Epilepsia, 51(4):592–601, 2010
doi: 10.1111/j.1528-1167.2009.02306.x

FULL-LENGTH ORIGINAL RESEARCH

Interictal EEG spikes identify the region of electrographic seizure onset in some, but not all, pediatric epilepsy patients

***Eric D. Marsh, *Bradley Peltzer, *Merritt W. Brown III, *Courtney Wusthoff, †Phillip B. Storm Jr, ‡Brian Litt, and *Brenda E. Porter**

***Division of Child Neurology, Department of Neurology and Pediatrics, Children's Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.; †Department of Pediatric Neurosurgery, Children's Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.; and ‡Departments of Neurology and Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.**

Summary

Purpose: The role of sharps and spikes, interictal epileptiform discharges (IEDs), in guiding epilepsy surgery in children remains controversial, particularly with intracranial electroencephalography (IEEG). Although ictal recording is the mainstay of localizing epileptic networks for surgical resection, current practice dictates removing regions generating frequent IEDs if they are near the ictal onset zone. Indeed, past studies suggest an inconsistent relationship between IED and seizure-onset location, although these studies were based upon relatively short EEG epochs.

Methods: We employ a previously validated, computerized spike detector to measure and localize IED activity over prolonged, representative segments of IEEG recorded from 19 children with intractable, mostly extratemporal lobe epilepsy. Approximately 8 h of IEEG, randomly selected 30-min segments of continuous interictal IEEG per patient, were analyzed over all intracranial electrode contacts.

Results: When spike frequency was averaged over the 16-time segments, electrodes with the highest mean spike frequency were found to be within the seizure-onset region in 11 of 19 patients. There was significant variability between individual 30-min segments in these patients, indicating that large statistical samples of interictal activity were required for improved localization. Low-voltage fast EEG at seizure onset was the only clinical factor predicting IED localization to the seizure-onset region.

Conclusions: Our data suggest that automated IED detection over multiple representative samples of IEEG may be of utility in planning epilepsy surgery for children with intractable epilepsy. Further research is required to better determine which patients may benefit from this technique a priori.

KEY WORDS: Spike density, Intracranial EEG, Seizure onset, Pediatric epilepsy.

Epilepsy surgery is performed in patients with medically refractory epilepsy and evidence of localized or regional seizure onset on noninvasive preoperative testing. Intracranial electroencephalography (IEEG) monitoring or intraoperative electrocorticography (ECoG) is often performed to tailor resections, especially in those patients with extratemporal epilepsy. Both techniques have inherent advantages and disadvantages. Intracranial electrode implantations have increased morbidity, and do not always capture seizures or improve localization. ECoG typically does not capture seizures, and can be affected by type and depth of anesthesia, and by artifact in the operating room. The limitations of both techniques may reduce postoperative seizure freedom, and new methods to improve presurgical localization of epileptic networks are greatly needed. This study analyzes interictal spike occurrence over prolonged epochs of IEEG to determine if quantitative analysis can improve localization of the seizure onset zone prior to surgery. If successful, this technique may decrease morbidity and duration of hospital stay, and potentially improve outcome in patients undergoing epilepsy surgery; it also might be extrapolated to patients undergoing ECoG during surgical resection.

Interictal epileptiform discharges (IEDs) have been hypothesized to play a role in seizure generation; however, their relationship to seizure onset has been difficult to define (see Staley et al., 2005 for review). The localization value of IEDs may relate to the modality used to record this activity. Scalp EEG is the most imprecise

Accepted July 24, 2009; Early View publication September 22, 2009.
Address correspondence to Eric D. Marsh, M.D., Ph.D., Division of Child Neurology, Children's Hospital of Philadelphia, Abramson Research Building, Room-502A, 3400 Civic Center Boulevard, Philadelphia, PA 19104, U.S.A. E-mail: marshe@email.chop.edu

method for localizing IEDs, owing to its comparatively poor spatial resolution. Magnetoencephalography (MEG) has much better spatial resolution for surface sources, but signals beyond a depth of a centimeter fall off rapidly. Consequently, epileptic networks involving deep structures, such as the hippocampus, are not well ''imaged'' by MEG. Still, both of these noninvasive techniques can be used to tailor epilepsy surgical resections. ECoG provides much higher spatial resolution and good quality signals; however, the technique is limited by restricted surgical time and confounding of anesthesia, and frank seizures are rarely captured, except in severe cases. Therefore, it is important to understand how frequently IEDs identify the area of seizure onset to improve surgical outcome.

Several studies utilizing both long-term IEEG and ECoG report that resections incorporating a ''significant'' portion of regions generating interictal spikes and sharp waves, in addition to the ictal onset zone, improve seizure freedom postoperatively (Wyllie et al., 1987; Paolicchi et al., 2000; Krsek et al., 2008). Regions of spiking on subdural and depth electrodes usually extend beyond the seizure onset zone, and in some reports, they appear to represent multiple distinct independent spiking foci (Hufnagel et al., 2000; Kobayashi et al., 2001). One study found that electrodes with the highest frequency of interictal spiking were within the seizure onset zone 100% of the time, but in another study, frequency of interictal spiking could identify the seizure onset zone in only ~50% of the patients (Hufnagel et al., 2000; Asano et al., 2003). The reason for this variability is not clear, although there were differences in methodologies and predominant pathology. Both groups analyzed relatively brief periods of IEEG, which could have undersampled IED distributions. These studies suggest that spiking is part of the dysfunctional ''epileptogenic zone,'' but further studies are needed to determine if there is a quantitative relationship between IEDs, seizure onset, and surgical outcome.

