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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Early detection rate changes from a brain-responsive neurostimulation system predict efficacy of newly added antiseizure drugs

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Abstract

Objective: Brain-responsive neurostimulation (RNS System, NeuroPace) is used to treat medically refractory focal epilepsy and also provides long-term ambulatory neurophysiologic data. We sought to determine whether these data could predict the clinical response to antiseizure drugs (ASDs).

Methods: First, newly added medications were identified in RNS System patients followed at a single epilepsy center. Daily detection rates including "episode starts" (predominantly interictal activity) and "long episodes" (often electrographic seizures) were compared before and after ASD initiation. Efficacy was determined from documentation of clinical improvement and medication retention. Next, the analysis was repeated on an independent sample of patients from a multicenter long-term treatment trial, using an efficacy measure of ≥50% reduction in diary-recorded seizure frequency after 3 months.

Results: In the single center cohort, long episodes, but not episode starts, had a significantly greater reduction in the first week for clinically efficacious compared to inefficacious medications. In this cohort, having no long episodes in the first week was highly predictive of ASD efficacy. In the multicenter cohort, both long episodes and episode starts had a significantly greater reduction for effective medications starting in the first 1-2 weeks. In this larger dataset, a ≥50% decrease in episode starts was 90% specific for efficacy with a positive predictive value (PPV) of 67%, and a ≥84% decrease in long episodes was 80% specific with a PPV of 48%. Conversely, a <25% decrease in long episodes (including any increase) or a <20% decrease in episode starts had a predictive value for inefficacy of >80%.

Significance: In RNS System patients with stable detection settings, when new ASDs are started, detection rates within the first 1-2 weeks may provide an early, objective indication of efficacy. These data could be used to identify responses to medication trials early to allow more rapid medication adjustments than conventionally possible.

KEYWORDS
antiepileptic drugs, biomarker, brain stimulation, intracranial EEG, outcome prediction, responsive neurostimulation

1 | INTRODUCTION

One of the challenges in optimizing medications for patients with epilepsy is the length of time necessary to identify which regimens are effective or ineffective. Although many antiseizure drugs (ASDs) are available, depending on a patient's seizure frequency, it can take years of trials to find the most effective regimen.[1] A biomarker that could be used to assess response to ASDs prior to observing changes in clinical seizure frequency could be of benefit. Despite observed changes in cortical excitability associated with changes in ASDs,[2,3] there is no well-accepted biomarker for efficacy, particularly for focal epilepsy.

Brain-responsive neurostimulation is a recent therapeutic option for adults with medically intractable focal epilepsy.[4,5] A unique characteristic of this system is that it provides intracranial electrocorticographic (ECoG) data over long time periods (years), which have not been available outside of small series.[6,7] These long-term measurements have previously been used to identify the predominant focus in patients with bitemporal epilepsy[8] and characterize temporal cycles of epileptic activity.[9–11]

Recently, a retrospective study of the chronic ambulatory ECoG data provided by the RNS System (NeuroPace) demonstrated that quantitative changes in the data could differentiate between clinically beneficial and not beneficial responses to ASDs.[12] However, the timescale assessed during this study was on the order of months. At this timescale, the benefit over patient reporting is limited. If evident early enough, however, these changes might be practical for predicting clinical efficacy.

Here, we extend the previous study by assessing the changes in the ECoG data within the first few weeks following the addition of a new ASD. We also assess the predictive value of the data for identifying ASD additions that result in clinically significant reductions in seizures. Our results and those of prior work[8,11] point toward the potential role of diagnostic ambulatory ECoG to guide treatment and forecast changes in seizure frequency.

Key Points

- Electrographic detections by the RNS System decrease within 1-2 weeks following the addition of medications that are efficacious.
- Electrographic detections by the RNS System do not decrease within 1-2 weeks following the addition of medications that are inefficacious.
- Long-term ambulatory electrocorticography provides early and objective data that may be used to optimize medical therapy for epilepsy.

2 | MATERIALS AND METHODS

2.1 | RNS System

The RNS System includes a neurostimulator placed within the cranium and connected to 1-2 leads that are placed according to the patient's seizure focus or foci. After the device is implanted, an epileptologist defines criteria for detection based on ECoG recordings of seizure onsets. Such patterns, termed "episode starts," occur many more times than clinical seizures and often include brief bursts or epileptiform activity or interictal activity. Detection of these episode starts triggers electrical stimulation, which is titrated to optimize seizure frequency, battery life, and patient comfort. A subset of the episode starts progress to "long episodes," in which the ECoG pattern of concern persists for a preset duration. The physician sets this long episode threshold to identify periods of sustained detections, typically abnormal electrographic events that persist for 10-60 seconds; most commonly, the threshold is set at 20-30 seconds. These long episodes typically represent electrographic seizures or prolonged abnormal epileptiform activity and typically occur more often than clinical seizures.[13,14] Despite the observation that long episodes occur more frequently than clinical seizures, these events are significantly correlated with clinical outcome.[15] The neurostimulator log includes a near-continuous record of the hourly rates of episode starts and long episodes.

