studies [18,22,23]. In one previous study, preictal changes were also observed in SCS as measured by the similarity of the EEG to reference periods, providing evidence that like CS, SCS may be preceded by preictal changes [24].

The ability to predict subclinical seizures could yield considerable benefit. On the one hand, it could help to avert symptoms that, although having no apparent clinical manifestation, may affect the cognition of the patient and decrease his or her quality of life. If SCS could be predicted reliably, their occurrence could be prevented or aborted with automated intervention devices, thereby preventing the disabling cognitive effects. Here, the benefit to the patient has to be weighed against the effects of the intervention techniques and possible side effects. Whether it would be adequate to give the patient an actual warning would have to be considered on an individual basis, in light of the severity of the impairment of the SCS, the possibility of the patient to prevent seizure occurrence on short notice, and the concrete psychosocial situation of the patient.

On the other hand, the previously mentioned evidence suggests that the distinction between CS and SCS is less clear-cut than the names suggest. For at least a subset of patients with SCS, it can be assumed that behavioral or cognitive changes could be detected if appropriate tests were implemented during seizure occurrence [1], making them "clinically unobserved clinical seizures." Moreover, from a prediction point of view, CS and SCS may have similar or even identical precursors. Hence, it could be hard to distinguish them in advance: Correct predictions of SCS would be regarded as incorrect predictions if only CS are taken into account. Therefore, prediction performance may be negatively affected if prediction analysis is restricted to clinically manifest seizures.

In the following, we study surface and intracranial long-term recordings of 21 patients with partial epilepsy who had SCS during presurgical monitoring. Based on the mean phase coherence, a method that estimates the degree of interaction between signals derived from pairs of channels of the electroencephalogram (EEG) [25], we analyze prediction performance for CS and SCS.

The article is structured as follows. First, the patient collective studied, the data recording and processing, and the technique employed to preselect auspicious features are described. Then, the approach to alarm generation and evaluation is introduced, including means to statistically validate prediction performance. In the Results, observed prediction performance is presented. Subsequently, the suitability of SCS predictions is discussed and conclusions are drawn.

2. Methods

2.1. Patient characteristics

Surface and intracranial EEG recordings of patients with pharmacoresistant focal epilepsies who underwent presurgical evaluation were compiled as part of the EPILEPSIAE EU project [26]. Recordings were obtained at the epilepsy units of the University Hospital Freiburg, Germany; the Pitié-Salpêtrière Hospital, Paris, France; and the Hospitais de Universidade de Coimbra, Portugal. The retrospective evaluation of the data received prior approval by the ethics committees of the respective hospitals.

To be included in this study, subjects had to have had at least five CS and at least five SCS separated by at least 2 hours. Additionally, all "interictal" periods between CS and SCS had to total at least 3 days, to allow adequate estimation of false prediction rates. Some patients experienced SCS almost continuously over the whole recording period; prediction performance could not be studied in these patients. Hence, we excluded all patients from the analysis for whom SCS covered more than half of the recording, considering a preictal period of 1.5 hours and a postictal period of 0.5 hours. Among the 192 patients available in the database at the beginning of the study—of whom 141 had temporal epilepsies, 23 frontal epilepsies, and 74 other types of epilepsy—65 patients showed SCS. Of these, 21 patients who were screened for SCS for the whole recording duration met the inclusion criteria.

Patient characteristics are summarized in Table 1, grouped by origin of epilepsy (temporal lobe in 11 patients, frontal in 5 patients, and other origin in 5 patients). Fifteen patients had had invasive recordings, and 6 patients surface recordings. For invasive recordings, subdural strip and grid electrodes and/or depth electrodes were used. EEG recordings were obtained using digital video/EEG systems (Neurofile NT in Freiburg, Nicolet in Paris, and Micromed in Coimbra). Sampling rates of 256, 400, 512, 1024, and 2048 Hz were used, and data were filtered for line noise at 50 Hz.

To standardize annotations, a common protocol was established in all centers. Four seizure types were considered: SCS, simple partial seizures, complex partial seizures, and secondarily generalized seizures. SCS were defined as electrographic seizures without observed subjective or objective neurological or somatic manifestations [1,2,27–29]. The electrographic seizure onset of both CS and SCS was defined as the time of onset of a clear-cut seizure pattern, either rhythmic activity, repetitive spiking, or amplitude depression with evolution in morphology, spatial extension, and/or frequency. For clinically manifest seizures, clinical seizure onset was also defined as the first clear-cut subjective symptom or objective sign related to an ongoing epileptic seizure. To evaluate predictions, we considered electrographic seizure onset as proposed in [18]. For clinically manifest seizures for which no electrographic onset could be determined, clinical onset was used instead.

2.2. Extraction and preselection of features

For each pair of electrode contacts on each patient, the mean phase coherence (MPC) was estimated by applying a sliding-window analysis, using a window of 30 seconds' duration shifted by 5 seconds [25]. The MPC was based on a reconstruction of the analytical signal by means of the Hilbert transform. The deviation of phase differences from the uniform distribution was quantified as

$$R_{n,m}^2 = \left\langle \cos\Phi_{n,m} \right\rangle^2 + \left\langle \sin\Phi_{n,m} \right\rangle^2,$$

where $\Phi_{n,m}$ denotes the differences in the instantaneous phases of signals m and n [25,30]. The MPC R is limited to values in [0, 1]. For uniformly distributed phases, $R_{n,m}$ would be zero, whereas for highly coherent phases $R_{n,m}$ approaches one.

