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# Using pre-surgical suspicion to guide insula implantation strategy

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ABSTRACT

*Rationale:* Insular epilepsy can be a challenging diagnosis due to overlapping semiology and scalp EEG findings with frontal, temporal, and parietal lobe epilepsies. Stereotactic electroencephalography (sEEG) provides an opportunity to better localize seizure onset. The possibility of improved localization is balanced by implantation risk in this vascularly rich anatomic region. We review both safety and pre-implantation factors involved in insular electrode placement across four years at an academic medical center.

*Methods:* Presurgical data, operative reports, and invasive EEG summaries were retrospectively reviewed for patients undergoing invasive epilepsy monitoring on the insula from 2016 through 2019. EEG reports were reviewed to record the presence of insula ictal and interictal involvement. We recorded which presurgical findings suggested insular involvement (insula lesion on MRI, insula changes on PET/SPECT/scalp EEG, characteristic semiology, or history of failed anterior temporal lobectomy). The likelihood of pre-sEEG insular onset was categorized as low suspicion if no presurgical findings were present ("rule out"), moderate suspicion if one finding was present, and high suspicion if two or more findings were present.

*Results:* 76 patients received 189 insular electrodes as part of their implantation strategy for 79 surgical cases. Seven patients (8.9%) had insular ictal onset. One clinically significant complication (left hemiparesis) occurred in a patient with moderate suspicion for insular onset. There were 38 low suspicion cases, 36 moderate suspicion cases, and 5 high suspicion cases for pre-sEEG insula ictal onset. Two low suspicion (5.3%), three moderate suspicion (8.6%), and two high suspicion (40%) cases had insular ictal onset.

*Conclusions:* The insula can safely receive sEEG. Having two or more presurgical factors indicating insular onset is a strong, albeit incomplete, predictor of insular seizure onset. Using pre-implantation clinical findings can offer clinicians predictive value for targeting the insula during invasive EEG monitoring.

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## 1. Introduction

Insular epilepsy can be challenging to localize. Two common pre-surgical diagnostic points, ictal semiology and scalp electrophysiology, often have overlapping features with other anatomic localizations [1]. A large variety of ictal electrophysiologic patterns occur due to the insula's interconnection with the frontal, temporal, and parietal lobes [2]. While some semiologies such as laryngeal constriction, hemi-body paresthesia, pronounced nausea/vomiting, and other autonomic disturbances more specifically implicate the insula [3], insular epilepsy can manifest with semiology classically associated with temporal or frontal lobe epilepsy [4]. This has led to a consideration of insular epilepsy as a "great mimicker." [4].

For patients with drug resistant epilepsy (DRE), intracranial electroencephalography can be utilized to better localize the seizure onset zone and inform subsequent therapy. When a deeper structure such as the insula is considered, stereotactic electroencephalography (sEEG) better localizes seizure onset compared to subdural electrode implantation on the cortical surface [5]. Still, the insula sEEG surgical approach remains challenging. The Sylvian fissure hides the insula, so the most direct access still requires traversing either the frontal or temporal lobe [6]. Furthermore, the anatomical proximity of the middle cerebral artery and its branches within the sylvian fissure carry the potential for significant hemorrhagic concerns when placing depth electrodes [7–9].

As insular epilepsy mimics common epilepsy localizations, it may be overlooked when hypothesizing targets for sEEG monitoring. For this reason, insula investigation has been suggested to be "neglected" in planning for sEEG [10]. Building on this, Alomar et al. suggested insula localization needs to be considered with temporal or frontal lobe-like epilepsy with somatosensory symptoms or parietal lobe-like epilepsy with perioral parasthesias [7]. On the other hand, common "mimicking" semiologies may result in patients having varied clinical suspicion causing difficulty in discerning which patients should receive insular investigation. Given the challenging surgical approach, balancing pre-surgical evidence versus surgical risk for insular investigation remains difficult.

In patients with characteristic semiology and clinical data, insula monitoring in DRE offers an opportunity to correctly localize seizure onset for patients to improve outcomes. This retrospective study examines safety data, rate of insula localization, and pre-implantation hypotheses for insula targeted sEEG at the University of Kansas Comprehensive Epilepsy Center from 2016 to 2019. Our study utilizes previously reported sEEG data [9] focusing specifically on patients whose sEEG included insular electrodes.

