Epilepsy & Behavior 37 (2014) 291–307

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy

Sriram Ramgopal [a,b], Sigride Thome-Souza [a,c], Michele Jackson [a], Navah Ester Kadish [a,i], Iván Sánchez Fernández [a], Jacquelyn Klehm [a], William Bosl [d], Claus Reinsberger [e,g,h], Steven Schachter [f], Tobias Loddenkemper [a,*]

[a] Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Boston, MA, USA
[b] Department of Pediatrics, Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[c] Psychiatry Department of Clinics Hospital of School of Medicine of University of Sao Paulo, Brazil
[d] Department of Health Informatics, University of San Francisco School of Nursing and Health Professions, San Francisco, CA, USA
[e] Edward B. Bromfield Epilepsy Center, Dept. of Neurology, Brigham and Women's Hospital, Boston, MA, USA
[f] Department of Neurology, Harvard Medical School, Boston, MA, USA
[g] Institute of Sports Medicine, Department of Exercise and Health, Faculty of Science, University of Paderborn, Germany
[h] Institute of Sports Medicine, Faculty of Science, University of Paderborn, Warburger Str. 100, 33098 Paderborn, Germany
[i] Department of Neuropediatrics and Department of Medical Psychology and Medical Sociology, University Medical Center Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany

ARTICLE INFO

Article history:
Received 17 April 2014
Revised 4 June 2014
Accepted 10 June 2014
Available online 29 August 2014

Keywords:
Accelerometry
Artificial neural network
Automated seizure detection
Closed-loop methods
ECG-based seizure detection
EEG-based seizure detection
Fourier
Higher-order spectra
Markov modeling
Support vector machine

ABSTRACT

Nearly one-third of patients with epilepsy continue to have seizures despite optimal medication management. Systems employed to detect seizures may have the potential to improve outcomes in these patients by allowing more tailored therapies and might, additionally, have a role in accident and SUDEP prevention. Automated seizure detection and prediction require algorithms which employ feature computation and subsequent classification. Over the last few decades, methods have been developed to detect seizures utilizing scalp and intracranial EEG, electrocardiography, accelerometry and motion sensors, electrodermal activity, and audio/video captures. To date, it is unclear which combination of detection technologies yields the best results, and approaches may ultimately need to be individualized. This review presents an overview of seizure detection and related prediction methods and discusses their potential uses in closed-loop warning systems in epilepsy.

1. Introduction

Epilepsy is one of the most common neurological disorders and occurs with an incidence of 68.8/100,000 person-years [1]. The age-adjusted incidence of epilepsy is estimated to be 44/100,000 person-years [2]. Despite the introduction of new antiepileptic drugs in the last decades, one-third of people with epilepsy continue to have seizures despite treatment [3]. However, even when seizures are well controlled, self-reported quality of life is significantly lowered by the anxiety associated with the unpredictable nature of seizures and the consequences therefrom [4].

Some of the difficulties in managing treatment-refractory epilepsy can be ameliorated by the ability to detect clinical seizures. This information might be useful both in developing accurate seizure diaries and in providing therapies during times of greatest seizure susceptibility. The ability to rapidly and accurately detect seizures could promote therapies aimed at rapidly treating seizures. The capability to detect seizures early and anticipate their onset prior to presentation would provide even greater advantages. These early detection and prediction systems might be able to abort seizures through

Abbreviations: SVM, support vector machine; ANN, artificial neural network; PCA, principal component analysis; SEN, sensitivity; SPEC, specificity; FPR, false-positive rate; PPV, positive predictive value.

* Corresponding author at: Harvard Medical School, Division of Epilepsy and Clinical Neurophysiology, Fegan 9, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115, USA. Tel.: +1 617 355 2443; fax: +1 617 730 0463.
E-mail address: tobias.loddenkemper@childrens.harvard.edu (T. Loddenkemper).

http://dx.doi.org/10.1016/j.yebeh.2014.06.023

Table 1
Selected seizure detection systems.

Author, year	Measuring device/seizures detected	Detection algorithm	Results
Electroencephalography/electrocorticography			
Webber, 1996 [5]	EEG (24–40 channels)/seizures not stated	ANN classification system	SEN of 76% and FPR of 1 event/h
Pradhan, 1996 [6]	EEG (8 channels)/seizures not stated	Wavelet transformation feature acquisition, ANN classification	SEN of 97% and SPEC of 89.5%
Gabor, 1998 [7]	EEG (8 channels)/seizures not stated	Self-organizing neural network with unsupervised training	SEN of 92.8% and FPR of 1.35 events/h
Wilson, 2004 [8]	EEG (8–32 channels)/seizures not stated	Combined algorithm (utilizes matching pursuit, small neural networks, and clustering algorithm)	SEN of 76% and FPR of 0.11 events/h
Wilson, 2005 [9]	EEG (single channel selected)/CPS, secondary GS and primary GS	Used a trained probabilistic neural network for rapid detection of seizures	SEN of 89% and FPR of 0.56 events/h
Alkan, 2005 [10]	EEG (4 channels)/absence seizures	Comparison of linear regression systems and ANN classification systems	ANN-based systems found to be greater. ANN-based system provided greater accuracy compared with linear regression
D'Alessandro, 2005 [11]	Intracranial EEG/seizures not stated	Genetic algorithm for signal processing, probabilistic neural network for classification	100% prediction of seizures within 10 min prior to onset
Arabi, 2006 [12]	EEG/neonatal seizures	Used linear correlation feature selection methods and back propagation neural network for classification. Used in detection of neonatal seizures	SEN of 91% and FPR of 1.17 events/h
Casson, 2007 [13]	Ambulatory EEG	Continuous wavelet transform	Over 90% of spike detection
Chan, 2008 [14]	Intracranial EEG/PS	SVM system	SEN of 80–98%, FPR of 38%
Netoff, 2009 [15]	EEG (6 channels)/PS	Cost-sensitive SVM system	SEN of 77.8%, no false positives detected
Chua, 2009 [16]	EEG/PS	Data processing by higher-order spectra analysis followed by classification by the Gaussian mixture model or SVM	Accuracy of 92–93%
Mirowski, 2009 [17]	EEG/PS	Variable feature extraction methods used followed by patient-specific machine learning-based classifiers	Convolutional networks combined with wavelet coherence yielded sensitivity of 71% and no false positives
Sorensen, 2010 [18]	EEG (3 channels)/GTCS, SPS, CPS	Features classified by matching pursuit algorithm and classified by SVM	SEN of 78–100 and FPR of 0.16–5.31 events/h
Chisci, 2010 [19]	EEG (multichannel)/focal seizures	Least-squares parameter estimator for extraction followed by SVM classification	SEN of 100%
Peterson, 2011 [20]	EEG (single channel)/absence seizures	Wavelet transform followed by SVM classification used to detect absence seizures using single-channel EEG	SEN of 99.1% and PPV of 94.8%
Temko, 2011 [21]	EEG (8 bipolar)/neonatal seizures	Fast Fourier transform used for feature extraction followed by SVM classification. Used to detect neonatal seizures	SEN adjustable, with 89% SEN yielding one false detection/h
Acharya, 2011 [22]	EEG/seizures not stated	Higher-order spectra-based feature extraction followed by SVM	Detection accuracy of 98.5%
Kharbouch, 2011 [23]	Intracranial EEG/focal epilepsy	Multistep feature extraction system followed by SVM classifier, individualized for patients	Detected 97% of seizures, FPR of 0.6 events/day
Liu, 2012 [24]	Intracranial EEG/GTCS, SPS, CPS	Wavelet decomposition-based feature extraction followed by SVM classification	SEN of 94.5% and SPEC of 95.3%
Xie, 2012 [25]	EEG (6 channels)/focal seizures, others not stated	Feature extraction by wavelet-based sparse functional linear model and 1-NN classification method	Has 99–100% classification accuracy
Direito, 2012 [26]	EEG (multichannel)/focal seizures	Markov modeling classification system. Identified four states — preictal, ictal, postictal, and interictal	Point-by-point accuracy of 89.3%
Rabbi, 2012 [27]	Intracranial EEG/GTCS, SPS, CPS	Used fuzzy algorithms for feature extraction for classification	SEN of 95.8% and FPR of 0.26 events/h
Implanted advisory system			
Cook, 2013 [28]	Intracranial implanted device/partial-onset seizure	Cluster computing system at NeuroVista (one algorithm for each patient)	SEN of 65%–100%
Electromyography			
Conradsen, 2010 [29]	Features extracted from surface electromyography acceleration and angular velocity/seizure-like movements performed by healthy volunteers	Classification based on SVM	SEN of 91–100% and SPEC of 100%
Conradsen, 2012 [30]	Electromyography and motion sensor features/motor seizures, seizure-like movements performed by healthy volunteers	Discrete wavelet transformation/wavelet packet transform techniques used to extract features. SVM classification system	Evaluated healthy subjects simulating seizures. SEN of 91–100% and SPEC of 100%

Electrocardiogram			
Greene, 2007 [31]	ECG/newborn seizures	Processing of 41 heart timing variables	SEN of 62.2% and SPEC of 71.8%
Malarvili, 2009 [32]	ECG/newborn seizures	Utilizes heart rate from ECG and classifies using statistical methods seizures from nonseizure events	SEN of 85.7% and SPEC of 84.6%
Jeppesen, 2010 [33]	ECG/temporal lobe epilepsy	Time–frequency features from ECG extracted followed by wrapper-based feature selection technique.	Reciprocal power peaks from 10 s preictal to 24 s postictal were 2.96–93.63 times higher than in control
Doyle, 2010 [34]	ECG/newborn seizures	SVM-based classifier using features extracted from heart rate variability	SEN of 60% and SPEC of 60%
Accelerometry			
Nijsen, 2005 [35]	3-D accelerometers used on both legs and arms and on the chest/myoclonic, tonic, tonic–clonic, startle, SPS, CPS	Patterns for simple motor seizures ascertained based on visual inspection of data	Typical seizure patterns were noted in 95% of motor seizures
Nijsen, 2007 [36]	3-D accelerometers used on both legs and arms and on the chest/myoclonic, clonic, and tonic seizures	Use of linear threshold function to determine the presence of nocturnal seizures	SPEC of 100% and PPV of 52–93%
Cuppens, 2009 [37]	3-D accelerometers on wrists and ankles/frontal lobe seizures with motor manifestations	Algorithm uses standard deviations of moving epochs and uses moving average filter to detect nocturnal frontal lobe seizures	SEN of 91.7% and SPEC of 83.9%
Nijsen, 2010 [38]	3-D accelerometers and video-EEG used on both legs and arms and on the chest/myoclonic, clonic, tonic seizures, and CPS	Short-time Fourier transform, Wigner distribution, continuous wavelet transform, and model-based matched wavelet transform	Short-time Fourier transform: SEN of 71% and PPV of 16%. Using Wigner distribution: SEN of 34% and PPV of 15%. Using continuous wavelet transform: SEN of 80% and PPV of 16%. Using model-based matched wavelet transform: SEN of 80% and PPV of 15%
Lockman, 2011 [39]	Single 3-D accelerometer worn on the wrist/tonic–clonic seizures	Pattern recognition algorithm detects seizure events	Detects tonic–clonic seizures. SEN of 87.5%. 204 false positives
Kramer, 2011 [40]	Single 3-D accelerometer worn on the wrist/tonic, GTCS	Time domain- and frequency domain-based algorithm	Identified 91% of clonic or tonic, tonic–clonic, or secondarily generalized seizures
Van de Vel, 2012 [41]	One 3-D accelerometer on each limb/hypermotor seizures	Movement detection system followed by feature extraction	SEN of 96% and PPV of 58%
Dalton, 2012 [42]	Accelerometer-based kinematic sensor/DTW algorithm	Motor patterns of epileptic seizures	SEN of 91% and SPEC of 84%
Beniczky, 2013 [43]	Single 3-D accelerometer worn on the wrist/GTCS	Time domain- and frequency domain-based algorithm	SEN of 91% and FPR of 0.2 events/day
Video detection systems			
Karayinnis, 2004 [44]	Video segments of seizures/neonatal myoclonic and focal clonic seizures	Neural network model	SEN > 90%, SPEC > 95%
Cuppens, 2010 [45]	Epilepsy monitoring unit-derived video segments/GTCS	Optical flow algorithm	Detection of seizures from video recordings using trial in pediatric nighttime seizures
Cuppens, 2012 [46]	Nocturnal video	Spatiotemporal interest points	SEN of 75% and PPV of 85%
Lu, 2013 [42]	Quantify limb movements	Gaussian mixture models	Performance compared with EEG
Mattress sensor			
Carlson, 2009 [47]	Microphone under mattress/tonic–clonic seizures	Activated by tapping noises/bedspring noises. Designed to detect nocturnal seizures	SEN of 62.5% and SPEC of 90.4%
Narechania, 2011 [48]	Quasi-piezoelectric sensor/tonic–clonic seizures	Activated by rhythmic movements	Detected 80% of seizures, 14 false alarms occurred during periods of patient wakefulness
Audio classification			
Bruijne, 2009 [49]	Signal enhancement, audio analysis, and classification	Seizure classification based on temporal and spectral sounds	Good performance for sounds during and after seizures
Seizure-alert dogs			
Strong, 1999 [50]	Trained dog	Elicits behaviors (barking, pawing) minutes prior to seizures	Anecdotal evidence of seizure giving warnings from 15 to 45 min prior to seizure onset

AAN: artificial neural networks; CPS: complex partial seizures; GS: generalized seizures; GTCS: generalized tonic–clonic seizures; PS: partial seizures; SPS: simple partial seizures; SVM: support vector machine; SEN: sensitivity; SPEC: specificity; FPR: false-positive rate; PPV: positive predictive value.

targeted therapies. Such systems would also be able to prevent accidents and limit injury.

