17

Preliminary Report

PREDICTION OF SEIZURES DURING SLEEP

GROUP 17: JACK LIN, JOSH OLICK-GIBSON, NIKHIL PATEL

OCTOBER 6TH, 2017

1.0 Background

Sixty-five million people around the world have epilepsy. In the United States, 1 in 26 people will develop epilepsy at some point in their life. Epilepsy is a condition characterized by disturbances in the electrical activity in the brain, resulting in a seizure. Symptoms of a seizure can range from a minor space out (absence seizure) to severe convulsions (tonic-clonic seizures). Typically, epilepsy is diagnosed in a person who has had two or more seizures, or had one seizure with a high risk for future episodes. Types of seizures are classified by where they begin in the brain. Focal onset seizures originate in a group of cells in one side of the brain. Generalized onset seizures originate in groups of cells in both sides of the brain. Types of generalized onset seizures include tonic-clonic (also known as "convulsive"), absence, and atonic. Treatments for epilepsy include seizure medication, devices, surgery, and dietary therapy. These treatments have proven to be effective in many, but not all, epileptic individuals. For 1 in 3 people with epilepsy, there is currently no available treatment that controls their seizures. In rare instances, epilepsy can even lead to death [1].

Sudden Unexpected Death in Epilepsy (SUDEP) is believed to be the leading cause of epilepsy-related deaths, affecting 1 in 1000 people with epilepsy. SUDEP is cited as the cause of death in an epileptic person when no other cause of death is found. For this reason, most cases of SUDEP are not diagnosed in individuals until an autopsy is performed. Although the specific causes of SUDEP are relatively unknown, several potential risk factors have been identified. People who experience generalized tonic-clonic seizures are at the highest risk for SUDEP. Other risk factors include, but are not limited to, abrupt changes in medication, excessive drinking, using illegal substances, having epilepsy for more than 15 years, and having seizures during sleep [1].

Although very little is known about the causes of SUDEP, experts in the medical community generally agree that the incidence of SUDEP can be reduced through improved early detection methods and monitoring of patients when they are about to have or are actively suffering from a seizure [2].

2.0 Clinical Need

There is a need to alert individuals who are at high risk for seizure during sleep to an impending epileptic event to decrease the frequency of Sudden Unexpected Death in Epilepsy (SUDEP).

3.0 Project Scope

This project proposes to deliver a safe, comfortable, and easy to use device that can be worn overnight. It will use available physiological data to accurately predict an impending seizure, and will alert the user and emergency medical services a short time (on the order of minutes) before the seizure begins. The proposed device will be delivered to Dr. David Lardizabal and the BME 401 instructors, including the necessary software for seizure prediction and a user manual for safe operation by the end of April 2018.

4.0 Existing Solutions

4.1 Commonly Used Methods for Seizure Detection

The primary methods used for seizure detection currently are wristbands/watches, cell phones, and mattress sensors. All of these methods rely primarily on accelerometry to detect active seizures and some use additional signals such as pulse or electrodermal activity. Many of these devices are also capable of alerting a caregiver if an active seizure is occurring. One device on the market that is commonly used is the Embrace wristband by Empatica (shown in

Figure 1). This wristband uses an accelerometer, a gyroscope, an electrodermal activity sensor, and a peripheral temperature sensor to detect an ongoing seizure. When an event is detected, the wristband uses a bluetooth connection to a phone to alert preprogrammed caregivers so that the patient can get the help they need [3]. While this is an effective tool that is easy to use, there are a wide array of activities that could produce the same signals as a seizure using this method and could lead to false alarms. It is also unlikely that this wristband is being worn during sleep and therefore is unable to make detections during that time. Additionally, this device cannot predict a seizure before it happens and is therefore putting the patient at greater risk for SUDEP. See more existing devices in Appendix B.

Figure 1: Front and back views of the Empatica E3 wristband show the wide array of sensors available to collect user data [3]

Other methods that have been used to detect seizures include video detection, audio classification, and seizure alert dogs. While these methods are all effective in certain instances, they all have severe limitations. Video detection is limited by what can be seen by the camera and have a limited view. Similarly, audio classification requires that a microphone is listening at all times and will be impeded by any background noise. Seizure alert dogs are commonly used for many seizure patients, but are only valuable as long as the dog is awake, alert, and watching the patient. This means that they are not able to assist while they are asleep. Research that has explored these possible solutions is described in Appendix C.

4.2 EEG and ECoG Based Seizure Detection and Prediction

The majority of the research that has been performed with the goal of accurate detection and prediction of seizures has been done using electroencephalography (EEG) and electrocorticography (ECoG). Because the cause of a seizure is sudden and disorganized electrical activity in the brain, collecting data on brain signals is an effective method of determining if an individual is about to have or is currently having a seizure. It is common to apply a machine learning method in these experiments as shown in Figure 2 [4].

