Published in final edited form as:
Clin Neurophysiol. 2023 June ; 150: 49–55. doi:10.1016/j.clinph.2023.02.180.

Spike height improves prediction of future seizure risk

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Abstract

Objective: We evaluated whether interictal epileptiform discharge (IED) rate and morphological characteristics predict seizure risk.

Methods: We evaluated 10 features from automatically detectable IEDs in a stereotyped population with self-limited epilepsy with centrotemporal spikes (SeLECTS). We tested whether the average value or the most extreme values from each feature predicted future seizure risk in cross-sectional and longitudinal models.

Results: 10,748 individual centrotemporal IEDs were analyzed from 59 subjects at 81 timepoints. In cross-sectional models, increases in average spike height, spike duration, slow wave rising slope, slow wave falling slope, and the most extreme values of slow wave rising slope each improved prediction of an increased risk of a future seizure compared to a model with age alone ($p<0.05$, each). In longitudinal model, spike rising height improved prediction of future seizure risk compared to a model with age alone ($p=0.04$)

Conclusions: Spike height improves prediction of future seizure risk in SeLECTS. Several other morphological features may also improve prediction and should be explored in larger studies.

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Author contributions

CJC conceived and designed the analysis and wrote the paper. DSC and GX collected the data, performed the analysis, and wrote the paper. JJ and MBW contributed analysis tools. MAK, ERS, and UTE designed the analysis.

Disclosure

CJC has consulted for Biogen Inc and Ovid Pharmaceuticals. MAK has consulted for Biogen Inc. None of the other authors have any disclosures to report.

Significance: Discovery of a relationship between novel IED features and seizure risk may improve clinical prognostication, visual and automated IED detection strategies, and provide insights into the underlying neuronal mechanisms that contribute to IED pathology.

Keywords

Interictal epileptiform discharges; Rolandic epilepsy; self-limited epilepsy with centrotmporal spikes (SeLECTS); Electroencephalography (EEG) biomarker

1. Introduction

Interictal epileptiform discharges (IEDs) recorded on the scalp EEG are a well-recognized biomarker of epilepsy. Defined as brief (<250 ms) electrical discharges, IEDs are present in nearly all cases of epilepsy, independent of etiology (Staley and Dudek, 2006). The presence of IEDs is the most widely utilized, and sensitive, biomarker to estimate seizure risk (Staley and Dudek, 2006; Kanemura et al., 2015; Shinnar et al., 1994; Wirrell, 2010). However, IEDs are not specific for epilepsy. For example, IEDs are present in 0.5-2.4% of the general population without a seizure history (Bennett, 1967; Olofsson, Peterson, Sellden, 1971; Gregory, Oates, Merry, 1993) and can persist for years after seizure resolution (Kramer et al., 2019; Xie et al., 2018; Kobayashi et al., 2010; Bouma et al., 1997; Van Klink et al., 2016; Chen et al., 2019). Thus, improved non-invasive biomarkers are required to better classify patients at risk of a future seizure (Engel, 2011).

IEDs are composed of a large negative spike followed by a slow wave. Due to the low inter-rater reliability between experts in detecting individual IED events (13-18%) (Webber et al., 1993; Scheuer, Bagic and Wilson, 2017), but improved agreement when determining whether at least one IED is present (kappa 0.83, Stroink et al., 2006), prior work evaluating IEDs as a biomarker for seizure risk focused on the presence or absence of IEDs as a binary classifier. However, IEDs are highly variable in rate and several other quantifiable morphological characteristics, such as the amplitude, duration, and slope of both the spike and slow-wave components (Bagheri et al., 2017; Halford, 2009, Kural et al., 2020). With the introduction of reliable, reproducible, automated approaches to detect IEDs (Jing et al., 2020; Jing et al., 2020), these variable and rich features can now be more accurately quantified. However, the utility of spike morphological measurements even with reliable approaches to quantification may be limited by the impact of spike location and brain anatomy on surface measures. This challenge can be mitigated by analyzing spikes across subjects with normal cerebral anatomy and the same spike location.