If all possible pairs of electrode contacts were considered, a multitude of potential features would be derived. For an automatic preselection of features carrying possibly predictive information, a preselection method was proposed recently that takes the ratio of global variance to local variance of the features into account [31]. This ratio is defined as

$$S_k = \frac{2\sigma_{k,\mathrm{global}}^2}{\sigma_{k,\mathrm{local}}^2},$$

where

$$\sigma_{k,\mathrm{global}}^2 = \frac{1}{N-1}\sum_{i=1}^{N}\left(x_k^i - \overline{x_k}\right)^2$$

is the variance of the feature time series x_k, containing N samples, and

$$\sigma_{k,\mathrm{local}}^2 = \frac{1}{N-2}\sum_{i=1}^{N-1}\left(\Delta x_k^i - \overline{\Delta x_k}\right)^2$$

Table 1
Characteristics of patients with respect to temporal, frontal, or other lobar origin of epilepsy.

ID	Recording type	Age	Gender	Electrode type	CS type	Number of CS(CS >2 h)	Number of SCS(SCS >2 h)	Recording duration (h)	Outcome
Patients with epilepsy of temporal lobe origin									
1	Scalp	15	F	10–20	SP, CP, SG	5 (5)	7 (6)	92.9	Ia
2	Scalp	47	M	10–20	CP, SG, UC	7 (6)	365 (12)	178.Pa2	No surgery
3	Scalp	62	F	10–20	CP	6 (6)	11 (9)	162.2	No surgery
4	Inv.	3	F	g,s	CP, UC	7 (7)	7 (5)	197.0	IIIa
5	Inv.	11	F	d,s	SP, CP, UC	14 (14)	22 (20)	155.0	Ia
6	Inv.	15	M	g,d,s	CP, UC	19 (15)	43 (8)	199.8	Ia
7	Inv.	23	M	d	CP, UC	52 (32)	109 (35)	424.1	Ib
8	Inv.	29	F	d	SP, CP, UC	9 (9)	6 (5)	183.1	Ia
9	Inv.	37	F	d	SP, CP, SG, UC	7 (7)	71 (31)	260.1	Ia
10	Inv.	53	F	d,s	SP, CP	6 (6)	26 (13)	164.4	Ia
11	Inv.	63	F	d,s	CP, UC	21 (9)	11 (6)	118.9	No surgery
Patients with epilepsy of frontal lobe origin									
12	Scalp	31	M	10-20	SP,CP,UC	15 (11)	45 (16)	162.6	Ib
13	Inv.	11	M	g	SP,CP,UC	54 (12)	164 (18)	141.4	Ia
14	Inv.	36	M	d	UC	12 (12)	10 (10)	211.7	IIb
15	Inv.	38	M	d	SG,UC	5 (5)	18 (7)	341.5	No surgery
16	Inv.	48	F	g,s	SP,UC	94 (15)	1816 (18)	244.7	IIb
Patients with epilepsy of other origin									
17	Scalp	31	F	10-10	CP,SG,UC	8 (7)	450 (18)	159.4	IIIa
18	Scalp	46	F	10-20	SP,CP,UC	11 (10)	6 (5)	203.7	No surgery
19	Inv.	22	M	d	SP,CP,SG,UC	26 (5)	119 (9)	113.2	No surgery
20	Inv.	32	F	d	SP,CP,UC	9 (7)	15 (5)	151.6	IVb
21	Inv.	35	M	d,s	SP,CP,SG,UC	26 (16)	20 (15)	180.0	No surgery
Ø		32.8				19.7 (10.3)	159.1 (12.9)	192.6	

Note. Scalp and invasive recordings were obtained with the 10–20 or 10–10 system for scalp recordings and with depth (d), grid (g), and strip (s) electrodes for invasive recordings. Clinical seizures (CS) were classified as simple partial (SP), complex partial (CP), secondarily generalized (SG), or unclassified (UC). Outcome was classified according to a modified Engel classification [41].

is the variance of the differences $\Delta x_k^i = x_k^{i+1} - x_k^i$ between subsequent samples. The arithmetic mean of x_k is denoted by $\overline{x_k}$, and the arithmetic mean of Δx_k by $\overline{\Delta x_k}$. To include a limited number of features exhibiting the highest variance ratios, for each patient, we selected the 15 channel pairs for which the respective features exhibited the highest values of S. As the time of occurrence of seizures is not taken into account for this preselection method, it may be applied to the data that are analyzed subsequently for prediction purposes.

To remove possible outliers in the feature time series, a median filter with 4-minute window length was used.

2.3. Seizure prediction characteristics

To analyze the predictive performance of triggered alarms, we apply the so-called seizure prediction characteristics [32]. Here, alarms are raised whenever the feature crosses a predefined threshold, predicting upcoming seizures. The alarm has to be followed by an interval that should be free of any seizure, the intervention time (IT), which should enable an intervention (cf. Fig. 1). The seizure is predicted to occur during the seizure occurrence period (SOP). If a seizure indeed occurs during the SOP, the alarm can be regarded as correct; otherwise, it would be false. After an alarm, no further alarms are triggered until either SOP + IT passes or a seizure occurs. During refractory periods of 30 minutes after each seizure, no alarms are triggered. As no false alarms could occur during these periods, the respective intervals are not regarded in the calculation of the rate of false predictions. If seizures follow each other too closely, that is, within the duration of SOP + IT, the latter seizure is not considered predictable and the respective periods are excluded from the analysis.

