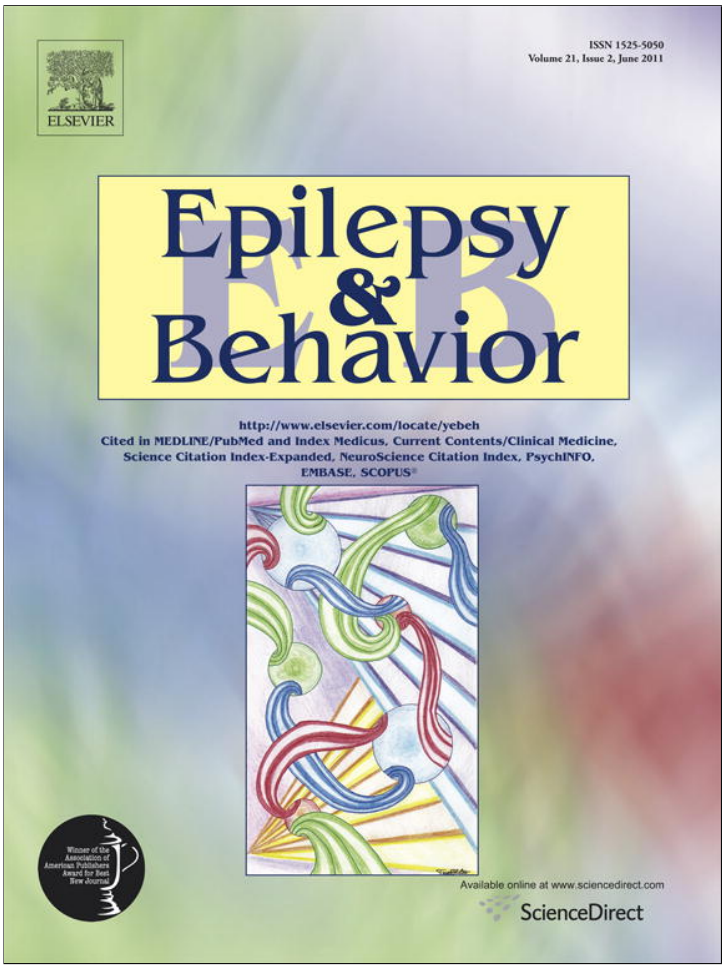

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Are prodromes preictal events? A prospective PDA-based study

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ABSTRACT

Up to 29% of patients with epilepsy report "prodromal" sensations more than 30 minutes prior to seizures. We developed and implemented an objective methodology to prospectively assess the sensitivity and specificity of these subjective experiences using personal digital assistants (PDAs). The key property, in contrast to paper-based diaries, is the internal recording of the patient's entering time of prodromes and seizures. Of 500 patients with epilepsy interviewed, 31 claimed to sense prodromal symptoms at least 30 minutes before seizure onset. Eleven of them agreed to participate in a 4-week study to objectively measure their prospective prediction performance. In 9 patients returning data, the majority of prodrome entries were not followed by seizures or were identified only retrospectively. Statistical analysis revealed that no patient could outperform a nonspecific random predictor when predicting seizures based on the occurrence of prodromes, and that the group performance matched precisely the expected result for a by-chance prediction. These results question the predictive value of "prodromes" and the specificity of their occurrence in the preictal period.

1. Introduction

Epileptic seizures are often preceded by subjective sensations, which are interpreted by the patients as precursors of the upcoming seizure. Epileptic *auras* are ictal events manifesting only as alterations in subjective perception, are not recognizable from outside, and mostly occur several seconds up to a few minutes before seizure onset. In contrast, sensations preceding a seizure by a period of hours up to days are commonly called *prodromes*. In a Hungarian multicenter study 19.6% of all patients reported experiencing prodromes characterized by nonspecific vegetative, affective, or cognitive symptoms [1]. Hughes et al. reported that 29% of patients with epilepsy [2], and Schulze-Bonhage et al. reported that 6.2%, claimed to have experienced prodromal symptoms [3]. The underlying physiology is currently not understood, and the validity of prodromes for seizure prediction has not yet been assessed prospectively.

