FULL-LENGTH ORIGINAL RESEARCH

Modeling seizure self-prediction: An e-diary study

*†Sheryl R. Haut, †‡Charles B. Hall, *†Thomas Borkowski, §Howard Tennen, and †‡Richard B. Lipton

Epilepsia, 54(11):1960–1967, 2013
doi: 10.1111/epi.12355

Summary

Purpose: A subset of patients with epilepsy successfully self-predicted seizures in a paper diary study. We conducted an e-diary study to ensure that prediction precedes seizures, and to characterize the prodromal features and time windows that underlie self-prediction.

Methods: Subjects 18 or older with localization-related epilepsy (LRE) and ≥3 seizures per month maintained an e-diary, reporting a.m./p.m. data daily, including mood, premonitory symptoms, and all seizures. Self-prediction was rated by, "How likely are you to experience a seizure (time frame)?" Five choices ranged from almost certain (>95% chance) to very unlikely. Relative odds of seizure (odds ratio, OR) within time frames was examined using Poisson models with log normal random effects to adjust for multiple observations.

Key Findings: Nineteen subjects reported 244 eligible seizures. OR for prediction choices within 6 h was as high as 9.31 (CI 1.92–45.23) for "almost certain." Prediction was most robust within 6 h of diary entry, and remained significant up to 12 h. For nine best predictors, average sensitivity was 50%. Older age contributed to successful self-prediction, and self-prediction appeared to be driven by mood and premonitory symptoms. In multivariate modeling of seizure occurrence, self-prediction (2.84; CI 1.68–4.81), favorable change in mood (0.82; CI 0.67–0.99), and number of premonitory symptoms (1.11; CI 1.00–1.24) were significant.

Significance: Some persons with epilepsy can self-predict seizures. In these individuals, the odds of a seizure following a positive prediction are high. Predictions were robust, not attributable to recall bias, and were related to self-awareness of mood and premonitory features. The 6-h prediction window is suitable for the development of preemptive therapy.

KEY WORDS: Seizure prediction, Self-prediction, Localization-related epilepsy, Seizure diary, Electronic diary, Premonitory symptoms, Seizure precipitants.

The unpredictability of seizures remains one of the most challenging aspects of epilepsy (Murray, 1993; Fisher, 2000). Simply knowing when a seizure is coming, may in itself, reduce the burden of unpredictability and improve health-related quality of life (Schulze-Bonhage & Buller, 2008). For the most part, efforts to predict seizures have relied on electroencephalography (EEG) data, although the concept of self-prediction of seizures by persons with epilepsy has been the focus of increasing research and discussion (Spector et al., 2000; Lee & No, 2005; Schulze-Bonhage et al., 2006; Haut et al., 2007a; Dionisio & Tatum, 2010; DuBois et al., 2010). In questionnaire studies, many patients report a "pre-seizure state" characterized by prodromal or premonitory symptoms (Hughes et al., 1993; Rajna et al., 1997; Lee & No, 2005; Petitmengin et al., 2006; Schulze-Bonhage et al., 2006; Scaramelli et al., 2009); more recently, prodromes and seizure self-prediction have been investigated in prospective studies (Haut et al., 2007a; DuBois et al., 2010; Maiwald et al., 2011).

In a paper diary study, we showed that a subset of patients with localization-related epilepsy (LRE) successfully predicted their seizures over a 24 h window (Haut et al., 2007a). We conceptualize seizure self-prediction as a conscious or subconscious awareness of prodromal features, trigger factors, and possibly unmeasured variables such as state correlates of electrophysiologic changes.

To further explore the nature of clinical seizure self-prediction, we conducted an e-diary study that is the basis of the present report. We also included an extensive inventory of trigger factors, premonitory symptoms, and measures of mood, thereby expanding our ability to characterize the preictal state. Based on these data, we reported clinical features

Accepted August 3, 2013; Early View publication September 20, 2013.
*Montefiore-Einstein Epilepsy Center; †Departments of Neurology; ‡Epidemiology and Population Health, Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, New York, U.S.A.; and §Community Medicine, University of Connecticut School of Medicine, Storrs, Connecticut, U.S.A.

Address correspondence to Sheryl R. Haut, Epilepsy Management Center, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467-2490, U.S.A. E-mail: sheryl.haut@einstein.yu.edu

of the preictal state, demonstrating that mood changes and premonitory features predicted seizure occurrence over 12 h (Haut et al., 2012).