To determine whether distinct IED morphological characteristics improve prediction of seizure risk among patients with IEDs, we evaluated the relationships between IED rate and morphological features and seizure risk in a cohort of children with self-Limited Epilepsy with centrotemporal spikes (SeLECTS, also called Rolandic epilepsy) (Specchio et al., 2022). Focusing on SeLECTS provides several advantages for this analysis. First, this common, non-lesional developmental epilepsy has a well-characterized and self-limited seizure course (Ross et al., 2019) allowing us to test the ability of IED features to predict seizure risk over the course of resolving disease. Second, SeLECTS is electrographically stereotyped, characterized by distinct focal spikes in the centrotemporal regions, thereby minimizing the impact of variations in brain anatomy on morphological measures (Herman, 2011; Tenney et al., 2016).

We hypothesized that IED rate and morphological features would predict seizure risk in children with SeLECTS with persistent IEDs, thereby improving prediction beyond the presence of IEDs alone. Identification of a relationship between novel IED features and seizure risk would directly improve patient care, help inform automated IED detection strategies, and provide insights into the underlying neuronal mechanisms that contribute to IED pathology.

2. Methods

2.1 Subjects

This project was approved by the institutional review board at Massachusetts General Hospital (MGH). EEG and clinical data from two databases were reviewed for inclusion in this study. These included: 1) All subjects with a diagnosis of SeLECTS seen between June 2001 and June 2017 at MGH with available clinical information on the date of the most recent seizure relative to an EEG recording (n=130), and 2) All subjects with SeLECTS enrolled in a prospective study between 01/2014 and 06/2019 that included the date of the most recent seizure relative to an EEG recording (n=34). For 1), patients were identified via search of the institutional EEG database for the words “rolandic,” “sleep-activated,” “sleep activated,” “benign,” “BECTS,” “ECTS,” “centrotemporal,” “centro-temporal,” or “horizontal dipole” and clinical chart review confirming the history of a seizure, sleep-activated centrotemporal discharges on EEG, and a clinical diagnosis of SeLECTS by a child neurologist (Xie et al., 2018). For 2), subjects enrolled in the prospective study with a clinical diagnosis of SeLECTS by a child neurologist following International League Against Epilepsy criteria, including both a history of focal motor or generalized seizure and an EEG showing sleep-activated centrotemporal spikes were included (Berg et al., 2010). Subjects with a history of only a single clinical seizure were included (n = 1) if clinical and EEG features led to the diagnosis of SeLECTS (Fisher et al., 2014). For both 1) and 2), patients with a history of autism spectrum disorder, mental retardation, or other unrelated neurological disease were excluded while children with attention disorders and mild learning difficulties were included, as these profiles are consistent with known SeLECTS comorbidities (Wickens,et al., 2017).

Of the 164 subjects identified for inclusion, 48 were excluded because raw EEG recordings were not available, leaving 178 raw EEG recordings from 116 subjects available for analysis. Of these, 40 EEGs were excluded because stage 2 non-rapid eye movement sleep (N2) was not recorded, leaving 138 EEG recordings from 93 subjects. Of these, 25 EEGs were excluded because these recordings had no IEDs or IEDs were not maximal in the centrotemporal regions (e.g., C3, C4, T3, or T4) resulting in 112 EEG recordings from 79 unique subjects. After manual removal of grossly artifactual detections, 80 EEG recordings from 59 unique subjects had persistent IED detections and were included in the subsequent analysis.

2.2 EEG Data Acquisition

EEG data obtained in the clinical MGH EEG lab included electrooculogram (two channels), EEG (19 channels, Ag/AgCl electrodes placed according to the 10-20 international system referred to the second cervical spinous process: FP2, F4, C4, P4, O2, F8, T4, T6, Fz, Cz, Pz, Fp1, F3, C3, P3, O1, F7, T3, and T5), and electrocardiogram using a standard clinical recording system (Xltek, a subsidiary of Natus Medical). Signals were sampled at 256 or 512 Hz. In database 2, EEG data were recorded with a 70-channel cap based on the 10-10 electrode placement system at a 2,035 Hz sampling rate (Easycap, Vectorview, Elekta-Neuromag, Helsinki, Finland) with additional electrodes placed at T1 and T2 locations.