In 2007, Haut et al. performed the first investigation of whether patients with epilepsy can predict their own seizures [4]. On the basis of seizure diary entries, they assessed a mean specificity of 83.2% and a sensitivity of 31.9%. The criteria on which patients based their predictions were not specified. In the accompanying editorial, Litt and Krieger pointed out that a methodology based on patient recordings in a diary does not ensure a true prospective assessment [5]. In particular, a response bias cannot be excluded by this approach. Furthermore, it remained unclear if patients based their predictions on the subjective experience of prodromes or if other factors contributed to their predictive performance. To account for this and to specifically address prodrome-based predictions, we performed a study using personal digital assistants (PDAs) and implemented specially designed software for prospective assessment. Analysis of recording times of prodromes and seizures provided evidence of a considerable retrospective attribution of symptoms as preseizure events. We defined a successful prediction as being followed by a seizure within 24 hours.

The following questions were addressed:

1. Sensitivity: What percentage of seizures is preceded by prodromes?
2. Specificity: Are the entered prodromes specific for upcoming seizures?
3. Consistency and compliance: Are entries in free and triggered mode coherent, and are patients compliant during the study period?
4. Reporting bias: Is there evidence for the retrospective attribution of symptoms experienced as prodromal events?

2. Methods

2.1. Patients

In a multicenter assessment of premonitory symptoms, 500 patients from three German epilepsy centers (251 males, 249 females, mean

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age 38.1 years) were interviewed about prodromal symptoms at least 30 minutes before seizure onset [3]. Thirty-one patients claimed to have sensed prodromal symptoms, 11 of whom agreed to take part in the present study. These patients (mean age 39 years, range 20–52 years, 9 females) had focal (10) or generalized (1) epilepsy and gave their informed consent to participate in this study. They recorded prodrome and seizure events for a period of 1 month by means of personal digital assistants (PDAs) provided by the Epilepsy Center Freiburg. The study was approved by the local ethics committee.

2.2. Personal digital assistant-based data acquisition

Three Palm-based programs were developed by the authors for assessment of prodromes and seizures. Programs 1 and 2 allowed for active entries by the patient of experienced seizures and prodromes at freely chosen time points (Fig. 1, left). Selectable prodromal symptoms comprised headache, depression, irritability, and other. The severity of the seizure could be mild, medium, severe, or unknown. In addition to the time point and symptoms specified by the patient, entry time was also stored. In a third program the participant was queried twice per day by the PDA to affirm if a prodrome has occurred during the preceding 12 hours (Fig. 1, right). Alarm sound and time for the regular entries were selected according to individual patient preferences.

Patients were instructed regarding the handling of the devices, the software, and their tasks in an ambulatory setting at the Freiburg Epilepsy Center. The PDA, a short documentation, a recharging unit, and a prepaid parcel were provided to the patients to perform the study and to mail the devices back to the hospital. The patients showed no difficulty in understanding the task or using the handheld device. Each observation covered a 4- to 5-week long period.

2.3. Data analysis

2.3.1. Sensitivity

For assessment of the predictive power of an alarm system with respect to regularly occurring events, suitable statistics have been suggested in the context of EEG-based seizure prediction [e.g., 6–8]. On this basis, we here applied the *seizure prediction characteristic* [9,10]. A prodromal event is classified as a correct prediction if a seizure occurs within a certain period after the event, called the *seizure occurrence period* (SOP). Sensitivity can then be determined as the fraction of correctly predicted seizures to all seizures. As the SOP increases, so does sensitivity, as the probability of a seizure occurring within an SOP rises. We investigated SOPs up to 24 hours [11].

2.3.2. Specificity

Prodromes without subsequent seizures during the SOP were classified as false predictions. The number of false predictions per period, the *false prediction rate* (FPR), serves to quantify how specific prodromal events are with respect to the prediction of epileptic seizures. It is important to note that even with a nonspecific by-chance prediction, high sensitivity can be achieved if long periods are allowed for the occurrence of seizures or if high rates of false predictions are tolerated. This is especially important for the analysis of prodromes, where the assumed SOP can be several hours to 24 hours long [11]. Therefore, we calculated whether the patient's prodrome-based prediction was significantly better than results based on random predictions.

2.3.3. Consistency and compliance

Free and regular prodrome entries should correlate; that is, the query following a free entry should be affirmed positively and vice versa. This cross-checking allows the consistency of the data to be controlled and may be used to identify memory problems of the patients. In addition, the continuity of compliance was analyzed based on the presence or absence of alarm-triggered, regular entries. If these questions were not answered for 36 hours or longer, the *inactive* period was excluded from further statistical analysis. This approach is not feasible in paper-and-pencil-based studies, but is necessary to avoid a decrease in the false prediction rate based on the duration of inactive periods.

