Multifocal Source Localizations from Interictal Epileptiform Discharges (IEDs) and Seizures as Traveling Waves

C. LaGamma[1], D. McAuliffe[2], J. Diamond[3] and K. Zaghloul[3]

1. Penn State College of Medicine, Hershey, Pennsylvania, USA
2. Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania, USA
3. Surgical Neurology Branch, National Institutes of Health, Bethesda, Maryland USA
clagamma@pennstatehealth.psu.edu, danielle.mcauliffe12@gmail.com,
joshua.diamond@nih.gov, kareem.zaghloul@nih.gov

***Abstract*— Post-surgical outcomes for drug-resistant epilepsy continue to be suboptimal, particularly in the setting of multifocal epilepsy. This is due in part to the fact that the mechanisms of seizure onset and spread, particularly in multifocal disease, remain incompletely understood. Seizures may spread contiguously, as traveling waves, or via underlying structural connectivity. Distinct foci may have differing significance for seizure generation.**

Here, we take advantage of a recently-developed algorithm that captures time differences of traveling waves at adjacent electrodes for seizure source localization. We identify seizure source locations from 36 patients in interictal epileptiform discharges (IEDs) and during seizures. We visually counted foci of activity, and scored whether foci were resected. Next, we divided localization results into separate foci in an automated fashion, using k-means clustering. IED foci tend to be larger, but less dense, than seizure foci.

Next, we asked how much of each focus should be resected to yield an Engel 1 outcome. We found that a resection extent of 50%, in seizure foci, and 75%, in IED foci, was best at stratifying patients into those with good outcome and poor outcome. On average, patients had 3 seizure foci that were at least 50% resected and on average had 1 IED focus with at least 70% resection. Finally, we asked about overlap of IED and seizure foci. We found that the degree of overlap was significantly greater in Engel 1 patients. Understanding of the extent and nature of multifocality in epilepsy may help improve post-surgical outcomes.

Keywords*— *seizure localization, multifocal epilepsy, IEDs, traveling waves.

I. Introduction

Drug-resistant epilepsy is characterized by the failure to achieve seizure freedom despite optimal medical management. Patients with drug-resistant epilepsy may be eligible for surgical resection [1][2]. Resection procedures are often preceded by invasive recordings with intracranial electroencephalography (iEEG) for localization of seizure onset zones [3][4].

One of the principal challenges that may arise from invasive recordings is the presence of multifocal epilepsy [5]. Post-surgical outcomes have been found to be worse in the setting of multifocal disease [6]. Pathologic synchronization across multiple lesions may underlie the difficulty achieving seizure freedom for patients with multifocal disease burden [7][8]. However, the extent to which focal site number and extent of resection of foci contribute to outcome remains poorly understood.

Here, we aim to assess multifocality of seizure localizations and post-surgical outcomes using qualitative and quantitative approaches. We use a previously developed approach for localization of both ictal and interictal discharges [9][10]. There are multiple prevailing theories regarding the spread of epielptic activity including using functional connectivity, white matter tracks, local spread, and traveling waves [11],[12],[13],[14],[15]. This approach offers that epileptic activity can be conceptualized as emitting from a traveling wave. When using electrodes as sensors, an epileptic focus can be algorithmically identified. A limitation to this approach is the lack of inclusion of multiple types of spread, however the integration of techniques is currently under investigation. Previous work, however, did not consider the impact of multifocality on post-surgical outcomes. Here, we show that multifocal disease is very common in our patient population. We identify a critical proportion of foci that should be resected to achieve a good outcome: 50% of seizure foci, and 70% of interictal epileptiform discharge (IED) foci. Finally, we show that seizure freedom is most likely if resected seizure and IED foci are overlapping.

II. Methods

36 participants with drug-resistant epilepsy (35.7 +/- 10.3yrs; 16 female) were implanted with subdural and depth electrodes. Surgical procedures and video-EEG monitoring were performed at the Clinical Center at the National Institutes of Health (NIH) for all patients. The research protocol was approved by the Institutional Review Board, and informed consent was obtained from all participants. The average number of seizures recorded per participant was 4.94, with 178 total seizures recorded across participants. Of 36 patients, 17 (47%) had an Engel 1 outcome after surgery, indicating seizure freedom. The remaining 19 patients (53%) of patients had outcomes of Engel 2 (n=9), Engel 3 (n=7) and Engel 4 (n=3).

