Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study

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Summary

Background Seizure prediction would be clinically useful in patients with epilepsy and could improve safety, increase independence, and allow acute treatment. We did a multicentre clinical feasibility study to assess the safety and efficacy of a long-term implanted seizure advisory system designed to predict seizure likelihood and quantify seizures in adults with drug-resistant focal seizures.

Methods We enrolled patients at three centres in Melbourne, Australia, between March 24, 2010, and June 21, 2011. Eligible patients had between two and 12 disabling partial-onset seizures per month, a lateralised epileptogenic zone, and no history of psychogenic seizures. After devices were surgically implanted, patients entered a data collection phase, during which an algorithm for identification of periods of high, moderate, and low seizure likelihood was established. If the algorithm met performance criteria (ie, sensitivity of high-likelihood warnings greater than 65% and performance better than expected through chance prediction of randomly occurring events), patients then entered an advisory phase and received information about seizure likelihood. The primary endpoint was the number of device-related adverse events at 4 months after implantation. Our secondary endpoints were algorithm performance at the end of the data collection phase, clinical effectiveness (measures of anxiety, depression, seizure severity, and quality of life) 4 months after iniation of the advisory phase, and longer-term adverse events. This trial is registered with ClinicalTrials.gov, number NCT01043406.

Findings We implanted 15 patients with the advisory system. 11 device-related adverse events were noted within four months of implantation, two of which were serious (device migration, seroma); an additional two serious adverse events occurred during the first year after implantation (device-related infection, device site reaction), but were resolved without further complication. The device met enabling criteria in 11 patients upon completion of the data collection phase, with high likelihood performance estimate sensitivities ranging from 65% to 100%. Three patients' algorithms did not meet performance criteria and one patient required device removal because of an adverse event before sufficient training data were acquired. We detected no significant changes in clinical effectiveness measures between baseline and 4 months after implantation.

Interpretation This study showed that intracranial electroencephalographic monitoring is feasible in ambulatory patients with drug-resistant epilepsy. If these findings are replicated in larger, longer studies, accurate definition of preictal electrical activity might improve understanding of seizure generation and eventually lead to new management strategies.

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Introduction

Epilepsy is a common and serious group of neurological disorders that is characterised by recurrent seizures and affects more than 60 million people worldwide. 30–40% of cases are not adequately controlled with current treatments.[1] Resective surgery, though often effective, is either not appropriate or not available for most patients with inadequately controlled epilepsy. Although the morbidity and mortality associated with epilepsy is largely related to the immediate effects of loss of consciousness, such as falls and injury, and the life-threatening risk of status epilepticus, the inherent unpredictability of seizures contributes substantially to the risk of injury, mortality, and psychosocial disability. Quality-of-life impairments associated with epilepsy compare unfavourably with those associated with many other chronic illnesses, such as hypertension, diabetes, and heart disease,[2] and the uncertainty of seizure occurrence is a major component of this impairment.[3]

Although the occurrence of seizures is deemed unpredictable, evidence shows that changes occur in the brain before attacks. This evidence is provided by anecdotal reports of prodromes, which have been described by patients or noted by caregivers and feature subtle changes in behaviour, in the hours or sometimes days before a seizure occurs. Additionally, functional MRI studies[4–6] and near-infrared spectroscopy[7,8] have shown that perfusion increases before seizures. Transcranial magnetic stimulation experiments have shown that the

brain is in a hyperexcitable state before seizures.[9,10] Other techniques, including auditory and visual steady-state responses[11] and direct electrical stimulation[12] of the brain, suggest that cortical hyperexcitability is a precursor to epileptic seizures. These findings suggest that seizures might be anticipated by careful observation of the brain. Reliable anticipation of seizure occurrence could allow patients to avoid dangerous situations and enable administration of treatments, such as electrical stimulation or acute drug delivery, targeted to when a seizure is likely to occur, rather than chronic administration, which is current clinical practice.

The seizure advisory system is a hand-held device that receives and analyses electroencephalography (EEG) signals recorded directly from the surface of the brain, and then provides a visual and audible signal showing the likelihood of a seizure in the minutes or hours ahead. Here we report the results of the first study to assess the safety and efficacy of the seizure advisory system in patients with drug-resistant epilepsy.

Methods

Study design and participants

See Online for appendix

Before our study, NeuroVista (Seattle, WA, USA) assembled a large database of scalp and intracranial electroencephalograms (EEGs) recorded during assessments of epilepsy-monitoring units at several academic centres. A development and validation test library of intracranial subdural grid EEG recordings from 49 patients (total duration 7192 h) was derived from these data.