This article describes currently available detection and prediction systems for epileptic seizures. We explore the potential application of such systems in ambulatory monitoring and closed-loop models for individual patient care. We also describe how population-based prediction algorithms may be used to formulate prediction models to anticipate seizures.

2. Seizure detection

Seizure detection systems are capable of detecting ongoing seizures and provide clinicians with detailed seizure data useful for the management of epilepsy. Closed-loop systems built around seizure detection might also be able to provide rapid therapy in response to seizures early in their clinical onset, thereby limiting the complications or potentially arresting the spread of seizures.

A seizure detection system must be able to determine the presence or absence of ongoing seizures. A variety of algorithms of different biometric signals can do this even prior to clinical onset of a seizure (Table 1). All seizure detection algorithms involve two main steps. First, appropriate quantitative values or features, such as EEG features, movements, or other biomarkers, must be computed from the data. Second, a threshold or model-based criteria must be applied to the features to determine the presence or absence of a seizure. This second step, called classification, might be as simple as thresholding a value or might require models derived from modern machine learning algorithms [51,52]. Features are computed in a manner that is generally a compromise between the need for speed and the need for detection accuracy and might be preceded by a preprocessing or filtering step (Table 2; for further details, please refer to supplementary document). Derivation of a model from machine learning algorithms is done during a training phase and involves three substeps: preprocessing or filtering, feature computation, and feature reduction or feature extraction (Fig. 1). Each of these processes is a field of active, specialized research and will not be elaborated further here [66]. Derivation of appropriate features for seizure detection depends on the physiological data that are measured. It is helpful to keep in mind that the training or supervised learning phase involves the following steps that are carried out separately on previously recorded data from a large population:

1. Feature computation
   a. Preprocessing or filtering
   b. Feature computation
   c. Feature reduction or extraction
2. Training or supervised learning: During this step, model parameters that determine criteria for the presence or absence of seizures are computed. The criteria might apply to a whole population of patients, to specific subpopulations, or to individual patients. This step involves considerable computation and is performed offline before implementation for real-time seizure detection. It can also be updated as more data are collected.

Real-time classification requires computation of signal features, followed by computation of the classification outcome from the previously learned model. This step must be optimized for speed to be useful. Some of the most common algorithms for each of these steps are discussed below in the setting of EEG recordings.

2.1. EEG and electrocorticography

Measurements of brain electrical activity with EEG have long been one of the most valuable sources of information for epilepsy research and diagnosis, yet this rich resource may still be underutilized. Electroencephalography carries a large amount of complex information that is valuable in detecting ongoing seizures. Automated methods of EEG analysis are emerging from the concept that normal brain dynamics, which involve limited, transient synchronization of disorganized neural activity, evolve into a persistent, highly synchronized state that incorporates large regions of the brain during epileptic seizures [67]. While EEG provides a great wealth of data that can be interpreted via automated

Table 2
Analytic methods for seizure detection.

Feature computation	
Line length	Fast algorithm to compute the sum of vertical change time windows. Sensitive to variations in EEG signal, amplitude, and frequency [53].
Frequency or Fourier analysis	Identify frequencies related to seizure activity. This method has a training phase involving EEG examination to determine the magnitude ratio and time length associated with seizures. Can be tailored to suit individual patient profiles [54].
Wavelet transformations	A filtering process that can be used to decompose time series into components [55]. A wavelet decomposition results in components at multiple levels of resolution (computational microscopes) [56]. This system has been evaluated in both intracranial and surface EEG recordings [13,57,58].
Principal component analysis (PCA)	Identify the set of principal components using orthogonal transformation and sorted by variance. Real-time or "dynamic" PCA is computing principle components quickly in sliding window of features [59].
Higher-order spectra analysis	Similar manner to spectral decomposition to compute features of the EEG signal. High predictive value in the identification of normal, interictal, and ictal EEGs [22].
Classification methods	
Support vector machines	A method that includes data transformed by a nonlinear kernel function to find complex relations among features separating classes of interest. Variations have been developed for classifying different types of ictal events from within patients [60].
Artificial neural networks	Originally inspired by models that attempted to emulate biological neural networks [51,61]. Linear features include amplitude, slope, curvature, rhythmicity, and frequency of EEG components [5].
Fuzzy logic models	Many-valued logic method which incorporates multiple variables and gives output as a gradient rather than a simple binary function. Initially designed to mimic human control logic. Relies on empirically based algorithms. Widely used in systems engineering and is finding new uses in many medical applications [62–64].
Markov modeling	A prediction or classification algorithm used to predict the transition from one state to another, such as preictal to ictal. In the learning phase, a time sequence of features is computed for the EEG signal, and the Markov model is built [65].
Learning system	
AutoLearn system	It is software that uses an artificial neural network classifier with spectral features to detect seizures. The use of an individualized machine learning system used to overcome interindividual and intraindividual heterogeneity in focal seizures resulted in a 97% detection rate [23].

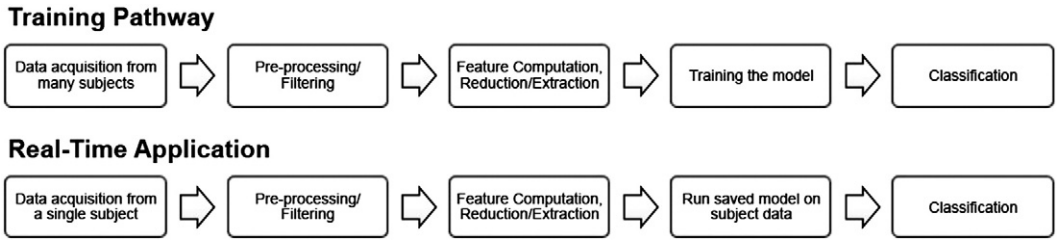

Fig. 1. Steps involved in feature extraction and classification for seizure detection and prediction. Seizures are detected using a sequential process of steps. During the training phase, features are computed from a large number of patients to optimize the model. During the implementation phase, real-time data are acquired from an individual patient, and features are computed. Data from the saved model are applied for classification.

methods, it can be difficult for patients to wear the EEG electrodes for prolonged periods of time, and prolonged surface electrode recordings may become difficult to read because of increasing impedance. Additionally, some patients may develop skin abrasions due to prolonged exposure to surface electrodes.

2.2. ECG

Epileptic seizures can cause short-term and long-term heart rate disturbances [53]. Changes in heart rate and conduction have been shown to be important autonomic biomarkers in epilepsy, as well as play a pivotal role in SUDEP pathophysiology. Tachycardia can occur prior to and during complex partial and tonic–clonic seizures, which might be related to discharges in the right insular cortex [68]. An evaluation of ECG changes in a cohort of 58 patients found that tachycardia occurred during the seizures in more than 85% of patients [69]. Ictal tachycardia is particularly noted in cases of generalized tonic–clonic epilepsy and temporal and frontal lobe epilepsies [69,70]. Importantly, tachycardia has been noted to precede seizures in some patients with temporal lobe epilepsy and, thus, might be useful in seizure prediction [71,72]. On the other hand, bradycardia seems to be involved with a nonclear brain network [73], sometimes with involvement of the left hemisphere (insular cortex and amygdala) [74]. Bradycardia and conduction disorders were also observed in temporal lobe seizures leading to secondary syncope [75]. Postictal hypotension has been shown to be another important autonomic biomarker measure with strict correlation with postictal generalized EEG suppression after generalized tonic–clonic seizures [76].

The utilization of cardiac cues in seizure detectors has been most commonly applied to newborns, in whom signs of seizures are subtle [77,78]. Because EEG use in newborns is difficult and requires specialist interpretation, adjunct systems based on changes in heart rate might be particularly useful in neonatal intensive care units. Computing features from ECG signals can require several steps, just as in EEG analysis. A promising approach computes heart rate using an automatic QRS detection algorithm from which various spectral features are calculated. A two-phase wrapper-based feature selection technique is then applied to rapidly reduce the feature set. Three classification schemes were tested, including a linear discriminator and k-nearest neighbor method, for classifying the reduced feature set. The system achieved sensitivities and specificities of greater than 85% [32].

The use of cardiac-based seizure warning systems in older individuals is complicated by complex changes in the ECG that occur in physiological and pathological conditions, such as exercise, emotional states, disease states, and in response to the 24 h circadian rhythm. Nonetheless, the system carries potential. In a limited study of six patients with temporal lobe epilepsy, power spectral analysis of heart rate variability demonstrated the ability of such a system to provide warnings. In some detected seizures, the algorithm was activated prior to clinical seizure onset, indicating that this method may be useful as a seizure predictor [33]. A closed-loop system based on ECG detection systems using VNS as an output mechanism is currently under evaluation (http://clinicaltrials.gov/ct2/show/NCT01325623). Results from this study have been announced by the sponsor (http://www.marketwatch.com/story/cyberonics-announces-results-from-the-e-36-study-of-vns-therapy-delivered-by-the-aspiresrtm-generator-2013-12-08).

2.3. Accelerometry

Accelerometers are devices that detect changes in velocity and direction. The so-called "3-D accelerometers" are capable of detecting changes in the x, y, and z planes. The use of motion sensors in seizure detection is relatively new. These systems may serve in the detection of motor seizures, such as tonic–clonic or myoclonic seizures. Accelerometers are only useful in the detection of ongoing seizures. Specificity may also be a problem, as many sudden motions, such as stumbling, may be similar to seizure movements.

The first actigraphs were applied in a pilot trial of 18 patients, reported in 2005, and these relied primarily on expert interpretation of the recording system [35]. In this study, Cluitmans and colleagues used motion sensors on the wrists, ankles, and chest and were able to detect 48% of seizures.

The SmartWatch, manufactured by Smart Monitor, Inc. (www.smart-monitor.com), is a similar device that can be worn on the wrist or ankle and utilizes pattern recognition and feature analysis in its built-in seizure detection algorithm. The SmartWatch can also synchronize with a smartphone application (app) via Bluetooth to transmit seizure data to the user's mobile phone. The app can then contact caretakers to alert them of ongoing seizures. In a pilot study, 7 out of 8 tonic–clonic seizures were detected [39]. Using our previous language for seizure detection and classification, the velocity, acceleration, and other data provided by motion sensors are either used as feature data directly or are computed into secondary features. Classification algorithms, as discussed above, are then trained to distinguish normal movements from seizure movements. An active cancel button can be used to decrease false-positive results over time.

A recent prospective trial evaluated the use of another three-dimensional accelerometer, the Epi-Care Free device (Danish Care Technology ApS, Sorø, Denmark). The device is worn as a wristwatch and contains a three-dimensional accelerometer and a transmitter that can send real-time accelerometric information to a control unit. In a prospective trial in 20 patients who had 39 generalized tonic–clonic seizures during the trial period, the system was able to detect 35 (89.7%) seizures. The device had a false-positive rate of 0.2 seizures/day [43].

Accelerometers have also been evaluated in other types of motor seizures. Further refinements by Cluitmans and colleagues in detection algorithms improved the sensitivity and decreased the false-positive rate in the detection of nocturnal [36] and myoclonic seizures [38,79]. These systems used linear threshold, time-scale, and time–frequency functions. When compared with video-EEG results and different accelerometers for the detection of nocturnal hypermotor seizures, the wristwatch was found to have a sensitivity of over 90% [41,80].

Ep Detect (www.epdetect.com) is a smartphone app designed to capture tonic–clonic seizures using the device's built-in accelerometer. The app is currently in beta testing.

Use of accelerometry carries a number of drawbacks. Most obviously, it can only be used in a select portion of seizures that have well-defined motor activity. Distinct patterns have been determined by Cluitmans for myoclonic, tonic, tonic–clonic, clonic, and complex motor seizures [35]. Additionally, trials of accelerometry often have high false-positive rates [36,39], presumably, because of various nonseizure movements, such as stumbles, sports or video games, which create motion data that cannot yet easily be distinguished from seizures. As with EEG and ECG data, this could be due to inherent limitations in the data themselves, or, perhaps, better learning algorithms will be able to find subtle distinctions between seizure and nonseizure motions. Accelerometry might be useful in predicting motor seizures and has the advantage that sensors can be worn relatively unobtrusively, i.e., on the wrist or ankle, instead of wearing electrodes on the head as required for EEG recordings.