Source localizations from traveling wave calculations from both IED discharges and seizure data were used to characterize multifocality of epileptic sources. We used a source localization technique that treats pathologic signals as traveling waves [11]. This allows us to capture differences in time or in phase of these signals across adjacent electrodes. These differences can then be used to mathematically determine the discharge source. This technique has been reported in previous work [10] [16], and borrows from similar techniques used in geophysics and acoustics.

Source localization algorithm was used in a 2 hour awake baseline for IEDs and during all recorded seizures. Next, raters blinded to outcome qualitatively scored number of foci and whether they were resected to determine whether foci offered additional information surrounding outcomes and to motivate a quantitative analysis. A quantitative analysis involved a clustering algorithm of localizations to define the foci, and determine characteristics including spatial radius, density, fractional size, and amount resected. This also allowed us to compare these measures between foci defined by IED localizations and foci defined by seizure localizations. To understand how outcomes are impacted by resections of foci defined by both IEDs and by seizures, we iteratively thresholded the percent of foci resected to maximize differences between outcomes. We used these thresholds to determine the number of foci resected that resulted in seizure free patients. Finally we determined the overlap of seizure and IED foci that were resected in patients with seizure freedom.

III. Rater scoring

Researchers who were involved with this work (C.L. and D.M.) analyzed the results of the seizure and IED localization procedure. Localizations were then grouped into foci, and foci were graded as to whether they were fully, partially, or not resected. Raters were blinded to patient outcomes. For each patient, foci were assigned a 0, 0.5, or 1 corresponding to the rater resection determination (none, partial, or full, respectively) and this was averaged between raters to generate the Average Rater Score (ARS) and then across foci to compute and average Focus Resection Score (Figure 1, equation 2). This was contrasted with Gross Resection Score, where the same ratings were given, but considering that all localizations were a single focus. This contrast helped to distinguish whether foci information offered additional information to understanding differences in outcomes compared with total gross resection percentages.

$$GrossResectionScore = ARS \tag{1}$$

$$FocusResectionScore = \frac{1}{nFoci}\sum_{i=i}^{nFoci} ARS \tag{2}$$

Raters were reliable for both resection score and number of foci, with a fleiss kappa of 0.84 and 0.46 respectively. Every patient was rated as having multiple foci, for both

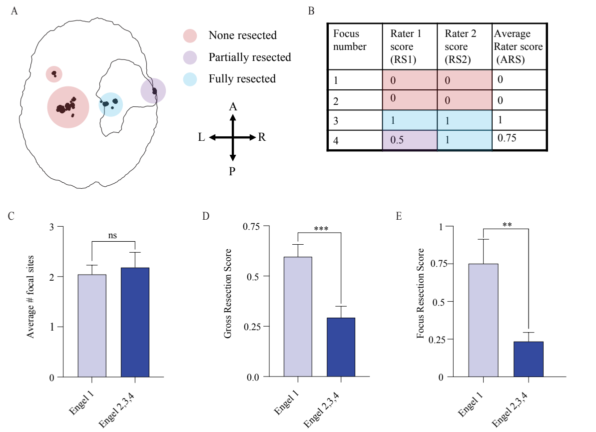

Figure 1. **Rater-determined foci** A. Example of rater scoring foci localizations for a single seizure. Red shading demonstrates two labeled foci where raters independently deemed none was resected, blue shows full resection, and purple shows partial resection. B. Rater Scoring system example. Raters scored no resection as 0, full as 1 and partial as 0.5. C. Average number of Foci for seizures did not differ between patients with an Engel 1 outcome, patients with all other outcomes. D. Gross resection score was considered as the ARS if all localizations were considered in 1 focus. E. The average of the Average Rater Score(ARS) for each foci was considered in the Focus Resection Score. Both Gross Resection and Focus Resection Score were significantly different between between Engel 1 and all other outcomes. Error bars represent + SEM. * p < 0.05, ** p < 0.01, *** p < 0.001, n.s. = not significant

seizures and IEDs. Both the Focus Resection Scores (m = 0.75, 0.23, p<0.01), and Gross Resection Score (m = 0.59, 0.29, p<0.01) for each patient, significantly differed between patients with Engel 1 and other Engel outcomes despite the number of foci being similar between outcome groups (m = 2.0, 2.1, p=n.s.). This observational study motivated us to approach these findings quantitatively.