In our experience, clinicians usually settle on a stable set of detection parameters within a year after implantation, with few or no changes afterward. Periods of 1 year or greater of seizure freedom occur in approximately 13%-15% of patients.[16] For patients who do not become seizure-free, medication trials often continue afterward. This situation provides an unprecedented opportunity to observe long-term ambulatory ECoG responses to newly added medications.

2.2 | Single center analysis

We identified all patients implanted with RNS Neurostimulators and Leads followed at the Yale Comprehensive Epilepsy Center as of the end of 2016. Similar to the clinical trials for the RNS System, patients

implanted with the neurostimulator at Yale were refractory to medications and typically not resective surgical candidates, because they had seizures arising from either eloquent cortex or the bilateral mesial temporal lobes, and/or they had undergone a prior resection and could not have additional surgery due to the risk for neurological deficit. As part of standard clinical care, data from the device, including the hourly counts of episode starts and long episodes, are uploaded to a server by the patient intermittently. We downloaded the daily episode start and long episode rates for all identified patients for further analysis. We reviewed the medical record to identify all changes to ASDs since RNS System implantation. Classification of efficacy was determined independently by two investigators (I.H.Q. and M.R.M.), blinded to RNS System data, and a consensus was reached in all cases in which there was any discrepancy. The clinicians who provided the initial documentation were not blinded to the neurostimulator data, however.

The response to each new medication was classified as efficacious if there was a documented improvement in seizure frequency or severity in the chart based on the opinion of the provider and patient. In cases where a seizure diary was available, the documented impression was supplemented by evaluation for a ≥50% reduction in seizure frequency over the prior 3 months. Medications that were continued indefinitely with no documentation indicating that seizures worsened or did not improve were also counted as efficacious. Medication trials in which documentation indicated no improvement or worsening of seizures, or in some cases diary review showing increased seizure frequency, were classified as inefficacious. Trials in which side effects prevented an adequate trial or in which there were confounding changes to the device settings were excluded. Similarly, trials during which other ASDs were simultaneously tapered off were excluded. Patients consented to share their clinical information under the auspices of the Yale University Human Investigation Committee.

2.3 | Multicenter analysis

All patients enrolled in the NeuroPace Long-Term Treatment (LTT) study were screened electronically for newly added ASDs. These patients had previously completed an initial 2-year study and were enrolled in the LTT study to collect an additional 7 years of safety and efficacy data. During the open-label LTT study, medication changes were permitted. Patients consented to share information including device data, seizure diaries, and medication logs under protocols approved by the institutional review board at each center. The study was registered on www.clinicaltrials.gov (NCT00572195).

Medication additions were retrospectively identified from detailed medication logs maintained as part of the trial. These medication additions were excluded if there were no diary data, if there were any other medication changes within ±3 months, or if there were any changes to neurostimulation detection settings within ±3 months. Because all these patients had diaries, clinical efficacy of each newly added medication was defined with a standardized measure as a ≥50% reduction in seizure frequency in the 3 months after the medication was added relative to the 3 months beforehand.

2.4 | Statistical analysis

Correlations between changes in detection rates (either episode starts or long episodes) and medication efficacy were calculated using an analysis of covariance (ANCOVA)-based linear model in which the average preaddition (before addition of a new medication) baseline detections were used as a covariate. In the larger, multicenter dataset, two additional covariates were added to the model as potential confounders. The first of these was the medication name, to account for the possibility of differential effects between medications. The second was the patient ID, to account for some patients having multiple medication trials and possibly having patient-specific responses. Akaike information criteria (AIC) was applied to determine whether either of these values added to the accuracy of the model.

To establish a potential biomarker, episode start and long episode rates were divided by patient-specific preaddition baseline values to form a post (after new medication) to pre ratio (hereafter referred to as *detection change ratio*) for different times of interest (1 week and 3 months for the single center analysis, and each of the first 4 weeks for the subsequent multicenter analysis). Detection change ratios for episode starts and long episodes were evaluated for predictive power by the area under the curve of the receiver operating characteristic (ROC). Detection change ratios for episode starts and long episodes were also compared directly between efficacy groups using a two-way Wilcoxon rank sum test (Mann-Whitney) as a supplement to the covariate analysis described above. Statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Single center cohort

Twenty RNS System patients were identified who had a total of 61 new ASDs added after implantation. Twenty-two of these medication additions met eligibility criteria. The remaining additions were excluded due to programming

changes, changes to other medications, or early discontinuation due to side effects. Fifteen of these medication additions were classified as effective, and seven were classified as ineffective (Table S1). The most frequent additions were lacosamide (five, three effective), clobazam (five, four effective), and zonisamide (four, three effective).

