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Forecasting cycles of seizure likelihood

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Abstract

Objective: Seizure unpredictability is rated as one of the most challenging aspects of living with epilepsy. Seizure likelihood can be influenced by a range of environmental and physiological factors that are difficult to measure and quantify. However, some generalizable patterns have been demonstrated in seizure onset. A majority of people with epilepsy exhibit circadian rhythms in their seizure times, and many also show slower, multiday patterns. Seizure cycles can be measured using a range of recording modalities, including self-reported electronic seizure diaries. This study aimed to develop personalized forecasts from a mobile seizure diary app.

Methods: Forecasts based on circadian and multiday seizure cycles were tested pseudoprospectively using data from 50 app users (mean of 109 seizures per subject). Individuals' strongest cycles were estimated from their reported seizure times and used to derive the likelihood of future seizures. The forecasting approach was validated using self-reported events and electrographic seizures from the Neurovista dataset, an existing database of long-term electroencephalography that has been widely used to develop forecasting algorithms.

Results: The validation dataset showed that forecasts of seizure likelihood based on self-reported cycles were predictive of electrographic seizures for approximately half the cohort. Forecasts using only mobile app diaries allowed users to spend an average of 67.1% of their time in a low-risk state, with 14.8% of their time in a high-risk warning state. On average, 69.1% of seizures occurred during high-risk states and 10.5% of seizures occurred in low-risk states.

Significance: Seizure diary apps can provide personalized forecasts of seizure likelihood that are accurate and clinically relevant for electrographic seizures. These results have immediate potential for translation to a prospective seizure forecasting trial using a mobile diary app. It is our hope that seizure forecasting apps will one day give people with epilepsy greater confidence in managing their daily activities.

KEYWORDS

circadian rhythms, epilepsy, mobile health, multiday rhythms, seizure cycles, seizure forecasting

1 | INTRODUCTION

Medically refractory epilepsy is a condition associated with persistent uncertainty. Most people with epilepsy report that, regardless of seizure frequency, it is the unpredictability of when seizures will occur that is the most debilitating aspect of their condition.¹ A forecast of seizure likelihood could provide immense benefits to people with epilepsy, especially for those with refractory seizures. More than 30% of all people with epilepsy cannot control their seizures with medication,² and for decades, new drugs have mostly failed to improve overall rates of seizure freedom.³ Surveys have shown that seizure forecasting is considered a highly attractive management option by people with uncontrolled seizures.¹ At the same time, epilepsy research has uncovered numerous factors affecting seizure likelihood from long-term trends in behavioural, environmental, and physiological data. For example, some people are more prone to seizures due to stress,⁴ poor sleep,⁵ exercise,⁶ diet,⁷ weather,⁸ alcohol use,⁹ poor drug adherence,¹⁰ and a multitude of other factors. Investigating the utility of these seizure risk factors and developing personalized forecasting devices is now a key goal for clinical epilepsy management.¹

The first prospective clinical trial of seizure forecasting in humans used an intracranial implant to record long-term, continuous electroencephalography (EEG).¹¹ Using the same data, subsequent studies have improved the accuracy of seizure forecasts.^{12,13} A key development has been the understanding that seizure onset is modulated by patient-specific, cyclic patterns.¹⁴⁻¹⁶ The rhythmic nature of epilepsy has been well documented for centuries; however, it has only recently become clear that an individual's seizure cycles can be used to develop personalized forecasts of future seizure likelihood.^{13-14,17,18} Although changes in EEG signal characteristics provide the clearest biomarker to track cycles of seizure likelihood,^{16,18,19} it is possible to measure individual cycles using only self-reported seizure diaries.¹⁵ Therefore, for some people, seizure diaries alone may provide a clinically useful forecast of future high or low seizure risk periods.

It is now recognized that estimating the probability of someone having a seizure in the near future is more feasible than trying to predict the exact timing of their next seizure.^{12,17,20} There are increasing efforts to develop a clinical seizure forecasting device¹ and understand user requirements.²¹⁻²³ Patient surveys have confirmed that probabilistic forecasts are considered useful and that perfect accuracy is not a requirement of such devices.^{21,23} For practical reasons, externally worn devices are rated more desirable than implanted recording devices in surveys.²³ There is increasing availability of wearable technology for seizure detection and forecasting.²⁴⁻²⁶ Furthermore, many seizure triggers that have been shown to be useful biomarkers of seizure likelihood can

Key Points

- Personalized forecasts based on circadian and multiday seizure cycles were tested pseudoprospectively using data from a mobile seizure diary app (50 users)
- Forecasts of seizure likelihood based on self-reported cycles were predictive of electrographic seizures for approximately half the validation cohort (n = 8)
- Forecasts using only mobile app diaries had an average accuracy of 69.1% (14.8% of time in warning) and allowed users to spend an average of 67.1% of their time in a low-risk state
- Seizure diary apps can provide personalized forecasts of seizure likelihood that are accurate and clinically relevant for electrographic seizures

be measured noninvasively. For instance, self-reported stress is predictive of seizures.^{27,28} Heart rate^{29,30} and other physiological signals monitored from a smartwatch device³¹ have also been used to forecast seizure likelihood. It is possible that these noncerebral biomarkers of seizure likelihood are useful because the same fundamental rhythms that modulate many aspects of human physiology also drive seizure risk.