IV. Foci characteristics

Using k-means clustering, we algorithmically defined foci from both IED and seizure localizations (Figure 2A) with a max possible cluster count of 8, the maximum number of foci identified by raters. These characterizations elucidate differences between seizure and IED foci. All statistics between IED foci and seizure foci were computed using a ranksum given their non normal distributions. Mean and p-values will be reported for characteristics as (mean of IED foci, mean of seizure foci, and p-value).

We measured the focus radius, calculated by obtaining the maximum pairwise Euclidean distance over all localized points in that focus (Figure 2B). IED foci cover more space (m = 15.91, 5.97 mm p=<0.001). These results agree with prior findings that the region giving rise to IEDs often contains, but is larger than, the seizure onset zone [17][18][19][10]. We calculated the focus density (Figure 2C) as the number of localizations in each focus, divided by the radius of that focus. This can be thought of as a measure of precision of that focus. IED foci are less dense (m=17.18, 83.71 pts/focus p<0.001). The cluster count metric (Figure 2D) tells us the percentage that each focus contributes to the total number of localizations. This may help determine whether there tend to be major or minor foci, on the one hand, or foci which are more evenly distributed, on the other, in either condition. These were not significantly different between conditions and the foci on average amassed to contain about a quarter of the total amount of localizations (m= 0.24, 0.29 %, p= n.s.). The average percent of resection for each focus (Figure 2E) was calculated by dividing the amount of resected source points, in each focus, by the total number of source points in that focus. Resection percentage of foci did not differ between groups and skewed towards 0 or 1, that is, foci were mostly close to fully or not at all resected (m = 0.25, m=0.35 % , p = n.s.).

V. Resection outcomes

We were interested in considering the relationship between extent of resection of seizure and IED foci and outcome. Therefore, for all patients in both IED and seizure conditions, we counted the number of foci that were resected to a particular threshold. We utilized multiple thresholds at 10% intervals to identify which threshold had the maximum difference between outcome groups. This in effect can be thought of as choosing the threshold which was best in distinguishing the two outcomes, much like maximizing the area under the receiver operating characteristic curve.

Figure 3 shows four of the threshold distributions. Over all patients, having at least 50% of seizure foci removed and having at least 70% of IED foci removed were the thresholds that showed significant difference in distributions between outcome groups (p<0.001,p<0.001 respectively). We were interested to find this, as it may seem contradictory to the foci resection characteristics. That is, most foci were close to completely or not at all resected (Figure 2E). However, our results suggest that the foci which are truly partially resected are important in differentiating between good and poor outcomes.

We then asked, in patients that are seizure free, how many foci were resected at these thresholds? When we used this threshold for only Engel 1 outcome patients (n=17), we obtained an average of 1.10 IED foci that were at least 70% resected. Non Engel 1 patients had an average of 0.2 IED foci at least 70% resected. For seizure localizations, Engel 1 patients had an average of 2.95 foci that were at least 50% resected where non Engel 1 patients had an average of 0.56. As described above, IED foci are often broader than seizure foci and may contain regions of only potentially-epileptogenic tissue. On the other hand, seizure foci are often more compact, but may be distributed. Our results suggest that resection of both regions may have importance for seizure freedom.