2.4. Video detection systems

A variety of models have been developed to detect seizures using video monitoring. Video systems analyze a variety of elements in order to detect seizures. Motion trajectory methods are based on the path of moving objects through space over time. Other elements used in analysis include velocity, area, angular speed, and duration [81]. Some of the video analysis techniques are based on the use of markers, which use detectable objects worn on joints and extremities of patients [82]. Marker-free methods have also been developed and have been tried in newborn, pediatric, and adult groups [37,44,45,83]. Current video detection systems are limited by the area that is covered by the video camera and by the inability of detectors to capture events which occur when patients are obscured from view, such as under covers.

2.5. Mattress sensor

The MP5 mattress monitor (Medpage Ltd., UK) is designed to detect seizures occurring during sleep. Placed between the mattress and box spring, the microphone in the monitor detects tapping and spring noise and has an adjustable sensitivity. In a study of 64 subjects having 8 tonic–clonic seizures, the system was capable of detecting 5 (62.5%) events. The device suffered from a poor positive predictive value of 3.3%. Its high negative predictive value of 99.8%, however, may give patients with these seizures a greater sense of security [47].

The Emfit movement monitor (Emfit Ltd., Finland) is a quasi-piezoelectric seizure detector placed under the mattress system that can alert caregivers to unexpected motor activity. The system also utilizes a bedside monitor. In a trial with 22 patients, the system was able to detect 80% of seizures [48].

2.6. Baby monitors

Baby monitors typically use a night-vision camera, a microphone, and, often, a Wi-Fi connection. Baby monitors have been used by parents to increase the awareness of potential seizures, such as in the Baby Ping system (www.babyping.com). They have not been employed to date in an automated seizure warning system.

2.7. Other seizure detection systems

The potential for seizure-alert dogs to detect seizures is supported by anecdotal evidence [50], and such dogs might even decrease the frequency of seizures in some patients [84]. Based on available studies, dogs can detect seizures after seizure onset and alert others, but dogs are not reliable in seizure prediction [85]. However, evidence is conflicting, and more research is needed to understand these findings and the means by which dogs might be able to detect oncoming seizures [86].

In-vivo experiments in rats using optical coherence tomography showed that near-infrared light could register the progression of seizures. This technique has been able to produce high resolution depth resolved cross-sectional images facilitating identification of changes in cortical tissue before and after seizures [87]. Another technique is near-infrared spectroscopy, a noninvasive method that has proven better than SPECT in detecting an epileptogenic focus [88]. Other methods by which seizure detection can be done include measurement of hormone levels [89], nonformed vocalizations, and extraocular movements.

3. Seizure prediction

Predicting seizures potentially carries even greater advantages compared with seizure detection. Such devices might be useful both in preventing accidents and in improving outcomes, ultimately allowing early treatment or even prevention of seizures. A survey of 141 patients with epilepsy found that more than 90% of respondents believed that the development of means to predict seizures was important. These patients voiced a preference for sensitivity over specificity in seizure prediction [90]. Prediction systems must be able to identify preictal changes that – if present – occur within minutes, hours, or days prior to seizures. Note that the features used to predict seizures in advance may or may not be the same as those used to detect the presence of a seizure.

3.1. EEG and electrocorticography

Electroencephalography changes preceding seizures can theoretically be detected to permit anticipation of oncoming seizures. The evaluation of EEGs from a series of patients with mesial temporal lobe epilepsy, for example, suggests that EEG changes can be noted as early as 7 h prior to seizure onset [91]. The first EEG-based attempts at identifying preictal patterns relied primarily on linear approaches for computing features of the EEG on a sliding window [92,93]. These models gave way to nonlinear signal processing methodologies, which analyzed the spontaneous formation of spatial, temporal, and spatiotemporal patterns.

Seizure prediction based on real-time EEG presents a number of challenges compared with retrospective methods of EEG analyses. Algorithm-based EEG analysis is complicated by the fact that EEG manifestations of seizures differ widely between patients and even within the same patient. Techniques which interpret EEG findings to provide seizure predictions utilize a variety of different strategies for feature calculation and supervised learning.

Various features have been computed from EEG time series in order to detect changes immediately prior to the onset of seizures. These include some of the more traditional frequency-based methods discussed below, as well as more recent measures derived from complex system theory. For example, permutation entropy was found to change significantly up to 5 s before seizure onset in rat models of absence epilepsy [94]. Kolmogorov entropy, correlation dimension [95], relative wavelet energy [96], and approximate entropy [97] have all demonstrated some success for detecting preseizure onset periods but could not distinguish healthy controls from people with epilepsy during seizure-free periods. Mixed results have been reported for automated seizure detection algorithms based on four different measures (principal eigenvalue, total power, Kolmogorov entropy, and correlation dimension). The algorithms were found to be patient age-specific, and no one algorithm performed well on all patients [98]. These studies strongly suggest that the information contained in EEG data relevant to seizure

detection has not yet been fully exploited, and continued research is needed. Alternatively, individual patient-based detector training may be necessary to increase sensitivity and specificity.

Many of the above mentioned techniques have been applied towards identifying a preictal phase which can be used in seizure prediction. In one study, higher-order spectral features computed from a sample of 300 EEGs displayed unique ranges for normal, preictal, and seizure classes that could be used for seizure prediction [99]. Trials with recurrent neural networks have detected preictal stages which occur minutes before clinical seizures [100]. Another study, utilizing probabilistic neural networks, was able to predict 100% of seizures within a 10-minute prediction horizon [11]. Cost-sensitive SVM are a modification of the traditional SVM that can be employed to give different weights to different classes of information, a system that could be useful in the differentiation of interictal and preictal activities. A prospective study used a cost-sensitive SVM to classify linear features computed from a frequency decomposition of the EEG. Results from 9 patients with 45 seizures found this approach to have a sensitivity of 78% and a zero false-positive rate [15]. Trials evaluating fuzzy logic systems for seizure prediction are underway [27,101].

While the majority of research in seizure warning systems has focused on EEG-based methods for seizure detection, this approach implies a number of limitations. Currently available systems suffer from poor sensitivity and specificity, though these systems are constantly being refined. Few of these methods have been tested prospectively. It is not yet known if the limits of seizure detection with EEG are due to inherent limits in brain electrophysiology, EEG hardware quality, or algorithms used to analyze these data. New features that are highly predictive of seizure onset may be found. Additionally, better classification algorithms will identify novel patterns within known features. Very large numbers are needed to find subtle patterns in EEG features and to assess the accuracy of these seizure detection methods. Studies with smaller numbers may report higher numbers of false-positive conclusions [102]. The use of EEG in the outpatient setting for long durations is poorly tolerated by most patients, though this may be partially alleviated by the use of electrocorticography.

3.2. Electrical probing of cortical excitability

Electrical probing is able to actively test brain excitability by means of stimulation and recording of the response, thereby providing measures of the excitability of the stimulated cortex. [103]. Specifically, a transcranial magnetic or electrical probe is used to deliver a stimulus to the brain, and the transient or steady-state response is measured. The signal is then processed, and the neural excitability is estimated by extracting a feature of EEG responses using the mean phase variance, meaning the variation in the instantaneous frequency of the responses. In a limited trial carried out in two patients, the technique was demonstrated to have features which vary with the sleep/wake state, interictal discharges, and epileptic seizures.

3.3. Long-term implanted advisory system

Intracranial electroencephalography in patients with refractory epilepsy has been developed as a feasible tool in seizure prediction in ambulatory patients. An Australian group [28] implanted 15 patients with a seizure advisory device and found high rates of sensitivity, ranging from 65 to 100%, with no significant impact on quality of life, severity of seizures, and measures for anxiety and depression disorders.

4. Combined methods for seizure detection

Multiple applied methods can be used to further improve the sensitivity and specificity of seizure detection. The general approach is similar to that used with individual data sources: first, features must be computed from the measured quantities; second, simple thresholding or a more extensive training process must be used with real data to determine how the features can be used to detect or predict seizures. The thresholding process, when using multiple data sources, can provide a higher degree of resolution in detecting events. Combinations of seizure detection methods could possibly be individualized for patients to provide optimal seizure detection. A number of trials have evaluated combined systems on seizure detection (Table 3).

4.1. Combined EEG systems

Seizure detection systems may implement a variety of methods for computing signal features, reducing the feature set or creating new features. One or more classification or learning algorithms might be used to determine how to map the features to the patient's state, and to elicit whether a binary classification (seizure/no seizure) or a more refined classification (normal, preictal, ictal, and postictal, for example) is more appropriate. The use of too many features can result in reduced prediction accuracy due to the 'curse of dimensionality' [51]. Determination of the best features and the best classification methods is an area of active research. A hybrid classification system, called EPILAB, is MATLAB-based software that attempts to use multiple algorithms to anticipate seizures. The system utilizes algorithms from univariate (single-EEG channel) and multivariate (multiple EEG channels) data [107]. Trials studying the predictive value of this system are underway (www.epilepsiae.eu), and software is publically available.

4.2. Combined accelerometry and electrodermal activity methods

The use of electrodermal activity has recently been attempted in seizure detection. Sweat secretion during seizures is thought to relate to changes in sympathetic activity [108]. Additionally, autonomic changes may correlate with postictal suppression on EEG [109]. The use of electrodermal activity has been applied in a biofeedback system in adult epilepsy and has shown promising results [110]. The use of a wearable device to monitor both electrodermal activity and accelerometry has been attempted for seizure detection (Fig. 2). Data from both sensors are used to compute a larger set of features that are then used to train

Table 3
Methods utilizing a combination of more than one data input for seizure detection.

Author, year	Measuring devices	Algorithm	Results
Greene, 2007 [104]	Retrospective review of EEG/ECG data/infant seizures	Both patient-specific and patient-independent algorithms using statistical classifier methods	Patient-specific system — SEN of 98% and FPR of 13.2%; patient independent system — SEN of 81% and FPR of 29%
Shoeb, 2009 [105]	Combined EEG and ECG data/simple partial, complex partial, and generalized seizures	Patient-specific detector with adaptive ECG algorithm	Detected all seizures, FPR of 0.4 events/h
Poh, 2012 [106]	Wrist band sensor utilizes accelerometric data and conductance/generalized tonic–clonic seizures	Generalized tonic–clonic seizures detected via SVM	SEN of 94% and FPR of 0.74 events/day

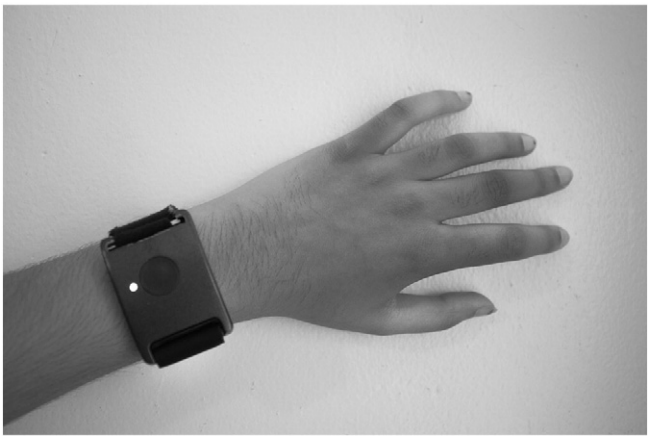

Fig. 2. A wristband sensor measures a combination of accelerometric and electrodermal data. The combination of accelerometric and electrodermal activity provides superior sensitivity than any single system used alone. The device is currently being tested as a seizure detection system.

a classification algorithm, such as an ANN or SVM. One such system used 19 features, including time, frequency, and nonlinear measures [111]. In a trial conducted on a series of 80 patients, seven of whom had generalized tonic–clonic seizures, the combined electrodermal and accelerometry system was able to correctly identify 94% of such seizures using an SVM to classify the feature set. The system had a false-positive rate of 0.74 seizures over 24 h and was able to detect seizure onset on an average of 31 s following clinical seizure manifestations [106]. The use of electrodermal activity, in addition to accelerometry, provides additional sensitivity compared with models that utilize the latter alone [106]. Further studies will need to be done to assess the viability of these models in the outpatient setting.

4.3. Combination of ECG and EEG data

Seizure detection systems utilizing both ECG and EEG data have been developed. The EPILAB system, for example, is able to incorporate both ECG and EEG data [107]. In a retrospective study evaluating the detection of newborn seizures, extraction of both EEG and ECG features provided a high degree of accuracy [112].

Another study utilized an ECG-based and an EEG-based system to demonstrate the potential of these two modalities to complement each other. The study, performed on patients undergoing inpatient video-EEG, utilized trained seizure detection algorithms with features computed from patient-specific data. As with all supervised learning algorithms, prior training is required with data segments that have been labeled by a neurologist who is able to differentiate ictal and nonictal events. Detected seizure events activated a vagal nerve stimulator, which can potentially arrest seizure activity. A limited trial of the system was performed on a series of five patients undergoing video-EEG with simple partial, complex partial, and generalized seizures. The system was able to detect 5/5 seizures and had a false-positive rate of one every 2.5 per h [105].

