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SUPPLEMENT ARTICLE

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Machine learning and wearable devices of the future

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Abstract

Machine learning (ML) is increasingly recognized as a useful tool in healthcare applications, including epilepsy. One of the most important applications of ML in epilepsy is seizure detection and prediction, using wearable devices (WDs). However, not all currently available algorithms implemented in WDs are using ML. In this review, we summarize the state of the art of using WDs and ML in epilepsy, and we outline future development in these domains. There is published evidence for reliable detection of epileptic seizures using implanted electroencephalography (EEG) electrodes and wearable, non-EEG devices. Application of ML using the data recorded with WDs from a large number of patients could change radically the way we diagnose and manage patients with epilepsy.

KEYWORDS

epilepsy, machine learning, seizure detection, seizure prediction, wearable devices

1 | WEARABLE DEVICES

Wearable devices (WDs) are becoming widely used, and their impact is significant in education, communication, navigation, and entertainment. This trend has already reached healthcare applications, including epilepsy: WDs have been developed for seizure detection and prediction. There are thousands of WDs on the market that measure health parameters and biosignals.[1] Market research reports have predicted an exponential growth in this field,[2,3] and it is likely that this will extend to applications in the field of epilepsy too. In this section, we discuss why there is need for seizure detection and prediction using WDs, highlight the critical aspects in clinical validation studies of WDs, summarize the current evidence for the accuracy of WDs, and describe how the recorded data could be used to broaden the clinical yield of the WDs in epilepsy.

1.1 | Why do we need WDs in epilepsy?

There is a well-documented need for seizure detection and prediction, using WDs.[4-8] The unpredictable nature of seizure occurrence is distressing and disabling for patients and caregivers, and affects their quality of life, leading to social isolation. Automated seizure alarms calling for help are especially important for generalized tonic-clonic seizures (GTCS) including focal-to-bilateral tonic-clonic seizures, since these seizure types are associated with the highest morbidity and mortality. Each year 25% of the patients with

GTCS experience serious accidental injury related to the seizure.[9] GTCS during the preceding year was associated with a 27-fold increased risk of sudden unexpected death in epilepsy (SUDEP), and the combination of not sharing a bedroom and having at least one GTCS per year had a 67-fold increased risk of SUDEP.[10] Studies in the epilepsy monitoring units demonstrate that patients and caregivers typically underreport their seizures.[11] Seizure diaries derived from seizures reported by patients and caregivers are unreliable, yet they constitute the input for therapeutic decisions in clinical practice and for the outcomes in drug trials. An objective quantification of seizure burden could improve clinical decision-making and the quality of the drug trials. A reliable seizure-detection system could trigger antiseizure therapy, so that the patients are exposed to this on demand, and not throughout the whole interictal period.

Key Points

- Automated analysis of scalp electroencephalography (EEG) can detect seizures with a sensitivity of 75%-90%
- Using intracranial EEG and deep learning, seizures can be predicted with a sensitivity of 79%
- Noninvasive wearable devices can detect generalized tonic-clonic seizures with a sensitivity of 90%-96%

1.2 | Design of clinical validation studies of seizure detection using WDs

Due to the obvious need for seizure-detection devices, and spurred by advances in electronics and signal analysis, development of seizure-detection devices has been the goal of many groups and has led to more than 3000 articles on this topic.[12] However, despite the rapid technological development, the clinical evidence for the diagnostic accuracy of these WDs is disappointingly scarce, and this limits their integration into a formal medical decision processes and reimbursement by healthcare providers. Most of the published clinical validation studies have a poor design with numerous potential biases.[12] To help estimate the robustness of the evidence behind WDs for seizure detection, standards have been proposed.[13] Depending on how studies address four key features that are important for seizure-detection devices (subjects, recordings, data analysis, alarms, and reference standard), studies are classified into five phases (0-4), similar to drug trials, where phase 3 studies provide compelling evidence (equivalent to randomized-controlled trials for therapeutic intervention studies) and phase 4 studies provide in-field assessment of usability.

1.3 | EEG-based seizure detection

There is robust evidence published showing that seizures can be detected using scalp electroencephalography (EEG), with a sensitivity between 75% and 90%, and false alarm rates (FARs) between 0.1 and 5 per hour.[14] Although such applications can be useful for data segmentation in long-term video-EEG monitoring, their application for ultra-long-term monitoring in the ambulatory, outpatient setting is limited by their technical feasibility. In addition, patients want to avoid stigma and do not want to wear devices that cannot be concealed.[15] EEG electrodes can be hidden, using auricular devices (similar to hearing aids). However, performance of EEG-based seizure detection decreases when only few electrodes and reduced spatial sampling is used,[14] and convincing evidence for the accuracy of these devices is still lacking. An alternative approach is using WDs with subcutaneous EEG electrodes. This minimally invasive approach showed promising results in a study where signals were visually evaluated by experts.[16] However, the utility of these signals for automated detection still needs to be investigated systematically. Although patients are reluctant to have intracranial electrodes implanted merely for seizure detection, they may accept this invasive approach when the seizure detection triggers a therapeutic action, such as the closed-loop system of the responsive neurostimulation device.[17] By using a high-frequency stimulation that stops seizures at their onset, promising results have been achieved: Median percentage of seizure reduction was between 44% and 71%, increasing over time.[17]