Changes in long episodes in the first few days were often dramatic and visually evident on graphs of a patient's detection counts (Figure 1). Efficacious medication trials often produced a sharp drop in long episodes that was more prominent than an individual patient's downward fluctuations. Inefficacious medication trials typically showed no change, or sometimes an increase, in long episodes.

In the first 7 days after ASD initiation, long episode rates declined more for medication trials that were efficacious than for those that were inefficacious at 3 months ($P = .03$ without accounting for confounders, or $P < .0001$ when accounting for patient-specific effects, ANCOVA). Corresponding differences were evident in the detection change ratios ($P < .001$, Mann-Whitney), which were 0.47 ± 0.13 (n = 14) in the efficacious group and 1.5 ± 0.25 (n = 8) in the inefficacious group (Figure 2A).

Episode starts were also evaluated (Figure 2B). In the first 7 days after ASD initiation, episode starts were not any lower for efficacious than inefficacious medications ($P = .26$, n = 22, ANCOVA). There was no patient-specific effects ($P = .87$, n = 22). Detection change ratios for this measure also did not differ between efficacy groups ($P = .07$, n = 22).

There were five medication additions in which the long episodes dropped completely to zero in the first 7 days (three clobazam, two pregabalin, one lacosamide). All of these cases were ultimately judged to have clinical efficacy (specificity and positive predictive value of 100%). There were no medications that were judged clinically inefficacious in which the 7-day detection change ratio dropped to <50%, whereas this occurred for 32% of efficacious cases.

From this single center cohort, although the sample size was limited, the 7-day long episode normalized ratio was an excellent predictor of response with area under the curve = 0.93. An optimal cutoff to determine efficacy was a 20% decrease in long episodes (Youden *J* statistic). There were 12 cases in which long episodes dropped by 20% or more, and all of them were later judged to have clinical efficacy. Of the remaining 10 cases, seven were judged to be ineffective. Thus, this cutoff yielded a positive predictive value of 100% and negative predictive value of 70%, with 79% sensitivity and 100% specificity.

3.2 | Multicenter analysis: Clinical efficacy of medication trials

To validate our single center results, we obtained longitudinal data from the 230 patients in the NeuroPace LTT trial for independent analysis.[16] Patients from the initial single center (Yale) analysis were excluded to ensure an independent

FIGURE 1 Examples of daily long episode (LE; red) and episode start (ES; blue) rates 90 days before and after the dates of new medication trials (vertical dashes). A, Daily LE and ES rates in a single patient following a trial of a clinically efficacious medication (clobazam in this case). LEs declined by 83% in the first 7 days (highlighted region). ESs did not decline as significantly. The patient ultimately had a 71% reduction in clinical seizures after the addition of clobazam. B, Daily LE and ES rates in a single patient following a trial of a clinically inefficacious medication (zonisamide in this case). LEs increased by 65% in the first 7 days, likely as part of the patient's typical cycles. The patient discontinued the medication after 5 months due to lack of clinical response

sample. Trials in which other medication changes were also made were excluded. Lamotrigine trials (17 cases, of which four were efficacious) were excluded, because the required very slow titration rate made short-term biomarker evaluation impractical. Patients lacking diary data were excluded. Cases in which no seizures were reported in the 3 months prior to the medication addition were excluded, because clinical efficacy could not be determined reliably.

Three hundred thirty-seven medication trials from 152 patients remained for analysis prior to final censoring steps (Table 1; Figure 3). Some of these patients were only included at early time points due to subsequent detection setting changes. Ninety-seven trials (29%) were classified as efficacious and 240 (71%) as inefficacious based on an efficacy criterion of ≥50% reduction in reported clinical seizure frequency. Of the 152 patients, 69 had a single medication trial included in the analysis, 31 had two trials, and 21 had three trials. Twenty percent of patients (n = 31) had four or more trials included, with a maximum of seven in two patients (Figure S1). Two hundred twelve trials were selected that had corresponding detection count data available for subsequent statistical analysis.

3.3 | Multicenter analysis: Long episode counts

Because having no long episodes in the first week appeared to be an important (although insensitive) sign of efficacy in the single center data, this was evaluated in the multicenter dataset, prior to more comprehensive analysis for detection change ratios (for which we also censored for stimulation changes and accounted for confounding variables). In the first week (n = 204), having no long episodes had a sensitivity of 23%, specificity of 81%, positive predictive value of 34%, and negative predictive value of 71%. In the second

TABLE 1 Medication trials in the multicenter dataset listed with efficacy results based on 50% or greater seizure freedom after 3 months

