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Seizure forecasting using minimally invasive, ultra-long-term subcutaneous EEG: Generalizable cross-patient models

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Abstract

This study describes a generalized cross-patient seizure-forecasting approach using recurrent neural networks with ultra-long-term subcutaneous EEG (sqEEG) recordings. Data from six patients diagnosed with refractory epilepsy and monitored with an sqEEG device were used to develop a generalized algorithm for seizure forecasting using long short-term memory (LSTM) deep-learning classifiers. Electrographic seizures were identified by a board-certified epileptologist. One-minute data segments were labeled as preictal or interictal based on their relationship to confirmed seizures. Data were separated into training and testing data sets, and to

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compensate for the unbalanced data ratio in training, noise-added copies of preictal data segments were generated to expand the training data set. The mean and standard deviation (SD) of the training data were used to normalize all data, preserving the pseudo-prospective nature of the analysis. Different architecture classifiers were trained and tested using a leave-one-patient-out cross-validation method, and the area under the receiver-operating characteristic (ROC) curve (AUC) was used to evaluate the performance classifiers. The importance of each input signal was evaluated using a leave-one-signal-out method with repeated training and testing for each classifier. Cross-patient classifiers achieved performance significantly better than chance in four of the six patients and an overall mean AUC of 0.602 ± 0.126 (mean ± SD). A time in warning of 37.386% ± 5.006% (mean ± std) and sensitivity of 0.691 ± 0.068 (mean ± std) were observed for patients with better than chance results. Analysis of input channels showed a significant contribution ($p < .05$) by the Fourier transform of signals channels to overall classifier performance. The relative contribution of input signals varied among patients and architectures, suggesting that the inclusion of all signals contributes to robustness in a cross-patient classifier. These early results show that it is possible to forecast seizures training with data from different patients using two-channel ultra-long-term sqEEG.

Keywords

deep neural networks; epilepsy; LSTM neural networks; machine learning; seizure forecasting; subcutaneous EEG

1 | INTRODUCTION

Many people with epilepsy continue to have seizures despite optimized medication therapy, surgical treatments, and neuromodulation therapy. The unpredictability of seizures is reported to be one of the most disabling aspects of epilepsy,[1,2] and forecasting seizures could help patients manage activities or facilitate targeted therapies.[3–8] Electroencephalography (EEG) has been the modality most studied for the development of seizure forecasting algorithms. However, a significant limitation to forecasting has been the scarcity and technical difficulty of ultra-long-term EEG recordings, as well as the invasiveness of intracranial EEG (iEEG) recordings.[9–11] New subcutaneous EEG (sqEEG) recording systems have shown promise in enabling ultra-long-term monitoring to better inform treatment in epilepsy.[12] Preliminary analysis of the data has shown excellent long-term stability[13] and that electrographic seizure monitoring and analysis of long-term cycles of seizure risk with these data are possible.[14] These devices may be attractive as part of a seizure-forecasting system, offering continuous monitoring and a modest burden to the patient,[15] although with limited spatial coverage.

Neural networks have shown great promise for recognizing patterns in data, with various applications in medicine, health care, and specifically epilepsy.[16–18] Recurrent neural networks (RNN)[19] are neural networks with hidden states allowing them to retain past and current information and determine the current outputs, thus making them better with sequential information. Long short-term memory (LSTM) networks[20] are a type of RNN capable of learning long-term dependencies in time-series data, thereby overcoming the

RNN difficulty of preserving information over many timesteps. An LSTM unit comprises three gates (input, forget, and output) cooperating to decide whether to retain or ignore the hidden state information. Bidirectional LSTM (BiLSTM) networks[21,22] are a fusion of the standard LSTM networks and bidirectional RNN (BRNN)[23] that use a two-way input: first, in the forward direction and second in the reverse direction, where both are connected to the same output layer.