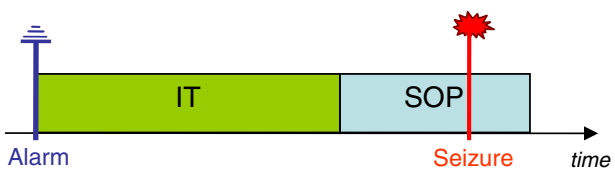
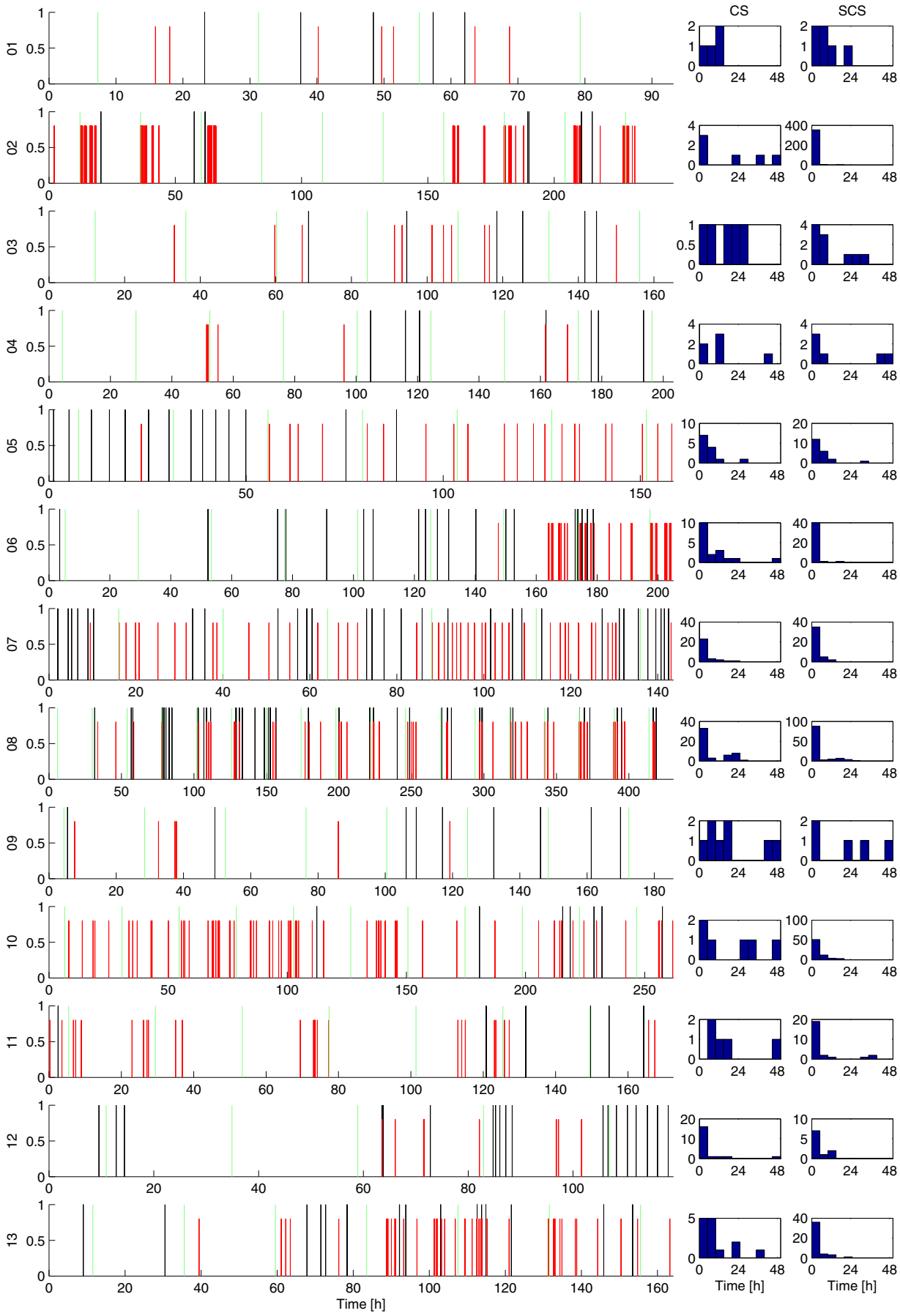


Fig. 1. Schematics of the seizure prediction characteristics. An alarm is followed by a time period reserved for an intervention, the intervention time (IT). This should be free of any seizure, so that an intervention can be applied. The seizure is expected to occur during the seizure occurrence period (SOP). If this is the case, the alarm was a correct prediction.

For this study, we varied the duration of the IT between 10 and 60 minutes to determine an optimal IT for each patient. The SOP was chosen to last 30 minutes, which had been found to be a reasonable duration in previous studies [33,34].

In the analysis of the predictive performance of a prediction method, sensitivity as well as specificity has to be considered. Sensitivity is the ratio of correctly predicted seizures; specificity can be quantified by the rate of false predictions. To limit the specificity to clinically relevant values, a maximum false prediction rate FPR_{max} of 0.15 false prediction per hour is defined [cf. 32].This value can be adjusted depending on the type of intervention.

