BRIEF COMMUNICATION

Epilepsia

Incomplete resection of the intracranial electroencephalographic seizure onset zone is not associated with postsurgical outcomes

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Abstract

Delineation of seizure onset regions using intracranial electroencephalography (icEEG) is vital in the surgical workup of drug-resistant epilepsy cases. However, it is unknown whether the complete resection of these regions is necessary for seizure freedom, or whether postsurgical seizure recurrence can be attributed to the incomplete removal of seizure onset regions. To address this gap, we retrospectively analyzed icEEG recordings from 63 subjects, identifying seizure onset regions visually and algorithmically. We assessed onset region resection and correlated this with postsurgical seizure control. The majority of subjects had more than half of their onset regions resected (82.46% and 80.65% of subjects using visual and algorithmic methods, respectively). There was no association between the proportion of the seizure onset zone (SOZ) that was subsequently resected and better surgical outcomes (area under the receiver operating characteristic curve [AUC] < .7). Investigating the spatial extent of onset regions, we found no substantial evidence of an association with postsurgical seizure control (all AUC < .7). Although seizure onset regions are typically resected completely or in large part, incomplete resection is not associated with worse postsurgical outcomes. We conclude that postsurgical seizure recurrence cannot be attributed

to an incomplete resection of the icEEG SOZ alone. Other network mechanisms beyond icEEG seizure onset likely contribute.

KEYWORDS

epilepsy surgery, intracranial EEG, onset detection, seizure freedom

1 | INTRODUCTION

When medications fail to control seizures in focal epilepsy, surgical resection is a potential curative solution.[1] Such surgeries aim to resect or disconnect epileptogenic tissue with the ultimate goal of postsurgical seizure freedom.[2] During presurgical evaluation, a battery of assessments across modalities are used to localize tissue believed to be involved in epileptogenesis.[3] More complex cases require intracranial electroencephalographic (icEEG) recordings to localize epileptogenic tissue.[4] The seizure onset zone (SOZ) identified on the icEEG is a proxy for the epileptogenic zone and is thus used to guide surgical resections[5] where appropriate.

When considering epilepsy as a network disorder,[6] however, it is unclear whether complete removal of seizure onset regions is necessary to attain seizure freedom postsurgically. Past investigations have reported contradictory findings. Khan et al.[7] report that more complete resections of icEEG seizure onset channels are not associated with postsurgical seizure freedom in children; yet numerous papers discuss "incomplete resection" as a mechanism of surgical failure[8,9]. Related to this, the common wisdom that "diffuse onsets," or multifocal onsets, are more likely to yield postsurgical seizure recurrence, also remains untested.

To this end, we assessed the overlap between seizure onset and resected regions to determine whether resecting a larger proportion of the onset region was associated with postsurgical seizure freedom.

2 | MATERIALS AND METHODS

2.1 | Subject details

In this retrospective study, 63 subjects with medically refractory focal epilepsy underwent video icEEG monitoring (stereo-EEG [SEEG] and electrocorticography [ECoG]) within the epilepsy monitoring unit at the UK's National Hospital for Neurology and Neurosurgery (NHNN). All subjects had subsequent surgical resections, with postsurgical outcomes recorded at year 1 consistently. International League Against Epilepsy (ILAE) 1–2 was labeled as a "favorable" outcome, as there were no debilitating postsurgical seizures experienced; ILAE 3+ was labeled as an "unfavorable" outcome. Surgical outcome

groups did not differ in age, sex, surgery type, or disease duration (see Suppl. S2). Anonymized data were collected from NHNN; all analyses were completed following approval from the Newcastle University Ethics Committee (reference: 28280/2023).

2.2 | EEG preprocessing

For each seizure recorded using icEEG, we obtained 120 s of activity before onset. Only spontaneous seizures were assessed; seizures arising from stimulation were excluded. Prior to analysis, all data were resampled to 512 Hz. An iterative noise detection algorithm was used to identify preictal noise, which was validated by visual inspection. On a within-subject basis, channels identified as noisy were removed from all seizures (see Suppl. S3.1). When seizures occurred in close succession, we retained only the lead seizure. Recordings were rereferenced to a common average reference, notch filtered at 50 Hz (and harmonics) with a 2-Hz window to remove line noise. Recordings were then band-pass filtered between .5 and 200 Hz using a fourth-order, zero-phase shift Butterworth filter.

2.3 | Onset detection and mapping to regions

Two methods were used to identify onset regions; clinically labeled onset regions (CLOs) were identified through visual inspection by the clinical team, and automatically labeled onset regions (ALOs) were identified using a computational algorithm. Regionwise onsets were subsequently compared against resections using the same parcellation scheme.

