PROF. DAVID B GRAYDEN (Orcid ID : 0000-0002-5497-7234)

DR. PHILIPPA J KAROLY (Orcid ID : 0000-0002-9879-5854)

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Seizure forecasting and cyclic control of seizures

Rachel E. Stirling[1], Mark J. Cook[2], David B. Grayden[1], Philippa J. Karoly[1,2]

1. Department of Biomedical Engineering, The University of Melbourne, Australia
2. Graeme Clark Institute & St Vincent's Hospital, The University of Melbourne, Australia

Corresponding author: Philippa J. Karoly, Graeme Clark Institute, The University of Melbourne, 203 Bouverie St Carlton VIC 3053 Australia, karolyp@unimelb.edu.au

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Key points:

- Seizure forecasting is a key goal of the epilepsy community, but many parameters and requirements remain unknown.
- Existing seizure prediction algorithms often rely on short term EEG data and have not been tested in prospective clinical settings.
- Non-invasive biomarkers of seizure likelihood, e.g. heart rate and stress levels, are being explored alongside advances in wearable technology.
- Emerging evidence of robust, individual seizure cycles over circadian and multiday timescales should guide forecasting strategies.

- Longitudinal clinical trials of seizure forecasting should be undertaken to understand user requirements and clinical effectiveness.

Abstract

Epilepsy is a unique neurological condition characterised by recurrent seizures, where causes, underlying biomarkers, triggers and patterns differ across individuals. The unpredictability of seizures can heighten fear and anxiety in people with epilepsy, making it difficult to take part in day-to-day activities. Epilepsy researchers have prioritised developing seizure prediction algorithms to combat episodic seizures for decades, but the utility and effectiveness of prediction algorithms has not been thoroughly investigated in clinical settings. In contrast, seizure forecasts, which theoretically provide the probability of a seizure at any time (as opposed to predicting the next seizure occurrence), may be more feasible. Many advances have been made over the past decade in the field of seizure forecasting, including improvements in algorithms as a result of machine learning and exploration of non-EEG based measures of seizure susceptibility, such as physiological biomarkers, behavioural changes, environmental drivers and cyclic seizure patterns. For example, recent work investigating periodicities in individual seizure patterns has determined that more than 90% of people have circadian rhythms in their seizures, and many also experience multi-day, weekly or longer cycles. Other potential indicators of seizure susceptibility include stress levels, heart rate and sleep quality; all of which have the potential to be captured non-invasively over long time scales. There are many possible applications of a seizure forecasting device, including improving quality of life for people with epilepsy, guiding treatment plans and medication titration, optimising pre-surgical monitoring and focusing scientific research. In order to realise this potential, it is vital to better understand the user requirements of a seizure forecasting device, continue to advance forecasting algorithms and design clear guidelines for prospective clinical trials of seizure forecasting.

Keywords: epilepsy; seizure cycles; seizure forecast; seizure prediction; circadian rhythms; multiday rhythms

Introduction

Epilepsy is a unique neurological condition because seizures are relatively rare for most people; yet seizures can be very disruptive, as they come with little or no warning. While

surgical interventions and anti-epileptic drugs (AEDs) treat most people successfully, it is estimated that 30% of people are refractory to conventional interventions[1,2]. People with epilepsy are more likely to experience depression, anxiety and low self-esteem, compounded by psychological factors including fear of seizures, perceived stigma and discrimination, together with side effects of their medication[3]. Of these comorbidities, Arthurs et al. (2010) found fear to be the most insidious aspect of epilepsy as seizures cannot be anticipated[4]. A 2016 survey also found 'unpredictability' to be the most debilitating characteristic of living with epilepsy, particularly for people who experience less frequent seizures (e.g., monthly or yearly)[5]. Quality of life could be dramatically improved with a clinically useful seizure forecasting device. Developing such a device, a 'seizure gauge', is now a key goal of the epilepsy community[6] and it is increasingly accepted that a seizure forecast algorithm may be more feasible than a seizure prediction algorithm. A seizure forecast should provide users with the likelihood (or probability) of a seizure occurring at any time, rather than attempt to provide a precise prediction of the time at which a seizure will occur[7,8].

The primary application of a seizure gauge is to inform people with epilepsy and their caregivers of their risk of having a seizure, providing more control over their day-to-day activities, just as a weather forecast can be used to plan what to wear, what mode of transport to use, and whether to carry an umbrella. Knowing when seizures are more likely or less likely has the potential to improve quality of life, reduce anxiety and possibly reduce the chance of sudden, unexpected death. As well as informing individuals' lifestyle choices, seizure forecasts may be used to guide treatment plans. Medication or electrical stimulation could be titrated based on times of high or low seizure risk, thereby potentially reducing costs and side effects[9–11]. The utility of delivering medication at times of day when seizures are more commonly observed (chronotherapy) has been explored with some success[12]; however, medication titration has not been trialled using personalised seizure forecasts. Additionally, an individual's seizure forecast could be used to optimise the timing of diagnostic or pre-surgical monitoring, which typically rely on ambulatory video-electroencephalography with low yield[13].

Although seizure forecasting is now considered possible, each application comes with its own unique challenges to clinical implementation. A key hurdle is to develop forecasting devices that are acceptable to users in terms of both performance and useability (e.g. invasiveness, comfort, cost)[6,14]. Additional technical challenges include the need to run personalized

algorithms that can detect patient-specific biomarkers of seizure likelihood, seizure triggers and patterns, while remaining computationally feasible to run in real time[15,16]. This review covers some of these challenges while focusing on the key advances in the development of practical seizure forecasts for clinical applications. The following sections review the requirements of clinical seizure forecasting, then discuss recent developments in forecasting algorithms, particularly the increasing focus on circadian and multi-day cycles of seizure likelihood that may have enormous implications for forecasting. We then review practical biomarkers of seizure likelihood and finally speculate on some future applications of seizure forecasts.