Our primary aim in the present report is to confirm clinical seizure self-prediction utilizing electronic data capture to provide time-stamped data collection, thereby reducing the potential for retrospective reporting and recall bias. Furthermore, because of the collection of exposure data twice daily and the time-stamped reporting of seizure onset, we are in a strong position to explore a number of secondary aims, including the following: defining time frames of seizure occurrence following self-prediction; assessing self-prediction as an outcome in its own right, independent of accuracy; identifying components of self-prediction and ultimately to improve its accuracy; and finally, determining the separate and joint effect of seizure self-prediction, mood and change in mood, as well as premonitory features on the subsequent occurrence of seizures. Insights into the predictability of seizures could lead to a novel approach to epilepsy treatment, namely, preemptive therapy during the preictal state.

Methods

Subject recruitment

Study inclusion criteria have been reported (Haut et al., 2012). Briefly, eligible subjects were ≥18 years old, had focal epilepsy (previously termed), and reported ≥3 seizures per month. Subjects who reported seizure self-predictive ability and/or awareness of seizure precipitants were preferentially recruited. Subjects with a history of nonepileptic seizures were excluded. The Montefiore Medical Center Institutional Review Board approved the study, and all subjects provided informed consent.

Localization was defined as temporal, frontal, or extratemporal lobe epilepsy; multifocal epilepsy; focal epilepsy with unknown localization; and generalized epilepsy. Localization was considered unknown in subjects with a history of partial seizures, normal or nonlocalizable EEG and magnetic resonance imaging (MRI) data, and no inpatient epilepsy monitoring information.

Data collection

Diary training and data entry

Design of the e-diary has been described (Haut et al., 2012). The study utilized a Palm-based electronic Patient Reported Outcome (ePRO) program developed by Symfo (Boston, MA). Subjects accessed a questionnaire in response to preprogrammed alarms. Questions were linked to each other with branching logic. Data were transmitted to a central server that was accessible to the investigators through a secure web portal.

Data were collected twice daily at two fixed intervals scheduled 12 h apart (a.m. and p.m.), and by patient initiation in relation to seizure or premonitory symptoms. Once data was entered, it was no longer available for editing by the subject (no back-entry). Each diary entry began with a stem question, "How are you feeling right now?" Response options included: not anticipating a seizure; anticipating a seizure; currently experiencing a seizure; and recovering from a seizure. When subjects reported "currently experiencing a seizure," the diary directed them to exit and return to the diary after the seizure concluded. Diary completion was monitored biweekly, and subjects were contacted for diary nonadherence.

Seizure prediction, premonitory symptoms, and precipitants

Seizure self-prediction, potential seizure precipitant, and premonitory symptom data were collected during each a.m. and p.m. diary entry. Seizure self-prediction was assessed by the following question: How likely are you to experience a seizure [today (a.m. diary)/in the next 24 h (p.m. diary)]? Reponses included: Almost certain (>95% chance); Very likely (75–94% chance); Fairly likely (50–74% chance); Quite unlikely (25–49% chance); Very unlikely (<25% chance).

Data on potential seizure precipitants was collected as previously described (Haut et al., 2012). Six items from the mood circumplex (Larsen & Diener, 1992) were assessed twice daily on a visual analog scale in response to the questions "how ('happy, sad, relaxed, nervous, lively, bored') are you feeling right now?" Other precipitant data included hours of sleep, menstrual status, alcohol use, and medication compliance.

Eighteen premonitory symptoms were chosen based on previously reported symptoms in epilepsy and migraine studies (Hughes et al., 1993; Rajna et al., 1997; Giffin et al., 2003; Schulze-Bonhage et al., 2006; Scaramelli et al., 2009). Data on these symptoms were collected as, "Are you experiencing any of the following?" followed by multiple choice menus, with an opportunity to add open-ended responses.

Of 22 subjects, 2 (9%) uploaded <30 days of diary data and were eliminated from this analysis. Twenty subjects (91%) uploaded ≥90 diary days. One of these subjects, who reported daily seizures, was eliminated from the analysis due to the seizure prediction horizon windows. This left a study sample of 19 subjects.

Statistical analysis

We defined the primary measure of patients' ability to predict seizures to be the odds ratios associating the individual's self prediction with the occurrence of a seizure at varying time frames after the prediction averaged over all the patients' diary reports.