This study used long-term, self-reported data from a mobile seizure diary to determine whether seizure cycles can provide a useful forecast of future seizure likelihood. The results provide a proof-of-concept that forecasting seizure cycles is practical and accurate and has the potential to be used as a clinical management tool. Mobile tools to forecast seizure cycles have wide-ranging applications including for improved clinical trial design, treatment titration, and long-term management for people with epilepsy.

2 | MATERIALS AND METHODS

2.1 | Data

This study used long-term data from a mobile seizure diary app (Seer Medical) to develop and test seizure forecasts. Forecasts were also generated using only the self-reported events from the Neurovista dataset, an existing set of long-term, continuous EEG and seizure annotations that have been widely used to develop forecasting algorithms.¹¹ The Neurovista dataset enabled forecasts based on self-reported seizures to be evaluated against electrographic seizures, and also provided a comparison of noninvasive forecasting performance to state-of-the-art seizure prediction.

2.1.1 | Mobile app data

The Seer app is a freely available mobile diary for reporting seizures and medications. Currently, there are >500 active users. This study used a subset of 50 users with a clinical epilepsy diagnosis, at least 30 reported seizures (mean = 109 seizures), and at least 2-month recording duration (mean = 48 weeks). Although users can report information such as seizure type and duration, this study only used the times of reported seizures. This study was approved by the St Vincent's Hospital Human Research Ethics Committee (HREC LRR 165/19).

2.1.2 | Continuous EEG data

The Neurovista study collected continuous intracranial EEG data from 15 subjects for a period of 6 months to 2 years. Further information on data collection and participants are reported by Cook et al.¹¹ This study used only the seizure times reported during the 6 month to 2 year recording period. Electrographic seizures were automatically annotated by an onboard EEG-based detection algorithm. All seizure detections were confirmed by trained epileptologists. Self-reported events were based on diaries kept by participants and caregivers, which were subsequently combined with EEG annotations and stored as electronic records. In addition to diary data, the Neurovista device included an audio recording feature that was automatically activated when suspect epileptiform EEG activity was detected by the on-board algorithm. The audio recordings were used to aid confirmation of clinical seizures, and for some subjects, audio recordings provided substantial assistance in seizure detection. However, to provide a direct comparison with mobile app data, the current study primarily considered events based on participants' diaries. The human research ethics committees of the participating institutes approved the Neurovista

study and subsequent amendments. All patients gave written informed consent before participation.

2.2 | Forecasting seizure cycles

An overview of the forecasting method is shown in Figure 1. An individual's strongest circadian ("fast") and multiday ("slow") cycles were estimated from their reported seizure times using the magnitude of the resultant vector, or synchronization index (SI), measured over a range of potential cycle periods. The SI is given by:

$$SI = \frac{1}{N} \left| \sum_{n=1}^N e^{i\theta_n} \right| \quad (1)$$

where N is the total number of seizures and each seizure is represented as a vector on the unit circle, $e^{i\theta_n}$, where i represents the imaginary number. The angle, θ_n , ranges from 0 to the period of the cycle being estimated (ie, 24 hours for a circadian cycle). For this study, fast cycle periods were assumed to be between 6 and 48 hours, with a 6-hour increment; that is, the strongest cycle for each individual, defined as the period with maximum SI, was selected from seven candidate periods (6, 12, 18, 24, 36, 42, and 48 hours). This range of fast cycle periods enabled the detection of approximate daily cycles rather than true circadian rhythms. Slow cycles were assumed to have periods of >3 days, with a maximum allowed period of 2 months or one-fifth of the recording duration (whichever was lowest). For instance, a person with 10 weeks of data could have a maximum slow cycle of 2 weeks, whereas someone with 1 year of data could have a slow cycle of up to 2 months. The increment for slow cycles was 1 day; that is, the strongest cycle for an individual, defined as the period with maximum SI, was selected from candidate periods of [3, 4, 5 days, ...] up to the maximum allowed period. Only significant cycles were used to develop seizure forecasts.

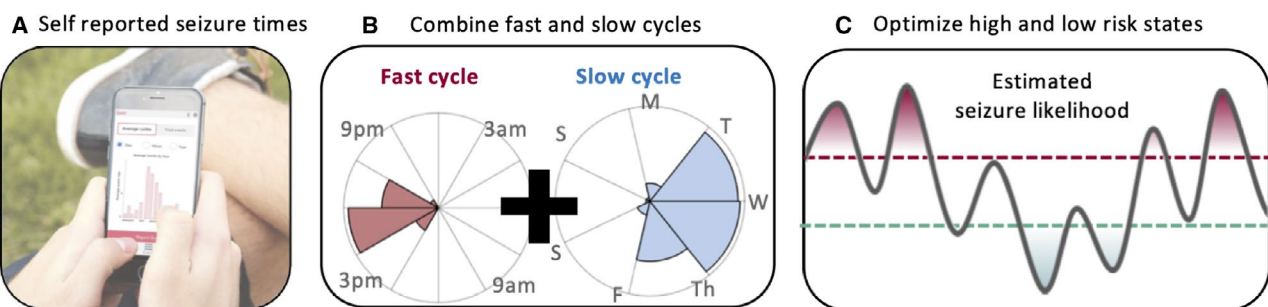


FIGURE 1 Schematic of seizure forecasting method. A, Development of forecasts initially required at least 30 seizure times to be reported in the mobile app. B, Self-reported seizure times were represented as cyclic histograms with different periods. The strongest fast and slow cycles were estimated based on the synchronization index of seizure histograms. In the example, a 24-h and a 7-d cycle are shown. C, The estimated seizure likelihood was calculated by combining the fast and slow cycles. High- and low-risk forecasts (dashed red and green lines) were optimized based on historical data