This process begins by collecting data from the patient which is then processed using a feature extraction algorithm. These algorithms extract meaningful pieces of information from the ECG or ECoG signal, called features. Feature computation occurs in three steps: preprocessing, feature computation, and feature reduction. Preprocessing is often used to convert the signal into another form that may be easier to manipulate or may involve removing segments of data that are not usable. The features are then computed from the signal using methods that depend on both the signal type and features being computed. Commonly used feature extraction algorithms include Fourier analysis, wavelet transformations, and principal component analysis. Finally, with feature reduction, the available features are combined using either feature selection (choosing the most meaningful subset of the computed features) or feature extraction (compressing the

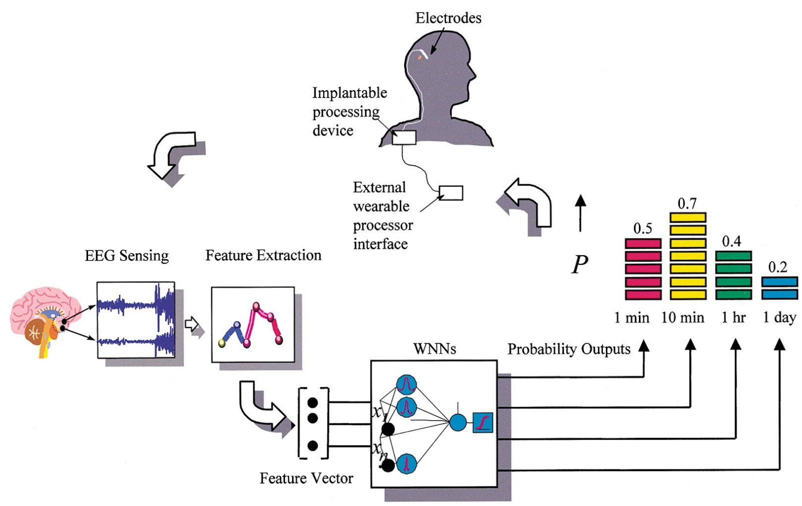


Figure 2: Overview of a theoretical ECoC machine learning prediction algorithm as outlined by Litt et al. Data is first collected from the patient through implanted electrodes (top). Analysis is performed on this data that extracts meaningful features to produce a feature vector (left). This feature vector first used to train a classifier, such as a Wavelet Neural Network (WNN, bottom). After training, this classifier can compute the likelihood of the user having a seizure and use that information to make a prediction and alert the patient [4].

information in the computed features into fewer features). Some of the features that were used in the identified studies include mean, correlation dimension, power, etc. This data is then used to determine if the patient is ictal (having a seizure) or preictal (about to have a seizure) using a machine learning classifier. The classifier is trained using a portion of the available data that is known to be collected during an ictal, pre-ictal, or interictal (normal) period. The trained classifier can then be tested on new signals to determine the state of the patient at the time the data was collected [5].

Several researchers using this method have produced accurate classifiers, however, they are dependent on EEG data which is difficult to collect outside of a lab or medical setting. Patients are not able to sleep with EEG electrodes on, and often these are not tolerated well for long periods of time. An intracranial EEG would eliminate this problem, but would require the patient to undergo an arduous surgery process to have the electrodes inserted.

Most research into these techniques has not involved real-time prediction, but rather has used data from past seizures to construct a classifier that is tested on other EEG/ECoG data that has already been collected. Appendices C and D technology that has been developed using this technique. Many of these classifiers are able to achieve a sensitivity above 90% [5]. One example of this is the work done by D'Alessandro et al. in 2005 to produce a probabilistic neural network classifier. In this study, data was collected using 8 intracranial EEG channels. Among 25,872 possible features computed among the 8 electrodes, a reduced search space of 800 electrodes was used. The classifier was trained using 4 hours of baseline data and 10 minutes of preictal data for the first 4 clinical seizures. This classifier was able to predict 100% of seizures up to 10 minutes before they occurred with a false positive rate of 1.1/hour [6]. While this data is effective for predicting seizures within a helpful timeframe, it is only able to do so after the seizure has occurred and was not tested using a real time application.

4.3 Seizure Detection Using Non-EEG Signals

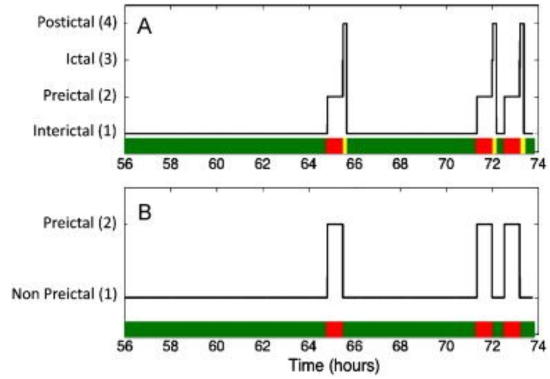


Figure 3: Time series encoding the classification of the cerebral states for three seizures using both four class encoding (A) and two class encoding (B) using the EPILAB software. (Green = interictal period, red = preictal period, and yellow = ictal/postictal period) [7].

While most research uses EEG and ECoG, there has been exploration into the use of other signals, such as ECG. Teixeira et al. developed a software package, EPILAB, that provides researchers with a simple user interface for efficiently analyzing long term EEG and ECG data in the context of seizure prediction. EPILAB can construct classifiers of various types using over 35 univariate and multivariate features from both EEG and ECG data. It uses these classifiers to determine if the subject is in an interictal, preictal, ictal, or postictal state. A variety of user settings allow flexibility with respect to feature extraction and analysis, classifier training, and prediction [7]. Figure 3 shows a sample time series output of using the software, showing that it was able to successfully identify the preictal period.

4.4 Real-time Seizure Prediction

It should also be noted that most current research analyzes data after the seizure has occurred, rather than in real time. Cook et al., however, did perform one such experiment and demonstrated successful real-time seizure prediction. In this study, 15 patients were implanted with an intracranial EEG advisory system. These patients then underwent a 1 month advisory period during which data was recorded and used to construct an individualized prediction algorithm for each patient. Patients then entered a 3 month advisory phase and were given warning of an impending seizure with lights that indicated low, moderate, and high likelihood. The system was able to predict seizures with sensitivities ranging from 65-100% with no significant deterioration in effectiveness over time [8].