Practical requirements of seizure forecasting

A seizure forecasting system may combine user data from various sources, including continuous electroencephalography (EEG), clinical records, wearables and other mobile devices, determining patient-specific triggers using measurements from physiological, behavioural and environmental biomarkers. These biomarkers - such as heart rate, sleeping patterns and weather – can be integrated by a forecasting algorithm to output a probability of seizure likelihood. The clinical requirements of a forecaster, such as forecasting horizon (minutes, hours, days) and presentation (score, categorical risk level, etc), are still unclear, and will be discussed further in this section. An overview of a seizure forecasting system is shown in Figure 1.

Historically, it has been difficult to compare performances of different seizure forecasting algorithms or even to ascertain what makes a seizure forecaster clinically useful. Forecasting algorithms have been evaluated using various performance metrics and guidelines, such as sensitivity, specificity, time spent in false warning, false prediction rate per hour, mean prediction time, receiver operating characteristic (ROC) curves or area under the ROC curve (AUC)[15,17]. The inconsistency in choice of performance metrics, and somewhat arbitrary selection of many algorithm parameters, makes it difficult to compare forecasting approaches. For instance, the seizure occurrence period (SOP) is a parameter that is highly variable throughout the literature on seizure prediction algorithms, ranging from 2 minutes in one study[18] to 150 minutes in another[19]. The SOP represents the maximum time within which a seizure can occur after a positive prediction (or high-risk warning) before it is considered a false positive. The problem with these inconsistencies is that the SOP time can

drastically alter algorithm performance. For example, one study comparing SOP times on the same algorithm improved sensitivity from 19% to 73% simply by increasing the time from 2 minutes to 40 minutes, both of which are considered acceptable SOP choices[18].

Furthermore, traditional metrics may not be appropriate when evaluating probabilistic forecasts, as many are designed for binary predictions where the output is either true (a seizure will occur) or false (a seizure will not occur). Intuitively, one can immediately tell if a binary prediction is "right" or "wrong". On the other hand, multiple seizures are required to assess the accuracy of a forecast that outputs the probability of having a seizure. Hence, the shift to forecasting seizure probabilities requires a corresponding shift in performance measures that are based on a probabilistic framework[20]. More generally, the performance of any prediction (binary classifier or probability) cannot be rigorously evaluated until enough seizures are recorded to determine statistical significance. While there is no prescribed threshold on the required number of seizures, many past studies used data with less than ten seizures per patient[21]. Low seizure numbers were considered a leading cause of the inability of many prediction algorithms to generalise to new data[22].

The minimum accuracy required for a forecaster to be considered clinically useful is another uncertainty in seizure forecasting requirements and may depend on the intended application. Recent surveys have established that people with epilepsy and their caregivers would prefer a forecasting device to be accurate at least 90% of the time, although this depends on the user[14,23]. Some responders would use a device that was inaccurate up to 30% of the time[14], and others argued that, without 100% accuracy, a forecasting device could do more harm[23]. Forecasts used for medication titration (without overall dose reduction), responsive stimulation, scheduling pre-surgical monitoring or to refine seizure detection devices may not require perfect accuracy, as these applications are routinely unassisted and could benefit from additional awareness of seizure timing without compromising current standard of care. On the other hand, forecasts used for prescriptive purposes, such as day-to-day activity modification, tapering down medication or alerting caregivers and people with epilepsy about seizure risk, may be detrimental to health and safety without a higher degree of accuracy. Due to the lack of prospective data from seizure forecasting devices in real-world applications, there are limited resources to adequately review these differing requirements. While the aforementioned surveys provide useful information, assessment of clinical utility must ultimately be derived from clinical trials. In the only prospective forecasting trial to

date, Cook et al. (2013) demonstrated that most subjects found a forecasting device valuable despite less than perfect sensitivity (median 60%) and time in warning of up to 30%[24,25], although these results were based on small user cohort (11 subjects) primarily assessing device safety rather than forecasting performance.

In addition to performance standards, the required warning period of a clinically useful forecasting device and the relative utility of predicting periods of low seizure risk, high seizure risk, or both, also remain unknown. As with performance, these requirements are likely to depend on the specific application and user preferences. It is understood from surveys that people with epilepsy and their caregivers would prefer a device that *predicts* seizures with a shorter warning time[14,23] of less than 10 minutes, with 3 to 5 minutes being most preferred in one survey[4]. However, it is not clear how these desired prediction horizons translate to a *forecasting* device, where the objective is to provide the probability of a seizure, rather than a binary yes or no prediction. Cook et al. (2013) provided a gauge of seizure risk (low/moderate/high) with warning times between 5 and 960 minutes (average of 114 ± 151 minutes), where the device was reported clinically useful by most participants[24,26]. This insight suggests that users may benefit from warnings several hours in advance. Recently, the prospect of forecasting seizures days in advance has also been proposed[27], as longer warning times may be desirable for certain applications. For example, medical professionals may want a device that provides daily probabilities so they can choose to schedule diagnostic monitoring on a day when seizure risk is high. Thus, the application of the forecaster should be taken into consideration when it is designed.

To date, most seizure forecasting algorithms have utilised EEG or measures derived from EEG (such as rates of epileptic discharges), typically obtained from implanted devices. Invasive or even minimally invasive monitoring may not be well tolerated; for instance, Janse et al. (2019) reported that externally worn devices were ranked more favourably than subcutaneous or implantable devices as a seizure forecasting device[14]. More recently, there has been a growing focus on developing seizure forecasts from peripheral signals obtained from wearable devices, such as heart rate[28–30], or even environmental risk factors, such as time of day[31]. New technology utilising wearable EEG electrodes may also provide a promising solution for long-term seizure forecasting[6].