1.4 | Seizure detection using non-EEG WDs

At present, all seizure detection WDs with a satisfactory level of performance, validated in phase 3 studies are using non-EEG modalities,[12] and algorithms based on biomarkers derived from exploratory studies,[18,19] rather than machine learning (ML). Although major progress has been made in the field of EEG-based seizure detection and prediction using ML, there is much need for improvement in the field of non-EEG WDs. Currently, their applicability is restricted to GTCS.[12] Although detection of this seizure type is the most important one for prevention of the morbidity (injuries) and mortality (SUDEP) associated with seizures, detection of other seizure types would be desirable for objective seizure quantification.

In a phase 3 study, a bracelet accelerometer WD detected GTCS with a sensitivity of 90% (95% confidence interval [CI] 76%-97%), with false alarm rate of 0.2 per day and a mean latency of 55 seconds.[19] A WD recording surface electromyography (EMG) from the biceps muscle had a sensitivity of 94% (95% CI 86%-100%), false alarm rate of 0.7 per day (0.01/night), and a median detection latency of 9 seconds in a phase 3 clinical validation study.[20] A multimodal WD, designed for nocturnal surveillance, based on accelerometry and heart-rate (photoplethysmography) in a bracelet placed on the upper arm, detected major motor seizures with a median sensitivity per patient of 86% (for GTCS: 96%), and a false alarm rate of 0.03 per night, in a phase 3 validation study.[21]

Currently there is no convincing evidence for the reliability of non-EEG-based WD for detecting nonconvulsive seizure types. An electrocardiography (ECG)–based algorithm implemented into a vagus nerve stimulation (VNS) device, detected seizures with a sensitivity of 59%, and a very high false alarm rate 7.15 per hour.[22] Although this is suitable when the objective is triggering VNS, it is not feasible for triggering alarms or for objective seizure quantification. A promising approach was based on heart-rate variability, calculated from signals recorded with an ECG WD.[23] This approach worked only in patients with marked ictal autonomic changes (approximatively half of the recruited patients); yet in this subgroup, it achieved a detection sensitivity of 90% (95% CI 77%-97%) for nonconvulsive seizures, with a false alarm rate of 1.0 per day (0.11/night), in a phase 2 validation study.[23] Further, phase 3 studies are needed for elucidating the reliability of WDs for detecting nonconvulsive seizure types.

1.5 | Further applications of WDs in epilepsy

False alarms constitute a challenge for using WDs for objective seizure quantification, even for devices targeting GTCS, where sensitivities >90% have been achieved. A possible way of addressing this could be the visual assessment by experts of the recorded signals during the detected epochs. For surface EMG signals, this method yielded a specificity of 100%.[24] However, this requires specific expertise, not widely available. Therefore, further improvement of the performance using ML is needed.

Another possible application of WD detecting GTCS is differential diagnostics. Although distinguishing GTCS from convulsive psychogenic nonepileptic seizures (PNES) is not difficult for an epilepsy expert, they are not available in the emergency rooms. In the recently published Established Status Epilepticus Treatment Trial, 10% of the enrolled patients, considered to have convulsive status epilepticus in an in-hospital setting, turned out to have PNES.[25] Algorithms can distinguish between GTCS and convulsive PNES with an accuracy of 95%.[25]

Besides detecting GTCS, the biosignals recorded by WDs could contribute to their characterization and risk assessment. Algorithms based on surface EMG were able to identify GTCS with long postictal generalized EEG suppression (PGES),[26] a surrogate marker of SUDEP.

2 | MACHINE LEARNING

The increasing availability of WDs and minimally invasive implanted devices for epilepsy monitoring is driving exponential growth of data. It is no longer feasible for these data to be evaluated by expert human reviewers, and computer-aided or computer-driven approaches are necessary. Machine learning (or ML) has increasingly been seen as a powerful solution for managing vast quantities of epilepsy data.[27] The field of ML encompasses a diverse array of algorithms used to train mathematical models, ranging from linear classifiers parameterized by just a few variables to deep neural networks with millions of parameters that must be fitted ("learned").[28] To-date, ML has shown great promise in health care, from cancer diagnosis to seizure detection[29-31]; however, its dynamic nature and vast data requirements are present challenges for traditional medical regulatory systems.[32]

There are many possible uses for ML approaches in epilepsy, ranging from diagnosis and treatment selection to seizure forecasting and surgical planning. For instance, ML algorithms have demonstrated effectiveness for automated detection of seizures from diagnostic scalp EEG.[14] ML can also be used to guide clinical decision-making and treatment selection. Recently, deep learning was used for automatic selection of electrical stimulation parameters after training on a large database of patient EEG characteristics and associated treatment outcomes.[33] ML has also been used with retrospective data to accurately predict drug resistance,[34] effectiveness of antiepileptic drugs,[35] and surgical outcomes[36] and effective treatment.[37] The aforementioned studies have shown promising results on retrospective data; however, there are still limited examples of the successful application of ML in clinical epileptology.