Prior studies have identified sleep state, seizures, and medication withdrawal as variables that alter the frequency and to some extent the regional localization of IEDs (Gotman & Marciani, 1985; Marciani et al., 1985; Gotman & Koffler, 1989; Sammaritano et al., 1991; Spencer et al., 2008). The extent of variability in discharge frequency and localization may vary between temporal and extratemporal IEEG, especially over longer periods of IEEG (Spencer et al., 2008). Investigators analyzing recordings from human temporal lobe epilepsy, for the most part, have not been able to identify changes in IED activity prior to a seizure (Lieb et al., 1978; Lange et al., 1983). Mixed results on changes in IEDs following medication withdrawal have been reported, and several studies have reported decreases in spike frequency post seizure (Gotman & Marciani, 1985; Gotman & Koffler, 1989; Spencer et al., 2008). The variability in IED frequency and spatial extent with sleep state and seizure activity suggest that there are fluctuations in this activity over time, although the mechanism for the variability is not well understood. For example, during non-REM (rapid eye movement) sleep there is not only an increase in IEDs, but also an extension of the spiking area (Sammaritano et al., 1991; Staba et al., 2002).

Here we have set out to map the frequency of IEDs in long-term IEEG recordings in a group of children with intractable epilepsy, with the goal of determining if the location of frequent IEDs is a surrogate marker for seizure onset.

Methods

Clinical data

The Children's Hospital of Philadelphia (CHOP) Institutional Review Board approved this study. IEEG recordings were obtained prospectively from 30 patients undergoing subdural electrode implantation for epilepsy surgery between 2003 and 2007. All IEEGs were recorded with Grass-Telefactor 128 Electrode CTE EEG machine using 16-bit amplifiers (Astro Med Corp., West Warwick, RI, U.S.A.) sampled at 200 samples/s/electrode. Analog antialiasing bandpass filter (frequency cut-offs at 0.1- and 70-Hz) and notch filter (null at 60 Hz) were used for signal conditioning. Recordings were reviewed in a referential montage, and marked by two reviewers to identify seizure onset times, morphology, and electrode locations.

All clinical data, including seizure type, and presurgical and postsurgical data were obtained by retrospective chart review. The primary neurologist's seizure outcome assessment was graded using a modified Engle scale at last patient contact (Engel et al., 1993).

Patient selection

From 30 consecutively consented patients, 19 patient's IEEGs were selected for the current study. Patients were chosen using the following criteria: detailed IEEG seizure markings were present, recordings were continuous and predominantly artifact free, and interictal epileptiform activity was present. If any of the criteria were not met, the patient was excluded from the study. Of the patients who did not meet criteria, incomplete recordings and excessive artifact were the reasons for exclusion in six patients. Lack of or very rare IEDs excluded five patients.

Seizure onset determination

Two clinical epileptologists marked seizure onset times and locations. Clinical reports were consulted, but the entire recording was reviewed for the presence of seizures. All electrographic seizures were marked for times of unequivocal electrical seizure onset and earliest electrical change (Litt et al., 2001). Final consensus between the two IEEG readers established which electrodes were involved at seizure onset and the exact onset times for each seizure. All electrodes determined to be involved at the unequivocal electrographic onset were included in the

seizure-onset zone calculations. A description of the electrographic onset was recorded as attenuated with low-voltage fast activity, repetitive spiking, or rhythmic slow wave onsets.

IED detection

An automated detector was used that was developed by our group, implemented in MATLAB (Natick, MA, U.S.A.), and previously validated against human markings (Brown et al., 2007). Briefly, the detector is mimetic-based and models IEDs as deflections in the IEEG satisfying three criteria: (1) a peak amplitude greater than a threshold value based on the background IEEG, (2) a characteristic width of the spike component lasting between 30 and 300 ms, and (3) an after-going slow wave with a duration of 100–500 ms.

For this study the detector was ''tuned'' for each patient's IEDs by first selecting representative IEEG epochs containing electrodes with both characteristic epileptiform activity and no IEDs. The detector's output was plotted against the IEEG and reviewed independently by two epileptologists for the threshold settings with the highest true-positive and lowest false-positive detections. Reviewers had to qualitatively agree with the spike detections (approximately 50% accuracy was used, as this is the previously quantified accuracy of the detector) or the detector thresholds were recalculated. Therefore, using the current spike detector, spikes will be missed, as well as incorrectly identified, but within a patient's IEEG, consistent spike morphologies should be identified using our computer detection system. Once a threshold was selected, the detector analyzed the full dataset (described in subsequent text). In addition, the quantitative detection maps generated by collating detector outputs by channel were reviewed and compared to the pattern of detection with the epileptologist's interpretation of the most active spike foci.

Segment selection and data analysis

The full duration of each patient's IEEG recording was divided into 30-min segments. A MATLAB random number algorithm reordered the segments, with the first 16 being reviewed. If the randomly chosen segment contained a seizure or was interrupted by file change, the next segment in the list was used. After the original segment selection was completed, three segments, determined to be unusable due to artifacts, were discarded. This resulted in three patients having only 15, 30-min segments for analysis.

The selected segments were analyzed using the predetermined thresholds and the output sorted by electrode and segment. Mean, range, variance, and standard deviation of spikes per 30 min were calculated. The mean spike density (spikes/30 min/electrode) was plotted in X–Y coordinates. The entire process is shown in Fig. 1. The location of each electrode was extracted from surgical photographs, schematic drawings, and postimplant magnetic resonance imaging (MRI), when available. Mean IED densities were graphed on the X–Y coordinate plots of the grids.