4.5 Patents and Related Technology

There are a number of patents that describe technology similar to those described above. One patent published by Leyde and Dilorenzo in 2007 broadly outlines this method of determining a patient's neurological state by collecting EEG data, analyzing the signal using a machine learning process and predicting the likelihood of a patient having a seizure [9]. There is also a series of patents that describe standard seizure detection methods such as those that can be placed under a mattress or can be worn on the patient's wrist [10].

There is also a significant amount of overlap in the technology used to detect seizures as the technology used to detect sleep apnea. There are three primary types of home sleep test monitors used for sleep apnea: Type II, Type III, and Type IV. Each of these monitors measures a different number of channels to measure different types of signals (ranging from 7 channels on Type II to 1 or 2 channels on Type IV) [11]. A patent for a Type III monitor invented by Bowers and Kienle describes one of these devices that includes an SaO_2 sensor, a breathing sensor, a snorting sensor, and a head position sensor [12]. A typical monitor setup can be seen in Figure 4. Some sleep apnea monitors, such as the one previously described, do not provide a method of sleep apnea detection, and require manual scoring of results. Others, such as one designed by Bsoul et al. are capable of detecting sleep apnea in real time by extracting features from ECG data and using a support vector machine to make a determination of whether the patient is experiencing sleep apnea [13]. Similar devices have been used in an attempt to reduce the frequency of sudden infant death (SID) during sleep. A device designed by Kim in 1996 describes the use of pulse oximetry and video monitoring to determine when to set off an alarm that alerts parents that their child is at risk for SID [14].

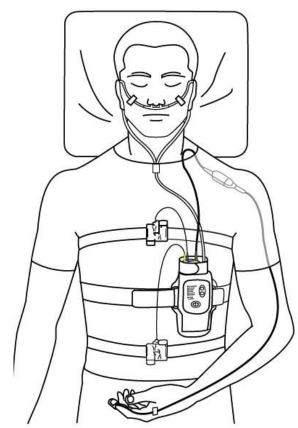


Figure 4: Typical setup for a home sleep apnea test [11].

5.0 Design Specifications

Because the market for a seizure detection device consists of epileptic individuals, it is crucial to consider the parameters of such a device that these patients deem most important. A study performed by Shulze-Bonhage et al. determined what these parameters were. Most patients preferred to be alerted by an acoustic warning, as opposed to a visual warning or a warning via text message. Furthermore, the majority of patients surveyed in the study preferred to be alerted to a seizure less than one hour before it occurred. If the prediction window were any longer than this, patients would feel heightened anxiety due to anticipation of the impending seizure. The patients' primary concern with such a device was its sensitivity—that is, how readily it could detect a seizure and alert the patient. Additionally, the importance of the device's specificity was considered by most patients to be secondary to its sensitivity [15]. These specifications are outlined in Tables 1 and 2, in addition to others deemed relevant by the authors of this preliminary report.

Table 1: Sensor Specifications

Specification	Unit	Value	Description
Safety	Unitless	Unitless	Device should be safe to wear during sleep. It should not contain sharp edges or cords that can tangle, and should be properly insulated
Comfort	Unitless	Unitless	Device should not prevent the user from sleeping comfortably
Size	cm	cm	Device size should not hinder the patient's ability to sleep and should be large enough to be able to collect the relevant data
Weight	g	g	Device weight should not hinder the patient's ability to sleep
Operating time	Hours	12 Hours	Device should be operational throughout the night

Table 1: Sensor Specifications (continued)			
Specification	Unit	Value	Description
Consumer Cost	$	$1,000	Device consumer cost is predicted by client to be of similar cost to current AED devices
Production Cost	$	$300	Device production cost is estimated to be ⅓ of the consumer cost
Transmission	unitless	unitless	Device should transmit signals wirelessly to the receiver
Software Platform	unitless	unitless	Device should be able to collect the necessary data and send them to the receiver

Table 2: Receiver Specifications			
Specification	Unit	Value	Description
Software platform	Unitless	Unitless	Device software should process data with minimal delay, predict an impending seizure, and send an alert to the patient and EMS
Prediction Interval	Min	5-60 min	Device should be able to alert the patient of impending seizure 5 to 60 min prior to onset
Prediction Alert	Unitless	Unitless	Device should acoustically alert the patient when an impending seizure is predicted
Detection Alert	Unitless	Unitless	Device should alert emergency services when an active seizure is detected
Reliability (Repeatability)	Unitless	0.9	Consistency in measurements taken by the device across multiple trials
Sensitivity	%	90%	Device should accurately predict an impending seizure within a certain percentage
Range	m	20 m	Device should be able to receive signals from the sensor within 20 meters
Security	%	100%	Data collected will only be accessible to the user and to emergency services

6.0 Preliminary Design Schedule

See Appendix A for the preliminary design schedule.