The pros and cons of the detection and prediction methods for epilepsy described in this manuscript are detailed in Table 4, as well as the devices currently available or under research in Table 5.

5. Electronic seizure record applications

Several electronic mobile applications have been developed to electronically track seizure information, including type, frequency, and duration (Table 6). These electronic seizure record applications replace paper seizure logs and have become a tool to help patients, families, and clinicians capture accurate seizure data. Seizure record applications allow families to easily record seizures in an electronic format that is user-friendly, mobile, and easily accessed by their treating epileptologist.

Currently, there are several applications already available on the market. At the forefront, SeizureTracker (www.seizuretracker.com) and My Epilepsy Diary (http://www.epilepsy.com/seizurediary) are mobile seizure diary applications that track seizure activity, preevent and postevent activities, medication schedules, and appointments (Tables 6, 7). SeizureTracker and My Epilepsy Diary allow users to input seizure episode characteristics, such as seizure type, date, time, duration, frequency, medication, triggers, and mood. SeizureTracker also allows the user to record and upload seizure videos. Both applications provide detailed seizure reports, graphs charting seizure duration, frequency, and medication schedule, and have also developed a unique clinician portal system that allows the clinician to access the patient's seizure data online. Furthermore, SeizureTracker developed The Seizure Tracker Clinical Trial Monitoring Tool in collaboration with the Neurocognition in Tuberous Sclerosis Complex Clinical Trial (NCT01289912). The Seizure Tracker Clinical Trial Monitoring Tool is an electronic logging system that tracks multicenter enrollment.

Epi & Me (http://epiandme.com/), Epilepsia App (https://itunes.apple.com/us/app/epilepsia-app/id589429873?mt=8), Epilepsy Action (http://app.epilepsy.org.uk/), Epilepsy Guide App (https://itunes.apple.com/us/app/epilepsy-guide/id375345255), and Young Epilepsy (http://youngepilepsy.org.uk/all-about-epilepsy/epilepsy-app) are other mobile seizure diary applications. Epilepsy Guide App, Seizure Disorder Coach (http://resqrsoftware.com/seizure.php), Epilepsy Action, and Young Epilepsy are emergency guides that educate users on emergency steps that need to be taken during seizures (Tables 5, 6).

Table 4
Pros and cons of detection methods.

Method	Pros	Cons
Electroencephalography	Noninvasive with valuable data in detecting epileptic seizures.	Low spatial resolution (limited to seizures with EEG correlation).
Electrocorticography	Seizure prediction with 10 min of horizon and electrographic seizures.	Invasive procedure and follow-up in hospital environment.
Implanted advisory system	Seizure prediction with long-term EEG ambulatory monitoring using an algorithm for each patient.	Invasive procedure with serious adverse events.
Electromyography	Technique with high sensitivity and low false detection rate.	No studies with people with epilepsy. Only effective in some types of motor seizures.
Electrocardiogram	Narrow relation of tachycardia in periictal phase. On the other hand, bradycardia is sometimes observed in lateralization to left hemisphere.	Rhythmic cardiac changes can be observed in other physiological and pathological conditions, especially in older patients.
Accelerometry	Able to detect movement changes in x, y, and z planes. Used in seizures with motor component.	Any sudden movement can be registered as a seizure event.
Video detection systems	Feasible methods in recognizing kinematic patterns of seizure phenomena.	Limited to a subset of epileptic seizures.
Mattress sensor	Identification of nocturnal seizures, especially tonic–clonic seizures.	Presented a high negative predictive value (99.8%).
Audio classification	Good performance for a subset of patients who produce sounds during and after seizures.	Not applicable for patients who do not produce sounds during his/her seizures.
Seizure-alert dogs	Able to give alert before the seizures for recognition of specific changes in his/her owner.	Likely not monitoring patients while the dogs sleep; cannot distinguish between epileptic and nonepileptic seizures.

Table 5
Currently available devices.

Company	Brand name	Device type	Article published	Available on market	Signal processing	Website
ActiGraph	wGT3X, wActiSleep, GT3X, ActiSleep	Watch activity monitor	No	Yes	Triaxis, solid state accelerometer ambient light photodiode	http://www.actigraphcorp.com
Advanced Brain Monitoring	X series — EEG wireless monitoring	EEG headsets with 4 (×4), 10 (×10), or 24 (×24) channels	No epilepsy	Yes	Wireless EEG	http://advancedbrainmonitoring.com
Affectiva	Affectiva/Q Sensor	Wristband	Poh et al. [106,109,111,113] and Fletcher et al. [114]	Temporally interrupted	Electrodermal activity, triaxis accelerometer and body temperature	www.affectiva.com
Air Brain System/Kwansei Gakuin University	Air Brain System	Portable EEG telemetry system using 3G network with a smartphone	Honda et al. [115]	No	3G, Wi-Fi connection to smartphone	http://eudl.eu/doi/10.4108/icst.bodynets.2013.253918
Alert-It	Ep-It Companion Monitor (S1029)	Bed motion monitor (accelerometer under mattress)	No	Yes	Wireless to radio transmitter wired to nurse call, telephone dialer, or remote bell	http://www.alert-it.co.uk
	Ep-It Guardian Monitor (P139)	Bed motion monitor (accelerometer under mattress)	No	Yes	Wireless to radio transmitter wired to nurse call, telephone dialer, or remote bell	
	Badge-it	Panic button	No	Yes	Wireless to radio transmitter wired to nurse call, telephone dialer, or remote bell	
Ashametrics Company	Wrist LifeBand, Ankle LifeBand, Chest LifeBand	Wristband, ankleband, and chestband	Rajan et al. [116] and Fletcher et al. [114]	Yes	Skin conductance, three-axis accelerometer, ambient temperature sensor, real-time clock with quartz crystal precision and autosync with phone; chestband (+ECG heart monitor)	
BioLert	EpiLert	Watch-like sensor system	Kramer et al. [40]	Yes	Wireless transmission	http://www.biolertsys.com
Baby Ping	Baby Ping	Baby monitor — video, audio, and night-vision camera	No	Yes	3G, 4G, Wi-Fi connection	www.babyping.com
The Bhutan Epilepsy Project/ Grand Challenges Canada	2014 The Bhutan Epilepsy Project	Portable EEG telemetry system using 3G network with a smartphone	Hodson [117], Scholey [118], and Yang [119]	No	3G, Wi-Fi connection to smartphone	http://www.bhutanbrain.com
Capture Proof	Capture Proof	HIPAA compliant platform to share medical videos	No	Yes	Wireless transmission	www.captureproof.com
Cyberonics Inc.	Aspire	Cardiac abnormalities during epileptic seizures	No	No	System linked to VNS system (closed-loop)	http://clinicaltrials.gov/ct2/show/NCT01325623
Danish Care ApS	Epi-Care Free Device	Wristband — accelerometer	Beniczky et al. [120]	Yes	Wireless transmission — pager and mobile phone	http://danishcare.dk/uk
	Epi-Care 3000	Bed motion monitor (accelerometer under mattress)	No	Yes	Wireless call — SMS message, pager, or emergency phone	
D.C.T. Associates Pty Ltd.	Vigil-Aide	Vibration motion (on bed or in pouch/ belt): audible, vibratory, or visual (flashing lights)	No	Yes	Radio transmission by coded signal	http://www.dctassociates.com.au/convul.htm
Movisens	Electrodermal activity sensor	Electrodes (palm, sole of foot, and finger)	No	Yes	Raw signals of electrodermal activity, 3-axis acceleration, air pressure, and temperature	http://www.movisens.com
Emfit	Emfit Seizure Monitor	Bed motion sensor (accelerometer under mattress)	Narechania et al. [48]	Yes	Wireless transmission	http://www.emfit.com
Empatica	E3 Wristband	Wristband and free mobile phone application	No	Yes	Photoplethysmography, electrodermal activity, triaxis accelerometer, body temperature, and heat flux	https://www.empatica.com
EpDetect	EpDetect	Free mobile phone application (accelerometer)	No	Yes	Wireless transmission — SMS messaging, movement detection, and GPS system	http://www.epdetect.com
EpiCall Ltd.	EpiCall	Sticker placed on the side of the face with electrooculograph and photoplethysmograph electrodes	No	No	Monitoring seizure biomarkers (heart rate and extraocular eye movements)	http://clinicaltrials.gov/ct2/show/NCT01436695
Garmin	Garmin Forerunner 310X	Watch	No	Yes	Heart rate monitor	http://www.heartratemonitors.com
Holst Centre/IMEC, Hobo Heeze BV		Armband with chest electrodes	Massé et al. [121] and van Elmpt et al. [122]	No	Prototypes using electroencephalogram, electrocardiogram, and accelerometer	http://www.hoboheeze.nl/engels/episode.html
IctalCare A/S	IctalCare 365	Body-worn "ePatch" attached to the upper arm	Conradsen et al. [123]	No	Wireless surface electromyography (sEMG)	http://ictalcare.com/

(continued on next page)

Table 5 (*continued*)

Company	Brand name	Device type	Article published	Available on market	Signal processing	Website
Medpage	MP5	Bed motion sensor and vocalization microphone (accelerometer under mattress and microphone)	Fulton et al. [124] and Carlson et al. [47]	Yes	Wireless transmission — radio pager	http://www.medpageusa.com
	MP2	Bed motion sensor (accelerometer under mattress)	No	Yes	Wireless transmission — a radio alarm pager and/or a desktop alarm receiver	
	ST2	Bed motion sensor and breathing cessation monitor (accelerometer under mattress)	Fulton et al. [124]	Yes	Wireless transmission — radio pager	
Mio Alpha	Mio Alpha Strapless	Watch	No	Yes	Heart rate monitor	http://www.alphaheartrate.com
Sensorium	Sensealert-102/EP200	Bed motion sensor (accelerometer under mattress)	No	Yes	Digital microprocessor — radio transmission	http://www.sensorium.co.uk
Sparkfun	ADLX330	Wristband	Bayly et al. [125]	Yes	Triple axis accelerometer	https://www.sparkfun.com
Smart Monitor Corp.	SmartWatch	Wristwatch	Lockman et al. [39]	Yes	Android application — Bluetooth signal	http://www.smart-monitor.com
Polar	H1, H2, H7	Body strap	No	Yes	Heart rate monitor	http://www.polar.com
	FT1, FT2, FT60, FT80, FT40, FT7	Watch	No	Yes	Heart rate monitor	
Shilene.com	Seizure Alert and Recorder	Free mobile phone application (accelerometer under development)	No	No	Wireless transmission — SMS messaging, movement detection, and GPS system	http://shilene.com/
Suunto	M5, Suunto Quest	Watch	No	Yes	Heart rate monitor	www.suunto.com
Timex	Timex Heart Rate Monitor	Watch	No	Yes	Heart rate monitor	www.timex.com
Vahlkamp	Epi-Watcher	Bed motion sensor (accelerometer under mattress)	No	Yes	Wireless (radio waves) alarm bell and wired version integrated. Transmit spoken message to preprogrammed numbers	http://www.vahlkamp.nl/Epi-Watcher_gb.html

Table 6
Electronic seizure record applications.