2.1 | Challenges to clinical application of ML

Challenges to the practical implementation of ML in the clinic include regulatory concerns, large data requirements, and unclear performance benchmarks. Medical regulatory bodies are not traditionally equipped to assess algorithms that may continually learn and update as new data are collected; however, the U.S. Food and Drug Administration (FDA) is increasing the scope for ML software to be approved and regulated.[38] In addition to learning dynamically, ML often requires large, consistent data sets to train algorithms. Missing data or unreliable data annotations can greatly degrade the performance of ML models.[39] The requirement for high-quality data curation is heightened when creating corpora from multiple centers; however, efforts to standardize the storage of epilepsy-relevant data elements are underway.[40] Finally, to ensure that ML is practical for real-world applications, it is crucial to carefully define the problem and understand performance requirements in a clinical setting. Particularly in epilepsy, where clinical definitions are constantly evolving,[41] it is important to carefully consider what training and benchmarking data sets are used to develop ML algorithms.

Despite the aforementioned challenges, seizure detection and forecasting are notable examples where ML has been successfully applied in a clinical setting. ML algorithms in conjunction with WDs have been approved for clinical use in the field of automated seizure detection. For instance, a multimodal WD based on accelerometry and electrodermal activity (EDA) has obtained clearance from the FDA. With an algorithm developed using ML, the multimodal WD detected GTCS with high sensitivity (92%-100%) and low false alarm rate (0.2-1/day), in phase 2 studies.[42] In the diagnostic space, ML approaches can expedite clinical review of diagnostic scalp EEG,[43-45] although currently there are relatively few approved algorithms for automated EEG review.[14] ML has also been extensively applied to the problem of seizure forecasting. For example, ML was used in a successful clinical trial for an implantable seizure warning device.[46] A key goal of the epilepsy community is to provide forecasting technology to people with epilepsy,[47] and ML is likely to play a vital role in next-generation forecasting technology.[48,49] The following sections discuss the utility of ML for seizure detection and forecasting in more detail.

2.2 | Lessons from long-term EEG

ML has been well developed for applications requiring long-term EEG analysis, in particular for seizure detection and forecasting. Both detection and forecasting are examples of epilepsy applications that have drawn on the crowd-sourced data science competition, Kaggle, to help develop ML algorithms.[31,50,51] An important driver of these competitions has been the availability of large curated data sets of continuously recorded, prolonged EEG. All three Kaggle competitions drew on the same NeuroVista databases of ambulatory EEG from either canines or humans.[52] An earlier initiative created an open source data set of continuous EEG for a seizure prediction competition that was used to train and test ML algorithms.[53,54] Similarly, a scalp-EEG database used to develop ML approaches for seizure detection was made freely available and has been cited by hundreds of subsequent studies employing ML for seizure detection or prediction.[55] Another freely available data platform was developed to share neuroimaging data for epilepsy research.[56] These publicly available, curated datasets of EEG with labeled epileptic events have been an important driver of ML applications in epilepsy.

The availability of long-term EEG has provided several lessons that have guided ML approaches. For instance, a finding from the NeuroVista human and canine studies has been that signal features of the EEG were not stable over time,[57,58] and seizures also showed long-term electrographic changes.[59] These dynamics required ML models to be retrained once data had stabilized. Long-term fluctuations in the EEG signal highlight the benefits of ML, which can learn continuously as new data are collected. ML analysis of long-term EEG has also shown there are limitations of data-driven algorithms. For people with rare seizures, there may never be enough data to train reliable, patient-specific models for seizure detection or forecasting. For seizure detection, it may be sufficient to train generalized algorithms that can be applied to patient populations. However, seizure forecasting is considered highly patient-specific,[48] and seizure detection may be further improved with personalized data.[60,61] In cases where training examples (ie seizures) are limited, ML may ultimately be outperformed by less data-hungry methods. For instance, recent forecasting approaches using simple cyclic models of seizure susceptibility have shown more robust seizure prediction compared to complex ML models.[62,63]

2.3 | ML for seizure detection from EEG

There has been significant interest in developing generalizable algorithms that can be trained to recognize epileptic activity in EEG data. The aforementioned Kaggle competition utilized human and canine implanted EEG recordings to develop a generalized seizure-detection algorithm.[31] The winning entrants reported an area under the curve (AUC) of >0.97, using a random forest classifier, demonstrating the utility of ML for automated seizure detection from long-term EEG. A recent review of seizure detection from scalp EEG reported good performance from ML algorithms (neural network, support vector machine), with sensitivities between 75% and 90% and false-positive rates of between 0.1 and 5 per hour.[14]