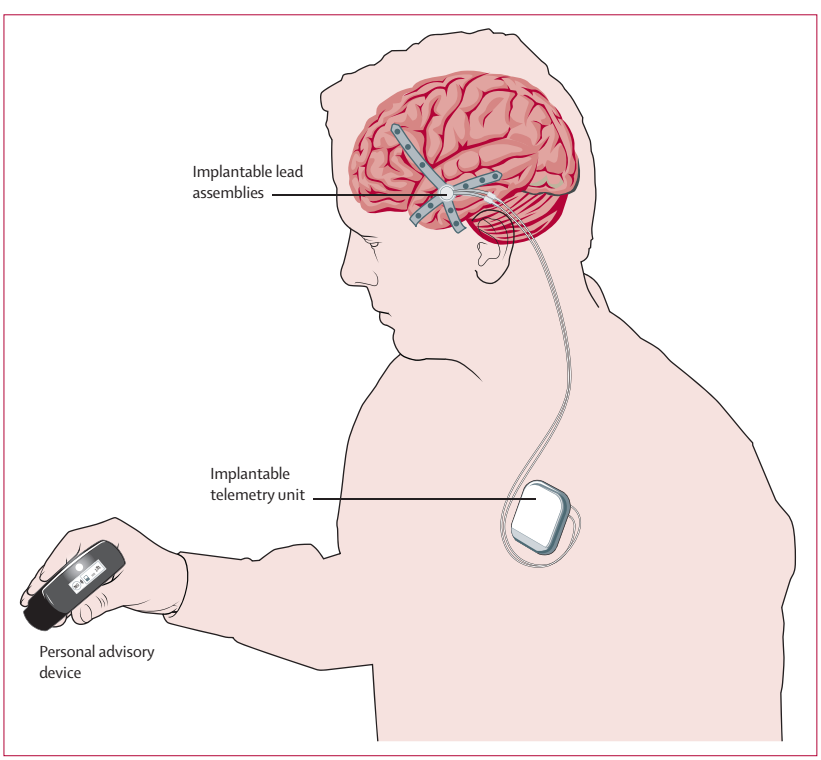

***Figure 1*: Major components of seizure advisory system**
Intracranial electrode arrays (location shown by grey areas) were used to collect intracranial electroencephalogram (EEG) data on the cortical surface. Leads were connected to a subclavicularly placed implanted telemetry unit, which wirelessly transmitted data to an external, hand-held personal advisory device. The external device received the telemetered EEG, applied an algorithm to the data, and displayed the resultant information as a series of advisory lights—blue (low), white (moderate), or red (high) indicators—in addition to an audible tone or vibration, or both. The hand-held device could be worn on the belt or carried in a bag.

A purpose-built cluster-computing environment was developed to assist in the search for a suitable algorithm on the basis of previously developed methods.[13] The resulting prototype algorithm showed good performance. However, this early work had several limitations. Even with the application of the development and validation test library, conservative analysis methods often made meaningful differences between algorithm variants difficult to show. A major limitation was the possibility of errors that arise from multiple comparisons and overinterpretation of the data, the effects of drug changes, and the changes that can result during the surgical recovery period. Steps were taken to avoid errors arising from multiple comparisons and overinterpretation of the data, and we did experiments to examine the effects of variation in the data that might arise from tapering of drugs or recovery after surgery. Previously, the seizure advisory system was deployed in dogs.[14]

We designed a feasibility study to provide safety and proof-of-concept efficacy data for the seizure advisory system in patients with medically refractory epilepsy. The study was done at three clinical centres in Australia—Austin Health, the Royal Melbourne Hospital, and St Vincent's Hospital, all of which are part of the Melbourne University Epilepsy Group. The human research ethics committees of the participating institutes approved the study and subsequent amendments. All patients gave written informed consent before participation.

We recruited patients within our practices between March 24, 2010, and June 21, 2011. Enrolment dates were broadly defined prospectively to provide reasonable enrolment windows. We decided to conclude the study early on Oct 19, 2012, because of uncertainties about whether funding for the study would continue, to ensure optimum management of patients. Patients were selected mainly on the basis of suitable seizure frequency (between 2 and 12 seizures per month); patients were adults who had a level of independence sufficient to make the device useful in the management of daily activities. Complete lists of inclusion and exclusion criteria are in the appendix. Patients reported baseline seizure rates for the 3 months before enrolment. Patients meeting the inclusion criteria were implanted with the seizure advisory system and initially entered a data collection phase, during which intracranial EEGs were recorded but the hand-held device gave no advisories to the patients. When sufficient data were gathered, a patient-specific algorithm was created and then assessed against performance criteria. If the algorithm met these performance criteria, the patient entered the advisory phase, during which the device was enabled to provide visual and audible advisories.