7.0 Team Responsibilities

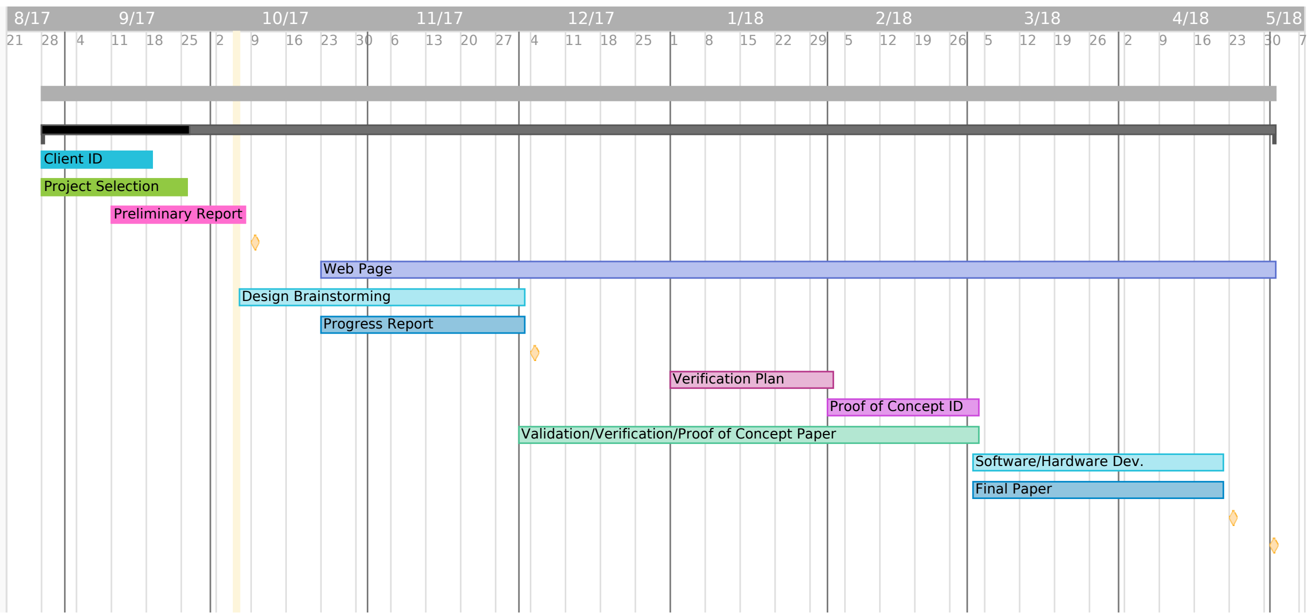
Table 3: Team Responsibilities			
Responsibility	Jack Lin	Josh Olick-Gibson	Nikhil Patel
Written Reports	x	x	x
Weekly Reports	x	x	x
Website	x		
Software Development			x
Hardware Development	x	x	
Preliminary Presentation			x
Progress Presentation	x		
V&V Presentation		x	
Poster	x	x	x
Final Presentation	x	x	x

8.0 Conclusion

There is a need to alert high risk epileptic individuals to an impending seizure. Over the past twenty years, the scientific and medical community has performed a substantial amount of research on seizure detection methods, ranging from EEG and ECoG to seizure alert dogs. Many potential solutions have emerged from this research, but not without limitations. The existing solutions to this problem primarily suffer from high false alarm rates, inaccessibility to the patient during sleep, and lack of real-time seizure prediction. This project aims to meet the need for a device that will address these limitations.

Appendix A: Preliminary Design Schedule

SUDEP	start	end	12%
	08/28/17	**05/01/18**	**12%**
Client ID	08/28	09/18	100%
Project Selection	08/28	09/25	100%
Preliminary Report	09/11	10/06	100%
Preliminary Presentation	10/09	10/09	0%
Web Page	10/23	05/01	0%
Design Brainstorming	10/06	12/01	0%
Progress Report	10/23	12/01	0%
Progress Report Presentation	12/04	12/04	0%
Verification Plan	01/01	02/01	0%
Proof of Concept ID	02/01	03/02	0%
Validation/Verification/Proof of Conc...	12/01	03/02	0%
Software/Hardware Dev.	03/02	04/20	0%
Final Paper	03/02	04/20	0%
Prototype Demo	04/23	04/23	0%
BME day	05/01	05/01	0%



Appendix B: Existing Device Solutions

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 (x4), 10 (x10), or 24 (x24) channels	No	Yes	Wireless EEG	http://advancedbrainmonitoring.com
Affectiva		Wristband	Poh et al. and Fletcher et al.	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.	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. and Fletcher et al.	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.	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, Scholey, and Yang	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.	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.	Yes	Wireless transmission	http://www.emfit.com
Empatica [66]	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. and van Elmpt et al.	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.	No	Wireless surface electromyography (sEMG)	http://ictalcare.com/
Medpage	MP5	Bed motion sensor and vocalization microphone (accelerometer under mattress and microphone)	Fulton et al. and Carlson et al.	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.	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.	Yes	Triple axis accelerometer	https://www.sparkfun.com

Company	Brand name	Device type	Article published	Available on market	Signal processing	Website
Smart Monitor Corp.	SmartWatch	Wristwatch	Lockman et al.	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

Author, year	Measuring Device	Detection algorithm	Results
Electroencephalography/ electrocorticography			
Webber, 1996	EEG (24-40 channels)	ANN classification system	SEN of 76% and FPR of 1 event/h
Pradhan, 1996	EEG (8 channels)	Wavelet transformation feature acquisition, ANN classification	SEN of 97% and SPEC of 89.5%
Gabor, 1998	EEG (8 channels)	Self-organizing neural network with unsupervised training	SEN of 92.8% and FPR of 1.35 events/h
Petrosian, 2000	EEG (32 channels), Intracranial EEG	Recurrent Neural Networks (RNN) combined with wavelet processing	Detected preictal stages iwthin minutes of seizure onset
Wilson, 2004	EEG (8-32 channels)	Combined algorithm (utilizes matching pursuit, small neural networks, and clustering algorithm)	SEN of 76% and FPR of 0.11 events/h
Wilson, 2005	EEG (single channel selected)	Used a trained probabilistic neural network for rapid detection of seizures	SEN of 89% and FPR of 0.56 events/h
Alkan, 2005	EEG (4 channels)	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 [6]	Intracranial EEG	Genetic algorithm for signal processing, probabilistic neural network for classification	100% prediction of seizures within 10 min prior to onset
Arabi, 2006	EEG	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	Ambulatory EEG	Continuous wavelet transform	Over 90% of spike detection
Chan, 2008	Intracranial EEG	SVM system	SEN of 80-98%, FPR of 38%
Netoff, 2009	EEG (6 channels)	Cost-sensitive SVM system	SEN of 77.8%, no false positives detected
Chua, 2009	EEG	Data processing by higher-order spectra analysis followed by classification by the Gaussian mixture model or SVM	Accuracy of 92-93%
Mirowski, 2009	EEG	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	EEG (3 channels)	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	EEG (multichannel)	Least-squares parameter estimator for extraction followed by SVM classification	SEN of 100%
Peterson, 2011	EEG (single channel)	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	EEG (8 bipolar)	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	EEG	Higher-order spectra-based feature extraction followed by SVM	Detection accuracy of 98.5%
Kharbouch, 2011	Intracranial EEG	Multistep feature extraction system followed by SVM classifier, individualized for patients	Detected 97% of seizures, FPR of 0.6 events/day

