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## FULL-LENGTH ORIGINAL RESEARCH

# Factors correlated with intracranial interictal epileptiform discharges in refractory epilepsy

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## Abstract

**Objective:** This study was undertaken to evaluate the influence that subject-specific factors have on intracranial interictal epileptiform discharge (IED) rates in persons with refractory epilepsy.

**Methods:** One hundred fifty subjects with intracranial electrodes performed multiple sessions of a free recall memory task; this standardized task controlled for subject attention levels. We utilized a dominance analysis to rank the importance of subject-specific factors based on their relative influence on IED rates. Linear mixed-effects models were employed to comprehensively examine factors with highly ranked importance.

**Results:** Antiseizure medication (ASM) status, time of testing, and seizure onset zone (SOZ) location were the highest-ranking factors in terms of their impact on IED rates. The average IED rate of electrodes in SOZs was 34% higher than the average IED rate of electrodes outside of SOZs (non-SOZ;  $p < .001$ ). However, non-SOZ electrodes had similar IED rates regardless of the subject's SOZ location ( $p = .99$ ). Subjects on older generation ( $p < .001$ ) and combined generation ( $p < .001$ ) ASM regimens had significantly lower IED rates relative to the group taking no ASMs; newer generation ASM regimens demonstrated a nonsignificant association with IED rates ( $p = .13$ ). Of the ASMs included in this study, the following ASMs were associated with significant reductions in IED rates: levetiracetam ( $p < .001$ ), carbamazepine ( $p < .001$ ), lacosamide ( $p = .03$ ), zonisamide ( $p = .01$ ), lamotrigine ( $p = .03$ ), phenytoin ( $p = .03$ ), and topiramate ( $p = .01$ ). We observed a nonsignificant association between time of testing and IED rates (morning–afternoon  $p = .15$ , morning–evening  $p = .85$ , afternoon–evening  $p = .26$ ).

**Significance:** The current study ranks the relative influence that subject-specific factors have on IED rates and highlights the importance of considering certain factors, such as SOZ location and ASM status, when analyzing IEDs for clinical or research purposes.

## KEYWORDS

clinical factors, demographics, epilepsy, interictal epileptiform discharges, intracranial monitoring

## 1 | INTRODUCTION

In addition to seizures, persons with epilepsy are burdened with interictal epileptiform discharges (IEDs); IEDs are transient electrographic periods where populations of pathologically connected neurons partake in hypersynchronous firing.<sup>1,2</sup> Although the specific mechanism connecting IEDs and seizure activity remains a matter of debate, IEDs have been shown to be associated with unfavorable clinical symptoms, such as increased seizure frequency and severity<sup>3–6</sup> and reduced quality of life.<sup>7–9</sup> Several recent studies also reported a correlation between increased IEDs and impaired cognition and memory.<sup>10–12</sup> However, many of these studies were limited by (1) the use of scalp electroencephalography (EEG), which is inferior to intracranial EEG for detecting and localizing IEDs, and (2) the low number of subjects performing standardized tasks.<sup>13</sup> The latter limitation is especially noteworthy, provided that IED rates may be dependent on cognitive activity. Thus, a particular strength of this current study was that all patients performed a standardized task, controlling for their attention levels.

These previous studies showed that IEDs were related to sleep patterns,<sup>14</sup> mood disorders,<sup>15</sup> hormone levels (e.g., menstrual cycle hormones<sup>16</sup> and cortisol<sup>17</sup>), age,<sup>18</sup> and time-dependent fluctuations,<sup>19,20</sup> but have mostly examined factors independently. Goncharova et al<sup>3</sup> also demonstrated a relationship between antiseizure medications (ASMs) and IEDs, where IED rates decreased with ASM tapering epochs, then increased after this tapering period in 79 subjects with scalp EEG. Jointly, these findings convey that specific factors influence IED rates, and expose the need to examine these factors in aggregate, to better understand how they relate to IEDs.

Our study's primary purpose was to determine whether specific characteristics were correlated with differences in intracranial IED rates in refractory epilepsy. We expanded on previous work by utilizing 150 subjects with intracranial stereo-EEG implants to rank the relative importance of subject-specific factors, in terms of their association with IED rates. We then performed a detailed analysis of the highest-ranking factors. Based on previous reports, we predicted that ASM status, age, seizure onset zone (SOZ) location, and time of testing would be the highest-ranking factors associated with IED rates. However, the relative rank of these factors remains unknown. We also hypothesized that intracranial IED rates would be higher in electrodes near the SOZ relative to areas outlying the SOZ (non-SOZ) and

## Key Points

- ASM status and SOZ location are important influencers of IED rates
- Irrespective of the SOZ location, intracranial electrodes in the SOZ had higher overall IED rates than electrodes outside of the SOZ
- Older generation and combined generation ASM regimens were associated with significant reductions in IED rates
- Carbamazepine, levetiracetam, lacosamide, zonisamide, lamotrigine, phenytoin, and topiramate significantly reduced IED rates
- Specific factors should be considered when analyzing IEDs for either clinical or research purposes

that IED rates would be higher in mesial structures relative to neocortical structures. Our final hypothesis was that specific ASMs, such as levetiracetam and lamotrigine, would have higher predicted IED rate reductions than other ASMs, as these ASMs were previously shown to reduce IEDs.<sup>21,22</sup> The results of this study are essential for understanding the influence that specific factors have on IED rates, which may otherwise confound clinical and research interpretations of intracranial IEDs.