2.3.4. Reporting bias

The PDA-based approach allows the storage of the exact entry recording times of seizures and prodromes. We analyzed if reporting bias occurred, that is, if sensations before a seizure were reinterpreted as prodromal events retrospectively. If so, the corresponding prodromes were excluded from further analysis.

3. Results

During a 4- to 5-week period, five of nine patients experienced 1–18 seizures, and eight of nine patients reported 3–26 prodromes. One patient did not experience any event, and patients 10 and 11 completed the study too early or lost data because of failure to

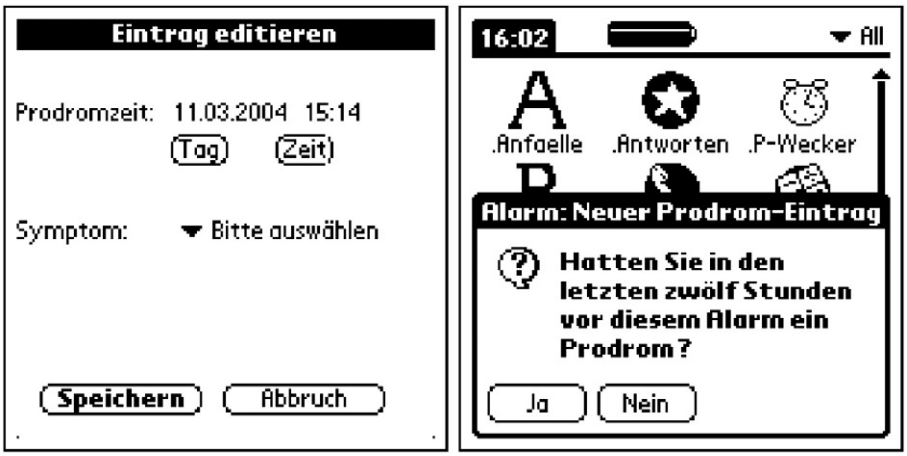

Fig. 1. Example dialogues from the prodrome programs. Left: Active adding of a prodromal event by day, time, and symptom (headache, irritability, depression, and other). Beyond the user-specified prodrome time, the saving time is also recorded to serve as an objective criterion. A similar dialogue enables saving of seizure events. Right: Regular prompting of the patient about seizures in the last half-day: "Did you experience a prodrome in the last 12 hours before this alarm? Yes or No."

Table 1
Numbers of seizures, prodromes, and positive answers of all patients.

ID No.	Age	Sex	Seizures	Free prodrome entries	Triggered positive prodrome entries
1	40	f	18	14 (H,I,D,O)	12
2	43	f	7	4 (O)	7
3	20	f	2	17 (H,I,D,O)	19
4	39	f	1	26 (I,O)	21
5	40	f	1	5 (O)	5
6	52	f	0	14 (H,I,D,O)	10
7	39	m	0	0	13
8	20	f	0	0	3
9	45	m	0	0	0
10	41	f	Did not finish the study		
11	52	f	Device not recharged		

Note. Eleven patients affirmed the ability to sense prodromal symptoms and agreed to store seizure and prodromal events for at least 4 weeks in a PDA. During this period, five patients experienced between 1 and 18 seizures, three patients sensed only prodromes, one patient was not affected by any event, and two patients did not finish the study or lost all records. The Triggered Positive Prodrome Entries column reflects how often the participants affirmed a prodrome in the preceding 12 hours within the regular query dialogue. Selectable prodromal symptoms comprised headache (H), irritability (I), depression (D), and other (O). Seizures were categorized as mild, medium, severe, or unknown.

recharge the device. Table 1 summarizes the experienced seizures and prodromes of all participants. Fig. 2 provides an overview of events and compliance for patient 1, who experienced the largest number of seizures.

3.1. Sensitivity of prodrome-based seizure prediction

The five patients with at least one seizure had a total of 29 seizures and 66 prodromes within 161 days. Twelve seizures were preceded by a prodrome within 24 hours, corresponding to a sensitivity of 41.4%. Comparative calculation for an unspecific periodic predictor with a given seizure occurrence period of 24 hours resulted in a sensitivity of 41.0%. Fourteen percent of prodromes were entered only after the seizure had occurred. None of the patients claiming to experience characteristic sensations preceding seizures performed better than random prediction.