In addition to detecting seizures, automated detection of interictal epileptiform discharges is of paramount importance for the diagnostic workup of patients with epilepsy. There is an increasing amount of long-term video-EEG monitoring, including home monitoring. The analysis of this huge amount of data is facilitated by reliable, automated spike detection. ML algorithms were able to identify EEG epochs without spikes, thus excluding them from visual analysis.[64] In a clinical environment, deep learning was found to be robust for automated review and quantification of epileptic discharges in patients with generalized epilepsy.[44,65] Another recently published large-scale study, also used a deep learning–based detection algorithm for epileptiform EEG discharges that was validated against scorings of experts, with remarkable results.[43]

A challenge facing automated seizure detection is a lack of consensus on what constitutes epileptic activity. Different specialists often do not agree on whether an EEG waveform is epileptiform or not, which makes it difficult to train and evaluate ML algorithms.[66] Seizure detection may also be highly context-dependent. In a diagnostic setting, it may be important to detect all epileptiform discharges as well as to detect and quantify the type of electrographic seizures. On the other hand, for ongoing management, it may only be important to monitor clinically relevant events.

2.4 | ML for seizure forecasting from EEG

Seizure detection and seizure forecasting are inextricably linked, because reliable seizure detection is vital to develop seizure forecasts.[47,67] A variety of ML algorithms have been used for seizure prediction with both EEG and data from WDs, although these have primarily used a retrospective approach to develop and test forecasting algorithms, rather than evaluating performance within a prospective real-world trial.[68,69]

One clinical trial for an implantable seizure advisory device demonstrated successful use of ML for seizure forecasting in a prospective setting.[46] The device used a decision tree-type classifier with hand-coded features (line length and power in various frequency bands) and, in the human trial, classifiers were trained after 4 months of recording. Results were promising, with seizure prediction accuracy of 100% in some cases; however, for other participants, ML classifiers failed to produce useful forecasts. A subsequent Kaggle competition on three of the most challenging patients showed significant improvements, finding that algorithms must be sufficiently flexible to deal with patient-specific pre-ictal signals.[50] An earlier Kaggle competition[51] also showed strong results from ML approaches, with the winning entrant showing an AUC of 0.82 using a weighted combination of a neural network, support-vector machine, and random forest. More recently, forecasting with the canine data was further improved in performance (sensitivity 0.79, time in warning 0.18) and computational efficiency using deep learning.[70]

A range of ML approaches have been applied for seizure prediction using databases of scalp EEG, with excellent performance reported from various deep learning methods.[52,71] However, the comparatively short duration of scalp EEG recordings limits the ability to rigorously test seizure-prediction methods. Studies using scalp EEG for seizure prediction are typically developed with fewer than 10 seizures per individual, thereby limiting the ability to train ML algorithms and leading to poor generalizability on unseen data.[72,73]

2.5 | ML for seizure detection and prediction from WDs

Signals from WDs, measured during phase 0 to phase 2 trials,[13] have used a variety of ML methods to detect and forecast seizure events. Combined accelerometry and electrodermal activity recordings have been used as inputs for support vector machine models to detect tonic-clonic seizures.[74,75] Similarly, these signals have been used in a hybrid k nearest neighbor and random forest algorithm.[76] The aforementioned studies used the same FDA-approved wrist-worn seizure-detection watch. However, due to the small number of recorded seizures and inconsistent seizure definitions used, it is difficult to assess the relative merits of these ML methods. Furthermore, existing studies reported only retrospective seizure-detection results using the smartwatch device. Prospective studies are underway using the same device[42]; although, to the best of our knowledge, the results are not yet published. As well as wrist-worn sensors, EMG signals have been relatively widely used as features for ML algorithms in seizure detection. Larsen et al[77] used surface EMG recorded from deltoid electrodes to derive features for a random forest classifier to detect GTCSs, with excellent sensitivity (median = 1.0, min = 0.5).

In addition to seizure detection, ML has been applied to detect pre-ictal signal features from WDs. Heart rate has been most commonly used for seizure forecasting from WDs, and pre-ictal heart rate changes have been documented in early studies.[78] More recently, ECG has been shown to anticipate seizures utilizing deep learning methods to extract predictive features.[79] Another study used ECG signals with a support vector machine to develop patient-specific seizure-prediction algorithms.[80] This study used 15 patients with different seizure types and reported average sensitivity of 89%, with predictive signals obtained up to 20 minutes prior to seizures.[80] Although heart rate and WDs have shown some early promise in seizure-forecasting studies, their predictive utility has yet to be tested in a prospective setting.[80,81]

The application of ML to WD data for seizure forecasting may be on a trajectory similar to that seen with seizure forecasting from EEG, where early results are promising, but issues remain with clinical translation. It is not clear that the computational complexity of many ML techniques is warranted, when simpler predictive models based on known physiological phenomena may perform better. For example, phenomena such as circadian and multiday cycles of seizure occurrence have proven valuable in forecasting applications.[62,63] Furthermore, ML models typically require more training data compared to other models (ie, feature thresholding). Larger data requirements introduce a trade-off between patient-specific models that require many seizures for each individual, vs generic models, which are faster to train but may generalize poorly to individuals.[49] Studies may struggle to demonstrate statistical significance due to limited numbers of seizures per patient. Comparisons between ML methods remain difficult due to variations in devices, definitions of seizure types, and inclusion criteria. Many of these early challenges can be addressed with the public availability of large, standardized data sets of WD signals from people with epilepsy, as has been undertaken with EEG recordings.