Medication	Ineffective trials	Effective trials	All trials	Effective trials, %
Lacosamide	74	20	94	21
Clobazam	19	22	41	54
Levetiracetam	13	16	29	55
Pregabalin	22	3	25	12
Zonisamide	11	7	18	39
Topiramate	10	5	15	33
Clonazepam	11	1	12	8
Felbamate	9	3	12	25
Perampanel	8	4	12	33
Carbamazepine	8	3	11	27
Rufinamide	11	0	11	0
Phenytoin	5	2	7	29
Valproate/valproic acid	5	2	7	29
Eslicarbazepine	5	1	6	17
Ezogabine	4	1	5	20
Oxcarbazepine	5	0	5	0
Gabapentin	3	1	4	25
Lorazepam	0	4	4	100
Phenobarbital	4	0	4	0
Tiagabine	3	1	4	25
Vigabatrin	2	1	3	33
Diazepam	2	0	2	0
Midazolam	2	0	2	0
Acetazolamide	1	0	1	0
Cannabidiol	1	0	1	0
Ethosuximide	1	0	1	0
Primidone	1	0	1	0

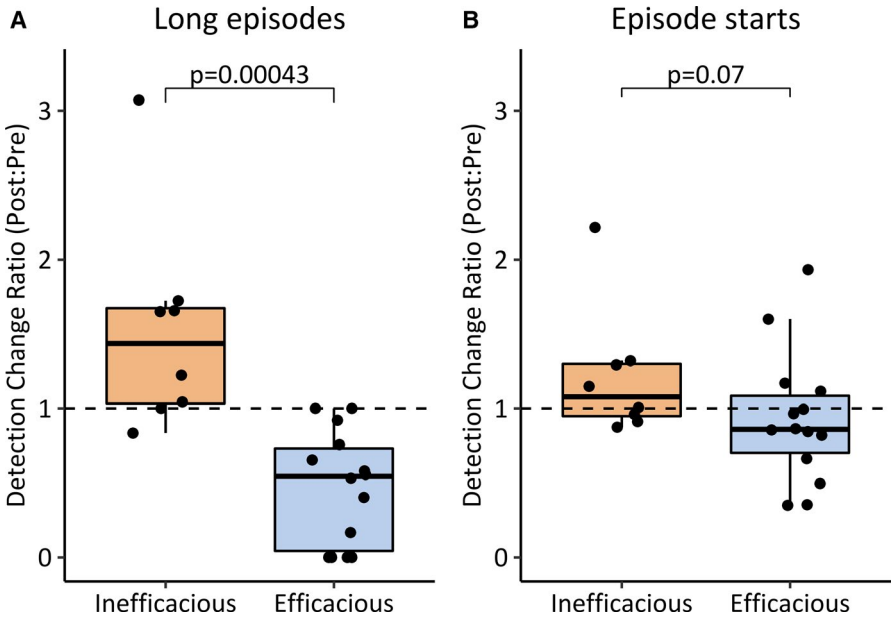
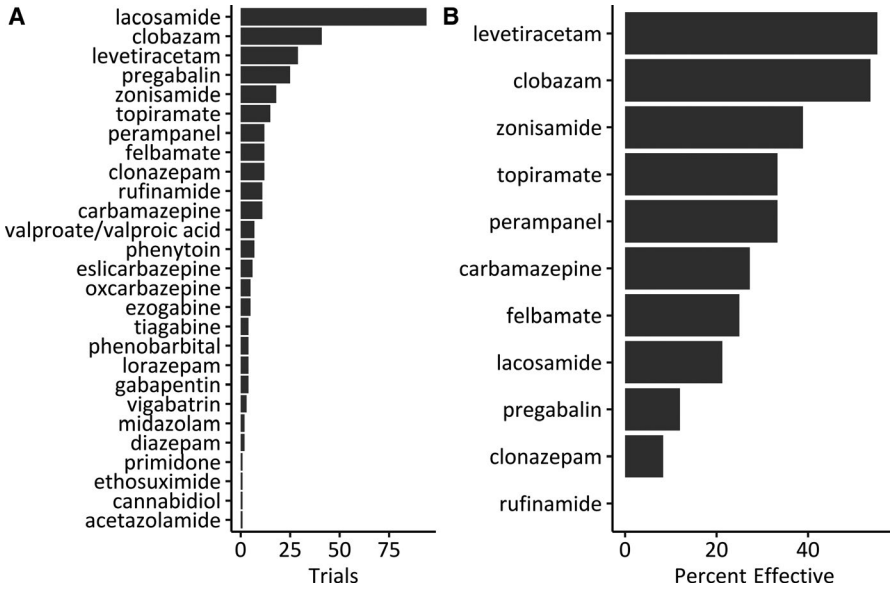


FIGURE 2 Summary of detection change ratios for long episodes (A) and episode starts (B) per medication trial from the single center dataset for inefficacious (orange) and efficacious (blue) trials after 1 week. Long episode ratios showed a decrease after 1 week for medication trials that were clinically effective. Detection ratios represent the mean postmedication change in daily detection rate compared to the 3-month premedication change detection rate. Boxes represent median and interquartile range; whiskers represent the smaller of 1.5 × interquartile range or the limit of the data. Significance values shown are based on a Mann-Whitney *U* test on ratios

FIGURE 3 A, Medications included in the multicenter dataset, excluding lamotrigine. Lacosamide was by far the most common, followed by clobazam, levetiracetam, and pregabalin. B, Medication efficacy (percentage of trials that had a minimum of 50% improvement in clinical seizure frequency)



week (n = 202), having no long episodes had a sensitivity of 41%, specificity of 84%, positive predictive value of 43%, and negative predictive value of 77%.