Author, year	Measuring Device	Detection algorithm	Results
Liu, 2012	Intracranial EEG	Wavelet decomposition-based feature extraction followed by SVM classification	SEN of 94.5% and SPEC of 95.3%
Xie, 2012	EEG (6 channels)	Feature extraction by wavelet-based sparse functional linear model and 1-NN classification method	Has 99-100% classification accuracy
Direito, 2012	EEG (multichannel)	Markov modeling classification system. Identified four states - preictal, ictal, postictal, and interictal	Point-by-point accuracy of 89.3%
Rabbi, 2012	Intracranial EEG	Used fuzzy algorithms for feature extraction for classification	SEN of 95.8% and FPR of 0.26 events/h
Implanted advisory system			
Cook, 2013	Intracranial implanted device	Cluster computing system at NeuroVista (one algorithm for each patient)	SEN of 65%-100%
Electromyography			
Conradsen, 2010	Electromyography	Features extracted from surface electromyography acceleration and angular velocity/seizure-like movements performed by healthy volunteers	SEN of 91-100% and SPEC of 100%
Conradsen, 2012	Electromyography and motion sensor features	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	ECG	Processing of 41 heart timing variables	SEN of 62.2% and SPEC of 71.8%
Malarvili, 2009	ECG	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	ECG	Time-frequency features from ECG extracted followed by wrapperbased 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	ECG	SVM-based classifier using features extracted from heart rate variability	SEN of 60% and SPEC of 60%
Accelerometry			
Nijsen, 2005	3-D accelerometers used on both legs and arms and on the chest/myoclonic, tonic, tonic-clonic, startle, SPS, CPS	Typical seizure patterns were noted in 95% of motor seizures	
Nijsen, 2007	3-D accelerometers used on both legs and arms and on the chest/myoclonic, clonic, and tonic seizures	SPEC of 100% and PPV of 52-93%	

Author, year	Measuring Device	Detection algorithm	Results
Cuppens, 2009	3-D accelerometers on wrists and ankles/frontal lobe seizures with motor manifestations	SEN of 91.7% and SPEC of 83.9%	
Nijsen, 2010	3-D accelerometers and video-EEG used on both legs and arms and on the chest	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	Single 3-D accelerometer worn on the wrist	Pattern recognition algorithm detects seizure events	Detects tonic-clonic seizures. SEN of 87.5%. 204 false positives
Kramer, 2011	Single 3-D accelerometer worn on the wrist	Time domain- and frequency domain-based algorithm	Identified 91% of clonic or tonic, tonic-clonic, or secondarily generalized seizures
Van de Vel, 2012	One 3-D accelerometer on each limb	Movement detection system followed by feature extraction	SEN of 96% and PPV of 58%
Dalton, 2012	Accelerometer-based kinematic sensor	Motor patterns of epileptic seizures	SEN of 91% and SPEC of 84%
Beniczky, 2013	Single 3-D accelerometer worn on the wrist	Time domain- and frequency domain-based algorithm	SEN of 91% and FPR of 0.2 events/day
Video detection systems			
Karayinnis, 2004	Video segments of seizures	Neural network model	SEN N 90%, SPEC N 95%
Cuppens, 2010	Epilepsy monitoring unit-derived video segments	Optical flow algorithm	Detection of seizures from video recordings using trial in pediatric nighttime seizures
Cuppens, 2012	Nocturnal video	Spatiotemporal interest points	SEN of 75% and PPV of 85%
Lu, 2013	Quantify limb movements	Gaussian mixture models	Performance compared with EEG
Mattress sensor			
Carlson, 2009	Microphone under mattress	Activated by tapping noises/bedspring noises. Designed to detect nocturnal seizures	SEN of 62.5% and SPEC of 90.4%
Narechania, 2011	Quasi-piezoelectric sensor	Activated by rhythmic movements	Detected 80% of seizures, 14 false alarms occurred during periods of patient wakefulness
Audio classification			
Bruijne, 2009	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			

Author, year	**Measuring Device**	**Detection algorithm**	**Results**
Strong, 1999	Trained dog	Anecdotal evidence of seizure giving warnings from 15 to 45 min prior to seizure onset	N/A

