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RESEARCH ARTICLE

Quantitative analysis of visually reviewed normal scalp EEG predicts seizure freedom following anterior temporal lobectomy

Yogatheesan Varatharajah[1,2] | **Boney Joseph**[2] | **Benjamin Brinkmann**[2] | **Marcia Morita-Sherman**[3] | **Zachary Fitzgerald**[3] | **Deborah Vegh**[3] | **Dileep Nair**[3] | **Richard Burgess**[3] | **Fernando Cendes**[4] | **Lara Jehi**[3] | **Gregory Worrell**[2]

[1]Department of Bioengineering, University of Illinois at Urbana Champaign, Urbana, Illinois, USA

[2]Departments of Neurology and Physiology & Biomedical Engineering, Mayo Clinic, Rochester, Minnesota, USA

[3]Epilepsy Center, Cleveland Clinic, Cleveland, Ohio, USA

[4]Department of Neurology, University of Campinas UNICAMP, Campinas, Brazil

Correspondence
Yogatheesan Varatharajah, Department of Bioengineering, University of Illinois at Urbana Champaign, Urbana, IL 61801, USA.
Email: varatha2@illinois.edu

Gregory Worrell, Mayo Systems Electrophysiology Laboratory, Department of Neurology, Mayo Clinic, Rochester, MN, 55905, USA.
Email: worrell.gregory@mayo.edu

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Abstract

Objective: Anterior temporal lobectomy (ATL) is a widely performed and successful intervention for drug-resistant temporal lobe epilepsy (TLE). However, up to one third of patients experience seizure recurrence within 1 year after ATL. Despite the extensive literature on presurgical electroencephalography (EEG) and magnetic resonance imaging (MRI) abnormalities to prognosticate seizure freedom following ATL, the value of quantitative analysis of visually reviewed normal interictal EEG in such prognostication remains unclear. In this retrospective multicenter study, we investigate whether machine learning analysis of normal interictal scalp EEG studies can inform the prediction of postoperative seizure freedom outcomes in patients who have undergone ATL.

Methods: We analyzed normal presurgical scalp EEG recordings from 41 Mayo Clinic (MC) and 23 Cleveland Clinic (CC) patients. We used an unbiased automated algorithm to extract eyes closed awake epochs from scalp EEG studies that were free of any epileptiform activity and then extracted spectral EEG features representing (a) spectral power and (b) interhemispheric spectral coherence in frequencies between 1 and 25 Hz across several brain regions. We analyzed the differences between the seizure-free and non–seizure-free patients and employed a Naïve Bayes classifier using multiple spectral features to predict surgery outcomes. We trained the classifier using a leave-one-patient-out cross-validation scheme within the MC data set and then tested using the out-of-sample CC data set. Finally, we compared the predictive performance of normal scalp EEG-derived features against MRI abnormalities.

Results: We found that several spectral power and coherence features showed significant differences correlated with surgical outcomes and that they were most pronounced in the 10–25 Hz range. The Naïve Bayes classification based on

Lara Jehi and Gregory Worrell: Co-senior authors

those features predicted 1-year seizure freedom following ATL with area under the curve (AUC) values of 0.78 and 0.76 for the MC and CC data sets, respectively. Subsequent analyses revealed that (a) interhemispheric spectral coherence features in the 10–25 Hz range provided better predictability than other combinations and (b) normal scalp EEG-derived features provided superior and potentially distinct predictive value when compared with MRI abnormalities (>10% higher F1 score).

Significance: These results support that quantitative analysis of even a normal presurgical scalp EEG may help prognosticate seizure freedom following ATL in patients with drug-resistant TLE. Although the mechanism for this result is not known, the scalp EEG spectral and coherence properties predicting seizure freedom may represent activity arising from the neocortex or the networks responsible for temporal lobe seizure generation within vs outside the margins of an ATL.

KEYWORDS

anterior temporal lobectomy, machine learning, normal scalp EEG, quantitative EEG analysis, temporal lobe epilepsy, surgery outcomes

1 | INTRODUCTION

Temporal lobe epilepsy (TLE) is a common type of drug-resistant epilepsy, and anterior temporal lobectomy (ATL) is a widely performed and successful intervention with class 1 evidence of efficacy from randomized clinical trials.[1,2] Despite the recent advances in brain imaging, electroencephalography (EEG) monitoring, and surgical technologies, up to one third of patients do not achieve long-term seizure freedom after ATL.[3,4] Therefore, the identification of prognostic factors that can help predict the likelihood of seizure freedom following ATL remains of great clinical interest. Several previous studies have reported that ictal EEG patterns, interictal EEG abnormalities, magnetic resonance imaging (MRI) structural abnormalities, and their relationship to the resected area are useful for prognosticating surgical outcomes following ATL.[5,6] However, the potential value of quantitative analysis of normal interictal scalp EEG, that is, in the absence of interictal epileptiform abnormalities or focal slowing, remains unknown for such prognostication. Because nearly 50% of routine EEG studies and 10% of prolonged video-EEG studies in patients with known epilepsy do not contain any recognizable epileptiform activity,[7,8] the ability to predict ATL outcomes using normal scalp EEG findings could prove useful as a cost-effective and expeditious additional feature for evaluating surgical candidacy and predicting outcomes.

EEG is a cornerstone in the evaluation of drug-resistant epilepsy. There is extensive literature on visual and quantitative approaches applied to scalp EEG data for identifying interictal epileptiform activity, seizures, and propagation patterns with the aim of mapping the epileptogenic zone and predicting outcomes.[3–5,9,10] Similarly, there is a large body of literature on visual and quantitative methods applied to invasive intracranial EEG data to answer the same research questions.[11–14] Spectral power and coherence measures are

Key points

- We performed a machine learning analysis to evaluate whether visually reviewed normal presurgical scalp electroencephalography (EEG) findings without any interictal abnormalities can predict the outcomes following an anterior temporal lobectomy.
- We achieved an area under the curve of 0.78 in predicting outcomes using a leave-one-out cross-validation in a data set including 41 patients from the Mayo Clinic.
- Independent testing of the machine learning model on a data set including 23 patients from the Cleveland Clinic yielded an area under the curve of 0.76.
- Our results provide strong evidence that quantitative analysis of normal scalp EEG can help in the prognostication of anterior temporal lobectomy outcomes.

among the common quantitative measures studied using both scalp and intracranial EEG.[15–21] More recently, the investigation of high-frequency oscillations recorded on scalp EEG[22–24] and interictal spikes from combined scalp and intracranial EEG[25] have received significant interest in the study of outcome prognostication. However, the evaluation of interictal EEG without epileptiform activity or slowing, that is, visually classified normal EEG by an epileptologist, has received less attention.