All EEG data were visually inspected by a board-certified neurophysiologist (CJC) and channels with significant artifact were excluded from analysis. Since IEDs are activated during non-rapid eye movement sleep in this disease, to maintain a consistent state of consciousness across recordings, all available N2 data per EEG were selected for analysis following standard sleep staging criteria (Grigg-Damberger et al., 2007). Additional clinical data were collected for each subject, including age, sex, medication use, and duration seizure free. In a large prospective cohort of 60 children with SeLECTS followed for a mean of 16 years from epilepsy onset through resolution, we have previously demonstrated that duration seizure free provides a reliable measure of future seizure risk (see Figure 4 in Ross et al., 2020). For example, after 1 month seizure free, the risk of future seizure is 86% and after 60 months seizure free, the risk of a future seizure is ~ 0.

2.3 Automated IED Detection

For automated IED detection, only the 10-20 channels were used. IEDs were detected using SpikeNet, a validated automated spike detection program found to perform equivalent to human experts, but with better reproducibility (Jing et al., 2019). Briefly, SpikeNet’s preprocessing steps include 0.0-64.0 Hz band-pass filtering, application of a notch filter, downsampling to 128.0 Hz and referencing channels to the average reference. The SpikeNet detector had lower calibration errors than other commercially available detectors (Jing et al., 2019). Since children with SeLECTS can have unilateral or bilateral involvement, for each EEG, we focused our analysis on the hemisphere with the highest spike rate. To reduce noise due to false detections, but also minimize subjectivity in IED detection, candidate IEDs (n=12,838) were manually reviewed and only false detections due to gross artifacts were removed (n=2,160, 16.73%).

2.4 IED Morphologic Features

After IED detection, for each subject, we evaluated IED rate along with 9 morphological features in each IED spike, including: spike falling height, spike rising height, spike rising slope, spike falling slope, spike duration, slow wave rising slope, slow wave falling slope, slow wave duration, slow wave falling height (Figure 1). For each subject, we then computed the mean for each feature across all IEDs. Then, we computed the mean of the largest 10% of values (e.g., the largest 10% of spike heights), provided at least 10 spike detections were present in the EEG recording. If only 10 spikes were available, the single largest value from the 10 spikes was included for each feature.

2.5 Statistical Analysis

We hypothesized that, among patients with IEDs, IED rate and measures of spike and slow wave morphological features would predict seizure risk. To test this hypothesis, we developed generalized linear mixed effects models (gamma distribution, log link) of duration seizure free with subject-specific intercepts to account for multiple EEG visits by some subjects.

As age strongly predicts seizure risk in this self-limited disease, we constructed a baseline model with predictor age for comparison to all other models (Equation 1). We evaluated whether antiseizure medication (ASM) or each IED feature improved prediction of seizure risk compared to the model with age alone (Equation 2). To identify collinear IED features among the IED features that improved prediction of seizure risk, we applied hierarchical clustering using a distance measure of one minus the sample correlation between features. Then, among the IED features that improved prediction of seizure risk, we created models for all pairs of non-collinear features (Equation 3). We express the models for seizure risk as,

$$\log(Seizure\,risk) \sim 1 + age + (1 \mid subject) \tag{Eq .1}$$

$$log(Seizure\,risk) \sim 1 + age + IED\,feature\,or\,ASM + (1 \mid subject) \tag{Eq .2}$$

$$log(Seizure\,risk) \sim 1 + age + IED\,feature\,X + IED\,feature\,Y + (1 \mid subject) \tag{Eq .3}$$

where age, each IED feature (spike rate, spike rising height, spike rising slope, spike duration, spike falling slope, spike falling height, slow wave rising slope, slow wave duration, slow wave falling slope and slow wave falling height), and antiseizure medication use (ASM) are fixed effects and $(1 \mid \text{subject})$ is a subject specific intercept (i.e., random effect). Nested model comparisons were performed using the log likelihood ratio test, and goodness-of-fit was evaluated by inspecting the quantile-quantile (Q-Q) plot of the deviance residuals (Lee et al., 2006).