Seizure forecasting has been shown previously to be most accurate when developed for a specific patient,[9,24–27] training on early data and generating forecasts prospectively. However, the prediction performance is typically driven by the availability of training data, and the lack of a large amount of data (especially preictal) is particularly challenging during the early phases of monitoring when minimal training data are available. Generalized, cross-patient seizure-forecasting algorithms have been developed for iEEG[25] and multimodal wearable signals[28] and have achieved better than random results in a significant proportion of patients studied. The variability between individuals is challenging when identifying subtle preictal changes in a generalized, cross-patient seizure-forecasting system. However, the possibility of forecasting seizures immediately at the outset of monitoring, prior to the availability of patient-specific training data, and using periodic retraining with patient-specific collected data may be attainable with sufficient data and innovative normalization strategies.

The work presented here evaluated a generalized cross-patient seizure forecasting algorithm approach from ultra-long-term sqEEG using LSTM neural networks. This study also explored the input channel importance to intrapatient seizure-forecasting performance.

2 | METHODS

2.1 | Subcutaneous EEG data

This study evaluated patients with refractory focal epilepsy that recorded ultra-long-term subcutaneous EEG (sqEEG) using the 24/7 EEG SubQ system from two centers: a completed study at Zealand University Hospital (ZUH), Denmark,[15] and an ongoing study (ClinicalTrials.gov NCT04061707) at King's College London (KCL), UK.[14] This system consists of an implanted three-contact lead wire and ceramic housing inserted unilaterally with a brief local anesthetic procedure. An external data logger connects to the implant housing via induction, powering the implant and recording data at 207 Hz. The data are bandpass filtered at [0.5, 48] Hz with a finite-impulse-response equiripple design and 40 dB attenuation filter. In both cohorts, electrographic seizures were then identified by a team of board-certified epileptologists in a visual review of the data while considering patient-specific seizure signatures. At KCL, the EEG was reviewed on a dedicated software (UNEEG Episight) assisted by a high-sensitivity automated seizure detector (unpublished) and a review of a random sample of 6-h epochs comprising 10% of the whole recording. If seizures missed by the detector were found, the whole data set was reviewed. At ZUH, the EEG was visually inspected based on 10-min time-frequency epochs and potential seizures reviewed in the time domain.

2.2 | Training and testing data

Based on confirmed seizures identified by a board-certified epileptologist, data were labeled as preictal or interictal epochs as follows: preictal data segments were defined 1 h with a set-back of 5 min before seizure onset for lead seizures, which were defined as seizures separated from preceding seizures by at least 4 h (see an example of sqEEG signal at the defined pre-ictal data segment and at the time of a lead seizure in Figure 1). Clustered (i.e., nonlead) seizures were excluded from the analysis. Interictal data segments were identified from seizure-free periods at least 1 day apart from any seizure. In the leave-one-patient-out analysis, the classifier was tested on each patient in turns using all other patient's data as a training set (see Table 2). For inclusion in the analysis, we required that (1) the training data included a minimum of three 60-min preictal epochs, (2) the testing data included a minimum of four 60-min preictal epochs, (3) the training data included a total of interictal segments at least three times the total of preictal segments, and (4) the testing data included at least as many interictal segments as preictal segments (see Table 2).

2.3 | Neural network architectures

In our preliminary analysis, seven architectures were evaluated in a single patient study,[29] and the three architectures with the best forecasting performance were included in this study. Architecture 1 (3 LSTM), the architecture previously presented in Nasseri et al.[30] consisted of three consecutively connected unidirectional LSTM layers with 200 hidden layers each, followed by one dropout layer with a rate of 0.2. For architecture 2 (5 LSTM), we increased the number of LSTM layers in conjunction with reducing the number of hidden layers. Thus the architecture consisted of five consecutively connected unidirectional LSTM layers with 25 hidden layers each. For architecture 3 (2 BiLSTM), we investigated the capabilities of a simple BiLSTM architecture consisting of two bidirectional LSTM layers with 10 hidden layers each per direction. All architectures end with a sigmoid activation function output layer to generate the classification. The architectures differ in their input (as described in subsequent text). See Table 1 for a summary of architectures and Figure S1 for illustration of the architectures.