Multiple studies have reported that quantitative analysis of EEG segments without interictal epileptiform abnormalities can reveal subtle nonspecific abnormalities in the normal brain function of patients with epilepsy.[26–34] These electrophysiological changes are hypothesized to arise from epilepsy-related pathologic changes such as neuronal loss, gliosis, and synaptic and network changes. They may also reflect interictal dysfunction in memory and cognition because the same neuronal-glial circuits underlying seizure generation in TLE may subserve normal brain functions.[35,36] The EEG biomarkers of normal brain function investigated in previous studies include alpha activity during eyes-closed wakefulness,[26–29] spectral connectivity measures based on phase-locking factor[30–32] and weighted partial directed coherence,[33] and EEG-based local and global synchrony measures.[34] Furthermore, several of those studies showed that the changes in EEG biomarkers of normal brain function can help determine, a) drug resistance,[26,27,29] b) focal vs generalized origin of seizures,[30,32] and c) seizure-generating hemisphere in focal epilepsy.[26] Building on those findings, we hypothesize that biomarkers of normal EEG can help predict the likelihood of seizure recurrence following ATL.

To test that hypothesis, we analyzed presurgical scalp EEG studies of 41 Mayo Clinic (MC) and 23 Cleveland Clinic (CC) patients who underwent ATL for drug-resistant TLE. We used an unbiased automated tool to select eyes-closed awake epochs in scalp EEG recordings determined by epileptologists to be free of any epileptiform activity or other abnormalities and calculated spectral power and interhemispheric spectral coherence measures between 1 and 25 Hz at several brain regions covered by the extended 10–20 scalp EEG montage. We then analyzed the group statistical differences within those measures based on at least 1 year of follow-up for seizure freedom and used a machine learning analysis to quantify the predictability of surgery outcomes. Furthermore, we compared the predictability of normal scalp EEG-derived features with MRI abnormalities to evaluate whether there is a distinct, additional predictive value in normal scalp EEG.

2 | MATERIALS AND METHODS

2.1 | Study participants

In this retrospective cohort study, we identified 64 patients who underwent ATL for drug-resistant epilepsy at the Mayo Clinic (41 patients) and Cleveland Clinic (23 patients). We used the inclusion criterion that either their routine outpatient EEG or the first day of prolonged video-EEG study was interictally normal (i.e., free of interictal epileptiform abnormalities, focal slowing, or excessive fast activity). We used this inclusion criterion to ensure that the EEGs we later analyzed did not contain any interictal abnormalities. In the case of prolonged video-EEG studies, we did not place any restrictions beyond the first day. All patients except one had their habitual seizures recorded during the video-EEG study. Although this is a select cohort, it reflects the purpose of our study to determine if quantitative analysis of visually reviewed normal scalp EEG can predict ATL outcomes. Our study was approved by the institutional review boards of the respective institutions.

2.2 | Presurgical evaluations

All patients underwent comprehensive evaluations for epilepsy surgery that included (a) neurological history and examination, (b) routine scalp EEG, (c) MRI, and (d) prolonged video-EEG to record their seizures. All patients had abnormal video-EEG results, including recorded seizures prior to ATL. In addition, some patients underwent positron emission tomography (PET), single-photon emission computerized tomography (SPECT), magneto-electroencephalography (MEG), and intracranial EEG (iEEG) monitoring as indicated by the clinical evaluation. (See Table S1 for detailed results of the clinical evaluation.)

2.3 | Surgery and outcomes

All patients underwent standard ATL, which included anterior temporal neocortex and amygdalahippocampal resection.[2,4,5] To binarize seizure outcomes following ATL, we used Engel IA-IB or International League Against Epilepsy (ILAE) class 1–2 outcomes during the first year following ATL as the threshold to determine seizure-free outcomes. In the above-identified cohort, 30 MC and 16 CC patients experienced seizure-free outcomes for at least 1 year following ATL.

2.4 | EEG acquisition

The EEG studies at MC were recorded using the XLTEK EMU40EX headbox (from Natus Medical Incorporated) using 31 channels according to the extended 10–20 localization system[37] at a sampling rate of 256 Hz. The EEG studies at CC were recorded using the Nihon Kohden JE-921A, JE-120A, and JE-208A headboxes (Nihon Kohden Corporation) using the same extended 10–20 localization system at a sampling rate of 200 Hz.

2.5 | Data curation and preprocessing

We analyzed exactly one EEG per participant, which included 42 routine (32 MC and 10 CC) and 22 prolonged epilepsy monitoring unit (EMU; 9 MC and 13 CC) studies. To be consistent with the effect of antiseizure medications (ASMs), we discarded the EEG recorded beyond the first day of prolonged EMU studies when ASMs are tapered. All EEG preprocessing was performed using the MNE library in the Python programming language.[38] The EEG recordings were bandpass-filtered within 0.5–30 Hz, and artifact components reflecting electrocardiography and eye movements were removed using the signal subspace projection method implemented in the MNE library.[21]

2.6 | Eyes-closed epoch selection

We then selected multiple 10 s-long eyes-closed awake (EC) epochs (maximum of six epochs per participant) using an automated algorithm (58 participants had 6 EC epochs, and 6 participants had <6 epochs). The automated algorithm included the following steps: (a) divide the preprocessed EEG recording into epochs of 10 s; (b) automatically score sleep stages using a previously published algorithm[39]; (c) select epochs that do not contain eye blinks from the epochs scored as "awake" by the sleep staging algorithm[38]; (d) rank those eyes-closed epochs in order of spectral power in the alpha frequency range (8–12 Hz) in posterior channels (O1 and O2); and (e) select the first six epochs (fewer if six epochs were not available) with the highest posterior alpha power. This approach was able to successfully extract six EC epochs from 58 of the 64 EEG records and two to six EC epochs from the rest of the EEG records.

2.7 | Feature extraction

For each epoch, we estimated the power spectral density (PSD, in decibels) at frequencies between 1 and 25 Hz (25 integer frequencies) using a Welch fast-Fourier transform approach[1] across all EEG channels. Those PSD values were then aggregated among the channels located in prefrontal (Fp1 and Fp2), frontal (F3, F7 and F4, F8), temporal (T7 and T8), central (C3 and C4), parietal (P3, P7 and P4, P8), and occipital (O1 and O2) regions to estimate the PSD values for those respective regions. Note that the PSD values in the left and right hemispheres were averaged to produce a single PSD value per region. Hence, this process yielded $N_s \times 6 \times 25$ features per patient (6 regions and 24 frequencies), where N_s is the number of epochs. Similarly, we also estimated the interhemispheric spectral-coherence density (ISD) for each region (magnitude squared spectral coherence[2] between the channels in the left and right hemispheres of the respective region) at the same frequencies, which yielded another $N_s \times 6 \times 25$ features per patient.

2.8 | Feature normalization

Prior to any statistical or machine learning analysis, PSD features were normalized to eliminate any systematic differences in data acquisition. We calculated a grand average of the total spectral power between 1 and 25 Hz (among all channels and participants) for the two data sets and divided the individual spectrums using that average. We performed this normalization separately for the two data sets because of the differences in the range of absolute spectral power values observed. We did not normalize ISD features, as they were already normalized within the 0–1 range.

2.9 | Statistical analyses

We first analyzed the statistical differences within the PSD and ISD features between seizure-free and non–seizure-free groups. To do so, we aggregated the PSD and ISD values within delta (1–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), and beta (13–25 Hz) bands. We then calculated Pearson correlations between the band-limited PSD and ISD values and surgery outcomes and performed a Mann-Whitney-Wilcoxon test between those features conditioned on the surgery outcomes with Bonferroni correction for multiple comparisons.

