Seizure prediction

Professor Mark Cook
is the Chair of Medicine and Director of Neurosciences at St. Vincent's Hospital, Melbourne. Professor Cook specialises in the treatment of epilepsy and is recognised internationally for his expertise in epilepsy management; particularly imaging and surgical planning.

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Correspondence address:
Professor Mark Cook,
Chair of Medicine,
St. Vincent's Hospital,
Department of Medicine,
The University of Melbourne,
PO Box 2900,
Fitzroy VIC 3065, Australia.

Seizure prediction is of obvious clinical relevance, as for many patients with epilepsy the largest part of their disability results from the unpredictable nature of the seizures. It is this component which has the greatest ramifications for driving, other dangerous activities, and work. As well the fear of having a seizure in public often restricts socialisation, with all the consequences of the isolation that results.[1,2] Much of the stigma associated with the condition could be alleviated if people could anticipate their seizures and take necessary steps to make themselves safe, and modify their environment. Conceivably having accurate seizure prediction strategies could also permit administration of acutely acting anticonvulsant therapies. Seizure prediction systems may allow new insights into the natural history of the condition, and associated co-morbidities.

It has been recognised for many years that there are changes in cerebral activity that occur some time prior to seizures. To some extent the clinical evidence for this has been anecdotal, with reports of carers and patients who seem to be able to recognise changes in behaviour some time prior to the event, often surprisingly accurately.[3] This is difficult to validate however, and it is possible they are often describing subtle seizure activity rather than a distinct prodrome.

Imaging studies have shown conclusively that there are changes in brain function that develop some time before seizures occur, and this has been demonstrated across a number of modalities.[4,5] The changes reflect brain network activity distinct from typical electroencephalographic seizures, and the EEG correlates of these changes are often unclear.

Many attempts at predicting seizures have been undertaken over the years, with limited success until recently. Artifact and limited spatial resolution limit the utility of scalp EEG, and so intracranial EEG data is typically used. The majority of previous approaches have typically used mathematical algorithms estimating entropy, correlation dimension, and Lyapunov exponents.[6,7] There has recently been interest in using EEG synchronisation analysis,[8-10] as these measures are thought to be correlates of cortical activity. Unfortunately these algorithms have not delivered reproducible outcomes.[11,12]

Recent interest in devices intended to abolish or modulate seizures through direct stimulation of cortical areas responsible for stimulation of deep cerebral structures[13,14] has led to the development of implantable therapeutic devices for epilepsy, and the recent completions of two major trials. The first of these systems is a closed loop device, which detects and responds to individual events.[15] The second is an open loop system that provides regular stimulation to the anterior thalamic nucleus to supress seizures presumably by modulating cortical excitability.[16] The results of the trials show sufficient promise to warrant further exploration of such therapies. An attractive application of seizure prediction systems would be to link them to seizure suppression systems of this type, as it may allow more effective therapy, and as well have significant implications for the power requirements of these devices if utilisation could be better managed.

Therapeutic strategies are currently based around chronic administration of a medication to prevent often relatively infrequent but unpredictably occurring events. Accurate prediction may direct therapies toward short acting anticonvulsant agents, not a focus of drug development in this field to date, with a limited number of agents used in this manner. Similar approaches may ultimately allow safer driving and make occupational hazards less of an obstacle to employment.

We have recently completed a trial of an implanted device to predict seizures.[17] This system was developed by the Neurovista Corporation, and consists of a set of intracranial electrodes, which are placed subdurally via a small craniotomy to lie on the surface of the brain and continuously record cerebral electrical activity. This is conducted via a lead to a subclavicular unit that transmits the data wirelessly to a hand-held device, which contains algorithms developed for each individual based on analysis of at least five seizures. The EEG is filtered and various features of interest extracted, these are then analysed with respect to later seizures, and the features that correlate best coded into the hand held unit. This then processes in real time the data being transmitted from the implanted unit, and recognises the features that allow accurate seizure prediction. The hand held unit has a series of lights to indicate the risk of seizure in the minutes or hours ahead, a red light indicates a high risk, white light a moderate risk, and blue light no risk. Various statistical criteria were established to test the predictive capabilities of the device.

The system also had other features, it allowed the patient to record audio to annotate the record, and as well would automatically record audio when a seizure was detected (rather than predicted). This feature was surprisingly useful, allowing the identification of events not reported by the patient.

Fifteen subjects were enrolled in the study; all had 2-12 disabling partial onset seizures/month; a lateralised epileptogenic zone; and no history of psychogenic seizures. After the surgery they entered a data collection phase to allow the training of an algorithm, and if the algorithm met satisfactory performance criteria the hand held unit was activated to give advice regarding seizure likelihood. The study was intended to provide advice on safety as well as accuracy and the utility of seizure prediction.

Eleven of the 15 subjects completed the data

collection period, and of these 10 met the criteria that had been set around algorithm performance, and went on to the advisory Phase.

The study demonstrated that ambulatory intracranial EEG monitoring is safe, with a complication rate similar to that of other implanted devices of this type, and that the majority of study subjects met criteria for enabling seizure advisories.

There were a number of unexpected findings in the study, most significantly that patients generally underestimated the number of seizures they had. It has long been known from inpatient telemetry studies that patients underestimate the number of events[18,19] by a factor of 2-3 times, but in fact the variation was much greater than that with some patients underestimating by over 100 events per month. To complicate matters further, the misreporting varied within subjects month to month, preventing the application of any 'correcting factor'. Given seizure management is based chiefly on patient seizure estimates of frequency, this has significant clinical implications. As well the assessment of new anticonvulsant medications is also performed in this manner, and these findings place all this on much less certain ground. Some subjects had fewer seizures than they reported, and some turned out to be reporting other events as seizures, such as migraines. A few individuals took additional benzodiazepine therapy when the light changed to red on their device, though anecdotally this seemed to be useful, the low numbers meant statistical analysis was not possible.

The practical utility of the system varied between patients. One early concern had been that anxiety would increase if patients were warned in advance of seizure, but this did not occur – patients are already anxious about unpredictable seizures and this was not magnified. Patients with very frequent seizures were often a little frustrated however to find the device was frequently warning them of an impending event. Though this information was accurate, it did not always benefit them greatly. For others though the information was life changing, allowing much greater independence, level of activity, and confidence. It allowed others to take appropriate action to avoid embarrassment in the work place, and others to discontinue planned potentially hazardous activities such as swimming.

This was a very preliminary study of what is the first device to allow successful seizure prediction, but the potential to improve quality of life for people with this devastating and unpredictable condition is obvious. As well we have seen unexpected outcomes with better understanding of the natural course of the illness, and this has significant implications for day-to-day management and future drug assessment. ◆

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