To analyze whether the observed prediction sensitivities are statistically significant, we compared the results with the critical sensitivity of an analytical random predictor that does not exploit any information contained in the EEG [35,36]. Only if the observed sensitivity exceeds the performance of the random predictor can it be considered significant. For the analytical random predictor, the SOP, FPR_{max}, and number d of parameter settings used for the prediction method are taken into account. The parameter d allows correction for multiple testing, which occurs if parameters are optimized in a retrospective fashion. In this study, this is the case for the duration of the IT and the best of the 15 preselected features that are chosen for each patient. In the following, we consider two different assumptions: complete dependence and complete independence of the features. For the former, the six different durations of IT are taken into account by setting d equal to 6, leading to the lower critical sensitivity. For the latter, d is set to a statistically more conservative value of $d = 6 \times 15 = 90$ to correct also for the 15 features analyzed for each patient. This constitutes the upper critical sensitivity of the random predictor.



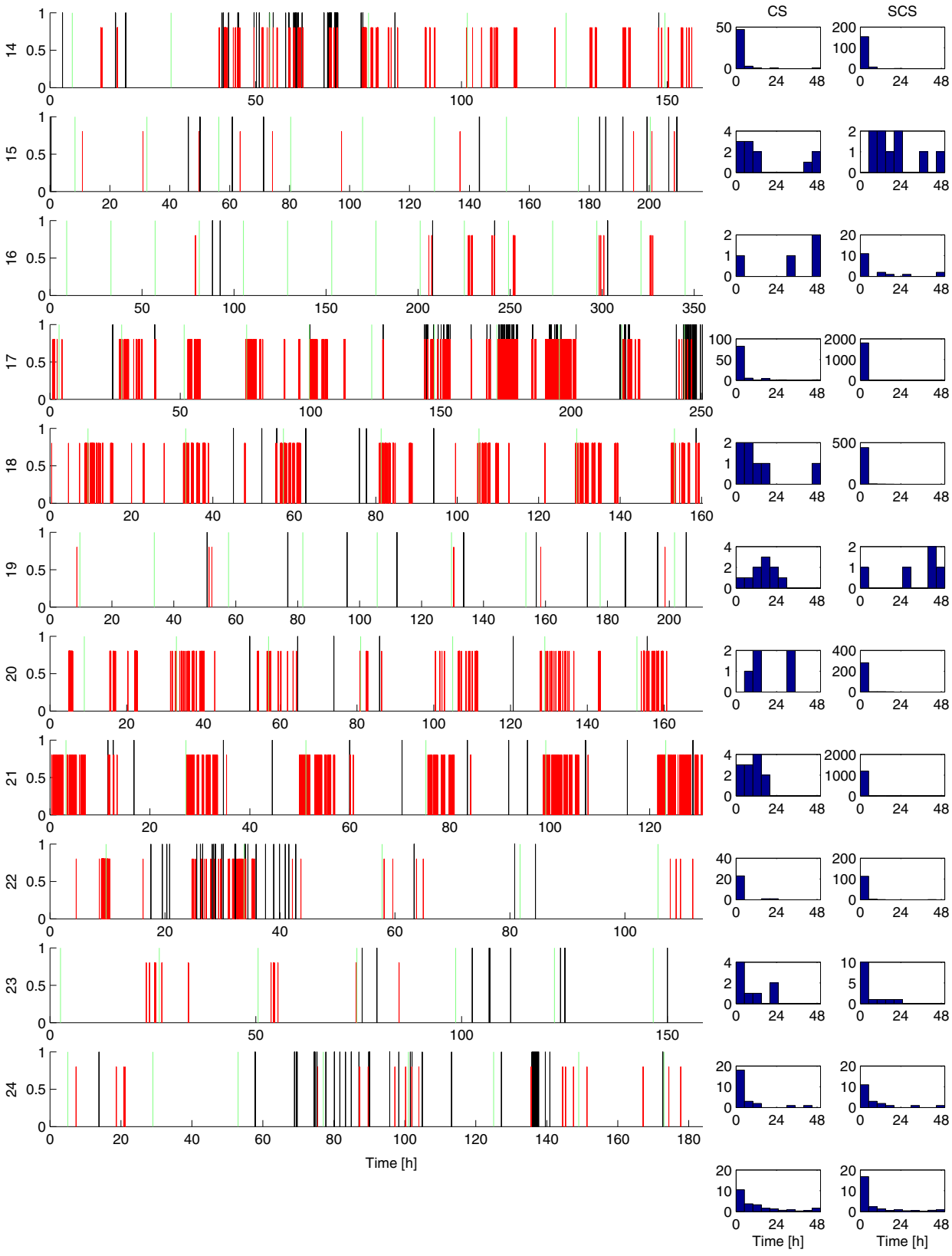


Fig. 2. Occurrences of clinically manifest seizures (CS, black) and subclinical seizures (SCS, red) during the recording periods of all patients. Midnight is marked by green lines; recording gaps are shaded in gray. Also shown are histograms of the interseizure intervals observed for CS and SCS, that is, the number of interseizure intervals that have a certain duration. The bin at 48 hours also contains all longer intervals. Last row: Histograms of interseizure intervals of both CS and SCS pooled for all patients; here, each patient's seizures are weighted with a total weight of 1.