	Age (years)	Sex	Age at diagnosis (years)	Antiepileptic drugs	Epileptogenic zone	Previous resection
Patient 1	26	Male	4	Clonazepam, levetiracetam, lamotrigine, valproate	Parietal-temporal	No
Patient 2	44	Male	12	Lacosamide, lamotrigine, oxcarbazepine, valproate	Occipitoparietal	No
Patient 3	22	Female	16	Carbamazepine, lamotrigine, phenytoin	Parietal-temporal	Yes
Patient 4	61	Male	48	Carbamazepine, lacosamide, lamotrigine, topiramate, phenytoin	Parietal-temporal	No
Patient 5	20	Female	1	Clonazepam , lamotrigine, oxcarbazepine, topiramate	Frontotemporal	Yes
Patient 6	62	Male	37	None	Temporal	No
Patient 7	52	Male	26	Carbamazepine, clonazepam, levetiracetam	Frontotemporal	No
Patient 8*	48	Male	20	Carbamazepine, levetiracetam	Frontotemporal	Yes
Patient 9	51	Female	10	Carbamazepine	Occipitoparietal	No
Patient 10	50	Female	15	Levetiracetam, oxcarbazepine, zonisamide	Frontotemporal	Yes
Patient 11	53	Female	15	Lacosamide, phenytoin, perampanel	Frontotemporal	No
Patient 12	43	Male	20	Lamotrigine, lacosamide, phenytoin, retigabine	Temporal	No
Patient 13	50	Male	20	Carbamazepine, clonazepam, levitiracetam, lacosamide	Temporal	Yes
Patient 14	49	Female	4	Clonazepam, oxcarbazepine	Parietal-temporal	No
Patient 15	36	Male	5	Carbamazepine, lacosamide, perampanel, topiramate	Temporal	Yes

Drugs were used throughout the study, with variations according to clinical parameters (ie, toxic effects).*Patient 8 had previous vagus nerve stimulation.

Table 1: **Demographics of patients at baseline**

Procedures

Our primary endpoint was the number of device-related adverse events at 4 months after implantation. We standardised the definition of such events with the Medical Dictionary for Regulatory Activities. Our secondary endpoints were algorithm performance at the end of the data collection phase, clinical effectiveness 4 months after initiation of the advisory phase, and adverse events and clinical effectiveness 12 and 24 months after implantation.

The major components of the seizure advisory system are shown in figure 1. A cluster-computing system at NeuroVista was used to configure algorithms for each patient (appendix). Two silicon implantable lead assemblies, each with eight platinum iridium contacts distributed across two electrode arrays, collected intracranial EEGs on the cortical surface. The lead assemblies were designed with materials and geometries similar to those of commercially available cortical strip electrodes that are routinely used in epilepsy-monitoring units, but have increased robustness and tolerance to flexural stresses.

The leads were tunnelled down the neck and terminated at a subclavicularly placed, titanium-encased, hermetically sealed, implantable telemetry unit, which sampled 16 channels of intracranial EEGs acquired at 400 Hz and wirelessly transmitted these data to an external, hand-held personal advisory device. The leads did not deliver any type of electrical energy or stimulation to the patient. The implantable telemetry unit was inductively recharged through an external charging accessory. The implantable portions of the system were designed for long-term implantation but could be removed with standard surgical techniques.

After collection of demographic data and medical histories, and clinical assessments at baseline, the advisory systems were surgically implanted. Leads were placed via a small craniotomy regionally and unilaterally over the quadrant believed to contain the epileptogenic zone (as determined by previous EEG, imaging studies, or seizure type; appendix). In patients with bilateral temporal lobe onset seizures, leads were placed over the hemisphere that generated the most frequent, stereotypical seizures. We verified system operation and integrity before wound closure.

After patients recovered from surgery, the data collection phase began. We did postoperative examinations before discharge and 6 weeks after surgery, and neurological examinations and cognitive assessments at baseline and 4 months, 1 year, and 2 years after surgery. The cognitive battery designed to detect any decline in cognitive function included the Wechsler abbreviated scale of intelligence (vocabulary and matrices subtests), Rey auditory verbal learning test (forms AB and CD), brief visuospatial memory test–revised (forms 1–4), trail making test (A and B), Wechsler memory scale–working memory index (spatial span, letter-number sequencing), Wechsler adult intelligence scale (3 digit symbol and symbol search), Boston naming test, judgment of line orientation test, and grooved pegboard test.

At least one month of EEGs containing at least five leading seizures had to be recorded during the data collection phase to develop an algorithm. For the purpose of this study, and for a conservative estimation of performance, we defined a lead seizure as a clinical seizure that is preceded by a minimum of 8 h of interictal data. Accumulated EEGs were annotated by NeuroVista clinical staff and verified by study investigators on the

	Adverse events		Serious adverse events	
	4 months after implantation	12 months after implantation	4 months after implantation	12 months after implantation
Device migration	1	..	1	..
Device-related infection	..	1	..	1
Reaction at site of medical device	1	1	..	1
Postoperative nausea	1	..	..	..
Postoperative vomiting	1	..	..	..
Procedural headache	5	..	..	..
Procedural pain	1	..	..	..
Seroma	1	..	1	..

Adverse events total includes serious adverse events. For the primary endpoint, we followed up adverse events for 4 months after implantation of the device (12 months for secondary endpoints). No further device-related adverse events were noted before study termination; five of the 12 remaining (when the study was terminated) implanted patients reached the endpoint of 24 months after implantation.