Seizure occurrence was modeled as a binary outcome. Odds ratios of seizure occurrence were calculated between individual predictive choices, and also for "positive predictions," being defined as a response of either "almost

certain," "very likely," or "fairly likely" combined versus negative predictions ("fairly unlikely" or "very unlikely"). Logit-normal random effects models fit by maximum likelihood were used to estimate the odds ratios. A random intercept took into account individual differences in predictive ability and the repeated within-person measurements across multiple days of diary data. The odds ratio has the interpretation of the ratio of an individual's odds of seizure for one prediction level divided by the same individual's odds of seizure at the baseline "very unlikely" prediction level. STATA versions 11 and 12 (StataCorp) were used for data analyses. In a series of models, we estimated the relative odds of seizure for a given level of prediction over 6, and 12 h. We also estimated the relative odds of seizure over specified nonoverlapping time intervals including 0–<4, 4–<6, 6–<12, 12–<18, and 18–<24.

We previously showed that positive mood items were associated with a decreased risk of seizure, whereas negative mood items had similar magnitudes of effect on seizure probability but in the opposite direction. Accordingly, we combined all six mood measures into a single summary metric, reverse scoring the negative mood items, as previously described (Haut et al., 2012). This summary measure was treated as a continuous interval scale predictor, which we refer to as "favorable mood." In addition, we calculated the change in the value of this mood measure from the corresponding (a.m. or p.m.) diary from the previous day, for a summary measure referred to as "favorable change in mood." Similarly, the number of significant premonitory features reported in a single diary was also used as a continuous interval scale predictor.

Results

The 19 subjects were predominantly female (84%), and had a median age of 35 years with mean duration of epilepsy 16.1 years. Median frequency was 3.5 seizures per 30 days. Epilepsy localization was temporal (n = 14); frontal (n = 1); extratemporal other (n = 2); and nonlocalizable (n = 2).

Diaries were completed for a median of 103 days (range 50–151). Subjects provided 1,680 a.m. entries, 1,594 p.m. entries, and reported 258 seizures. Fourteen seizures were excluded: Five occurred as a first diary entry with no preceding diary data; nine occurred >24 h after last diary entry due to missed diaries. Therefore, the analyses presented were performed on of the remaining 244 seizures.

Accuracy of seizure self-prediction by level of predictive certainty

Patient assessments of the likelihood of seizures were distributed as follows across the 3,274 diary reports eligible for analysis: almost certain (15), very likely (77), fairly likely (346), quite unlikely (985), and very unlikely (1,851) (Table 1). The OR for seizure occurrence as function of level of self-prediction options is presented over 6 h and 12 h prediction windows (Table 1). For example, the relative odds of seizure occurrence within 12 h following positive prediction were 5.36 (CI 1.37–21.00) for "almost certain," and 5.05 (CI 2.46–10.39) for "very likely," compared to the reference group "very unlikely." The OR for these response options at 6 h were even more robust at 9.31 (CI 1.2–45.23) for almost certain and 8.78 (CI 3.84–20.06) for "very likely," albeit with very large confidence intervals because of the reduced number of events.

Table 1. Relative odds of seizure by level of self-prediction at 6 h and 12 h

Patient reported likelihood of seizures (self-prediction)	Odds Ratio of seizure within time window compared to reference group "very unlikely"	95% Confidence interval	p-Value
6 h time window			
Almost certain	**9.31**	1.92,45.23	0.006
Very likely	**8.78**	3.84,20.06	<0.001
Fairly likely	**4.68**	2.53,8.63	<0.001
Quite unlikely	**1.20**	0.65,2.20	NS
Very unlikely	1.0	Reference	–
12 h time window			
Almost certain	**5.36**	1.37,21.00	0.016
Very likely	**5.05**	2.46,10.39	<0.001
Fairly likely	**4.15**	2.51,6.85	<0.001
Quite unlikely	**1.34**	0.87,2.08	NS
Very unlikely	1.0	Reference	–

Odds Ratios of seizure occurrence within 6 or 12 h following specific prediction choices. Each choice is compared to the reference group "very unlikely."

Individual self-prediction odds ratios for each participant ranged from 0 to 16, reflecting heterogeneity in individual predictive ability. Nine of the 19 subjects were able to predict their seizures to a statistically significant degree. In this group of better predictors, the adjusted odds ratio for seizure given positive prediction was 6.44 (CI 3.70–11.25; $p < 0.0001$) over 12 h. The adjusted odds for the group of 10 nonpredictors was nonsignificant.

For self-prediction to usefully identify periods of increased risk for intervention, adequate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are required. Overall, 7/19 subjects had a sensitivity of 30% or higher. Nearly all of the subjects (16/19) had a specificity of 83% or higher, and most (14/19) had a specificity of at least 90%. Twenty percent of responses of "almost certain" and "fairly certain" were followed by a seizure, whereas 15% of "very likely" responses were followed by a seizure. Negative diary responses were significantly less likely to be followed by a seizure (4% for quite unlikely and 3% for very unlikely).