2.3.1 | Magnetic resonance imaging processing for identifying regions and resected tissue

To map electrode coordinates to brain regions, we used the same methods as described previously.[10,11] We used FreeSurfer to generate volumetric parcellations of each subject's preoperative magnetic resonance imaging (MRI)

according to the Lausanne-120 atlas.[12,13] Each electrode contact was assigned to the closest gray matter volumetric region within 5 mm. Contacts >5 mm from gray matter regions were excluded from further analysis.

To identify which regions were resected, we used previously described methods.[10,14] We registered the postoperative MRI to the preoperative MRI and manually delineated the resection cavity, accounting for postoperative brain shift and sagging. Electrode contacts within 5 mm of the resection were labeled as resected. Regions with >25% of their electrode contacts removed were considered as resected for downstream analysis (see Taylor et al.[10]). Figure 1A displays an example subject′s implantation and subsequent resection.

2.3.2 | Automatically localized onset

Our seizure onset localization method extends the "Imprint" algorithm.[15] For each icEEG time series (see Figure 1B for an sample subject′s icEEG time series), we computed eight markers of EEG activity (line length, energy, and band powers in δ, θ, α, β, low-γ, and high-γ bands). This was done at the channel level for the preictal and ictal periods using 1-s windows with a 7/8-s overlap.

Mahalanobis distance was employed to identify abnormal (pathological) activity across all eight markers, considering the covariance structure of markers. A baseline distribution of median absolute deviation (MAD) scores for Mahalanobis distances was established for each channel, with each window scored against all other time windows in the preictal segment. Noise, such as interictal epileptiform discharges, was eliminated from the preictal segment (see Suppl. S3.2). Subsequently, seizure activity in the ictal segment was identified by MAD scoring each window against the corresponding baseline distribution of Mahalanobis distances in the channel. Seizure activity was defined as MAD scores > 3 persisting for at least 80% of a 9-s window. Any channels with activity commencing within 1 s of the first detected activity were labeled as seizure onset. Channelwise onsets (Figure 1C) were then localized to regions of interest (referred to as regions in this work) according to the Lausanne-120 atlas[13] (Figure 1D). To summarize onset channels across seizures in a given subject, we retained any regions that were involved in at least 50% of seizures (Figure 1E,F).

2.3.3 | Clinically labeled onset

Seizure onset channels were labeled based on visual inspection of icEEG by an expert team at the NHNN. Regions involved in rapid propagation (up to 3 s after onset) were also included in the definition of the seizure onset zone. When multiple seizures occurred within the same subject, we obtained one CLO per subject. This was done by considering the channels involved most frequently across clinically relevant focal seizure onsets, as indicated by the clinical team.

Clinically labeled onsets were localized to regions using the Lausanne-120 parcellation scheme (Figure 1G).

2.4 | Comparing the proportion of onset resected and onset size across outcome groups

Regions in the ALO and CLO were directly compared against resection (Figure 1F,G). The proportion of subsequently resected onset regions was compared across outcome groups. We examined onset sizes, both as a count of regions and a proportion of the implantation, across all subjects. We computed the area under the receiver operating characteristic curve (AUC) using logistic regression models comparing outcome groups; the associated p-values were computed using permutation tests with 1000 permutations. AUC thresholds reported follow previous conventions[16]; an AUC≥.7 was considered acceptable, and an AUC<.7 was considered unacceptable (i.e., the model is not able to distinguish outcome groups). Probability values based on permutation tests are reported for reference.

2.5 | Code availability

Onset detection code is available at https://github.com/SGascoigne97/ictal_onset. Analysis code is available at https://github.com/SGascoigne97/onset_analysis.

3 | RESULTS

3.1 | icEEG seizure onset regions tend to be resected, but more complete resections are not associated with more favorable surgical outcomes

First, we investigated whether seizure onset regions tend to be resected and found this to be the case in most subjects. The median proportion of CLOs and ALOs resected was 80% (median proportion: 80% ILAE 1–2, 75% ILAE 3+) and 100% (median proportion: 100% ILAE 1–2, 100% ILAE 3+), respectively. More than half of CLOs and ALOs were resected in 82.46% (47/57) and 80.65% (50/62) of subjects, respectively. Furthermore, there was no significant
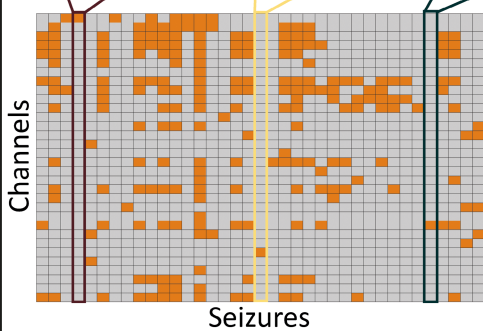
Example Subject

