



## Commentary

## Seizure Prediction Is Possible—Now Let's Make It Practical



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People living with uncontrolled epilepsy face the constant fear of seizures. The mental toll of anticipation and uncertainty surrounding the random occurrence of seizures may actually be more stressful than the embarrassment, injury, or death caused by the seizure itself. In a recent US poll of patients and caregivers by the Epilepsy Foundation, the unpredictability of seizures was the most impactful aspect of epilepsy, and there is great interest in providing warning to patients when seizures are more likely—a “seizure prediction” device (Dumanis et al., 2017). However, whether such a device is feasible, both scientifically and practically, has been an unanswered question.

Seizure prediction has been the goal of many researchers ever since digital EEG arrived in the 1990's. Early work presented a myriad of individual algorithms but had concerns about validation, then progressed greatly once centers began sharing data and developed methods to assure statistical rigor (Mormann et al., 2007; Snyder et al., 2008). Those new guidelines culminated in a clinical trial in Melbourne Australia, in which patients had continuous EEG recorded from indwelling intracranial electrodes over several months, attached to a portable device designed to signal the risk of imminent seizures (Cook et al., 2013). That trial demonstrated that seizure prediction was possible in some people, though the trial and the sponsor company (NeuroVista) both terminated, in large part because there were several patients in whom the device did not work well using the initial prediction algorithms. While this may appear like a failed trial, it provided the crucial groundwork for the field to progress. One new development is in terminology: the strategy is really better described as “forecasting” rather than prediction, as identifying periods of increased risk is more physiological than true prediction of a seizure event (especially since a patient may take measures to prevent a seizure). The next step was further optimization and a worldwide seizure prediction competition using data from epileptic dogs and two patients from the Melbourne study, which demonstrated remarkable success (Brinkmann et al., 2016). A follow up competition on Kaggle.com recently completed with many algorithms that clearly beat a chance predictor, this time with data from the patients that were unsuccessful in the original Melbourne trial. These results prove that seizure

prediction/forecasting is a reality, and that there are many potential successful algorithms.

Perhaps the most important contribution of the early work has been the acquisition and availability of the chronic human recordings. These data have led to several new findings, most recently that there are long term seizure patterns on the scale of days, weeks, and months (Karoly et al., 2017; Baud et al., 2018). These findings have verified what patients have been saying for years: both men and women often have seizures at the same time of the day or month, which can be exploited to improve the accuracy of seizure prediction algorithms (Karoly et al., 2017).

In summary, we have now shown that seizure prediction works on a computer...but is it practical for clinical use? The NeuroVista device required a handheld pager-like device that contained a processor, and patients had to recharge batteries regularly. The algorithms in the Kaggle competition are not subject to any processor or battery constraints, and many of them were very complicated and power-intensive. And power is the primary question: complex algorithms require processors, and processors use up battery power very fast (as any smartphone user can attest). Thus, the next step in translating seizure prediction to patients is to address the concern of feasibility.

In *EBioMedicine*, Kiral-Kornek and colleagues utilize a new device that is designed specifically to perform complex algorithms with ultra-low power (Kiral-Kornek et al., 2018). The device is “neuromorphic”, meaning its design mimics brain physiology, and is capable of an advanced machine learning technique known as Deep Learning. Deep Learning is truly a “black box” approach: the goal is to teach the device to produce desired outputs given specific inputs, and it automatically develops the internal logic necessary to make the correct distinction. This method, a newcomer to the field of seizure prediction, is perfectly suited to answer the problem of feasibility: it uses extremely low power and can adapt to each patient individually.

Adapting Deep Learning to seizure prediction required a very novel approach. In order to present the device with readable information, segments of EEG were transformed into 2-D images of their instantaneous power spectra. The device then learned how to distinguish literal “snapshots” from pre-ictal (before a seizure) and inter-ictal (not before a seizure) EEG, using graphical interpretation to identify brain states that forecast imminent seizures. Their final results were comparable with the efficacy of past successful published prediction algorithms using the same patients (Cook et al., 2013; Karoly et al., 2017), with some

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important differences. First, the algorithm's efficiency allowed them to analyze months at a time, much longer than in previous studies. Second, the predictive functionality was maintained over all patients over the entire duration of the study, automatically tuning to maximize the response. Third, the algorithm could be adaptively tuned to patient preference (i.e. having warnings that are either more sensitive or more specific), which is one of the features most desired by patients (Schulze-Bonhage et al., 2010). Although these features are not necessarily unique to Deep Learning, this is the first time a single strategy has been able to accomplish them all. However, an important limitation was that it was unable to identify "safe times" accurately, in which seizures were less likely (the identification of safe times was a feature of the NeuroVista device, and is highly desired by patients). One unexpected result of this work is that the algorithm worked best if only the most recent 30 days of data were used, i.e. providing longer term recordings was not helpful. This suggests some degree of month-long plasticity in EEG signals that has not been previously recognized, and which requires adaptive algorithms such as deep learning to uncover.

This work officially heralds the transition to translation of advanced seizure forecasting. The era of "building a better mousetrap", with new algorithms that provide incremental improvement over past prediction results, is all but over: there are literally hundreds of successful algorithms in the Kaggle competitions. But clearly there are several aspects that need to be improved. In the current work, the authors address two of them: how can increasingly complex algorithms be implemented on an implantable device, and how can they adapt to patient preference? The neuromorphic chip provides an intriguing solution to both questions. Deep Learning uses very low power yet has tremendous capacity to forecast oncoming seizures, while also providing straightforward tunability. This device, or others that provide similar low power solutions, have opened a new era of possibility.

There are still further challenges to address for clinical seizure forecasting. To date, the focus has been almost exclusively on intracranial cerebral voltage data. Not only is this invasive, it may not provide all the necessary information. There are many other potential modalities, particularly those with wearable technologies and new sensors, that may provide complementary data that could improve efficacy or reduce invasiveness (Dumanis et al., 2017). Another limitation is that past work has focused only on typical EEG frequencies (under 30 Hz), but there is a great deal of experimental work showing that higher resolution (up to 500 Hz or higher) reveals additional information such as High

Frequency Oscillations, that could be very helpful in seizure prediction algorithms. Finally, the clinical approval process will be a challenge, as a "forecasting device" has very little precedent, and it is difficult to judge the risk/benefit ratio when there is no obvious intervention. Approval will require government agencies to approach these devices with a new perspective. These new technologies and techniques provide ample room for growth, though always with the stipulation that the technique be clinically feasible. Patients have spoken—they want seizure prediction. But moving it into reality will require a careful balance between clever techniques and attention to patient preference. This work provides an important first step in the right direction.

## Disclosure

The author has no conflicts of interest.

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