Mobile application	Founder	App purpose	Device type	Clinical trial	Available on market	Website
Cleveland Clinic MyEpilepsy	The Cleveland Clinic Foundation	Seizure diary, educational tool, and emergency guide	iPad only	No	Yes	http://my.clevelandclinic.org/mobile-apps/epilepsy-app.aspx
E-Action Info: your epilepsy resource	UCB Pharma SA, Logicopolis Technology Inc., CPC Healthcare Communications Toronto	Educational tool and link to my epilepsy diary	iPhone, iPad, iPod Touch	No	Yes	http://www.e-action.ca/Home.aspx?lang=en
Epi & Me	Gilles Huberfeld, UCB Pharma S.A. France/Brain and Spine Institute	Seizure diary	iPhone, iPad, iPod Touch	No	Yes	http://epiandme.com/
Epilepsia App	Soda Virtual	Seizure diary	iPhone, iPad, iPod Touch	No	Yes	https://itunes.apple.com/us/app/epilepsia-app/id589429873?mt=8
Epilepsy Action	Epilepsy Action British Epilepsy Association	Seizure diary, educational tool, emergency guide, and call helpline feature	Android MDA, iPhone, iPad, iPod Touch and, online account	No	Yes	http://app.epilepsy.org.uk/ https://www.epilepsy.org.uk/
Epilepsy App	Adiljan Abdurihim and Andrius Januska	Seizure diary and alarm with SMS messaging and GPS system	Android MDA	No	Yes	https://play.google.com/store/apps/details?id=no.hig.stud.bachelor.epilepsyapp
Epilepsy Guide App	National Society for Epilepsy	Seizure diary and emergency guide	Android MDA, iPhone, iPad, iPod Touch	No	Yes	http://www.epilepsysociety.org.uk/
Epilepsy Manager Pro/ Epilepsy Manager 2/ Epilepsie	Julia Bechman	Seizure diary	Android MDA, iPhone, iPad, iPod Touch	No	Yes	https://itunes.apple.com/us/app/epilepsy-manager-pro/id766021861?mt=8
My Epilepsy Diary	Dr. Robert Fisher and Patty Shafer, RN Epilepsy Foundation	Seizure diary	Android MDA, iPhone, iPad, iPod Touch, and online account	No	Yes	www.epilepsy.com/seizurediary
Seizure Diary	Gavin Harris	Seizure diary	iPhone, iPad, iPod Touch	No	Yes	https://itunes.apple.com/us/app/seizure-diary/id402201129?mt=8
Seizure Disorder Coach	Think Safe Inc.	Emergency guide	iPhone, iPad, iPod Touch	No	Yes	http://resqrsoftware.com/seizure.php
Seizure Journal for Parents	Cloud Med LLC	Seizure diary	iPhone, iPad, iPod Touch	No	Yes	https://itunes.apple.com/us/app/seizure-journal-for-parents/id420054138?mt=8
Seizures	Dmitry Ulupov, Satoru Systems	Seizure diary	iPhone, iPad, iPod Touch	No	Yes	http://satorusystems.com/seizures.html
Seizure Tracker	Rob and Lisa Moss/Seizure Tracker LLC	Seizure Diary	Android MDA, iPhone, iPad, iPod Touch, and online account	NCT01289912	Yes	www.seizuretracker.com
Young Epilepsy	Young Epilepsy, The National Centre for Young People with Epilepsy	Seizure diary, educational tool, emergency guide, and call helpline feature	Android MDA, iPhone, iPad, iPod Touch	No	Yes	http://youngepilepsy.org.uk/all-about-epilepsy/epilepsy-app
Your Epilepsy Diary	Neal Daringer	Seizure diary	Android MDA	No	Yes	https://play.google.com/store/apps/details?id=org.daringer.EpApp2

MDA: mobile device app.

Table 7
Features available in various electronic seizure record applications.

Mobile application	Calendar view	Video	Data input reminders	Data output	Patient seizure profile	Clinician portal to manage multiple accounts
Cleveland Clinic MyEpilepsy	Yes	No	Yes	Yes	No	Yes
Epi & Me	Yes	Yes	No	No	No	No
Epilepsia App	Yes	Yes	Yes	Yes	Yes	No
Epilepsy Action	Yes	No	No	Yes	Yes	No
Epilepsy App	Yes	No	Yes	Yes	No	No
Epilepsy Guide App	Yes	No	No	No	Yes	No
Epilepsy Manager Pro/Epilepsy Manager 2/Epilepsie	Yes	No	Yes	Yes	No	No
My Epilepsy Diary	Yes	No	Yes	Yes	Yes	Clinician portal
Seizure Diary	Yes	No	No	Yes	Yes	No
Seizure Disorder Coach	No	No	No	No	No	No
Seizure Journal for Parents	Yes	No	No	No	No	No
Seizures	Yes	No	No	Yes	No	No
Seizure Tracker	Yes	Yes	Yes	Yes	Yes	Valet system
Young Epilepsy	Yes	Yes	Yes	Yes	Yes	No
Your Epilepsy Diary	Yes	No	No	No	No	No

6. Population health data in disease and outcome prediction

The use of population health data has the potential to provide individualized care in epilepsy by utilizing information derived from large groups of individuals. Successful examples of population-based data have been seen in infectious diseases. Use of population health data, for example, improved the ability of models in diagnosing pertussis [126] and hand, foot, and mouth disease [127]. The application of population health data can also extend beyond its application towards diagnostics and can even investigate outcomes or adverse effects. A logistic regression model, termed the predictive pharmacosafety network, for example, was applied retrospectively to predict unknown drug adverse effects over a 5-year period. This model achieved a relatively high area under the receiver operating curve, suggesting that this type of modeling can be used in determination of unknown adverse effects and drug interactions by the use of large amounts of population-based data [128].

6.1. Prediction models in epilepsy

Prediction models in epilepsy may also be based on correlations between seizure occurrence during certain times of the day and during different states of arousal on the basis of patient age, seizure localization, and seizure semiology [129–131]. These data can be used to develop prediction models that utilize individual variables to predict the timing of greatest seizure risk. The use of large-scale population health data can serve as a source of information for improving the accuracy of similar individualized prediction models. Additionally, these data sets might permit the determination of other important information, such as the medication efficacy, disease progression, and prognostic factors. In a trial conducted on 20 adult patients taking levetiracetam who self-reported mood changes, it was determined that patients taking the drug were more likely develop aggressive moods over the course of therapy and that changes in aggressive mood were maximal during daytime [132]. Such models hold promise if expanded upon in a larger scale.

6.2. Automated detection systems in prediction models

Traditionally, seizure logs or diaries have been used by clinicians to determine the periods of greatest seizure susceptibility. Automated seizure detection systems can serve as a supplement or replacement for patient diaries for a number of reasons. Patients and/or their parents may not document all seizures if they are required to enter the data manually. Certain types of seizures, such as complex or simple partial seizures, may be subclinical and not fully observed. Seizures that occur when the patient is asleep might be similarly missed. A study performed on patients undergoing video-EEG found that patients were unaware of approximately half of their clinical seizures [133]. Behavioral factors may affect seizure reporting as well; for example, caregivers and patients may be more vigilant when monitoring seizures while switching between antiepileptic medications [104]. Such factors may confound accuracy of seizure logs. Detection systems may fill this gap in seizure documentation in the future by providing more objective and real-time data collection. Additionally, automated seizure detection methods can provide information specific to the seizure tracking method, such as EEG, ECG, or electrodermal data [109]. The use of seizure detectors may, thus, be able to overcome some of the barriers to data collection, patient monitoring, and prediction modeling.

7. Seizure detectors, data processing, and closed-loop systems

The use of seizure detectors may indicate deterioration, prevent harm during treatment, and ultimately improve patient outcomes. Such monitoring may be accomplished by a closed-loop system, in which seizures can be detected or even anticipated and responded to in real-time.

7.1. Closed-loop systems

Closed-loop systems provide an active feedback loop. In the medical setting, the term refers to systems that monitor a patient's physiological parameters and responds in an automatic or semiautomatic manner in order to keep this parameter within specified limits. Closed-loop systems have most frequently been applied in emergency and intensive care settings, where systems monitor vital signs and respond appropriately to maintain these parameters within a determined range [134] (Fig. 3).

Closed-loop models have been proposed in several medical subspecialties, including anesthesia [135] and diabetology. In neurology, closed-loop strategies have been proposed in the treatment of movement disorders [136]; in the assistance of cognitive recovery following acquired brain injury [137]; and in the acute management of strokes [138], epileptic seizures [139], and other chronic conditions with recurring events.

7.2. Closed-loop treatment in epilepsy

Closed-loop systems are analogous to physiological feedback systems. They consist of a measuring or detection device, data transmission, data processing, and a corrective response within an output loop. The approach to feature selection, reduction, and classification is similar, with perhaps higher specificity, since the response of the system to false-positive detections (when there is no seizure) could be undesirable.

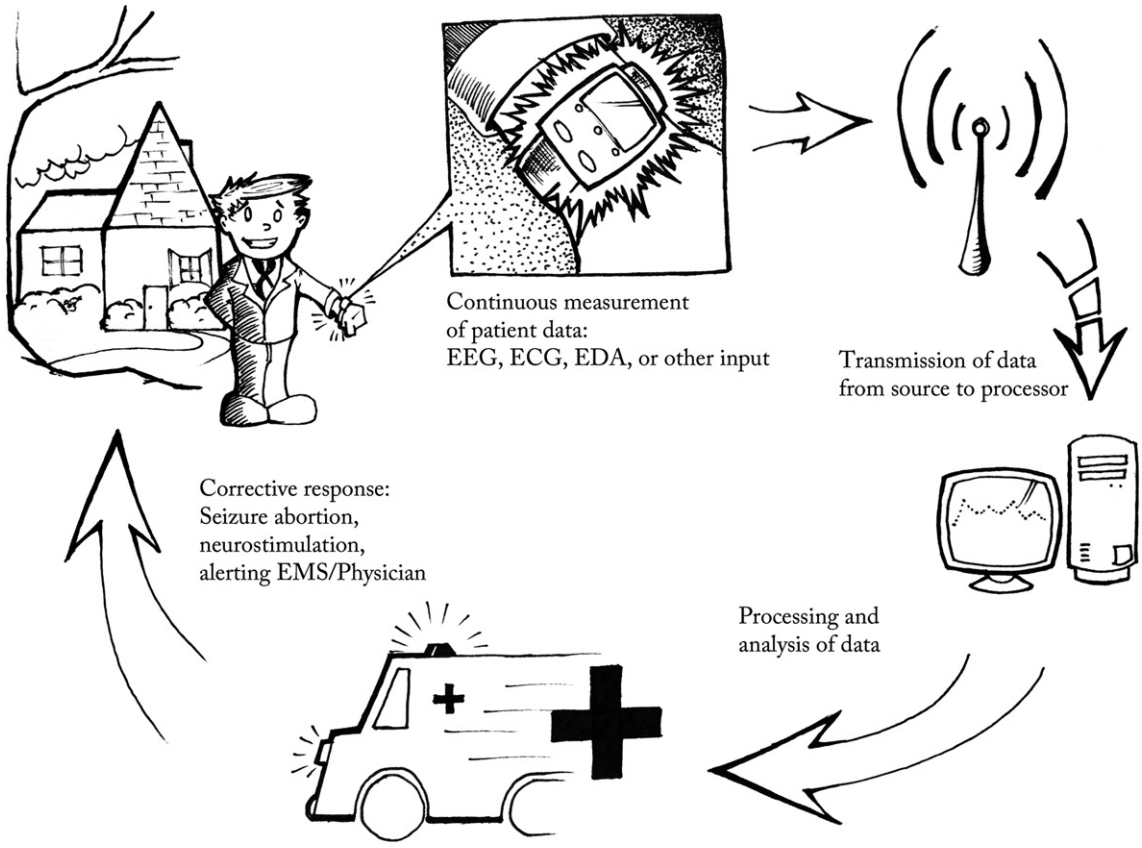

Fig. 3. Components of a closed-loop system. Data are collected continuously from patients using a variety of methods (electroencephalography, electrocardiography, electrocorticography, electrodermal activity, or accelerometry.) Data are transmitted from site of collection and subsequently processed. Events are classified. Ictal events, when detected, lead to a corrective response and can include abortive pharmacotherapy, neurostimulation, or contacting caretakers or emergency medical services.

7.3. Measuring device

Reproducible data in a closed-loop system must be continually collected and processed. A variety of sensor and detector tools have been previously discussed.

7.4. Data transmission

Following data acquisition, the information must be transmitted to a system. This will permit data analysis and processing. Such a system should ideally accommodate rapid and secure collection and analysis of real-time data.

Experimental models of closed-loop systems have been tested on inpatients admitted for video-EEG, such as in a recently developed model in which vagal nerve stimulation is triggered upon detection of seizure activity [105]. A closed-loop system in the outpatient setting, however, should ideally employ wireless systems that do not interfere with day-to-day living. In some experimental models, the use of wireless data transmission using wireless local area network (Wi-Fi) [140] or Bluetooth [39] has been carried out successfully. While these two systems are limited to proximity to a wireless receiver, similar systems using mobile telecommunication technology could be developed.

For some devices, such as newer commercial EEG headsets, signal processing, including feature calculation and classification, can be performed in processors installed on the device itself, eliminating the need for transmission of the raw data. For example, the b-alert system (http://www.bmedical.com.au/shop/neuroscience/b-alert-x4-wireless-eeg.htm) contains a lightweight processor on the EEG headset itself that performs feature calculation and classification. A learning algorithm is also built into the onboard processor to enable the headset to adapt to individual users. The output has been used to evaluate EEG detection of motor and cognitive performance in surgical residents when fatigued after on-call shifts [141]. If such a device was designed for seizure detection, a positive signal could be relayed directly from the onboard processor to an intervention device, such as a vagal nerve stimulator. This could utilize a dedicated signal, avoiding the possibility of interference or interception. An encrypted result could also be transmitted to a local smartphone for transmission to a health-care provider.

Data transmission is vulnerable to interception, which can result in compromise, loss, or corruption of private health information. The need for secure standards in data transmission are, thus, of paramount importance. A variety of steps have been developed to ensure the security of transmitted information. The recent demonstration of the E-SAP authentication protocol is an example of such a system developed for this purpose. The data transmitted by this system are encrypted and allow for access by selected professionals and, thus, for patient care to be uninterrupted by privacy needs [142].