Author, year	Measuring Device	Detection algorithm	Results
Litt, 2001 [61]	Intracranial EEG (3-14 days, continuous)	Visual review of epileptologists to identify the earliest EEG change associated with seizures and the the unequivocal EEG onset of seizures	Able to detect signals of seizures several hours (~7) before the seizure actually occurs (however this identification occurred after the fact)
Li, 2007	Rat EEG	Threshold for the permutation or sample entropy (decrease in the entropy/less stability in entropy indicates an impending seizure state)	Mean anticipation time for permutation = 4.9s (with 54% pre-ictal detection) and for sample = 3.7s (with 21% pre-ictal detection)
Van Drongelen, 2003	Surface EEG (2 patients) and Intracranial EEG (3 patients)	Time series analysis using Kolmogorov entropy	Anticipation times between 2 and 40 minutes; As effective as the more commonly used correlation dimension in anticipating seizures
Bruioka, 2005	EEG (no further information)	Evaluated approximate entropy (ApEn) in EEG and found it was significantly decreased during epileptic seizures	Unlear if this was used for prediction, I couldn't get access to the full paper
Chua, 2009	EEG (128 channel)	Exploit higher order spectra (bicoherence patterns and bispectra entropies) using Fourier transforms to extract features used to train a classifier	Identified features that are specific to the pre-ictal EEG using the bispectrum magnitude plot and the bicoherence plot
D'Alessandro, 2005 [6]	Intracranial EEG	Train a neural network classifier to predict on a 10 minute prediction horizon using a set of seizure data and test on the remaining data. The classifier continues to train and learn over time	Sensitivity of 100% and 1.1 False positives/hour, Able to predict about 6.5-8 minutes before seizure onset
Netoff, 2009	Intracranial EEG	Training using oartial pre-ictal data from the 5 minute interval before seizure onset from 45 seizures on a support vector machine classifier and then testing on the remaining data	Sensitivity of 77.8% with no false positives
Cook, 2013 [22]	Intracranial EEG	After implantation, at least 1 month of data was collected in order to develop a personalized algorithm for the patient; after that, a handheld device indicated low, medium, or high likelihood of seizure	Sensitivities of 65-100% in 11 patients (using real time seizure prediction)
Teixeira, 2011 [53]	EEG and ECG	Collection of over 35 time/frequency domain features based on univariate and multivariate analysis that are used to construct classifiers of various types	High sensitivity and low false positive rate (varies depending on the predictor that is used)
Yuan, 2017	Intracranial EEG	Used diffusion distance (DD) from iEEG recordings. DD extracted from wavelet decomposition of EEG signals, fed this into a Bayesian Linear Discriminant Analysis (BLDA) classifier.	Sensitivity of 85.11% for seizure occurrence period of 30 min, sensitivity of 93.62% for a seizure occurence period of 50 min, both with seizure prediction horizon of 10 sec. False prediction rate 0.08/h
Karoly, 2017	ECoG	Compared results of an electrocorticography-based logistic regression model, a circadian probability, and a combined electrocorticography and circadian model. Used to calculate the probability of a seizure in a given time	Prediction sensitivity ranged from 45% to 76%

Author, year	Measuring Device	Detection algorithm	Results
Hasan, 2017	EEG	Extracted features including approximate entropy (ApEn), standard deviation (SD), standard error (SE), modified mean absolute value (MMAV), roll-off (R), and zero crossing (ZC). Used the k-nearest neibours (k-NN) algorithm for the classification of epilepsy, then used regression analysis to predict the epilepsy level.	Obtained up to 60% classification accuracy
Yang, 2016	Anterior thalamic signals (EEG)	Generic Osorio-Frei algorithim (GOFA)	In temporal lobe epileptic rats, ANT LFP is feasible to predict seizures with minimal false-positives and no false-negatives

References

1. Shafer, P. epilepsy.com. *Epilepsy Foundation* (2014). Available at: https://www.epilepsy.com.
2. Devinsky, O. *Orrin Devinsky MD Talks About SUDEP*. (2013).
3. Empatica Inc. Empatica. (2017). Available at: www.empatica.com.
4. Litt, B. *et al.* Epileptic seizures may begin hours in advance of clinical onset: A report of five patients. *Neuron* 30, 51–64 (2001).
5. Ramgopal, S. *et al.* Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. *Epilepsy and Behavior* 37, 291–307 (2014).
6. D'Alessandro, M. *et al.* A multi-feature and multi-channel univariate selection process for seizure prediction. *Clin. Neurophysiol.* 116, 506–516 (2005).
7. Teixeira, C. A. *et al.* EPILAB: A software package for studies on the prediction of epileptic seizures. *J. Neurosci. Methods* 200, 257–271 (2011).
8. Cook, M. J. *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.* 12, 563–571 (2013).
9. Leyde, K. & Dilorenzo, D. Methods and Systems for Recommending an Appropriate Action to a Patient for Managing Epilepsy and Other Neurological Disorders. (2007).
10. Singh, B. Seizure and Movement Monitoring Apparatus. (2001).
11. Smith, W. No Title. *Medscape* (2015).
12. Bowers, D. & Kienle, G. Sleep Apnea Monitor. (1989).
13. Bsoul, M., Minn, H. & Tamil, L. Apnea MedAssist: Real-time sleep apnea monitor using single-lead ECG. *IEEE Trans. Inf. Technol. Biomed.* 15, 416–427 (2011).
14. Kim, B. Sudden Infant Death Syndrome Monitor. (1996).
15. Schulze-Bonhage, A. *et al.* Views of patients with epilepsy on seizure prediction devices. *Epilepsy Behav.* 18, 388–396 (2010).
16. Kwan, P. & Brodie, M. J. Early identification of refractory epilepsy. *N. Engl. J. Med.* 342, 314–9 (2000).
17. Pradhan, N., Sadasivan, P. K. & Arunodaya, G. R. Detection of Seizure Activity in EEG by an Artificial Neural Network: A Preliminary Study. *Comput. Biomed. Res.* 29, 303–313 (1996).
18. 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.* 20, 749–55 (2012).
19. Xie, S. & Krishnan, S. Wavelet-based sparse functional linear model with applications to EEGs seizure detection and epilepsy diagnosis. *Med. Biol. Eng. Comput.* 51, 49–60 (2013).
20. Direito, B. *et al.* Modeling epileptic brain states using EEG spectral analysis and topographic mapping. *J. Neurosci. Methods* 210, 220–229 (2012).
21. Rabbi, A. F. & Fazel-Rezai, R. A fuzzy logic system for seizure onset detection in intracranial EEG. *Comput. Intell. Neurosci.* 2012, (2012).
22. 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.* 117, 328–340 (2006).
23. Conradsen, I. *et al.* Seizure onset detection based on a Uni- or Multi-modal Intelligent Seizure Acquisition (UISA/MISA) system. in *2010 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC'10* 3269–3272 (2010). doi:10.1109/IEMBS.2010.5627218

