Of seizure prediction, statistics, and dogs: A cautionary tail
Brian Litt and Abba Krieger
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The idea of predicting seizures seems simple enough. A patient gets a feeling that a seizure may happen, or a computer algorithm detects some physiologic indication of an impending event, then the patient or computer records the time. Within some predetermined period a seizure either occurs or does not, and the process is repeated until there is adequate power to assess the predictor’s reliability. Haut et al.\(^1\) demonstrate that this task is more complex in practice than in theory, particularly when patients are doing the reporting. Straightforward but difficult-to-answer questions abound. Did a seizure really occur? Were patients unaware of seizures, a common problem reported by Blum et al.\(^2\)? Were questionnaires filled out prospectively, or did patients “cheat” after the fact? Is patient accuracy based upon knowing their regular cycles, or upon changes in brain physiology prior to each seizure? Was prediction performance better than random guessing? These are questions Haut et al. confront in their study.

Why the focus on predicting seizures? The single most problematic aspect of epilepsy, according to patients in one large survey, is uncertainty about if and when a clinical event may occur.\(^3\) In addition, understanding seizure generation may enable new therapies, such as implantable devices, to help the one-third of the world’s 60 million patients with epilepsy whose seizures cannot be controlled by medication.\(^4\) Identifying periods of time when the probability of seizures is increased also offers patients an opportunity to avoid dangerous situations such as driving during these times, and to take medications that might prevent seizures from happening, with enough warning. Haut et al. conclude that a subset of patients with epilepsy can predict their seizures, in a welcome, statistically rigorous supplement to a frequently quoted study of self-reported patient prodromes by Ranja et al.\(^5\) Haut et al.’s conclusions, however, need to be interpreted with some caution.

There are at least three sources of potential bias in this study. First, the pool of 134 subjects is not randomly chosen from a well-defined population, raising the question of selection bias. Nonresponse bias is potentially of more concern. Specifically, it is not clear that the 71 responders are representative of all patients enrolled, and whether failure to send back diaries was influenced by a lack of ability to predict seizures. If this is the case, then the results of the study might reflect the outcomes of subjects who are better predictors, and the number of predictors begins to approach what might be expected by chance alone. There is, however, no compelling reason to believe that the 71 responders were not representative of the entire enrolled group.

The third and perhaps most serious concern is response bias. The data in this study are self-reported. A willingness of subjects to please investigators might have led to reports that improperly demonstrated prediction. There is no way to tell if this was the case. Aware of this issue, the authors point out that much of the literature related to antiepileptic drug therapy is based upon similar patient reports, with some validation.

Once one accepts the data as representative, and without measurement error, then the statistical analysis is compelling. Twelve of the 76 individuals were able to predict seizures over the subsequent 24 hours, compared to the 3 to 4 subjects we would have expected to produce positive results at the 0.05 significance level by chance alone. (In this analysis, each individual is determined to be a predictor by tests performed only upon that individual’s perfor-
formance [within subject]. This introduces the problem of multiplicity, as 71 separate tests are being performed. A more refined analysis [e.g., Bonferroni, or the Seims procedure] could be performed to avoid the possibility of potentially erroneously labeling an individual as a predictor. This is balanced against the issue of power, which may have mistakenly labeled individuals as nonpredictors, due to insufficient data.) The notion that some patients might be better predictors than others is not unreasonable, and perhaps is more likely due to the proximity of their seizure generators to eloquent cortex than to any special ability.

Of interest, the authors note that predictors tended to be younger and to have more seizures. The latter point raises an interesting issue, which may be related to statistical power. It may be that because of too few seizures during the sample period, the authors actually misclassified some patients with lower seizure frequencies who were good predictors as non-predictors, because of insufficient data.

These issues aside, the study by Haut et al. is important both for its results and rigorous methods, and suggests opportunities to eliminate reliance upon self-reported data in future studies. A computer or handheld electronic time-marking device could track patient predictions. Seizures could be validated by recording simultaneous EEG with patient predictions, either in an epilepsy monitoring unit, or better, as outpatients, via an external ambulatory EEG monitor or implantable device. In this setting, a device that records continuous EEG for prolonged periods, perhaps for months at a time, would be preferable to one that detects seizures with a certain unknown imperfect sensitivity and specificity. This leaves us for now with Haut et al.’s provocative results. The authors have clearly done an excellent job assessing their data, but their conclusions must be considered in the setting of potential errors introduced by patient self-reporting.

The two accompanying articles on seizure predicting dogs provide examples of how misleading self-reporting errors can be. Enthusiasm remains high for dogs that can protect their owners by detecting or predicting seizures; however, most studies rely upon patient and family reports of dog and patient behavior. There are dogs that can detect when their owners are having seizures, and summon help or stand by them to ward off potential dangers.7 Seizure prediction by dogs, however, has not been validated in rigorous studies, despite anecdotal reports in the lay press.7 In an interesting twist, three recent small studies, two appearing in this issue of Neurology, demonstrate that seizure prediction dogs were more likely to respond to nonepileptic, psychogenic seizures than epileptic events.8,9,10 In “Wag the dog: Skepticism on seizure-alert canines,” Doherty and Haltiner present the example of a dog whose warning behavior for both a husband and wife was triggered by nonepileptic psychogenic seizures.9 In “Pseudoseizure dogs,” Krauss et al. observed patients and dogs together in an epilepsy monitoring unit and found that in one case, dog behavior (licking the owner’s face) actually triggered nonepileptic psychogenic events.10 Both studies suggest a potential therapeutic effect in owning such dogs, but that the benefit is more likely to be psychological than neurologic. In both studies it was only objective validation of patient-reported events that led the appropriate diagnosis and conclusions.

In sum, Haut et al. present their provocative results carefully, and confront potential confounders directly. Their results are not overstated, and their conclusions are only limited by the quality of the data and patient-reporting study design. Their results, however, are sufficiently interesting and important that they cautiously support the conclusion that there are physiologic precursors to seizures, perceptible in some patients, and hence a potential to intervene to obtain better seizure control.

References
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