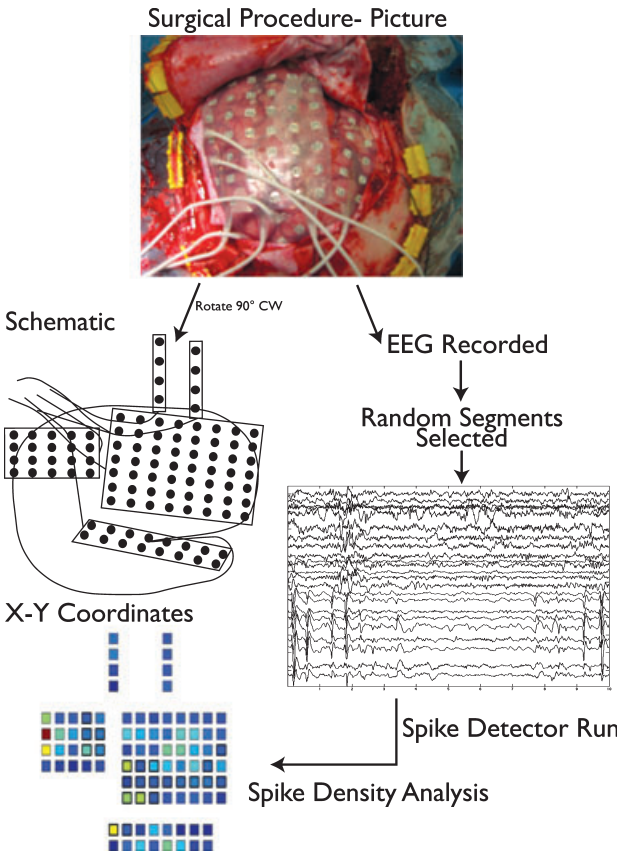

Figure 1.
Procedure for mapping spatial relationship of electrodes, spike density, and seizure-onset electrodes. A picture of the brain with electrodes is taken in the operating room at the time of implantation. A map of the electrode contacts is created to identify electrode numbers and location. The spike detector is run, and a color-coded map of spike density is created, Red>>>Blue. The seizure-onset electrodes are then overlaid on the spike density map by a thick dark line around the onset electrodes.

Statistical analysis

All graphs were qualitatively assessed for correlation between maximal IED density and seizure onset. Quantitative assessment was performed using a *t* test to compare mean spike values in channels at or away from seizure-onset location. All calculations were performed in MATLAB using the statistical toolbox. The mean spike density in the seizure-onset electrodes versus electrodes that were not part of the seizure onset was analyzed. Our original question was to determine if the IED could identify the seizure-onset electrodes. Our null hypothesis was no difference in mean spiking between seizure onset and other

electrodes existed. Significance and ''tails'' were set to the default values of 0.05 and ''both.''

Because we found a mixture of patients with and without IED correlation to seizure onset we decided to determine if variation in spiking over time could account for the varied results. Intrapatient segmental variation was tested in three ways: First, the *t*-test was calculated for each 30-min segment individually to test for variability of seizure onset with spike density across segments for a single patient. Second, a segment-versus-segment test of differences within each patient was performed using an *F* test to compare the total variance of all electrodes to each segmental variance, with a null hypothesis that no difference in variance existed across segments. Third, an electrode-by-electrode *F* test statistic compared the total variance against the segmental mean variance. A single sided *F* test was used, as we were interested only in if the electrode variance was greater than the total variance. This method allowed us to test the hypothesis that spiking in a subset of the electrodes varied more than the overall variability.

Clinical data were analyzed for differences in patients with and without spike density and seizure-onset correlation using the Fisher's exact *t*-test for seizure outcome, pathology, and seizure-onset morphology.

Results

Patient characteristics

Nineteen patients were analyzed: eight female, aged 1–20 years (mean 12 years) at time of epilepsy surgery. Electrode coverage is described in Table 1, with most patients having multilobar coverage. Cortical dysplasia Palmini type 2a was the pathologic diagnosis in 14 of the 18 patients who underwent resection (Palmini et al., 2004). Two patients had Palmini type 2b dysplasia, one patient had evidence of hemorrhage, and one had a chronic infarction. Postoperative seizure freedom occurred in 10 patients (Engel class I), whereas 5 others were felt to demonstrate significant seizure improvement (Engel class III; See Table 1 for details).

Seizure onset/IEEG selection

Seizure-onset electrodes for all patients ranged between 3 and 102 contacts, with a median of 13 involved electrodes. This was 4–82% of the total electrodes on any given patient. The types of seizure onsets on IEEG were rhythmic spiking in 12 patients and low-voltage attenuation in 5 patients; 1 patient had a mixture of seizures with rhythmic spiking and low-voltage attenuation with fast activity. Only one patient had rhythmic slowing at seizure onset.

The 15 or 16 randomly selected 30-min IEEG sections covered wake and sleep segments as well as preictal and postictal recording states. Seven and one-half or 8 h of total IEEG was analyzed per patient, comprising between 2.5 and 16.7% of each patients total recording. Analysis of IED frequency per 30-min segment per electrode was calculated and compared to the location of the seizure-onset zone.

Mean spike density analysis

Mean spike densities (spikes/30 min/electrode) across all processed data epochs for each patient were compared to

Table 1. Clinical data

Patient #	Implant location	Clinical seizures	Subclinical seizures	Pathology	Outcome	F/U-years	Correlation	Seizure onset-type
1	L Fr, Par	1	14	2A	3	6.7	N	Spiking
2	R Fr	18	None	2A	4	5.5	N	Spiking
3	R Fr, Par	2	3	2A	4	4.9	N	Spiking
4	L Par, Temp, Fr Occ	2	None	2A and Gliosis	1	4.8	N	Spiking
5	L Fr, Par, Temp	4	14	2A and Cell loss	3	3.5	Y	Spiking
6	L Fr, Par	45	2	2A	3	3.2	Y	Low voltage attenuation
7	R Fr, Par	7	None	Hemorrhage	1	2.3	Y	Spiking
8	R Fr, Par	None	202	2B	1	2.9	N	Spiking
9	R Fr, Par, Temp	None	229	2A	1	2.1	N	Spiking
10	R Fr, Par, Temp	15	2	2A	3	3.2	Y	Low voltage attenuation
11	Bi-Occ, Par	10	12	No Resection			Y	Low voltage attenuation
12	L Temp, Par	1	4	2a and MTS	1	1	N	Rhythmic slowing
13	R Fr, Par, Temp	37	17	2A	1	2.4	Y	Spiking
14	L Fr	1	None	2A	3	1.9	Y	Spiking
15	L Fr	12	10	2B	1	0.2	Y	Low voltage attenuation
16	L Temp, Fr, Occ	19	None	Chronic Infarction	1	1.3	Y	Spiking low voltage attenuation
17	R Fr	1	81	2A	4	1.5	N	Spiking
18	R Fr	2	None	2A	1	1	Y	Spiking
19	R Temp, Par, Occ	15	None	2A	1	0.9	Y	Low voltage attenuation