## 2 | MATERIALS AND METHODS

## 2.1 | Participants

Data were collected as part of an ongoing research collaboration registered as “An Investigator-Initiated, Prospective, Multicenter, Controlled Feasibility Study of Direct Brain Recording and Stimulation for Memory Enhancement” (ClinicalTrials.gov identifier: NCT04286776). Informed consent was obtained from each subject, and the institutional review board approved the research protocol at each of the eight testing centers (protocol #: MEMES-001).

This data were analyzed from 150 persons with refractory epilepsy who underwent a surgical procedure to implant stereo-EEG contacts within the brain parenchyma. Electrodes were placed to best localize the SOZ. These



subjects each performed a uniform free recall memory task multiple times during their long-term stereo-EEG monitoring, resulting in a total of 399 unique experiment sessions with intracranial stereo-EEG recordings. The median number of sessions per subject was two (interquartile range = 1–3). We confirmed that IED rates were stable over time (i.e., in subsequent sessions for the same subject) by including session number as a predictor after controlling for ASM status and SOZ location in a hierarchical linear model ( $p = .65$ ).

The number of sessions with ASMs was limited because most subjects were taken off ASMs for intracranial monitoring, as seizures were desired to localize SOZs. Additionally, several subjects had missing ASM data and were excluded from the ASM analyses in this study. This resulted in 81 subjects on at least one ASM during the time of testing, contributing 165 unique testing sessions, and 28 subjects with a record of no ASM during the time of testing, contributing 67 unique testing sessions. Our study only included nonstimulation testing sessions collected before any brain stimulation was performed. All testing sessions were conducted at least 4 h after the most recent seizure activity, and sessions were excluded if a seizure occurred during that testing session. Data collection was performed after the patient was stable and transferred to the epilepsy monitoring unit, providing a minimum recovery period of at least 24 h postimplantation. Other subject demographic and clinical characteristics are reported in Table 1.

## 2.2 | Free recall memory task

Subjects performed a delayed free recall memory task with a bedside laptop. The task consisted of an encoding phase, delay phase, and retrieval phase (Figure 1A). During the encoding phase, subjects were asked to memorize 12 random nouns from a pool of English nouns (<http://memory.psych.upenn.edu/WordPools>). Words were sampled without replacement from the word pool and were presented for 1600 ms with blank interstimulus intervals of 800–1200 ms. We used data from tasks where the words were categorized (categorical free recall) and completely independent (free recall). The encoding phase was followed by a 20-s distractor phase, which consisted of arithmetic problems presented as  $X + Y + Z = ?$  where  $X$ ,  $Y$ , and  $Z$  were set to random single-digit integers. The subjects were then given 30 s to recall as many words as possible from the preceding list, in any order. Each subject performed up to 25 recall lists per session and completed multiple testing sessions over the course of several days.<sup>23</sup> Generally, the goal at each testing center enrolled in this multicenter trial was to collect as many unstimulated free recall sessions as possible.

**TABLE 1** Subject characteristics

	Overall, N = 150
Age, y	
Mean (SD)	37.1 (11.5)
Sex, n (%)	
Male	78 (52.0%)
Female	72 (48.0%)
Years of education	
Mean (SD)	13.7 (2.23)
Handedness, n (%)	
Ambidextrous	6 (4.0%)
Left	17 (11.3%)
Right	127 (84.7%)
Age at seizure onset, y	
Mean (SD)	17.0 (13.2)
History of prior resection, n (%)	
Yes	30 (20.0%)
No	120 (80.0%)
History of TBI, n (%)	
Yes	9 (6.0%)
No	141 (94.0%)
Number of implanted channels	
Mean (SD)	123 (40.4)
SOZ, n (%)	
Multifocal SOZ <sup>a</sup>	77 (51.3%)
Focal SOZ	73 (48.7%)
Normalized IED rate, IEDs/h <sup>b</sup>	
SOZ, mean (SD)	6.53 (17.47)
Non-SOZ, mean (SD)	.34 (.50)
Combined, mean (SD)	.60 (.72)