2.10 | Classification framework

We then employed a Naïve Bayes (NB) classification approach using both the PSD and ISD features to

predict surgery outcomes. We chose to utilize the NB classifier for this task because of the relatively small sample size. This approach was evaluated using a leave-one-patient-out cross-validation strategy within the MC data set and tested using the out-of-sample CC data set. We assigned labels of "1" and "0" to seizure-free and non–seizure-free outcomes, respectively. During model training, we treated each epoch from a patient's EEG as a separate sample with the same outcome label as the patient and developed a classifier that predicted the probability of seizure freedom for an unseen epoch in the testing set. Note that the epochs of a single patient were never shared between the training and the testing sets during each cross-validation. We calculated the class probabilities in this fashion for all epochs in the data set and compared them with the ground truth labels to plot the receiver-operating characteristic (ROC) curve for the Mayo data set. In addition, we utilized the trained model during each cross-validation and predicted the class probabilities for the CC data set. We then averaged the predicted probabilities across all cross-validations to calculate the final probabilities, which were used to plot the ROC curve for the CCF data set. Furthermore, the predicted probabilities of all the epochs of a single patient were averaged to produce the probability for that patient. Using the patient-level probabilities, we also plotted patient-level ROC curves to ensure that the window-level classification translated well to individual patients. Apart from the area under the ROC curve (AUC) metric, we calculated other metrics such as precision, recall, and F1 score as the weighted averages of the respective individual class-specific metrics at an operating point on the ROC curve that provided the best sensitivity and specificity.[40] This process is illustrated in Figure 1.

3 | RESULTS

3.1 | Study participants

Table 1 describes the participants of this study, which included 41 TLE patients from MC and 23 TLE patients from CC. All participants were 18 years or older, and 30 MC and 16 CC patients were seizure-free for at least 1 year following ATL. Twenty-seven MC patients (65.9%)

TABLE 1 Participants of our study and their classifications based on 1-year outcomes of anterior temporal lobectomy, sex, age, seizure focus lateralization, general MRI abnormalities, and mesial temporal sclerosis

	Mayo Clinic	Cleveland Clinic
Number of patients	41	23
1-year seizure freedom following ATL	30	16
Sex (female)	15	14
Age at EEG in years, mean (range)	38.43 (18–69)	44.3 (23–77)
Left TLE	15	9
Abnormal MRI	27 (20 seizure-free)	15 (11 seizure-free)
Normal MRI	14 (10 seizure-free)	8 (5 seizure-free)
Mesial temporal sclerosis	11 (10 seizure-free)	12 (9 seizure-free)
Absence of mesial temporal sclerosis	30 (20 seizure-free)	11 (7 seizure-free)

Abbreviations: ATL, anterior temporal lobectomy; EEG, electroencephalography; MRI, magnetic resonance imaging; TLE, temporal lobe epilepsy.

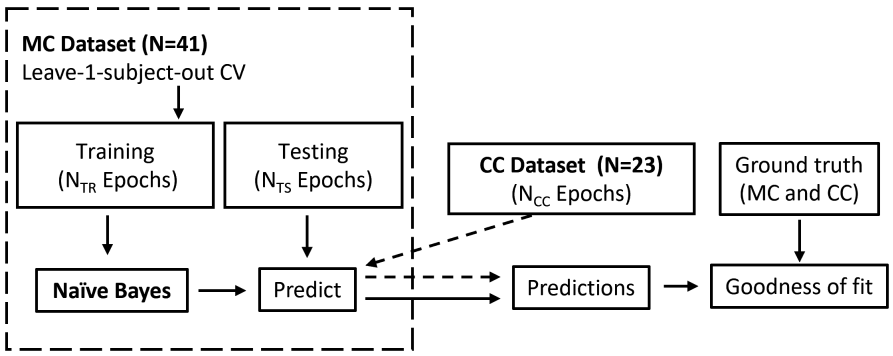

FIGURE 1 Classification of ATL outcomes using power spectral and interhemispheric coherence features extracted from presurgical routine EEG studies. We employed a Naïve Bayes classification approach using a leave-one-patient-out cross-validation within the MC data set and out-of-sample testing of the CC data set. ATL, Anterior temporal lobectomy; CC, Cleveland Clinic; EEG, electroencephalography; MC, Mayo Clinic

and 15 CC patients (65.2%) showed abnormalities in MRI during presurgical evaluation, and 11 MC patients (26.8%) and 12 CC patients (52.2%) were determined to have mesial temporal sclerosis (MTS) on pathology assessment of resected tissue. Among those with abnormal MRI, 20 MC patients (74.1%) and 8 CC patients (73.3%)

