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Seizure Detection, Seizure Prediction, and Closed-Loop Warning Systems in Epilepsy

S Ramgopal
S Thome-Souza
M Jackson
N E. Kadish
I Sanchez Fernandez

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Review

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

Sriram Ramgopala, Sigride Thome-Souza, Michele Jackson, Navah Ester Kadisha, Iván Sánchez Fernández, Jacquelyn Klehm, William Bosl, Claus Reinsberger, Steven Schachter, Tobias Loddenkemper

*Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children’s Hospital, Boston, MA, USA
**Department of Pediatrics, Children’s Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
***Psychiatry Department of Clinics Hospital of School of Medicine of University of Sao Paulo, Brazil
****Department of Health Informatics, University of San Francisco School of Nursing and Health Professions, San Francisco, CA, USA
*****Edward B. Bronfman Epilepsy Center, Dept. of Neurology, Brigham and Women’s Hospital, Boston, MA, USA
******Department of Neurology, Harvard Medical School, Boston, MA, USA
*******Institute of Sports Medicine, Department of Exercise and Health, Faculty of Science, University of Paderborn, Germany
********Institute of Sports Medicine, Faculty of Science, University of Paderborn, Warburger Str. 100, 33098 Paderborn, Germany
*********Department of Neuropediatrics and Department of Medical Psychology and Medical Sociology, University Medical Center Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany

Abstract

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

Greene, 2007 [31] ECG/newborn seizures Processing of 41 heart timing variables
Utilizes heart rate from ECG and classifies using statistical methods
Seizures from nonseizure events
SEN of 62.2% and SPEC of 71.8%
SEN of 85.7% and SPEC of 84.6%

SVM-based classifier using features extracted from heart rate variability
Reciprocal power peaks from 10 s preictal to 24 s postictal were 2.96–93.63 times higher than in control
SEN of 60% and SPEC of 60%

Jeffepesen, 2010 [33] ECG/temporal lobe epilepsy
SEN of 62.2% and SPEC of 71.8%

Doyle, 2010 [34] ECG/newborn seizures

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
Use of linear threshold function to determine the presence of nocturnal seizures
SEN of 91.7% and SPEC of 83.9%

Nijsen, 2007 [36] 3-D accelerometers used on both legs and arms and on the chest/myoclonic, tonic, tonic–clonic, and tonic seizures
Algorithm uses standard deviations of moving epochs and uses moving average filter to detect nocturnal frontal lobe seizures
Typical seizure patterns were noted in 95% of motor seizures
SEN of 100% and PPV of 52–93%

Cuppens, 2009 [37] 3-D accelerometers on wrists and ankles/frontal lobe seizures with motor manifestations
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%

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

Pattern recognition algorithm detects seizure events
Time domain- and frequency domain-based algorithm
Identified 91% of clonic or tonic, tonic–clonic, or secondarily generalized seizures

Kramer, 2011 [40] Single 3-D accelerometer worn on the wrist/tonic, GTCS

Van de Vel, 2012 [41] One 3-D accelerometer on each limb/hypermotor seizures
Movement detection system followed by feature extraction
Motor patterns of epileptic seizures
SEN of 96% and PPV of 58%

Time domain- and frequency domain-based model
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

Karayiannis, 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
SEN of 75% and PPV of 85%

Cuppens, 2012 [46] Nocturnal video
Spatiotemporal interest points
Performance compared with EEG

Lu, 2013 [42] Quantify limb movements

Mattress sensor

Activated by tapping noises/bedspring noises. Designed to detect nocturnal seizures
SEN of 62.5% and SPEC of 90.4%

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

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>
<thead>
<tr>
<th>Feature computation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line length</td>
</tr>
<tr>
<td>Frequency or Fourier analysis</td>
</tr>
<tr>
<td>Wavelet transformations</td>
</tr>
<tr>
<td>Principal component analysis (PCA)</td>
</tr>
<tr>
<td>Higher-order spectra analysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support vector machines</td>
</tr>
<tr>
<td>Artificial neural networks</td>
</tr>
<tr>
<td>Fuzzy logic models</td>
</tr>
<tr>
<td>Markov modeling</td>
</tr>
</tbody>
</table>

| 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 intrindividual heterogeneity in focal seizures resulted in a 97% detection rate [23]. |
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 [53]. 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 [54].