For the nine subjects described earlier who were best able to predict their seizures, median/mean sensitivity was

Table 2. Predictive accuracy of seizure self-prediction[a] for seizure occurrence over various nonoverlapping time intervals

Time frame from diary entry to seizure (h)	Odds ratio of seizure for positive prediction compared to reference group "very unlikely"	95% Confidence interval	p Value
0<4	**4.02**	2.14–7.54	<0.001
4–<6	**6.72**	2.48–18.2	<0.001
6–<12	**2.81**	1.54–5.13	<0.001
12–<18	0.99	0.43–2.27	0.10
18–<24	0.88	0.38–2.07	0.77

Odds ratios of seizure occurrence within specified time frames following a positive prediction (almost certain, very likely, fairly likely)[a], compared to the reference group "very unlikely."
Significant values indicated in bold.

50%/34%; median/mean specificity was 95%/92%, median/mean PPV was 16%/23%, and median NPV was 97%/96%.

Time frame for seizure self-prediction

The odds ratios for overall seizure self-prediction for positive responses (including all three positive choices) as estimated from the logit normal models for time intervals ranging from 4 to 24 h is presented (Table 2). The odds ratios were statistically significant for time intervals up through 12 h, and were most robust between 4 and 6 h, where the odds of experiencing a seizure in the 4–6 h following a positive response were nearly seven times greater than the odds of a seizure following a response of "very unlikely." The OR of seizure occurrence following a positive diary prediction does not achieve statistical significance after 12 h.

Who successfully predicted seizures?

Duration of epilepsy, seizure frequency, and seizure localization were not associated with seizure prediction; however, older individuals were better able to predict their seizures. There was a significant association between patient age and self-prediction ability ($p = 0.041$). Every year of age difference increased the odds of successful prediction by 5.23% (odds ratio estimate for interaction 1.05; CI 1.00–1.11).

Determinants of positive seizure self-prediction independent of accuracy

Next, we examined the preictal features related to seizure self-prediction, independent of accuracy (Fig. 1A). All six mood items (happy, relaxed, lively, nervous, sad, and bored) were significantly related to seizure self-prediction. In univariate analysis (Fig. 1A, column 1) the "favorable mood" composite score was associated with a reduced risk of a positive seizure prediction (OR 0.21, CI 0.16–0.27), indicating that for each standard deviation increase in favorable mood composite the odds of a positive prediction decreases substantially. Similarly, a favorable change in mood was associated with a reduction in the relative odds of seizure prediction (OR 0.40, CI 0.33–0.49) (Fig. 1A, column 1). However, only favorable mood remains significant when combining both variables in a model.

Similarly, all 10 premonitory features that predicted seizure occurrence (blurred vision, light sensitivity, dizziness, feeling emotional, concentration difficulty, hunger/food cravings, noise sensitivity, tired/weary, thirst, difficulty with thoughts) were also associated with seizure self-prediction, and total number of premonitory features was utilized as a composite score for modeling. In univariate analysis, the presence of each additional premonitory symptom nearly tripled the chance of making a seizure self-prediction (Fig. 1A, column 1).

Other precipitants, including hours of sleep, menstrual phase, alcohol use, and medication compliance, were not associated with reporting a seizure self-prediction. As indicated in Fig. 1A, there is variance for seizure prediction not shared by mood and premonitory symptoms; this variance is likely attributable to other unmeasured variables.

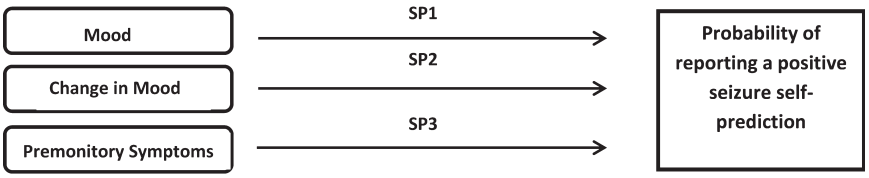
In multivariate logistic regression modeling to assess the degree to which self prediction was driven by mood and premonitory symptoms, both mood and premonitory symptoms remained significant (Fig. 1A, column 2) in the expected directions. Although the significance of the mood variable was modestly attenuated from 0.21 to 0.32 in the multivariate models, the significance of premonitory symptoms remains largely nonattenuated.

Seizure occurrence based on self-prediction, mood, and premonitory features

We next modeled actual seizure occurrence related to the separate and joint influence of self-prediction, mood, and premonitory symptoms (Fig. 1B). In a series of univariate analyses (Fig. 1B, column 1), positive self-prediction was the single strongest predictor of seizures. Favorable mood and favorable change in mood were protective, whereas increased number of premonitory features was a risk factor in these univariate models. Combining the mood variables, only favorable change in mood remained an independent predictor. Combining favorable change in mood and premonitory symptoms, each remained significant (Fig. 1B, column 2).