For architectures 2 (5 LSTM) and 3 (2 BiLSTM), the preictal and interictal data epochs were divided into 1-min nonoverlapping segments and preprocessed, starting with per-segment mean subtraction, low pass filtered by Butterworth 5th order with a cutoff at 25 Hz, and down-sampled by a factor of 2. The fast Fourier transform (FFT) of signals was calculated for each channel as an additional input channel to emphasize frequency information within the data. In addition, the time of day (TOD) represented as the hour part of the 24-h time of the 1-min epoch was added as an input channel to allow the algorithm to learn any circadian periodicities in the patient's seizure pattern. To compensate for the heavily unbalanced data ratio in training, noise-added copies of preictal data segments were generated by adding random white noise uniformly distributed over [0,1) and then multiplied by the segment's median. Finally, the entire data set (training and testing) was normalized (z-score), using the training data's mean and standard deviation. For architecture 1 (3 LSTM)—our initial architecture—the data were preprocessed similarly without filtering, down-sampling, or including the TOD channel.

2.4 | Relative contributions of input channels

A leave-one-signal-out analysis was performed to evaluate the relative contributions of each input signal to the seizure-forecasting algorithm performance. To better assess interpatient variability in the relative contributions of different input signals, training and testing were performed using each patient's data separately, with the earliest third of the recorded data used for training and the latter two thirds of data for testing. Architectures 2 (5 LSTM) and 3 (2 BiLSTM) were trained and tested with different input channels removed in turns, creating separate classifiers without: TOD channel, two FFT channels, two data channels, and each of the two recorded channels (data and FFT). This was done five times to account for the random initial weight assignment during training, and a mean area under the curve (AUC) was calculated. The AUC with the omitted signal was compared to the AUC of the complete classifier to quantify each signal's importance to the forecasting performance.

2.5 | Statistical analysis

The area under the receiver-operating characteristic (ROC) curve (or AUC) was used to evaluate the performance of the different architectures. The results were assessed by taking the mean probability of five consecutive 1-min segments; then the maximum probability from every 60 min (12 values of five consecutive 1-min segments) was identified. Forecasting performance was also evaluated using sensitivity, corresponding to the particular decision threshold chosen, false alarms in the percentage of hours per day calculated as the sum of false positives (total hours in warning) divided by the sum of predictions (total hours), mean preseizure alerts in minutes, and *p*-values to identify better than chance performance for each architecture were computed using the method presented in Snyder et al.[31] The results were further validated by calculating improvement over chance[24] (IoC) against a random classifier with randomized seizure times for each patient[32] (averaged across 100 times per patient). Python (3.7.8),[33] TensorFlow (2.4.1),[34] and MATLAB (MathWorks, R2019b) were used for signal classification and analysis in this study.

3 | RESULTS

3.1 | Subcutaneous EEG data

Our analysis included six patients who had completed monitoring, had full data annotations, and satisfied the training and testing criteria. Demographic and data information are summarized in Table 2.

3.2 | Forecasting performance

The AUC-ROC for architecture 1 (3 LSTM), which achieved the best results among architectures studied, is illustrated in Figure 2. Forecasting performance for architecture 1 is summarized in Table 3 (see Table S1 for architectures 2 and 3 forecasting performance). Architecture 1 produced a mean AUC of 0.602 ± 0.126 (mean ± standard deviation [SD]) for six classifiers. Four of six performed better than chance with a mean sensitivity of 0.691 ± 0.068 (mean ± SD), and false-alarm rate per day of 37.4% ± 5.0% (mean ± SD), preseizure warning of 31.8 ± 4.3 (mean ± SD) min, and IoC of 0.342 ± 0.077 (mean ± SD). When including all seizures, lead and clustered, in the testing data set, architecture 1, produced

similar performance with a mean AUC of 0.599 ± 0.130 (mean ± SD), and four of six classifiers show better than chance performance with a mean sensitivity of 0.666 ± 0.059 (mean ± SD) and mean false-alarm rate per day of 37.6% ± 3.6% (mean ± SD). Additional forecasting performance results are summarized in Table S2.