Significance was assessed using the Rayleigh test for nonuniformity of circular distributions ($P < .05$).³²

Individuals' strongest cycles were iteratively updated with each new seizure based on an exponentially weighted history of past seizure times; that is, the sum for the weighted SI of N seizures, SI_w , became:

$$SI_w = \frac{1}{\sum w_n} \left| \sum_{n=1}^N w_n e^{i\theta_n} \right|, \quad (2)$$

where $w_n = 1 - (1 - \alpha)^n$ is the weight applied to the n th seizure and $\alpha = 0.8$. The value of α was chosen somewhat arbitrarily; however, in this study, α had only minor effects on forecasting performance. In a longer-term, prospective study, the weighting on past events may be more important, and future work will focus on evaluating alternative weighting schemes. To estimate seizure likelihood, the phases of the fast and slow cycles, ϕ_{slow} and ϕ_{fast} , were derived for each 1-hour sliding window (with 5-minute overlap) over the recording duration:

$$\phi_i[t] = 2\pi \left\lfloor \left\lfloor \frac{t - t_0}{T_i} \right\rfloor \right\rfloor \quad (3)$$

where T_i is the period of the strongest cycle (ie T_{fast} or T_{slow}) and $\lfloor \cdot \rfloor$ indicates the modulo operator (the remainder after division). The phase, ϕ_i , is a function of time, t (hours), and t_0 represents the time of the most recent seizure (as the estimated fast and slow cycle periods, T_i , were updated after each seizure). The phase was then quantized into 20 equally spaced bins, from 0 to 2π . The probability of seizure occurrence with respect to each phase, $P[\phi_{slow}]$ and $P[\phi_{fast}]$, was calculated from the histogram of previous seizure times.

The final probability of seizure occurrence at each time, $P[t]$, was obtained as the product of the log-odds of each probability, $P[\phi_{slow}]$ and $P[\phi_{fast}]$:³³

$$P[t] = \frac{p}{1+p}$$

$$p = a \left(\frac{P[\phi_{fast}[t]]}{1 - P[\phi_{fast}[t]]} \right)^{\frac{a}{2}} \left(\frac{P[\phi_{slow}[t]]}{1 - P[\phi_{slow}[t]]} \right)^{\frac{a}{2}}, \quad (4)$$

where $a \in [0, \infty)$ is a systematic bias term reflecting the accuracy of the forecast ($a < 1$ indicates overconfidence and $a > 1$ indicates underconfidence). In this study, we have set $a = 1$, which is an unbiased forecast. However, in eventual real-world applications, a can be used to iteratively calibrate the forecast based on past performance. High- and low-risk warning thresholds were computed using a pseudoprospective brute force optimization that maximized the time spent in low-risk periods and number of seizures classified in high-risk periods.¹⁸

Forecasts were updated every hour and evaluated pseudoprospectively, using only the historical seizure record to compute the likelihood of future seizure occurrence ($P[T]$ in Equation 4). At least 10 seizures were required to initiate the seizure forecast, which was then iteratively updated after each seizure. Only the lead seizure within each 1-hour window was used; subsequent seizures within the same hour were removed before calculating and evaluating forecasts. Performance was evaluated based on the percentage of seizures in high (low) risk and the total duration spent in high (low) risk, after setting optimal thresholds for high- and low-risk warnings. Thresholds were also optimized pseudoprospectively using only previous seizures, that is, high and low thresholds were iteratively updated after each new seizure occurrence. Times where neither the high- nor low-risk thresholds were exceeded (ie, the forecast seizure likelihood was below the high-risk threshold and above the low-risk threshold) were considered moderate risk.

A 5-minute intervention period was used for evaluation; that is, seizures were only considered to be correctly predicted if the high-risk warning was on for at least 5 minutes before onset. Note that because seizure likelihood was calculated using a 1-hour sliding window with 5-minute overlap, this effectively meant that the minimum intervention period was between 5 and 10 minutes. Sensitivity improvement over chance was calculated based on the proportion of seizures and time in high risk to assess whether the high-risk forecast sensitivity was significantly better than chance performance.³⁴

Performance was also measured using the receiver operating characteristic (area under the curve [AUC]). The AUC addresses the ability of a classifier to discriminate between interictal and preictal data and is the preferred measure for many studies benchmarking multiple seizure forecasting algorithms.^{34,35} The AUC was also used to assess forecasting performance compared to chance level forecasting. The 95% confidence intervals of the AUC were calculated according to the procedure outlined by Hanley and McNeil.³⁶ These AUC confidence intervals were then compared to the chance level AUC. Chance level AUCs were approximated by computing the forecasting performance from shuffled seizure times (note that the theoretical chance level AUC is 0.5).