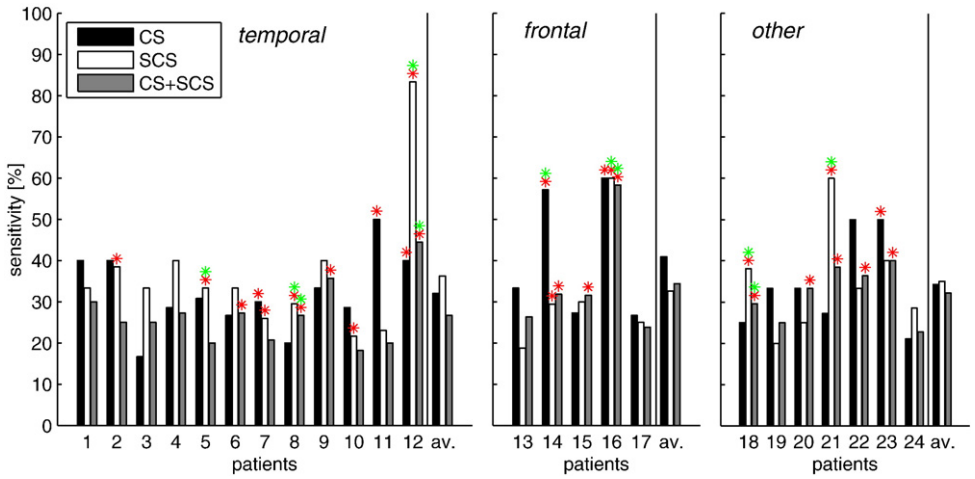


Fig. 3. Prediction sensitivities and average values for patients with temporal, frontal, and other epilepsies. Shown are the sensitivities for predictions of clinically manifest seizures (CS) and subclinical seizure (SCS) and a joint prediction of both CS and SCS. Sensitivities that exceed the lower critical sensitivity of the analytical random predictor are marked by one (red) asterisk; those that exceed the upper critical sensitivity, additionally be a second (green) asterisk.

In this study, predictive sensitivity was analyzed for CS as well as SCS. Additionally, the two types of seizures were also pooled to determine the prediction of all electrographic seizures that occurred.

To quantify how many of the false alarms that are triggered during predictions of CS would indeed be correct predictions of SCS if these were also be considered, we determined the fraction of false alarms that were followed by a SCS during the subsequent SOP. To validate whether the observed fraction is above chance level, we used nonparametric Mann–Whitney–Wilcoxon signed rank sum tests [37] to test whether it was significantly larger than for false alarms distributed randomly during the recording period.

3. Results

3.1. Distribution of clinical and subclinical seizures

There was an average of 19.7 CS per patient (range: 5–94). If only unclustered seizures, that is, seizures separated by more than 2 hours, are considered, the average is 10.3 seizures per patient (range: 5–32) (cf. Table 1). For all patients, the average number of SCS was 159.1 (range: 6–1816). The majority of these seizures were clustered; if only those separated by more than 2 hours are considered, the average is 12.9 per patient (range: 5–35).

The distribution of both CS and SCS over the recording period is illustrated in Fig. 2, together with histograms of the interseizure intervals. It can be observed that several patients, for example, patients 7, 16, 17, and 19, had frequent clusters of both CS and SCS. In general, SCS are more strongly clustered than CS, as is visible in the histograms in Fig. 2. In addition, the circadian dependence of seizure occurrence can clearly be identified for some patients: patients 7 and 16 for both CS and SCS, and patient 17 for SCS.

3.2. Prediction performances depending on site of origin

The performance of the preselected MPC features in predicting CS or SCS or CS + SCS is illustrated in Fig. 3. Results are summarized in Table 2. For a SOP of 30 minutes and a FPR_{max} of 0.15/hour, the average sensitivity for CS is 32.2% for patients with temporal lobe epilepsies, 40.9% for patients with frontal lobe epilepsies, and 35.9% for the remaining patients. For several patients sensitivity was as high as 50–60%, and for some it was below 20%. For SCS, average sensitivity was 37.2% for patients with temporal lobe epilepsies, 32.6% for patients with frontal lobe epilepsies, and 32.0% for patients with other epilepsies (range: 18.8–83.3%). There were no significant differences in performance between the different patient groups as assessed with a nonparametric Kruskal–Wallis test [38].

In comparison to the lower critical sensitivity of the analytical random predictor, statistically significant sensitivities were achieved for 5 of all 21 patients for CS, for 8 of 21 patients for SCS, and for 10 of 21 patients for pooled CS + SCS. Considering the upper critical sensitivity, this was true for 1 of 21 patients for CS, 5 of 21 patients for SCS, and for 4 of 21 patients for CS + SCS. Hence, the number of patients with significant prediction performance increases considerably when SCS are taken into account. A detailed breakdown for the different patient groups is found in Table 2.

3.3. Prediction performance depending on type of recording

In Fig. 4 and Table 2, prediction performance is summarized with respect to type of EEG recording: invasive and scalp. Average

Table 2
Prediction performance with respect to different patient categories (all, temporal/frontal/other, invasive/scalp).