***Table 2*: Device-related adverse events and serious adverse events**

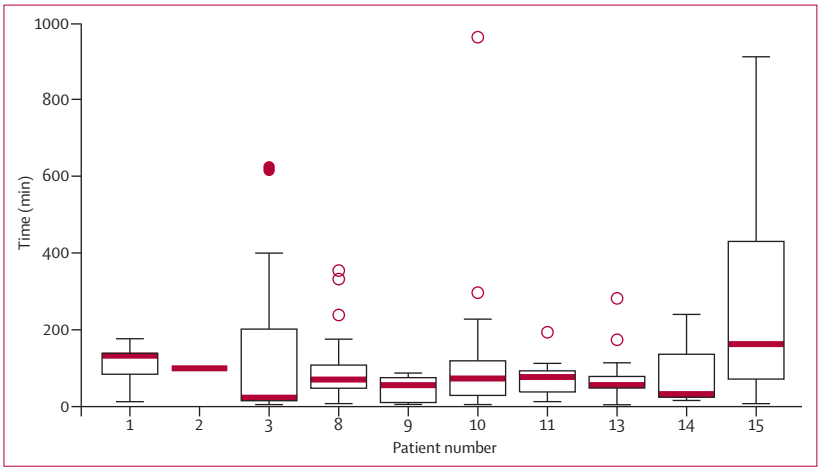

***Figure 2*: Box plots of time between start of the red advisory and seizures, by patient**
Solid lines represent medians, top whiskers maxima, bottom whiskers minima, box tops 75th percentiles, box bottoms 25th percentiles, and circles outliers.

basis of patients' diaries, hand-held audio recordings, and a seizure detection algorithm based on an unsupervised learning approach that identifies significant outliers in features of EEGs that are associated with seizures.[15] Only electrographic events that were judged by a reviewer to be associated with clinical manifestations (seizure diary or audio recordings; ie, clinically correlated seizures) or those that were electrographically similar in onset, propagation, and spread to clinically correlated seizures (ie, clinical equivalent seizures) were used to train the algorithm. For the purpose of algorithm training, we assumed that similar electrographic presentations were of similar clinical relevance. We assessed stationarity of algorithm features generated from EEGs by noting the trajectory of the processed signal in the space defined by the algorithm feature vector.

The personal advisory device received and processed the EEG data in real time on the basis of the patient's unique algorithm. Outputs show the patient's likelihood of having a seizure via a series of advisory lights—blue (low likelihood), white (moderate likelihood), or red (high likelihood) indicators—and an audible tone or vibration, or both. The personal advisory device stored EEGs and advisories on standard flash memory cards for subsequent analysis. It also supported audio recordings, both those manually triggered by the patient for diary purposes and those automatically activated when a seizure was detected by the system to help to establish a clinical correlate with intracranial EEG activity.

During the study, patients recorded seizures via diary or patient-initiated audio recordings on the hand-held device, or both. These records were supplemented by automatically activated audio recordings that were made when the device detected events, which allowed identification of unreported clinical seizures, through sounds made by patients or the responses of bystanders.

We prospectively assessed algorithm performance 4 months after initiation of the advisory phase. Additionally, when applicable, we assessed clinical effectiveness measures with the quality of life in epilepsy survey, Beck depression inventory, Beck anxiety inventory, multidimensional health locus of control scale, Liverpool seizure severity scale, and caregiver burden inventory at 4 months, and compared results with those at baseline.

Statistical analysis

As an invasive first-in-man study, a sample size of ten patients was originally established to assess risk and benefit. After successful enrolment and implantation of the first ten patients, we expanded the study to 15 patients.

In view of the varied and inconsistent definition of seizure, the gold standard for algorithm assessment included only clinically correlated seizures.[16–18]

To begin the advisory phase, individualised algorithms had to meet two criteria—sensitivity of the red advisory indicator had to be superior to a time-matched chance indicator and not inferior to (ie, lower limit 95% CI of the proportion of seizures anticipated not lower than) 65% and the blue indicator had to have a false-negative rate that was superior to a time-matched chance indicator (significance level of 0·05 for both criteria). Red indicators had to precede a seizure by 5 min to be deemed a true-positive, and a seizure could not occur within 5 min of a blue advisory to qualify as a true-negative. If only one criterion was satisfied, advisory indicators could be enabled independently to provide solely high or low likelihood advisories. We used a leave-one-out cross-validation to estimate performance.[13] Patients, investigators, and other reviewers of EEGs (ie, NeuroVista personnel) were not privy to advisory indicators during the data collection phase. If neither criterion was met, the system was explanted and the patient discontinued the study.

We calculated sensitivity for the high likelihood advisory and the significance of the advisory performance compared with a time-matched chance indicator. When a