Recent developments in seizure forecasting

In the past decade, great strides have been made in the area of seizure forecasting. In 2005, the first international collaborative workshop on seizure prediction was held, and an open-access prediction database and competition was launched in 2007 to facilitate comparison between methods[32]. This heralded a new era of improved metrics and rigorous evaluation of seizure forecasting. In 2009, a prospective human trial was initiated using an implanted device, the NeuroVista device[25], that collected intracranial recordings of 15 people with epilepsy and forecast seizures in real time. The NeuroVista device predicted patients' seizures with 65-100% sensitivity. Similar advancements using implantable seizure forecasting devices were also made in naturally occurring canine epilepsy[33,34]. In 2014, two large-scale crowdsourcing competitions were launched to allow the machine learning community to tackle seizure detection and forecasting algorithm development[17,35], which paved the way for a subsequent competition[36]. More recently, several studies have quantified seizure cycles over daily and multiday time scales across numerous datasets[37–41] which have important implications for seizure forecasting. Theoretical understanding of the dynamic principles underlying pre-ictal brain dynamics has also advanced in the last decade[42,43], providing new insight into the predictability of seizures[44,45]. The growth of mobile health technology and digital seizure diaries has driven new discoveries[46], even enabling diaries to provide a basic measure of seizure likelihood[47]. Alternatives to EEG have also been used in seizure prediction with varying degrees of success, including heart rate variability, wearable sensor data and self-prediction[29,48]. However, use of invasive EEG data has achieved the best seizure prediction results to date[35,36,49]. Table 1 summarises some of the key papers over the past decade, showing successive developments that have built towards the current state-of-the-art in seizure forecasting.

Seizure prediction algorithms have traditionally taken a classification approach, decoding data into pre-ictal, inter-ictal and post-ictal states. Various classification algorithms have been applied to seizure prediction with the field becoming increasingly reliant on machine learning, including techniques such as feature thresholding[35], linear classifiers[50], Bayesian networks[17], support vector machines[51], k-nearest neighbours[19] and neural networks[52]. In particular, utilising the machine learning community through crowdsourcing has been demonstrated to yield rapid advancements in seizure detection and forecasting algorithms[17,36,53]. In 2014, the first Kaggle seizure prediction contest was entered by over 500 teams[17]. The top performing team in this competition ensembled three different algorithms with their own features and classifiers: LassoGLM, support vector machine and random

forest classifiers. This combination outperformed other teams who used neural networks and k-nearest neighbours. However, it was uncertain whether these algorithms would generalise to long-term human data. In 2018, a follow-up Kaggle competition on seizure forecasting was conducted[36] with data from three patients from the long-term NeuroVista dataset (minimum of 374 recording days). The winner of this competition, entered by 478 teams, also ensembled distinct machine learning classifiers, with numerous feature combinations. Competition algorithms were evaluated on continuous EEG data and performed better than random and periodic predictors for patients that previously had poor seizure prediction outcomes; i.e., where sensitivity was low and time in warning was high[25,36]. These studies demonstrate the usefulness of combining outputs from multiple distinct algorithms.

Other machine learning algorithms have shown impressively high accuracy using open source datasets, both in terms of sensitivity and specificity. For instance, studies have achieved 100% accuracy and false positive rates of close to zero on the Freiburg dataset, with prediction horizons on the order of several hours[50,51]. Similarly high accuracy and low false positive rates are not exclusive to the Freiburg dataset[52]. Despite impressive performance, it is critical to note that these results were based on limited seizures per person during the study period (range of 3 to 8). When limited seizures are used in a retrospective setting, it is possible to 'overtrain' algorithms to perfectly predict test data yet fail to generalise to unseen data, as small datasets cannot afford to include training, validation and test sets[35]. In contrast, crowdsourced algorithms using long-term EEG data (hundreds of seizures per subject) have so far failed to achieve perfect accuracy despite improvements in machine learning[36], highlighting the importance of considering dataset size when comparing algorithm performance.

Over the past decade, theories underpinning seizure forecasting have also evolved. Seizure prediction algorithms had commonly developed under the assumption that seizures follow a pre-ictal brain state, defined retrospectively as some time period immediately preceding seizure onset and marked by a measurable change in brain dynamics. On the other hand, probabilistic forecasting aims to detect brain states when seizures are more likely but not certain (so called "pro-ictal" states)[54,55] in a manner that considers information across multiple time scales and modalities. Pro-ictal states may or may not lead to the occurrence of a seizure. It is also possible for seizures to occur in nominally low-risk states. Figure 2 illustrates this distinction between pre-ictal and pro-ictal states. The hypothesis that a

measurable pre-ictal state exists has long been supported by evidence that seizures often occur at transition points in the brain state, such as between sleep and wake states[56], and that mood and behavioural changes are noticeable in the hours leading up to a seizure[57]. Pre-ictal states are further substantiated by evidence of seizure self-prediction, the notion that some people with epilepsy can sense when a seizure is imminent[58], although in many cases the seizure is likely to have already started[57]. Evidence of altered pre-ictal dynamics from neuroimaging[59] has inspired many researchers to look for predictable features in the window prior to seizure onset. However, the success of this approach has been limited[22] and it is possible that seizure transitions are not always characterised by a deterministic state[60]. Additionally, restricting seizure prediction methods to consider a limited pre-ictal time window reduces the ability to incorporate known rhythms over longer, multi-day timescales, which are discussed in detail in the following section.

Table 1. Advances in seizure forecasting over the past decade that highlight key developments towards state-of-the-art forecasting performance.

Cycles of seizure susceptibility

In many cases, the problem of seizure forecasting can be cast as developing a model of past seizure times in order to predict future risk. Many models of seizure times have been considered, including the possibility that seizure onset is noise driven or follows a random process[60]. On the other hand, epileptic seizures have long been known to follow consistent cyclic patterns[61]. These patterns are often patient-specific, but may follow circadian, multi-day or seasonal rhythms[37,38,40,62]. Many decades ago, Griffiths (1938) noted some people experienced seizures only in the morning or at night and some followed regular monthly cycles, speculating that this could follow other physiological cycles such as the hormonal or menstrual cycles[61]. However, other people with epilepsy experience cycles that follow no known physiological variables, such as every 3 or 5 weeks or, in one unique case, regular seizures in one month followed by no seizures in the next month[61]. More recently, Cook et al. (2014) found long-memory dynamics governed seizure timing with highly patient-specific time scales of days to weeks[39]. Subsequent studies on the same database showed cyclic patterns were evident over years, with 92% of people showing strong circadian (24 hour) rhythms and 25% showing approximate weekly cycles[37]. Spencer et al. (2016) also found consistent circadian and/or ultradian patterns in 98% of participants with an implanted EEG

device[62]. Furthermore, there is evidence that interictal epileptiform activity oscillates with similar multi-day periods[38,40] and that these rhythms persist for up to 10 years[40]. Importantly, analogous circadian and multi-day (weekly and monthly) cycles have been observed in long-term animal recordings from both canine epilepsy[41,63] and rodent models[64]. Animal studies showed multi-day rhythms were independent of AEDs and not purely exogenous (driven by environmental factors)[41,64]. The long temporal scales of epileptic rhythms (from weeks to months) pose an interesting challenge for seizure forecasting, which has traditionally considered seizure prediction horizons of minutes to hours.