Patient category	Type of seizure	Mean sensitivity (min–max)	Number of patients exceeding	
			Lower critical value	Upper critical value
All	CS	35.2% (16.7–60.0%)	5	1
	SCS	34.9% (18.8–83.3%)	8	5
	CS + SCS	29.8% (18.2–58.3%)	10	4
Temporal	CS	32.2% (16.7–50.0%)	2	0
	SCS	37.2% (21.6–83.3%)	5	3
	CS + SCS	27.2% (18.2–44.4%)	4	2
Frontal	CS	40.9% (26.7–60.0%)	2	1
	SCS	32.6% (18.8–60.0%)	2	1
	CS + SCS	34.4% (23.8–58.3%)	3	1
Other	CS	35.9% (21.1–50.0%)	1	0
	SCS	32.0% (20.0–40.0%)	1	1
	CS + SCS	30.7% (22.7–40.0%)	3	1
Invasive	CS	36.7% (20.0–60.0%)	5	1
	SCS	36.7% (21.6–83.3%)	6	4
	CS + SCS	30.9% (18.2–58.3%)	9	3
Scalp	CS	31.4% (16.7–40.0%)	0	0
	SCS	30.3% (18.8–38.5%)	2	1
	CS + SCS	26.8% (25.0–30.0%)	1	1

Note. Mean, minimum, and maximum sensitivities are given for predictions of clinical seizures (CS), subclinical seizures (SCS), and pooled CS and SCS (CS + SCS). Additionally, the numbers of patients with sensitivities exceeding the lower and upper critical values are specified.

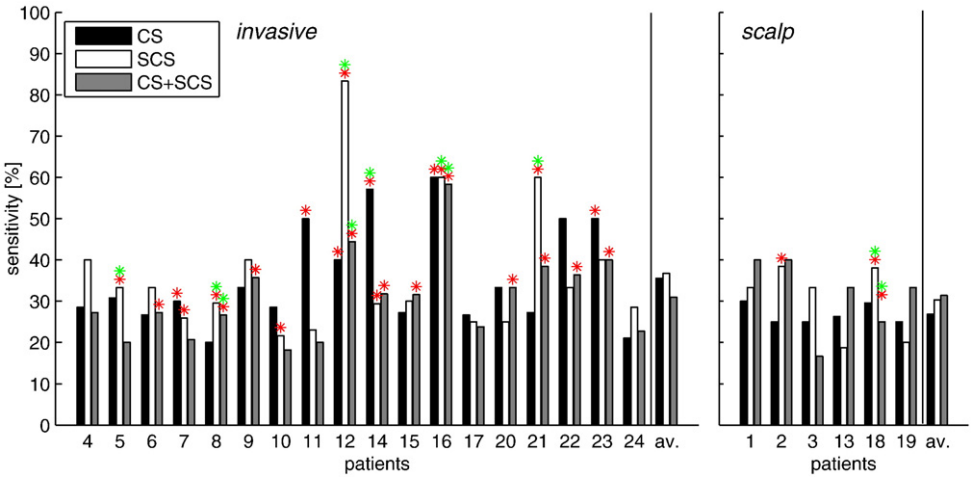


Fig. 4. Same as for Fig. 3 with respect to invasive or scalp recordings.

sensitivities for patients with invasive recordings are 36.7% for CS, at 36.7% for SCS, and 30.9% for CS + SCS. For patients with scalp recordings, sensitivities were 31.4% for CS, 30.3% for SCS, and 26.8% at CS + SCS. No significant differences between patient groups were detected with a Kruskal–Wallis test.

Concerning the numbers of patients with significant prediction performance, considerable differences are observed between the groups. Among the 15 patients with invasive recordings, sensitivities exceeded the lower critical sensitivity for 5 patients for CS, 6 patients for SCS, and 9 patients for CS + SCS, and exceeded the upper critical sensitivity for 1 patient for CS, 4 patients for SCS, and 3 patients for CS + SCS. In contrast, among the 6 patients with scalp recordings, sensitivities exceeded the lower critical sensitivity for no patient for CS, 2 patients for SCS, and 1 patient for CS + SCS, and exceeded the upper critical sensitivity for no patient for CS and 1 patient each for SCS and CS + SCS.

3.4. Analysis of false alarms for predictions of CS

In analyses of correlations of false alarms triggered during the prediction of CS, on average, for all patients, about 9.1% of the false alarms were followed by a SCS during the subsequent SOP (cf. Table 3). Although for several patients no false alarms were followed by a SCS, for others up to 30.8% preceded a SCS. For 9 patients, more false alarms were followed by a SCS than expected by chance (cf. Table 3).

4. Discussion

Increasing evidence suggests that SCS are of clinical relevance [1,2,8,39]. Although, by definition, no clinical signs are observed during the occurrence of SCS, they may nonetheless alter cognitive performance, as found in previous studies [e.g., 6]. The distinction between CS and SCS is inherently ambiguous, even if conventional neuropsychological testing is performed. It can be expected that for many SCS, clinical correlates could have been found if the appropriate modality had been tested for.

In our study, when analyzing the predictive power of SCS in 21 patients with focal epilepsies, sensitivities similar to those for CS were observed. This was the case for patients with different epilepsy localizations (temporal, frontal, and other). Although the absolute sensitivities achieved do not seem sufficient for application in a clinical setting for most patients, they may yet be beneficial for, for example, automatic closed-loop intervention systems as compared with chronic interventions To further improve prediction performance, several approaches could be combined [34], or circadian rhythms of seizure occurrence could be taken into account. If sensible for the desired type of intervention, higher sensitivities could be achieved by increasing the duration of the SOP or FPR_{max}.