L, Left; R, right; Fr, frontal; Par, parietal; Temp, temporal; Occ, occipital; Bi, bilateral; Pathology; MTS, mesial temporal sclerosis, Palmini grading system (Palmini et al., 2004); Outcome, Engel grading system (Engel et al., 1993).

that patient's seizure-onset zone (Figs. 2 and 3). Qualitative assessment by two IEEG readers using the color-coded maps revealed 10 of 19 patients had overlap between the electrode with highest spike density and seizure-onset electrodes (Fig. 2). A *t* test was calculated to quantify overlap between spike density and seizure onset. Eleven of the 19 patients (57.89%) had mean spike densities in the seizure-onset channels that were significantly different from all other channels ($p < 0.05$; Table 2). The results of four additional patients trended toward significant correlation between spike density and location of the seizure-onset zone. Of the eight patients for whom IED density was not statistically different in seizure onset and all other channel locations, four of eight appeared to have seizure onsets that surrounded or abutted the region of highest spike density, whereas the remaining four patients appeared to have no pattern of overlap or correlation between the two variables (Fig. 3). Overall the majority of patients have mean spike counts that are highest in the seizure-onset region.

Intersegment variability

We assessed if IED correlation with seizure-onset electrode contacts remained constant across all the segments (Fig. 4). Two tests were performed. First, the *t* test was performed on each data segment individually. In the 11 patients described earlier with significant correlation between IEDs and seizure-onset zone, up to 11 (range 0–11) of the p-values of the 16 individual segments was >0.05 (Table S1). In patients with the lowest p-values ($p < 0.001$), there were fewer segments (range 0–6) that had p-values >0.05. For patients whose 16-segment average showed no significant correlation ($p > 0.05$) there also was variability between segments, with zero to six segments having significant correlation ($p < 0.05$) between

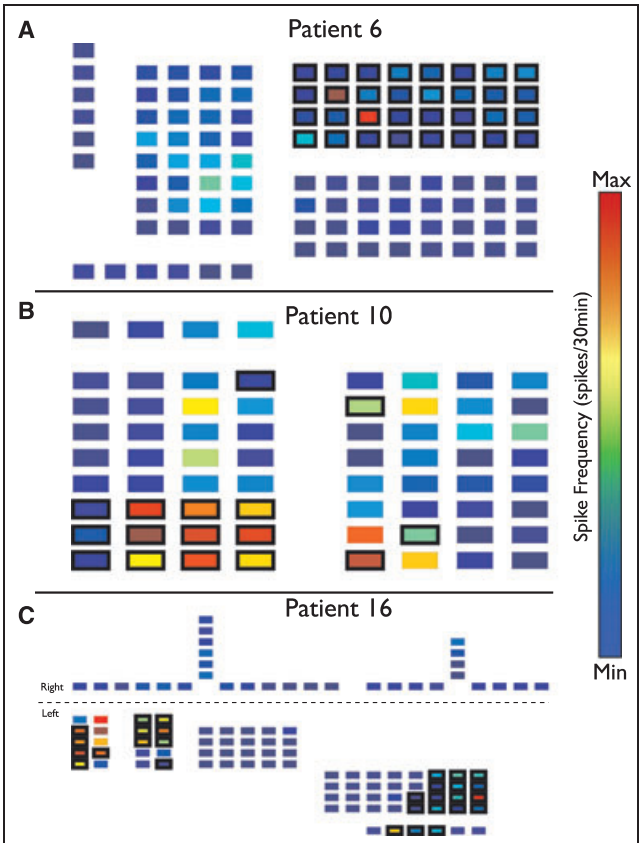

Figure 2.
Three patients demonstrating strong correlation of spike frequency with seizure-onset electrodes. Electrode maps of patients 6, 10, and 16 demonstrating areas of frequent spikes, as represented by brighter colors, are predominantly in the seizure-onset electrodes, shown by a dark outline. Some electrodes with frequent spikes remain outside the seizure-onset region in all the patients. Mean spike frequency for the entire intracranial electroencephalography (IEEG) is plotted.
Epilepsia © ILAE

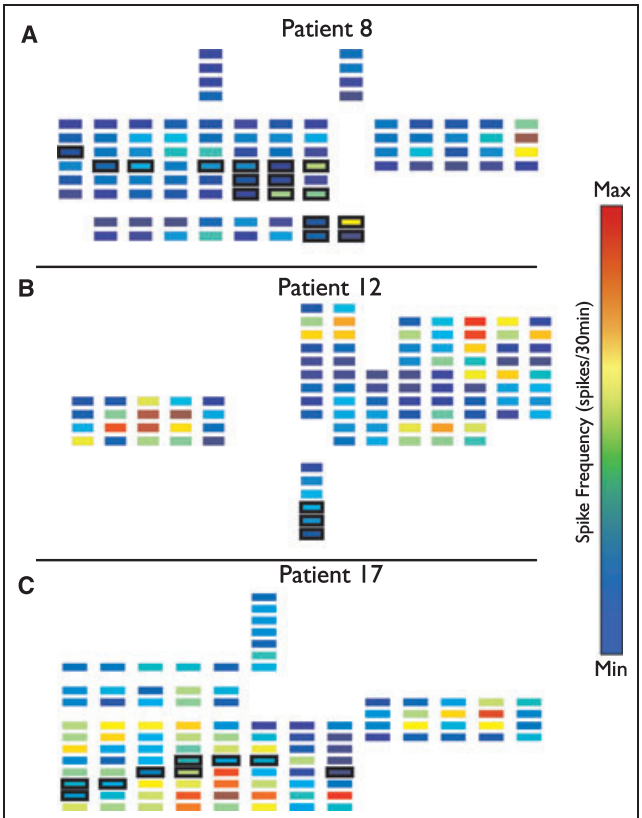

Figure 3.
Three patients demonstrating a lack of correlation of spike frequency with seizure-onset electrodes. Electrode maps of patients 8, 12, and 14 demonstrating areas of frequent spikes, as represented by brighter colors, are predominantly outside the seizure-onset electrodes, shown by a dark outline. Although some of the electrodes with frequent spiking are within the seizure-onset region. Mean spike frequency for the entire intracranial electroencephalography (IEEG) is plotted.
Epilepsia © ILAE