To test whether IED features found significant in the cross-sectional model remained significant in a longitudinal model, we analyzed the relationships including only the subset of subjects with multiple visits, using Eq 1-3.

3. Results

3.1 Data and characteristics

80 EEG recordings from 59 subjects (26F, ages at recording: 2.9-15.1 years old) were included. A total of 10,748 individual centrotemporal IEDs during N2 sleep were analyzed. EEG N2 sleep duration was an average of 17.7 minutes per subject (range: 1.9-79.5 minutes). The mean number of IEDs per EEG was 134 (range of 1-1419). The mean duration seizure free for the subjects at the time of the EEG visits was 11.3 months (range 0-51 months). 30 subjects (50.9%) were taking antiseizure medications (ASMs) at the time of the EEG recording.

3.2 Spike morphological features vary across and within patients

Visual inspection of IEDs revealed marked morphological diversity in spike and wave amplitude, duration, and slopes both within the same subject and across different subjects (Figure 2A-C). Distributions of the mean IEDs features across subjects tended to be unimodal (Figure 2D).

3.3 Age predicts seizure risk

Consistent with prior reports (Callenbach et al., 2010), we found that in this self-limited developmental epilepsy, age (p=0.001, effect size 0.245 days/year, 95% CI [0.111 0.380]) had a strong positive relationship with duration seizure free in cross-sectional analysis. In SeLECTS, for each year increase in age, the duration to the next seizure increased by a factor of 28%. Current ASM use was not a significant predictor of seizure risk (p=0.14) and inclusion of ASM was not found to improve the model with age alone (likelihood ratio test p=0.14). Similarly, in longitudinal analysis, age had a strong positive relationship with duration seizure free (p=0.008, effect size 0.235 days/year, 95% CI [0.064 0.406]); for each year increase in age, the duration seizure free increased by a factor of 26%. Current ASM use was not a significant predictor of seizure risk (p=0.4) and inclusion of ASM did not improve the model with age alone (likelihood ratio test p=0.4).

3.4 IED morphological features improve prediction of seizure risk in cross-sectional models

Several IED morphological features improved prediction of seizure risk compared to a model with age alone. Among the spike features (B-F in Figure 1), spike rising height (B, likelihood ratio test: p=0.011) and spike duration (D, likelihood ratio test: p<0.001) improved prediction of seizure risk compared to the model with age alone. Among the slow wave features (G-J in Figure 1), slow wave rising slope (G, likelihood ratio test: p=0.048) and slow wave falling slope (I, likelihood ratio test: p=0.025) improved prediction of seizure risk compared to the model with age alone (Table1).

3.5 Spike height improves prediction of seizure risk in longitudinal analysis.

In subjects with multiple visits, spike height improved prediction of future seizure risk compared to the model with age alone (p=0.040) and was found trending (p=0.073, effect size −0.011 per μV, 95% CI [−0.024 0.0011]). None of the other IED features identified from cross-sectional analysis improved the prediction of future seizure in the longitudinal model compared to the model with age alone.

3.6 Multicollinearity in IED morphological features

Visual inspection of scatterplots and clustering analysis revealed that spike rising height (B) and spike duration (D) were collinear and slow wave rising height (G) and slow wave falling height (I) were collinear (Figure 3). To test whether combinations of IED features improved prediction of seizure risk, we considered each combination of non-collinear features (i.e., B and G; B and I, D and G, D and I; Figure 3). We found no combination of features improved model fit compared to the model with age and spike duration alone in cross-sectional or longitudinal analysis.

3.7 The most extreme IED morphological features do not improve prediction of seizure risk

To evaluate whether extreme IED morphological values predict seizure risk, we considered the largest 10% of measurements from subjects with at least 10 IEDs to evaluate (n=59). In this cohort, age was again found to have a positive linear relationship with seizure risk (p=0.001, effect size 0.213 days/year, 95% CI [0.053 0.373]). Following a similar analysis approach as above, we find only one feature - slow wave rising slope - improved prediction of seizure risk compared to the model with age alone (log likelihood ratio test, p=0.002, Table 1).