3.3 | Relative contributions of input channels

The relative contributions of input signals to the forecasting performance for architectures 2 (5 LSTM) and 3 (2 BiLSTM) are shown in Figure 3. For architecture 2, input channels importance analysis showed a significant difference ($p < .05$) between classifiers using all channels and classifiers without the FFT of EEG signals. Generally, the relative contributions of signals varied between patients and architecture (see Figure S2 for architectures 2 and Figure S3 for architectures 3).

4 | DISCUSSION

We have demonstrated better than chance results forecasting seizures using two-channel sqEEG data recorded over months in a small cohort of people with epilepsy, using algorithms trained on recordings from other individuals. Forecasting seizures using a cross-patient training/testing approach has proven to be quite challenging using other data sources,[25,28] and this is also the case here when compared to an intrapatient training and testing approach applied to the same data set (Viana et al., current issue). These initial results on a limited data set are encouraging and support the feasibility of this approach. Given the strong dependence of deep-learning algorithms on exceedingly large training data sets, it seems likely that the accuracy will improve significantly with the expansion of available training data. In theory, the supply of training data for a cross-patient forecasting classifier is nearly infinite, whereas the potential supply of training data for a single-patient classifier is limited to what has been recorded previously by that patient. As a relatively new data source, sqEEG has been recorded from a small number of patients with epilepsy. As these devices see increasingly widespread use, the data available for algorithm training and development will increase commensurately, likely leading to improved performance. The data scarcity problem is further exacerbated because seizures are rare events, and machine learning algorithms need abundant examples of both classes of data to learn the differences between them. In addition, epilepsy as a disease characterized by diverse EEG patterns[35] further expands the amount of data needed to implement a general-use seizure-forecasting algorithm successfully, and initially efforts may be most successful if focused on groups of patients with similar seizure-onset zones and EEG patterns.

Regardless of these challenges, however, the cross-patient approach to forecasting seizures has great promise and should not be overlooked. The single-patient approach to training and testing requires a period of recording and annotation in order to train an algorithm successfully, and during this period a cross-patient algorithm could provide seizure warnings. Subsequently, recorded data could then be used to progressively retrain the algorithm, adapting it to that particular person’s data patterns. When sqEEG gains widespread use and data become abundantly available, algorithms trained with vast stores of interictal and preictal EEG may add robustness to forecasts, particularly to changing EEG

patterns. It may also be possible to leverage similar data sources to expand training data, which may be especially helpful in the case of a relatively new device.

The relative contributions of the input signals showed heterogeneous results in this patient group, even among the four patients for whom forecasts were significantly better than chance (see Figures S2 and S3). Most likely the significant dependence on the FFT inputs observed for architecture 2 (5 LSTM) is driven by the heavy reliance on these signals for patients S02 and E09 (see Figure S2). The time-of-day channel, in particular, showed interpatient differences, contributing positively to performance for patients S01, S02, and E09, but apparently hindering performance for patients E02 and E04, as AUCs in both architectures increased when this feature was removed. It seems likely that patients with a strong and stable circadian pattern of seizures may benefit from the inclusion of this signal. In contrast, patients with an unstable or changing circadian pattern might have degraded performance. In aggregate, these differences may have aided performance in the cross-patient case, as the training data encompassed a broader range of signal dependencies. In general, improved forecasting performance beyond what is reported here is needed to achieve acceptance in real-world clinical applications. The necessary performance to achieve routine usability depends upon the use case: for patient alerts, false positives can contribute to alert fatigue and discourage use, whereas for neuromodulation or responsive pharmacotherapy false alerts have a low penalty but missed seizures are problematic. We believe that increasing training data, adding long-term cyclical seizure risk, and ensembling cross-subject and intrasubject classifiers can provide significant improvement in performance.