3 | RESULTS

3.1 | Can people self-report their seizure cycles?

We had previously demonstrated that seizure cycles can be measured from self-reported seizure times.¹⁵ The current

study presents a retrospective validation that self-reported cycles correspond to true underlying epileptic rhythms, rather than just forecasting behavioral cycles governing when individuals are more or less likely to report their seizures. The Neurovista dataset was used to determine whether self-reported seizure cycles aligned with cycles derived from electrographic seizures. Figure 2 shows that 11 of 15 Neurovista subjects (73%) had circadian cycles that were not significantly different using self-reported (diary) events compared to electrographic seizures ($P > .05$ using Kuiper test for circular distributions). Three subjects (S2, S3, and S5) did not have enough diary events to make a comparison. Nine subjects (60%) had multiday cycles that were not significantly different using diaries compared to electrographic seizures (see Figure S1). This suggests that although participants vastly underreported the total number of seizures, the underlying circadian and multiday trends can still be determined. There was a preference for individuals to report fewer seizures at night (Figure S2). In comparison, audio

confirmations were higher at night and lower during the day, perhaps reflecting less background noise during the night. In general, audio confirmations improved the alignment of circadian rhythms (Figure S3). Overall, these data suggest that self-reported seizures identified clinically relevant cycles for most people with epilepsy, albeit based on a relatively small validation cohort with refractory, focal epilepsy.

Figure 3 shows a comparison of forecasting performance using either self-reported (diary) or electrographic seizures from the Neurovista cohort. Both forecast models were evaluated using electrographic seizures. This comparison provided a unique opportunity to benchmark the performance of forecasts based on self-reported seizures against confirmed electrographic seizures, ensuring that forecasts were not merely useful at predicting users' reporting habits. This benchmarking is critical to provide confidence in the clinical utility of forecasts based on mobile diaries alone.

Forecasts were developed for subjects with at least 30 seizures (11 subjects had >30 electrographic seizures, eight