2.6 | New developments in ML for seizure detection and forecasting

The advent of minimally invasive, implantable devices to record long-term, continuous EEG promise to improve ML, with the potential to greatly change the practice of epileptology.[48,49] Current incarnations of these devices are designed for monitoring and do not deliver therapeutic stimulation, as the goal is to establish accurate seizure counts to replace unreliable seizure diaries.[82] Accordingly, such devices will be reliant on automated methods of seizure detection, as the volume of streaming data cannot be feasibly analyzed by human reviewers. The continuous EEG recorded from these minimally invasive implant devices promises to provide a valuable data source to develop and test methods of automated seizure detection. Nevertheless, the first subcutaneous EEG devices are still in early phase clinical trials,[83] so the promise of ML for sub-scalp EEG remains to be tested prospectively in large patient cohorts.

Subcutaneous EEG and automated seizure detection will have flow-on benefits for seizure forecasting by providing a more accurate record of seizure activity. Recently it has been shown that the past history of seizure times can be used to establish cyclic trends and forecast seizure likelihood.[63,84] However, an accurate record of seizure times is critical.[63] Forecasts based on epileptic rhythms also become more accurate when long-term EEG is available to measure cyclic trends.[62,85] In addition, the inclusion of other physiological signals measured from WD, or even environmental conditions may also improve seizure detection and forecasting performance.[47]

3 | FUTURE PERSPECTIVES

There is a huge potential benefit in using WD for seizure detection, prediction, and characterization. This could help prevent the morbidity and mortality associated with seizures, and address the anxiety generated by the unpredictability of seizure occurrence. Objective quantification of seizure burden could help in tailoring the therapy to the needs of the individual patients (precision medicine) and improve the quality of the therapeutic studies. Despite the considerable progress in this field, we are still far from this goal. At present there is convincing evidence only for detection of GTCS, using non-EEG WDs. Further development is needed to: (a) reduce the false alarm rate, which at present is the main obstacle for using WDs for quantification of the burden of GTCS; (b) to reliably detect all seizure types—including the nonconvulsive seizures, which is still a challenging; (c) to develop seizure prediction using noninvasive modalities; and (d) to develop methods for objective risk assessment of the recorded seizures. Application of ML using the data recorded with WDs from a large number of patients could be a game changer in this field. The authors encourage groups working on these topics to share anonymized data recorded with WDs and to establish large databases to facilitate development and validation of novel algorithms.

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REFERENCES

1. Jo A, Coronel BD, Coakes CE, Mainous AG 3rd. Is there a benefit to patients using wearable devices such as fitbit or health apps on mobiles? A systematic review. Am J Med. 2019;132(12):1394–400.e1.
2. Juniper Research; 2014. [cited 2020 Mar 2]. Available from https://www.juniperresearch.com/press/press-releases
3. Technavio; 2016. Global outlook for the smart wearable healthcare devices and services market. [cited 2020 Apr 5]. Available from https://www.technavio.com/report/global-machine-machine-m2m-and-connected-devices-smart-wearable-healthcare-devices-and
4. Schulze-Bonhage A, Sales F, Wagner K, Teotonio R, Carius A, Schelle A, et al. Views of patients with epilepsy on seizure prediction devices. Epilepsy Behav. 2010;18:388–96.