When compared with video-EEG results and different accelerometers used to decrease false-positive results over time. 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–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
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 publicly 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.

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


### Table 4

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

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.
<table>
<thead>
<tr>
<th>Company</th>
<th>Brand name</th>
<th>Device type</th>
<th>Article published</th>
<th>Available on market</th>
<th>Signal processing</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>ActiGraph</td>
<td>wGT3X, wActiSleep, GT3X, ActiSleep</td>
<td>Watch activity monitor</td>
<td>No</td>
<td>Yes</td>
<td>Triaxis, solid state accelerometer ambient light photodiode, Wireless ECG</td>
<td><a href="http://www.actigraphcorp.com">http://www.actigraphcorp.com</a></td>
</tr>
<tr>
<td>Advanced Brain Monitoring Affectiva</td>
<td>X series — EEG wireless monitoring Affectiva/Q Sensor</td>
<td>EEG headsets with 4 (×4), 10 (×10), or 24 (×24) channels Wristband</td>
<td>No</td>
<td>No epilepsy</td>
<td>Wireless EEG</td>
<td><a href="http://advancedbrainmonitoring.com">http://advancedbrainmonitoring.com</a></td>
</tr>
<tr>
<td>Alert-It</td>
<td>Ep-It Companion Monitor (ST029)</td>
<td>Bed motion monitor (accelerometer under mattress)</td>
<td>No</td>
<td>No</td>
<td>Wireless to radio transmitter wired to nurse call, telephone dialer, or remote bell</td>
<td><a href="http://www.alert-it.co.uk">http://www.alert-it.co.uk</a></td>
</tr>
<tr>
<td>Ashametrics Company</td>
<td>Wrist LifeBand, Ankle LifeBand, Chest LifeBand</td>
<td>Wristband, ankleband, and chestband</td>
<td>Rajan et al. [116] and Fletcher et al. [114]</td>
<td>Yes</td>
<td>Skin conductance, three-axis accelerometer, ambient temperature sensor, real-time clock</td>
<td><a href="http://www.ashametrics.com">http://www.ashametrics.com</a></td>
</tr>
<tr>
<td>BioLert Company</td>
<td>Baby Ping Baby Ping</td>
<td>Watch-like sensor system Baby monitor — video, audio, and night-vision camera</td>
<td>Kramer et al. [40]</td>
<td>Yes</td>
<td>3G, 4G, Wi-Fi connection</td>
<td><a href="http://www.biolertsy.com">http://www.biolertsy.com</a></td>
</tr>
<tr>
<td>The Bhutan Epilepsy Project/ Grand Challenges Canada Capture Proof</td>
<td>2014 The Bhutan Epilepsy Project Capture Proof</td>
<td>Portable EEG telemetry system using 3G network with a smartphone HIPAA compliant platform to share medical videos</td>
<td>No</td>
<td>No</td>
<td>3G, Wi-Fi connection to smartphone</td>
<td><a href="http://www.bhutanbrain.com">http://www.bhutanbrain.com</a></td>
</tr>
<tr>
<td>Cyberonics Inc.</td>
<td>Aspire</td>
<td>Cardiac abnormalities during epileptic seizures</td>
<td>No</td>
<td>No</td>
<td>System linked to VNS system (closed-loop)</td>
<td><a href="http://www.clinicaltrials.gov/ct2/show/NCT0268623">http://www.clinicaltrials.gov/ct2/show/NCT0268623</a></td>
</tr>
<tr>
<td>Danish Care ApS</td>
<td>Epi-Care Free Device Epi-Care 3000</td>
<td>Wristband — accelerometer Bed motion monitor (accelerometer under mattress)</td>
<td>Beniczky et al. [120]</td>
<td>Yes</td>
<td>Wireless transmission — pager and mobile phone, Wireless call — SMS message, pager, or emergency phone</td>
<td><a href="http://www.dansichcare.dk/uk">http://www.dansichcare.dk/uk</a></td>
</tr>
<tr>
<td>Movisens</td>
<td>Electrodensital activity sensor</td>
<td>Electodes (palm, sole of foot, and finger)</td>
<td>No</td>
<td>Yes</td>
<td>Raw signals of electrodensital activity, 3-axis acceleration, air pressure, and temperature</td>
<td><a href="http://www.movisens.com">http://www.movisens.com</a></td>
</tr>
<tr>
<td>Empatica</td>
<td>E3 Wristband</td>
<td>Wristband and free mobile phone application</td>
<td>No</td>
<td>No</td>
<td>Photoplethysmography, electrodermal activity, triaxis accelerometer, body temperature, and heat flux</td>
<td><a href="https://www.empatica.com">https://www.empatica.com</a></td>