4. Discussion

Reliable, non-invasive biomarkers are required to predict seizure risk in both epileptogenesis and epilepsy remission and inform treatment decisions (Engel, 2011). Here, we studied a unique population of patients with a self-limited epilepsy syndrome and identified several IED features that improved prediction of seizure risk beyond the presence of IEDs alone. These findings leverage new features of this canonical non-invasive epilepsy biomarker to improve estimates of seizure risk and our understanding of the components of epileptiform activity that may be most pathogenic.

Consistent with previous studies in SeLECTS, here we also did not find a significant relationship between spike rate and seizure risk (Kramer et al., 2019; Xie et al., 2018; Van Klink et al., 2016). Outside of SeLECTS, the relationship between spike rate and seizure frequency has been mixed. Some studies have found increased spike rate correlates with increased seizure frequency and the development of chronic epilepsy (Kanemura et al., 2015; White et al., 2010) while others found that interictal activity increases after a seizure but does not predict the probability of future seizure occurrence (Gotman and Marciani, 1985; Gotman and Koffler, 1989). These mixed results may be due at least in part to spike detection approaches. Prior studies have relied on visual analysis, where inter-rater agreement in identifying spikes is low (Barkmeier et al., 2012; Black et al., 2000; Scheuer, Bagic, and Wilson, 2016). Here we used an automated approach and only removed false detections due to clear artifactual activity, allowing for reproducibility of detection criteria and results. We also focused on a stereotyped idiopathic focal epilepsy and evaluated only the most active spike population in the centrotemporal regions during N2 sleep. Despite reducing variability due to etiology, localization, state of consciousness, and spike detection, we were unable to identify a relationship between spike rate and seizure risk.

Observations from animal models suggest that IEDs represent abnormally enhanced synchronization of large neuronal populations (Bragin et al., 2000; Truccolo et al., 2014). Thus, IED morphological features are expected to directly reflect the underlying pathological neuronal dynamics, including the size of the network and the degree of the synchronization. In this study, after controlling for age, we found a negative relationship between four IED morphological features and duration seizure free. In each case, an increase in each measure (spike height, spike duration, slow wave rising slope, slow wave falling slope) predicted a shorter duration seizure free, which strongly correlates with increased future seizure risk in SeLECTS (Ross et al., 2020). Together, these results indicate that the shape of the spike and slow wave changes dynamically with disease resolution. This could be related to factors such as size and synchronization of neuronal networks underlying spike generation or potentially a change in the orientation of the cortical spike source (Gregory and Wong, 1984).

In our cross-sectional and longitudinal analysis, we found that spike height consistently improved prediction of future seizure risk. In the cross-sectional model, when considering the average of all IED features, a 10 μV decrease in spike height corresponds to a 9% increase in duration seizure free. In the longitudinal model, a 10 μV decrease in spike height corresponds to a 10% increase in duration seizure free. Duration seizure free is directly related to the probability of a future seizure, for example an increase in duration seizure free from 10 months to 11 months decreases the probability of a future seizure from 47% to 44% (Ross et al., 2020). Thus, relatively small incremental changes in these morphological features can have a measurable impact on future seizure risk. In our cross-sectional analysis, our findings suggest that several other morphological features may also improve prediction of future seizure risk, however this relationship was not observed in the longitudinal model. This may be related to the small number of longitudinal subjects included in our analysis and these features could be further explored in future studies.

A potential limitation of this cross-sectional study is the use of duration seizure-free as a surrogate for seizure risk. A longitudinal study across the course of epilepsy could further validate our observations by directly recording changes in spike frequency and morphology within subjects compared to direct measures of their future seizure rate. In this investigation, studying SeLECTS provided several advantages, however, our focus on a homogeneous population limits the generalizability of our findings to other types of epilepsy. In addition, future work utilizing electrical source imaging could more precisely localize the epileptogenic focus and propagation of spikes over disease resolution (Nemtsas et al., 2017).