Sensitivity was also calculated for a variable SOP, which is the period after a prediction during which a seizure is considered to be correctly predicted. For longer SOPs, the chance increases to predict a seizure even by a nonspecific random predictor. For the best performing patient, patient 1, Fig. 3 compares sensitivity depending on SOP with the performance of a random predictor having the same number of false predictions per hour. In all SOPs considered, lasting 30 minutes to 24 hours, the random predictor could not significantly be outperformed.

3.2. Specificity of prodromes for upcoming seizures

Three patients reported up to 13 prodromes but did not experience any seizures during the 4-week period analyzed. Six patients (Nos. 3–8, Table 1) experienced significantly more prodromes (13.3 ± 8.6, mean $\pm$ SD) based on the triggered entries than seizures (0.7 ± 0.8). In some of them, the rates of both free and triggered entries of prodromes were more than 10 times higher than the rates of seizures. All patients entered prodromes that were not followed by seizures (false positives). This shows that prodrome-like sensations were not specific indicators of an upcoming seizure in any patient.

As a measure of prediction performance, a combination of correct positive and negative predictions has also been used [4]. In our patients experiencing seizures, this performance based on 24-hour seizure prediction was 68.9%.

3.3. Consistency and compliance

Consistency of prodrome entries was evaluated by comparing free entries by the patient with PDA-triggered entries every 12 hours. In patients 1–5, free entries were followed by a positive affirmation in 71, 100, 53, 100, and 86% of cases. Positive entries of prodromes triggered by the PDA were preceded by free entries in 58, 43, 11, 67, and 80%. PDA-based data acquisition allowed detection of periods of noncompliance, showing periods without any spontaneous or

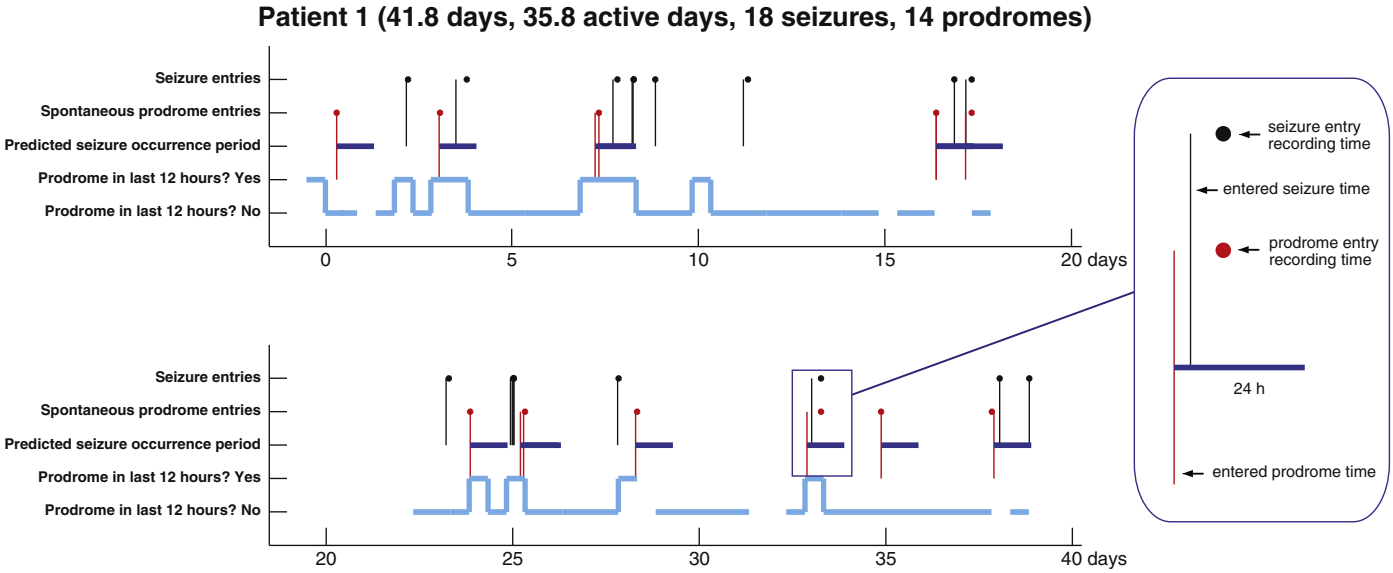

Fig. 2. Overview of events and patient compliance. Patient 1 participated for 42 days and had 18 seizures and 14 prodromes. The upper row represents the experienced seizures (black vertical lines) and their recording times (black dots). Similarly, the middle row shows the stored prodromes (red vertical lines) and their recording times (red dots). Each prodrome is followed by a 24-hour seizure SOP (blue horizontal lines). If a seizure occurs within a SOP, it is classified as correctly predicted by the corresponding prodrome for a SOP of 24 hours. The lower rows display the answers of the triggered prodrome entries. Upper levels of the light blue line belong to periods in which one or more prodromes should have occurred if the patient made consistent entries. The line is interrupted if no answer is given by the patient for a triggered event.