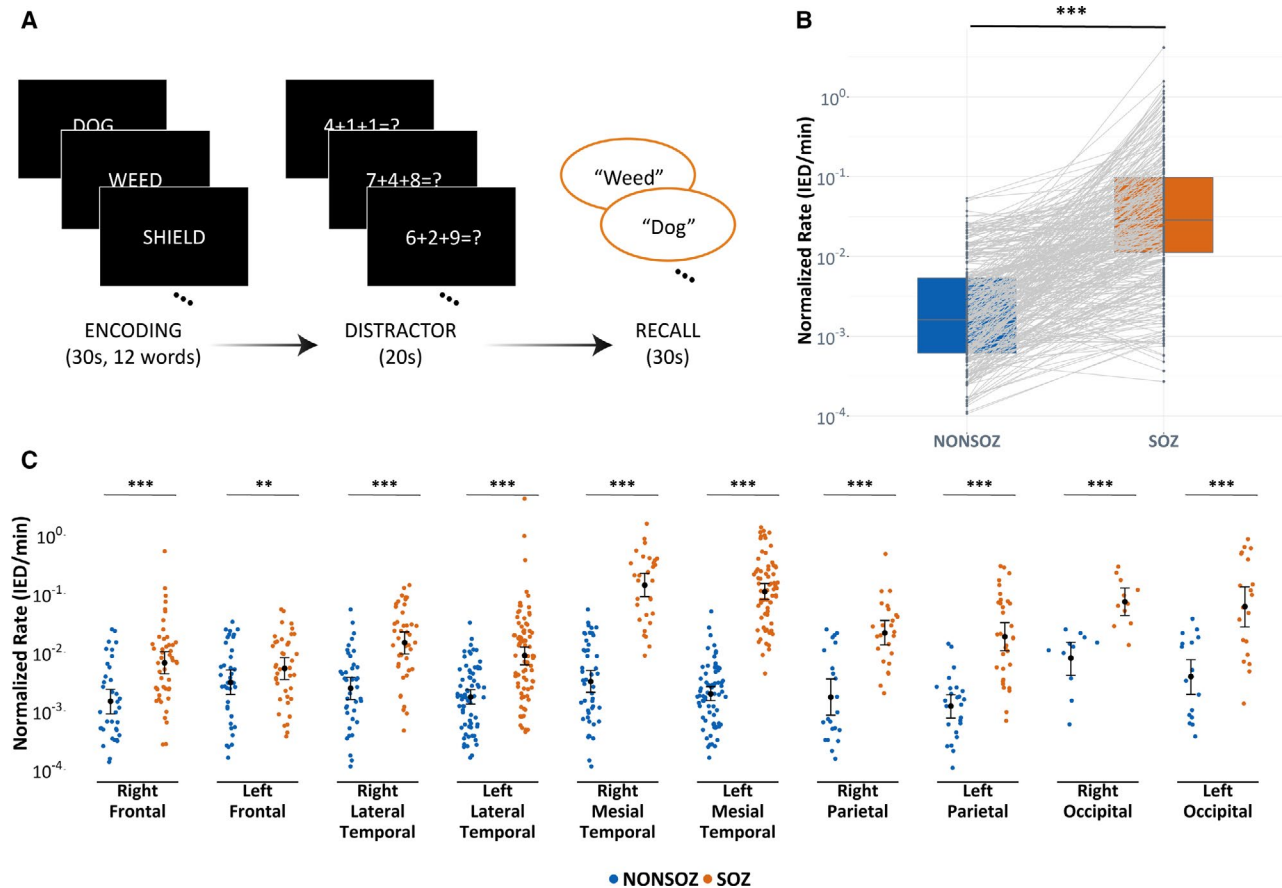
Abbreviations: IED, interictal epileptiform discharge; SOZ, seizure onset zone; TBI, traumatic brain injury.

<sup>a</sup>Multifocal SOZs were most commonly in neighboring brain regions (e.g., lateral temporal and mesial temporal regions).

<sup>b</sup>Normalized IED rates were calculated per session per contact by dividing initial IED rates by the total number of contacts in each region; thus, these normalized rates represent the average number of IEDs detected by each individual contact per hour. SOZ refers to average IED rates of contacts in the SOZ. "Non-SOZ" refers to average IED rates of contacts outside of the SOZ. "Combined" refers to global IED rates averaged across all contacts.

## 2.3 | Intracranial stereo-EEG recordings

Intracranial stereo-EEG data were recorded using depth electrodes (contacts spaced 2.2–10 mm apart) with recording systems at each testing site. For this study, we only included subjects with depth electrodes due to the low number of subjects with surface electrodes (i.e., grids or strips) in our dataset. These recording systems included Quantum LTM (Natus), Grass Telefactor, Nihon-Kohden, and custom



**FIGURE 1** Interictal epileptiform discharge (IED) rates are higher in seizure onset zones (SOZs). (A) For each trial of the free recall task, subjects were asked to encode 12 nouns, then performed an arithmetic distraction that was followed by the verbal recall phase. (B) Linear mixed-effects models revealed that IED rates were higher for contacts in the SOZ relative to contacts outside of the SOZ (non-SOZ;  $p < .001$ ). (C) IED rates were also shown to be higher in the SOZ relative to the non-SOZ, irrespective of the SOZ location ( $p < .01$ ); however, there was no difference in IED rates between the stratified non-SOZ regions ( $p = .99$ ). Bars represent 95% confidence intervals.  $**p < .01$ ,  $***p < .001$

Medtronic EEG systems. Electrode locations were determined by the clinical care team and were selected solely based on clinical monitoring needs. All signals were sampled at either 500, 1000, or 1600 Hz and were either bipolar referenced or referenced to a common contact placed intracranially, on the scalp, or on the mastoid process. Thus, we re-referenced all recordings to an averaged referential montage. Stereo-EEG recordings were also linearly detrended and notch-filtered at 60 Hz and its odd harmonics. The signal was then low-pass filtered with a Butterworth filter at 250 Hz, and high-pass filtered with a Butterworth filter at 1 Hz. Recordings were downsampled to 500 Hz; then, recording channels were excluded if the signal was greater than three standard deviations from the mean value across other recording channels.

## 2.4 | Anatomical localization

Intracranial electrodes were localized using computed tomography (CT) and magnetic resonance imaging (MRI)

coregistration provided with the RAM dataset. Hippocampal subfields and MTL cortices were automatically labeled in a preimplant, T2-weighted MRI using the automatic segmentation of hippocampal subfields multiatlas segmentation method.<sup>24</sup> Advanced Normalization tools were then used to coregister postimplant CT images with presurgical T1/T2 weighted scans.<sup>25</sup> The Desikan–Killany–Tourville atlas was utilized to obtain parcellated cortical areas in different lobes.<sup>26</sup> Two neuroradiologists then reviewed the final electrode position labels for all subjects.<sup>27</sup> Figure S1 depicts the spatial distribution of these localized electrodes on an average brain.