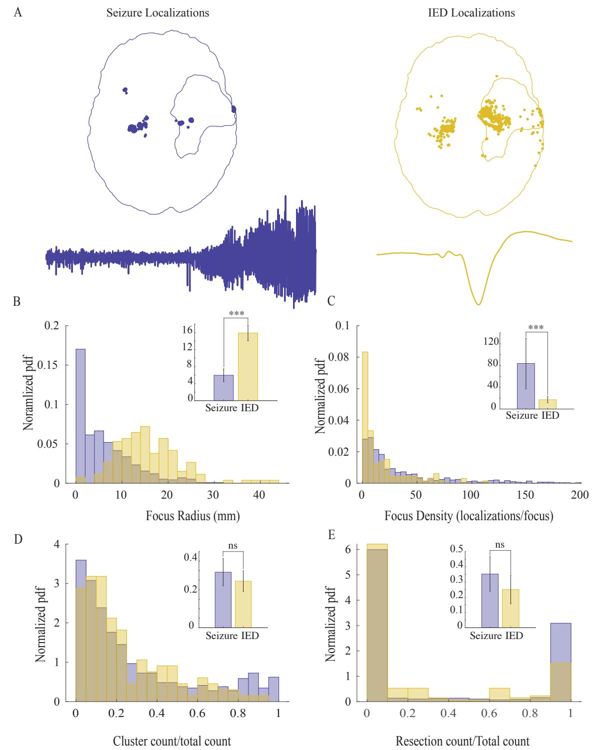

Figure 2. **Focus characteristics** A. Representative patient diagram of seizure source localization throughout the brain (left) and IED source localization (right). B. Histogram showing quantitative comparison of seizure versus IED foci radius. Inset represents comparison of average radii between seizure and IED foci. C. Histogram showing quantitative comparison of seizure versus IED foci site density. Inset represents comparison of average radii between seizure and IED density. D. Representative patient diagram of IED localization throughout the brain (left) and IED activity tracing (right). E. Histogram showing quantitative comparison of seizure versus IED percent contribution of a particular foci's localization to the overall number of localizations. Inset represents comparison of average seizure versus IED foci percent contribution. (F) Histogram showing quantitative comparison of the percent of points within a foci that were resected between seizure and IED foci data. (n = 579 for seizure foci; 132 for IED foci). Error bars represent + SEM. * p < 0.05, ** p < 0.01, *** p < 0.001, n.s. = not significant, IED = interictal epileptiform discharge.

VI. Overlap resections by outcome

In the previous section, we showed that, in patients with Engel 1 outcome, on average, 70% of one IED focus and 50% of three seizure foci were resected. Next, we sought to determine the extent to which these