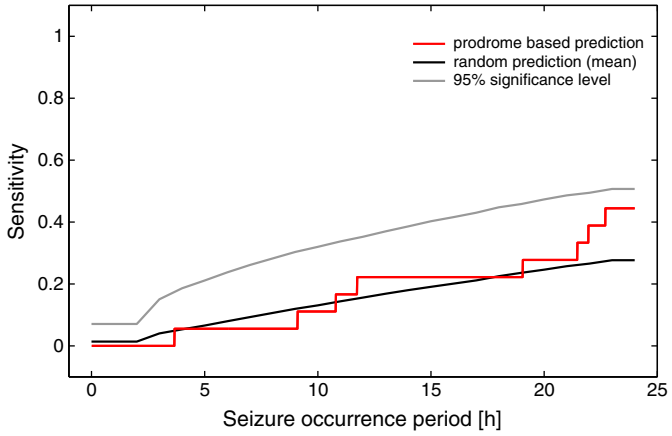

Fig. 3. Predictive power of prodromal symptoms in patient 1. Sensitivity of a seizure prediction method depends on the SOP, which is the interval after a prodromal event for which a seizure is considered to be correctly predicted. Patient 1 had the best predictive power of all patients, but could not surpass a random predictor significantly for SOPs between 0 and 24 hours.

triggered entries (86, 73, 69, 100, and 100% of study duration). In addition to only 73% active participation, patient 2 did not report free entries on days 12 and 13 despite positive answers to the regular queries. Here, the variable consistency and compliance limited the value of the data for a statistical assessment of predictive power. This effect would go unnoticed in a paper-and-pencil-based approach.

3.4. Reporting bias

A possible reporting bias was assessed particularly for patients with a large number of active entries. There was evidence of retrospective attribution of prodromes to the preseizure period. For example, patient 1 saved two prodromes following a seizure but indicated a time of occurrence before seizure onset (see inset, Fig. 2). The PDA-based assessment of the time of entry thus showed that in this case sensations were classified as seizure precedents only retrospectively. In a nonprospective setting, this could have been mistaken as evidence of positive predictive performance.

4. Discussion

The occurrence of prodromes before seizures has been suggested in many textbooks and reported in several studies [1–3]. Prospective studies on their predictive value are, however, not available. The best study performed so far suggesting that patients may be able to predict upcoming seizures was performed by Haut et al. and was based on seizure diaries [4]. Our study focuses specifically on the seizure prediction performance of prodromes and demonstrates that these events are not a reliable, statistically significant basis on which patients can predict their own seizures.

There are a number of factors that contribute to the discrepancy with the results of Haut et al. First, we analyzed prodrome-based predictions, whereas Haut et al. did not ask patients to specify reasons for anticipating a seizure. It may be assumed that they based their predictions not only on prodromes but on knowledge of trigger factors, including sleep disturbances and emotional distress, that have been found to be significant predictors of subsequent seizures [4]. Furthermore, it may well be that additional knowledge of irregular intake of medication or of associations of seizures with certain periodic events, as in catamenial epilepsy in the perimenstrual period, may have contributed to their predictions.

Haut and colleauges' study was performed using seizure diaries, which may allow for cheating [5] or involuntary retrospective attribution of events as preictal (although a prospective analysis appears to support the data, personal communication). In addition, the statistics differed: whereas our study compared patients´ performance in a pseudo-prospective way, Haut et al. used a retrospective multivariate analysis. In our patients, the sensitivity of correct positive predictions was 41.4% (corresponding to 41% of patients considering a seizure extremely likely in Haut and colleagues' group, and to the 41% that a totally nonspecific random predictor achieves at the same false-positive rate as of our patients); this performance, thus, is not statistically different from random predictions with identical long SOPs. When considering also correct negative predictions of seizures not occurring within the next day, our patients with at least one seizure had 62.4% correct negative predictions. This does not, however, imply statistically significant performance, because for patients with a relatively low seizure frequency, random predictors achieve a similarly high performance (e.g., in patients with 5 seizures per month, continuous negative prediction of a seizure for the next 12 hours will result in 55/60 or 91.7% "correct" predictions).