7.5. Data processing

Data processing systems interpret the signals collected by the biometric device to determine the patient's status and assess the probability of imminent or ongoing seizures. Data processing systems should be able to determine the patient's current seizure risk by the use of real-time data in a rapid, efficient manner. The methods discussed above for feature calculation and classification of real-time EEG, ECG, and accelerometry data are examples of the data processing systems required for closed-loop systems. The success of a data processing system is determined by parameters of sensitivity, specificity, and predictive values. A frequently provided parameter in automated seizure detectors is the “false alarm rate” which, in turn, is related to the frequency of

false-positive results. Although the steps and algorithms required for closed-loop systems are similar to those for seizure predictors, the requirements for processing time are often more stringent, as activation of an intervention in time to prevent the seizure or warn a patient of its onset must be rapid. The false alarm rate tolerance is also likely to be quite strict.

7.6. Response system

The response system of the closed-loop device can take many forms. Basic forms of the device can warn the patient or caretakers. In epilepsy, an example for such a device is the SmartWatch, which sends alerts to smartphones and can then automatically alert caregivers or healthcare providers [143]. Alternatively, the system could initiate an activity, such as medication administration or activation of a neurostimulator, which could potentially preemptively stop a seizure from developing. The response system could also involve notifying a patient's caretakers, physician, or emergency medical services, such as through a smartphone or a pager device. The EpiLert system, (Biolert Ltd., Even Yehuda, Israel) provides an example of a possible response mechanism. The unit is able to detect movements (accelerometer) and transmits a message using a wireless system to a cell phone, the Internet, and a landline telephone and also has a GPS component that facilitates instantaneous help (www.biolertsys.com).

Neurostimulators are promising tools for the treatment of seizures. The responsive neurostimulation system (Neuropace Inc., Mountain View, CA) is an implantable device designed for the treatment of refractory partial epilepsy. This system is able to identify abnormal activity in the brain and immediately deliver electrical pulses in order to normalize brain activity even before the patient presents any signs or symptoms of seizure. There is also an external component that allows the physician to analyze brain activity in real-time and adjust parameters according to the seizure pattern of each patient (http://www.neuropace.com/product/overview.html). The Neuropace system is also unique in that it is able to detect both clinical and electrographic seizures. A randomized, double-blind, multicenter, sham-controlled study with 191 patients using the RNS system provided Class I evidence for this device. There was a reduction in seizure frequency ($p = 0.012$) in comparison with the placebo group, with no mood or cognitive adverse events [144].

Another promising technique in rapid seizure treatment is deep brain stimulation (DBS) of the thalamus. The technique uses stimulation in the various nuclei of the thalamus [126,127], and its goal is to modulate the brain. The target of stimulation in different studies includes the centromedian and anterior nucleus of the thalamus [126,127]. This technique demonstrated efficacy in selected groups of patients, and anterior thalamic stimulation has received European CE Mark approval for refractory epilepsy in 2010 but is not approved in the US.

A sufficiently accurate seizure prediction system may be useful in aborting imminent clinical seizures through other means. Rapidly acting benzodiazepines, delivered through multiple routes (intravenous, intranasal, intramuscular, rectal, and inhaled and, possibly, through microcatheters in the vicinity of the seizure focus in the brain), may prevent seizures before they occur. Other techniques for seizure abortion have been studied in animals. A Peltier cooler was successfully used in rapidly arresting in vitro hippocampal seizures in rodent studies [145]. Another in vitro study demonstrated the ability of UV light to elicit gamma amino butyric acid secretion and secondarily attenuate seizures [146]. Local drug delivery systems might serve a similar effect [147].

8. Trials of seizure detectors and predictors

Seizure detection can occur at multiple levels. To date, investigators have developed systems for anticipating or detecting epileptiform activity and then using a closed-loop strategy to arrest further progression. However, knowledge of epileptogenesis, or the degenerative changes that occur to predispose an individual towards having seizures, continues to grow. The ability to detect and treat seizures could potentially be applied at an earlier phase in order to determine and prevent the risk of future seizure predisposition.

8.1. EEG/electrocorticography-based models

A number of models have studied the viability of early warning systems in epilepsy. The most commonly employed models utilize neurostimulators, such as deep brain stimulation or vagal nerve stimulation, as an output method.

8.1.1. Animal models

An animal model, using Long–Evans rats with spontaneous spike-and-wave discharges or pentylenetetrazol-induced seizures, has shown potential as an EEG-based seizure prediction system. In a study analyzing the viability of a closed-loop system, rats were monitored by continuous EEG, which was wirelessly transmitted to a microcontroller unit. The output of the device was via a neurostimulator situated at the zona incerta. The system was found to have a detection accuracy of 92% and a latency period of 0.6 s. The system was able to suppress 90% of seizures in rats with spontaneous discharges and 60–70% of seizures in rats with pentylenetetrazol-induced seizures [140].

8.1.2. Human studies

The recently published prospective trial of a closed-loop system utilizing VNS as an output and the NeuroPace system which have already been mentioned [105], and more recently the combination of ECG-VNS has been in development. An early warning system which had been under development by NeuroVista monitors electrocorticography continuously in the ambulatory setting and wirelessly transmits its data to a handheld receiver. The system displays colors on the receiver demonstrating the risk of seizure at any given period.

Optogenetics may prove to be an important method to further explore genetic alterations in seizure activity. Opsins are used to selectively control neurons, leading to better understanding of pathophysiology [148]. The first studies in animal models have shown promising results, but more data are needed before this information can be applied as a therapeutic approach in humans [149].

9. Challenges

9.1. Technical

The development of new devices in epilepsy is moving forward, though serious challenges need to be addressed. Patients need devices that are sufficiently accurate and which can be used with minimal adverse effects and discomfort. Other important concerns are the reliability in real-time transmission of the data, a precise description of seizures, the need for 24-hour services to attend to events, and limitations in portable batteries.

9.2. Regulatory

After the idea for a new device, the research and development have a long journey to take to reach patients. The first step is to establish relationships with collaborators representing multiple areas of expertise (clinical, technical, and industrial). The next step is validation of the technology towards proof of principle and value and, finally, implementation and commercialization.

In the USA, the Food and Drug Administration (FDA) is responsible for the regulation of medical devices. This regulatory framework includes the definition of the device, device classification, pathways to market, clinical trials, and total product life cycle, in order to know if the device is safe and effective. In addition, it is important to know whether or not the device presents a low risk and is exempt from

intense premarket evaluation, and if it is in compliance with good manufacturing practices.

9.3. Payor

Seizure detection systems are resource intensive. There are some questions that need to be addressed before commercialization of the product: a) market need; b) market competition; c) time and capital requirements needed to create prototypes; d) the price and maintenance of a patent; e) time needed for return on investment; and f) presence of similar and/or superior treatments. Once on the market, devices can be replaced quickly by a new model, an increasing issue for FDA.

9.4. Research funding

There are a few partnering organizations that support the innovation and early development of new devices in epilepsy. One example is the Center for Integration of Medicine & Innovative Technology (CIMIT), a nonprofit consortium that created a model to accelerate translation medical research, especially medical device development (www.cimit.org). Another example is the Epilepsy Therapy Project of the Epilepsy Foundation.

10. Future directions

Collaboration among engineers, physicians, and industries towards the invention of new technologies or improvement of older ones will allow for a better approach towards prevention, detection and prediction of seizures. This will ultimately lead towards more precise diagnoses, individualization of treatment, and accurate guidance for neurosurgical interventions. The conception of a closed-loop system and prompt intervention has the potential for a better quality of life for patients and their caretakers.

11. Conclusion

Seizure detection and prediction provide new and individually targeted opportunities for the diagnosis and intervention in the management of epilepsy. These systems may allow for the detection of seizures prior to their clinical onset. Furthermore, these systems might be used in accident prevention and seizure tracking and could further be useful in closed-loops to facilitate seizure abortion. Beyond their uses in immediate patient care, these systems may allow for increased granularity of neuroepidemiologic data, thereby permitting improved seizure prediction and risk factor assessment.

Conflict of interest

Claus Reinsberger and Tobias Loddenkemper have accepted a donation of Q-sensors from Affectiva, Inc. for scientific studies. No other conflicts of interest.

Disclosures

Sriram Ramgopal, William Bosl, Navah Kadish, Michele Jackson, Iván Sánchez Fernández, and Jacquelyn Klehm have nothing to disclose.

Sigride Thome-Souza is supported by a grant from the Ciências Sem Fronteiras (CNPq), Ministry of Science Technology and Innovation, and Ministry of Education, Federal Government, Brazil.

Claus Reinsberger received funding from the Epilepsy Foundation of America (EF-1179308 and EF-213882).

Steven Schachter has received funding from the Center for Integration of Medicine and Innovative Technology for seizure detection-related projects.

Tobias Loddenkemper serves on the Laboratory Accreditation Board for Long-term (Epilepsy and ICU) Monitoring (ABRET); performs video-EEG long-term monitoring, EEGs, and other electrophysiological studies at Children's Hospital Boston and bills for these procedures (20%); receives support from NIH/NINDS, is supported by a Career Development Fellowship Award from Harvard Medical School and Children's Hospital Boston, by the Program for Quality and Safety at Children's Hospital Boston; receives funding from the American Epilepsy Society/Epilepsy Foundation of America, and from the Center for Integration of Medicine & Innovative Technology (CIMIT), Cure, Danny Did Foundation, HHV6 Foundation; and received investigator initiated research support from Lundbeck and Eisai Inc.

Acknowledgments

The authors would like to thank Alexander Mylavarapu, MD, for his assistance with Fig. 2. This study was supported by the Danny Did foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2014.06.023.

References

[1] Christensen J, Vestergaard M, Pedersen MG, Pedersen CB, Olsen J, Sidenius P. Incidence and prevalence of epilepsy in Denmark. Epilepsy Res 2007;76:60–5.
[2] Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. Epilepsia 1993;34:453–8.
[3] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–9.
[4] Camfield P, Camfield C. Idiopathic generalized epilepsy with generalized tonic–clonic seizures (IGE–GTC): a population-based cohort with >20 year follow up for medical and social outcome. Epilepsy Behav 2010;18:61–3.
[5] Webber WR, Lesser RP, Richardson RT, Wilson K. An approach to seizure detection using an artificial neural network (ANN). Electroencephalogr Clin Neurophysiol 1996;98:250–72.
[6] Pradhan N, Sadasivan PK, Arunodaya GR. Detection of seizure activity in EEG by an artificial neural network: a preliminary study. Comput Biomed Res 1996;29:303–13.
[7] Gabor AJ. Seizure detection using a self-organizing neural network: validation and comparison with other detection strategies. Electroencephalogr Clin Neurophysiol 1998;107:27–32.
[8] Wilson SB, Scheuer ML, Emerson RG, Gabor AJ. Seizure detection: evaluation of the Reveal algorithm. Clin Neurophysiol 2004;115:2280–91.
[9] Wilson SB. A neural network method for automatic and incremental learning applied to patient-dependent seizure detection. Clin Neurophysiol 2005;116:1785–95.
[10] Alkan A, Koklukaya E, Subasi A. Automatic seizure detection in EEG using logistic regression and artificial neural network. J Neurosci Methods 2005;148:167–76.
[11] D'Alessandro M, Vachtsevanos G, Esteller R, Echauz J, Cranstoun S, Worrell G, et al. A multi-feature and multi-channel univariate selection process for seizure prediction. Clin Neurophysiol 2005;116:506–16.
[12] Aarabi A, Wallois F, Grebe R. Automated neonatal seizure detection: a multistage classification system through feature selection based on relevance and redundancy analysis. Clin Neurophysiol 2006;117:328–40.
[13] Casson AJ, Yates DC, Patel S, Rodriguez-Villegas E. Algorithm for AEEG data selection leading to wireless and long term epilepsy monitoring. Conf Proc IEEE Eng Med Biol Soc 2007;2007:2456–9.
[14] Chan AM, Sun FT, Boto EH, Wingeier BM. Automated seizure onset detection for accurate onset time determination in intracranial EEG. Clin Neurophysiol 2008;119:2687–96.
[15] Netoff T, Park Y, Parhi K. Seizure prediction using cost-sensitive support vector machine. Conf Proc IEEE Eng Med Biol Soc 2009;2009:3322–5.
[16] Chua KC, Chandran V, Acharya UR, Lim CM. Automatic identification of epileptic electroencephalography signals using higher-order spectra. Proc Inst Mech Eng H 2009;223:485–95.
[17] Mirowski P, Madhavan D, Lecun Y, Kuzniecky R. Classification of patterns of EEG synchronization for seizure prediction. Clin Neurophysiol 2009;120:1927–40.
[18] Sorensen TL, Olsen UL, Conradsen I, Henriksen J, Kjaer TW, Thomsen CE, et al. Automatic epileptic seizure onset detection using matching pursuit: a case study. Conf Proc IEEE Eng Med Biol Soc 2010;2010:3277–80.
[19] Chisci L, Mavino A, Perferi G, Sciandrone M, Anile C, Colicchio G, et al. Real-time epileptic seizure prediction using AR models and support vector machines. IEEE Trans Biomed Eng 2010;57:1124–32.
[20] Petersen EB, Duun-Henriksen J, Mazzaretto A, Kjaer TW, Thomsen CE, Sorensen HB. Generic single-channel detection of absence seizures. Conf Proc IEEE Eng Med Biol Soc 2011;2011:4820–3.
[21] Temko A, Thomas E, Marnane W, Lightbody G, Boylan G. EEG-based neonatal seizure detection with Support Vector Machines. Clin Neurophysiol 2011;122:464–73.