## 2.5 | Automated IED detection

We utilized an automated IED detector that was validated and performed comparably to multiple clinicians and other published IED detectors.<sup>28</sup> This template-matching IED detector cross-correlated a 60-ms triangular template with

preprocessed stereo-EEG, then normalized the cross-correlation by the median standard deviation from 1-s sliding windows.<sup>28</sup> The absolute value of the normalized cross-correlation was then filtered with a specified detection threshold, marking local peaks above that threshold as IEDs. Our detector collapsed temporally overlapping detections into a single marked event and conservatively excluded IEDs occurring within 3 s of another IED to handle bursts of spikes or high-frequency activity.<sup>29</sup> We tuned our IED template to minimize the number of artifactual IED detections while optimizing the number of true positive IED detections (Figure S2). Lastly, we rejected IEDs that occurred for less than 10 ms or more than 100 ms to eliminate artifactual detections missed by our template-matching detector. Although our detector may have overcounted IEDs, false positive IEDs were assumed to be evenly distributed, minimally biasing the true positive distribution.<sup>5</sup> Our final IED set consisted of 43 308 IEDs.

## 2.6 | IED rate calculation

IED rates were calculated by dividing the total number of IEDs that occurred during a subject testing session by the total duration of each session; this provided us with IEDs per minute. Montreal Neurological Institute coordinates for each contact were used to obtain brain locations for all implanted electrodes in the RAM dataset. The RAM dataset also contained SOZ labels for each subject, as determined by the clinical team at each of the eight testing centers. For our study, contact locations were refactored as frontal, lateral temporal, mesial temporal, parietal, or occipital. We then divided initial IED rates by the total number of contacts in each region to normalize subject IED rates. These normalized IED rates were also used to calculate average IED rates for regions inside (SOZ) and outside (non-SOZ) the subjects' SOZs. The averaging and normalization procedures were necessary to allow for the comparison of IED rates between different brain regions and subjects,<sup>30,31</sup> especially to account for differences in the stereo-EEG coverage between neocortical and mesial regions.

## 2.7 | Statistical methods

We first examined whether there was a difference in IED rates inside versus outside of the SOZ. We utilized linear mixed-effects models to determine statistical significance, as these models accounted for repeated subject observations and heterogeneity in the data between subjects (i.e., unequal electrode sampling between each anatomical region). The dependent variable for our model was log-transformed normalized IED rates, and the fixed effect was SOZ status (SOZ,

non-SOZ). Random slopes and intercepts were added for each subject. We next examined whether the location of the SOZ influenced whether there was a significant difference between IED rates inside versus outside of the SOZ. Similar linear mixed-effects models were employed after stratifying contacts based on hemisphere-specific SOZ locations (e.g., left frontal, right frontal).

After comparing the IED rates of electrodes located in SOZs versus outside of SOZs (non-SOZ), we examined whether there was a difference in IED rates between the different SOZ locations. That is, we averaged the normalized IED rates for electrodes located within stratified SOZs, then used a linear mixed-effects model to test whether there was an overall variation in IED rates between the different SOZs. Of note, we added an interaction term to account for whether a subject had focal or multifocal SOZs when appropriate in our models. This interaction term controlled for whether the observed effect was being driven by the presence of focal versus multifocal SOZs, and our mixed models accounted for the correlated, repeated measures produced by including subjects with multifocal SOZs in multiple groups. We performed Tukey honestly significant difference (HSD) test as a post hoc, pairwise comparison of all possible SOZ combinations.

Provided the in-depth coverage of stereo-EEG, we also evaluated whether IED rates were higher in mesial structures relative to neocortical structures and whether there was a difference in IED rates between common mesial structures. Common mesial structures classified in the RAM dataset include the hippocampus, amygdala, perirhinal cortex, entorhinal cortex, and parahippocampal gyrus. Similar to previous analyses, an analysis of variance was utilized to assess this overall difference.

The next part of our analysis was aimed at ranking clinical and demographic characteristics in terms of which factor had the strongest influence on global IED rates. We utilized a dominance analysis to establish the relative importance of a predictor by computing the contribution a factor makes, in terms of variance, to the outcome.<sup>32–34</sup> In other words, a factor is considered more important than another factor if it contributes a higher proportion to the outcome in models consisting of all possible combinations of predictors.<sup>35–37</sup> In evaluating all combinations of predictors, the dominance analysis also dealt with the issue of multicollinearity. We computed the general dominance by calculating the average variance explained by a predictor and compared this to the average variance explained by other predictors obtained in other submodels. General dominance weights were averaged over 1000 bootstrapped samples for each predictor to demonstrate the relative proportion of  $r^2$  attributable to a predictor. Here, larger  $r^2$  values correspond to higher relative importance for the predictor.<sup>33</sup> We refactored categorical variables for this analysis to prevent an overemphasis of factors with a large

number of values, as this would falsely inflate a category's relative importance; this also minimized the bias attributable to consuming varying degrees of freedom.

Following our dominance analysis, we evaluated the relationship between ASM status and IED rate, as this was the factor with the highest relative importance. We built linear mixed-effects models to examine the relationship between IED rates and ASM generation, in addition to specific, commonly prescribed ASMs in the RAM dataset. These models contained log-transformed normalized, global IED rates as the dependent variable, ASM generation or ASM name as categorical predictors, and random effects for each unique subject. Subjects on multiple ASMs were included in multiple ASM groups; however, our mixed-effects models accounted for these repeated measures. An interaction term was also added for whether the ASM was part of a monotherapy or polytherapy treatment regimen. Predicted IED rate changes were calculated by subtracting 1 from the exponentiated parameter estimates and converting the result to a percentage. Reference groups for these ASM models were subjects on no current ASM ( $n = 67$ ). We excluded the following ASMs with fewer than five subjects: gabapentin, divalproex sodium, perampanel, felbamate, rufinamide, primidone, and ASMs categorized as Other.

Lastly, we used linear mixed-effects models to examine the relationship between IED rates and time of testing. Testing times were discretized into the following time windows: morning (6 a.m.–12 p.m.), afternoon (12 p.m.–5 p.m.), and evening (5 p.m.–9 p.m.). This model contained log-transformed normalized, global IED rates as the dependent variable, time of testing as a categorical predictor, and random effects for each unique subject while controlling for ASM status and SOZ location.