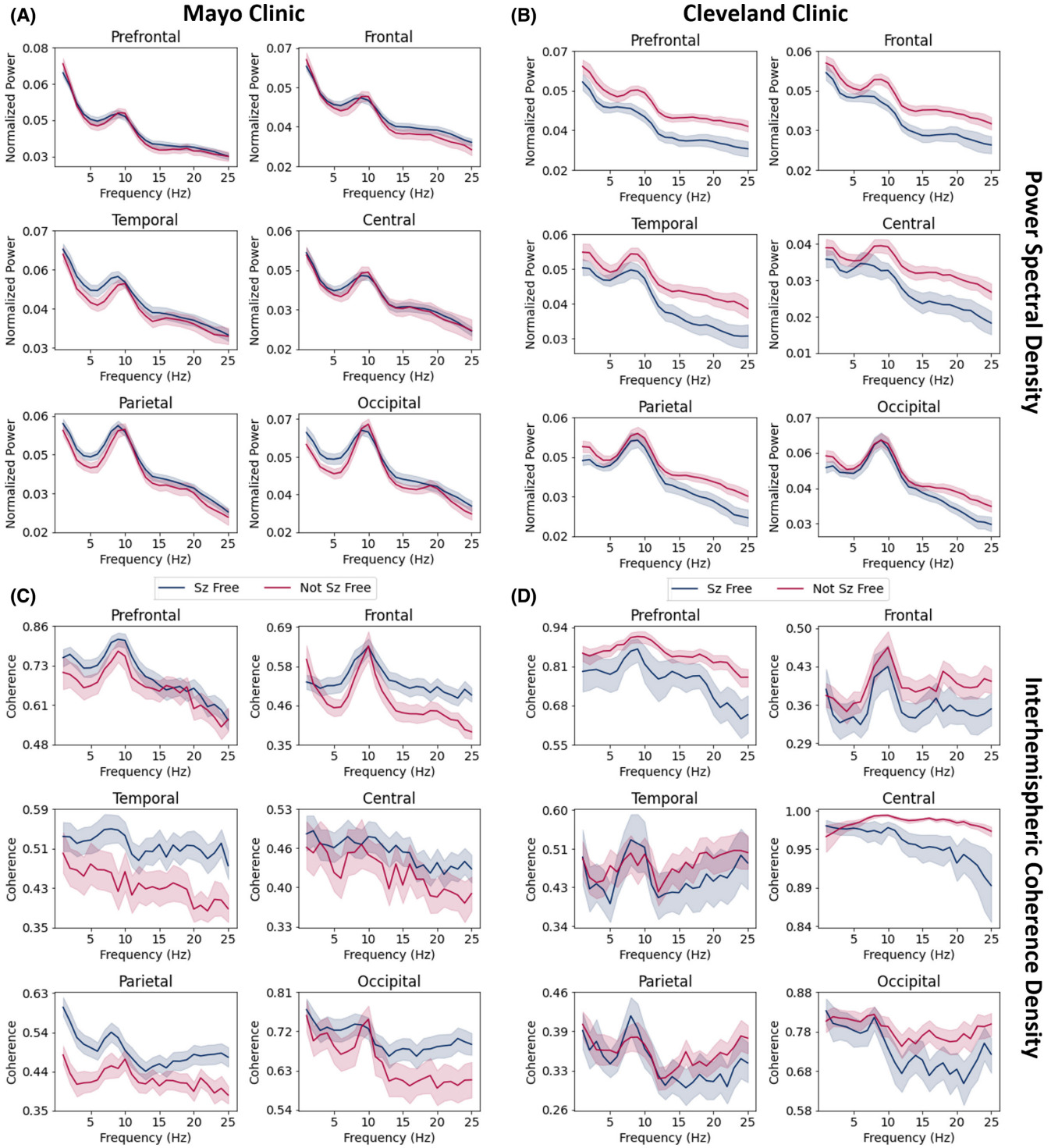

FIGURE 2 Power spectral (A-B) and spectral coherence-based (C-D) differences between MC and CC patients based on seizure-free outcomes following ATL. We estimated power spectral and spectral coherence densities using the Welch FFT approach at every integer frequency between 1 and 25 Hz. We then aggregated those densities among the channels located in prefrontal (Fp1 and Fp2), frontal (F3, F7 and F4, F8), temporal (T7, T9 and T8, T10), central (C3 and C4), parietal (P3, P7 and P4, P8), and occipital (O1 and O2) regions to estimate regional power spectral and regional interhemispheric spectral coherence densities. The power spectral densities were then normalized across the two populations within 1–25 Hz to harmonize the two data sets. Here solid lines indicate average values and shaded areas indicate 95% confidence intervals. ATL, Anterior temporal lobectomy; CC, Cleveland Clinic; FFT, Fast Fourier Transform; MC, Mayo Clinic

were seizure-free for 1 year following ATL. Similarly, among those with MTS, 10 MC patients (90.9%) and 9 CC patients (75%) were seizure-free for 1 year following ATL. Additional details regarding each individual participant can be found in Table S1.

3.2 | Comparison of spectral features

Figure 2 illustrates the average spectral differences between MC and CC patients who experienced 1-year seizure freedom following ATL and those who did not. Here we analyzed normalized regional power spectral and interhemispheric spectral coherence densities at every integer frequency between 1 and 25 Hz (as described in Methods). Figure 2A,B suggest that the PSD values of those who were seizure-free are, on average, higher than those who were not. Similarly, Figure 2C,D indicates that the ISD values of those who were seizure-free are higher in frontal, temporal, parietal, and occipital regions in frequencies above 10 Hz. The lower frequency behavior (i.e., 1–10 Hz), however, is more complex and does not appear consistent across both cohorts.

To further quantify the differences, we aggregated the PSD and ISD values within delta (1–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), and beta (13–25 Hz) bands. We then (a) calculated the Pearson correlations between the band-limited PSD and ISD values and surgery outcomes and (b) performed a Mann-Whitney-Wilcoxon test between the features conditioned on the surgery outcomes with the application of Bonferroni correction for multiple comparisons. The results of these analyses are shown in Figure 3. Those results indicate that both MC and CC data sets show significant differences between patients who experienced seizure freedom following ATL and those who did not. However, we note that the commonalities between the two data sets (MC and CC) are complex, although we observed somewhat consistent patterns in ISD features above 10 Hz across several brain regions (prefrontal, frontal, parietal, and occipital).

3.3 | Classification of seizure freedom following ATL using normal interictal scalp EEG

We performed several classification experiments between the patients who experienced 1-year seizure freedom following ATL and those who did not, using the framework

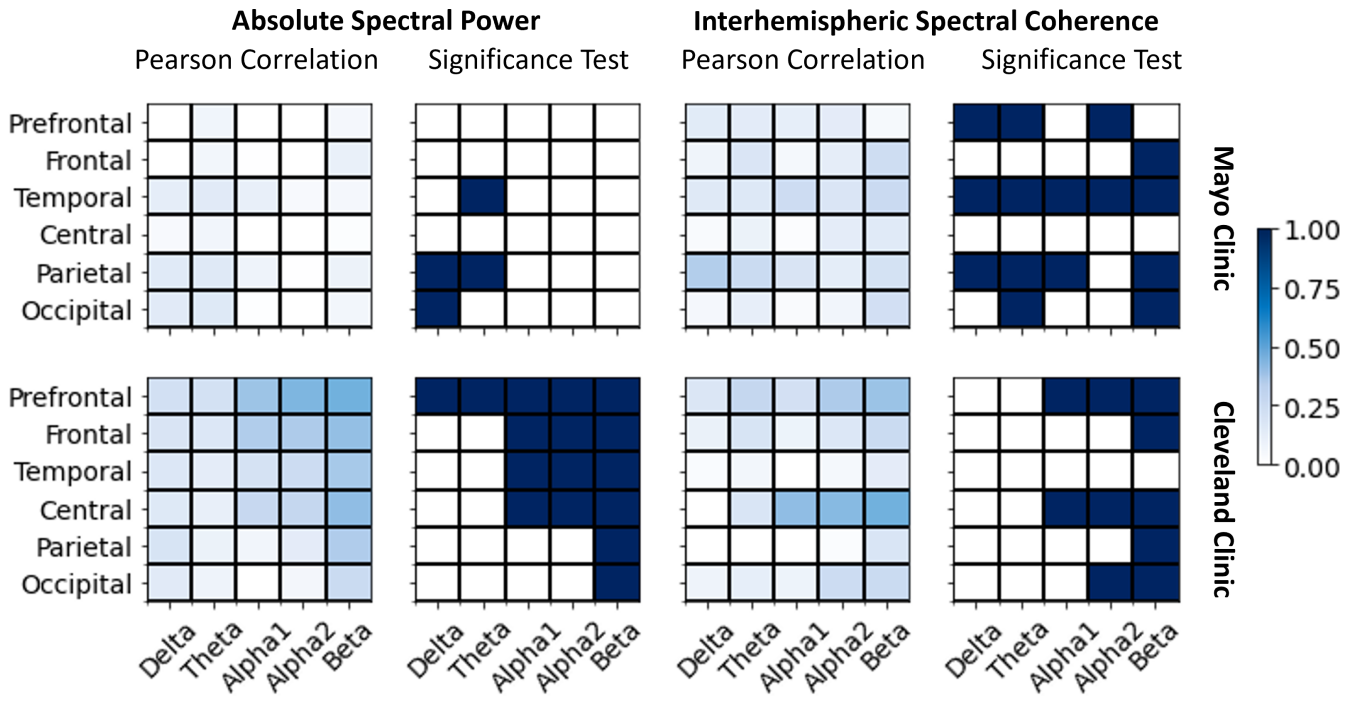

FIGURE 3 Statistical differences of power spectral density and interhemispheric spectral coherence density features between patients who experienced seizure freedom following anterior temporal lobectomy and those who did not. Those features were aggregated among six brain regions and five frequency bands prior to analyses. We then calculated Pearson correlations and performed Mann-Whitney-Wilcoxon tests between the two sets of features conditioned on the surgery outcomes with the application of Bonferroni correction for multiple comparisons. For Pearson correlation, blue entries indicate positive correlations (>0) with darker colors indicating stronger correlations. For significance tests, dark blue entries indicate statistically significant differences ($p < .05$), and white entries indicate nonsignificant differences ($p > .05$)