We conclude that the morphological features of IEDs predict seizure risk in children with SeLECTS with persistent IEDs, thereby improving prediction beyond the presence of IEDs alone. These findings have direct implications for patient care, help inform visual and automated IED detection strategies, and ultimately may provide insights into the underlying neuronal mechanisms that contribute to IED pathology.

Funding Information

This work was supported by NIH NINDS R01NS115868.

Data availability statement

Derivative deidentified data to reproduce the findings of this paper are available by request from the corresponding author.

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Highlights

1. Interictal epileptiform discharge (IED) characteristics improve prediction of seizure risk in patients with IEDs.
2. Increased spike height correlates with increased seizure risk.
3. Increased spike duration and increased slow wave rising and falling slopes may correlate with increased seizure risk.

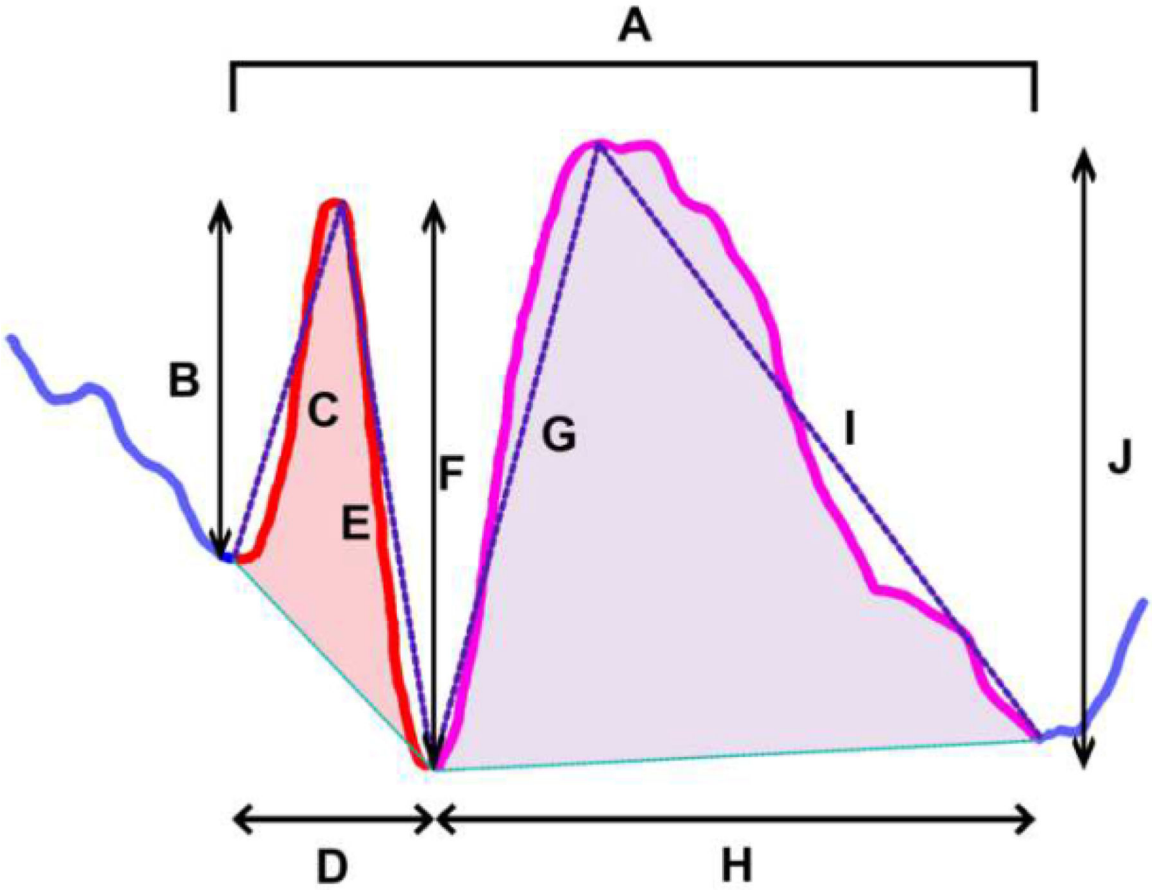

Figure 1. IED morphological characteristics. The spike wave complex

(A) consists of 9 features: (B) Spike rising height, (C) Spike rising slope, (D) Spike duration, (E) Spike falling slope, (F) Spike falling height, (G) Slow wave rising slope, (H) Slow wave duration, (I) Slow wave falling slope, (J) Slow wave falling height.