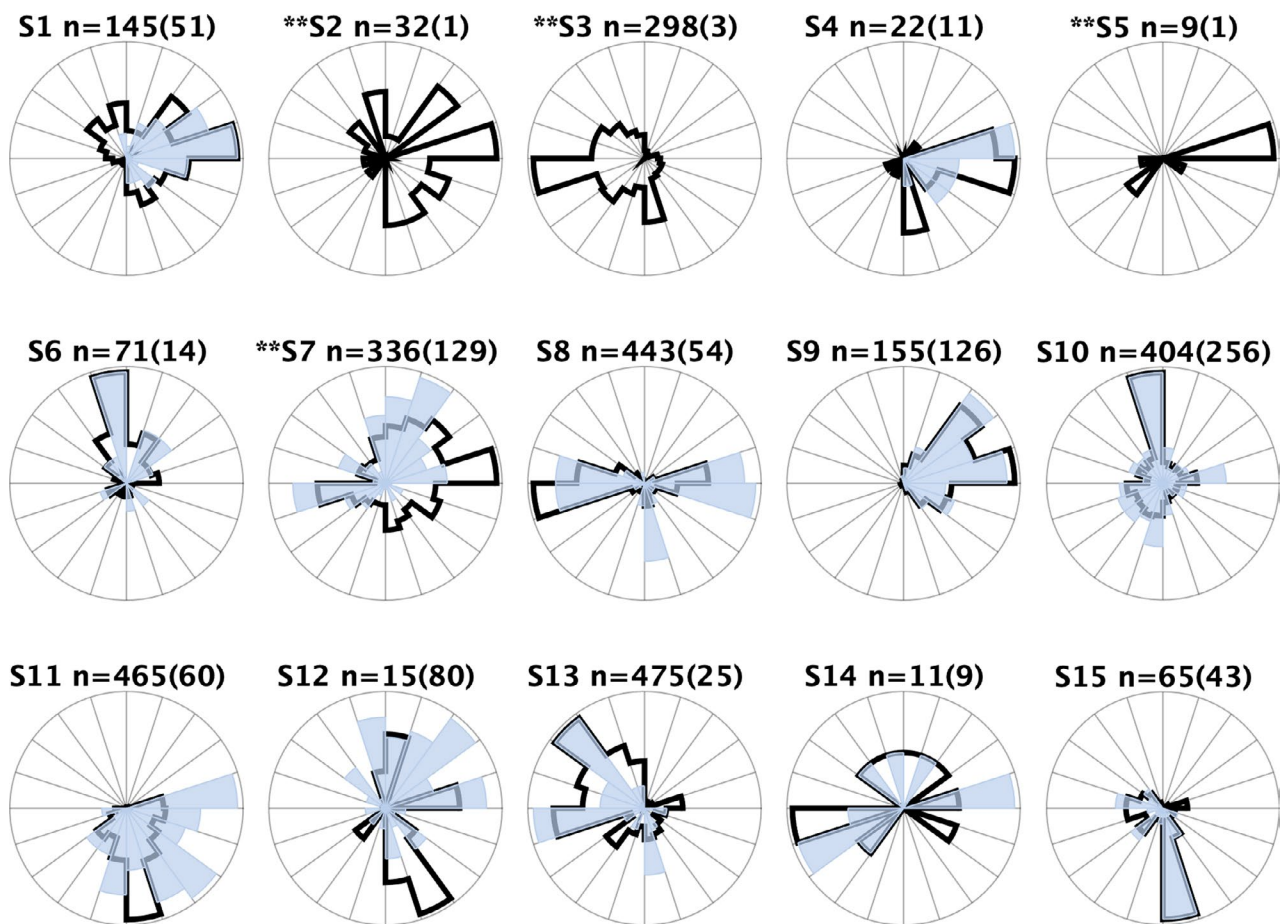


FIGURE 2 Alignment of seizure cycles based on self-report and electroencephalogram for the Neurovista cohort. Each circular histogram shows the circadian distribution of seizure cycles based on self-reported events (light blue) and electrographic seizures confirmed by expert reviewers (black lines). Total seizure numbers for each subject are given above each plot (with self-reported event counts in parentheses). Subject (S) 7 had significantly different cycle distributions using Kuiper test for circular distributions (** $P < .01$). Subjects 2, 3, and 5 did not have enough self-reported events for a comparison to be made

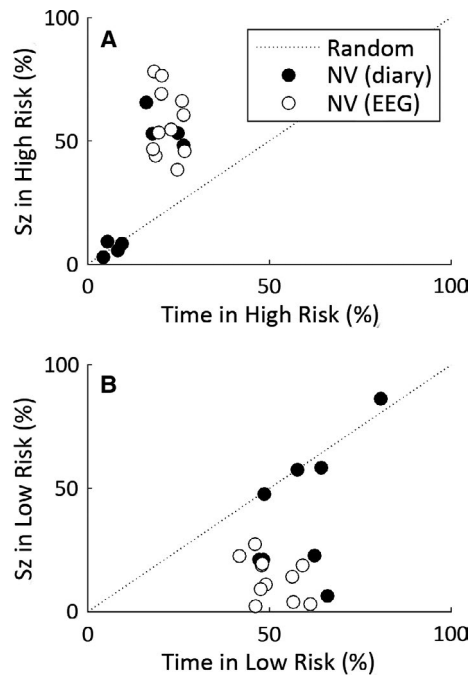


FIGURE 3 Validation of forecasting performance based on self-reported seizure cycles. Comparison of forecasting accuracy uses self-reported events (black) and electrographic seizures (white) from the Neurovista (NV) cohort. Note that only individuals with at least 30 seizures were included. Forecasting performance was evaluated for electrographic seizures (Sz). A, Percentage of time in high risk (x-axis) compared to accuracy, or proportion of seizures reported during high-risk states (y-axis). A good forecast is near the top left corner (100% accuracy, with the minimum number of hours in high risk). B, Percentage of time in low risk (x-axis) compared to the proportion of seizures in low-risk states (y-axis) reported. A good forecast is near the lower right corner, indicating maximal time in low risk without any seizures occurring. EEG, electroencephalogram

subjects had >30 self-reported seizures). Using electrographic seizures to develop forecasts resulted in a mean time in high risk of 20.5%, with 59.5% of seizures occurring in this state. The mean time in low risk was 55.6%, with 13.0% of seizures. The mean time in moderate risk was 23.9%, with 27.5% of seizures. However, when only self-reported seizures were used to develop forecasts, several individuals showed a marked decline in forecasting performance. Based on self-reported forecasts, four of the eight Neurovista subjects showed performance not significantly different from random performance ($P > .05$ using the sensitivity improvement over chance metric) for high-risk warning states. The other half of the subjects fell solidly within the low- or high-risk clusters. There was no significant correlation between reporting accuracy and forecasting accuracy (see Figure S4). This result shows that forecasts based on self-reported events may provide an accurate forecast of the likelihood of clinical electrographic seizures for approximately half of the cohort, whereas the other half of this group would produce inaccurate self-report forecasts.

3.2 | Forecasting accuracy

We tested whether a seizure forecasting model developed from self-reported seizures could be used to forecast future self-reported events using the mobile app diary data. Figure 4 shows an example of what forecasting seizure likelihood looked like using data recorded via the mobile app. The individual shown had an average of 2.8 seizures per week. Over the year of pseudoprospective evaluation, their forecast showed 18.7% of the time in high risk, with most seizures (59.3%) reported in this state. The individual's forecast showed 55.1% of the time in low risk, and 10 of their seizures (8.9%) occurred during low-risk periods. The rest of the time (26.2%) was spent in the moderate risk state. Figure S5 shows two other examples of subjects with different forecasting outcomes. The supplementary examples show that diary forecasts can provide useful information for individuals with a range of seizure rates, including an individual with a lower reported rate of 1.4 seizures per week who had no seizures occurring during low-risk periods, as well as a subject with a high rate of 24.2 seizures per week.