## 2. Methods

### 2.1. Data collection and assessment of insula suspicion

This retrospective study was approved by the Institutional Review Board at the University of Kansas Medical Center. The neurosurgery operative reports and invasive monitoring reports were retrospectively reviewed for all adult patients undergoing sEEG from January 2016 to December 2019. Patients who received electrodes targeted to the insula were identified based on anatomically labeled electrode trajectories which were subsequently verified by visual inspection of neuroimaging. Patients selected to receive insular sampling were chosen during epilepsy surgery conference by presurgical characteristics described below as well as consideration of the 2018 Chassoux et al. paper suggesting insula investigation, particularly in temporal lobe epilepsies [11]. Only patients with at least one insular electrode were included in the present analysis.

Medical records from the presurgical, perioperative, and post-operative periods were further examined to assess for surgical complication. It is worth noting that standard clinical practice at our site includes radiologic data being reviewed and interpreted independently by the treating epileptologist and at epilepsy surgery conference in addition to the radiologist report in guiding patient care. Documentation from the most recent outpatient follow up to date (2022) was used to determine subsequent surgical intervention and present Engel Surgical Outcome Score [12]. Following initial collection, these data were reviewed and independently verified by the patient's respective epileptologist.

Further chart review was performed to record seizure onset zone, abnormal sEEG interictal activity, and first and second sites of sEEG seizure spread. This data was obtained from the final sEEG report from each patient's respective intracranial video EEG. In this final report, the epileptologist had assigned insula involvement as seizure onset, first spread, second spread, interictal spiking, or no

**Table 1**
Criteria used to assign insula suspicion groups.

| Diagnostic History | Positive Finding Criteria |
|---|---|
| MRI | Structural abnormality |
| PET | Hypometabolism |
| SPECT | Ictal Hyper-perfusion |
| Scalp EEG | Ictal or interictal findings suggesting insula involvement (i.e., "atypical" temporal findings like immediate co-existing parasagittal chain involvement, non F7/F8, T7/T8, or FT9/FT10 interictal epileptiform discharge localizations) |
| **Clinical History** | |
| Characteristic Semiology | Autonomic features, throat sensations, etc. |
| Prior Failed Anterior Temporal Lobectomy (ATL) | Continued seizures following ATL |

Criteria for suspicion groups were categorized as either diagnostic (imaging, or other procedure) vs. clinical. Each criterion was given equal weight for ascribing pre-implantation suspicion. (MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography).

involvement.

Following epileptologist verification of surgical, sEEG, and outcome data, the same epileptologist indicated which pre-implantation findings suggested insula involvement. We predefined three suspicion groups; low suspicion had no factors, medium suspicion with one factor, and high suspicion with two or more positive criteria. The low suspicion group included both MRI-negative (non-lesional) and extra-insular lesional patients. Pre-implantation findings considered are included in Table 1 below.

### 2.2. Statistical analysis

Descriptive statistics were used to analyze data for patient demographics, electrode trajectories, and non-insula seizure onset. We then employed the use of a Chi-Square Test as follows. First, we compared insular seizure onset in high suspicion patients against the combination of moderate and low suspicion patients. Next, we compared insula onset in moderate vs. low suspicion patients, in addition to insular onset and first spread in moderate vs. low suspicion. Lastly, rates of positive semiology vs. all other features were compared among patients with insula onset. As reported below, three patients were implanted in the insula twice during our study period. Because this represents a low amount of our total patients and they did not demonstrate significant findings or alterations to our study data and inclusion or exclusion of these three patients did not change the statistically significant results, we completed our Chi-Square calculations as if each admission were a unique encounter. Power analysis was performed using G*Power 3 [13].

## 3. Results

### 3.1. Overview and demographics

Of the 131 patients receiving sEEG from 2016 to 2019 previously described in Miller et al., 76 (58.0%) patients received insula electrodes across 79 hospital admissions. Demographic data for these 79 admissions are summarized in Table 2 below.

### 3.2. Insula electrode procedural details and complication rate

Of the 1603 sEEG electrodes reported by Miller et al., 189 electrodes were implanted to target the insula. Remaining electrodes were distributed between the frontal, temporal, and parietal lobes based on consideration for an insular epilepsy localization as suggested by Chassoux et al. In the 79 epilepsy monitoring admissions targeting the insula, the average patient received 2.39 insula electrodes per investigation. The implantation trajectory varied based on patient factors and surgeon/epileptologist preference. One hundred seven electrodes were implanted from a superior (oblique) trajectory, 79 from a lateral (orthogonal) trajectory, and 3 from a posterior (*trans*-parietal) trajectory (Fig. 1).

