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SCOPE-mTL: A non-invasive tool for identifying and lateralizing mesial temporal lobe seizures prior to scalp EEG ictal onset

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HIGHLIGHTS

- Computer algorithms can detect temporal lobe seizures on scalp EEG before an ictal pattern arises.
- Lateralization of seizures is also possible on scalp EEG before a visible ictal pattern arises.
- Analysis of the pre-ictal scalp EEG can add valuable information to guide presurgical evaluation.

ABSTRACT

Objective: In mesial temporal lobe (mTL) epilepsy, seizure onset can precede the appearance of a scalp EEG ictal pattern by many seconds. The ability to identify this early, occult mTL seizure activity could improve lateralization and localization of mTL seizures on scalp EEG.

Methods: Using scalp EEG spectral features and machine learning approaches on a dataset of combined scalp EEG and foramen ovale electrode recordings in patients with mTL epilepsy, we developed an algorithm, SCOPE-mTL, to detect and lateralize early, occult mTL seizure activity, prior to the appearance of a scalp EEG ictal pattern.

Results: Using SCOPE-mTL, 73% of seizures with occult mTL onset were identified as such, and no seizures that lacked an occult mTL onset were identified as having one. Predicted mTL seizure onset times were highly correlated with actual mTL seizure onset times ($r = 0.69$). 50% of seizures with early mTL onset were lateralizable prior to scalp ictal onset, with 94% accuracy.

Conclusions: SCOPE-mTL can identify and lateralize mTL seizures prior to scalp EEG ictal onset, with high sensitivity, specificity, and accuracy.

Significance: Quantitative analysis of scalp EEG can provide important information about mTL seizures, even in the absence of a visible scalp EEG ictal correlate.

1. Introduction

The first phase in epilepsy presurgical evaluation uses scalp EEG monitoring to record seizures, with the intent of lateralizing and localizing the seizure onset zone. While scalp EEG is non-invasive and cost-effective, several drawbacks frequently hamper interpretation of these recordings. First, scalp EEG recordings are prone to extracerebral artifacts. Myogenic artifacts at the start of a seizure can obscure cerebral activity, making it difficult to lateralize or localize seizure onsets. Second, scalp EEG has poor sensitivity for deep brain structures. Seizures that arise from the mesial temporal lobe (mTL) can occur without any obvious scalp EEG ictal correlate, or may develop a scalp EEG ictal correlate only once the seizure has propagated beyond these deep structures (Ebersole and Pacia, 1996; Pacia and Ebersole, 1997; Risinger et al., 1989; Sakai et al., 2002). Propagated seizures may manifest on scalp EEG as midline or diffuse changes that are neither lateralizing nor localizing (Lieb et al., 1976; Spencer et al., 1985). In other cases, a significant electroclinical delay may cast doubt on scalp EEG ictal findings, even if they are lateralizing or localizing.

These factors limit interpretation of seizure recordings on scalp EEG and often result in the decision to pursue more invasive investigations with depth electrodes or subdural grids. Yet, invasive recordings are costly and carry substantial risk. In many cases,

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Abbreviations: mTL, mesial temporal lobe.

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intracranial electrodes are needed, but the available data provide little lateralizing or localizing information to guide placement of these electrodes. Development of methods that reduce the need for invasive studies, or that provide better guidance for placement of intracranial electrodes to improve the yield of these studies, is needed.

The goal of this study was to develop signal processing and computational tools to augment the utility of scalp EEG in assessing seizure onset and lateralization during Phase 1 presurgical studies. mTL epilepsy is one of the most common human focal epilepsies, and many of the aforementioned problems with scalp EEG recordings are particularly evident in mTL epilepsy. Scalp EEG ictal patterns for mTL seizures often represent propagated ictal activity, with focal mTL ictal activity starting tens of seconds before the appearance of a scalp EEG ictal pattern. The ability to identify this focal, occult mTL ictal activity in the pre-ictal scalp EEG recording, before significant seizure propagation occurs and before artifacts from clinical symptoms obscure the recording, could add valuable lateralizing and localizing information to the traditional visual interpretation of seizure recordings.