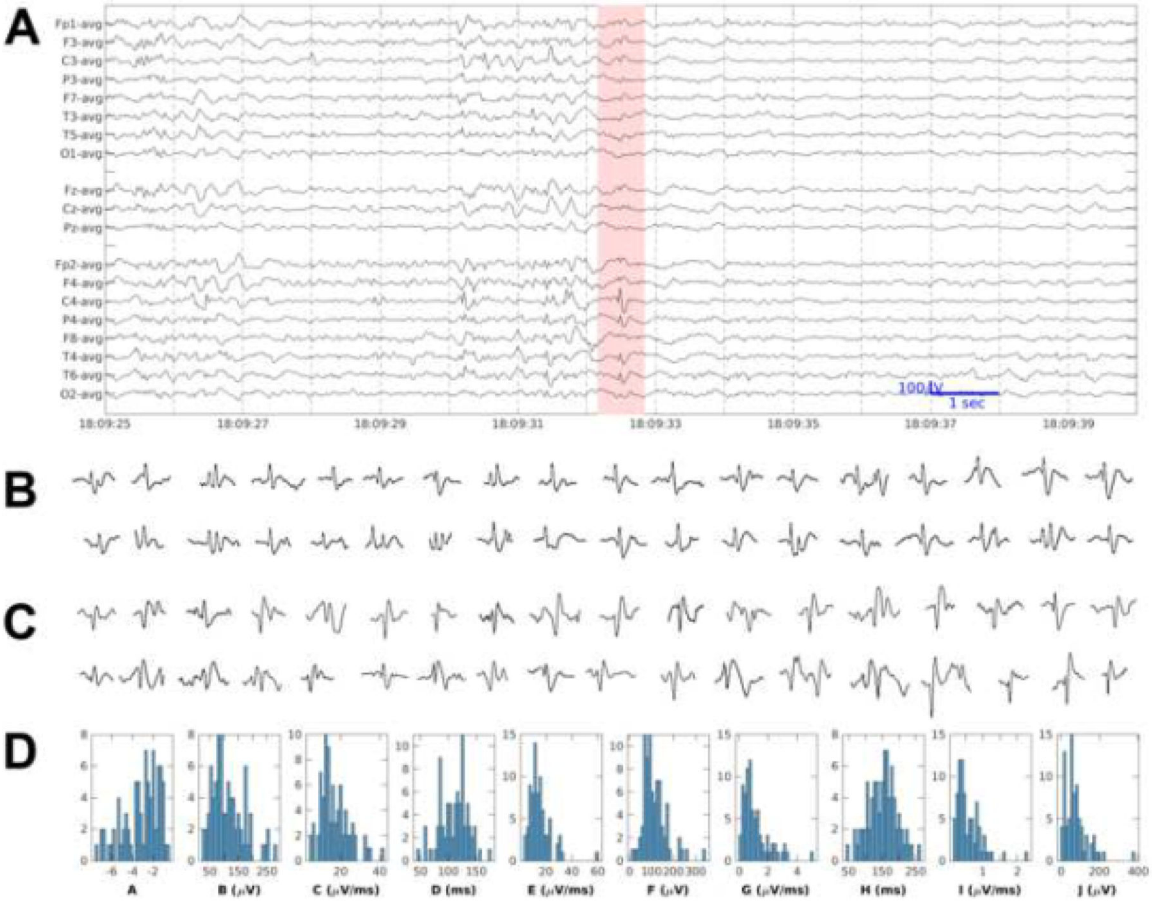

Figure 2. Example IED detections and distributions of IED features.