Although these results are encouraging, it should be noted that the small number of patients in this study and the shared temporal lobe localization of seizures in this cohort may limit broad applicability of this method. In addition, the subscalp EEG recording device is limited in its coverage and laterality (unless multiple devices are used), and we do not know if this method will be able to forecast seizures in patients with multifocal or bilateral seizures onsets. Although we believe the system will be able to forecast extratemporal seizures with adjustment to the electrode's position at implant to cover the area of seizure onset, we do not have evidence yet to confirm this. In addition, sqEEG signals are more susceptible than iEEG to myogenic and other artifacts, and it is possible that such artifacts may prevent successful seizure forecasting in some situations where invasive EEG-based forecasting would have succeeded.

Seizure forecasting has advanced in recent years through multiple avenues, including iEEG, wearable devices, and electronic diaries. Seizure-forecasting approaches using long-term multi-day cycles of seizure risk, and acute seizure forecasting are complementary, and both methods, along with cross-patient and single-patient approaches, may be combined to create a comprehensive system to optimize accuracy. sqEEG is especially well suited to the long-term use needed for chronic application of seizure forecasts because of its ability to be used for long periods with a relatively minimal patient burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST

JDH is an employee of UNEEG medical A/S. ESN and DF are employees and shareholders of Seer Medical. BHB has equity in Cadence Neurosciences, has research funding from Seer Medical, and has received research devices from Medtronic Inc. at no cost. MPR has been a member of ad hoc advisory boards for UNEEG medical A/S. PFV received a payment from UNEEG medical A/S for data annotation in an unrelated research study. TWK consults for UNEEG medical A/S. No other authors have conflicts to declare. 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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Key points

- These early results suggest that seizure forecasting is possible with a cross-patient classifier trained on two-channel ultra-long-term subcutaneous electroencephalography (EEG) recordings.
- Seizure forecasting with a cross-patient algorithm achieved better than chance performance for four of six classifiers.
- Input channel importance showed high relevance of frequency spectrum information to the performance of the algorithm.