5. Hoppe C, Feldmann M, Blachut B, Surges R, Elger CE, Helmstaedter C. Novel techniques for automated seizure registration: patients' wants and needs. Epilepsy Behav. 2015;52:1–7.
6. Van de Vel A, Smets K, Wouters K, Ceulemans B. Automated non-EEG based seizure detection: do users have a say? Epilepsy Behav. 2016;62:121–8.
7. Tovar Quiroga DF, Britton JW, Wirrell EC. Patient and caregiver view on seizure detection devices: a survey study. Seizure. 2016;41:179–81.
8. Patel AD, Moss R, Rust SW, Patterson J, Strouse R, Gedela S, et al. Patient-centered design criteria for wearable seizure detection devices. Epilepsy Behav. 2016;64:116–21.
9. Salas-Puig X, Iniesta M, Abraira L, Puig J. Accidental injuries in patients with generalized tonic-clonic seizures. A multicenter, observational, cross-sectional study (QUIN-GTC study). Epilepsy Behav. 2019;92:135–9.
10. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: a nationwide population-based case-control study. Neurology. 2020;94(4):e419–29.
11. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol. 2007;64:1595–9.
12. Beniczky S, Jeppesen J. Non-electroencephalography-based seizure detection. Curr Opin Neurol. 2019;32:198–204.
13. Beniczky S, Ryvlin P. Standards for testing and clinical validation of seizure detection devices. Epilepsia. 2018;59(Suppl 1):9–13.
14. Baumgartner C, Koren JP. Seizure detection using scalp-EEG. Epilepsia. 2018;59:14–22.
15. Bruno E, Simblett S, Lang A, Biondi A, Odoi C, Schulze-Bonhage A, et al. Wearable technology in epilepsy: the views of patients, caregivers, and healthcare professionals. Epilepsy Behav. 2018;85:141–9.
16. Weisdorf S, Duun-Henriksen J, Kjeldsen MJ, Poulsen FR, Gangstad SW, Kjaer TW. Ultra-long-term subcutaneous home monitoring of epilepsy-490 days of EEG from nine patients. Epilepsia. 2019;60:2204–14.
17. Skarpaas TL, Jarosiewicz B, Morrell MJ. Brain-responsive neurostimulation for epilepsy (RNS® System). Epilepsy Res. 2019;153:68–70.
18. Beniczky S, Conradsen I, Pressler R, Wolf P. Quantitative analysis of surface electromyography: biomarkers for convulsive seizures. Clin Neurophysiol. 2016;127:2900–7.
19. Beniczky S, Polster T, Kjaer TW, Hjalgrim H. Detection of generalized tonic-clonic seizures by a wireless wrist accelerometer: a prospective, multicenter study. Epilepsia. 2013;54:e58–61.
20. Beniczky S, Conradsen I, Henning O, Fabricius M, Wolf P. Automated real-time detection of tonic-clonic seizures using a wearable EMG device. Neurology. 2018;90:e428–34.
21. Arends J, Thijs RD, Gutter T, Ungureanu C, Cluitmans P, Van Dijk J, et al. Multimodal nocturnal seizure detection in a residential care setting: a long-term prospective trial. Neurology. 2018;91:e2010–9.
22. Boon P, Vonck K, van Rijckevorsel K, Tahry RE, Elger CE, Mullatti N, et al. A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. Seizure. 2015;32:52–61.
23. Jeppesen J, Fuglsang-Frederiksen A, Johansen P, Christensen J, Wüstenhagen S, Tankisi H, et al. Seizure detection based on heart rate variability using a wearable electrocardiography device. Epilepsia. 2019;60:2105–13.
24. Beniczky S, Conradsen I, Moldovan M, Jennum P, Fabricius M, Benedek K, et al. Quantitative analysis of surface electromyography during epileptic and nonepileptic convulsive seizures. Epilepsia. 2014;55:1128–34.
25. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med. 2019;381:2103–13.
26. Arbune AA, Conradsen I, Cardenas DP, Whitmire LE, Voyles SR, Wolf P, et al. Ictal quantitative surface electromyography correlates with postictal EEG suppression. Neurology. 2020. https://doi.org/10.1212/WNL.0000000000009492
27. Abbasi B, Goldenholz DM. Machine learning applications in epilepsy. Epilepsia. 2019;60:2037–47.
28. Bishop CM. Pattern recognition and machine learning. New York, NY: Springer-Verlag; 2006.
29. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015;521:436–44.
30. Muse ED, Barrett PM, Steinhubl SR, Topol EJ. Towards a smart medical home. Lancet Lond Engl. 2017;389:358.
31. Baldassano SN, Brinkmann BH, Ung H, Blevins T, Conrad EC, Leyde K, et al. Crowdsourcing seizure detection: algorithm development and validation on human implanted device recordings. Brain. 2017;140:1680–91.
32. Shah P, Kendall F, Khozin S, Goosen R, Hu J, Laramie J, et al. Artificial intelligence and machine learning in clinical development: a translational perspective. Npj Digit Med. 2019;2:1–5.
33. Desai SA, Tcheng T, Morrell M. Transfer-learning for differentiating epileptic patients who respond to treatment based on chronic ambulatory ECoG data. In: 2019 9th International IEEE/EMBS Conference on Neural Engineering (NER), 2019; p. 1–4.
34. An S, Malhotra K, Dilley C, Han-Burgess E, Valdez JN, Robertson J, et al. Predicting drug-resistant epilepsy – a machine learning approach based on administrative claims data. Epilepsy Behav. 2018;89:118–25.
35. Yao L, Cai M, Chen Y, Shen C, Shi L, Guo YI. Prediction of antiepileptic drug treatment outcomes of patients with newly diagnosed epilepsy by machine learning. Epilepsy Behav. 2019;96:92–7.
36. Memarian N, Kim S, Dewar S, Engel J, Staba RJ. Multimodal data and machine learning for surgery outcome prediction in complicated cases of mesial temporal lobe epilepsy. Comput Biol Med. 2015;64:67–78.
37. Devinsky O, Dilley C, Ozery-Flato M, Aharonov R, Goldschmidt Y, Rosen-Zvi M, et al. Changing the approach to treatment choice in epilepsy using big data. Epilepsy Behav. 2016;56:32–7.
38. Proposed regulatory framework for modifications to artificial intelligence/machine learning (AI/ML)-based software as a medical device (SaMD) [Internet]. FDA. 2019 [cited 2020 Apr 20]. Available from https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device
39. Batista GE, Monard MC. An analysis of four missing data treatment methods for supervised learning. Appl Artif Intell. 2003;17:519–33.
40. Goldenholz DM, Moss R, Jost DA, Crone NE, Krauss G, Picard R, et al. Common data elements for epilepsy mobile health systems. Epilepsia. 2018;59:1020–6.
41. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30.
42. Regalia G, Onorati F, Lai M, Caborni C, Picard RW. Multimodal wrist-worn devices for seizure detection and advancing research: focus on the Empatica wristbands. Epilepsy Res. 2019;153:79–82.