Individual seizure patterns may help to develop algorithms for seizure susceptibility. It has recently been demonstrated that including circadian rhythms of seizures can improve forecasting accuracy[31] and these patterns can probabilistically forecast seizure occurrence both alone and in conjunction with machine learning models[31,36]. In a similar vein, multiday cycles measured from long-term, intracranial EEG were also shown to be closely associated with seizure occurrence[40,44]. These cycles have been used to forecast seizures with accuracy surpassing all other methods[44] and can provide prediction horizons of a day or more[27]. The ability to forecast seizures using slow cyclic rhythms suggest that long time scales are important to measure seizure likelihood and highlight the existence of periodicities where seizures become more likely to occur (the pro-ictal period shown in Figure 2). In line with this, it has been suggested that seizures may not occur as a result of a chain reaction of predictable events that lead to the onset of a seizure, but rather as the crossing of a tipping-point or critical transition, analogous to 'the last straw which breaks the camel's back'[45]. A critical transition can be thought of as the change from normal brain activity to a seizure state. In theory, a system experiences a period of decreased resilience, or critical slowing, as it approaches a critical transition[42]. Critical slowing is often marked by delayed recovery to a state of equilibrium after a perturbation and an increase in system sensitivity[42–44]. Biomarkers of critical slowing associated with these critical transitions have been investigated prior to seizure onset/offset[44,45,65], and in relation to cortical excitability and AED concentration[63,66] in human and animal studies. Notably biomarkers of critical slowing have been shown to periodically fluctuate over timescales from hours to days[44,63], with a phase-locked relationship to seizure occurrence[44]. On the other hand, studies investigating critical slowing over shorter time scales (minutes to hours) have found no evidence for critical slowing prior to epileptic seizures[67,68]. Irrespective of the mechanisms underlying seizure cycles, it is

becoming clear that such prevalent, consistent rhythms are highly valuable in forecasting applications.

Practical biomarkers of seizure susceptibility

In the past decade, many studies have demonstrated the accurate seizure forecasting (Table 1), showing that is it possible to perform better than chance at detecting pro-ictal states. Despite the robustness of these forecasting approaches, they may not all be appropriate for clinical use. Methods of seizure forecasting must be practical for long-term, continuous use and so potential biomarkers of seizure likelihood should be evaluated based on feasibility in addition to accuracy. An overview of current biomarkers and recording modalities is shown in Figure 3. As previously described, signal features from continuous EEG have been used extensively to develop seizure forecasts, with circadian and multi-day cycles measured from intracranial EEG proving to be the most accurate biomarker of seizure susceptibility[44]. However, to date, chronic EEG recordings have only been possible with invasive implantable monitoring devices. Implanted EEG devices that are currently available in some countries are designed for therapeutic stimulation and have limited data telemetry capabilities for real-time forecasting[69,70]. Other chronically implantable EEG devices capable of continuous telemetry are under investigation in some research settings[71]. Wearable EEG recording devices are also becoming available[72] and minimally-invasive, sub-scalp electrodes are undergoing early trials[73]. However, it remains to be seen whether forecasting biomarkers developed from invasive cortical electrodes can be translated to scalp or sub-scalp EEG signals. The limited availability of chronic EEG recording has driven the search for alternative biomarkers of seizure susceptibility[6].

Physiological, Behavioural and Environmental Drivers

The underlying drivers of epileptic seizures are not well understood and may vary between individuals. Hormonal and other physiological variables fluctuate and cycle over the mammalian lifespan and have been hypothesised to mechanistically determine cyclic patterns in epilepsy[74]. Mechanisms that govern the hibernation, menstruation, reproductive and sleep cycles are examples of potential biological drivers. For instance, key circadian regulators, including glucocorticoids[75] and melatonin[76], modulate cortical excitability and fluctuate with the circadian cycle. Other cyclic hormones implicated in seizure onset include oestrogen, progesterone[77] and prolactin[78]. Currently, there is no conclusive evidence to show that these

biological variables have long-term predictive value for measuring seizure likelihood, and forecasts that look at a single biomarker, such as cortisol levels, may be clinically useful for some participants but not for others[75]. For example, some women with epilepsy may have coordinated seizure rhythms and menstrual hormones[77], but men also experience near-monthly cycles with no known physiological correlation[37,40,61].

In addition to physiological variables, there are behavioural and environmental factors that are thought to increase seizure probability. Factors include alcohol or illicit drug usage[79], change in external temperature[80], missing a medication dose, sleep deprivation[46] and stress[48,58,81]. These seizure triggers are highly individual, so factors that increase the chance of a seizure in one person may have no effect on someone else. Precipitating factors are reported for around a third of seizures[46] and by over 60% of people with epilepsy[82]. The relationship between triggering factors and seizures is not straightforward and may depend on seizure duration or epilepsy syndrome[46,82]. However, individuals' triggers may be useful to improve forecasting potential[81]. .

Measurable physiological signals

Recently, there has been an interest in clinically viable forecasting methods based on data that is easily recordable and collected non-invasively, such as through a wearable device or mobile app. These devices offer a solution to measuring biomarkers of seizure likelihood that are practical over the long term (years). Potential measurements have been suggested in a recent workshop, such as cortisol levels, heart rate, weather, sleep quality, body temperature and blood oxygen levels[6]. Evidence linking these prospective biomarkers to seizure risk is limited but emerging and some, such as heart rate and sleep, have been extensively studied.