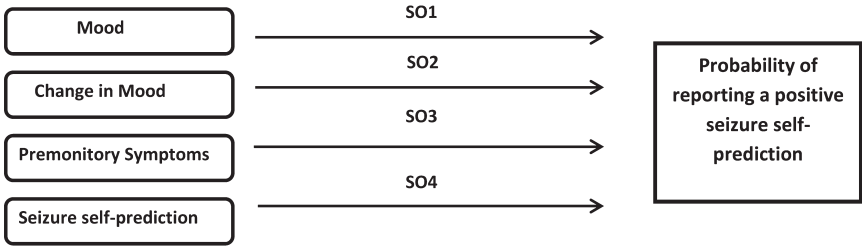
Multivariate models examining the detailed modeling of seizure occurrence are presented (Table S1). The addition of premonitory features attenuated the odds ratio for self-prediction from 3.8 (95% CI 2.44–5.94) to 2.92 (95% CI 1.75–4.85) (columns 1,4). In contrast, the addition of favorable change in mood does not substantially influence the OR of self prediction (column 5). In the final model (column 6), variables that remained significant included self-prediction (OR 2.84, 95% CI 1.68–4.81, $p < 0.001$), number of premonitory features (OR 1.11, CI 1.00–1.24, $p = 0.04$),

A The influence of mood, change in mood and premonitory features on self-predicting a seizure: Results from random effects logistic regression models.



Predictor variable	Univariate analysis	Multivariate modeling
Favorable current mood **(SP1)**	**0.21** (0.16-0.27 p<0.001)	**0.32** (0.22,0.46 p<0.001)
Favorable change in mood **(SP2)**	**0.40** (0.33,0.49 p<0.001)	0.91 (0.61,1.20 p=0.49)
Increased number of premonitory symptoms **(SP3)**	**2.88** (2.48-3.35 <0.001)	(2.08,2.82 p<0.001)

B The influence of mood, change in mood, premonitory features and seizure-self prediction on seizure occurrence: Results from random effects logistic regression models.



Predictor variable	Univariate analysis	Multivariate modeling
Favorable current mood **(SO1)**	**0.75** (0.61-0.91 p<0.004)	1.04 (0.81-1.33 P=0.75)
Favorable change in mood **(SO2)**	**0.71** (0.59-0.86 p<0.001)	**0.82** (0.67-0.99 p=0.038)
Increased number of premonitory symptoms **(SO3)**	**1.24** (1.13-1.35 p<0.001)	**1.11** (1.00-1.24 p=0.04)
Seizure self-prediction (SO4)	**3.8** (2.44-5.94 p<0.001)	**2.84** (1.68-4.81 p<0.001)

Figure 1.
(**A**) The direct effect of variables on the probability of self-predicting a seizure is denoted by SP1 (mood), SP2 (change in mood), and SP3 (premonitory features). The relative odds of seizure self-prediction as a function of each of these factors is shown for univariate models and after multivariate adjustment. Multivariate models are adjusted for all the factors shown. (**B**) The direct effect of variables on the probability of seizure occurrence is denoted by SO1 (mood), SO2 (change in mood), SO3 (premonitory features), and seizure self-prediction (SO4). The relative odds of seizure occurrence as a function of each of these factors is shown for univariate models and after multivariate adjustment below. Multivariate models are adjusted for all the factors shown.

and favorable change in mood (OR 0.82, CI 0.67–0.99, p = 0.04), but not favorable mood.

Discussion

This study demonstrates that 9 (43%) of 19 participants with refractory partial epilepsy were able to accurately predict their seizures, drawing on awareness of prodromal features such as mood and premonitory symptoms. Self-prediction was more accurate in participants who were more confident in the accuracy of their predictions. For the most confident prediction choices, the odds of seizure increased more than eightfold compared to times when seizures were thought to be "very unlikely" in unadjusted models. Self-prediction was most robust for prediction windows of 6 h or less, remaining highly significant over 12 h but not for longer time frames.

These results confirm and extend findings from our previous paper diary study with nightly measures (Haut et al., 2007a). The present report is more robust and informative because the electronic diary format provides time stamping, because exposures were captured twice daily, and because we included detailed inventories of mood and premonitory features. We also show that elements of the prodromal state play a large role in seizure self-prediction and ultimately, in accurate modeling of seizure occurrence.