43. Jing J, Sun H, Kim JA, Herlopian A, Karakis I, Ng M, et al. Development of expert-level automated detection of epileptiform discharges during electroencephalogram interpretation. JAMA Neurol. 2020;77(1):103.
44. Clarke S, Karoly PJ, Nurse E, Seneviratne U, Taylor J, Knight-Sadler R, et al. Computer-assisted EEG diagnostic review for idiopathic generalized epilepsy. Epilepsy Behav. 2019:106556. https://doi.org/10.1016/j.yebeh.2019
45. Scheuer ML, Bagic A, Wilson SB. Spike detection: inter-reader agreement and a statistical Turing test on a large data set. Clin Neurophysiol. 2017;128:243–50.
46. Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. Lancet Neurol. 2013;12:563–71.
47. Dumanis SB, French JA, Bernard C, Worrell GA, Fureman BE. Seizure forecasting from idea to reality. Outcomes of the My Seizure Gauge Epilepsy Innovation Institute Workshop. eNeuro. 2017;4:ENEURO.0349-17.2017.
48. Kuhlmann L, Lehnertz K, Richardson MP, Schelter B, Zaveri HP. Seizure prediction—ready for a new era. Nat Rev Neurol. 2018;14:618–30.
49. Freestone DR, Karoly PJ, Cook MJ. A forward-looking review of seizure prediction. Curr Opin Neurol. 2017;30:167–73.
50. Kuhlmann L, Karoly P, Freestone DR, Brinkmann BH, Temko A, Barachant A, et al. Epilepsyecosystem.org: crowd-sourcing reproducible seizure prediction with long-term human intracranial EEG. Brain. 2018;141:2619–30.
51. Brinkmann BH, Wagenaar J, Abbot D, Adkins P, Bosshard SC, Chen M, et al. Crowdsourcing reproducible seizure forecasting in human and canine epilepsy. Brain. 2016;139:1713–22.
52. Daoud H, Bayoumi MA. Efficient epileptic seizure prediction based on deep learning. IEEE Trans Biomed Circuits Syst. 2019;13:804–13.
53. Schelter B, Feldwisch-Drentrup H, Timmer J, Gotman J, Schulze-Bonhage A. A common strategy and database to compare the performance of seizure prediction algorithms. Epilepsy Behav. 2010;17:154–6.
54. Klatt J, Feldwisch-Drentrup H, Ihle M, Navarro V, Neufang M, Teixeira C, et al. The EPILEPSIAE database: an extensive electroencephalography database of epilepsy patients. Epilepsia. 2012;53:1669–76.
55. Shoeb AH, Guttag JV. Application of machine learning to epileptic seizure detection. In: Proceedings of the 27th International Conference on Machine Learning (ICML-10), 2010; p. 975–82.
56. Wagenaar JB, Worrell GA, Ives Z, Matthias D, Litt B, Schulze-Bonhage A. Collaborating and sharing data in epilepsy research. J Clin Neurophysiol. 2015;32:235.
57. Ung H, Baldassano SN, Bink H, Krieger AM, Williams S, Vitale F, et al. Intracranial EEG fluctuates over months after implanting electrodes in human brain. J Neural Eng. 2017;14:056011.
58. Davis KA, Ung H, Wulsin D, Wagenaar J, Fox E, Patterson N, et al. Mining continuous intracranial EEG in focal canine epilepsy: relating interictal bursts to seizure onsets. Epilepsia. 2016;57:89–98.
59. Ung H, Davis KA, Wulsin D, Wagenaar J, Fox E, McDonnell JJ, et al. Temporal behavior of seizures and interictal bursts in prolonged intracranial recordings from epileptic canines. Epilepsia. 2016;57:1949–57.
60. Qu H, Gotman J. Improvement in seizure detection performance by automatic adaptation to the EEG of each patient. Electroencephalogr Clin Neurophysiol. 1993;86:79–87.
61. Minasyan GR, Chatten JB, Chatten MJ, Harner RN. Patient-specific early seizure detection from scalp EEG. J Clin Neurophysiol. 2010;27:163.
62. Maturana MI, Meisel C, Dell K, Karoly PJ, D'Souza W, Grayden DB, et al. Critical slowing as a biomarker for seizure susceptibility. Nat Commun. 2020;11:2172.
63. Karoly PJ, Cook MJ, Maturana M, Nurse ES, Payne D, Brinkmann BH, et al. Forecasting cycles of seizure likelihood. Epilepsia. 2020;61:776–86.
64. Bagheri E, Jin J, Dauwels J, Cash S, Westover MB. A fast machine learning approach to facilitate the detection of interictal epileptiform discharges in the scalp electroencephalogram. J Neurosci Methods. 2019;326:108362.
65. Eden D, Nurse ES, Clarke S, Karoly PJ, Seneviratne U, Cook M, et al. Computer-assisted estimation of interictal discharge burden in idiopathic generalized epilepsy. Epilepsy Behav. 2020;105:106970.
66. Webber W, Litt B, Lesser RP, Fisher RS, Bankman I. Automatic EEG spike detection: what should the computer imitate? Electroencephalogr Clin Neurophysiol. 1993;87:364–73.
67. Baud MO, Rao VR. Gauging seizure risk. Neurology. 2018;91:967–73.
68. Gadhoumi K, Lina J-M, Mormann F, Gotman J. Seizure prediction for therapeutic devices: a review. J Neurosci Methods. 2016;260:270–82.
69. Stacey WC. Seizure prediction is possible-now let's make it practical. EBioMedicine. 2018;27:3–4.
70. Nejedly P, Kremen V, Sladky V, Nasseri M, Guragain H, Klimes P, et al. Deep-learning for seizure forecasting in canines with epilepsy. J Neural Eng. 2019;16:036031.
71. Hosseini M-P, Soltanian-Zadeh H, Elisevich K, Pompili D. Cloud-based deep learning of big EEG data for epileptic seizure prediction. In: 2016 IEEE global conference on signal and information processing (GlobalSIP). IEEE, 2016; p. 1151–5.
72. Alexandre Teixeira C, Direito B, Bandarabadi M, Le Van Quyen M, Valderrama M, Schelter B, et al. Epileptic seizure predictors based on computational intelligence techniques: a comparative study with 278 patients. Comput Methods Programs Biomed. 2014;114:324–36.
73. Feldwisch-Drentrup H, Schulze-Bonhage A, Timmer J, Schelter B. Statistical validation of event predictors: a comparative study based on the field of seizure prediction. Phys Rev E. 2011;83:066704.
74. Poh M-Z, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Sabtala MC, et al. Convulsive seizure detection using a wrist-worn electrodermal activity and accelerometry biosensor. Epilepsia. 2012;53:e93–7.
75. Onorati F, Regalia G, Caborni C, Migliorini M, Bender D, Poh M-Z, et al. Multicenter clinical assessment of improved wearable multimodal convulsive seizure detectors. Epilepsia. 2017;58:1870–9.
76. Heldberg BE, Kautz T, Leutheuser H, Hopfengärtner R, Kasper BS, Eskofier BM. Using wearable sensors for semiology-independent seizure detection-towards ambulatory monitoring of epilepsy. In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2015; p. 5593–6.
77. Larsen SN, Conradsen I, Beniczky S, Sorensen HB. Detection of tonic epileptic seizures based on surface electromyography. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:942–5.