Table 2. Statistical analysis of mean spike density versus seizure-onset zone

	Student's *t*-test		
Patient no.	p-value	Confidence interval	
1	0.1651	−141.126	814.633
2	0.0753	−4.136	83.911
3	0.0666	−0.783	23.146
4	0.0857	−4.043	60.275
5	0.0428	2.385	141.777
6	0.0008	24.168	89.988
7	<0.0001	58.327	140.061
8	0.0944	−11.793	146.329
9	0.0902	−134.965	9.961
10	<0.0001	106.352	217.163
11	0.04506	3.233	285.619
12	0.7355	−308.805	218.749
13	0.0022	36.568	162.536
14	0.0096	17.097	115.668
15	0.0011	27.989	110.452
16	<0.0001	391.836	635.981
17	0.3672	−202.757	75.618
18	0.0002	27.923	87.453
19	0.0001	30.864	90.932

For each patient, a Student's *t*-test was calculated. The resultant p-value and confidence interval of the difference of means of the 16-segment mean spike density and channels in or out of the seizure-onset zone is listed.

IED density and seizure-onset zone location. Only 1 of the 19 patients had no segments in which IED density did not correlate with seizure-onset zone location. Overall, 47.35% of the 302 IEEG epochs analyzed had IED densities that correlated with seizure-onset zones. Therefore, increased data sampling/averaging significantly improves the likelihood that IED distribution correlates with seizure-onset zone location.

To further assess the extent of variability between segments, an *F* test was performed to determine if the variance of IED density in each segment differed significantly from the mean variance of the grouped data epochs in each patient (Table S2). In almost all patients, this method found significant variability between epochs, with only one patient's data epochs demonstrating little variance from the mean. The other patients had between 5 and 13 segments whose individual epoch variances differed from the mean variance. Taken together these data suggest that there are significant differences in IED density localization between segments.

Interpatient and interelectrode variability

Among all patients the total number of IEDs per electrode varied from 0 to 5,997 per 30-min segment (a maximum of 3.33 IEDs/s/electrode were measured). The mean IED frequency across all epochs per electrode ranged from 15.93 to 1,092.12 discharges/electrode/30 min (Table 3). Because of this large variability, we asked if total IED number influenced the correlation between IED density and seizure onset. A linear regression analysis for the mean total IEDs per electrode and the 16-segment *t* test p-values did not produce a significant correlation ($p = 0.33$, Table 3). Comparison of the 16 segment p-values and either the range or the standard deviation of IEDs also did not correlate ($p = 0.83$ and 0.98, respectively, Table 3). Finally, a linear regression was performed for each patient, looking for a correlation between the number of total IEDs in a segment and the *t*-test p-value of that segment (Table S3). In 13 of the 19 patients (68.42%) the number of IEDs in a segment had no relationship to the p-value between seizure onset and IED density. For the six patients in whom there was a positive correlation, three demonstrated that a larger number of IEDs in a segment was associated with better agreement between IED generator and seizure-onset zone, and the opposite held true for 3 patients.

We performed an *F* test to determine if IED counts per electrode correlated with a global increase or decrease in IEDs in specific data epochs. An *F* test compared the variance of each electrode to the patient's mean variance, highlighting variability in the number of IEDs for a particular electrode compared to an increase or decrease in total IEDs for that segment. Between zero and 61 electrodes differed in the number of IEDs to a greater extent than the overall IED variance for a segment (i.e., *F* test $p < 0.01$ due to larger variability in an electrode compared to the entire segment; Table S4). Three patients had no electrodes, and another 6 of 19 had fewer than 10% of electrodes, with IED number varying more than the overall number of IEDs within epochs. However, the percentage of electrodes with IED variability greater than the overall variance did not distinguish patients with IED density correlation to seizure onset [15.7 ± 5% standard error of the mean (SEM)] to those without IED density correlation (6.7 ± 5% SEM). Together these data demonstrate that IED frequency changed over time in a given patient.

Spike correlation versus outcome/pathology

To determine if patients with and without IED density correlation to seizure-onset zone differed clinically, we performed a Fisher's exact test comparing the two groups for surgical outcome, pathology, and seizure-onset morphology on IEEG. There was no significant difference in postoperative outcomes ($p = 0.63$), or pathology IIa versus other (IIb, hemorrhage or infarction) ($p = 0.58$) between patients with and without IED correlation to seizure-onset zone. It is of interest to note that although only six patients had low-voltage attenuation as the first manifestation of their seizures, all six had correlation between frequency of IED and seizure-onset electrodes. In contrast, patients with spiking or slowing at seizure onset were mixed, with some demonstrating a correlation between high IED frequency and seizure-onset location ($n = 7$) and others no correlation ($n = 6$) (Fisher's exact *t* test $p < 0.05$).