Epileptic seizures can cause functional changes in the autonomic nervous system, affecting both the parasympathetic and sympathetic nervous systems[83]. These changes are known to be prominent at the onset of a seizure[84], though changes have also been detected prior to seizures[85] and after seizures[86]. Autonomic changes – often marked by tachycardia or bradycardia[87,88] – are patient specific and depend on several factors, such as AED usage[89], the type of seizure[28], the person's wakefulness/sleep state prior to a seizure[30], the lateralisation and localisation of the seizure[90] and age[91]. Heart rate variability (HRV), known to reflect autonomic nervous system function[89], has therefore been of interest to epilepsy researchers for years, not just in seizure prediction, but in treating refractory epilepsy with vagus nerve

stimulation[92]. Numerous studies analysing HRV have demonstrated significant changes in heart rate may occur approximately five minutes before a seizure[28,84,93,94]. More recently, Billeci et al (2018) detected earlier heart rate changes - up to 20 minutes prior to seizures - by taking a patient-specific approach[29]. Nevertheless, despite promising results, several limitations arise when considering applying these studies clinically. For instance, apart from one meta-analysis[93], sample sizes in the aforementioned studies were limited (ranging from 11 to 20), false prediction rates were high (up to 14 per hour[29]) and not all subjects showed strong prediction based on heart rate[93]. Furthermore, prediction horizons may not translate well from controlled study conditions to real-world settings, with many other confounding factors affecting heart rate changes[1].

The relationship between epileptic seizures and sleep has also been of interest to researchers for centuries[95,96]. Gowers (1885) observed that almost two-thirds of people with epilepsy experienced seizures exclusively during either the night or day. Since then, many studies have confirmed the existence of 'pure sleep epilepsy', albeit at a lower prevalence, and have highlighted that sleep – predominantly the stage of sleep – plays a role in seizure activity[95]. The complex role of sleep also depends on the type of epilepsy syndrome[95,97]. For example, the rate of epileptiform discharges has been shown to increase at sleep onset, but decrease at awakening in idiopathic generalized epilepsies; and this cyclic pattern persists irrespective of AEDs[97]. In seizure prediction, increased sleep was found to decrease self-reported seizure likelihood[81], and a combination of sleep staging and other information has shown significant predictive value using long-term electrographic seizure records[98]. . Evidently, sleep patterns may be a valuable physiological signal for seizure forecasters, and can be determined using non-EEG methods. However, the validity of sleep information has yet to be determined in a prospective seizure forecasting study.

It may be possible to use wristbands and smart watches to detect physiological variables that are useful for seizure prediction. Wearables have numerous benefits over traditional EEG monitoring devices, including affordability, fewer complications compared to invasive devices and attractiveness for people who wish to reduce the potential stigma associated with cumbersome external devices. Wearables can detect many distinct physiological signals simultaneously and have demonstrated utility in seizure detection applications[99,100]. Several automated seizure detection devices are already available on the market; see Elger and Hoppe (2018) for a recent review[100]. These wearable devices monitor physiological signals such as

electrodermal activity, accelerometry, body temperature, blood volume pressure, heart rate and activity levels, which can then be applied to other variables like sleep quality. There have been some positive developments in seizure prediction using data from wearable devices, although current studies remain limited with regard to accuracy and clinical validity[101,102].

Epilepsy seizure diaries have also shown promise as a source of diverse clinical insights[46], including as a measure of seizure risk[103]. Despite well documented inaccuracies and limitations inherent to seizure diaries[104], self-reported events remain the standard data source for medical practice and clinical trials in epilepsy. The widespread use of seizure diaries is likely to increase with the uptake of digital health tools and new applications for self-reported data[105]. Haut et al. (2007) demonstrated that an e-diary application could be used to forecast seizure risk based on a user's self-prediction and self-reported stress and anxiety levels[81]. Seizure self-prediction was confirmed in follow-up studies [48,58,81]. It has also been shown that cyclic seizure patterns can be detected from the timing of an individual's self-reported seizures[37]. For some people, cycles recorded from diaries were relevant to electrographic seizures and accurate forecasts were developed based entirely on self-reported events[47]. Seizure diaries and self-reported seizure risk factors are practical for long-term recording and, particularly for individuals who experience clear precipitants and patterns, may be a powerful input for personalised seizure forecasts.

In short, numerous types of physiological signals and self-reported data have shown promise in seizure forecasting, and have several advantages over traditional EEG methods. Algorithms that use wearable and mobile app data are still in early stages of development relative to EEG-based methods, and many potential variables are yet to be explored in long-term studies, such as cortisol levels and blood oxygen levels. Furthermore, the existence of longer, cyclic rhythms in physiological variables (other than EEG) has not been well studied, but could be a useful avenue to monitor seizure likelihood or even to identify the drivers behind periodic seizure patterns.

Applications of seizure forecasts

There are many potential applications of seizure forecasts. An accurate forecast may benefit people with epilepsy, their caregivers, medical professionals, researchers and pharmaceutical and medical device companies. However, as seizure forecasts are not in widespread clinical

use, the potential advantages remain mainly speculative, and individual preferences for different forecasting parameters further complicates assessment of the clinical utility of these systems. The clearest possible benefit is to improve the quality of life for people with epilepsy and their caregivers by reducing the debilitating effects of living with constant uncertainty[5]. Despite showing few symptoms apart from their seizures, people with epilepsy often avoid driving, cooking, working, and everyday situations that could expose them to humiliation or injury[106]. Most people with epilepsy and their caregivers are positive about the prospect of a seizure forecasting device[14], although people with years of actual experience with an implantable seizure warning device did not universally experience positive outcomes[24,25]. In the NeuroVista clinical study, most participants noticed an increased sense of control over daily activities, noticeable improvements in confidence and reductions in stress levels; contrary to this, one person reported feelings of self-estrangement and depression as a result of the implanted warning device[24].