Daily detection change ratios for long episodes had large variation, but upon averaging across cases displayed a downward trend following the date the medication was added in efficacious cases (Figure 4A). For inefficacious medication trials, there was actually an increase when evaluating the mean across cases. This increase in the mean of long episode detection change ratios for inefficacious medications represents skew from outliers and data that are not normally distributed; the rise is not seen when evaluating the median as in Figure 4C. To account for day-to-day variability, detection change ratios were binned in 1-week intervals. There was a significant difference between groups (clinical efficacy after 3 months) in long episode rates starting in the first week (week 1: $P = .036$, n = 181; week 2: $P = .0017$, n = 175; week 3: $P = 3.7\text{E-}5$, n = 168; week 4: $P = .0011$, n = 164).

Due to statistical concerns with comparing ratios and to allow for the contribution of confounding variables, we also

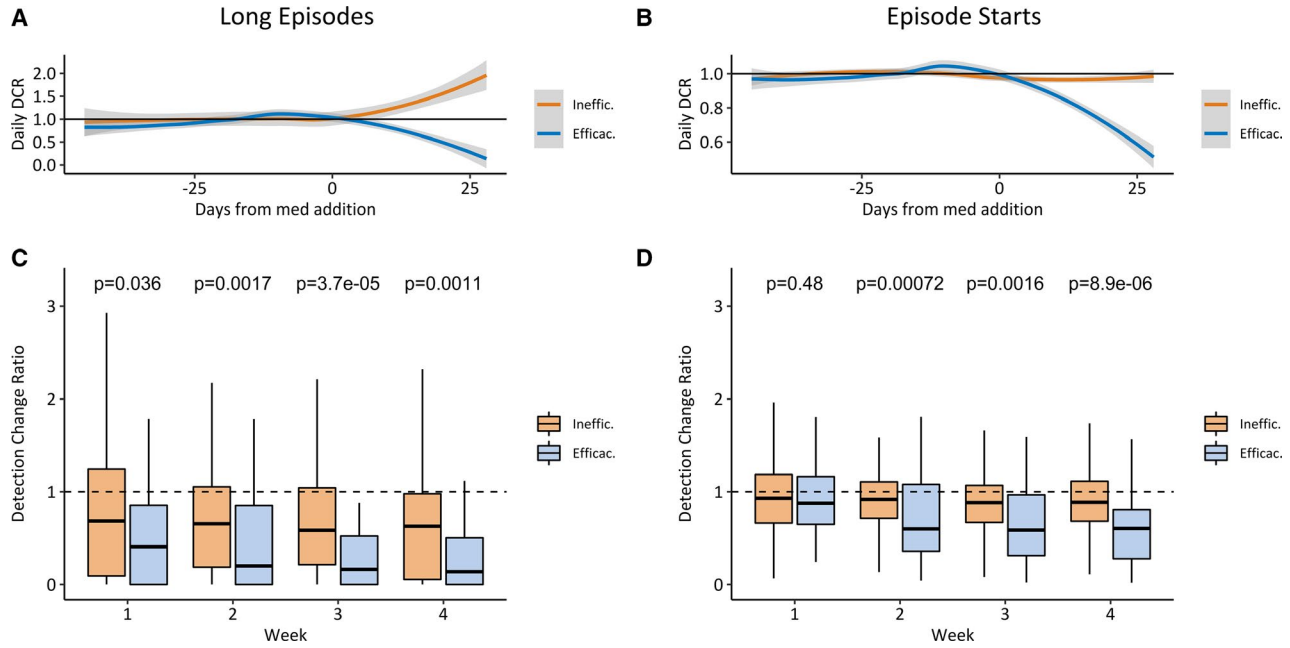


FIGURE 4 A, B, Trends of long episodes (A) and episode starts (B) averaged over all trials relative to individual baseline before and after medication trials from the multicenter dataset (locally weighted scatterplot smoothing fit with 95% confidence interval, span = 0.95, logarithmic scale) demonstrate a decrease in detection change ratio (DCR) after medication additions for efficacious trials (blue). C, Cumulative long episode rates (median ± interquartile range) following medication addition shows a decline in long episodes in the efficacious group from the first week and an increase in long episodes in the inefficacious group starting around weeks 1–2. D, A decline in episode starts was also significantly lower for efficacious medications starting in week 2. In the lower panels, horizontal lines represent the medians, boxes represent interquartile ranges, whiskers represent the smaller of 1.5 × interquartile range or total range of data. Significance values are from Mann-Whitney *U* test