described in Methods. The results of those experiments are shown in Table 2. First, we compared the predictability using all frequencies full bandwidth (1–25 Hz), low frequencies (1–9 Hz), and high frequencies (10–25 Hz), using the PSD and ISD values from all six brain regions (the first three rows of Table 2). Our results suggest that using all the frequencies (1–25 Hz) and high frequencies (10–25 Hz) provide relatively better classification performances between MC and CC data sets compared to lower frequencies (1–9 Hz). Second, we compared the contributions of PSD and ISD features within the low- and high-frequency range (rows 4–7). Our results indicate that ISD features, particularly in the 10–25 Hz frequency range, provide balanced predictability between MC and CC, compared to all other combinations. Overall, all the experiments provided classification performances substantially better than chance-level (>0.5), and ISD features in the 10–25 Hz range contributed the most to the classification performance. Figure 4A,B shows the ROC curves for MC and CC data sets at the window and patient levels for the classification using ISD features in the 10–25 Hz range across all six brain regions (corresponding to row 7 of Table 2). Figure 4C shows the confusion matrices for MC and CC data sets (at patient level) derived at an operating point that provided the best sensitivity and specificity for the respective ROC curve. The confusion matrices indicate that the proposed approach is very successful in identifying those who may experience seizure recurrence within the first year (top-left cell in each matrix).

3.4 | Comparison between normal scalp EEG and MRI abnormalities

Table 3 illustrates a comparison between features derived from normal interictal scalp-EEG segments and MRI abnormalities in predicting ATL outcomes at 1 year. Specifically, we compared the predictability of previously described scalp-EEG–derived ISD features in the 10–25 Hz frequency range (row 1) against (a) abnormal MRI findings (row 2) and (b) the presence of mesial temporal sclerosis (row 3). Our findings indicate that the features extracted from normal interictal scalp EEG segments provide superior predictability when compared with MRI abnormalities in both the MC and CC cohorts.

4 | DISCUSSION

4.1 | Main contribution of the study

The ability to predict surgical outcomes of anterior temporal lobectomy is of great clinical and research interest. Previous

TABLE 2 Results of classification experiments at the patient level

Spectral power		Spectral coherence		Mayo Clinic				Cleveland Clinic (out of sample)			
Regions	Frequencies	Regions	Frequencies	AUC	Precision	Recall	F1	AUC	Precision	Recall	F1
All	1–25 Hz	All	1–25 Hz	0.69	0.8	0.63	0.65	0.86	0.88	0.87	0.87
All	1–9 Hz	All	1–9 Hz	0.67	0.76	0.73	0.74	0.63	0.75	0.61	0.62
All	10–25 Hz	All	10–25 Hz	0.71	0.8	0.73	0.75	0.85	0.88	0.87	0.87
All	1–9 Hz	None	None	0.57	0.72	0.73	0.73	0.62	0.72	0.74	0.73
All	10–25 Hz	None	None	0.5	0.66	0.66	0.66	0.75	0.79	0.78	0.79
None	None	All	1–9 Hz	0.72	0.77	0.76	0.76	0.54	0.66	0.61	0.62
None	None	All	10–25 Hz	0.78	0.82	0.68	0.7	0.76	0.79	0.78	0.79

Note: A Naïve Bayes classifier was trained using the MC data set in a leave-one-patient-out cross-validation setting and tested on the out-of-sample CC data set. The area under curve metric was calculated by plotting the ROC curve, and other metrics were calculated at an operating point on the ROC curve that provided the best sensitivity and specificity.

Abbreviations: CC, Cleveland Clinic; MC, Mayo Clinic; ROC, receiver-operating characteristic.

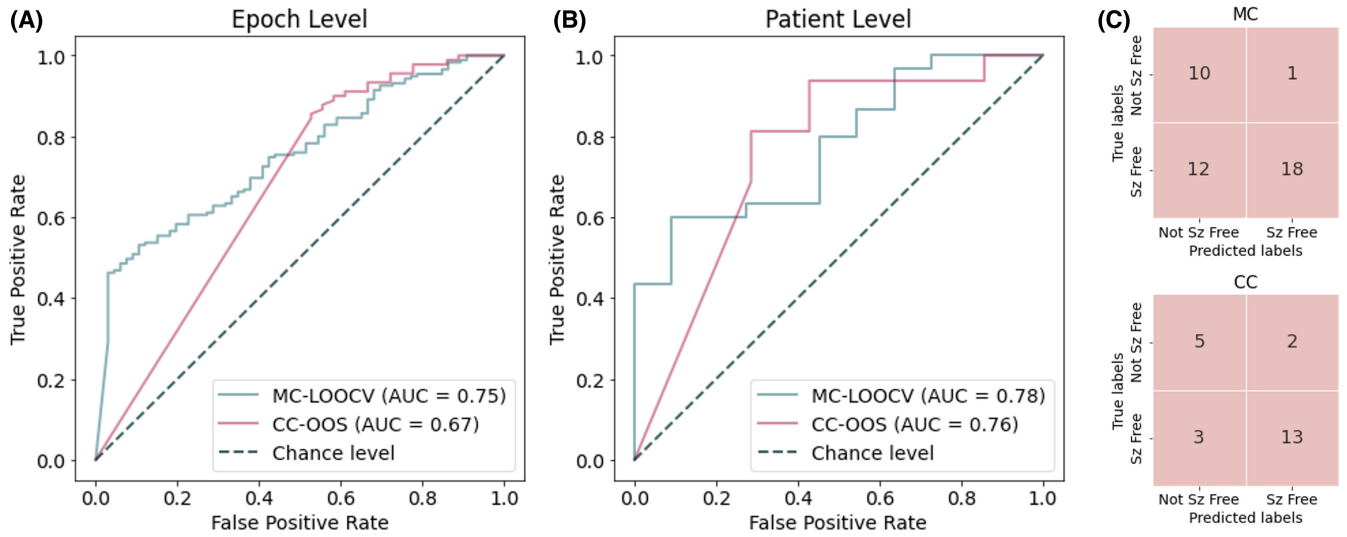

FIGURE 4 Epoch-level (A) and patient-level (B) receiver-operating characteristic (ROC) curves for MC and CC data sets obtained using a Naïve Bayes classifier trained with features including interhemispheric spectral coherence densities of all six brain regions within 10–25 Hz. The classifier was trained using the MC data set in a leave-one-patient-out cross-validation (LOOCV) setting and tested on the out-of-sample (OOS) CC data set. Note that the classifier was trained using features extracted from epochs, and then the predicted epoch-level probabilities were averaged to produce patient-level probabilities. Those probabilities were then used to plot ROC curves. (c) Confusion matrices for the MC and CC data sets (at patient level) were obtained using a threshold on the respective ROC curve that provided the best sensitivity and specificity. The cross-diagonal terms of the confusion matrices show correctly predicted outcomes. CC, Cleveland Clinic; MC, Mayo Clinic; ROC, receiver-operating characteristic