[22] Acharya UR, Sree SV, Suri JS. Automatic detection of epileptic EEG signals using higher order cumulant features. Int J Neural Syst 2011;21:403–14.
[23] Kharbouch A, Shoeb A, Guttag J, Cash SS. An algorithm for seizure onset detection using intracranial EEG. Epilepsy Behav 2011;22(Suppl. 1):S29–35.
[24] Liu Y, Zhou W, Yuan Q, Chen S. Automatic seizure detection using wavelet transform and SVM in long-term intracranial EEG. IEEE Trans Neural Syst Rehabil Eng 2012;20(6):749–55.
[25] Xie S, Krishnan S. Wavelet-based sparse functional linear model with applications to EEGs seizure detection and epilepsy diagnosis. Med Biol Eng Comput 2012;51(1–2):49–60.
[26] Direito B, Teixeira C, Ribeiro B, Castelo-Branco M, Sales F, Dourado A. Modeling epileptic brain states using EEG spectral analysis and topographic mapping. J Neurosci Methods 2012;210:220–9.
[27] Rabbi AF, Fazel-Rezai R. A fuzzy logic system for seizure onset detection in intracranial EEG. Comput Intell Neurosci 2012;2012:705140.
[28] Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, et al. 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 2013;12:563–71.
[29] Conradsen I, Beniczky S, Wolf P, Henriksen J, Sams T, Sorensen HB. Seizure onset detection based on a uni- or multi-modal intelligent seizure acquisition (UISA/MISA) system. Conf Proc IEEE Eng Med Biol Soc 2010;2010:3269–72.
[30] Conradsen I, Beniczky S, Wolf P, Kjaer TW, Sams T, Sorensen HB. Automatic multimodal intelligent seizure acquisition (MISA) system for detection of motor seizures from electromyographic data and motion data. Comput Methods Programs Biomed 2012;107:97–110.
[31] Greene BR, de Chazal P, Boylan GB, Connolly S, Reilly RB. Electrocardiogram based neonatal seizure detection. IEEE Trans Biomed Eng 2007;54:673–82.
[32] Malarvili MB, Mesbah M. Newborn seizure detection based on heart rate variability. IEEE Trans Biomed Eng 2009;56:2594–603.
[33] Jeppesen J, Beniczky S, Fuglsang-Frederiksen A, Sidenius P, Jasemian Y. Detection of epileptic-seizures by means of power spectrum analysis of heart rate variability: a pilot study. Technol Health Care 2010;18:417–26.
[34] Doyle OM, Temko A, Marnane W, Lightbody G, Boylan GB. Heart rate based automatic seizure detection in the newborn. Med Eng Phys 2010;32:829–39.
[35] Nijsen TM, Arends JB, Griep PA, Cluitmans PJ. The potential value of three-dimensional accelerometry for detection of motor seizures in severe epilepsy. Epilepsy Behav 2005;7:74–84.
[36] Nijsen TM, Cluitmans PJ, Arends JB, Griep PA. Detection of subtle nocturnal motor activity from 3-D accelerometry recordings in epilepsy patients. IEEE Trans Biomed Eng 2007;54:2073–81.
[37] Cuppens K, Lagae L, Ceulemans B, Van Huffel S, Vanrumste B. Detection of nocturnal frontal lobe seizures in pediatric patients by means of accelerometers: a first study. Conf Proc IEEE Eng Med Biol Soc 2009;2009:6608–11.
[38] Nijsen TM, Aarts RM, Cluitmans PJ, Griep PA. Time-frequency analysis of accelerometry data for detection of myoclonic seizures. IEEE Trans Inf Technol Biomed 2010;14:1197–203.
[39] Lockman J, Fisher RS, Olson DM. Detection of seizure-like movements using a wrist accelerometer. Epilepsy Behav 2011;20:638–41.
[40] Kramer U, Kipervasser S, Shlitner A, Kuzniecky R. A novel portable seizure detection alarm system: preliminary results. J Clin Neurophysiol 2011;28:36–8.
[41] Van de Vel A, Cuppens K, Bonroy B, Milosevic M, Van Huffel S, Vanrumste B, et al. Long-term home monitoring of hypermotor seizures by patient-worn accelerometers. Epilepsy Behav 2013;26:118–25.
[42] Lu H, Pan Y, Mandal B, Eng HL, Guan C, Chan DW. Quantifying limb movements in epileptic seizures through color-based video analysis. IEEE Trans Biomed Eng 2013;60:461–9.
[43] Beniczky S, Polster T, Kjaer TW, Hjalgrim H. Detection of generalized tonic–clonic seizures by a wireless wrist accelerometer: a prospective, multicenter study. Epilepsia 2013;54(4):e58–61.
[44] Karayiannis NB, Xiong Y, Frost Jr JD, Wise MS, Hrachovy RA, Mizrahi EM. Automated detection of videotaped neonatal seizures based on motion tracking methods. J Clin Neurophysiol 2006;23:521–31.
[45] Cuppens K, Lagae L, Ceulemans B, Van Huffel S, Vanrumste B. Automatic video detection of body movement during sleep based on optical flow in pediatric patients with epilepsy. Med Biol Eng Comput 2010;48:923–31.
[46] Cuppens K, Chen CW, Wong KB, Van de Vel A, Lagae L, Ceulemans B, et al. Using spatio-temporal interest points (STIP) for myoclonic jerk detection in nocturnal video. Conf Proc IEEE Eng Med Biol Soc 2012;2012:4454–7.
[47] Carlson C, Arnedo V, Cahill M, Devinsky O. Detecting nocturnal convulsions: efficacy of the MP5 monitor. Seizure 2009;18:225–7.
[48] Narechania AP, Garic II, Sen-Gupta I, Macken MP, Gerard EE, Schuele SU. Assessment of a quasi-piezoelectric mattress monitor as a detection system for generalized convulsions. Epilepsy Behav 2013;28:172–6.
[49] Bruijne GR, Sommen PCW, Aarts RM. Detection of epileptic seizures through audio classification. IFMBE Proceedings, 22; 2008. p. 1450–4.
[50] Strong V, Brown SW, Walker R. Seizure-alert dogs—fact or fiction? Seizure 1999;8:62–5.
[51] Marsland S. Machine learning: an algorithmic perspective. Boca Raton: CRC Press; 2009.
[52] Witten IH, Frank E. Data mining: practical machine learning tools and techniques. 2nd ed. Amsterdam; Boston, MA: Morgan Kaufman; 2005.
[53] Jansen K, Lagae L. Cardiac changes in epilepsy. Seizure 2010;19:455–60.
[54] Osorio I, Frei MG, Giftakis J, Peters T, Ingram J, Turnbull M, et al. Performance reassessment of a real-time seizure-detection algorithm on long ECoG series. Epilepsia 2002;43:1522–35.
[55] Walker JS. A primer on wavelets and their scientific applications. 2nd ed. Boca Raton: Chapman & Hall/CRC; 2008.
[56] Burke B. The mathematical microscope: waves, wavelets and beyond. In: Bartusiak MF, Burke B, Chaikin A, Greenwood A, editors. A positron named Priscilla: scientific discovery at the frontier. Washington, D.C.: National Academy of Sciences; 1994. p. 196–235.
[57] Khan YU, Gotman J. Wavelet based automatic seizure detection in intracerebral electroencephalogram. Clin Neurophysiol 2003;114:898–908.
[58] Saab ME, Gotman J. A system to detect the onset of epileptic seizures in scalp EEG. Clin Neurophysiol 2005;116:427–42.
[59] Xie S, Jin F, Krishnan S. Sparse approximation of long-term biomedical signals for classification via dynamic PCA. Conf Proc IEEE Eng Med Biol Soc 2011:7167–70.
[60] Tang Y, Durand D. A tunable support vector machine assembly classifier for epileptic seizure detection. Expert Syst Appl 2012;39:3925–38.
[61] Bishop CM. Pattern recognition and machine learning. New York: Springer; 2006.
[62] Bosl WJ. Systems biology by the rules: hybrid intelligent systems for pathway modeling and discovery. BMC Syst Biol 2007;1:13.
[63] Kriete A, Bosl W, Booker G. Fuzzy logic modeling of stress response in cell aging. Foundations of Systems Biology in Engineering Conference 2009; 2009 [Denver, Colorado].
[64] Rau G, Becker K, Kaufmann R, Zimmermann HJ. Fuzzy logic and control: principal approach and potential applications in medicine. Artif Organs 1995;19:105–12.
[65] Direito B, Teixeira C, Ribeiro B, Castelo-Branco M, Sales F, Dourado A. Modeling epileptic brain states using EEG spectral analysis and topographic mapping. J Neurosci Methods 2012;210(2):220–9.
[66] Osorio I, Lyubushin A, Sornette D. Toward a probabilistic definition of seizures. Epilepsy Behav 2011;22(Suppl. 1):S18–28.
[67] Iasemidis LD. Seizure prediction and its applications. Neurosurg Clin N Am 2011;22:489–506 [vi].
[68] Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology 1992;42:1727–32.
[69] Leutmezer F, Schernthaner C, Lurger S, Potzelberger K, Baumgartner C. Electrocardiographic changes at the onset of epileptic seizures. Epilepsia 2003;44:348–54.
[70] Opherk C, Coromilas J, Hirsch LJ. Heart rate and EKG changes in 102 seizures: analysis of influencing factors. Epilepsy Res 2002;52:117–27.
[71] Di Gennaro G, Quarato PP, Sebastiano F, Esposito V, Onorati P, Grammaldo LG, et al. Ictal heart rate increase precedes EEG discharge in drug-resistant mesial temporal lobe seizures. Clin Neurophysiol 2004;115:1169–77.
[72] Weil S, Arnold S, Eisensehr I, Noachtar S. Heart rate increase in otherwise subclinical seizures is different in temporal versus extratemporal seizure onset: support for temporal lobe autonomic influence. Epileptic Disord 2005;7:199–204.
[73] Healy B, Peck J. Bradycardia induced from stimulation of the left versus right central nucleus of the amygdala. Epilepsy Res 1997;28:101–4.
[74] Altenmuller DM, Zehender M, Schulze-Bonhage A. High-grade atrioventricular block triggered by spontaneous and stimulation-induced epileptic activity in the left temporal lobe. Epilepsia 2004;45:1640–4.
[75] Kohno R, Abe H, Akamatsu N, Oginosawa Y, Tamura M, Takeuchi M, et al. Syncope and ictal asystole caused by temporal lobe epilepsy. Circ J 2011;75:2508–10.
[76] Bozorgi A, Chung S, Kaffashi F, Loparo KA, Sahoo S, Zhang GQ, et al. Significant postictal hypotension: expanding the spectrum of seizure-induced autonomic dysregulation. Epilepsia 2013;54:e127–30.
[77] Clancy RR, Legido A, Lewis D. Occult neonatal seizures. Epilepsia 1988;29:256–61.
[78] Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. Arch Dis Child Fetal Neonatal Ed 2008;93:F187–91.
[79] Nijsen TM, Aarts RM, Arends JB, Cluitmans PJ. Model for arm movements during myoclonic seizures. Conf Proc IEEE Eng Med Biol Soc 2007;2007:1582–5.
[80] Dalton A, Patel S, Chowdhury AR, Welsh M, Pang T, Schachter S, et al. Development of a body sensor network to detect motor patterns of epileptic seizures. IEEE Trans Biomed Eng 2012;59:3204–11.
[81] Pediaditis M, Tsiknakis M, Leitgeb N. Vision-based motion detection, analysis and recognition of epileptic seizures—a systematic review. Comput Methods Programs Biomed 2012;108:1133–48.
[82] Li Z, Martins da Silva A, Cunha JP. Movement quantification in epileptic seizures: a new approach to video-EEG analysis. IEEE Trans Biomed Eng 2002;49:565–73.
[83] Karayiannis NB, Tao G, Frost Jr JD, Wise MS, Hrachovy RA, Mizrahi EM. Automated detection of videotaped neonatal seizures based on motion segmentation methods. Clin Neurophysiol 2006;117:1585–94.
[84] Strong V, Brown S, Huyton M, Coyle H. Effect of trained seizure alert dogs on frequency of tonic–clonic seizures. Seizure 2002;11:402–5.
[85] Ortiz R, Liporace J. "Seizure-alert dogs": observations from an inpatient video/EEG unit. Epilepsy Behav 2005;6:620–2.
[86] Brown SW, Goldstein LH. Can seizure-alert dogs predict seizures? Epilepsy Res 2011;97:236–42.
[87] Eberle MM, Reynolds CL, Szu JI, Wang Y, Hansen AM, Hsu MS, et al. In vivo detection of cortical optical changes associated with seizure activity with optical coherence tomography. Biomed Opt Express 2012;3:2700–6.
[88] Watanabe E, Nagahori Y, Mayanagi Y. Focus diagnosis of epilepsy using near-infrared spectroscopy. Epilepsia 2002;43(Suppl. 9):50–5.
[89] Aydin S, Dag E, Ozkan Y, Arslan O, Koc G, Bek S, et al. Time-dependent changes in the serum levels of prolactin, nesfatin-1 and ghrelin as a marker of epileptic attacks young male patients. Peptides 2011;32:1276–80.
[90] Schulze-Bonhage A, Sales F, Wagner K, Teotonio R, Carius A, Schelle A, et al. Views of patients with epilepsy on seizure prediction devices. Epilepsy Behav 2010;18:388–96.