We recently developed an algorithm to detect “scalp EEG-negative” mTL seizures (mTL seizures that occur entirely without a visible scalp EEG ictal correlate), using coherence features extracted from scalp EEG data (Lam et al., 2016). This work demonstrated that, even in the absence of a visible scalp EEG ictal correlate, quantitative scalp EEG measures could still provide evidence of ongoing mTL seizure activity. Here, we develop an algorithm, SCOPE-mTL (Surface Capture of Occult Pre-ictal Epileptiform activity in the mTL) that uses scalp EEG spectral features and machine learning approaches to detect early, occult seizure activity within the mTL, from pre-ictal scalp EEG recordings. SCOPE-mTL was able to identify occult mTL seizure onsets and to lateralize mTL seizures with high accuracy, using only the scalp EEG data that precedes the onset of visible ictal activity. Computational tools developed here and in the future can complement the information gleaned from traditional visual interpretation of the EEG, to augment the evaluation of scalp EEG seizure recordings, improve epilepsy surgical decision making and outcomes, and reduce the need for invasive intracranial investigations.

2. Methods

2.1. Patient population

We studied patients who underwent monitoring with simultaneous foramen ovale (FO) electrodes and scalp EEG electrodes at our institution between 2005 and 2016. Data was analyzed retrospectively under a protocol approved by our center’s Institutional Review Board. Patients with mTL epilepsy based on semiology, neurophysiology, and imaging were included for analysis. Patients with prior brain instrumentation or extra-temporal structural abnormalities were excluded.

2.2. Scalp EEG and foramen ovale electrode recordings

Four-contact FO electrodes (Ad-Tech, Racine, WI) were placed bilaterally under fluoroscopic guidance through the foramen ovale to lie near the mTL (Sheth et al., 2014; Wieser et al., 1985). Scalp electrodes were placed using the International 10–20 system with anterior temporal electrodes (T1, T2). All recordings were acquired using XLTEK hardware (Natus Medical Inc., Pleasanton CA) with data sampled at 256, 512, or 1024 Hz.

2.3. Identification of mTL seizures and marking seizure onsets

We reviewed clinical EEG reports to identify mTL seizures that developed a scalp EEG ictal pattern at some point during the seizure. Seizures in which the pre-ictal recording was compromised by excessive electrode artifacts were excluded from analysis.

Three epileptologists (ADL, DM, SFZ) independently reviewed the seizure recordings to mark seizure onset times and lateralization. All EEG readers had advanced fellowship training in epilepsy, and two of the three readers were board-certified in both clinical neurophysiology and epilepsy. The seizure dataset analyzed by the EEG readers included a mixture of mTL seizures in which the ictal onset on FO electrodes preceded the ictal activity on scalp EEG, as well as seizures in which the scalp EEG and FO ictal onset were near simultaneous. The readers did not know beforehand which type of seizure they were reviewing. To fully mimic a Phase 1 presurgical evaluation and to prevent any bias from the FO recordings, the scalp EEG data was reviewed first, blinded to the FO data, to determine the onset time and lateralization (left, right, or not lateralized) of the first definitively ictal pattern on scalp EEG. Reviewers could switch between longitudinal bipolar, referential, and average montages, and could adjust gain and filter settings as they typically would for clinical EEG interpretation. After marking scalp EEG ictal onset and lateralization, they were then allowed to view montages with FO electrodes, to mark the FO ictal onset time and lateralization. Consensus on ictal onset times (determined independently for scalp EEG and FOs) was reached when onset times marked by at least 2 of the 3 epileptologists were within 2 s apart. The consensus ictal onset time was the average of the ictal onset times in agreement. Consensus on ictal lateralization (determined independently for scalp EEG and FOs) was reached when at least 2 of the 3 epileptologists were in agreement on lateralization. A typical right mTL seizure with consensus FO and scalp EEG seizure onset times is shown in Fig. 1.

2.4. EEG processing and artifact detection

All analysis was performed in MATLAB (Mathworks, Natick, MA), using custom and freely available scripts, including EEGLab (Delorme and Makeig, 2004) and the Chronux toolbox (Mitra and Bokil, 2008). Scalp EEGs were formatted into a longitudinal bipolar montage with a coronal ring (T1-T3, T3-C3, C3-Cz, Cz-C4, C4-T4, T4-T2, T1-T2), resulting in 25 scalp EEG bipolar channels. Each EEG record was divided into one second epochs, and an automated artifact detection script was used to identify epochs with significant artifact (see Supplementary Methods).