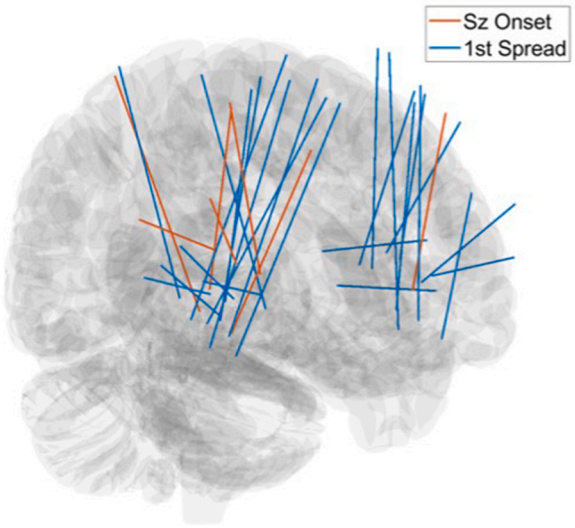
One clinically significant complication occurred. A right posterior insular electrode placed from a superior trajectory resulted in an intraparenchymal hemorrhage resulting in permanent hemiparesis. The resulting complication rate per electrode was 0.53%.

Additionally, one patient accidently removed two insular electrodes during monitoring. No harm occurred to this patient.

**Table 2**
Demographic characteristics.

| Gender | n | % of Total Admissions |
|---|---|---|
| Male | 37 | 46.8 |
| Female | 42 | 53.2 |
| **Age at Time of Surgery (Years)** | | |
| Mean = 37.9 | | |
| 20–32 | 28 | 35.4 |
| 32–44 | 29 | 36.7 |
| 44–56 | 17 | 21.5 |
| 56+ | 5 | 6.3 |
| **Patient Race** | | |
| White/Caucasian | 64 | 81.0 |
| Black or African American | 4 | 5.1 |
| American Indian or Alaskan Native | 1 | 1.3 |
| Asian | 0 | 0 |
| Native Hawaiian or Pacific Islander | 1 | 1.3 |
| Other or Not Reported | 9 | 11.4 |
| **Patient Ethnicity** | | |
| Hispanic, Latino, or Spanish Origin | 2 | 2.5 |
| Not Hispanic, Latino, or Spanish Origin | 75 | 94.9 |
| Other or Not Reported | 2 | 2.5 |

Overview of the patient demographics demonstrate relatively even male to female ratio. No children received insular electrodes during our study period.

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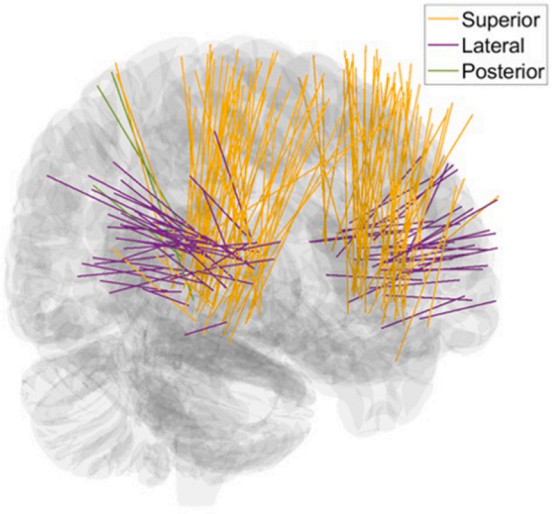


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**Fig. 1.** (a–b) Map of Insula Implantation Trajectories. The implantation trajectories for all sEEG electrodes targeting the insula in our patient set is shown (a). The seven electrodes (six right, one left) with insula seizure onset are shown in orange while the 25 sites of first seizure spread are in blue (b). All other trajectories, including superior, lateral, and posterior surgical approaches, are shown on the right. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

### *3.3. Rate of insula onset and insula spread*

Seven of 79 cases (8.9%) had insula sEEG seizure onset. Three of these cases demonstrated onset in the anterior insula, three in the posterior, and one showed both anterior and posterior onset. Most (5/7) of insular onset cases also had insula interictal spikes.