A) An example IED detection (time indicated by red shading) at C4. B, C) Several examples of IED detections (B) within the same recording in one subject, or (C) across different subjects, reveal marked variability in IED morphology across events. D) Distributions of the IED features across subjects are approximately unimodal. Here, **A** (natural logarithm of spike rate), **B** (Spike rising height), **C** (Spike rising slope), **D** (Spike duration), **E** (Spike falling slope), **F** (Spike falling height), **G** (Slow wave rising slope), **H** (Slow wave duration), **I** (Slow wave falling slope) and **J** (Slow wave falling height) correspond to the morphological features in Figure 1.

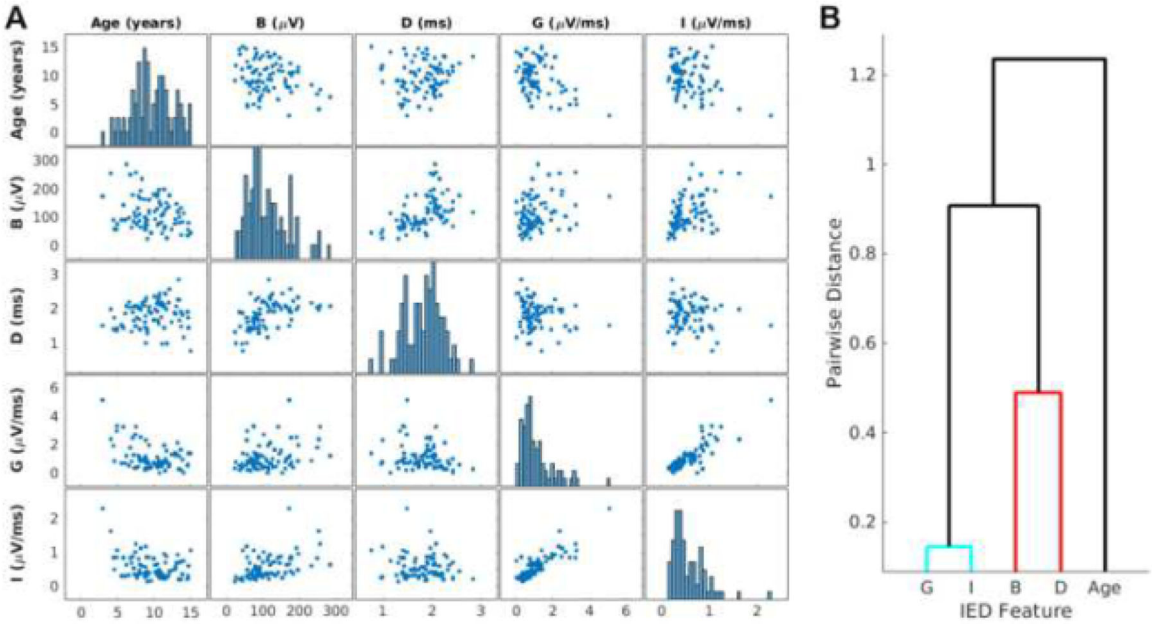

Figure 3. IED features cluster into two correlated groups.

A) Distributions (diagonal) and scatter plots (off-diagonal) of age and the four IED features identified to improve the model fit. B) Two clusters identify high correlation between G (slow wave rising slope) and I (slow wave falling slope), and high correlation between B (spike rising height) and D (spike duration).

Table 1.

IED features improve prediction of seizure risk beyond age alone.

Using the average IED values, four features (B, D, G, and I) improve prediction of seizure risk. Using only the extreme 10% of IED values, one feature (G) improves prediction of seizure risk. B: spike height, D: spike duration, G: slow wave rising slope, I: slow wave falling slope.

	Fixed Effect	p-value (Beta)	AIC	BIC	LLL	p-value (Compare)
All	**Age**	0.001	903.24	912.77	−447.62	
	B	0.011	898.75	910.66	−444.38	0.011
	D	0.006	891.21	903.12	−440.61	0.002
	G	0.033	901.35	913.26	−445.67	0.048
	I	0.014	900.24	912.15	−445.12	0.025
Largest 10%	**Age**	0.001	658.51	666.82	−325.25	
	G	0.029	650.65	661.04	−320.33	0.002