	Data collection phase (cross-validation estimate)						Advisory phase (prospective performance at 4 months)					
	Time in advisory (%)		High likelihood performance				Time in advisory (%)		High likelihood performance			
	High	Low	Seizures (n)	Sensitivity (%)	p	Phase duration (days)	High	Low	Seizures (n)	Sensitivity	p	Likelihood ratio
Patient 1	33	27	8 (16)	75%	0·0142 (0·0004)	95·8	27	7	7 (13)	86% (77%)	0·0017 (0·0002)	14·3 (8·0)
Patient 2	21	58	4	75%	0·0278	169·0	31	56	3	100%	0·0266	All*
Patient 3	42	Not enabled	37 (45)	65% (64%)	0·0026 (0·0013)	114·1	29	Not enabled	58 (106)	56% (45%)	<0·0001 (0·0001)	3·1 (2·1)
Patient 4†	15	46	8 (9)	71% (75%)	0·0009 (0·0002)	183·8	..	..	..	..	..	..
Patient 8	40	Not enabled	29 (65)	69% (63%)	0·0010 (0·0001)	143·0	28	Not enabled	36 (86)	63% (62%)	0·0003 (<0·0001)	4·4 (4·2)
Patient 9	36	19	15 (17)	67% (59%)	0·0120 (0·0401)	153·9	11	48‡	49 (52)	18%§(17%)	0·0839 (0·1419)	0·8
Patient 10	31	Not enabled	14 (20)	71% (75%)	0·0013 (<0·0001)	142·7	17	Not enabled	109 (164)	54% (51%)	<0·0001	5·8 (5·1)
Patient 11	30	20	20 (74)	93% (65%)	<0·0001	90·7	15	26	11 (39)	56% (39%)	0·0039 (0·0003)	5·1 (2·6)
Patient 13	35	Not enabled	17 (44)	73% (62%)	0·0021 (0·0004)	149·9	28	Not enabled	26 (113)	57% (50%)	0·0021 (<0·0001)	3·4 (5·1)
Patient 14	5	83	5 (6)	100%	<0·0001	467·9	3	88	3	100%	<0·0001	All*
Patient 15	18	Not enabled	5 (6)	100%	0·0002 (<0·0001)	157·5	41	Not enabled	21 (24)	71%	0·0034 (0·0019)	3·6 (3·5)

Performance data were assessed on the basis of correlated clinical seizures. Patients 5, 6, 7, and 12 did not proceed to the advisory phase, either because an adverse event led to device removal despite satisfactory preliminary data acquisition (patient 5), or because the algorithm generated on completion of the data collection phase did not meet the predetermined performance criteria (patients 6, 7, and 12). Assessments based on the use of clinical equivalent seizures in addition to correlated clinical seizures are provided in parentheses, when different. Likelihood ratio=([number of events in high advisory]/[time in high advisory])/([number of events in moderate advisory]/[time in moderate advisory]). *All events occurred during the high likelihood advisory. †Patient discontinued study because of adverse events before the 4 month advisory endpoint. ‡Negative predictive value <100%; all other low likelihood advisories had a negative predictive value of 100%. §Performance criteria were not satisfied prospectively.

Table 3: **Algorithm performance, by patient**

high chance likelihood indicator is applied to the data with the same proportion of time in high advisory, the significance value suggests the difference between chance prediction of events and actual sensitivity. We also calculated likelihood ratios to compare seizure rates between red and white advisories.

We did post-hoc analyses of individual patients' and overall population seizure reporting. We tested correlation between reported and recorded events with Spearman's rank correlation coefficient against the null hypotheses, which assumed that zero correlation existed. We deemed a p of 0·05 or less to be significant. We used R, JMP, Matlab, and purpose-built software for our analyses. This study is registered with ClinicalTrials.gov, number NCT01043406.

Role of the funding source

The sponsor had roles in study design; data collection, analysis, and interpretation; and writing of the Article. VR, WDS, DS, KL, and DH were employed by the sponsor; no other authors received compensation. All authors had full access to all study data. The corresponding author made the decision to submit the paper for publication.

Results

We enrolled 17 patients, two of whom dropped out before engaging in the study and are not included in further results. Nine men and six women (mean age 44·5 years [SD 13·0, range 20–62]) were implanted with the device. Six patients had undergone previous epilepsy resection, and one had used vagus nerve stimulation, which was explanted when the seizure advisory system was implanted (table 1).

Clinical effectiveness data are not available for 12 months after implantation because variability in duration of the data collection phase meant that assessments 12 months after implantation overlapped with assessments 4 months after advisory enablement in many patients. Because the study was concluded early, data were not gathered from most patients for 24 month endpoints.

Table 2 summarises device-related adverse events. At 4 months after implantation, two of 11 events were serious and necessitated intervention. In patient 5, during the data collection phase, the implantable telemetry unit fastening sutures were compromised and the device migrated (potentially aggravated by a fall during a seizure), causing substantial discomfort. The