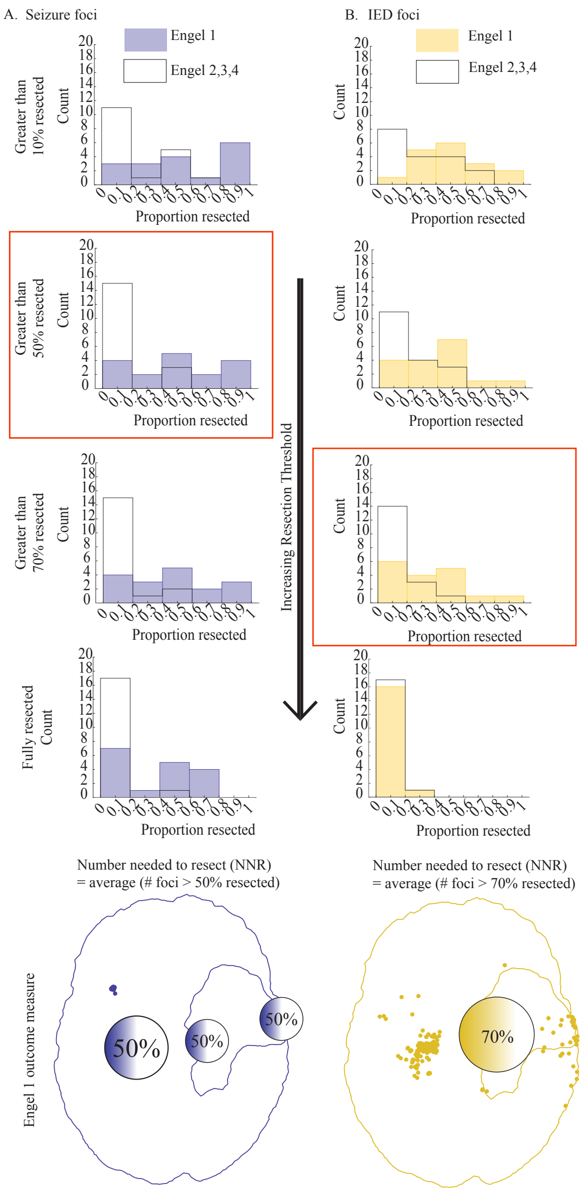

Figure 3. **Extent of resection of foci differs over Engel classes.** A. Histograms of the percent of foci that are at least 10% , 50% , 70% ,or 100% resected. Left column shows seizure foci, whereas the right shows IED foci. With seizure foci, the greatest separation between Engel class distributions distributions of these foci resection extents lies at 50% (Wilcox ranksum p=0.0007) and for IED foci, at 70% (p=0.002). This indicates that a 70% resection of IED foci and a 50% reduction of seizure foci can best distinguish between outcomes. Across patients, the average number of foci meeting these thresholds is 1 focus, for IEDs, and 3 foci, for seizures. respectively.

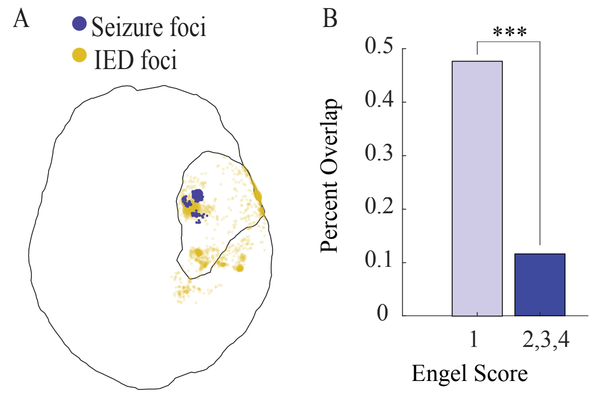

Figure 4. **Resection percent of the intersection between IED foci and seizure foci differs over Engel classes.** A. Representative patient with 3 Seizure foci overlapping with 1 IED focus. These seizure foci were completely resected and this IED focus was 98 % resected. B. Percent resection of overlap between seizure and IED foci across Engel 1 patients (n = 17) and all other Engel score outcomes (n = 19). * p < 0.05, ** p < 0.01, *** p < 0.001, n.s. = not significant

foci overlapped. Therefore, we took the intersection between IED and seizure foci to quantify overlap. We used an ROI-based approach to determine the brain surface vertices involved in IED foci. We were then able to ask about the number of intersecting vertices, in any comparison between a single IED focus (after ROI mapping) and a single seizure focus. We then took each seizure focus, and for any particular seizure focus, we found the single ROI-mapped IED focus that had the greatest percent overlap with that seizure focus. We then captured that territory of overlap, and asked about the proportion of that overlapping region that was resected. Among foci in Engel 1 patients, the 48% the intersection was resected, compared to 11% of the intersection in Engel class 2-4 patients.

VII. Summary

In the present work, we examined characteristics in multifocality as determined by localization of ictal and interictal discharges. We found that localizations identify multifocal disease in every patient, for both ictal and interictal data. This underscores the prevalence of multifocality in our patient population. We find that even partial resections of these foci may be sufficient to disrupt epileptogenic zones and impact surgical outcomes. This is evidenced by the strongest differences between groups having at least 50% of seizure and 70% of IED foci resected. Furthermore, when we look to see the average number of foci in patients that achieve and keep seizure freedom, we demonstrate that this is 3 seizure foci and 1 IED focus. This difference could be attributed to IED foci having larger spatial spread than the more precise seizure foci.

These results align with prior findings that the region giving rise to IEDs often contains, but is larger than, the seizure onset zone [17] [18] [19] [10]. IED foci are wider and more variable in their spatial spread. This may be related to differences in state, which affect IED propagation [9], whereas, seizures may be under a more narrow set of states, with more specific constraints. Additionally, IED activity may reflect the presence of tissue that is both actually, and also only *potentially*, epileptogenic. This underscores the importance of identifying overlapping foci when determining possible resection targets. The average percentage of seizure foci that overlapped with an IED foci and was resected was 48%. Therefore, these results may have clinical importance. iEEG results are strengthened when information from the IEDs and seizures are taken together. Clinicians could seek to resect particularly those regions in which IED and seizure activity overlap. Better understanding of the nature of multifocal epilepsy, including the interactions between interictal and ictal foci, may help improve post-surgical outcomes in drug-resistant epilepsy.

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