Figure 5 shows forecasting performance based on mobile app data. It can be seen that using mobile diaries, the mean high-risk accuracy was 69.1%, with users spending a mean of 14.8% of their time in high risk. The mean time in low risk was 67.1%, with an average of 10.5% of seizures occurring during low-risk states. The mean time in moderate risk was 18.1% with an average of 20.4% of seizures occurring during moderate risk states. The times and proportions of seizures occurring in low-, moderate-, and high-risk states were significantly different ($P < .01$ using the Wilcoxon rank sum test), as shown in Figure S6. Six of the 50 app users (12%) had zero reported seizures during their low-risk periods. All forecasts were significantly better than chance ($P < .01$ using the sensitivity improvement over chance metric). It is important to note that these results were evaluated based on self-reported seizures and may not reflect the performance if all electrographic seizures were recorded. However, the results suggest that clinically useful forecasts can be developed from mobile data alone, although it is anticipated that, for approximately half of people, mobile forecasts will not be accurate for predicting electrographic seizures, as shown from the Neurovista validation cohort (Figure 3).

Figure 6 shows the rate of true-positive compared to false-positive predictions for different thresholds of high-risk warnings using mobile app data. AUC provides a measure of forecasting performance without explicitly setting a warning threshold, where $AUC > 0.5$ indicates performance is better than chance level. Across the cohort, the mean AUC was 0.85 (range = 0.69–0.94). The 95% confidence intervals were computed for each AUC and compared to the AUC for chance performance. All individuals had AUCs that were significantly better than chance (95% confidence intervals were nonoverlapping).

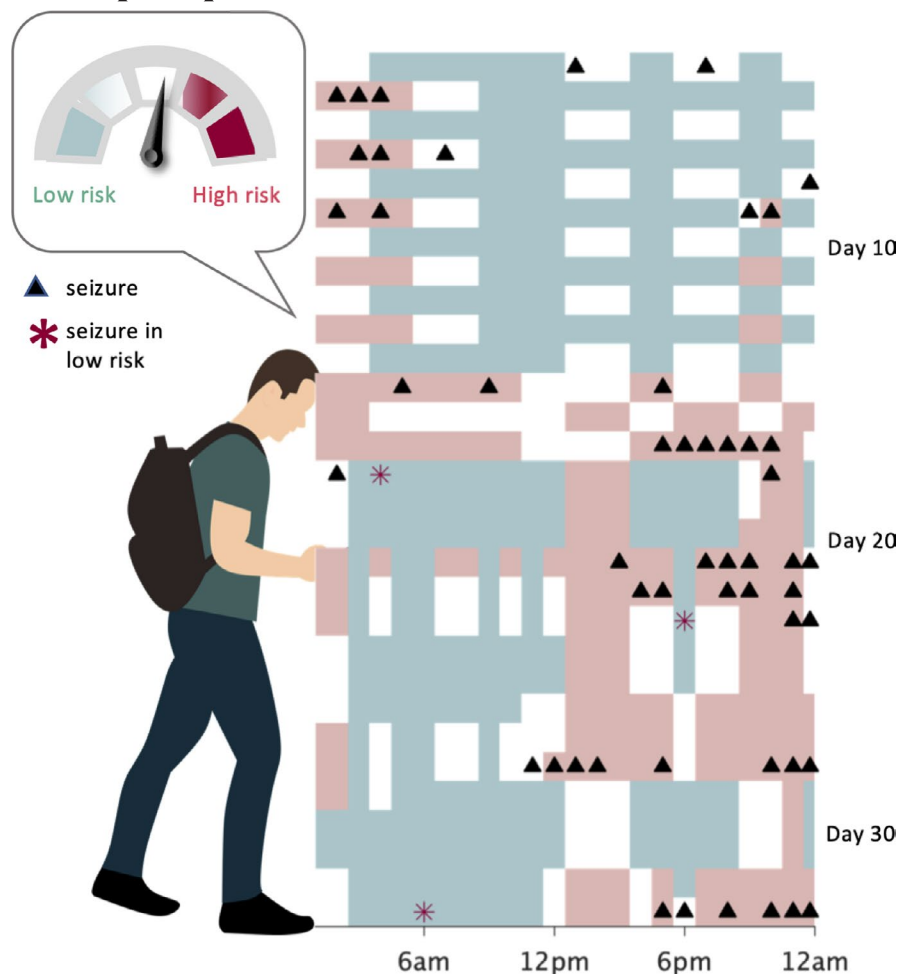


FIGURE 4 Output of a seizure forecast. Example data from an individual's high- and low-risk forecasts over a 30-day period (y-axis) are shown. The panel shows the pseudoprospective forecast output each day (x-axis). Red indicates times when the high-risk warning would be activated, green indicates time when the low-risk warning would be activated, and white shows times when the warning was moderate. Reported seizures are marked in black, and seizures that occurred during the low-risk state marked as red asterisks (in these data, three seizures occurred during low-risk periods). Note that individuals were not shown the output of their forecasts, and these data represent an example of pseudoprospective results only