TABLE 3 Comparison between the predictability of ATL outcomes using PSD and ISD features derived from normal scalp EEG segments and MRI abnormalities

	Mayo Clinic				Cleveland Clinic			
	AUC	Precision	Recall	F1	AUC	Precision	Recall	F1
Normal interictal scalp EEG	0.78	0.82	0.68	0.7	0.76	0.79	0.78	0.79
Abnormal MRI	—	0.61	0.58	0.60	—	0.62	0.61	0.62
Mesial temporal sclerosis	—	0.75	0.49	0.49	—	0.63	0.57	0.58

Abbreviations: ATL, anterior temporal lobectomy; ISD, interhemispheric spectral-coherence density; PSD, power spectral density.

studies have reported the impact of ictal and interictal EEG abnormalities and structural MRI abnormalities in prognosticating ATL outcomes.[4,5] However, to our knowledge, whether visually interpreted normal interictal EEG offers any prognostic value has not been considered previously. Here we analyzed multiple EEG features such as spectral power and interhemispheric spectral coherence within normal interictal EEG segments prior to surgery and demonstrated that there are substantial differences within those features between the TLE patients who experienced 1-year seizure freedom following ATL and those who did not achieve seizure-free outcomes. Furthermore, a machine learning analysis revealed that those EEG features could predict 1-year seizure freedom following ATL with AUCs greater than or equal to 0.75 in both the training and validation data set (MC) and in the out-of-sample testing data set from a different institution (CC). Further analyses showed that frequencies in the 10–25 Hz provided higher predictability compared to lower frequencies, particularly in ISD features. In addition, a comparison showed that the features extracted from normal scalp EEG provide superior predictability compared to MRI abnormalities in both the study cohorts. These findings provide strong evidence that quantitative analysis of normal interictal scalp EEG can help in the presurgical assessment of ATL candidates. Considering that routine scalp EEG is relatively inexpensive (compared to intracranial EEG and MRI), and that normal scalp EEG samples can be acquired in ambulatory settings, our findings can form the basis for novel and cost-effective ways to help assess the surgical candidacy of TLE patients, and, potentially, to identify candidates for iEEG monitoring prior to surgery.

4.2 | Interpretation of the results

A comparison of the spectral features, illustrated in Figure 2, indicates that spectral power and interhemispheric spectral coherence are significantly lower in several brain regions and frequencies for those who experienced seizure recurrence within 1 year of surgery. Although the exact mechanisms underlying this finding require further exploration, several factors could have contributed to this observation. Previous studies have reported that age at seizure onset, age at surgery, duration of epilepsy, and seizure frequency can influence outcomes of ATL, particularly in the long term.[41–44] A longer history and higher frequency of seizures may be associated with more severe chronic structural and functional abnormalities and can lead to progressive hippocampal injury and possibly the formation of secondary epileptogenic zones.[41] Furthermore, an association between the epilepsy duration and the bilateral decline of hippocampal volumes, brain glucose metabolism, and Wada hemispheric memory performance has been reported.[45] It is plausible that the spectral differences in visually interpreted normal interictal EEG segments represent an overall measure of epilepsy-related injury to the circuits involved in normal brain function.

Prior investigations using intracranial EEG show that the local synchrony is decreased surrounding the epileptogenic zone.[46–48] Because PSD is a measure of local synchrony and ISD a measure of interhemispheric network synchrony, the widespread decreased PSD and ISD in the patients with poor outcomes compared to those with good outcomes may reflect more severe and widespread epilepsy with more loss of local and network neuronal synchrony. On the other hand, the scalp EEG findings associated with good outcomes are those that are driven by anterior and/or mesial temporal lobe epileptogenic zone, which would be removed or disconnected by a standard ATL. Furthermore, we hypothesize that reduced scalp EEG power in the higher frequency range reflects abnormalities in the neocortex as opposed to deeper brain structures. In summary, we can speculate that changes in limbic networks associated with mesial temporal lobe epilepsy may be distinguishable with quantitative EEG measures used here and would characterize the patients most likely to have seizure-free outcomes after ATL surgery.

4.2.1 | Contribution of antiseizure medications

In addition, we considered whether the changes in EEG spectral power and coherence could be related to ASMs, particularly benzodiazepines.[49] However, as detailed in Table S1, only 2 MC patients (out of 41) and 3 CC patients (out of 23) were taking benzodiazepines at the time of EEG. Because the number of patients taking ASMs is relatively small compared to the total size of the cohort, we conclude that ASMs, and in particular benzodiazepines, cannot explain the population differences we observed between the seizure-free and non–seizure-free groups.

4.2.2 | Predictive value of normal scalp EEG when compared with MRI abnormalities

The presence of a distinct anatomical lesion identified by MRI is now arguably the most reliable predictor of seizure freedom following ATL.[5] However, our results indicate that normal scalp EEG–derived features provide superior and potentially distinct predictability of ATL outcomes compared to MRI abnormalities in the two cohorts we studied. Although this finding needs further validation in a larger population of patients, if validated, this finding could improve the current state of presurgical evaluations, particularly for those with normal MRI studies.

4.3 | Observations from a multicenter study

Replicating the results of machine learning–based analyses among multiple data sets, particularly when the data sets include physiological measurements such as EEG, is important to evaluate the potential for clinical translation. Our classification results were obtained by training a machine learning model using the EEG data acquired at MC and independently testing that model on out-of-sample EEG data acquired at CC. Although the ability to demonstrate similar predictability between the two data sets strengthens our findings, there were noticeable differences between the two data sets. First, the ranges of absolute spectral power values significantly differed between the two data sets. This observation is most likely a result of the different EEG acquisition systems used at the two institutions. Therefore, separate normalizations of the two data sets were necessary to evaluate them under the same machine learning framework. We normalized each data set using a grand average of the total spectral power between 1 and 25 Hz, calculated separately for each data set. However, we anticipate that control EEG data sets acquired using the respective acquisition conditions of the data sets will benefit future evaluations, including multicenter data sets. Second, even after normalization, we noticed that the group differences within the spectral features suggested inconsistent relationships in low frequencies (<10 Hz), particularly close to 1 Hz (Figure 2). This observation might result from hardware filter settings

of the respective acquisition systems and needs further exploration. However, both the data sets showed similar relationships in frequencies above 10 Hz. This effect is also evident in the classification results; we obtained relatively worse classification results when low-frequency features were used for classification, compared to higher frequencies (see Table 2). Nonetheless, we obtained better and more consistent results when features of frequencies above 10 Hz were utilized.