2.5. Spectral analysis

Multi-taper spectrograms were created from the bipolar scalp EEG channels (each normalized to zero-mean, unit-variance), using the Chronux script *mtspecgramc* with the following parameters: frequency range: 1–20 Hz, window: 2 s, step size: 1 s, time-bandwidth product: 2, tapers: 3. This provided a spectral resolution of 2 Hz. Average spectral power for each channel was calculated within four frequency bands (delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–20 Hz)), resulting in 100 channel-frequency combinations of spectral data (25 channels × 4 frequency bands).

2.6. Spectral feature extraction

We analyzed pre-ictal scalp EEG data, which we defined here as the 90 s of scalp EEG data immediately preceding the consensus scalp EEG ictal onset for each seizure (Fig. 2A). Within these 90 s, a feature vector was created for each 2-s window, with a 1-s

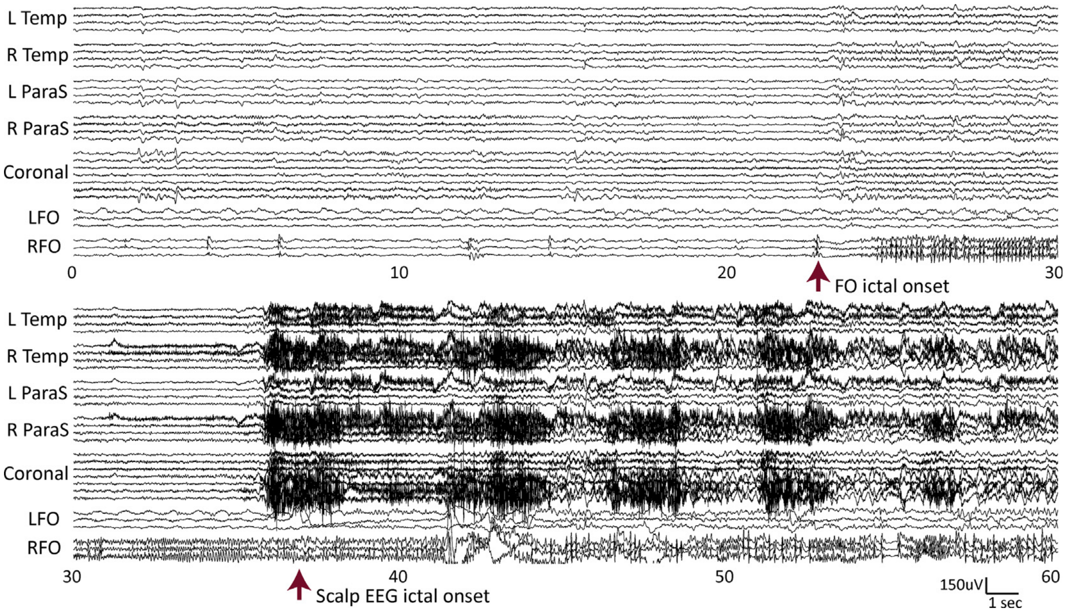

Fig. 1. Representative mTL seizure. The two panels show 60 s of continuous EEG recording, with seconds elapsed shown below each panel. Ictal activity first starts on the right FO electrodes, and there is a 14 s delay before a definite scalp EEG ictal pattern arises. While a change in background (onset of low amplitude, diffuse fast activity) is visible on the scalp EEG at the time of FO ictal onset, this occurs in the setting of a state transition (arousal from sleep) and was thus not deemed to be definitively ictal by the reviewers. While this fast activity is slightly more prominent over the right temporal region, subsequent appearance of myogenic artifact in this region also confounded interpretation of this pattern as definitively ictal. Arrows show consensus FO and scalp EEG ictal onset times, which were calculated as the average of the ictal onset times across reviewers in consensus. Scalp EEG is displayed as a longitudinal bipolar montage with coronal ring, with chains from top to bottom: left temporal chain (Fp1-F7, F7-T3, T3-T5, T5-O1), right temporal chain (Fp2-F8, F8-T4, T4-T6, T6-O2), left parasagittal chain (Fp1-F3, F3-C3, C3-P3, P3-O1), right parasagittal chain (Fp2-F4, F4-C4, C4-P4, P4-O2), coronal ring (Cz-C3, C3-T3, T3-T1, T1-T2, T2-T4, T4-C4, C4-Cz). FO electrodes (LFO = left FO, RFO = right FO) are shown in a unilateral bipolar montage (LFO1-LFO2, LFO2-LFO3, LFO3-LFO4; and RFO1-RFO2, RFO2-RFO3, RFO3-RFO4), where contact 1 is deepest. Calibration bar is shown in the lower right corner.