evaluated the raw long episode counts in a statistical model in which the patient-specific mean preaddition long episode rate was a covariate, as described for the single center analysis. Prior to adjustment for confounders, differences using this model were evident at weeks 1 ($P = .0004$), 2 ($P = .0011$), and 4 ($P = .001$), but not at week 3 ($P = .061$). Because individual medications appeared multiple times in the dataset, and in many cases individual patients had more than one medication trial, we tested the addition of these two potential confounders to the model. The highest quality model, balancing degrees of freedom and significance as evaluated by AIC, incorporated both ASD-specific effects and patient-specific effects (Table S2). The overall effect was not dependent on the ASD used (eg, in week 2, $P = .74$, $df = 21$). The effect did, however, vary by patient ($P = .0011$, $df = 103$). Using this combined model to account for confounders of patient-specific effects and ASD-specific effects, there was still a significant difference in long episodes between effective and ineffective medication trials. This difference in long episodes with this model (between 3-month clinical efficacy groups) was evident in each of the first 4 weeks after the ASD was started (week 1: $P = .00021$, $F = 15.6$; week 2: $P = 8.8E\text{-}5$, $F = 17.9$; week 3: $P = .0011$, $F = 12.0$; week 4: $P = .00068$, $F = 13.3$).

The accuracy of long episode detection change ratios (which are more easily implementable clinically but do not account for the confounders listed above) improved with time. The area under the curve of the ROC increased from 0.61 at 7 days to 0.67 at 14 days to 0.72 by 28 days (Figure 5B). The magnitude of the difference between groups and the ROC curves appeared to plateau from the second week onward, so this time point was evaluated further. In the second week there was no single cutoff in the normalized ratios for long episodes (not accounting for confounders) with both high sensitivity and high specificity. Several example cutoff values were analyzed further. A decrease in long episodes by 84% or more achieved specificity of 80% for efficacy (Figure 5A), with sensitivity for efficacious trials of 44% and positive predictive value for efficacy of 48%. An increase in long episodes by 10% or more was 80% specific for inefficacy (Figure 5B), with sensitivity for inefficacious trials of 52% and predictive value for inefficacious trials of 76%. An increase in long episodes by 80% or more was >90% specific for inefficacy, with predictive value for inefficacious trials of 75%.

A <25% decrease in long episodes (including any increase in long episodes) correctly predicted lack of efficacy in 80% of clinically inefficacious trials (ie, negative predictive value of 80%); this cutoff was similar to the one identified in the single center cohort.

Two patients were identified who had seven medication trials and were selected for more careful review. The first patient had a single efficacious medication trial (clobazam)