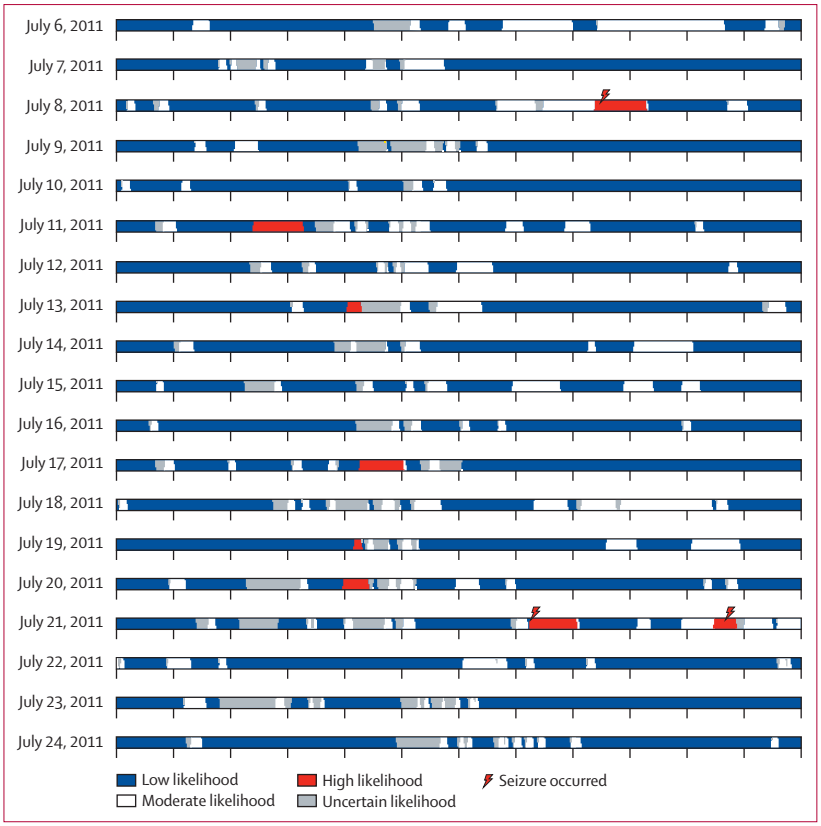

***Figure 3*: Excerpt from patient 2's advisory timeline**
Each horizontal row represents a day broken into 2 h periods. Within each line, pixel columns are 2·3 min in duration and are broken down vertically into 13·8 s pixels. During periods of uncertain likelihood, the algorithm could not provide advisories because of data loss. From top to bottom, left to right, warning times for seizures were 14·9 min, 6·3 min, and 29·7 min.

patient underwent a procedure to relocate and anchor the unit, and recovery was otherwise uncomplicated. Patient 13 had persistent headaches immediately after implantation and imaging showed fluid accumulation on the dura around the surgical wound. The patient had a second procedure to drain serous fluid from the site and then recovered uneventfully.

We noted two further serious adverse events at 12 months after implantation. Patient 4 presented with symptoms of infection 7 months after implantation. The infection site near the implantable telemetry unit was evacuated but incidental damage to the leads resulted in complete explantation during a subsequent procedure; the patient fully recovered. Patient 5 (who presented previously with device migration) experienced lead tautness, causing neck discomfort, which led her to request explantation. After the device was removed, a thick fibrotic capsule remained that was not resorbed (tethering), necessitating an additional cosmetic procedure (appendix). Minor problems reported by patients included prominence of the implantable telemetry unit and cosmetic aspects of device location (data not shown).

Compared with baseline, we noted no clinically significant neuropsychological changes in individual patients as measured by cognitive assessments 4 months after implantation (appendix).

When viewed from the perspective of the space defined by the algorithm feature vector, the region occupied by the processed iEEG signal typically drifted with time. This drift was prevalent in the days after implantation, which often prevented successful classification of events by the algorithm. This transient period was recorded in six patients and lasted from weeks to months, and in some cases necessitated extension of the data collection phase to allow data to become adequately stationary. 14 of 15 patients accrued the required EEGs during the data collection phase (the other patient discontinued because of tethering). 11 of these 14 patients had a trained algorithm that met enabling criteria for the high likelihood advisory and progressed to the advisory phase (which included enabling moderate-likelihood advisories). Eight patients' prospective performance 4 months after advisory enablement continued to satisfy criteria, and two patients had 100% sensitivity. Patient 4 advanced to the advisory phase, but explantation of the device because of infection was necessary before 4 months after implantation.

In addition to high-likelihood and moderate-likelihood advisories, low advisory (blue) was enabled in five patients, who were prospectively assessed. During the first four months of the advisory phase, four of these patients achieved 100% negative predictive value; the fifth had a negative predictive value of 98%. 4 months after advisory enablement, mean warning time of the red advisory was 114 min (SD, 151, range 5–960; figure 2). We detected no significant decline or improvement across the population in clinical effectiveness measures between baseline and 4 months after advisory enablement (appendix).

Table 3 shows individual algorithm performance in the data collection phase and the first 4 months of the advisory phase. Rather than specificity, which would be subjectively based on an arbitrarily chosen prediction horizon, we reported the time in high and low advisories as a proportion of valid EEGs. The remaining time was spent in the moderate advisory (data not shown). In two patients, all seizures occurred in the high likelihood advisory (table 3); in other patients, the likelihood of an event occurring in high likelihood advisory compared with moderate likelihood advisory varied substantially (mean 5·1 [SD 4·0]; table 3). Figure 3 shows a 19 day advisory timeline for one patient who achieved 100% sensitivity during the advisory phase.

Table 4 shows results of comparisons of individual patients' seizure reporting; figure 4 shows those of comparisons of the population's seizure reporting. We noted little correlation between reported and recorded events, and only five patients' correlations were significant.