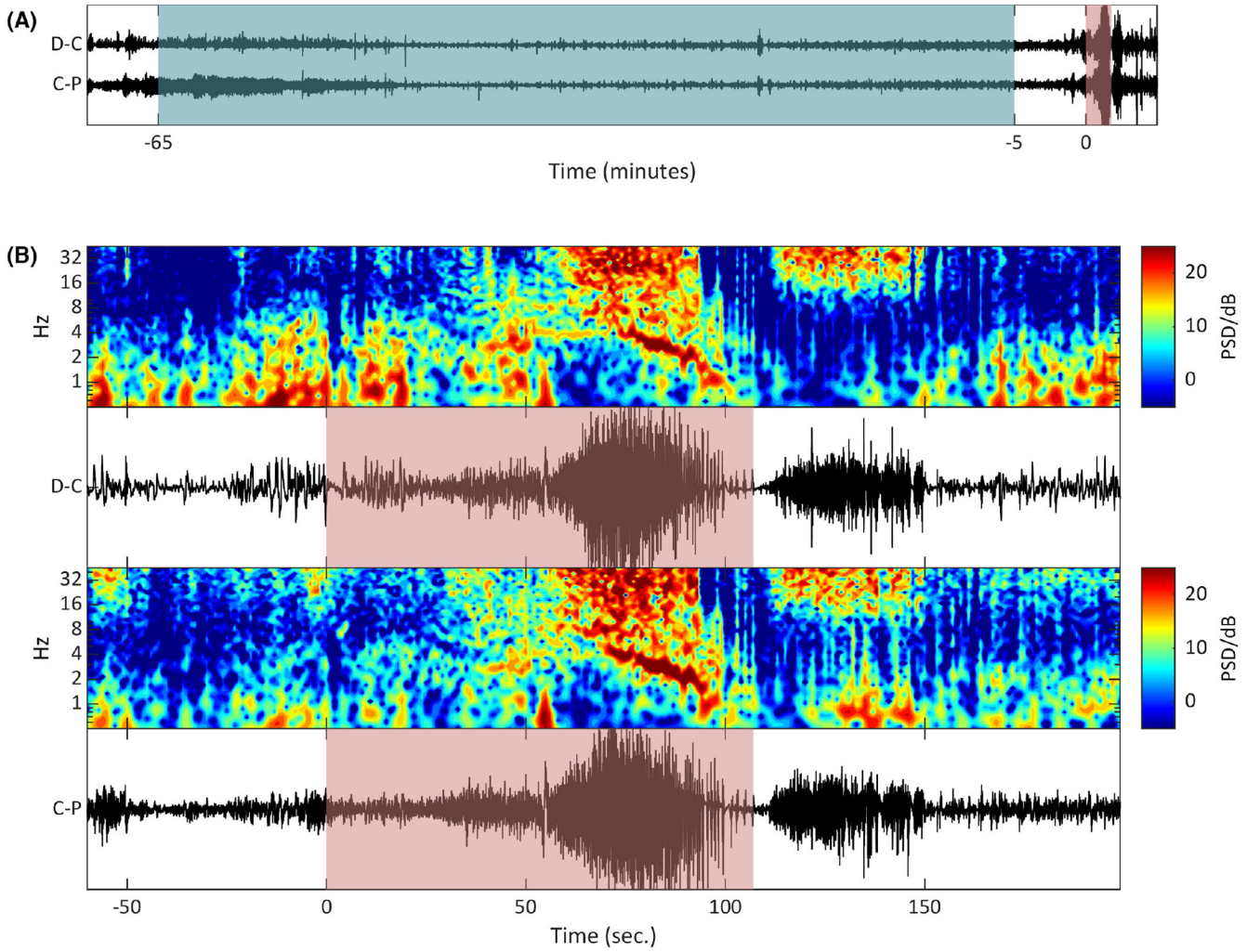

FIGURE 1.

Example of subcutaneous electroencephalography (sqEEG) signal at defined preictal data segment (panel A, light green) and at the time of a lead seizure (both panels, light red). Preictal data segments were defined as 1 h with a set-back of 5 min before seizure onset for lead seizures, which were defined as seizures separated from preceding seizures by at least 4 h. Panel B shows the raw EEG signal (D-C: distal to central channel, C-P: proximal to central channel) and time-frequency decomposition for each channel (performed via complex Morlet wavelet convolution, with wavelet frequencies between 0.5 and 40 Hz and number of cycles between 5 and 20, both logarithmically spaced)