Identifying the elements that contribute to seizure self-prediction offers the possibility of both understanding and improving self-prediction (Fig. 1A). The most significant variables associated with self-prediction were favorable mood and number of reported premonitory features. As both of these elements are relatively easy for patients to attend to and record, this observation offers the promise of improved self-prediction with use of education and training.

Mood and stress are reported to be among the strongest seizure precipitants in both questionnaire and prospective diary studies (Neugebauer et al., 1994; Spector et al., 2000; Nakken et al., 2005; Haut et al., 2007b, 2012; Sperling et al., 2008). In this e-diary study, current mood and not change in mood influenced self-prediction in multivariate models, whereas change in mood was associated with actual seizure occurrence. Training patients to be more aware of mood change from one day to the next might improve their ability to self-predict seizures accurately and yield more powerful models of seizure probability (Fig. 1B).

Premonitory symptoms make a strong contribution to self-prediction, which similarly offers opportunities to train patients about their own symptoms. Of note, premonitory features have been examined in a number of studies to date with conflicting results (Schulze-Bonhage et al., 2006; Maiwald et al., 2011; Haut et al., 2012), as was discussed in a recent review (Schulze-Bonhage & Haut, 2011).

In the modeling of seizure occurrence, self-prediction, favorable change in mood, and premonitory features remain independent predictors (Fig. 1B). The OR for the associations in multivariate modeling suggests that self-prediction and premonitory symptoms both contribute to accurately assessing the probability of seizure occurrence.

Significant seizure self-prediction has been similarly reported in the inpatient epilepsy monitoring setting (DuBois et al., 2010). Developing seizure self-prediction and seizure occurrence models may have important clinical implications. If "at risk" seizure states can be identified, interventions can range from taking precautionary measures to the actual use of preemptive therapies. Preemptive treatment will rely on robust modeling of seizure probability, of which seizure self-prediction may be a significant contributor. There is no evidence-based approach for pre-emptive therapy in adult epilepsy, although in practice clinicians may prescribe oral benzodiazepines for use in certain settings. If clinically based seizure prediction becomes more robust, candidate preemptive treatments might include short-term use of benzodiazepines, or even supplemental antiepileptic medications. The association between mood and prediction suggests the possibility of utilizing a behavioral intervention during periods of increased seizure risk. In fact, a randomized controlled e-diary trial of a behavioral intervention is currently being conducted (Polak et al., 2012).

As in other studies (Haut et al., 2007a; DuBois et al., 2010), predictive ability was not uniformly distributed among patients. The current cohort was enriched with subjects who described perceived self-predictive ability and/or awareness of precipitants, and almost 50% of the subjects demonstrated significant self-prediction. This percentage is much higher than in our previous study where 21% of the subjects were significant predictors. Here, older age was associated with better predictive ability, in contrast to our prior study where younger patients were better predictors, (Haut et al., 2007a). DuBois et al. (2010) reported that subjects with a longer duration of epilepsy were better at predicting "no-seizure" days. The current findings support the concept that longer experience with seizures is associated with more accurate prediction. DuBois et al. (2010) also found that higher seizure rates were associated with better prediction, which was not the case in our current study. This disparity may well relate to differences between outpatient and inpatient seizure frequencies.

Is self-prediction and seizure modeling ready for clinical use? Seizure self-prediction has a very high specificity (Haut et al., 2007a; DuBois et al., 2010), reflecting the accuracy of negative predictions. Successful negative prediction is important for preemption; if the intervention carries any risk, this will limit unnecessary treatment. A clinically relevant preemptive therapy also requires high sensitivity. In the group of predictors, median sensitivity and specificity were 50% and 95%. These numbers, although sufficient for a behavioral intervention, will not support a preemptive pharmacologic trial, but may be improved with training.

Our study has certain limitations. Our primary outcome measure is the occurrence of self-reported seizures as recorded using an electronic diary. This approach is vulnerable to errors of both underreporting or overreporting of seizures (Neugebauer, 1989; Blum et al., 1996; Tatum et al., 2001; Hoppe et al., 2007; Cook et al., 2013).

The accuracy of self-reported seizures is a concern, as recently reported in a long-term study using implanted electrodes, where disparities between reports of seizures in patient diaries and electrographic seizure patterns on EEG reached statistical significant in almost one-third of subjects (Cook et al., 2013). Although this area requires additional attention, continuous EEG monitoring is rarely available. As a consequence, we will continue to rely on self-report both in clinical trials and clinical practice for the foreseeable future. However, unless errors in seizure reporting are associated with the exposures of interest, we would expect our reported associations to get stronger with perfect reporting of seizure occurrence.