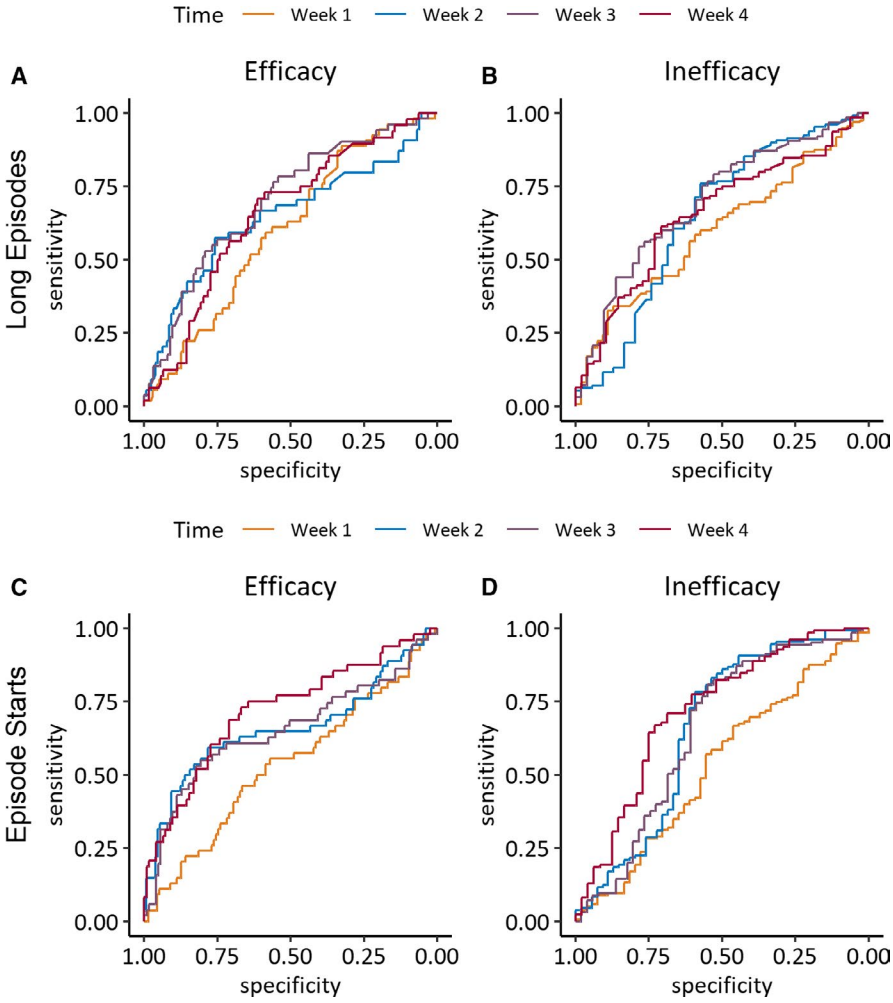


FIGURE 5 Receiver operating characteristic curves for ratio of long episodes (A, B) and episode starts (C, D) in each week divided by preaddition baseline. Performance of decrease in long episodes (A) or episode starts (C) in predicting medication efficacy gradually improves each week, with the largest change between the first and second week. Performance of increase in long episodes (B) or episode starts (D) in detecting medication inefficacy displays the expected inverse relationship to A and C. Area under the curve values at 1, 2, 3, and 4 weeks for long episodes are 0.60, 0.65, 0.70, 0.66 (or 0.72 for a cumulative change over all 4 weeks) and for episode starts are 0.53, 0.66, 0.65, 0.72, respectively

that was later censored due to programming changes. Of the other trials, there were no false positives in the 2-week-long episode detection change ratio. The second patient responded to none of the medication trials. This patient had three false positives: a case of clobazam with a long episode ratio in week 2 of 0.32 and clinical seizure reduction of 45%, a case of felbamate with a long episode ratio in week 2 of 0.37 and 69% increase in seizures, and a case of rufinamide with week 2 long episode ratio of 0.14 with 26% reduction in seizures.

3.4 | Multicenter analysis: Episode starts

Detection change ratios for episode starts showed a downward trend following the addition of an efficacious medication that was not seen in inefficacious cases (Figure 4A). Episode start detection change ratios were lower for efficacious ASDs (Figure 4B) starting in the second week (week 1: $P = .48$, n = 181; week 2: $P = .00072$, n = 175; week 3: $P = .0016$, n = 168; week 4: $P = 8.9\text{E-}6$, n = 164). As with long episodes, these differences were confirmed with a statistical model of raw detection counts. Differences were seen from the second week onward (week 1: $P = .33$, $F = 0.96$, residual $df = 186$; week 2: $P = .00036$, $F = 13.2$, residual $df = 180$; week 3: $P = .012$, $F = 6.4$, residual $df = 173$; week 4: $P = 8.2\text{E-}5$, $F = 16.3$, residual $df = 169$). Unlike with long episodes, for episode starts the addition of ASD or patient ID did not improve the model quality by AIC. Moreover, when these potential confounders were included, neither variable had a significant effect (ASD name: $P = .97$, $F = 0.45$, $df = 21$; patient ID: $P = .99$, $F = 0.57$, $df = 101$).

The area of the curve of the ROC for the episode start detection change ratio increased from 0.53 in the first week to 0.66 in week 2 and 0.72 by week 4. As with long episodes, several example cutoff values were analyzed. A decrease in episode starts of 50% or more was >90% specific for an efficacious medication (Figure 5C), with sensitivity of 44%, positive predictive value of 67%, and negative predictive value of 80%. An increase in episode starts of 30% or more was >90% specific for an inefficacious (Figure 5D) medication (with sensitivity for inefficacious trials of 12% and predictive value for inefficacy of 76%). A decrease in episode starts of <20% (including any increase) had a predictive value for an inefficacious medication, (ie negative predictive value) of 81%, with sensitivity for inefficacious trials of 68%.

4 | DISCUSSION

RNS System patients display a decrease in prolonged ECoG detections of ictal onset patterns ("long episodes") that is evident and statistically significant as early as 1 week after starting medication trials that are ultimately determined to have clinical efficacy. This pattern is not seen among inefficacious medication trials. These findings were seen via retrospective review at our single center and confirmed using data from a multicenter clinical trial. The difference between these groups suggests the utility of ambulatory intracranial ECoG as a potential biomarker to assess therapeutic responses in focal epilepsy within 1-2 weeks of starting a new medication. Other investigators have previously demonstrated that RNS System detection rates change in response to external factors such as caffeine,[17] antidepressant use,[18] and ASDs,[12] but the early use of these changes to predict medication responses at an early time point is a novel concept.