step-size between consecutive windows. Each feature vector represented the change in scalp EEG spectral content for that 2-s window, compared to a preceding 2-min baseline, with a 1-min buffer separating the baseline and two-second window. Each feature vector contained 100 spectral features (one for each channel-frequency combination), and each spectral feature was calculated as (Spectral power in window – Median spectral power in baseline)/(Median spectral power in baseline). Each feature vector was labeled based on whether or not there was ongoing occult mTL seizure activity (i.e., visible on FO electrodes only) during that 2-s window. A feature vector was discarded if its 2-s window contained an artifactual epoch or if artifactual epochs comprised over 20% of the 2-min baseline segment.

2.7. Development of SCOPE-mTL: building detectors for occult mTL seizure activity

Three different machine learning algorithms were used to build detectors for occult mTL seizure activity: (1) Support vector machine with Gaussian kernel, (2) Lasso regression, and (3) Ensemble *K*-nearest neighbors with random subspace. Implementation and optimization of parameters for each learning algorithm is described in the Supplementary Methods.

The overall scheme for training, cross-validation, testing, and generating graphical outputs for the detectors was the same for all algorithms (Fig. 2B). We used a leave-one-patient-out cross-validation approach, which estimates how well each detector's performance generalizes to seizures from new patients. For the 24 patients in our dataset, data from one patient was left out for testing, while data from the remaining 23 patients was used to train and optimize parameters for each machine learning algorithm. This procedure was repeated 24 times, leaving a different patient out each time, so that data from all patients was tested on independently.

For each learning algorithm, we built separate detectors to distinguish between left and right mTL occult seizure activity. We assumed that the scalp EEG signatures for left and right occult mTL seizure activity are similar but mirror images of one another. As our seizure dataset contained both left and right mTL seizures, we employed a strategy used previously to maximize the training data available for each detector (Lam et al., 2016). To train left mTL seizure detectors, we kept the scalp EEG data for all left mTL seizures intact and performed a left-right reflection of the scalp EEG data for all right mTL seizures, so that all seizures for training approximated left mTL seizures. The converse was done for training right mTL seizure detectors (Fig. 2C). As the same dataset is used to train both detectors, the left and right seizure detectors end up detecting essentially the same patterns, but on opposite sides of the EEG.

In practice, when and where a seizure occurs is not known *a priori*. As such, the feature vector for each 2-s window (data point) is processed by both left and right mTL seizure detectors, which independently output the probability that an occult seizure occurs in the left or right mTL, respectively, during those 2 s. To estimate the overall probability of an occult mTL seizure (regardless of lateralization) during each 2-s window, we generated a seizure probability distribution based on the combined outputs from the left and right mTL seizure detectors (see Supplementary Methods).

After optimization of the detectors and generation of the seizure probability distribution, the detectors were then tested on data from the left-out patient. For each algorithm, pre-ictal data points (feature vectors) for the left-out patient were processed by both left and right occult mTL seizure detectors, and the overall probability of an occult mTL seizure at each data point (based on combination of both left and right detector outputs) as well as