Another challenge in a seizure self-prediction study is that patients may be predicting a seizure during their aura, reporting the "ictal" and not "pre-ictal" state. Absent EEG monitoring, this possibility cannot be completely ruled out. However, the most accurate prediction window of this study was 4–6 h after a self-prediction, whereas a reported seizure would be expected to follow an aura report by minutes. Finally, although the number of subjects is modest, we had >3000 diary days and almost 250 seizures. The positive results support our feeling that the sample size is appropriate to confirm seizure self-prediction using electronic data capture.

There remains modeling evidence that as yet unmeasured variables are contributing to seizure self-prediction. These variables may represent other biologic phenomenon that

patients recognize as heralding a seizure, for example self-awareness of electrophysiologic changes. A follow-up study that includes continuous EEG monitoring, while logistically challenging, would likely clarify the phenomenon of self-prediction even further.

Our data confirm our previous findings that seizure self-prediction is possible for a subgroup of patients with epilepsy, and that in these individuals, the odds of a seizure following a positive prediction is high. Although these findings may only be generalizable to patients who report either self-predictive ability or awareness of seizure precipitants to their clinicians, prevalence studies indicate that this may be a substantial subgroup. Improvement in predictive ability will be necessary for a planned preemptive trial; this may be accomplished with education and training individuals on their own data, focusing on features of the prodromal state such as premonitory symptoms, and change in mood. Ultimately, EEG analysis may also be utilized in combination with self-prediction to enhance the effectiveness of both techniques. We anticipate that this work may represent a step toward a new paradigm of treatment, namely preemptive therapy for epilepsy.

Acknowledgments

The authors thank Dr. Solomon Moshé and Dr. Shlomo Shinnar for assistance in the study design and analysis.

Disclosure

Dr. Haut receives grant support from National Institute of Health (NIH) (RO1 NS053998) and the Shor Foundation for Epilepsy Research. She has consulted for Acorda, Upsher-Smith, and Impax. She is on the editorial boards of *Epilepsy and Behavior* and *Epilepsy Currents*. Dr. Hall receives or has received research support from the National Institute of Aging (NIA) (P01 AG03949, P01 AG027734, R01 AG022092, R01 AG034087, R21 AG036935), the National Center for Research Resources (UL1-RR025750-01), the National Cancer Institute (P30 CA13330-35), and the National Institute of Occupational Safety and Health (contracts 200-2011-39372 and 200-2011-39489 39379, and grants U01-OH10411 and U01-OH10412, the last as principal investigator). Dr. Borkowski has nothing to disclose. Dr. Tennen receives research support from the NIH 5P60AA003510-33, Center Component PI and Center Component Investigator; 5R01AA016599-03, Subcontractor; 5R01AA12827-07, Investigator; 1R01DA031275-01A1, Investigator. He serves as a consultant or has received honoraria from: John Wiley & Sons, and Best Practice Project Management. Dr. Richard B. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), RO1AG025119 (Investigator), RO1AG022374-06A2 (Investigator), RO1AG034119 (Investigator), RO1AG12101 (Investigator), K23AG030857 (Mentor), K23NS05140 901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial board of *Neurology*, has reviewed for the NIA and National Institute of Neurological Disorders and Stroke (NINDS), holds stock options in eNeura Therapeutics, serves as consultant, advisory board member, or has received honoraria from: Allergan, American Headache Society, Autonomic Technologies, Boehringer-Ingelheim Pharmaceuticals, Boston Scientific, Bristol Myers Squibb, Cognimed, Colucid, Eli Lilly, ENDO, eNeura Therapeutics, GlaxoSmithKline, Merck, Novartis, NuPathe, Pfizer, and Vedanta. 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.

References

Blum DE, Eskola J, Bortz JJ, Fisher RS. (1996) Patient awareness of seizures. *Neurology* 47:260–264.

Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, D;Souza W, Yerra R, Archer J, Litewka L, Hosking S, Lightfoot P, Ruedebusch V, Sheffield WD, Snyder D, Leyde K, Himes D. (2013) Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol* 12:563–571.

Dionisio J, Tatum WO. (2010) Triggers and techniques in termination of partial seizures. *Epilepsy Behav* 17:210–214.

DuBois JM, Boylan LS, Shiyko M, Barr WB, Devinsky O. (2010) Seizure prediction and recall. *Epilepsy Behav* 18:106–109.

Fisher RS. (2000) Epilepsy from the patient's perspective: review of results of a community-based survey. *Epilepsy Behav* 1:S9–S14.