In contrast to the PDA-based study reported here, a pencil-and-paper-based approach lacks objective time tracking and does not ensure the prospective nature of the recorded data [5]. In general, the retrospective nature of reported events makes possible a posteriori bias of symptom attribution as prodromes. The limited sensitivity of the symptoms described as prodromes is already suggested by the wide spectrum of symptoms reported in different studies of prodromes and by the occurrence of similar experiences in people without epilepsy. As Taylor concluded: "I have seen nothing clinically, or in the literature, that persuades me that the episodic expressions … that are said to presage seizures as a prodrome, do not also exist independently of the seizures they are said to presage" [12].

We here proposed and applied a method that avoids these problems and is appropriate to assessment of the validity of prodromes prospectively allowing for a statistical analysis similar to the evaluation of EEG data-based seizure prediction methods. The assessment of consistency, compliance, and reporting bias shows that the analysis of entry times is a necessary prerequisite for proper interpretation of acquired data. Thus, prodrome entries were shown to be dependent on the mode of acquisition (i.e., spontaneous vs triggered). Periods of noncompliance were detected that may not be discovered when paper-and-pencil-based seizure diaries are used. In particular, reporting bias was detected by demonstrating retrospective attribution of symptoms as prodromes in the postseizure period. Taking this into consideration and performing a statistical analysis of the predictive power of truly prospectively acquired prodrome entries, we found that prodromes not only were of limited sensitivity and of low specificity in the majority of patients, but also did not predict the occurrence of subsequent seizures better than chance in all patients.

This study is, on the one hand, limited because of the number of patients fulfilling the inclusion criterion of being subjectively convinced that they could predict seizures based on prodromal sensations, and by the requirement of a minimum seizure frequency of one per month. On the other hand, this limited group can be considered highly enriched as the subgroup of patients who are the best candidates for prodrome-based predictions was targeted. The fact that none of the patients was able to pass the threshold of statistical significance in a well-established test for the assessment of seizure prediction performance is of high relevance even if the patient cohort is limited. Statistical evaluation was chosen in a way that provided them with an optimal chance to surpass random prediction: A continuous assessment for variable possible seizure occurrence periods was performed, and the false-positive rate was chosen in a patient-optimized fashion that set the bar low to allow achievement of the best possible sensitivity. The negative result of the study was not foreseen by the study group, as the original intention was to identify patients with prodromes with positive predictive power and

recruit them for a study on electrophysiological correlates of valid prodromes.

Problems in achieving sufficient specificity with prodrome-based predictions is not surprising when considering the wide spectrum of prodromal sensations reported in the various studies assessing patient reports. "Prodromes" encompass a wide spectrum of bodily (mostly vegetative) sensations and emotional changes, which are, however, relatively specific to a given patient. The spectrum of prodromes (headache, irritability, mood changes, etc.) certainly shows a considerable degree of overlap with sensations experienced by persons without epilepsy without any relation to seizures and can thus be assumed not to be specific to the preictal period in the patient with epilepsy.

The results of this study thus support the critical view put forward by Taylor in an editorial comment in 2007 [12]: "only by reifying the 'epilepsy' as essentially consisting of the 'attacks' do the other manifestations seem to be 'prodromal'; they too may just be cyclical or occasional, and wrongly attributed to being the distant rumble of the eventual seizure." There is no good reason to believe that patients are voluntarily cheating in reporting the sensations regarded as "prodromal," but evidence is lacking that they are preictal and not just interictal. Thus, regarding the sensations experienced by patients as related to seizures may in fact be observer bias (be it the patient or the physician).

In summary, this first prospective assessment of prodromes calls into question the specificity of subjective experiences as seizure precursors. Sensitivity did not surpass random prediction despite the fact that the patient group was highly enriched in that only patients who were convinced that their feelings had a predictive value participated. Postseizure entries of prodromes may explain contradictory optimistic reports in paper-and-pencil-based studies. Retrospective attribution of subjective sensations as seizure precursors may provide a memory bias and obscure the nonspecific nature of these experiences [13]. Thus, even if particular sensations like "prodromes" occur in patients with epilepsy, there is yet a lack of evidence that they occur preictally rather than interictally and that they have a particular predictive relevance [12], similar to some EEG-based approaches that have been claimed to predict the occurrence of epileptic seizures [6,9,10,14].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.yebeh.2011.02.004.

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