</tr>
<tr>
<td>EpDetect</td>
<td>EpDetect</td>
<td>Free mobile phone application (accelerometer)</td>
<td>No</td>
<td>Yes</td>
<td>Wireless transmission — SMS messaging, movement detection, and GPS system</td>
<td><a href="http://www.epdetect.com">http://www.epdetect.com</a></td>
</tr>
<tr>
<td>EpiCall Ltd.</td>
<td>EpiCall</td>
<td>Sticker placed on the side of the face with electrodensital and photoplethysmograph electrodes</td>
<td>No</td>
<td>No</td>
<td>Monitoring seizure biomarkers (heart rate and extraocular eye movements)</td>
<td><a href="http://www.clinicaltrials.gov/ct2/show/NCT01436695">http://www.clinicaltrials.gov/ct2/show/NCT01436695</a></td>
</tr>
<tr>
<td>Garmin</td>
<td>Garmin Forerunner 310X</td>
<td>Watch</td>
<td>No</td>
<td>Yes</td>
<td>Heart rate monitor</td>
<td><a href="http://www.heartratemonitors.com">http://www.heartratemonitors.com</a></td>
</tr>
<tr>
<td>Holst Centre/JMEC, IctalCare A/S</td>
<td>IctalCare 365</td>
<td>Armiband with chest electrodes</td>
<td>Massé et al. [121] and van Elpitt et al. [122]</td>
<td>No</td>
<td>Prototypes using electroencephalogram, electrocardiogram, and accelerometer</td>
<td><a href="http://www.hobohreeze.nl/engels/epilepsie.html">http://www.hobohreeze.nl/engels/epilepsie.html</a></td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Company</th>
<th>Brand name</th>
<th>Device type</th>
<th>Article published</th>
<th>Available on market</th>
<th>Signal processing</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medpage</td>
<td>MP5</td>
<td>Bed motion sensor and vocalization microphone (accelerometer under mattress and microphone)</td>
<td>Fulton et al. [124] and Carlson et al. [47]</td>
<td>Yes</td>
<td>Wireless transmission — radio pager</td>
<td><a href="http://www.medpageusa.com">http://www.medpageusa.com</a></td>
</tr>
<tr>
<td></td>
<td>MP2</td>
<td>Bed motion sensor (accelerometer under mattress)</td>
<td>No</td>
<td>Yes</td>
<td>Wireless transmission — a radio alarm pager and/or a desktop alarm receiver</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>ST2</td>
<td>Bed motion sensor and breathing cessation monitor (accelerometer under mattress)</td>
<td>Fulton et al. [124]</td>
<td>Yes</td>
<td>Wireless transmission — radio pager</td>
<td>—</td>
</tr>
<tr>
<td>Mio Alpha Sensorium</td>
<td>Mio Alpha Strapless</td>
<td>Watch Bed motion sensor (accelerometer under mattress)</td>
<td>No</td>
<td>Yes</td>
<td>Heart rate monitor</td>
<td><a href="http://www.alphaheartrate.com">http://www.alphaheartrate.com</a></td>
</tr>
<tr>
<td></td>
<td>Sensealert-102/EP200</td>
<td>Wristband Bed motion sensor (accelerometer under mattress)</td>
<td>No</td>
<td>Yes</td>
<td>Digital microprocessor — radio transmission</td>
<td><a href="http://www.sensorium.co.uk">http://www.sensorium.co.uk</a></td>
</tr>
<tr>
<td>Sparkfun</td>
<td>ADLC330</td>
<td>Wristband Wristwatch</td>
<td>Bayly et al. [125]</td>
<td>Yes</td>
<td>Triple axis accelerometer</td>
<td><a href="https://www.sparkfun.com">https://www.sparkfun.com</a></td>
</tr>
<tr>
<td>Polar</td>
<td>FT1, FT2, FT60, FT80, FT40, FT7</td>
<td>Watch Seizure Alert and Recorder (accelerometer under development)</td>
<td>No</td>
<td>No</td>
<td>Wireless transmission — SMS messaging, movement detection, and GPS system</td>
<td><a href="http://shilene.com">http://shilene.com</a></td>
</tr>
<tr>
<td>Shilene.com</td>
<td>M5, Suunto Quest</td>
<td>Watch Free mobile phone application (accelerometer under development)</td>
<td>No</td>
<td>No</td>
<td>Wireless transmission — SMS messaging, movement detection, and GPS system</td>
<td><a href="http://www.shilene.com">http://www.shilene.com</a></td>
</tr>
<tr>
<td>Suunto</td>
<td>Timex Heart Rate Monitor</td>
<td>Watch Watch Heart rate monitor</td>
<td>No</td>
<td>Yes</td>
<td>Heart rate monitor</td>
<td><a href="http://www.suunto.com">www.suunto.com</a></td>
</tr>
<tr>
<td></td>
<td>Timex</td>
<td>Watch</td>
<td>No</td>
<td>Yes</td>
<td>Heart rate monitor</td>
<td><a href="http://www.timex.com">www.timex.com</a></td>
</tr>
</tbody>
</table>
### Table 6
Electronic seizure record applications.