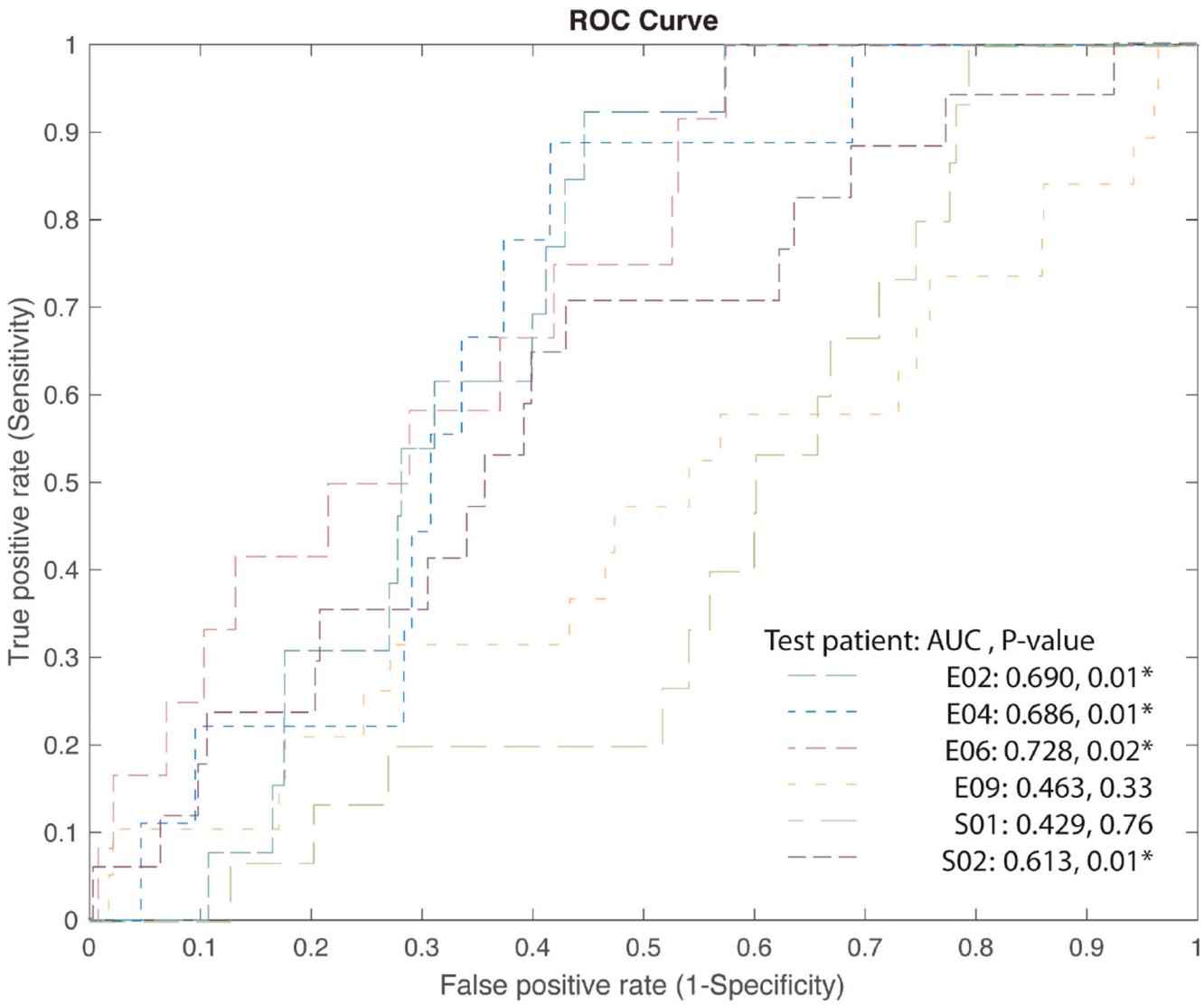

FIGURE 2.

Area under the receiver operating characteristic curve (AUC-ROC) for architecture 1 (3 long short-term memory [LSTM]). With a mean AUC of 0.602 ± 0.126 (mean ± standard deviation [SD]) and four of six generalized classifiers evaluated performed better than chance. *p-value <.05: better than chance performance