Of the remaining 72 non-insular onset cases, 44 (61.1%) indicated insular spread – 25 (34.7%) with first spread and 19 (26.4.9%) with secondary spread. Twenty-eight (38.9%) had no insular ictal involvement. Finally, 16 (22.2%) had interictal insular activity (Fig. 2).

Three patients were insula "re-implantation," meaning they had received insular electrodes in a previous sEEG admission occurring during the study period. None of these three repeat admissions demonstrated insula onset, but two demonstrated ictal spread (1 first-spread and 1 second-spread).

The temporal lobe (N = 49) was the most common ictal onset when the insula was not seizure onset (Fig. 3). One patient had simultaneous insular and temporal lobe onset. In 19 (38.8%) temporal onset cases, the insula was defined as the site of first ictal spread.

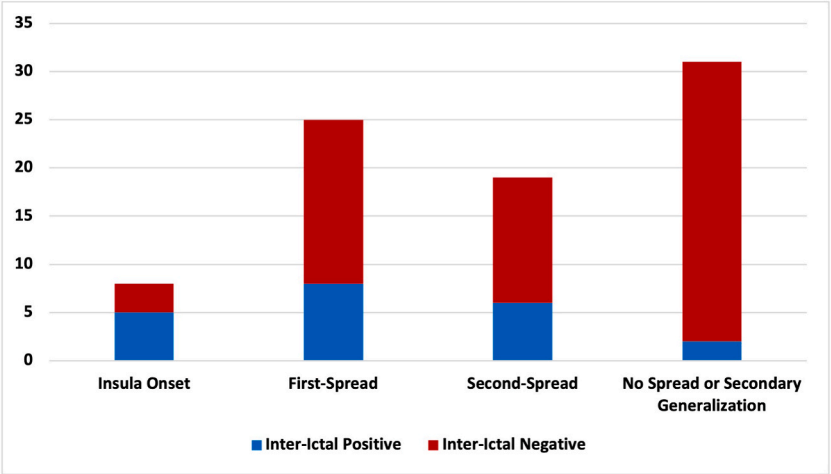


**Fig. 2.** Insula interictal activity stratified by ictal insula involvement. Even without insula onset, insula electrodes commonly demonstrated involvement in the epileptic network via ictal spread or interictal spiking.

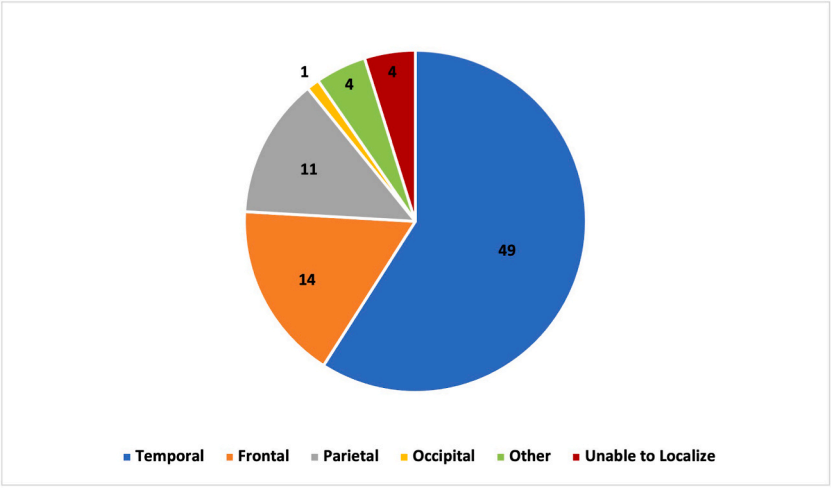


**Fig. 3.** Seizure Onset for Non-Insular Epilepsy Patients. Identified seizure onset in cases of non-insula onset. Seizures were most frequent from the temporal lobe. Some patients demonstrated multiple seizure types, resulting in 83 cases represented in this graph.

