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Machine learning and wearable devices of the future

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Summary

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 (WD). However, not all, currently available algorithms implemented in WD are using ML. In this review, we summarize the state of the art of using WD and ML in epilepsy, and we outline future development in these domains. There is published evidence for reliable detection of epileptic seizures using implanted EEG electrodes and wearable, non-EEG devices. Application of ML using the data recorded with WD 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

Key point box:

- Automated analysis of scalp 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%
- Non-invasive wearable devices can detect generalized tonic-clonic seizures with a sensitivity of 90-96%

1. Wearable devices

WD are becoming widely used, and their impact is significant in education, communication, navigation and entertainment. This trend has already reached healthcare applications, including epilepsy: WD have been developed for seizure detection and prediction. There are thousands of WD 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 WD, highlight the critical aspects in clinical validation studies of WD, summarize

the current evidence for the accuracy of WD and describe how the recorded data could be used to broaden the clinical yield of the WD, in epilepsy.

1.1 Why do we need WD in epilepsy?

There is a well-documented need for seizure detection and prediction, using WD[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 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 potentially 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.

1.2. Design of clinical validation studies of seizure detection using WD

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 three thousand papers on this topic[12]. However, in spite of the rapid technological development, the clinical evidence for the diagnostic accuracy of these WD is disappointingly scarce, and this limits their integration into 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 WD 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 randomised 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 EEG, with a sensitivity between 75% and 90%, and false alarm rates (FAR) 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 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 WD 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 systematically investigated. 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 WD

At present, all seizure detection WD with 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 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 WD. 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%CI: 76-97%), with false alarm rate of 0.2/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/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/night, in a phase-3 validation study[21].

Currently there is no convincing evidence for the reliability of non-EEG based WD for detecting non-convulsive seizure types. An ECG-based algorithm implemented into a vagal nerve stimulation (VNS) device, detected seizures with a sensitivity of 59%, and a very high false alarm rate 7.15/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 non-convulsive seizures, with a false alarm rate of 1.0 /day (0.11/night), in a phase-2 validation study[23]. Further, phase-3 studies are needed for elucidating the reliability of WD for detecting non-convulsive seizure types.

1.5. Further applications of WD in epilepsy

False alarms constitute a challenge for using WD for objective seizure quantification, even for devices targeting GTCS, where sensitivities over 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 PNES is not difficult for an epilepsy expert, they are not available in the emergency rooms. In the recently published ESETT trial, 10% of the enrolled patients, considered to have convulsive status epilepticus in an in-hospital setting, turned out to have psychogenic nonepileptic seizures (PNES)[25]. Algorithms can distinguish between GTCS and convulsive PNES with an accuracy of 95%[25].

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

2. Machine learning

The increasing availability of WD and minimally invasive implanted devices for epilepsy monitoring is driving exponential growth of data. It is no longer feasible for this data to be evaluated by expert human reviewers, and computer-aided or computer-driven approaches are necessary. Machine learning (ML) has increasingly 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 healthcare, 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 anti-epileptic 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 is collected, however the US 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 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 datasets 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 WD 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 per 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 datasets 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 dataset 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 researach[56]. These publicly available, curated datasets of EEG with labelled 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 is 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 (i.e. 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 machine learning 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 AUC of over 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 machine learning 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 detecting and quantifying 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 WD, 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 flexible enough 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 less than 10 seizures per individual, 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 WD

Signals from WD, 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. Furthermore, existing studies only reported 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 used sEMG recorded from deltoid electrodes to derive features for a random forest classifier to detect GTCSs, with excellent sensitivity (median = 1.0, min = 0.5)[77].

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 WD 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 similar trajectory that has been 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 (i.e. feature thresholding). Larger data requirements introduce a trade-off between patient-specific models that require many seizures for each

individual, versus 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. Comparison between ML methods remains 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 datasets 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 machine learning, 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].

Future Perspectives

There is a huge potential benefit in using WD for seizure detection, prediction and characterization. This could help preventing 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. In spite of 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 WD. Further development is needed to: 1) reduce the false alarm rate, which at present is the main obstacle for using WD for quantification of the burden of GTCS; 2) to reliably detect all seizure types – including the non-convulsive seizures, which is still a challenging; 3) to develop seizure prediction using non-invasive modalities; 4) to develop methods for objective risk assessment of the recorded seizures. Application of ML using the data recorded with WD 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 WD and establish large databases to facilitate development and validation of novel algorithms.

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Author SB served as a scientific consultant for Brain Sentinel and Epihunter. EN, PK, and MC are employed by Seer Medical. The remaining authors do not have any conflict of interest to disclose, related to this paper.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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