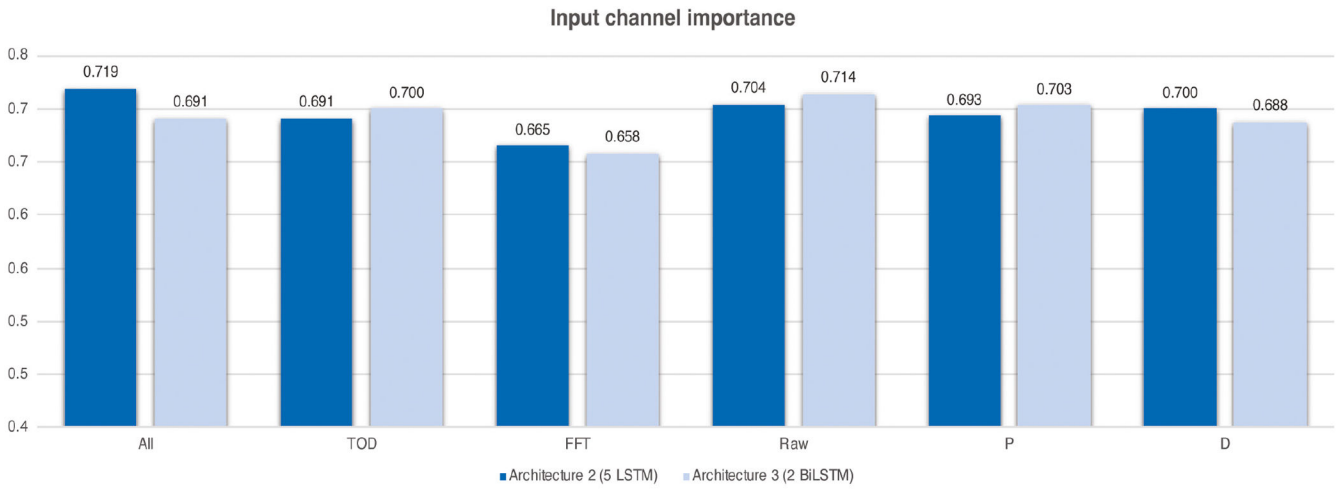

FIGURE 3.

Analysis of input channel importance and relative contribution to the prediction performance. For architecture 2 (5 long short-term memory [LSTM]), this analysis showed significantly poorer performance ($p < .05$) overall for classifiers without the fast Fourier transform (FFT) of electroencephalography (EEG) signals. The average AUC was calculated with time of day (TOD), FFT, Raw, P (proximal to central channel) and D (distal to central channel) channels removed. *X*-axis labels show the removed channel

TABLE 1

Architecture summary

Architecture		Number of channels	Number of LSTM layers	Number of hidden layers	Batch size
1	3 LSTM	4 (2 Raw, 2 FFT)	3	200	100
2	5 LSTM	5 (2 Raw, 2 FFT, TOD)	5	25	50
3	2 BiLSTM	5 (2 Raw, 2 FFT, TOD)	2	10	100

Note: Architecture 1 (3 LSTM) with two raw data channels and two FFT of signals channels to emphasize frequency information within the data. Architecture 2 (5 LSTM) and architecture 3 also include the TOD represented as the hour part of the 24-h time of the 1-min epoch to allow the algorithm to learn any circadian periodicities.

Abbreviations: BiLSTM, bidirectional long short-term memory; FFT, fast Fourier transform; LSTM, long short-term memory; TOD, time of day.

TABLE 2

Patient characteristics

Patient	Cohort	Age	Sex	Implant location	Seizure types	Preictal hours (Train/Test)	Interictal days (Train/Test)
S01	KCL	36	F	Left temporal	FAS; FIAS	4/11	50/138
S02	KCL	57	M	Right temporal	FAS; FIAS	12/5	1/21
E02	ZUH	33	F	Left temporal	FIAS; FBTCS	3/10	18/40
E04	ZUH	38	F	Left temporal	Uncertain	3/6	14/41
E06	ZUH	75	F	Left temporal	FIAS; FBTCS	8/4	7/30
E09	ZUH	27	F	Left temporal	FAS	8/11	8/37

Abbreviations: F, female; FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; KCL, King's College London; M, male; ZUH, Zealand University Hospital, Denmark.

TABLE 3

Generalized performance for architecture 1 (3 LSTM) (lead seizures)

Test	AUC	Sensitivity	False alarms (hours/day) [%][36]	Mean pre-seizure alert (min)	*p*-Value	Mean IoC (mean ± std)
S02	0.614	0.705 (12/17)	10.5 [43.6]	30.2	.01 *	0.274 ± 0.147
S01	0.430	0.2 (3/15)	6.5 [26.9]	37.2	.76	N/A
E09	0.463	0.315 (6/19)	6.5 [27.1]	31.5	.34	N/A
E06	0.729	0.666 (8/12)	8.9 [37.2]	35.2	.02 *	0.315 ± 0.163
E04	0.686	0.777 (7/9)	9.0 [37.4]	35.4	.01 *	0.454 ± 0.175
E02	0.690	0.615 (8/13)	7.5 [31.3]	26.5	.02 *	0.326 ± 0.230

Note:

* *p*-Value <.05: better than chance performance.

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