24. Conradsen, I. *et al.* Automatic multi-modal intelligent seizure acquisition (MISA) system for detection of motor seizures from electromyographic data and motion data. *Comput. Methods Programs Biomed.* 107, 97–110 (2012).
25. Chua, K. C., Chandran, V., Acharya, U. R. & Lim, C. M. Automatic identification of epileptic electroencephalography signals using higher-order spectra. *Proc. Inst. Mech. Eng. Part H J. Eng. Med.* 223, 485–495 (2009).
26. Netoff, T., Park, Y. & Parhi, K. Seizure prediction using cost-sensitive support vector machine. *Conf. Proc. ... Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf.* 2009, 3322–5 (2009).
27. Mirowski, P., Madhavan, D., LeCun, Y. & Kuzniecky, R. Classification of patterns of EEG synchronization for seizure prediction. *Clin. Neurophysiol.* 120, 1927–1940 (2009).
28. Sorensen, T. L. *et al.* Automatic epileptic seizure onset detection using matching pursuit: a case study. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2010, 3277–3280 (2010).
29. Chisci, L. *et al.* Real-Time Epileptic Seizure Prediction Using AR Models and Support Vector Machines. *IEEE Trans. Biomed. Eng.* 57, 1124–1132 (2010).
30. Petersen, E. B. *et al.* Generic single-channel detection of absence seizures. in *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS* 4820–4823 (2011). doi:10.1109/IEMBS.2011.6091194
31. Temko, A., Thomas, E., Marnane, W., Lightbody, G. & Boylan, G. EEG-based neonatal seizure detection with Support Vector Machines. *Clin. Neurophysiol.* 122, 464–473 (2011).
32. Acharya, U. R., Sree, S. V. & Suri, J. S. Automatic Detection of Epileptic EEG Signals Using Higher Order Cumulant Features. *Int. J. Neural Syst.* 21, 403–414 (2011).
33. Van de Vel, A. *et al.* Long-term home monitoring of hypermotor seizures by patient-worn accelerometers. *Epilepsy Behav.* 26, 118–125 (2013).
34. Kramer, U., Kipervasser, S., Shlitner, A. & Kuzniecky, R. A Novel Portable Seizure Detection Alarm System: Preliminary Results. *J. Clin. Neurophysiol.* 28, 36–38 (2011).
35. Lu, H. *et al.* Quantifying limb movements in epileptic seizures through color-based video analysis. *IEEE Trans. Biomed. Eng.* 60, 461–469 (2013).
36. Beniczky, S., Polster, T., Kjaer, T. W. & Hjalgrim, H. Detection of generalized tonic-clonic seizures by a wireless wrist accelerometer: A prospective, multicenter study. *Epilepsia* 54, (2013).
37. Karayiannis, N. B. *et al.* Automated detection of videotaped neonatal seizures based on motion tracking methods. *J. Clin. Neurophysiol.* 23, 521–531 (2006).
38. Cuppens, K., Lagae, L., Ceulemans, B., Huffel, S. Van & Vanrumste, B. Automatic video detection of body movement during sleep based on optical flow in pediatric patients with epilepsy. *Med. Biol. Eng. Comput.* 48, 923–931 (2010).
39. Cuppens, K. *et al.* Using spatio-temporal interest points (STIP) for myoclonic jerk detection in nocturnal video. in *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS* 4454–4457 (2012). doi:10.1109/EMBC.2012.6346955
40. Malarvili, M. B. & Mesbah, M. Newborn seizure detection based on heart rate variability. *IEEE Trans. Biomed. Eng.* 56, 2594–2603 (2009).
41. Greene, B. R., De Chazal, P., Boylan, G. B., Connolly, S. & Reilly, R. B. Electrocardiogram based neonatal seizure detection. *IEEE Trans. Biomed. Eng.* 54, 673–682 (2007).
42. Carlson, C., Arnedo, V., Cahill, M. & Devinsky, O. Detecting nocturnal convulsions: Efficacy of the MP5 monitor. *Seizure* 18, 225–227 (2009).