Giffin NJ, Ruggiero L, Lipton RB, Silberstein SD, Tvedskov JF, Olesen J, Altman J, Goadsby PJ, Macrae A. (2003) Premonitory symptoms in migraine: an electronic diary study. *Neurology* 60: 935–940.

Haut SR, Hall CB, LeValley AJ, Lipton RB. (2007a) Can patients with epilepsy predict their seizures? *Neurology* 68:262–266.

Haut SR, Hall CB, Masur J, Lipton RB. (2007b) Seizure occurrence: precipitants and prediction. *Neurology* 69:1905–1910.

Haut SR, Hall CB, Borkowski T, Tennen H, Lipton RB. (2012) Clinical features of the pre-ictal state: mood changes and premonitory symptoms. *Epilepsy Behav* 23:415–421.

Hoppe C, Poepel A, Elger CE. (2007) Accuracy of patient seizure counts. *Arch Neurol* 64:1595–1599.

Hughes J, Devinsky O, Feldmann E, Bromfield E. (1993) Premonitory symptoms in epilepsy. *Seizure* 2:201–203.

Larsen RJ, Diener E. (1992) Promises and problems with the circumplex model of emotion. *Pers Soc Psychol Rev* 13:25–59.

Lee SA, No YJ. (2005) Perceived self-control of seizures in patients with uncontrolled partial epilepsy. *Seizure* 14:100–105.

Maiwald T, Blumberg J, Timmer J, Schulze-Bonhage A. (2011) Are prodromes preictal events? A prospective PDA-based study *Epilepsy Behav* 21:184–188.

Murray J. (1993) Coping with the uncertainty of uncontrolled epilepsy. *Seizure* 2:167–178.

Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA. (2005) Which seizure-precipitating factors do patients with epilepsy most frequently report? *Epilepsy Behav* 6:85–89.

Neugebauer R. (1989) Reliability of seizure diaries in adult epileptic patients. *Neuroepidemiology* 8:228–233.

Neugebauer R, Paik M, Hauser WA, Nadel E, Leppik I, Susser M. (1994) Stressful life events and seizure frequency in patients with epilepsy. *Epilepsia* 35:336–343.

Petitmengin C, Baulac M, Navarro V. (2006) Seizure anticipation: are neurophenomenological approaches able to detect preictal symptoms? *Epilepsy Behav* 2:298–306.

Polak EL, Privitera MD, Lipton RB, Haut SR. (2012) Behavioral intervention as an add-on therapy in epilepsy: designing a clinical trial. *Epilepsy Behav* 25:505–510.

Rajna P, Clemens B, Csibri E, Dobos E, Geregely A, Gottschal M, György I, Horváth A, Horváth F, Mezöfi L, Velkey I, Veres J, Wagner E. (1997) Hungarian multicenter epidemiologic study of the warning and initial symptoms (prodrome, aura) of epileptic seizures. *Seizure* 6:361–368.

Scaramelli A, Braga P, Avellanal A, Bogacz A, Camejo C, Rega I, Messano T, Arciere B. (2009) Prodromal symptoms in epileptic patients: clinical characterization of the pre-ictal phase. *Seizure* 18:246–250.

Schulze-Bonhage A, Buller A. (2008) Unpredictability of seizures and the burden of epilepsy. In Schelter B, Timmer J, Schulze-Bonhage A (Hrsg) *Seizure prediction in epilepsy: from basic mechanisms to clinical applications*. Wiley, Berlin, pp. 1–10.

Schulze-Bonhage A, Haut SR. (2011) Premonitory features and seizure self-prediction: artifact or real? *Epilepsy Res* 97:231–235.

Schulze-Bonhage A, Kurth C, Carius A, Steinhoff BJ, Mayer T. (2006) Seizure anticipation by patients with focal and generalized epilepsy: a

multicentre assessment of premonitory symptoms. *Epilepsy Res* 70: 83–88.

Spector S, Cull C, Goldstein LH. (2000) Seizure precipitants and perceived self-control of seizures in adults with poorly controlled epilepsy. *Epilepsy Res* 38:207–216.

Sperling MR, Schilling CA, Glosser D, Tracy JI, Asadi-Poova AA. (2008) Self-perception of seizure precipitants and their relation to anxiety level, depression, and health locus of control in epilepsy. *Seizure* 17:302–307.

StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA http://www.stata.com.

Tatum WO 4th, Winters L, Gieron M, Passaro EA, Benbadis S, Ferreira J, Liporace J. (2001) Outpatient seizure identification: results of 502 patients using computer-assisted ambulatory EEG. *J Clin Neurophysiol* 18:14–19.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Variables associated with seizure occurrence.