### *3.4. Preimplantation findings*

There were 38 patients in the low suspicion (rule-out) group (7 non-insula lesional and 31 MRI-negative for any lesion). Among extra-insular lesional patients, the MRI findings included hippocampal sclerosis (3), malformation of cortical development (2),

**Table 3**
Patient count with specified positive criteria.

| Clinical Suspicion Group | Moderate (one pre-implantation finding) | High (≥ two positive pre-implantation) |
|---|---|---|
| Total Number of Patients | 36 | 5 |
| **Occurrences of Insula Pre-Implantation Findings** | | |
| Characteristic Semiology | 14 | 3 |
| MRI Positive | 11 | 3 |
| PET Positive | 5 | 2 |
| SPECT Positive | 1 | 1 |
| Prior Scalp EEG | 0 | 1 |
| Prior Failed ATL | 5 | 1 |

36 patients comprised the moderate suspicion group, with characteristic semiology being the most common cause of inclusion in this group. Likewise, semiology, along with MRI lesions, were common causes of high suspicion.

sphenoid wing encephalocele (1), and parietal pilocytic astrocytoma status-post resection (1). Table 3 delineates findings for the moderate and high suspicion groups.

The rates of insular onset and electrographic spread were tabulated for each of the three pre-implantation suspicion groups (Fig. 4). For the high clinical suspicion patients, 40% (2/5) had sEEG insular onset. In the moderate clinical suspicion group, 8.3% (3/36) patients demonstrated insular onset. Lastly, for the low suspicion patients, 5.3% (2/38) had sEEG-confirmed insular seizure onset. Patients with ≥2 pre-implantation findings were more likely to have insular onset, $X^2$ (1, N = 79) = 6.40, p < 0.02.

Comparison of the low and moderate suspicion categories yielded no difference in insular onset, $X^2$ (1, N = 74) = 0.28, p = 0.60. For the observed difference between moderate and low suspicion categories (8.3% vs 5.3%, respectively) approximately 3000 patients would be needed to identify a statistically significant difference with a power of 0.8. However, the moderate suspicion group did have more patients that were either insular onset or site of first spread (N = 20; 55.6%) compared to the low suspicion group (N = 9; 23.7%), $X^2$ (1, N = 74) = 7.88, p < 0.01. Thus, pre-implantation high clinical suspicion significantly improved prediction of insular onset seizures while moderate clinical suspicion identified patients more likely to have early insular ictal involvement.

Notably, semiology had the highest rate of predicting insular seizure onset (4/17–23.5%). In these four patients, two exhibited autonomic features in addition to dysarthria while the other two patients had painful seizures. In comparison, only three (12.5%) of the other 24 patients with clinical suspicion based on non-semiology findings were observed to have insular onset seizures. Still, this difference did not reach statistical significance, $X^2$ (1, N = 41) = 0.86, p = 0.36, for this sized patient population. Positive finding criteria for five insular onset patients in the moderate and high suspicion groups are detailed in Table 4.

### 3.5. Intervention and Engel scores

Sixty-eight patients of the entire cohort (91%) proceeded with surgical intervention. For patients with sEEG insular seizure onset, four of seven (57.1%) received surgical intervention targeting the insula. In the two cases of insular resection, pathology demonstrated non-specific findings of corpora amylacae and moderate hypercellularity. Additionally, two patients who did not demonstrate insular ictal onset on sEEG still received intervention on the insula as part of their treatment. These respective procedures are summarized in Table 5. Importantly, two patients with insular onset eventually received frontal lobe intervention due to demonstrated contribution to seizure onset from frontal electrodes and results of further sessions of invasive monitoring occurring outside of our study period.

## 4. Discussion

### 4.1. Utility of clinical suspicion estimates for implantation decision-making

In this study, we sought to identify if specific pre-surgical findings or some combination better predicted insular sEEG onset. We found no independent single factor significantly predicted insular onset. However, having ≥2 pre-surgical findings (our high suspicion group) was predictive of insula onset, while one finding predicted involvement via onset or first spread. These findings may provide guidance in deciding which patients warrant insula investigation. A primary goal of our "pre-implantation suspicion" subgroups was to minimize subsequent insular implantation and risk of unnecessary complications while maximizing accurate identification of insular seizure onset zones. Previous authors concluded that insula suspicion warrants sEEG monitoring with suggestive semiology, such as hypermotor seizures [3,14,15], an assertion with which our data is consistent. Similarly, the insula warrants investigation when clinical data suggests a temporal "plus" picture [1].