Because the long episode and episode start rates are readily available to the clinician, they provide an easy tool to assess medication responses in this patient population. Based on the multicenter data, we suggest that if episode starts or long episodes do not decline by at least 20%-25% in the first 1-2 weeks after starting a new ASD, it is unlikely that it will be clinically efficacious, and the trial might be terminated early in favor of another medication. If a decline of 50%-80% in either detection measure is seen in the first 1-2 weeks, it is likely the medication will be efficacious, and the medication should be continued if tolerated. If there is an indeterminate reduction of between 25% and 50%, then the medication could be efficacious, but it would be worthwhile to wait longer to see whether the effect is sustained. Of note, in the single center cohort, whenever the long episode rate dropped to zero, the medication was always efficacious, although this was less accurate in the multicenter cohort. Our overall results were independent of the specific ASD, although sample sizes for most of the medications were too small to draw individual conclusions.

Although less accessible to clinicians, there may be additional information in resting ECoG data that could supplement detection counts and increase predictive power.[12] The activity measured by the neurostimulator system may not have a scalp electroencephalographic (EEG) correlate. As a result, a scalp EEG solution is unlikely to provide information that is as useful as these intracranial features.

There was a significant patient-specific contribution to the correlation between short-term long episode frequency and longer-term seizure reduction. This finding suggests that in an individual patient, if short-term changes in long episodes are confirmed to be an accurate predictor after one or more medication trials, then short-term changes in long episodes following future trials in the same patient are more likely to be accurate predictors than the overall population of patients. This possibility needs to be verified. As the number of medication trials in RNS System patients available for analysis grows, this per-patient effect could be evaluated in further detail.

In addition to providing a shorter lag time than diaries or other patient reports, it could be argued that long episodes are an even better therapeutic target than reported clinical seizures. Although seizure diaries are a current standard in epilepsy research, their accuracy is known to be poor.[19–21] In the controlled environment of an inpatient video monitoring unit, <50% of all seizures (and <60% of bilateral tonic-clonic seizures) are reported.[21] Outpatient seizure reporting introduces further variability, because diaries may not be at hand or may be lost or forgotten. Intracranial ECoG-based detections provide an objective measure. Long episodes in particular often or usually represent electrographic seizures.[11] Moreover, recorded events that represent subclinical seizures may be important to treat as well. For example, "subclinical" focal discharges may impair memory[22] and reaction time.[23]

The results of this study also suggest the possibility of using long-term ECoG measurements for seizure forecasting. Although the study is limited to cases in which a new medication was added, this is one example of how clinical seizure frequency can be predicted before there is a clinical change. A key factor in such a forecasting endeavor appears to be the definition of an ECoG biomarker. More frequently detected patterns (episode starts) were not as useful a predictor, but longer, less frequently detected patterns (long episodes) were. As was done for the patients in this study, such events would need to be individualized in pattern and duration for optimal utility.

We applied our methodology to two populations of RNS System patients. The single center test set had two major limitations. First, the sample size was small. Second, the efficacy measure incorporated some subjectivity (documented clinical impression of the provider). We tried to offset these limitations, at least in part, by making the exclusion criteria rather strict (only about one-third of medication trials were able to be used). The provider who introduced new medications was not blinded to the neurostimulator data, so their clinical impression might have been influenced by it. The subjective measure does provide information not available from diary-provided seizure frequencies, however, such as seizure severity. Both of those limitations were addressed by the subsequent multicenter analysis, which also provided an independent, confirmatory patient sample. Another limitation that was common to both the single center and multicenter analyses was that both were retrospective. Additional, prospective studies will be necessary to confirm the observations presented here.

One other limitation of the study was the use of patient-reported seizures as the measure of clinical outcome. As many as 30%-50% of seizures are not reported by patients, for a variety of reasons.[21] However, self-reported seizure frequency remains the primary outcome measure of epilepsy treatment trials, and the seizure diary is still considered the gold standard.

Because patients in this study received neurostimulation, it is not known whether the results would remain significant for intracranial electrodes in the absence of stimulation. It is possible, for example, that stimulation is synergistic with ASDs and potentiates positive or negative changes in detection rates. To address this issue, a larger study of the type done by Cook et al[6] in which patients were implanted with intracranial electrodes for ambulatory monitoring, without stimulation, might be required. If our results extend to non-stimulated patients, then it may be possible to translate the ECoG biomarkers demonstrated in the current study to the large population of patients who are not otherwise candidates for neurostimulation, either through an implanted recording-only device or through other physiological measures from wearables or external devices that correlate with ECoG detections.

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CONFLICT OF INTEREST

L.J.H. has received consulting fees and honoraria from NeuroPace. T.L.S. has equity ownership/stock options with NeuroPace and is an employee of NeuroPace. 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

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

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