4 | DISCUSSION

It is well known that seizure diaries are inaccurate and not well correlated to true seizure rates.^{11,37} The presented results showed that, although diaries are an unreliable estimate of true seizure counts, they can be used to measure underlying epileptic rhythms (Figure 2). Because seizure cycles are repetitive, diary data can be treated as a noisy, under-sampled representation of these underlying patterns. In this way, many people's seizure rhythms were reliably measured from their diaries and could be used to forecast clinical electrographic seizures (Figure 3). Underreporting and a slight bias toward daytime reporting did not abolish overall cyclic trends, and the use of audio confirmation increased the number of recorded seizures and improved the estimation of seizure cycles (Figures S2 and S3). Interestingly, there was no correlation between seizure underreporting and forecasting performance (Figures S4), suggesting that poor diary compliance was not necessarily a barrier to developing seizure forecasts. This finding may be because other factors (ie, cycle strength) are more relevant to determine forecasting accuracy; however, a larger cohort would be needed to robustly assess which factors affect performance. On the other hand, when a minimum number of seizures

is required, underreporting can prevent or delay forecast development. Some subjects reported almost no seizures, which could reflect many possible factors, including postictal memory impairment, the available social support, or the subject's level of engagement and attention to detail during the study. On the whole, the retrospective validation of self-reported forecasting performance against electrographic seizures (Figure 3) suggested that seizure forecasting apps will be accurate and may be a clinically useful method for some people. Future work will focus on incorporating objective biomarkers of seizures from wearable devices and validating the clinical utility of the proposed seizure forecasting app in a prospective clinical trial.

Overall, the presented results showed that seizure diary apps have the potential to provide accurate, clinically useful, personalized forecasts of seizure likelihood. Forecasting results using seizure diaries showed state-of-the-art performance, with an average AUC of 0.85 (Figure 6). A recent Kaggle competition for seizure prediction using continuous intracranial EEG recorded from three subjects in the Neurovista cohort reported winning AUC results of 0.81 for the competition and 0.75 on the held-out dataset.¹³ Of course, these scores are not directly comparable to app forecasts, as they were derived from continuous intracranial EEG data with highly

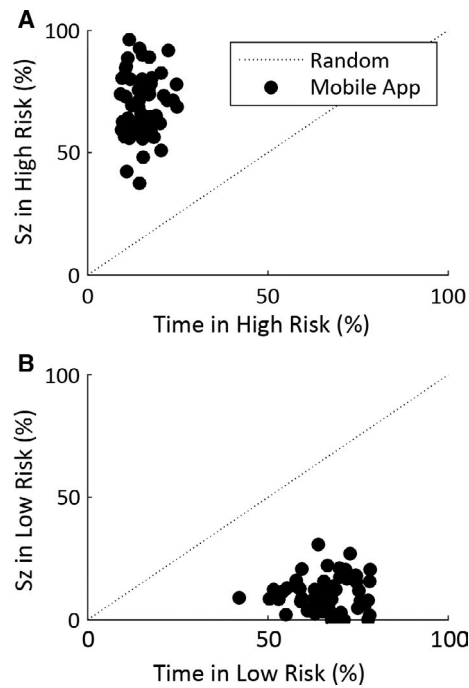


FIGURE 5 Forecasting performance using self-reported seizure cycles. Performance of high- and low-risk forecasts developed from mobile app data for 33 users is shown. A, Percentage of time in high risk (x-axis) compared to accuracy, or proportion of seizures (Sz) reported during high-risk states (y-axis). A good forecast is near the top left corner (100% accuracy, with the minimum number of hours in high risk). B, Percentage of time in low risk (x-axis) compared to the proportion of seizures in low-risk states (y-axis) reported. A good forecast is near the lower right corner, indicating maximal time in low risk without any seizures occurring

accurate seizure labeling; however, the comparison serves to highlight what is considered top range performance in seizure prediction using advanced machine learning. The current study showed forecasting accuracy of 69%, with app users spending, on average, less than one-fifth of their time with a high-risk warning (14.8%). A study using deep learning with the Neurovista data reported an average sensitivity of 69% and time in warning of 27%.³⁸ Moreover, forecasts based on seizure cycles naturally provide insight into times of low seizure likelihood. In this study, users were able to spend, on average, more than half their time in a low-risk state. Less than 10% of reported seizures occurred during the low-risk state, and 12% of users had no seizures in this state. Of course, it should be reiterated that this study only evaluated performance from users' self-reported events. It is anticipated that around half of the cohort would only show chance level performance for their electrographic seizures (Figure 3). However, the same forecasting strategy showed similar forecasting performance for both diary data and electrographic seizures (Figures 3 and 5). Therefore, performance is expected to improve as more accurate records of individuals' seizures become available, for instance, through new wearable or implantable technologies.