<table>
<thead>
<tr>
<th>Mobile application</th>
<th>Founder</th>
<th>App purpose</th>
<th>Device type</th>
<th>Clinical trial</th>
<th>Available on market</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleveland Clinic MyEpilepsy</td>
<td>The Cleveland Clinic Foundation</td>
<td>Seizure diary, educational tool, and emergency</td>
<td>iPad only</td>
<td>No</td>
<td>Yes</td>
<td><a href="http://my.clevelandclinic.org/mobile-apps/epilepsy-app.aspx">http://my.clevelandclinic.org/mobile-apps/epilepsy-app.aspx</a></td>
</tr>
<tr>
<td>E-Action Info: your epilepsy</td>
<td>UCB Pharma SA, Logicopolis Technology Inc., CPC Healthcare Communications Toronto Gilles Huberfeld, UCB Pharma S.A. France/Brain and Spine Institute</td>
<td>Educational tool and link to my epilepsy diary</td>
<td>iPhone, iPad, iPod Touch</td>
<td>No</td>
<td>Yes</td>
<td><a href="http://www.e-action.ca/Home.aspx?lang=en">http://www.e-action.ca/Home.aspx?lang=en</a></td>
</tr>
<tr>
<td>Epi &amp; Me</td>
<td>Soda Virtual</td>
<td>Seizure diary</td>
<td>iPhone, iPad, iPod Touch</td>
<td>No</td>
<td>Yes</td>
<td><a href="http://epiandme.com/">http://epiandme.com/</a></td>
</tr>
<tr>
<td>Epilepsy App</td>
<td>Epilepsy Action British Epilepsy Association</td>
<td>Seizure diary, educational tool, emergency guide</td>
<td>Android MDA, iPhone, iPad, iPod Touch and, online account</td>
<td>No</td>
<td>Yes</td>
<td><a href="https://itunes.apple.com/us/app/epilepsia-app/id5894298737mt=8">https://itunes.apple.com/us/app/epilepsia-app/id5894298737mt=8</a></td>
</tr>
<tr>
<td>Epilepsy Guide App</td>
<td>National Society for Epilepsy</td>
<td>Seizure diary and emergency guide</td>
<td>Android MDA, iPhone, iPad, iPod Touch</td>
<td>No</td>
<td>Yes</td>
<td><a href="http://www.epilepsysociety.org.uk/">http://www.epilepsysociety.org.uk/</a></td>
</tr>
<tr>
<td>Epilepsy Manager Pro/Epilepsy Manager 2/</td>
<td>Julia Bechman</td>
<td>Seizure diary</td>
<td>Android MDA, iPhone, iPad, iPod Touch</td>
<td>No</td>
<td>Yes</td>
<td><a href="https://itunes.apple.com/us/app/epilepsy-manager-pro/id7660218617nt=8">https://itunes.apple.com/us/app/epilepsy-manager-pro/id7660218617nt=8</a></td>
</tr>
<tr>
<td>My Epilepsy Diary</td>
<td>Dr. Robert Fisher and Patty Shafer, RN Epilepsy Foundation</td>
<td>Seizure diary</td>
<td>Android MDA, iPhone, iPad, iPod Touch, and online account</td>
<td>No</td>
<td>Yes</td>
<td><a href="http://www.epilepsy.com/seizurediary">www.epilepsy.com/seizurediary</a></td>
</tr>
<tr>
<td>Seizure Diary</td>
<td>Gavin Harris</td>
<td>Seizure diary</td>