The false discovery rate was controlled at .05 with the Benjamini–Hochberg procedure for all models.<sup>38</sup> Code for analyses in this study was written in R version 3.6.1 and Python version 3.6.7.

### 3 | RESULTS

#### 3.1 | Determining the association between SOZs and intracranial IED rates

There were significantly higher IED rates for electrodes in SOZ regions relative to non-SOZ regions (odds ratio [OR] = 1.34,  $p < .001$ ; Figure 1B). The model parameter estimates reflect the change in IED rates for each group relative to the reference group, reported here as ORs. After categorizing SOZs based on localized brain regions, we found that all hemisphere-specific SOZs, irrespective of the location, were associated with significantly higher IED rates compared to regions outside of the SOZ ( $p < .01$ ;

Figure 1C). We also found a significant overall difference in the average IED rates between different SOZ locations ( $p < .001$ ; Figure 2A). When stratified by the subject's SOZ location, there were no differences in the IED rates of electrodes in non-SOZ regions ( $p = .99$ ). In other words, IED rates in the SOZ were the only rates influenced by the location of the SOZ; IED rates in other brain areas were relatively constant, independent of the subject's SOZ location. Our pairwise comparison of these SOZ locations demonstrated that (1) mesial temporal regions had significantly higher IED rates than all other ipsilateral and contralateral neocortical areas, except the occipital lobes ( $p < .01$ ); (2) occipital lobes had higher IED rates than bilateral frontal lobes and ipsilateral lateral temporal lobes ( $p < .01$ ); and (3) parietal lobes had markedly higher IED rates than frontal lobes ( $p < .05$ ; Figure 2B). All pairwise comparisons from Tukey HSD test are depicted in Figure S3.

We also revealed that neocortical SOZs had an 89.81% reduced likelihood of IEDs per minute compared to mesial SOZs (OR = .1019,  $p < .001$ ; Figure 2C). An in-depth analysis of common mesial structures in the RAM dataset (hippocampus, amygdala, perirhinal cortex, entorhinal cortex, and parahippocampal gyrus) showed a nonsignificant difference in IED rates between mesial regions ( $p = .84$ ; Figure 2D). Thus, although SOZs in mesial structures had higher overall IED rates than neocortical SOZs, the specific mesial location of SOZs did not contribute to differences in IED rates.

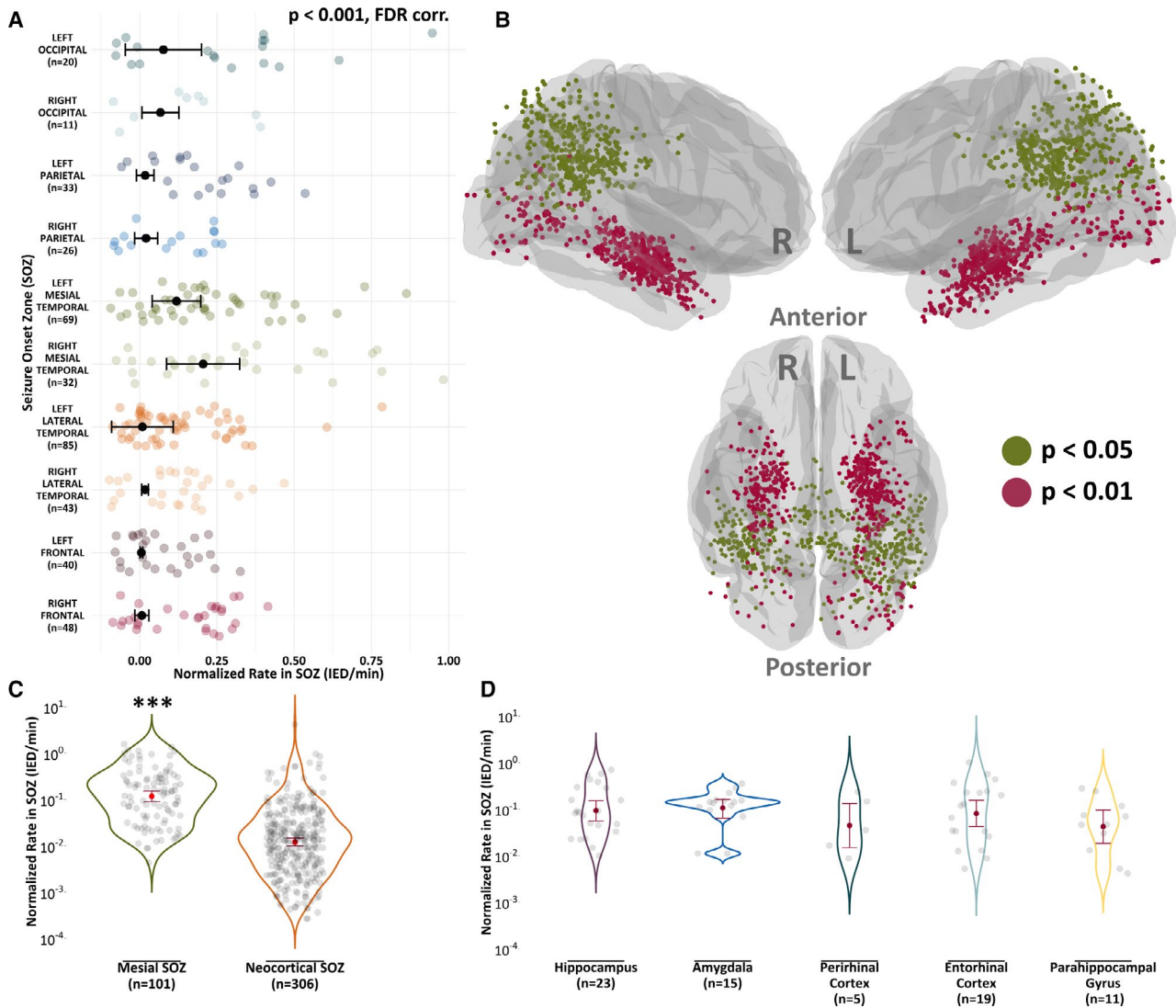
#### 3.2 | Ranking the relative influence that subject-specific factors have on IED rates