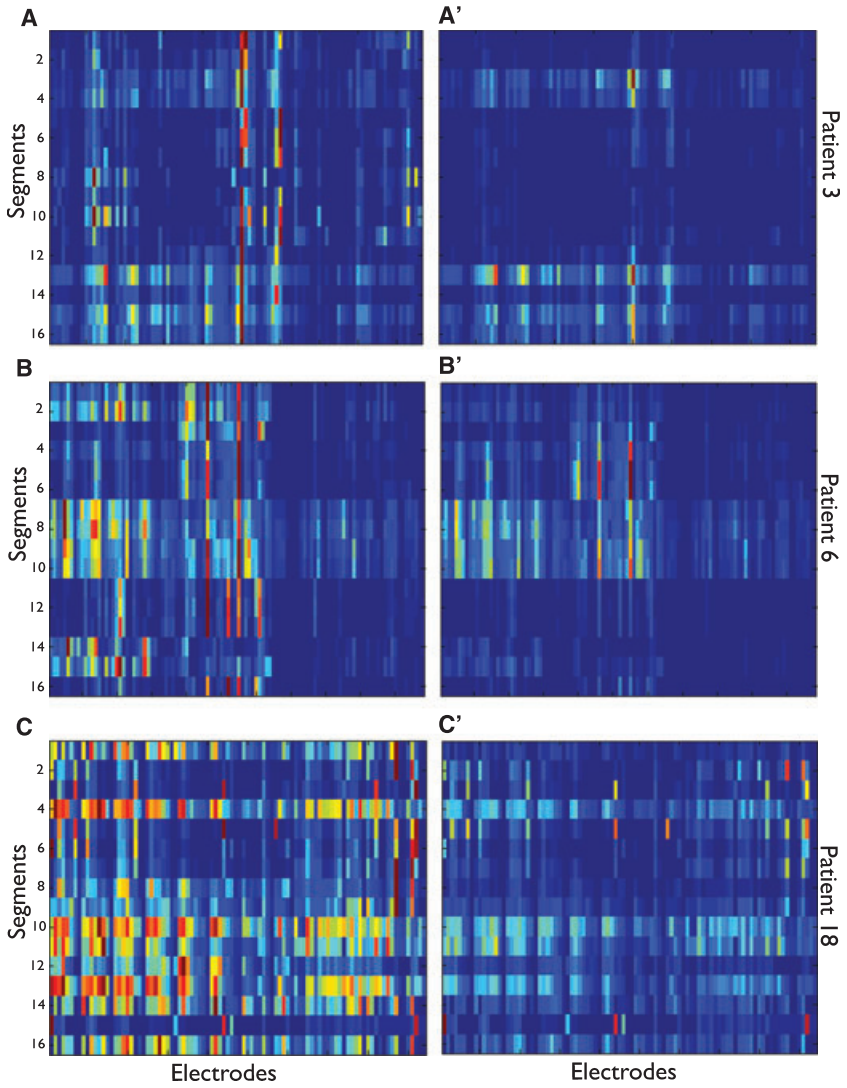

Figure 4.
Variability in electrodes with frequent spikes between 30-min segments and 8 h of intracranial electroencephalography (IEEG). (**A**) Patient 3: color-coded spike density for each 30-min segment was analyzed. Reading top to bottom of each figure shows each 1–16 random 30-min segments of EEG. From left to right shows each electrode; 1-# for that patient. The region of lowest to highest spiking, blue >>red, is shown for each of the 30-min segments, individually. The spike frequency is often but not always highest in the same set of electrodes. A′ is the same data as A, but plotted as the range of total spikes for each electrode relative to all electrodes over the full 8 h of data. Deep red represents the highest spike number for any electrode during all segments. The large variability in the number of spikes is evident, with some segments being mostly blue with fewer spikes, and other segments with more spiking. **B** and **B′**; **C** and **C′** is the same mapping paradigm as noted previously for patients 6 and 18. In both B and C there are two or even several patterns that emerge with frequent spikes in subsets of electrodes that seem to occur together in different 30-min segments. **B′** and **C′** demonstrate a great variability in the total number of spikes and their location over the entire 8 h of IEEG analyzed.

Discussion

Utilizing a computerized spike detection system to analyze long periods of IEEG, we identified correlation between interictal IED location and the seizure-onset zone in 11 of 19 patients. In the other eight patients, the mean distribution of interictal IEDs was a poor marker for identifying the seizure-onset region. In addition, when comparing across 16 different 30-min segments of IEEG for each individual patient, those with and without overall correlation, IED density varied significantly between sections for all but one patient. Therefore, in the majority of the patients, brief recordings of IEDs are unlikely to be useful in localizing seizure onset.

Table 3. Statistics of spiking for each patient

Patient no.	Spikes per segment		
	Mean	Range	SD
1	1,092.12	3,282.00	613.44
2	257.01	1,141.00	188.41
3	15.93	402.00	35.34
4	90.42	454.00	76.53
5	113.93	833.00	159.34
6	71.25	1,241.00	132.84
7	112.47	2,082.00	165.04
8	192.31	1,085.00	174.86
9	116.75	1,178.00	148.79
10	120.84	990.00	166.00
11	379.02	3,364.00	396.76
12	312.55	1,704.00	292.16
13	83.67	2,192.00	185.65
14	65.64	343.00	57.39
15	175.44	5,846.00	656.28
16	260.65	1,978.00	386.92
17	432.57	1,746.00	258.36
18	99.11	1,004.00	126.90
19	33.69	669.00	70.64

Statistics-regression of spike frequency and Spearman p-value

	R^2	p-value	Variance
Mean	0.054459816	0.336286908	58943.65334
Range	0.002624326	0.835014301	1874671.078
SD	2.74E–05	0.983043554	2034486.681

Listed is the mean, range, and standard deviation (SD) of the 16 segments for each patient. The lower part of the table lists the values of the regression analysis using the mean, range, and standard deviation (SD) from the table above correlated to the Spearman p-values from Table 2.

Prior studies have utilized short IEEG epochs to determine if IEDs can serve as a marker to identify seizure onset electrodes (Hufnagel et al., 2000; Asano et al., 2003). Asano et al., 2003 studied a patient population similar to our own, children mostly with cortical dysplasia, and found that the electrode with the highest IED frequency was contained within the seizure-onset region in 13 of 13 patients. IED frequency had the best correlation, although amplitude and leading spike were almost as good at identifying seizure-onset electrodes. In contrast, only 11 of 19 of our patients had the highest IED frequency within the seizure-onset zone. Our findings are in keeping with a larger study in adults and children also using a computer-based spike detector, where the seizure-onset electrode was within 2 cm of the maximal spike frequency electrode in only 53% of patients (Hufnagel et al., 2000).