<td>iPhone, iPad, iPod Touch</td>
<td>No</td>
<td>Yes</td>
<td><a href="https://itunes.apple.com/us/app/seizure-diary/id4022012797nt=8">https://itunes.apple.com/us/app/seizure-diary/id4022012797nt=8</a></td>
</tr>
<tr>
<td>Seizure Disorder Coach</td>
<td>Think Safe Inc. Cloud Med LLC</td>
<td>Emergency guide</td>
<td>iPhone, iPad, iPod Touch</td>
<td>No</td>
<td>Yes</td>
<td><a href="http://resqsoftware.com/seizure.php">http://resqsoftware.com/seizure.php</a></td>
</tr>
<tr>
<td>Seizure Journal for Parents</td>
<td>Dmitry Ulupov, Satoru Systems Rob and Lisa Moss/Seizure Tracker LLC</td>
<td>Seizure diary</td>
<td>iPhone, iPad, iPod Touch</td>
<td>No</td>
<td>Yes</td>
<td><a href="https://itunes.apple.com/us/app/seizure-journal-for-parents/id4200541387nt=8">https://itunes.apple.com/us/app/seizure-journal-for-parents/id4200541387nt=8</a></td>
</tr>
<tr>
<td>Young Epilepsy</td>
<td>Young Epilepsy, The National Centre for Young People with Epilepsy</td>
<td>Seizure diary, educational tool, emergency guide</td>
<td>Android MDA, iPhone, iPad, iPod Touch, and online account</td>
<td>No</td>
<td>Yes</td>
<td><a href="http://youngepilepsy.org.uk/all-about-epilepsy/epilepsy-app">http://youngepilepsy.org.uk/all-about-epilepsy/epilepsy-app</a></td>
</tr>
</tbody>
</table>

MDA: mobile device app.
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 sub-specialties, 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.
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 health-care 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 Epilept system, (Biolet 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.biolerlys.com).

Neurostimulators are promising tools for the treatment of seizures. The responsive neurostimulation system (Neurpace 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.neurpace.com/product/overview.html). The Neurpace system is also unique in that it is able to detect both clinical and electrogaphic 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 vent seizures before they occur. Other techniques for seizure abortion using benzodiazepines, delivered through multiple routes (intravenous, refractory epilepsy in 2010 but is not approved in the US.

terior thalamic stimulation has received European CE Mark approval for the regulation of medical devices. This regulatory framework in-

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

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Appendix A. Supplementary data

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References