Our bootstrapped general dominance values revealed that ASM status had the highest value ( $r^2 = .49$ ) and generally dominated all other predictors (Figure 3). This demonstrated that ASM status had the highest relative importance for explaining differences in IED rates. Here, ASM status represented a binary classification of whether the subject was on any ASM or no ASM. The next highest value was time of testing ( $r^2 = .09$ ), followed by SOZ location ( $r^2 = .01$ ; Figure 3). All other predictors showed minimal relative influences on IED rates (Figure 3). Of note, SOZ location and SOZ hemisphere were dichotomized for the dominance analysis to control for the degrees of freedom consumed by each predictor.

#### 3.3 | Effect of ASMs on IED rates

We observed a significant reduction in IED rates for subjects on older generation (OR = .09,  $p < .001$ ) and combined generation ASM regimens (OR = .23,  $p < .001$ ; Figure 4A). However, there was a nonsignificant association between newer generation ASM regimens and IED rates ( $p = .13$ ).





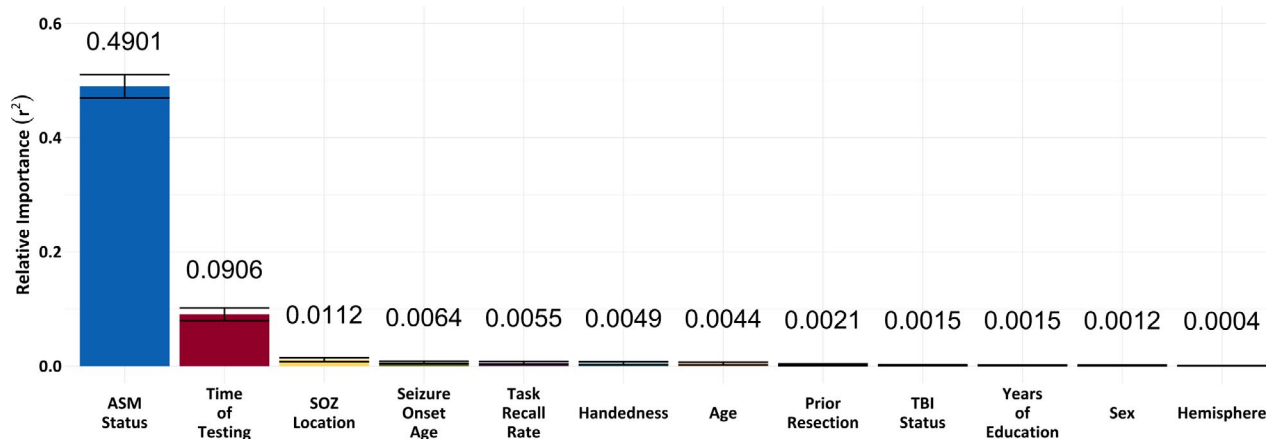
**FIGURE 2** Seizure onset zone (SOZ) location influences interictal epileptiform discharge (IED) rates. (A) Linear mixed-effects models were used to determine whether there were differences in IED rates between the different SOZs, stratified by brain region. Here, we used normalized IED rates computed solely from electrode contacts in SOZs. Analysis of variance (ANOVA) revealed that there were IED rate differences between the SOZs ( $p < .001$ ). FDR, false discovery rate. (B) Electrode contacts rendered on an average brain surface depict results from Tukey honestly significant difference test, a post-hoc test of the ANOVA in A. Colors represent significance values for contacts in SOZ brain regions that had significantly higher normalized IED rates than other SOZ brain regions. L, left; R, right. (C) IED rates were higher in mesial structures compared to neocortical structures ( $p < .001$ ). (D) There was a nonsignificant difference in IED rates between common mesial structures ( $p = .84$ ). Bars represent 95% confidence intervals. \*\*\* $p < .001$

As in other published works, we defined older generation ASMs as medications that were approved for the treatment of epilepsy prior to 1993.<sup>39</sup> In evaluating ASMs independently, our models revealed that being on any of the commonly prescribed ASMs present in the RAM dataset was associated with reduced IED rates. However, only seven of the 13 ASMs had statistically significant IED rate reductions. These ASMs included topiramate (OR = .61,  $p = .01$ ), zonisamide (OR = .53,  $p = .01$ ), lamotrigine (OR = .70,  $p = .03$ ), phenytoin (OR = .54,  $p = .03$ ), carbamazepine (OR = .42,  $p < .001$ ), levetiracetam (OR = .54,  $p < .001$ ), and lacosamide (OR = .68,  $p = .03$ ; Figure 4B).