43. 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* 18, 417–26 (2010).
44. Doyle, O. M., Temko, A., Marnane, W., Lightbody, G. & Boylan, G. B. Heart rate based automatic seizure detection in the newborn. *Med. Eng. Phys.* 32, 829–839 (2010).
45. Nijsen, T. M. E., Cluitmans, P. J. M., Arends, J. B. A. M. & Griep, P. A. M. Detection of subtle nocturnal motor activity from 3-D accelerometry recordings in epilepsy patients. *IEEE Trans. Biomed. Eng.* 54, 2073–2081 (2007).
46. 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. in *Proceedings of the 31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society: Engineering the Future of Biomedicine, EMBC 2009* 6608–6611 (2009). doi:10.1109/IEMBS.2009.5332557
47. Nijsen, T. M. E., Aarts, R. M., Cluitmans, P. J. M. & Griep, P. A. M. Time-frequency analysis of accelerometry data for detection of myoclonic seizures. *IEEE Trans. Inf. Technol. Biomed.* 14, 1197–1203 (2010).
48. Lockman, J., Fisher, R. S. & Olson, D. M. Detection of seizure-like movements using a wrist accelerometer. *Epilepsy Behav.* 20, 638–641 (2011).
49. Burioka, N. *et al.* Approximate entropy of the electroencephalogram in healthy awake subjects and absence epilepsy patients. *Clin. EEG Neurosci.* 36, 188–93 (2005).
50. Chua, K. C., Chandran, V., Rajendra Acharya, U. & Lim, C. M. Analysis of epileptic EEG signals using higher order spectra. *J. Med. Eng. Technol.* 33, 42–50 (2009).
51. Hasan, M. K., Ahamed, M. A., Ahmad, M. & Rashid, M. A. Prediction of Epileptic Seizure by Analysing Time Series EEG Signal Using k -NN Classifier. *Appl. Bionics Biomech.* 2017, (2017).
52. Karoly, P. J. *et al.* The circadian profile of epilepsy improves seizure forecasting. *Brain* 140, 2169–2182 (2017).
53. Alkan, A., Koklukaya, E. & Subasi, A. Automatic seizure detection in EEG using logistic regression and artificial neural network. *J. Neurosci. Methods* 148, 167–176 (2005).
54. Yang, A. chao *et al.* The ability of anterior thalamic signals to predict seizures in temporal lobe epilepsy in kainate-treated rats. *Epilepsia* 57, 1369–1376 (2016).
55. Narechania, A. P. *et al.* Assessment of a quasi-piezoelectric mattress monitor as a detection system for generalized convulsions. *Epilepsy Behav.* 28, 172–176 (2013).
56. De Bruijne, G. R., Sommen, P. C. W. & Aarts, R. M. Detection of epileptic seizures through audio classification. in *IFMBE Proceedings* 22, 1450–1454 (2008).
57. Yuan, S., Zhou, W. & Chen, L. Epileptic Seizure Prediction Using Diffusion Distance and Bayesian Linear Discriminate Analysis on Intracranial EEG. *Int. J. Neural Syst.* 0, 1750043
58. Strong, V., Brown, S. W. & Walker, R. Seizure-alert dogs--fact or fiction? *Seizure* 8, 62–65 (1999).
59. Petrosian, A., Prokhorov, D. & Homan, R. Recurrent neural network based prediction of epileptic seizures in intra-and extracranial EEG. *Neurocomputing* 30, 201–218 (2000).
60. Nijsen, T. M. E., Arends, J. B. A. M., Griep, P. A. M. & Cluitmans, P. J. M. The potential value of three-dimensional accelerometry for detection of motor seizures in severe epilepsy. *Epilepsy Behav.* 7, 74–84 (2005).
61. Wilson, S. B. A neural network method for automatic and incremental learning applied to patient-dependent seizure detection. *Clin. Neurophysiol.* 116, 1785–95 (2005).
62. Li, X., Ouyang, G. & Richards, D. A. Predictability analysis of absence seizures with permutation entropy. *Epilepsy Res.* 77, 70–74 (2007).

63. Van Drongelen, W. *et al.* Seizure anticipation in pediatric epilepsy: Use of kolmogorov entropy. *Pediatr. Neurol.* 29, 207–213 (2003).
64. Schulze-Bonhage, A. *et al.* Views of patients with epilepsy on seizure prediction devices. *Epilepsy Behav.* (2010). doi:10.1016/j.yebeh.2010.05.008
65. Tomson, T. sudep.org. *SUDEP Action* Available at: http://sudep.org.
66. Kharbouch, A., Shoeb, A., Guttag, J. & Cash, S. S. An algorithm for seizure onset detection using intracranial EEG. *Epilepsy Behav.* 22, (2011).
67. Casson, A. J., Yates, D. C., Patel, S. & Rodriguez-Villegas, E. Algorithm for AEEG data selection leading to wireless and long term epilepsy monitoring. in *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings* 2456–2459 (2007). doi:10.1109/IEMBS.2007.4352825
68. Wilson, S. B., Scheuer, M. L., Emerson, R. G. & Gabor, A. J. Seizure detection: Evaluation of the Reveal algorithm. *Clin. Neurophysiol.* 115, 2280–2291 (2004).
69. Nathan, V., Gope, C. & Nathan, A. Abnormal Motion Detector and Monitor. (2011).
70. Hauser, W. A., Annegers, J. F. & Kurland, L. T. Incidence of Epilepsy and Unprovoked Seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 34, 453–458 (1993).
71. Chan, A. M., Sun, F. T., Boto, E. H. & Wingeier, B. M. Automated seizure onset detection for accurate onset time determination in intracranial EEG. *Clin. Neurophysiol.* 119, 2687–2696 (2008).
72. Christensen, J. *et al.* Incidence and prevalence of epilepsy in Denmark. *Epilepsy Res.* 76, 60–65 (2007).
73. Camfield, P. & Camfield, C. Idiopathic generalized epilepsy with generalized tonic-clonic seizures (IGE-GTC): A population-based cohort with >20year follow up for medical and social outcome. *Epilepsy Behav.* 18, 61–63 (2010).
74. Webber, W. R. S., Lesser, R. P., Richardson, R. T. & Wilson, K. An approach to seizure detection using an artificial neural network (ANN). *Electroencephalogr. Clin. Neurophysiol.* 98, 250–272 (1996).
75. Gabor, A. J. Seizure detection using a self-organizing neural network: Validation and comparison with other detection strategies. *Electroencephalogr. Clin. Neurophysiol.* 107, 27–32 (1998).