4.4 | Limitations and future work

Replicating our findings on large multicenter data sets can help clarify the clinical value and potential pitfalls. A larger population-based data set will elucidate the independent predictive value of our finding when controlled for the effects of confounders such as age and medications.[50] In addition, the development of a clinically useful individualized EEG-based ATL outcome prognostication tool will require EEG recordings of healthy controls using the EEG acquisition systems at the respective medical centers. Our future efforts will focus on acquiring control EEG studies from multiple EEG acquisition systems for data normalization to ensure clinical translation.

Although our study utilized 1-year seizure freedom as a measure of outcomes, several studies have reported that the success rate of ATL keeps diminishing with longer follow-up periods.[41] In the future, we will investigate whether the same methodology can predict long-term outcomes beyond 1 year. We believe that our methodology can help quantify the changes in normal brain function following ATL (by comparing pre- and postoperative scalp EEG recordings) and hence may be useful in determining long-term outcomes even if the patient is seizure-free in the short term.

Furthermore, our study included awake eyes-closed EEG segments extracted from routine or the first day of prolonged EEG studies while the ASM effects were still present. However, it is possible that the pathological features in EEG are more identifiable during the time when ASMs are withdrawn or during other behavioral states, including slow-wave sleep. Therefore, in the future, we plan to analyze the predictability of ATL outcomes using EEG segments extracted from different stages of prolonged studies accounting for medication variability and behavioral states, including awake and sleep.

5 | CONCLUSION

Our results support that quantitative evaluation of interictal scalp EEG visually interpreted as normal by experienced epileptologists may help prognosticate seizure freedom after ATL in patients with drug-resistant TLE. Specifically, spectral power and interhemispheric coherence features extracted from normal scalp EEG segments during eyes-closed wakefulness showed significant differences between patients who became seizure-free and those who did not. Future studies focused on (a) larger and prospective patient cohorts, (b) effect of behavioral state, and (c) confounders such as age and medication effects can clarify the potential of using scalp EEG recordings to prognosticate surgical outcomes of ATL.

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CONFLICT OF INTEREST

Dr. Worrell has licensed intellectual property to NeuroOne Inc. and Cadence Neuroscience Inc. Dr. Brinkmann reports that he has licensed intellectual property to Cadence Neuroscience Inc. Dr. Cendes reports personal fees from UCB Pharma, grants from Sao Paulo Research Foundation (FAPESP), and grants from CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), outside the submitted work; and is a member of the editorial boards of the following journals: *Neurology*, *Epilepsy Research*, *Epilepsia* (Associate Editor), and *Frontiers in Neurology* (Specialty Chief Editor in Epilepsy). All other authors have nothing to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Yogatheesan Varatharajah https://orcid.org/0000-0002-4547-0036
Boney Joseph https://orcid.org/0000-0002-1576-9344
Benjamin Brinkmann https://orcid.org/0000-0002-2392-8608
Zachary Fitzgerald https://orcid.org/0000-0002-6702-1063
Fernando Cendes https://orcid.org/0000-0001-9336-9568
Lara Jehi https://orcid.org/0000-0002-8041-6377

ENDNOTES

[1] https://mne.tools/stable/generated/mne.time_frequency.psd_welch.html

[2] https://mne.tools/mne-connectivity/stable/generated/mne_connectivity.spectral_connectivity.html