Disparity between clinical events and reported events was substantial. Most patients underestimated the frequency of seizures (table 4). Reported and actual events varied unpredictably within patients from month to month (data not shown).

Discussion

Our study is the first to record long-term EEGs in an ambulatory setting in human beings and to show successful prospective seizure prediction. Implantation of the seizure advisory system was generally well tolerated, and the device met expectations about data acquisition and analysis, although improvements in the transmission quality from the implantable telemetry unit would be beneficial (panel).

Our study had some limitations. Patients had heterogeneous focal epilepsies, and all had longstanding refractory epilepsy. Several patients had undergone previous surgical procedures, and this population might not be representative of the broader group of patients with epilepsy. The stability of the features detected by the algorithm with increasing time is not yet clear. However, three patients have now had the device for more than 2 years and, notwithstanding algorithm retraining, prediction ability remains stable with time. Conceivably, some long-term EEG changes could confound the process, but such changes seem unlikely in view of the stability of recordings.

We did not expect the transient effects of surgery, which varied in length from weeks to months, on features of EEGs that temporally change. This finding might be pertinent to much seizure prediction research, which has been based mainly on data from epilepsy-monitoring units.

Although we did not develop a formal method to identify sleep or vigilance, two patients seemed to have advisories that were diurnal (appendix), which might be because of susceptibility of the algorithm feature selection (ie, identification of the metrics used to analyse the iEEG data [specifically for a preictal signal] that are most able to provide likelihood advisories) to the effects of sleep cycles. Future algorithms might benefit from development of features insensitive to sleep patterns and use of corrected assessments that account for performance achieved mainly through diurnal selection.

Algorithm selection and training were rigorously fixed (ie, cluster-computing architecture for algorithm development was locked) throughout both the data collection phase and the first 4 months of the advisory phase. The grouping of clinically correlated and clinical equivalent seizures provided more relevant training data for the prediction algorithm but reduced the probability of training for subclinical events (ie, events without clinically relevant manifestations).

Beyond 4 months in the advisory phase, we used various strategies for algorithm implementation, improvement, and training, making overall comparison difficult, and thus we have not reported results for algorithm performance in this period. Algorithm performance was generally maintained until study termination, but periodic retraining (roughly every 4 months) was sometimes necessary to either maintain or improve performance affected by feature temporal

	Estimated monthly seizure rate at enrolment	Mean monthly seizure rate during study	Mean monthly seizure rate captured by intracranial electroencephalography	Spearman's rank correlation coefficient (⍰)	p
Patient 1	4	5·37	14·17	0·71	0·0063
Patient 2	3	0·00	1·52	..	..
Patient 3	7	0·00	126·65	..	..
Patient 4	5	1·16	3·61	–0·26	0·5742
Patient 5	4	0·00	1·32	..	..
Patient 6	2	0·55	6·32	–0·40	0·2223
Patient 8	4	5·55	42·32	0·59	0·0356
Patient 9	10	22·52	30·37	0·74	0·0134
Patient 10	4	24·06	52·28	0·45	0·1472
Patient 11	8	11·21	102·50	0·25	0·4357
Patient 12	5	0·25	0·37	0·71	0·0097
Patient 13	7	0·99	25·74	0·86	0·0007
Patient 14	3	0·00	0·00	..	..
Patient 15	5	4·80	6·28	0·55	0·1328

We eliminated outliers 1·5 times or more outside the IQR, which resulted in zero values for some patients with infrequent seizures.

Table 4: **Seizure rates before and during the study, by patient**

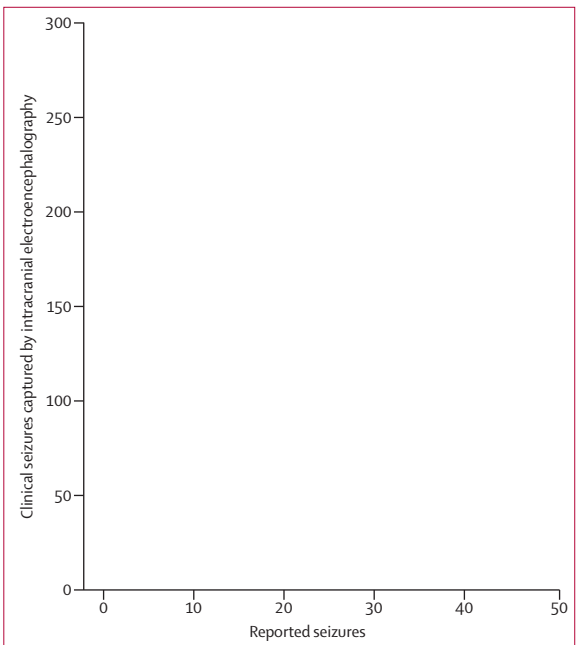

Figure 4: **Monthly seizure rates—reported seizures versus clinical seizures captured by intracranial encephalography**
Spearman's rank correlation (⍰)=0·48 (p<0·0001).