78. Zijlmans M, Flanagan D, Gotman J. Heart rate changes and ECG abnormalities during epileptic seizures: prevalence and definition of an objective clinical sign. Epilepsia. 2002;43:847–54.
79. Meisel C, Bailey KA. Identifying signal-dependent information about the preictal state: a comparison across ECoG, EEG and EKG using deep learning. EBioMedicine. 2019;45:422–31.
80. Billeci L, Marino D, Insana L, Vatti G, Varanini M. Patient-specific seizure prediction based on heart rate variability and recurrence quantification analysis. PLoS One. 2018;13:e0204339.
81. Ufongene C, El Atrache R, Loddenkemper T, Meisel C. Electrocardiographic changes associated with epilepsy beyond heart rate and their utilization in future seizure detection and forecasting methods. Clin Neurophysiol. 2020;131:866–79.
82. Elger CE, Hoppe C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. Lancet Neurol. 2018;17:279–88.
83. Weisdorf S, Gangstad SW, Duun-Henriksen J, Mosholt KSS, Kjær TW. High similarity between EEG from subcutaneous and proximate scalp electrodes in patients with temporal lobe epilepsy. J Neurophysiol. 2018;120:1451–60.
84. Karoly PJ, Goldenholz DM, Freestone DR, Moss RE, Grayden DB, Theodore WH, et al. Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. Lancet Neurol. 2018;17:977–85.
85. Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, et al. Multi-day rhythms modulate seizure risk in epilepsy. Nat Commun. 2018;9:88.

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