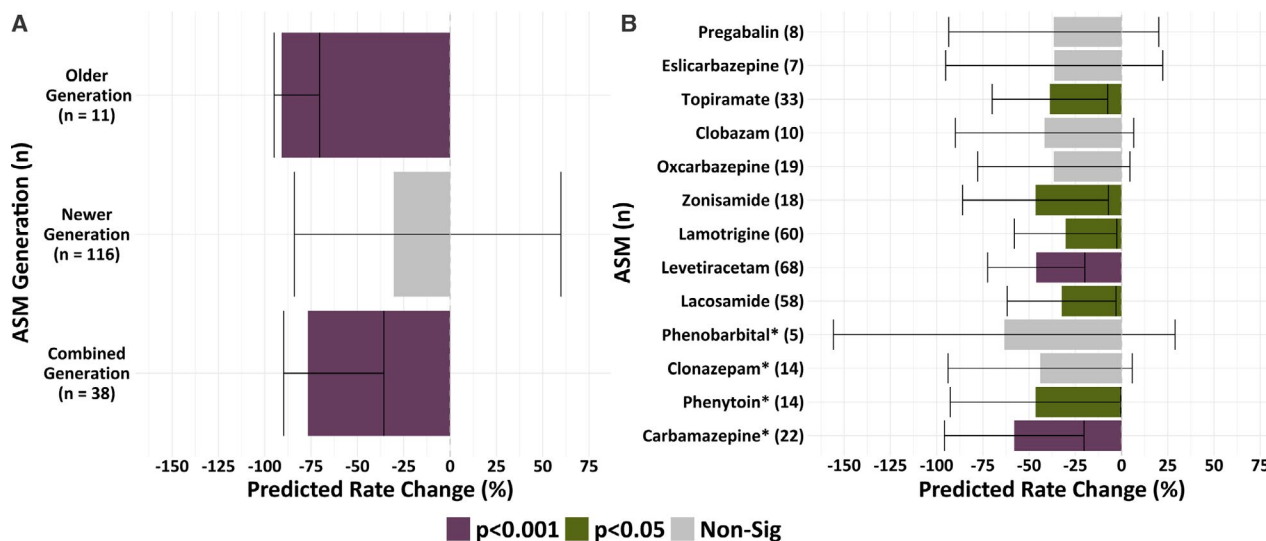
### 3.4 | Effect of time of testing on IED rates

There was a nonsignificant difference in the IED rates between the time windows (morning–afternoon  $p = .15$ , morning–evening  $p = .85$ , afternoon–evening  $p = .26$ ; Figure S4). The average normalized rate in the morning was .01 IEDs per minute (95% confidence interval [CI] = .008–.012), afternoon was .008 IEDs per minute (95% CI = .006–.01), and evening was .01 IEDs per minute (95% CI = .007–.013). Figure S4 illustrates that several of the subdivided 30-min time bins (e.g., 10 a.m.) had higher, albeit nonsignificant average normalized IED rates.





**FIGURE 3** General dominance analysis of subject-specific features. The bootstrapped general dominance analysis provided weights for each predictor to demonstrate the relative proportion of  $r^2$  attributable to that predictor. Larger  $r^2$  values represent higher relative importance of predictors relative to all possible combinations of predictors. General dominance values revealed that antiseizure medication (ASM) status had the highest relative importance ( $r^2 = .49$ ) and generally dominated all other predictors, followed by time of testing ( $r^2 = .09$ ), then seizure onset zone (SOZ) location ( $r^2 = .01$ ). All other predictors showed minimal relative importance for predicting interictal epileptiform discharge rate changes. Bars represent standard errors. TBI, traumatic brain injury



**FIGURE 4** Antiseizure medications demonstrate differences in interictal epileptiform discharge (IED) rate reductions. (A) There was a significant reduction in the predicted IED rate for subjects on older generation ( $p < .001$ ) and combined generation antiseizure medication (ASM) regimens ( $p < .001$ ) relative to the group taking no ASMs. (B) Our linear mixed-effects models revealed that seven of the ASMs were associated with significant overall IED rate reductions when referenced to the group taking no ASMs. Colors reflect significance values with false discovery rate controlled at a level of .05. Bars represent 95% confidence intervals. Asterisks denote older generation ASMs.  $n$  corresponds to the number of unique subject sessions contributing to each stratum. ASMs excluded due to a small number in our dataset were gabapentin, divalproex sodium, perampanel, felbamate, rufinamide, primidone, and ASMs categorized as Other

## 4 | DISCUSSION

Our findings evince that certain factors have a stronger association with intracranial IED rates in subjects with refractory epilepsy. Although we cannot establish the true direction of this association, we emphasize the importance of considering subject-specific differences in IED rates when evaluating IEDs for clinical or research purposes. We revealed that (1) the frequency of IEDs was not distributed

uniformly across the brain; (2) IED rates were higher for electrodes in the SOZ, relative to electrodes outside of the SOZ; and (3) certain SOZs, especially those in mesial temporal regions, had higher IED rates. In conjunction, these results suggest that IED rates were generally higher in SOZs and that hemisphere-specific SOZ locations significantly influenced IED rates. These intracranial findings align with previous observations by showing a higher percentage of IEDs per electrode in regions near the SOZ.<sup>4,8,30,40</sup>

However, we augment past studies by leveraging the power of a large stereo-EEG dataset to comprehensively examine different focal SOZs in both mesial and neocortical regions.

In evaluating the IED rates of electrodes outside of the SOZ (non-SOZ), but still stratified by the subject's SOZ location, we discovered that non-SOZ IED rates were similar, irrespective of the SOZ location. Nonetheless, previous studies demonstrated that IEDs outside of the SOZ impact memory encoding and retrieval,<sup>8,11</sup> indicating that low IED rates in non-SOZ brain regions are still detrimental. Our findings support the evaluation of IED rates for localizing SOZs<sup>41</sup> and reveal that global IED rates are likely attenuated when examining all electrodes in aggregate. The paradoxically low  $r^2$  observed for SOZ location (e.g., mesial temporal, lateral temporal) in our dominance analysis and the highly significant effects shown in the detailed, factor-level analysis further revealed the importance of considering the SOZ hemisphere (e.g., right or left) when investigating IED rates.