Interictal IEDs are clinically used in a variety of ways to help identify the region of surgical resection. Our data suggest that electrodes with the highest frequency of IEDs over long periods of IEEG correlate with the electrodes involved in the seizure onset in about two-thirds of pediatric patients with medically refractory epilepsy. When only a single 30-min segment of recording is used, there is less-consistent correlation between the electrodes generating IEDs and the seizure-onset zone. Indeed, in all but one patient, the IED density pattern in a random 30-min segment did not consistently correlate with seizure-onset zone. These data suggest that the use of short epochs of subdural electrode recordings to identify regions of highest spike density is generally insufficient to provide an accurate localization of IED density. However, because at least a single segment in all but one patient correlated with seizure onset, picking the correct time to quantify seizure density could help delineate the seizure-onset zone.

From a clinical perspective, can we use our findings to improve seizure-free outcomes following surgery? Previous reports utilizing IEEG, describe increased surgical success if both the area of ''prominent interictal spiking and background abnormalities'' and seizure onset are resected (Wyllie et al., 1987; Paolicchi et al., 2000; Krsek et al., 2008). Their findings imply a distinct location for IEDs and seizure onset in a subset of patients. Our data quantify this relationship that IEDs had a distinct localization from seizure onset in about 40% of our patients. A potential hypothesis from combining these studies is that IEDs have a distinct localization and a causal relationship to seizure generation. One complicating factor in this discussion is the issue of generators versus propagators of IEDs. It may be that regions generating IEDs may be vital to seizure generation, but that those that merely conduct discharges confound efforts to localize the ictal-onset zone. Further quantitative studies looking at IED timing, correlation, and propagation may shed considerable light on this issue. In the end, the question of what constitutes a seizure and what are the cellular and network elements that are necessary to generate it are central to this discussion.

A prominent finding in this study was the variability of IEDs in any given electrode over time, and relative changes in IED frequencies between electrodes over time. A number of physiologic factors likely play an important role in this variability. Prior studies in the temporal lobe have implicated sleep as being one of the major sources of variability in the location of IEDs over time (Sammaritano et al., 1991; Staba et al., 2002). The frequency of IEDs and their spatial spread were greater in slow wave sleep than in wakefulness or REM sleep. Increased number of IEDs following a seizure has been reported, which may be affected by postictal sleep state (Gotman & Marciani, 1985; Gotman & Koffler, 1989). Epilepsy syndrome and localization may also play a role in the relationship between IEDs, sleep, and seizures, particularly in temporal lobe epilepsy (Spencer et al., 2008). Our data suggest that there is a great deal of variability in frequency of IEDs in extratemporal epilepsy.

Another potential cause for IED variability, in addition to sleep state, is alterations in antiepileptic drug (AED) levels during the phase II surgical evaluation. Studies have reported a mixed relationship between IED frequency and AED levels (Rodin et al., 1974; Milligan et al., 1983; Gotman & Marciani, 1985; Gotman & Koffler, 1989; Spencer

et al., 2008). Many of the patients in our study had medication adjustments over the course of their IEEG monitoring. An additional consideration for the variability in IED number is whether data epochs are preictal. There is as of yet no consensus whether there is a reproducible change in the temporal distribution of IEDs as seizures approach (Lieb et al., 1978; Gotman et al., 1982; Lange et al., 1983; Katz et al., 1991). These factors were not examined in the current study.

Cortical dysplasia, Palmini grade 2A, was the most predominant finding on pathology, and these patients had IEDs that both correlated and did not correlate with seizure onset. Similar to prior studies in patients with cortical dysplasia (Turkdogan et al., 2005), we found a mixture of seizure-onset morphologies, including rhythmic spiking, low-voltage fast-activity onsets, and rhythmic slowing at onset. Of the 13 patients with a rhythmic spiking morphology at seizure onset, 7 had IED frequency correlating with seizure onset. In contrast, all the patients with the low-voltage seizure onset displayed a correlation between IED frequency and seizure onset, suggesting that IED frequency may be a better marker for seizure-onset electrodes in patients with low-voltage fast activity on IEEG at seizure onset. A prior study found improved surgical outcome in patients with low-voltage fast activity at seizure onset as compared to slower rhythmic spiking, suggesting that it might be a marker for improved outcome (Park et al., 2002). Although the low-voltage fast activity was more common in patients with IED correlation to seizure onset, it did not portend a better surgical outcome in our patients. We do not understand why the low-voltage fast activity at seizure onset correlates better with frequent IED than rhythmic slowing at seizure onset. There was not a difference between the two groups in the number of electrodes involved in seizure onset. One possibility is that we are missing the true seizure onsets in some patients, especially those with rhythmic slowing at onset. It will be important to replicate the correlation differences between findings on a second set of patients.

In this study we utilized automated, computer-based EEG analysis to quantify IEDs over long periods of IEEG, and we identified patients with and without a correlation between IED and seizure-onset regions. The improvement in computer technology over the last decade has allowed implementation of methods capable of easily analyzing IEDs over 8 h of IEEG in up to 140 electrodes per patient. Although our results are promising for using computer-based detection methods to quantify IEDs, it remains an open question as to how to best utilize and refine these methods to improve outcome from epilepsy surgery, shorten length of stay, and potentially maximize the utility of intraoperative ECoG during electrode placement and resection. Even more importantly, this study raises important questions about how seizures and interictal epileptiform discharges are generated in human brain, and how to define and map epileptic networks.

Acknowledgments

CURE and NINDS NS044869 funding for B.E.P and funding from the Woman's auxiliary of the Children's Hospital of Philadelphia for P.B.S. Funding from NINDS NS048598, NS041811-02, and CA084438-05, and the following foundations, Klingenstein, Dana, Epilepsy Research, Whitaker, and PA Tobacco Fund for Brian Litt. The authors would like to thank Dr. Abba Krieger for his review of the statistics used in the article.

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.

Disclosure: The authors have no conflict of interest to report.

References

Asano E, Muzik O, Shah A, Juhasz C, Chugani DC, Sood S, Janisse J, Ergun EL, Ahn-Ewing J, Shen C, Gotman J, Chugani HT. (2003) Quantitative interictal subdural EEG analyses in children with neocortical epilepsy. *Epilepsia* 44:425–434.

Brown MW III, Porter BE, Dlugos DJ, Keating J, Gardner AB, Storm PB Jr, Marsh ED. (2007) Comparison of novel computer detectors and human performance for spike detection in intracranial EEG. *Clin Neurophysiol* 118:1744–1752.