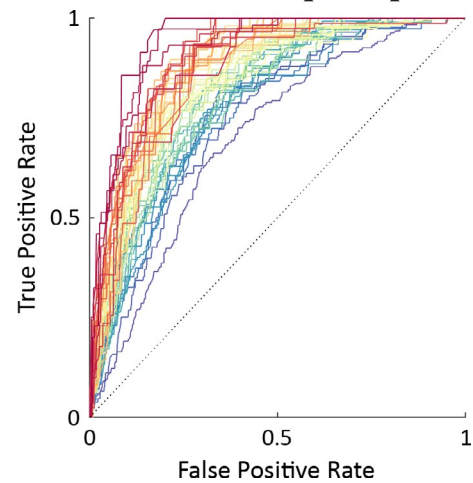


FIGURE 6 Receiver operating characteristic curves for seizure forecasts. The curves show the true-positive rate (y-axis) compared to the false-positive rate (x-axis) for each individual app user as the high-risk threshold is varied. An ideal forecast has area under the curve (AUC) = 1; chance level forecast has AUC = 0.5 (the diagonal line)

Furthermore, there are applications for forecasts of self-reported events, such as scheduling EEG monitoring, or improving analysis of clinical trial diaries.³⁹

Delivering seizure forecasts in a prospective trial is itself noninterventive in the sense that no direct therapy is given. Instead, users are only given information about their personalized seizure likelihood. However, reliable information may be a powerful antidote to the uncertainty of living with uncontrolled seizures. Furthermore, information about seizure likelihood can be used in conjunction with behavioral strategies to reduce seizure rates. For instance, it has recently been shown that stress management techniques could be targeted to days of heightened seizure risk to reduce seizure rates.⁴⁰ Forecasts may also be used to modulate medication or stimulation levels based on seizure likelihood. Such modulating chronotherapy has been used to time dosage of antiseizure medication, successfully reducing seizure rates.⁴¹ However, modulation of drug levels has not been investigated for individually tailored cycles or over longer timescales to account for multiday cycles of seizure likelihood. Seizure forecasting systems may also improve seizure detection and prediction accuracy by incorporating data from wearable or implantable monitoring devices.

Wearable devices have long been heralded as the next frontier in epilepsy management, both for their potential as automated seizure detectors and to provide advance warning of seizure onset.²⁴ However, wearable seizure monitors have faced several challenges, including their relevance for more subtle seizure types, high false alarm rates, and poor user experience.^{22,42} A forecasting app could potentially improve the detection performance of wearable devices by providing a prior probability of seizure likelihood. Similarly, physiological signals recorded from wearable devices could improve

forecasts of seizure cycles by providing a continuous measure of underlying rhythms, rather than discrete samples (seizure times). We have shown that fast and slow cycles of brain activity can be measured from continuous EEG across diverse frequencies and regions of cortex.¹⁸ These continuous cycles provided the most accurate estimate of seizure likelihood to date. More recently, cycles of interictal epileptiform were also used to provide a forecast of seizure risk over days.¹⁹ It is possible that cycles of epileptic brain activity can also be derived from auxiliary systems modulated by the brain, such as cardiac and pulmonary output or even mood and sleep. It is well known that both circadian and multiday cycles modulate many aspects of human health and disease,⁴³⁻⁴⁵ including heart disease,^{46,47} immune response,⁴⁸ and neurological and psychiatric disorders.^{49,50} However, a long-term study to identify cyclic rhythms of physiological signals in conjunction with cycles of seizure risk has not yet been undertaken. Ultimately, the ability to measure cycles from almost every biological process underscores the power of a simple, cyclic seizure forecast.

There is still no consensus on how accurate a seizure forecast must be to be clinically useful, nor for which epilepsy characteristics and patterns forecasting methods may prove most useful. Several studies have surveyed the views of people with epilepsy and caregivers on the subject of seizure forecasting. In one survey, participants reported that missed seizures were considered worse than false alarms, and that perfect accuracy was not considered a requirement for a forecasting device.²¹ Recently, Janse et al²³ showed that seizure forecasting devices were acceptable despite the potential for inaccuracy (up to “inaccurate 30% of the time”). Ultimately, post hoc studies and surveys can only provide an indicative measure of the utility and benefits of a seizure forecasting device. In a prospective setting, some people may find knowing times of safety to be more important than high-risk warnings. Some people are likely to tolerate false alarms poorly, whereas others would find a forecasting device very helpful. It is also unclear how many warning states users will find desirable. This study used three seizure likelihood states (low, medium, and high), based on the warning lights used in the original Neurovista study. We found that the times and proportions of seizures occurring in low-, moderate-, and high-risk states were significantly different (Figure S6), suggesting the division into three risk states can provide statistically meaningful information. However, in a prospective setting, users may prefer to be able to set their own warning states. As with many aspects of epilepsy treatment, the usefulness of seizure forecasting is likely to be patient-specific.

This study provided a proof-of-concept that seizure diary apps can provide personalized forecasts of seizure likelihood. We hypothesize that mobile apps to forecast cycles of seizure

likelihood have the power to improve quality of life for people with epilepsy, even without delivering direct intervention. In support of this hypothesis, we note that unpredictability is the primary disability of epilepsy,¹ and for people with refractory seizures, quality of life is far more strongly determined by the degree of drug-related side effects or depressive symptoms than by seizure frequency.⁵¹ Reliable seizure forecasting has the potential to improve quality of life by reducing uncertainty and improving mood. There is also scope for forecasting to reduce drug-related side effects through intelligent titration of medication. Ultimately, it is our hope that seizure forecasting apps provide another clinical tool to manage epilepsy.

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CONFLICT OF INTEREST

D.R.F., M.J.C., and P.J.K. each have a financial interest in Seer Medical. D.R.F., P.J.K., M.M., E.S.N., and D.P. receive a salary from Seer Medical. None of the other authors has any conflict of interest to disclose. 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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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