Seizure forecasting could also be used in clinical contexts to improve the yield of diagnostic or pre-surgical monitoring. Continuous EEG monitoring remains the standard approach for epilepsy diagnosis[107] as it is critical to capture an electrographic clinical seizure when distinguishing epileptic events from non-epileptic events, and there may be serious implications if a correct diagnosis is missed[108]. Nevertheless, rates of misdiagnosis in epilepsy are between 30% and 70%[109]. Inpatient EEG monitoring fails to capture seizures in up to one third of patients across both diagnostic and pre-surgical monitoring[13]. Scheduling EEG monitoring for times when more seizures are anticipated has the potential to improve the number of seizures recorded during testing. Diagnostic applications further motivate the development of non-invasive, predictive biomarkers including from seizure diaries and wearable devices.

As previously mentioned, seizures have historically been categorised into diurnal and nocturnal categories[9], and were often thought to follow other recurrent patterns, such as menstrual and lunar cycles because of their about-monthly periodicity. Recently, circadian patterns have been found to occur in 80-98% of people with epilepsy[37,62]. Chronotherapy, where medication doses are increased throughout the day when seizure susceptibility is high, often without changing total daily dose, utilises this concept and has previously been shown to improve outcomes for people with nocturnal seizures and non-responders to conventional

pharmacotherapy[11]. Applying chronotherapy for seizure cycles longer than 24 hours has exciting potential in conjunction with seizure forecasting, raising the possibility of administering higher doses during times of high seizure susceptibility and reducing or stopping doses during times of low seizure susceptibility[12]. For instance, increasing medication during menstruation has been postulated as a strategy for women with catamenial epilepsy[110], though clinical results have been inconsistent[111]. This cyclic titration has the potential to maximise therapeutic value and minimise total dosage, thereby reducing well-known adverse side effects of AEDs[112]. In future, a time-varying medication therapy, controlled by a seizure forecaster, may be delivered via implanted devices. Tailoring medication dosage to seizure susceptibility can also be applied to other therapies, such as responsive neurostimulation[10].

Conclusion

Numerous advances in seizure forecasting and scientific understanding of epilepsy have been made over the past decade, including access to long-term data, improved algorithm performance and converging evidence of predictable cyclic rhythms modulating seizures and epileptic activity. Despite this, the clinical feasibility of most algorithms remains unknown as the overwhelming majority of algorithms are built upon small data sets and often use invasively collected EEG data, which may not be possible or desirable for all users. Most importantly they have not been applied in prospective studies. Moreover, the requirements of a seizure forecasting device, such as the accuracy, forecasting horizon and display style, are unknown; although will likely be highly dependent on the intended application and user. To drive the next advances in seizure forecasting, we advocate for utilising circadian and multiday cycles measured from seizure times, epileptic activity or EEG biomarkers as the leading indicator of seizure susceptibility. In addition, it is important to validate alternative measures that may also be used to track multiscale cycles of seizure susceptibility, such as stress, hormone concentrations, blood glucose, heart rate, activity, sleep quality and temperature. The development of new wearable technologies will enable novel biomarkers for a seizure forecasting device to be explored, particularly biomarkers that can be measured chronically and non-invasively. Finally, we join the call to initiate new longitudinal clinical trials of seizure forecasting[6,15,16], in parallel with extensive user experience research to understand and meet users' expectations and requirements. To facilitate the next wave of seizure forecasting device trials, it is our hope that the epilepsy community will work to

develop clear guidelines for each phase of seizure forecasting trials, analogous to proposed standards for wearable seizure detection devices[113].

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Competing interests

PJK and MJC have a financial interest in Seer Medical. MJC has a financial interest in Epi-Minder. All other authors report no relevant interests.

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.

Table Captions

Table 1. Advances in seizure forecasting over the past decade that highlight key developments towards state-of-the-art forecasting performance.

Figure Captions

Figure 1: Overview of seizure forecasting. A. Forecasts should combine data from multiple sources including wearable and mobile devices, clinical records, and continuous neurophysiology (EEG). **B.** Measurements should cover diverse, patient-specific triggers including physiological, behavioural and environmental factors. **C.** Computational methods are used to integrate data sources and output a final probability of seizure likelihood. **D.** User interface requirements for a forecasting device are unclear, including parameters such as forecasting horizon (minutes, hours, days) and presentation (score, categorical risk level, etc).

Figure 2. Pre-ictal and pro-ictal states. The pre-ictal state is defined retrospectively as some window of time prior to seizure onset. In contrast, pro-ictal states, where seizures become more likely but not certain, may emerge transiently and have been observed to occur with periodic circadian and multiday cycles. Shown in the figure is an example of a daily cycle overlaid by an about-weekly (7-day) cycle of seizure likelihood.

Figure 3. Biomarkers and available recording devices. Many biomarkers have been related to seizure likelihood, including EEG features, heart rate, and other physiological and environmental factors. Current commercially available recording devices can continuously measure most relevant biomarkers. Devices include mobile seizure diary apps, wearable devices, wearable sensor patches, and deep brain stimulation (DBS) or responsive neurostimulation (RNS) devices. Long-term recording devices utilising sub-scalp recording electrodes and recording/stimulating cortical electrodes are currently in trial phase.