Engel J, Van Ness PC, Rasmussen TB, Ojemann LM. (1993) Outcome with respect to epileptic seizures. In Engel J (Ed.) *Surgical treatment of the epilepsies*. Raven Press, New York, pp. 609–622.

Gotman J, Ives J, Gloor P, Olivier A, Quesney LF. (1982) Changes in interictal EEG spiking and seizure occurrence in humans. *Epilepsia* 23:432–433.

Gotman J, Marciani MG. (1985) Electroencephalographic spiking activity, drug levels, and seizure occurrence in epileptic patients. *Ann Neurol* 17:597–603.

Gotman J, Koffler DJ. (1989) Interictal spiking increases after seizures but does not after decrease in medication. *Electroencephalogr Clin Neurophysiol* 72:7–15.

Hufnagel A, Dumpelmann M, Zentner J, Schijns O, Elger CE. (2000) Clinical relevance of quantified intracranial interictal spike activity in presurgical evaluation of epilepsy. *Epilepsia* 41:467–478.

Katz A, Marks DA, McCarthy G, Spencer SS. (1991) Does interictal spiking change prior to seizures? *Electroencephalogr Clin Neurophysiol* 79:153–156.

Kobayashi K, Merlet I, Gotman J. (2001) Separation of spikes from background by independent component analysis with dipole modeling and comparison to intracranial recording. *Clin Neurophysiol* 112:405–413.

Krsek P, Maton B, Jayakar P, Dean P, Korman B, Rey G, Dunoyer C, Pacheco-Jacome E, Morrison G, Ragheb J, Vinters HV, Resnick T, Duchowny M. (2009) Incomplete resection of focal cortical dysplasia is the main predictor of poor postsurgical outcome. *Neurology* 72:217–223.

Lange HH, Lieb JP, Engel J Jr, Crandall PH. (1983) Temporo-spatial patterns of pre-ictal spike activity in human temporal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 56:543–555.

Lieb JP, Woods SC, Siccardi A, Crandall PH, Walter DO, Leake B. (1978) Quantitative analysis of depth spiking in relation to seizure foci in patients with temporal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 44:641–663.

Litt B, Esteller R, Echauz J, D'Alessandro M, Shor R, Henry T, Pennell P, Epstein C, Bakay R, Dichter M, Vachtsevanos G. (2001) Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. *Neuron* 30:51–64.

Marciani MG, Gotman J, Andermann F, Olivier A. (1985) Patterns of seizure activation after withdrawal of antiepileptic medication. *Neurology* 35:1537–1543.

Milligan N, Oxley J, Richens A. (1983) Acute effects of intravenous phenytoin on the frequency of inter-ictal spikes in man. *Br J Clin Pharmacol* 16:285–289.

Palmini A, Najm I, Avanzini G, Babb T, Guerrini R, Foldvary-Schaefer N, Jackson G, Luders HO, Prayson R, Spreafico R, Vinters HV. (2004) Terminology and classification of the cortical dysplasias. *Neurology* 62:S2–S8.

Paolicchi JM, Jayakar P, Dean P, Yaylali I, Morrison G, Prats A, Resnik T, Alvarez L, Duchowny M. (2000) Predictors of outcome in pediatric epilepsy surgery. *Neurology* 54:642–647.

Park SA, Lim SR, Kim GS, Heo K, Park SC, Chang JW, Chung SS, Choi JU, Kim TS, Lee BI. (2002) Ictal electrocorticographic findings related with surgical outcomes in nonlesional neocortical epilepsy. *Epilepsy Res* 48:199–206.

Rodin EA, Rim CS, Rennick PM. (1974) The effects of carbamazepine on patients with psychomotor epilepsy: results of a double-blind study. *Epilepsia* 15:547–561.

Sammaritano M, Gigli GL, Gotman J. (1991) Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. *Neurology* 41:290–297.

Spencer SS, Goncharova II, Duckrow RB, Novotny EJ, Zaveri HP. (2008) Interictal spikes on intracranial recording: Behavior, physiology, and implications. *Epilepsia* 49:1881–1892.

Staba RJ, Wilson CL, Bragin A, Fried I, Engel J Jr. (2002) Sleep states differentiate single neuron activity recorded from human epileptic hippocampus, entorhinal cortex, and subiculum. *J Neurosci* 22:5694–5704.

Staley K, Hellier JL, Dudek FE. (2005) Do interictal spikes drive epileptogenesis? *Neuroscientist* 11:272–276.

Turkdogan D, Duchowny M, Resnick T, Jayakar P. (2005) Subdural EEG patterns in children with taylor-type cortical dysplasia: comparison with nondysplastic lesions. *J Clin Neurophysiol* 22:37–42.

Wyllie E, Luders H, Morris HH III, Lesser RP, Dinner DS, Hahn J, Estes ML, Rothner AD, Erenberg G, Cruse R, Friedman D. (1987) Clinical outcome after complete or partial cortical resection for intractable epilepsy. *Neurology* 37:1634–1641.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Studentized p-values for test of significance of spike density of each segment to seizure-onset zone. If p-value is <0.0001, then only 0.000 is shown.

Table S2. Variability of spiking does not correlate with significant *t*-test p-value. The variability of spiking in different segments was a potential reason for each segment within a patient having unlike p-values. A regression analysis between mean, range, variance, and standard deviation of a segment and that segment's *t*-test p-value was calculated (only regression to the mean of the segment is shown). The R-squared value (R^2), calculated p-value, and variance are listed.

Table S3. Variability of spiking between segments: The variability of spiking was tested by performing an *F* test of the mean spike variance for all segments of a patient and the variance of each segment. p-value of *F* test is listed. There was significant variability found. Seg, segment.

Table S4. Spike variability within a given channel across segments. An *F* test of equal variances was calculated for the mean spike variance of a patient and the variability of spiking in a given channel. The resultant p-value for each patient and each channel is listed. E#, electrode number; pt, patient number.

Please note: Wiley Periodicals is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.