[91] Litt B, Esteller R, Echauz J, D'Alessandro M, Shor R, Henry T, et al. Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. Neuron 2001;30:51–64.
[92] Viglione SS, Walsh GO. Proceedings: epileptic seizure prediction. Electroencephalogr Clin Neurophysiol 1975;39:435–6.
[93] Roby RJ, Lettich E. Proceedings: a simplified circuit for stimulus artifact suppression. Electroencephalogr Clin Neurophysiol 1975;39:435.
[94] Li X, Ouyang G, Richards DA. Predictability analysis of absence seizures with permutation entropy. Epilepsy Res 2007;77:70–4.
[95] van Drongelen W, Nayak S, Frim DM, Kohrman MH, Towle VL, Lee HC, et al. Seizure anticipation in pediatric epilepsy: use of Kolmogorov entropy. Pediatr Neurol 2003;29:207–13.
[96] Rosso OA. Entropy changes in brain function. Int J Psychophysiol 2007;64:75–80.
[97] Burioka N, Cornelissen G, Maegaki Y, Halberg F, Kaplan DT, Miyata M, et al. Approximate entropy of the electroencephalogram in healthy awake subjects and absence epilepsy patients. Clin EEG Neurosci 2005;36:188–93.
[98] Lee HC, van Drongelen W, McGee AB, Frim DM, Kohrman MH. Comparison of seizure detection algorithms in continuously monitored pediatric patients. J Clin Neurophysiol 2007;24:137–46.
[99] Chua KC, Chandran V, Acharya UR, Lim CM. Analysis of epileptic EEG signals using higher order spectra. J Med Eng Technol 2009;33:42–50.
[100] Petrosian A, Prokhorov D, Homan R, Dasheiff R, Wunsch Ii D. Recurrent neural network based prediction of epileptic seizures in intra- and extracranial EEG. Neurocomputing 2000;30:201–18.
[101] Rabbi AF, Aarabi A, Fazel-Rezai R. Fuzzy rule-based seizure prediction based on correlation dimension changes in intracranial EEG. Conf Proc IEEE Eng Med Biol Soc 2010;2010:3301–4.
[102] Feldwisch-Drentrup H, Schulze-Bonhage A, Timmer J, Schelter B. Statistical validation of event predictors: a comparative study based on the field of seizure prediction. Phys Rev E Stat Nonlin Soft Matter Phys 2011;83:066704.
[103] Freestone DR, Kuhlmann L, Grayden DB, Burkitt AN, Lai A, Nelson TS, et al. Electrical probing of cortical excitability in patients with epilepsy. Epilepsy Behav 2011;22(Suppl. 1):S110–8.
[104] Fisher RS, Blum DE, Diventura B, Vannest J, Hixson JD, Moss R, et al. Seizure diaries for clinical research and practice: limitations and future prospects. Epilepsy Behav 2012;24:304–10.
[105] Shoeb A, Pang T, Guttag J, Schachter S. Non-invasive computerized system for automatically initiating vagus nerve stimulation following patient-specific detection of seizures or epileptiform discharges. Int J Neural Syst 2009;19:157–72.
[106] Poh MZ, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Sabtala MC, et al. Convulsive seizure detection using a wrist-worn electrodermal activity and accelerometry biosensor. Epilepsia 2012;53:e93–7.
[107] Teixeira CA, Direito B, Feldwisch-Drentrup H, Valderrama M, Costa RP, Alvarado-Rojas C, et al. EPILAB: a software package for studies on the prediction of epileptic seizures. J Neurosci Methods 2011;200:257–71.
[108] Poh MZ. Continuous assessment of epileptic seizures with wrist- worn biosensors. Harvard-MIT Division of Health Sciences and Technology. Cambridge: MIT; 2011.
[109] Poh MZ, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Madsen JR, et al. Autonomic changes with seizures correlate with postictal EEG suppression. Neurology 2012;78:1868–76.
[110] Nagai Y, Goldstein LH, Fenwick PB, Trimble MR. Clinical efficacy of galvanic skin response biofeedback training in reducing seizures in adult epilepsy: a preliminary randomized controlled study. Epilepsy Behav 2004;5:216–23.
[111] Poh MZ, Loddenkemper T, Swenson NC, Goyal S, Madsen JR, Picard RW. Continuous monitoring of electrodermal activity during epileptic seizures using a wearable sensor. Conf Proc IEEE Eng Med Biol Soc 2010;2010:4415–8.
[112] Greene BR, Boylan GB, Reilly RB, de Chazal P, Connolly S. Combination of EEG and ECG for improved automatic neonatal seizure detection. Clin Neurophysiol 2007;118:1348–59.
[113] Poh MZ, Swenson NC, Picard RW. A wearable sensor for unobtrusive, long-term assessment of electrodermal activity. IEEE Trans Biomed Eng 2010;57:1243–52.
[114] Fletcher RR, Poh MZ, Eydgahi H. Wearable sensors: opportunities and challenges for low-cost health care. Conf Proc IEEE Eng Med Biol Soc 2010;2010:1763–6.
[115] Honda K, Kudoh SN. Air brain—the easy telemetric system with smartphone for EEG signal and human behavior. BODYNETS 2013. Boston, MA, United States: ICST; 2013. p. 343–6.
[116] Rajan S, Leonard N, Fletcher R, Casarjian B, Casarjian R, Cisse C, et al. Ambulatory autonomic activity monitoring among at-risk adolescent mothers. J Mob Technol Med 2012;1:25–31.
[117] Hodson H. Smartphone EEG to diagnose epilepsy in poor nations. In: New Scientist, editor. 2014 [Web: http://www.newscientist.com/article/dn24887-smartphone-eeg-to-diagnose-epilepsy-in-poor-nations.html#.U0v-KPldX76].
[118] Scholey L. University of Ottawa professor behind new epilepsy-screening app In: Metro Ottawa, editor. 2014 [Web: http://metronews.ca/news/ottawa/904279/university-of-ottawa-professor-behind-new-epilepsy-screening-app/].
[119] Yang J. Got epilepsy? Now there's an app for that. The World Daily Blog; 2014 [Web: http://www.thestar.com/news/the_world_daily/2014/01/got_epilepsy_now_theres_an_app_for_that.html].
[120] Beniczky S, Polster T, Kjaer TW, Hjalgrim H. Detection of generalized tonic–clonic seizures by a wireless wrist accelerometer: a prospective, multicenter study. Epilepsia 2013;54:e58–61.
[121] Massé F, Van Bussel M, Serteyn A, Arends J, Penders J. Miniaturized wireless ECG-monitor for real-time detection of epileptic seizures. Proceeding WH '10 Wireless, Health; 2010. p. 111–7.
[122] van Elmpt WJ, Nijsen TM, Griep PA, Arends JB. A model of heart rate changes to detect seizures in severe epilepsy. Seizure 2006;15:366–75.
[123] Conradsen I, Beniczky S, Wolf P, Jennum P, Sorensen HB. Evaluation of novel algorithm embedded in a wearable sEMG device for seizure detection. Conf Proc IEEE Eng Med Biol Soc 2012;2012:2048–51.
[124] Fulton S, Van Poppel K, McGregor A, Ellis M, Patters A, Wheless J. Prospective study of 2 bed alarms for detection of nocturnal seizures. J Child Neurol 2012;28:1430–3.
[125] Bayly J, Carino J, Petrovski S, Smit M, Fernando DA, Vinton A, et al. Time-frequency mapping of the rhythmic limb movements distinguishes convulsive epileptic from psychogenic nonepileptic seizures. Epilepsia 2013;54:1402–8.
[126] Fine AM, Reis BY, Nigrovic LE, Goldmann DA, Laporte TN, Olson KL, et al. Use of population health data to refine diagnostic decision-making for pertussis. J Am Med Inform Assoc 2010;17:85–90.
[127] Wang JF, Reis BY, Hu MG, Christakos G, Yang WZ, Sun Q, et al. Area disease estimation based on sentinel hospital records. PLoS One 2011;6:e23428.
[128] Cami A, Arnold A, Manzi S, Reis B. Predicting adverse drug events using pharmacological network models. Sci Transl Med 2011;3:114ra127.
[129] Ramgopal S, Shah A, Zarowski M, Vendrame M, Gregas M, Alexopoulos AV, et al. Diurnal and sleep/wake patterns of epileptic spasms in different age groups. Epilepsia 2012;53:1170–7.
[130] Ramgopal S, Vendrame M, Shah A, Gregas M, Zarowski M, Rotenberg A, et al. Circadian patterns of generalized tonic–clonic evolutions in pediatric epilepsy patients. Seizure 2012;21:535–9.
[131] Pavlova MK, Woo Lee J, Yilmaz F, Dworetzky BA. Diurnal pattern of seizures outside the hospital: is there a time of circadian vulnerability? Neurology 2012;78:1488–92.
[132] Frings L, Wagner K, Maiwald T, Carius A, Schinkel A, Lehmann C, et al. Early detection of behavioral side effects of antiepileptic treatment using handheld computers. Epilepsy Behav 2008;13:402–6.
[133] Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. Neurology 1996;47:260–4.
[134] Arney D, Pajic M, Goldman JM, Lee I, Mangharam R, Sokolsky O. Toward patient safety in closed-loop medical device systems. Proceedings of the 1st ACM/IEEE International Conference on Cyber-Physical Systems. Stockholm, Sweden: ACM; 2010. p. 139–48.
[135] Pauldine R, Beck G, Salinas J, Kaczka DW. Closed-loop strategies for patient care systems. J Trauma 2008;64:S289–94.
[136] Boraud T. Closed-loop stimulation: the future of surgical therapy of brain disorders? Mov Disord 2012;27:200.
[137] Schiff ND, Plum F, Rezai AR. Developing prosthetics to treat cognitive disabilities resulting from acquired brain injuries. Neurol Res 2002;24:116–24.
[138] Georgiadis D, Schwarz S, Kollmar R, Schwab S. Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. Stroke 2001;32:2550–3.
[139] Gigante PR, Goodman RR. Responsive neurostimulation for the treatment of epilepsy. Neurosurg Clin N Am 2011;22:477–80 [vi].
[140] Liang SF, Liao YC, Shaw FZ, Chang DW, Young CP, Chiueh H. Closed-loop seizure control on epileptic rat models. J Neural Eng 2011;8:045001.
[141] Kahol K, Smith M, Brandenberger J, Ashby A, Ferrara JJ. Impact of fatigue on neurophysiologic measures of surgical residents. J Am Coll Surg 2011;213:29–34 [discussion 34–6].
[142] Kumar P, Lee SG, Lee HJ. E-SAP: efficient-strong authentication protocol for healthcare applications using wireless medical sensor networks. Sensors (Basel) 2012;12:1625–47.
[143] SmartWatch motion detecting and alerting device [Web:http://www.smart-monitor.com/].
[144] Morrell MJ, RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77:1295–304.
[145] Hill MW, Wong M, Amarakone A, Rothman SM. Rapid cooling aborts seizure-like activity in rodent hippocampal–entorhinal slices. Epilepsia 2000;41:1241–8.
[146] Yang XF, Schmidt BF, Rode DL, Rothman SM. Optical suppression of experimental seizures in rat brain slices. Epilepsia 2010;51:127–35.
[147] Van Dycke A, Raedt R, Dauwe I, Sante T, Wyckhuys T, Meurs A, et al. Continuous local intrahippocampal delivery of adenosine reduces seizure frequency in rats with spontaneous seizures. Epilepsia 2010;51:1721–8.
[148] Chow BY, Han X, Dobry AS, Qian X, Chuong AS, Li M, et al. High-performance genetically targetable optical neural silencing by light-driven proton pumps. Nature 2010;463:98–102.
[149] Krook-Magnuson E, Armstrong C, Oijala M, Soltesz I. On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy. Nat Commun 2013;4:1376.