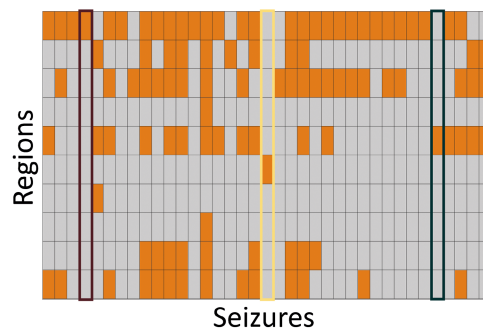

(A) Implantation and subsequent resection
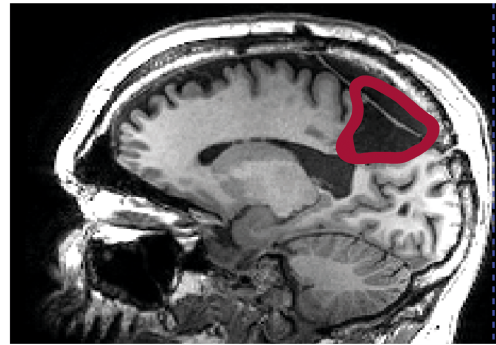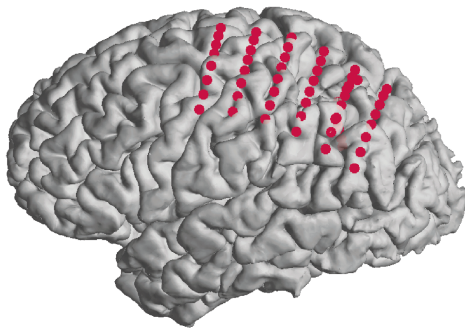
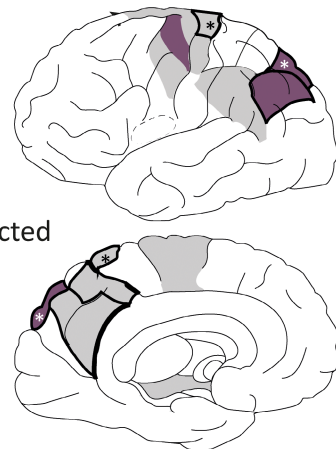**(B)** EEGs with automatically detected activity overlaid

| Automatically detected onset time
■ Seizure activity
■ Earliest activity

10s
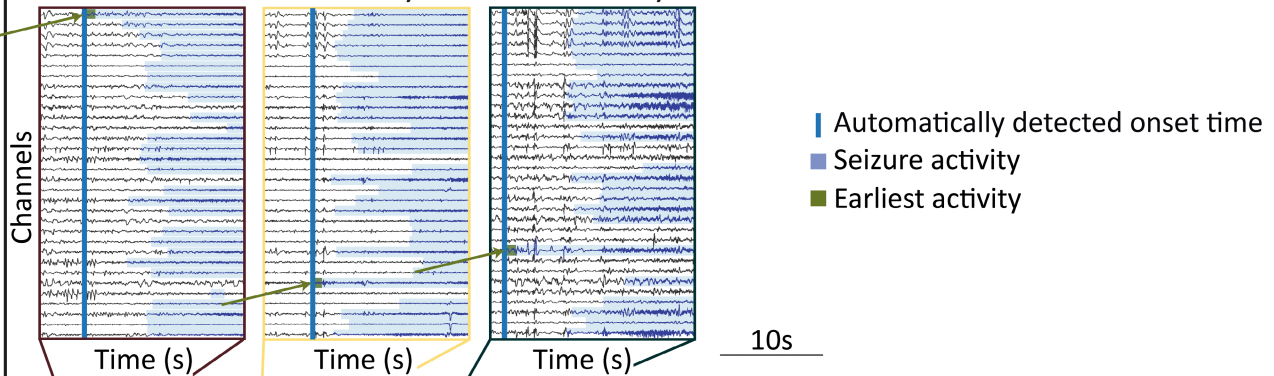
(C) Channel-wise onsets **(D)** Region-wise onsets **(E)** Consensus onset

(F) Consensus onset mapped onto brain **(G)** Clinically marked onset mapped onto brain