REFERENCES

1. Engel JJr, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012;307(9):922–30.

2. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001;345(5):311–8.
3. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain. 2005;128(Pt 5):1188–98.
4. Jeha LE, Najm IM, Bingaman WE, Khandwala F, Widdess-Walsh P, Morris HH, et al. Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. Neurology. 2006;66(12):1938–40.
5. Radhakrishnan K, So EL, Silbert PL, Jack CR, Cascino GD, Sharbrough FW, et al. Predictors of outcome of anterior temporal lobectomy for intractable epilepsy: a multivariate study. Neurology. 1998;51(2):465–71.
6. Azeem A, Ellenrieder N, Hall J, Dubeau F, Frauscher B, Gotman J. Interictal spike networks predict surgical outcome in patients with drug-resistant focal epilepsy. Ann Clin Transl Neurol. 2021;8(6):1212–23.
7. Uldall P, Alving J, Hansen LK, Kibaek M, Buchholt J. The misdiagnosis of epilepsy in children admitted to a tertiary epilepsy centre with paroxysmal events. Arch Dis Child. 2006;91(3):219–21.
8. Fitzgerald Z, Morita-Sherman M, Hogue O, Joseph B, Alvim MKM, Yasuda CL, et al. Improving the prediction of epilepsy surgery outcomes using basic scalp EEG findings. Epilepsia. 2021;62(10):2439–50.
9. Gilliam F, Bowling S, Bilir E, Thomas J, Faught E, Morawetz R, et al. Association of combined MRI, interictal EEG, and ictal EEG results with outcome and pathology after temporal lobectomy. Epilepsia. 1997;38(12):1315–20.
10. Schulz R, Luders HO, Hoppe M, Tuxhorn I, May T, Ebner A. Interictal EEG and ictal scalp EEG propagation are highly predictive of surgical outcome in mesial temporal lobe epilepsy. Epilepsia. 2000;41(5):564–70.
11. Jobst BC, Bartolomei F, Diehl B, Frauscher B, Kahane P, Minotti L, et al. Intracranial EEG in the 21st century. Epilepsy Curr. 2020;20(4):180–8.
12. Asano E, Juhász C, Shah A, Sood S, Chugani HT. Role of subdural electrocorticography in prediction of long-term seizure outcome in epilepsy surgery. Brain. 2009;132(Pt 4):1038–47.
13. Shah P, Bernabei JM, Kini LG, Ashourvan A, Boccanfuso J, Archer R, et al. High interictal connectivity within the resection zone is associated with favorable post-surgical outcomes in focal epilepsy patients. Neuroimage Clin. 2019;23:101908.
14. Lee RW, Hoogs MM, Burkholder DB, Trenerry MR, Drazkowski JF, Shih JJ, et al. Outcome of intracranial electroencephalography monitoring and surgery in magnetic resonance imaging-negative temporal lobe epilepsy. Epilepsy Res. 2014;108(5):937–44.
15. Jacobs J, Vogt C, LeVan P, Zelmann R, Gotman J, Kobayashi K. The identification of distinct high-frequency oscillations during spikes delineates the seizure onset zone better than high-frequency spectral power changes. Clin Neurophysiol. 2016;127(1):129–42.
16. Schindler K, Leung H, Elger CE, Lehnertz K. Assessing seizure dynamics by analysing the correlation structure of multichannel intracranial EEG. Brain. 2007;130(Pt 1):65–77.
17. Goodfellow M, Rummel C, Abela E, Richardson MP, Schindler K, Terry JR. Estimation of brain network ictogenicity predicts outcome from epilepsy surgery. Sci Rep. 2016;6:29215.
18. Rummel C, Abela E, Andrzejak RG, Hauf M, Pollo C, Müller M, et al. Resected brain tissue, seizure onset zone and quantitative EEG measures: towards prediction of post-surgical seizure control. PLoS One. 2015;10(10):e0141023.
19. Tomlinson SB, Porter BE, Marsh ED. Interictal network synchrony and local heterogeneity predict epilepsy surgery outcome among pediatric patients. Epilepsia. 2017;58(3):402–11.
20. Varatharajah Y, Berry B, Cimbalnik J, Kremen V, Van Gompel J, Stead M, et al. Integrating artificial intelligence with real-time intracranial EEG monitoring to automate interictal identification of seizure onset zones in focal epilepsy. J Neural Eng. 2018;15(4):046035.
21. Lundstrom BN, Meisel C, Van Gompel J, Stead M, Worrell G. Comparing spiking and slow wave activity from invasive electroencephalography in patients with and without seizures. Clin Neurophysiol. 2018;129(5):909–19.
22. Boran E, Sarnthein J, Krayenbühl N, Ramantani G, Fedele T. High-frequency oscillations in scalp EEG mirror seizure frequency in pediatric focal epilepsy. Sci Rep. 2019;9(1):16560.
23. Cai Z, Sohrabpour A, Jiang H, Ye S, Joseph B, Brinkmann BH, et al. Noninvasive high-frequency oscillations riding spikes delineates epileptogenic sources. Proc Natl Acad Sci USA. 2021;118(17):e2011130118.
24. Yang Y, Wang W, Wang J, Wang M, Li X, Yan Z, et al. Scalp-HFO indexes are biomarkers for the lateralization and localization of the epileptogenic zone in preoperative assessment. J Neurophysiol. 2021;126(4):1148–58.
25. Burkholder DB, Sulc V, Hoffman EM, Cascino GD, Britton JW, So EL, et al. Interictal scalp electroencephalography and intraoperative electrocorticography in magnetic resonance imaging-negative temporal lobe epilepsy surgery. JAMA Neurol. 2014;71(6):702–9.
26. Varatharajah Y, Berry B, Joseph B, Balzekas I, Pal Attia T, Kremen V, et al. Characterizing the electrophysiological abnormalities in visually reviewed normal EEGs of drug-resistant focal epilepsy patients. Brain Commun. 2021;3(2):fcab102.
27. Larsson PG, Kostov H. Lower frequency variability in the alpha activity in EEG among patients with epilepsy. Clin Neurophysiol. 2005;116(11):2701–6.
28. Knyazeva MG, Barzegaran E, Vildavski VY, Demonet J-F. Aging of human alpha rhythm. Neurobiol Aging. 2018;69:261–73.
29. Pyrzowski J, Siemiński M, Sarnowska A, Jedrzejczak J, Nyka WM. Interval analysis of interictal EEG: pathology of the alpha rhythm in focal epilepsy. Sci Rep. 2015;5:16230.
30. Pegg EJ, Taylor JR, Laiou P, Richardson M, Mohanraj R. Interictal electroencephalographic functional network topology in drug-resistant and well-controlled idiopathic generalized epilepsy. Epilepsia. 2021;62(2):492–503.
31. Chowdhury FA, Woldman W, FitzGerald THB, Elwes RDC, Nashef L, Terry JR, et al. Revealing a brain network endophenotype in families with idiopathic generalised epilepsy. PLoS One. 2014;9(10):e110136.
32. Woldman W, Schmidt H, Abela E, Chowdhury FA, Pawley AD, Jewell S, et al. Dynamic network properties of the interictal brain determine whether seizures appear focal or generalised. Sci Rep. 2020;10(1):7043.
33. Verhoeven T, Coito A, Plomp G, Thomschewski A, Pittau F, Trinka E, et al. Automated diagnosis of temporal lobe

epilepsy in the absence of interictal spikes. Neuroimage Clin. 2018;17:10–5.
34. Schmidt H, Petkov G, Richardson MP, Terry JR. Dynamics on networks: the role of local dynamics and global networks on the emergence of hypersynchronous neural activity. PLoS Comput Biol. 2014;10(11):e1003947.
35. Engel JJr, Brown WJ, Kuhl DE, Phelps ME, Mazziotta JC, Crandall PH. Pathological findings underlying focal temporal lobe hypometabolism in partial epilepsy. Ann Neurol. 1982;12(6):518–28.
36. Liu S, Parvizi J. Cognitive refractory state caused by spontaneous epileptic high-frequency oscillations in the human brain. Sci Transl Med. 2019;11(514):eaax7830.
37. Klem GH, Lüders HO, Jasper HH, Elger CThe ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl. 1999;52:3–6.
38. Gramfort A, Luessi M, Larson E, Engemann DA, Strohmeier D, Brodbeck C, et al. MEG and EEG data analysis with MNE-Python. Front Neurosci. 2013;7:267.
39. Vallat R, Walker MP. An open-source, high-performance tool for automated sleep staging. Elife. 2021;10:e70092.
40. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3(1):32–5.
41. Janszky J, Janszky I, Schulz R, Hoppe M, Behne F, Pannek HW, et al. Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. Brain. 2005;128(Pt 2):395–404.
42. Sirven JI, Malamut BL, O'Connor MJ, Sperling MR. Temporal lobectomy outcome in older versus younger adults. Neurology. 2000;54(11):2166–70.
43. Jeong SW, Lee SK, Kim K-K, Kim HO, Kim J-Y, Chung C-K. Prognostic factors in anterior temporal lobe resections for mesial temporal lobe epilepsy: multivariate analysis. Epilepsia. 1999;40(12):1735–9.
44. Bjellvi J, Olsson I, Malmgren K, Wilbe Ramsay K. Epilepsy duration and seizure outcome in epilepsy surgery: a systematic review and meta-analysis. Neurology. 2019;93(2):e159–66.
45. Jokeit H, Ebner A, Arnold S, Schüller M, Antke C, Huang Y, et al. Bilateral reductions of hippocampal volume, glucose metabolism, and wada hemispheric memory performance are related to the duration of mesial temporal lobe epilepsy. J Neurol. 1999;246(10):926–33.
46. Burns SP, Santaniello S, Yaffe RB, Jouny CC, Crone NE, Bergey GK, et al. Network dynamics of the brain and influence of the epileptic seizure onset zone. Proc Natl Acad Sci USA. 2014;111(49):E5321–30.
47. Khambhati AN, Davis KA, Lucas TH, Litt B, Bassett DS. Virtual cortical resection reveals push-pull network control preceding seizure evolution. Neuron. 2016;91(5):1170–82.
48. Warren CP, Hu S, Stead M, Brinkmann BH, Bower MR, Worrell GA. Synchrony in normal and focal epileptic brain: the seizure onset zone is functionally disconnected. J Neurophysiol. 2010;104(6):3530–9.
49. vanLier H, Drinkenburg WHIM, vanEeten YJW, Coenen AML. Effects of diazepam and zolpidem on EEG beta frequencies are behavior-specific in rats. Neuropharmacology. 2004;47(2):163–74.
50. Brown EN, Purdon PL. The aging brain and anesthesia. Curr Opin Anaesthesiol. 2013;26(4):414–9.

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