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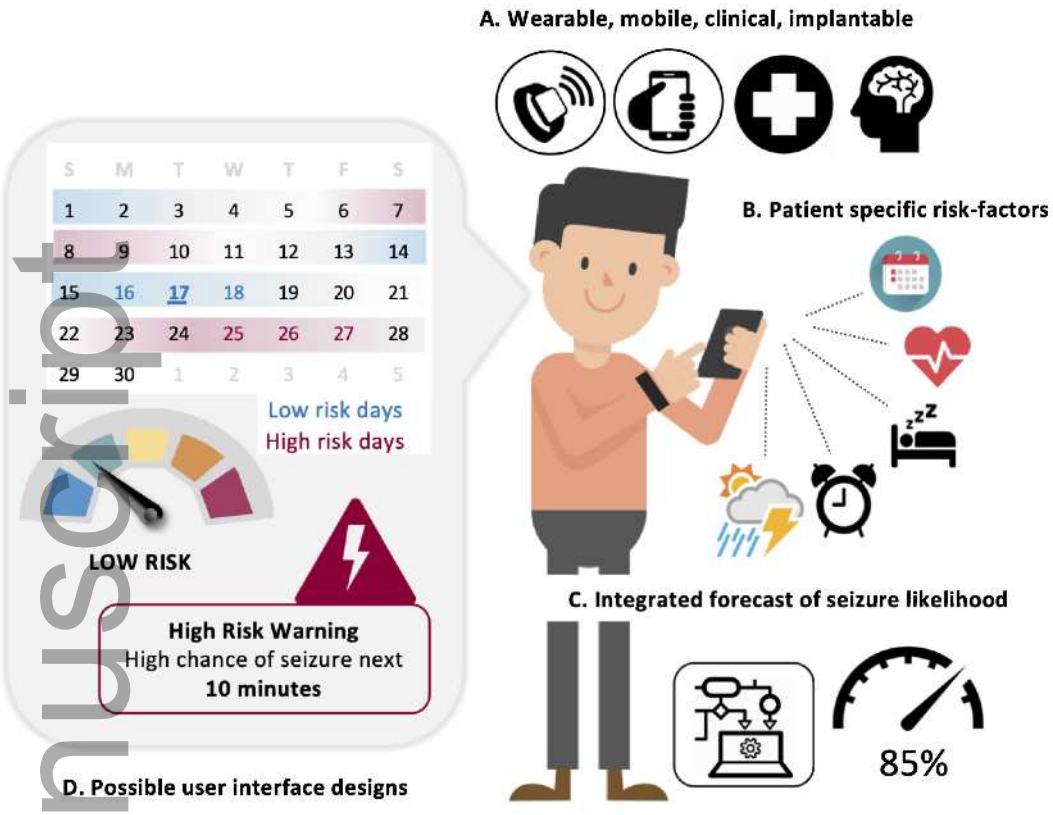
Table 1. Advances in seizure forecasting over the past decade that highlight key developments towards state-of-the-art forecasting performance.

Title (Authors)	**Year**	**Key Advancement**
A common strategy and database to compare the performance of seizure prediction algorithms. (Schelter et al.) *Epilepsy & Behaviour*	2010	Facilitation of a strong international research community based on open-access seizure prediction databases to enable comparison between methods.
Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. (Cook et al.) *Lancet Neurology*	2013	First real time prospective seizure warning device used in a human clinical trial.
Forecasting seizures in dogs with naturally occurring epilepsy. (Howbert et al.) *PLoS ONE*	2014	Seizure forecasting in a prospective trial for canines with epilepsy outperformed a Poisson chance predictor.

The dynamics of the epileptic brain reveal long-memory processes. (Cook et al.) *Frontiers in Neurology*	2014	Demonstrated long memory dynamics of seizure generation with multiday time scales of up to 40 days.
Crowdsourcing reproducible seizure forecasting in human and canine epilepsy. (Brinkmann et al.) *Brain*	2016	Demonstrated the usefulness of uniting machine learning community to develop a seizure forecasting algorithm.
The circadian profile of epilepsy improves seizure forecasting. (Karoly et al.) *Brain*	2017	Demonstrated that including circadian distributions of seizure times significantly improves forecasting accuracy.
Multi-day rhythms modulate seizure risk in epilepsy. (Baud et al.) *Nature Communications*	2018	Showed rates of interictal epileptiform activity oscillate with circadian and multi-day rhythms that may influence seizure likelihood.
Characteristics of large patient-reported outcomes: Where can one million seizures get us? (Ferastorou et al.) *Epilepsia Open*	2018	Highlighted that novel insights can arise from a large cohort of mobile seizure diaries. The same database has subsequently driven key advances in forecasting seizure risk from self-reported event times.
Epilepsyecosystem.org: crowd-sourcing reproducible seizure prediction with long-term human intracranial EEG. (Kuhlmann et al.) *Brain*	2018	Seizure prediction algorithms generated through a Kaggle competition produced better long-term results for study participants that previously achieved poor performance.
Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. (Karoly et al.) *Lancet Neurology*	2018	Showed circadian and multiday (weekly, monthly) cycles of seizure occurrence exist for most people with epilepsy, using a large cohort of seizure diaries
Patient-specific seizure prediction based on heart rate variability and recurrence quantification analysis (Billeci et al.) *PLoS ONE*	2018	Demonstrated the utility of an individualised approach to analyse pre-ictal changes in the autonomic nervous system. This highlights the potential for non-invasive ECG methods to predict seizures.
Deep learning for seizure forecasting in canines with epilepsy (Nejedly et al.) *Journal of Neural Engineering*	2019	Developed a fully automated, patient-specific seizure forecaster based on deep learning for canines with epilepsy.
Loss of neuronal network resilience precedes seizures and determines the ictogenic nature of interictal synaptic perturbations (Chang et al.) *Nature Neuroscience*	2019	Demonstrated that seizure emergence is a slow process characterised by progressive loss of resilience and critical slowing. This validates mathematical models and proposes a mechanistic basis for seizure clustering.

Seizure self-prediction in a randomized controlled trial of stress management (Privitera et al.) *Neurology*	2019	Found a significant relationship between seizure self-prediction and seizure occurrence at 6, 12 and 24 hours prior to a seizure.
Circadian and multiday seizure periodicities, and seizure clusters in canine epilepsy (Gregg et al.) *Brain Communications*	2020	Demonstrated that circadian and multiday cycles occur independent of AEDs in canines with naturally occurring epilepsy.
Forecasting Cycles of Seizure Likelihood (Karoly et al.) *Epilepsia*	2020	Demonstrated the feasibility of using seizure diaries to measure circadian and multi-day cycles and forecast seizure likelihood.
Critical slowing as a biomarker for seizure susceptibility (Maturana et al.) *Nature Communications*	2020	Demonstrated that seizure occurrence was consistently preceded by a critical transition in brain state heralded by critical slowing over multiple time scales. Biomarkers of critical slowing outperformed all previous approaches to forecast seizure likelihood.