Applying these principles, our clinically stratified cohorts expectedly demonstrate utility of insula sEEG targets when pre-implantation suspicions are present. Our high suspicion group yielded an insular onset rate of 40%. Even when positive for one

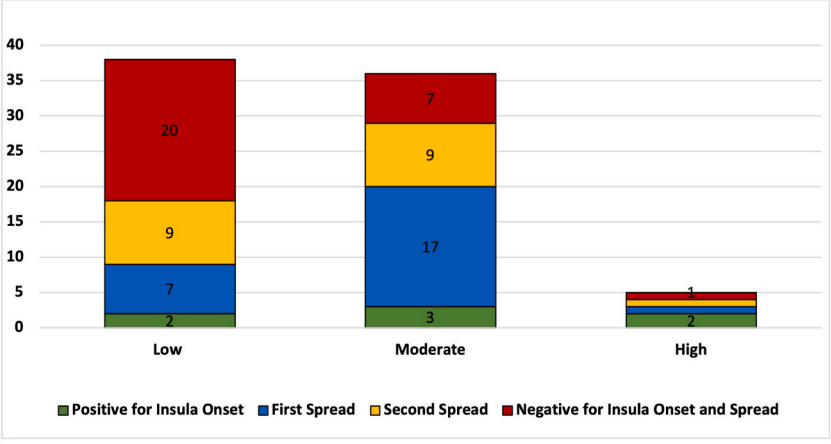


**Fig. 4.** Insula Ictal Involvement by Pre-Implantation Category. Insula onset rate increased with each step up in clinical suspicion. Note, of the high-risk group, one patient each had First Spread, Second Spread, and Negative involvement.

**Table 4**
Positive criteria found for insular seizure onset patients.

| Pre-Implant Suspicion | Semiology+ | MRI+ | SPECT+ | Scalp EEG+ | Prior ATL+ |
|---|---|---|---|---|---|
| **Mod 1** | X | | | | |
| **Mod 2** | X | | | | |
| **Mod 3** | | X | | | |
| **High 1** | X | | X | X | |
| **High 2** | X | | | | X |

Insula semiology was the most common finding among patients with insular onset. PET not included in table because no patient demonstrated positive findings. The two low suspicion patients are not listed since they did not have any specified features.

**Table 5**
Interventions targeting the insula in study population.

| Procedure & Laterality | Insula Involvement | Insula Interictal Spiking (Yes/No) | Engel Score & Time of Follow-Up (months) | Hemisphere of Language Dominance |
|---|---|---|---|---|
| RFA, Right | Ictal Onset | Yes | IIIA, 8.6 | Left |
| RFA, Bilateral | Ictal Onset | Yes | IVA, 32.1 | Left |
| RFA + Resection, Right | Ictal Onset | Yes | IIB, 6.5 | Left |
| Resection, Right | Ictal Onset | Yes | IIIA, 48.4 | Left |
| RFA, Left | First Spread | Yes | ID, 36.1 | Right |
| RNS, Left | Second Spread | No | IVC, 35.3 | Left |

Six procedures with intervention on the insula occurred in our study population. Results were not unexpectedly suboptimal as no total resections occurred in the cohort. (RFA = Radiofrequency ablation).

pre-implantation finding (imaging, semiology, or previous failed ATL), the insula was site of first spread nearly half of the time, demonstrating significant ictal involvement and the need to differentiate ictal onset and ictal spread. We conclude positive findings on clinical history and a variety of diagnostic techniques (scalp EEG, MRI, PET, SPECT) may serve as an indication for inclusion of insular interrogation. This is consistent with others' suggestions for a low threshold for insular exploration [7,15,16]. The rate of positive insular onset or spread appears to outweigh concern for surgical complication in these populations.

Still, should the insula be considered a candidate for sEEG exploration when there is no pre-implantation evidence of insular onset? Our population of "low suspicion" (i.e., rule out) still found significant insular involvement in 23.7% (onset in 5.2% and spread in 18.4%), rates that make this question less straightforward to answer than one hopes. Most involvement, though, stemmed from insular spread following temporal lobe onset (6 out of 7 instances of first spread in this group). Taken as a whole, our data suggest that implanting the insula for "rule out" cases should not be standard. Still, understandable clinician concern for missing insular onset that is well articulated in the literature [1,10,17] will appropriately put insula onset on the differential for many MRI negative cases. In other words, there will always be a tension in sEEG planning between concern for undersampling vs oversampling. Thus at the very least, we suggest caution in implanting "rule out" cases, although again, those investigations are not fruitless.