In contrast to patients with scalp recordings, significant prediction performance was observed for a larger fraction of the patients with invasive recordings in our study, especially for SCS and CS + SCS, for which the number of significant cases was considerably larger in comparison with that for CS. To some extent this can be explained by the approximately 25% larger number of (unclustered) seizures that are available for SCS than for CS, which improves the statistical power of the random predictor [36]. Hence, truly predictive performance can more easily be detected. However, when CS and SCS were considered together in a pooled analysis, no further increase in significant performance was observed compared with the results for SCS. Therefore it can be concluded that SCS can be predicted with an average sensitivity similar to that for CS, leading to a larger number of patients with significant performance. When CS and SCS are pooled, neither sensitivity nor number of significant cases changes considerably.

Table 3
Fractions of false alarms triggered by predicting CS that were followed by a SCS during the subsequent SOP.

Patient No.	Fraction of false alarms before SCS [%]	Significant
1	0.0	
2	14.3	sign.
3	0.0	
4	0.0	
5	5.9	
6	5.6	
7	8.7	sign.
8	4.8	sign.
9	13.0	
10	4.8	
11	20.0	sign.
12	14.3	sign.
13	30.8	sign.
14	5.3	sign.
15	3.3	sign.
16	0.0	
17	8.3	
18	0.0	
19	10.0	
20	0.0	
21	10.5	sign.
Ø	9.1	

Note. For each patient it was determined whether the observed fraction was significantly larger than that for randomly distributed false alarms (see text).

We analyzed whether the false alarms that are triggered when predicting CS are followed by SCS and found that on average, for all patients, about 9% of all false alarms preceded a SCS. This fraction was found to be significant in 9 of 21 patients. Hence, it can be concluded that a portion of the SCS are preceded by changes in neuronal dynamics similar to those that precede CS. However, because no significant increase in prediction performance was observed for a pooled analysis of CS and SCS, this may not be the case for all SCS. Additionally, a considerable proportion of false alarms are caused by other effects.

Although a previous study on a smaller group of patients found that prediction performance was similar for patients with scalp recordings and those with invasive recordings [40], the lower prediction performance for patients with scalp recordings observed in our study could be related to differences in the patient collectives investigated; ours was peculiar in that only patients with observed SCS were included. In general, for patients with SCS, some of these seizures may be missed by scalp recordings if they do not lead to visible changes in the surface EEG. This, in turn, would explain the decrease in prediction performance if, for example, an alarm that correctly predicts an unidentified SCS is classified as being incorrect.

To summarize, both performance of prediction methods and patients may benefit from the inclusion of SCS in seizure prediction algorithms. That is, prediction methods could improve performance by considering all types of electrographic seizures that occur, independent of whether clinical correlates are observed. This is especially the case for patients for whom the number of false alarms that are caused by preictal changes in SC can be reduced. In return, patients can also benefit from the additional prediction of their SCS and the ability to suppress the accompanying cognitive impairment if appropriate intervention techniques with relatively modest side effects can be applied.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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References