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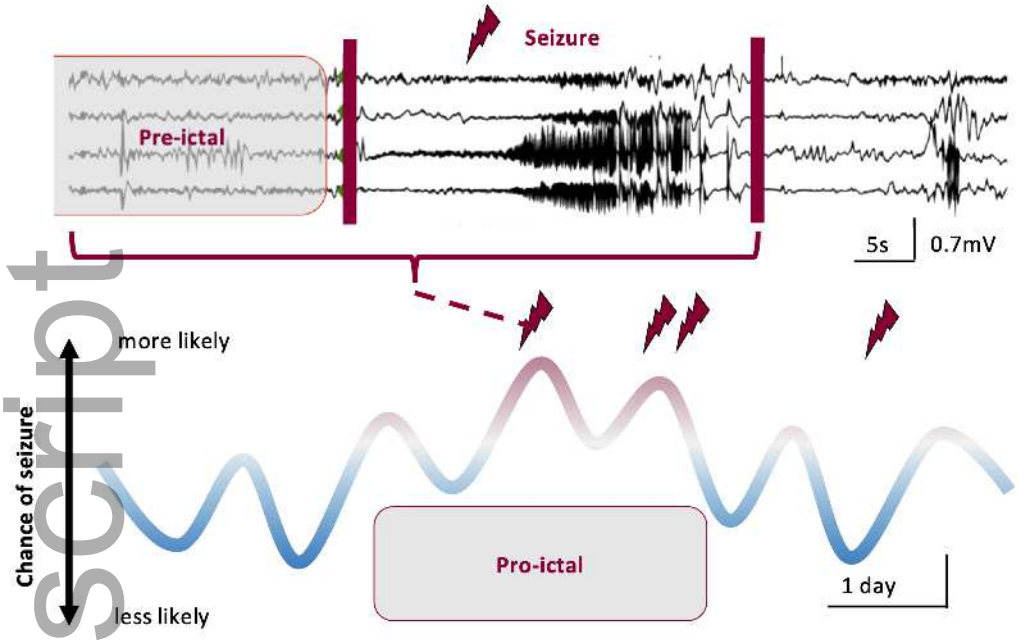

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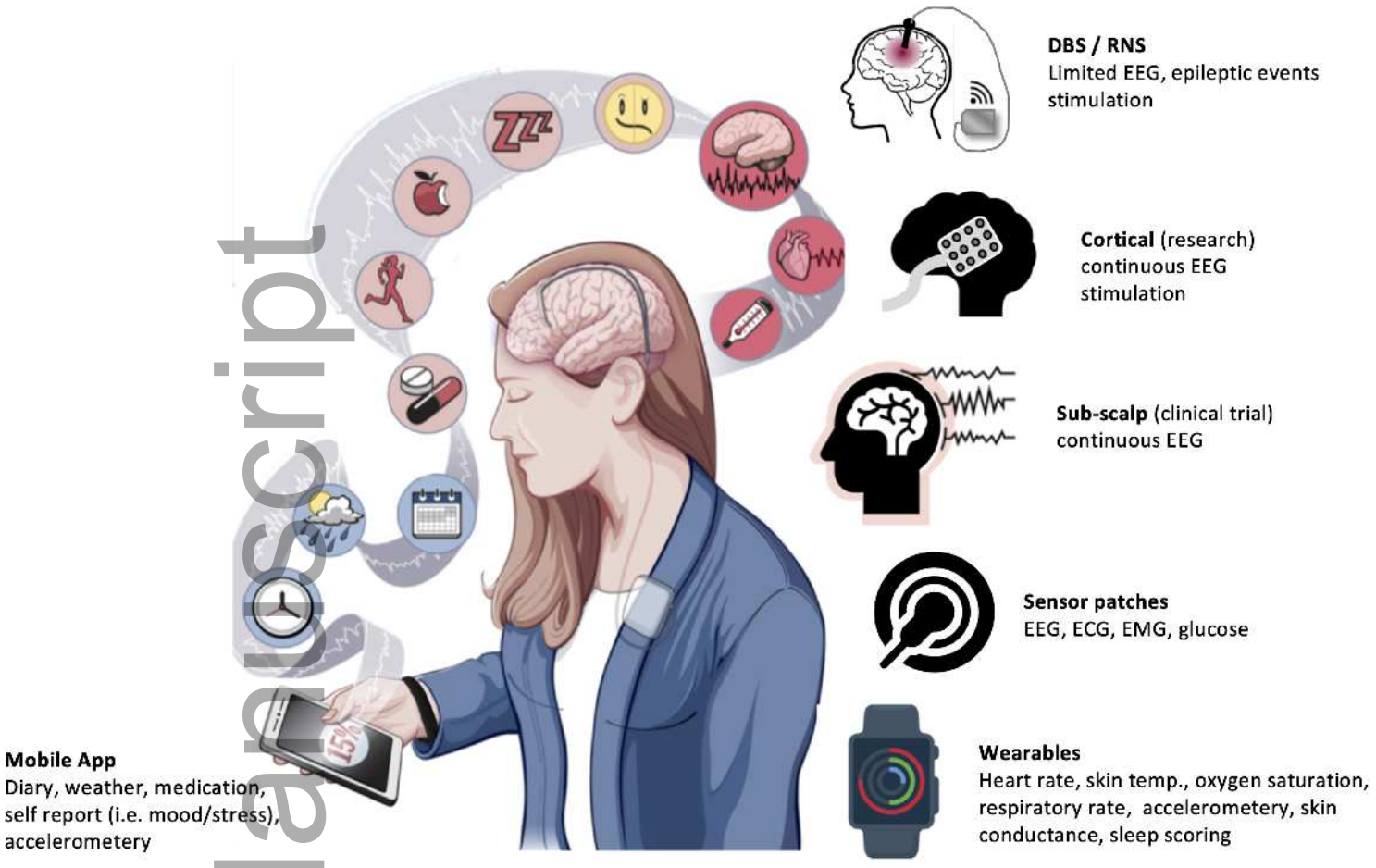

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