2 ALO regions
5 regions resected
1 onset region resected

50% of ALO resected

3 CLO regions
5 regions resected
2 onset regions resected

66.7% of CLO resected
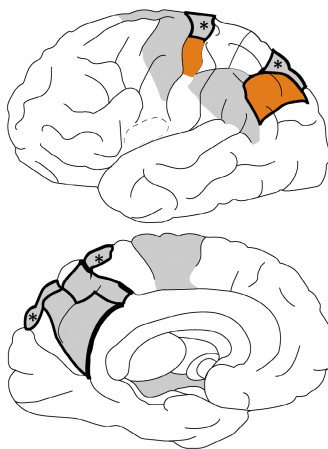
● ALO ● CLO ■ Implantation \ Resected regions ✳ Region seen in both views

FIGURE 1 Workflow from automatic seizure onset region detection for a sample subject. (A) Electrode location overlaid on subject's cortical surface (left) and postsurgical magnetic resonance image with resected region outlined in red (right). (B) Intracranial electroencephalographic time series for three focal seizures with detected seizure activity highlighted in blue. Automatically detected onset times are labeled in blue. First activity (i.e., onset) is highlighted in green and indicated with a green arrow. (C) Channelwise automatically detected seizure onsets for all seizures in this subject. (D) Regionwise automatically detected seizure onsets according to the Lausanne-120 atlas for all seizures in this subject. (E) Regionwise consensus onset determined using regions involved in at least 50% of seizures. (F) Consensus (i.e., present in ≥50% of seizure onsets) across automatically labeled onsets (ALO) mapped onto cortex with onset highlighted in orange and recorded (nononset) regions highlighted in gray. Resected regions are outlined in black. Onset/resected regions that can be seen in both views are marked with an asterisk. (G) Same as panel F but reporting the clinically labeled onset (CLO) instead. EEG, electroencephalogram.
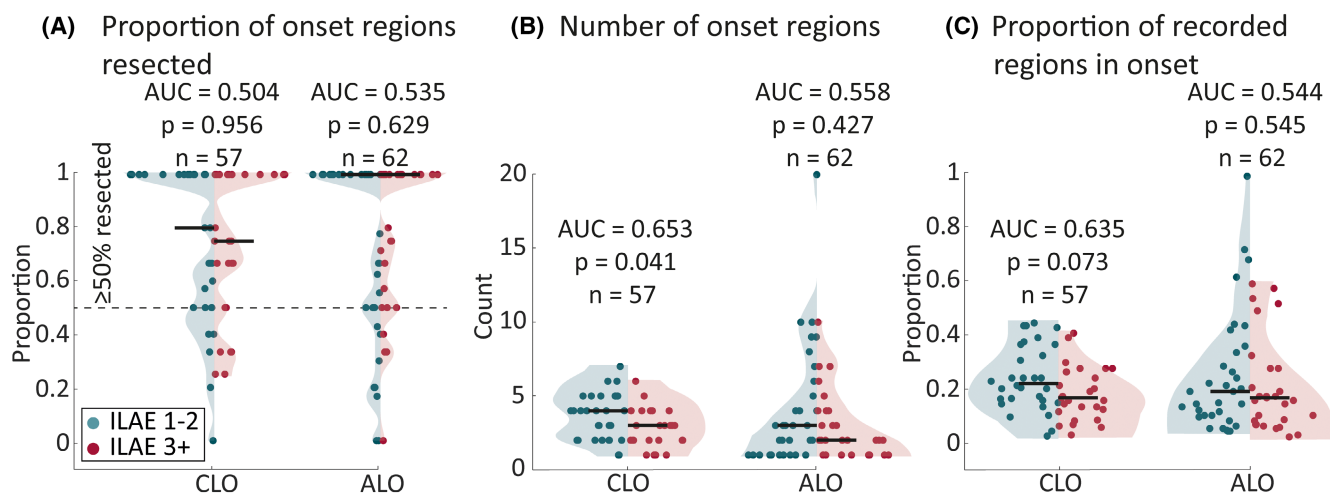

FIGURE 2 Comparing proportion of onset resected and counts of onset and resected regions across International League Against Epilepsy (ILAE) outcome groups. "Favorable" (ILAE 1–2) and "unfavorable" (ILAE 3+) surgical outcomes are displayed in green and pink, respectively. (A) Proportions of clinically labeled (CLO) and automatically labeled (ALO) onset regions resected across outcome groups are displayed on the left and right, respectively. (B) Counts of Lausanne-120 regions in CLO and ALO across outcome groups are displayed on the left and right, respectively. (C) Proportions of implanted Lausanne-120 regions that were included in CLO and ALO across outcome groups are displayed on the left and right, respectively. AUC, area under the receiver operating characteristic curve.

association between having a complete resection of onset and surgical outcome for CLOs ($\chi^2[1, 57] = .03$, $p = .87$) or ALOs ($\chi^2[1, 62] = .00$, $p = .99$). We found no difference in the proportion of onset regions resected across outcome groups for both CLOs and ALOs (both AUC < .7, $p > .05$; Figure 2A).