Panel: Research in context

Systematic review

We searched PubMed, Google Scholar, and IEEExplore with the terms "seizure prediction" and "epilepsy prediction" for human and animal studies published between Jan 1, 1965, and Oct 28, 2012. We did not restrict publications by language. We also hand-searched the proceedings of seizure-prediction workshops. We assessed all studies that had attempted to prospectively examine seizure prediction. Early attempts at accurate seizure prediction were limited by restricted datasets and uncertainty about whether prediction was possible, even in principle. Although some studies[19,20] had shown changes in the interictal period, sufficient sensitivity and specificity to afford clinically useful information has not been reported. Previously reported algorithms have been based on various approaches, including spectral analysis, measures of entropy, correlation dimension, short-term Lyapunov exponents, and intracranial electroencephalography (EEG) synchronisation analysis.[19–29]

Interpretation

Although previously reported algorithms have shown promise in some groups of patients in specific analytic conditions, the need to adopt rigorous methods that provide adequate protection from common analytic issues (eg, overtraining, in-sample testing) combined with an absence of suitable long-duration datasets has made satisfactory demonstration of performance difficult.[30–32] Our study is the first done in human beings that recorded long-term intracranial EEG data in an ambulatory setting with the intention of establishing the feasibility of seizure prediction (rather than detection only). Device performance met expectations for data acquisition and analysis, and we showed that successful seizure prediction is possible in some patients. We also noted substantial disparities between reported and detected events, which could have pronounced effects on analysis of patient-reported data in epilepsy, with implications for management of patients. Our proof-of-concept study shows that seizure prediction is possible and provides an important first step towards application of seizure-prediction techniques in development of new therapeutic strategies and perhaps eventually in clinical practice.

drift. Use of non-time-dependent features might negate the need for retraining in future. A patient in whom we deemed treatment unsuccessful went on to have a successful algorithm after an extended data collection phase beyond the stipulation of the protocol. Modified training strategies might eliminate the premature disqualification of patients in whom extended training periods are needed to develop algorithms.

The clinical usefulness of seizure prediction was inconclusive. Patients' abilities to interpret and apply predictive data to gain clinical benefit were anecdotally varied and unproven by quantitative metrics. Some patients had difficulty appreciating the importance of periods when the predicted likelihood of seizures was high, at least sufficiently so as to allow them to participate in daily activities. The high variability of seizure warning times also prevented a uniform response. Patients with the lowest proportions of time in the red advisory typically reported the highest satisfaction with the device and were able to make lifestyle adjustments, including avoiding swimming (ie, only swimming during low likelihood advisory), going to bed early, and warning bystanders. Awareness of device status did not cause heightened anxiety statistically or anecdotally.

Unexpectedly, the seizure advisory system provided insights into clinical management. Patient 7's algorithm did not meet enabling criteria and thus the patient did not proceed to the advisory phase, but EEG recorded by the system located a previously unidentified focal cortical dysplasia, which subsequently was successfully resected. Patient 12's seizure reporting differed substantially from the pattern shown by recorded EEGs, and subsequent inpatient video-EEG showed that several events were psychogenic. In patient 3, who reported drowsiness and impaired cognitive function in the morning that were previously thought to be caused by drugs, monitoring showed that these effects were probably caused by the 10–20 seizures she was having each night. Study investigators reviewed all seizure detection events to reduce the introduction of false-positive seizures during algorithm training and assessment.

Disparities in seizure frequency between patients' pre-enrolment estimates, seizure diaries during the study, and EEGs were often substantial. This relation varied highly from month to month, preventing the hypothetical application of a correction factor. Studies[33–35] of monitored inpatients have shown that more seizures occur than patients are typically aware of, but anticipation of how this finding would translate to the ambulant setting has been difficult. Our findings have pronounced implications for trials of new epilepsy treatments, which often rely on patient-reported events as the primary efficacy endpoint.

Three patients, two of whose advisory systems had to be removed, had noteworthy procedure-related complications—a similar complication rate to that described for devices such as implantable deep brain stimulators for Parkinson's disease (a meta-analysis[36] has shown hardware-related and infection-related complications in an estimated 17% of patients). Intracranial electrodes of the type used in our study have previously been used in long-term studies of epilepsy[37] and were not reported to be associated with any specific complications. Although uncommon, the development of thick fibrotic capsules after device removal has been identified in patients undergoing deep brain stimulation and is referred to as tethering.[38]

Our small proof-of-concept study shows that seizure prediction is possible and could lead to new therapeutic strategies and more independence for individuals with epilepsy.

Contributors

MJC, TJO'B, and SFB were the principal investigators and had roles in day-to-day management of the study and recruitment and assessment of patients. MM, AM, GF, WD'S, RY, JA, LL, SH, and PL were trial investigators and had roles in day-to-day management of the study and recruitment and assessment of patients. DH, KL, and DS had roles in study design and data analysis. VR helped with data analysis. WDS had a role in study design. MJC, TJO'B, SFB, DH, and KL wrote the Article.

Conflicts of interest

DH, VR, WDS, KL, and DS are employees of NeuroVista. The other authors declare that they have no conflicts of interest.

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