### *4.2. Comparison to internal and external safety data*

In the present study, we compare safety data described by Miller et al. to our isolated insula cohort. They found a hemorrhagic complication rate for all electrodes of 0.13% [9]. This represents an absolute risk increase of 0.40%, given our finding of a 0.53% hemorrhagic complication rate when isolating insula electrodes. With only one occurrence and a small number of insula electrodes in relation to overall electrode trajectories, it is challenging to precisely determine the risk. A power analysis assuming a doubling of risk from 0.13% to 0.26% and our case population with 18% of electrodes in insula reveals approximately 50,000 electrodes would be needed for a statistical power of 0.8. Therefore, it is not possible to determine statistically significant differences in risk of insular implantation with ours or most other single site datasets.

Despite the small sample size for comparison to internal data, our study can add to existing literature. Other institutions have concluded insula trajectories carry no increased rate of intracranial bleeding, although similar limitations of study power exist [7,14,18]. One meta-analysis concluded sEEG contains an overall hemorrhagic risk of 1.0%, with a 0.4% rate of "catastrophic intracranial hemorrhage" requiring surgical evacuation [19]. Our rate of insular hemorrhage appears to be comparable to that expected of sEEG procedures in general. Given the vascular anatomy and concealed location of the insula, it is likely implantation is more technically challenging and there is a small level of increased risk with insular implantation, but the data suggest the absolute increased risk is relatively small with appropriate surgical planning and expertise.

### *4.3. Diagnostic yield of seizure onset and irritative zones*

In this retrospective series of insula sEEG patients, the rate of identified ictal onset (8.9%) was similar to that found in the existing literature [7]. In our insula sEEG cohort, seizure onset in the temporal lobe remains the most identified localization. This is in

accordance with the temporal lobe being the most common epilepsy localization [20].

A sizable portion of our cohort still demonstrated interictal insular spiking despite an absence of insular ictal onset. Interictal activity may help define the epileptogenic network through characterization of the irritative zone [21]. With this in mind, we speculate the 16 patients with interictal activity still received diagnostic benefit by further description of the irritative zone. As some centers are understandably reluctant to resect the insula, particularly the dominant insula, better understanding the irritative zone in addition to the seizure onset zone may allow for consideration of other treatment strategies like RFA or regional RNS. That said, not considering resection plainly results in suboptimal surgical outcomes as reported previously [22].

### *4.4. Limitations*

Our study is limited by retrospective data collection. A second limitation was lack of time based definition of first and second electrographic spread as we instead relied on EEG reports for this data. As a result, precise replication of our insula ictal spread rates will be challenging. Similarly, we relied on sEEG final reports rather than the raw EEG data for the collection of our data. Future studies could employ a blinded review of the EEG recordings to remove any unintentional bias and improve standardization in assessing insula onset and interictal spiking.

### *4.5. Conclusions*

Insular epilepsy remains a challenging diagnostic endeavor. No single pre-implantation factor was observed to signal insula seizure onset, although semiology may be a factor worth further consideration in larger cohorts. Our study demonstrates that $\geq$2 pre-implantation positive findings does significantly raise the likelihood of an insular seizure onset while one pre-implantation factor strongly implies at least some insula involvement in the seizure. Using these pre-implantation factors to guide insula implantation decisions and strategies can help maximize sEEG diagnostic efficiency while minimizing neurosurgical risk.

## Ethics statement

This study was approved by the University of Kansas Medical Center Institutional Review Board STUDY00145156: "Human Neurophysiological Data Retrospective" in compliance with U.S. federal regulations for the ethical principles of respect, beneficence and justice set forth in *The Belmont Report*. As this study was retrospective after all treatments had been performed, deemed to be no more than minimal risk, and not practicable to contact all patients following hospital discharge, the requirement of separate written informed consent for this study was waived by the Institutional Review Board.

## Author contribution statement

Nathaniel Cameron: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Lane Fry, Christopher Miller: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Jean-Luc Kabangu, Bryan A. Schatmeyer: Contributed reagents, materials, analysis tools or data.

Carol M. Ulloa, Utku Uysal, Jennifer J. Cheng, Michael J. Kinsman: Analyzed and interpreted the data.

Adam G. Rouse, Patrick Landazuri: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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## Data availability statement

Data included in article/supp. material/referenced in article.

## Declaration of competing interest

The authors declare that no potential conflict of interest that could have appeared to influence the work reported in this paper.

## Acknowledgements

None.

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