We further assessed whether additional clinical factors were driving our results. The proportion of onset regions (CLO or ALO) resected did not differ substantially or significantly by seizure types experienced in the 12 months prior to surgery or presence of MRI lesions (see Suppl. S4.2).

3.2 | Larger onsets are not associated with surgical outcomes

We used the number of labelled onset regions as a proxy for seizure onset size as the regions in the Lausanne-120 parcellation scheme are approximately equally sized. For CLOs and ALOs, the median onset size was three regions (median onset size: four ILAE 1–2, three ILAE 3+) and two regions (median onset size: three ILAE 1–2, two ILAE 3+), respectively. The size of the SOZ was comparable between outcome groups using both methods (Figure 2B); the AUC for distinguishing outcome groups was < .7 (CLOs: $p = .041$, ALOs: $p > .05$).

In our data, there were only three clear cases of multifocal onsets; two had postsurgical seizure freedom, and one did not. When considering unifocal onsets only, we also found that onset size could not distinguish outcome groups (AUC < .7, $p > .05$; see Suppl. S4.5).

We also tested whether diffuse onsets were more frequently associated with worse seizure outcomes. We used the proportion of implanted regions in onset as a proxy for diffusivity and found that there were few patients with a consistently diffuse onset across seizures in ALOs or CLOs (see Figure 2C).

We did not find any association with postsurgical seizure outcomes (AUC < .7, p > .05).

4 | DISCUSSION

We observed that more complete resection of the icEEG SOZ, both clinically labeled and automatically detected, was not associated with better surgical outcomes, supporting the conclusion that surgical failure is not necessarily a result of incomplete resection of the SOZ as defined by icEEG. This is in line with the idea that postsurgical seizure freedom/relapse may be driven by network mechanisms beyond the seizure onset regions.[17] Here, we have included analyses using both clinically and automatically labeled SOZs to demonstrate the robustness of our results. Agreement was found between the two approaches, but a direct comparison of the approaches in terms of patient- and seizure-specific localization is reserved for future work.

The sampled subjects are those who required an intracranial investigation and subsequently proceeded to surgery. This is a highly heterogeneous cohort that does not represent the general epilepsy population. Our results are perhaps more specific to a difficult-to-treat adult cohort, given that these subjects required intracranial monitoring. Future work could incorporate data including both adult and pediatric cases. Potential mediating factors, for example, age and surgery/recording sites, should be investigated alongside icEEG-based seizure onset markers. We are, however, encouraged by findings similar to ours in a pediatric cohort.[7]

Outcome classification should not be seen as a static label; the definition of a "good" outcome could mean no abnormal activity at all (i.e., ILAE 1) or the absence of disabling seizures (i.e., ILAE 1–2). Future work must determine the appropriate definition of a good outcome with respect to the research aims. Additionally, continuation of antiseizure medications was not considered here; therefore, results should be repeated in a larger cohort where subjects can be further separated based on drug load following surgery.

Future work could also incorporate noninvasive techniques with whole-cortex coverage to capture potential abnormalities outside the recorded regions.[18,19] Even with the tailored approach of using SEEG or ECoG depending on the patient, intracranial recordings have limited spatial coverage, and therefore the seizure generators may not have been sampled. We conclude that a multimodal approach may offer more information about the mechanisms behind postsurgical seizure recurrence in epilepsy surgery.

An implication of our study for future research is that the identification of SOZ, particularly from icEEG, may need to be decoupled from the identification of epileptogenic regions. More specifically, stricter criteria should be applied when labeling regions "epileptogenic," as additional factors (e.g., imaging lesions) and their context within the wider network should be considered, as is the case in clinical practice.

This work demonstrates that seizure onset, both clinically labeled and automatically detected, tends to be resected. However, contrary to expectations, we did not find any evidence that resecting a larger proportion of the onset is associated with better surgical outcomes. This means that, in validating markers of epileptogenic brain regions, resection of the onset alone may not be a suitable ground truth.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

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