Our validation that intracranial IED rates were higher near the SOZ enabled us to more confidently compare the relative importance of SOZs and other subject-specific factors, as they relate to IED rates. We utilized the output from a bootstrapped general dominance analysis to rank the relative importance of factors for predicting differences in IED rates. Earlier reports examined the relationship between IEDs and subject-specific factors, such as age, antiepileptic medications, hormone levels, and multiday rhythms, yet this was mostly done in isolation.<sup>3,16,18,19</sup> Our study is the first to address this discrepancy by examining multiple subject-specific features in aggregate. We revealed that the top three factors influencing IED rates were ASM status (i.e., whether the subject was on at least one ASM or not on any ASMs), time of testing, and SOZ location, respectively.

It was unsurprising that ASM status ranked highly, as many previous studies showed an association between ASMs and IEDs.<sup>3,21,22,42</sup> We found that older generation and combined generation ASM regimens were associated with significant IED reductions; however, we acknowledge the possibility that subjects successfully treated with and remaining on older generation and combined generation ASM regimens may represent a different population than subjects on newer generation ASMs. Nevertheless, while these findings suggest that certain ASMs may have stronger influences on IEDs, it remains unclear whether using ASMs with a greater impact on IEDs will result in clinically significant improvements in cognition.<sup>8,10,11</sup>

Accordingly, we examined whether specific ASMs were associated with IED rate reductions relative to no ASM. Of the ASMs included in our analyses, carbamazepine, levetiracetam, lacosamide, zonisamide, lamotrigine, phenytoin, and topiramate demonstrated significant reductions in IEDs. As expected, levetiracetam and lamotrigine, two ASMs that have been previously shown to reduce IEDs, were included in this list.<sup>3,21,22</sup> However, we observed that carbamazepine

and levetiracetam had the most robust reduction in IEDs and should be considered if consistently lowering IED rates is of clinical interest, with the caveat that these considerations should not apply to specific pediatric epilepsies. Another clinical implication stems from Foster et al's finding that seizure frequency, rather than specific ASMs, was correlated with ASM-related cognitive dysfunction.<sup>43</sup> In union with our results, we divulge that IED rates, which are known biomarkers for cortical excitability and seizure frequency,<sup>5</sup> may be a potential metric for predicting cognitive side effects that coincide with ASM therapy in adults with epilepsy.

Although we observed a nonsignificant association between testing time and IED rates in our detailed, factor-level analysis, we attribute these null findings to the low temporal coverage of our data, especially because it excluded sleep states. Moreover, previous reports—explicitly designed to evaluate this question with either long-term scalp EEG or implanted brain devices—already demonstrated that time was significantly correlated with IEDs,<sup>19,44</sup> specifically, that the peak IED occurrence was in the evening, likely correlated with vigilance and sleep states, and that multiday IED rhythms were relatively stable within subjects.<sup>19,45</sup> Together with evidence that IED rates affect memory during sleep, we underscore the limitations imposed by low temporal coverage in the current dataset.<sup>46</sup>

Several provisos limit the implications of this study. We acknowledge that our mode of automated IED detection could introduce bias, as automated IED detection is not 100% concordant with human review.<sup>28,47</sup> However, this provides a method for objective signal processing of large potential deflections while avoiding potential inconsistencies of human review.<sup>48</sup> We also did not select subjects to specifically examine the relationship between subject-level factors and IED rates, so we were missing potentially relevant subject information, such as surgical outcome data. These data were not collected systematically between the study sites included in this multicenter study, creating the possibility that stereo-EEG missed or poorly covered SOZs. Our lack of pathology findings may bias results, as different pathologic etiologies of epilepsy could influence the rate and distribution of IEDs. We also did not have ASM blood levels at the time of testing and could not control for the impact that ASM tapering and neurosurgical procedures (e.g., stereo-EEG implant) had on IED rates.<sup>3</sup> ASM findings could additionally be influenced by type II error, as the effect sizes were similar between all ASMs regardless of statistical significance. Thus, nonsignificant ASM observations could be due to fewer subjects in those ASM groups, with an additional source of bias introduced due to missing ASM data.

The implications of our findings were further limited because we could not examine how ASMs impact seizure frequency and whether ASMs affect SOZ and non-SOZ IEDs equally. We concede that subjects were not randomized to come off or stay on ASMs. Consequently, the major contribution of ASM status in the general dominance analysis

could be confounded by factors other than the actual usage of ASMs. For instance, our lack of seizure information limited our ability to fully control for the relationship between ASM status and seizure frequency, a factor that may serve as a potential confound to the ASM findings. We also acknowledge potential bias from the heterogeneous number of sessions completed per subject. This arose due to several uncontrollable factors, mainly the varying lengths of implantation and the intracranial subjects' willingness to perform repeated experiment sessions. Despite these limitations, our study explores diverse focal epilepsies and provides the foundation for future research on this topic.

In summary, the current findings demonstrated that ASM status had the strongest influence on IED rates, followed by testing time and SOZ location. We revealed that IED rates were generally higher in SOZs and that electrodes distant from SOZs had similar IED rates, irrespective of the SOZ localization. We also showed that specific ASMs more strongly influenced IED rates; however, our work encourages future studies specifically designed to examine ASMs as they relate to interictal and ictal activity. These findings collectively provide new evidence for considering specific factors when analyzing IEDs for clinical or research purposes.

## 5 | ETHICAL PUBLICATION STATEMENT

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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## CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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