[1] Sperling MR, O'Connor MJ. Auras and subclinical seizures: characteristics and prognostic significance. Ann Neurol 1990;28:320–8.
[2] Zangaladze A, Nei M, Liporace JD, Sperling MR. Characteristics and clinical significance of subclinical seizures. Epilepsia 2008;49:2016–21.
[3] Binnie CD. Cognitive impairment during epileptiform discharges: is it ever justifiable to treat the EEG? Lancet Neurol 2003;2:725–30.
[4] Kasteleijn-Nolst Trenité DG, Vermeiren R. The impact of subclinical epileptiform discharges on complex tasks and cognition: relevance for aircrew and air traffic controllers. Epilepsy Behav 2005;6:31–4.
[5] Holmes GL, Lenck-Santini PP. Role of interictal epileptiform abnormalities in cognitive impairment. Epilepsy Behav 2006;8:504–15.
[6] Bridgman PA, Malamut BL, Sperling MR, Saykin AJ, O'Connor MJ. Memory during subclinical hippocampal seizures. Neurology 1989;39:853–6.
[7] Kobayashi E, Hawco CS, Grova C, Dubeau F, Gotman J. Widespread and intense BOLD changes during brief focal electrographic seizures. Neurology 2006;66:1049–55.
[8] Velkey A, Siegler Z, Janszky J, Duray B, Fogarasi A. Clinical value of subclinical seizures in children with focal epilepsy. Epilepsy Res 2011;95:82–5.
[9] Akman CI, Montenegro MA, Jacob S, et al. Subclinical seizures in children diagnosed with localization-related epilepsy: clinical and EEG characteristics. Epilepsy Behav 2009;16:86–98.
[10] Theodore WH, Fisher RS. Brain stimulation for epilepsy. Lancet Neurol 2004;3:111–8.
[11] Osorio I, Frei MG, Sunderam S, et al. Automated seizure abatement in humans using electrical stimulation. Ann Neurol 2005;57:258–68.
[12] Morrell M. Brain stimulation for epilepsy: can scheduled or responsive neurostimulation stop seizures? Curr Opin Neurol 2006;19:164–8.
[13] Stacey WC, Litt B. Technology insight: neuroengineering and epilepsy-designing devices for seizure control. Nat Clin Pract Neurol 2008;4:190–201.
[14] Schachter SC, Guttag J, Schiff SJ, Schomer DL, Contributors S. Advances in the application of technology to epilepsy: the CIMIT/NIO Epilepsy Innovation Summit. Epilepsy Behav 2009;16:3–46.
[15] Sunderam S, Gluckman B, Reato D, Bikson M. Toward rational design of electrical stimulation strategies for epilepsy control. Epilepsy Behav 2010;17:6–22.
[16] Stein AG, Eder HG, Blum DE, Drachev A, Fisher RS. An automated drug delivery system for focal epilepsy. Epilepsy Res 2000;39:103–14.
[17] Ebersole JS. In search of seizure prediction: a critique. Clin Neurophysiol 2005;116:489–92.
[18] Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. Brain 2007;130:314–33.
[19] Schelter B, Timmer J, Schulze-Bonhage A, editors. Seizure prediction in epilepsy: from basic mechanisms to clinical applications. Weinheim: Wiley-VCH; 2008.
[20] Arthurs S, Zaveri HP, Frei MG, Osorio I. Patient and caregiver perspectives on seizure prediction. Epilepsy Behav 2010;19:474–7.
[21] Schulze-Bonhage A, Sales F, Wagner K, et al. Views of patients with epilepsy on seizure prediction devices. Epilepsy Behav 2010;18:388–96.
[22] Osorio I, Frei MG, Sornette D, Milton J. Pharmaco-resistant seizures: self-triggering capacity, scale-free properties and predictability? Eur J Neurosci 2009;30:1554–8.
[23] Osorio I, Frei MG, Sornette D, Milton J, Lai YC. Epileptic seizures: quakes of the brain? Phys Rev E 2010;82:021919.
[24] Navarro V, Martinerie J, Quyen MLV, Baulac M, Dubeau F, Gotman J. Seizure anticipation: do mathematical measures correlate with video-EEG evaluation? Epilepsia 2005;46:385–96.
[25] Mormann F, Lehnertz K, David P, Elger CE. Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. Physica D 2000;144:358–69.
[26] Ihle M, Feldwisch-Drentrup H, Teixeira CA, et al. EPILEPSIAE: a European epilepsy database. Comput Methods Programs Biomed. E-Pub ahead of print.
[27] Babb TL, Wilson CL, Isokawa-Akesson M. Firing patterns of human limbic neurons during stereoencephalography (SEEG) and clinical temporal lobe seizures. Electroencephalogr Clin Neurophysiol 1987;66:467–82.
[28] Binnie CD, Marston D. Cognitive correlates of interictal discharges. Epilepsia 1992;33(Suppl 6):S11–7.
[29] Epstein MA, Sperling MR, O'Connor MJ. Cardiac rhythm during temporal lobe seizures. Neurology 1992;42:50–3.
[30] Rosenblum MG, Pikovsky AS, Kurths J. Phase synchronization of chaotic oscillators. Phys Rev Lett 1996;76:1804–7.
[31] Feldwisch-Drentrup H, Staniek M, Schulze-Bonhage A, et al. Identification of preseizure states in epilepsy: a data-driven approach for multichannel EEG recordings. Front Comput Neurosci 2011;5:32.
[32] Winterhalder M, Maiwald T, Voss HU, Aschenbrenner-Scheibe R, Timmer J, Schulze-Bonhage A. The seizure prediction characteristic: a general framework to assess and compare seizure prediction methods. Epilepsy Behav 2003;4:318–25.
[33] Schelter B, Winterhalder M, Feldwisch Genannt Drentrup H, et al. Seizure prediction: the impact of long prediction horizons. Epilepsy Res 2007;73:213–7.
[34] Feldwisch-Drentrup H, Schelter B, Jachan M, Nawrath J, Timmer J, Schulze-Bonhage A. Joining the benefits: combining epileptic seizure prediction methods. Epilepsia 2010;51:1598–606.
[35] Schelter B, Winterhalder M, Maiwald T, et al. Testing statistical significance of multivariate time series analysis techniques for epileptic seizure prediction. Chaos 2006;16:013108.
[36] Feldwisch-Drentrup H, Schulze-Bonhage A, Timmer J, Schelter B. Statistical validation of event predictors: a comparative study based on the field of seizure prediction. Phys Rev E 2011;83:066704.
[37] Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. Ann Math Stat 1947;18:50–60.
[38] Kruskal W, Wallis W. Use of ranks in one-criterion variance analysis. J Am Stat Assoc 1952:583–621.
[39] D'Ambrosio R, Miller JW. What is an epileptic seizure? Unifying definitions in clinical practice and animal research to develop novel treatments. Epilepsy Curr 2010;10:61–6.
[40] Schad A, Schindler K, Schelter B, et al. Application of a multivariate seizure detection and prediction method to non-invasive and intracranial long-term EEG recordings. Clin Neurophysiol 2008;119:197–211.
[41] Engel J, Rasmussen TB. Outcome with respect to seizures. In: Engel Jr J, editor. Surgical treatment of epilepsies. New York: Raven Press; 1993. p. 609–12.