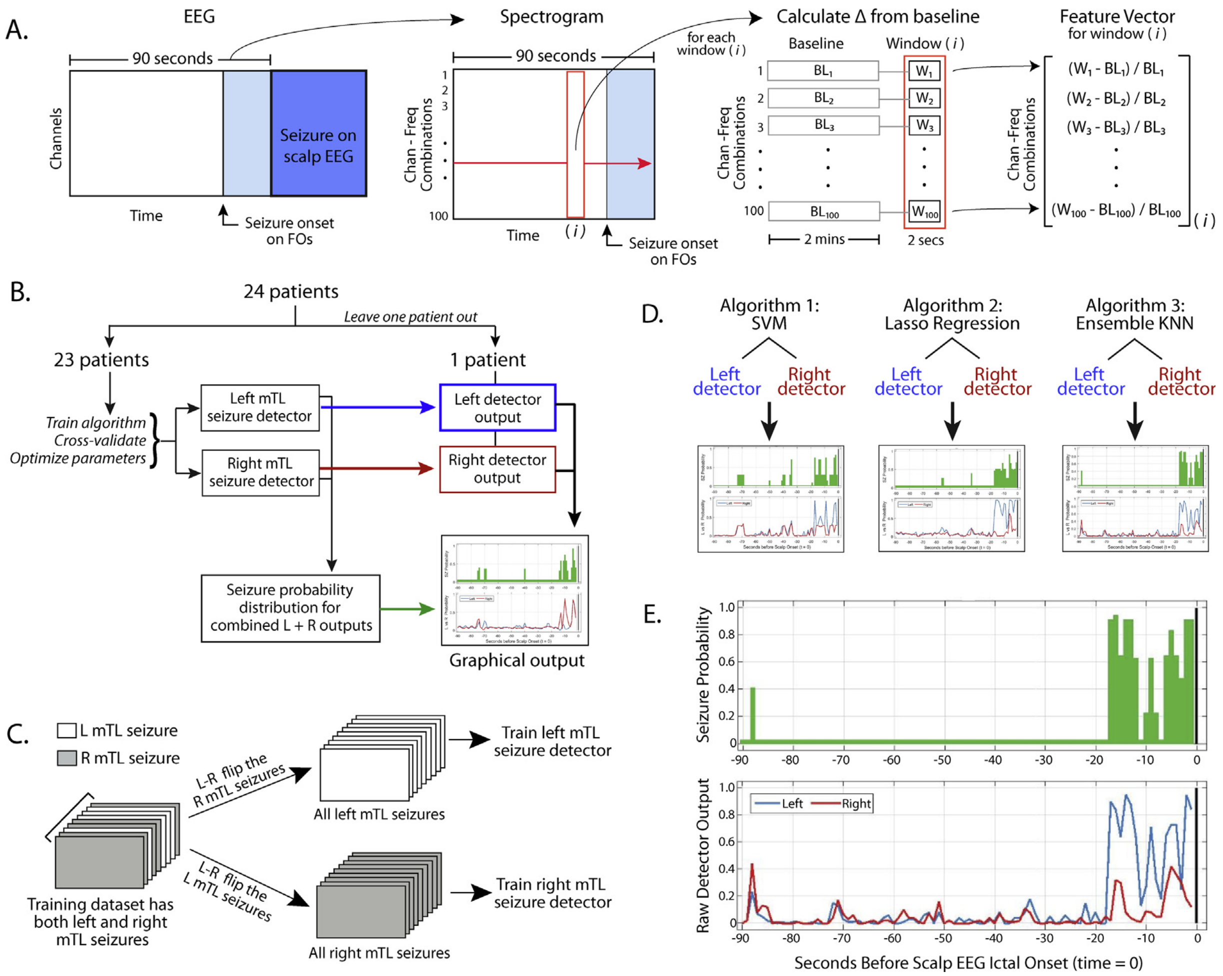

Fig. 2. Schematic of the SCOPE-mTL approach. (A) Extraction of spectral features from pre-ictal scalp EEG. Features are extracted from the 90 s of pre-ictal scalp EEG that immediately precede the scalp EEG ictal onset. Each feature vector represents the change in spectral content for a 2-s window, compared to a preceding 2-min baseline. (B) Leave-one-patient-out cross validation scheme. The left branch of the diagram shows training, cross-validation, and optimization of left and right mTL seizure detectors using data from all patients except the left-out patient. The right branch depicts testing the detectors using the left out patient and generating a graphical output based on the results. This approach is used for all 3 algorithms. (C) Method for left-right reflection of EEG data for seizures in order to train separate left and right mTL seizure detectors. (D) SCOPE-mTL graphical output reviewed for each seizure. The graphs show output from three algorithms that independently predict mTL seizure probability and lateralization. One of these graphs is shown in greater detail in (E), where the top plot (green bars) represents overall mTL seizure probability (based on combined outputs of left and right mTL seizure detectors), and the bottom plot shows raw output of the left (blue line) and right (red line) mTL seizure detectors (probability of mTL seizure in each detector).

the probabilities of left and right mTL seizure activity, were determined. This was repeated for all 3 algorithms, such that each algorithm provided an independent assessment of occult mTL seizure probabilities.

2.8. SCOPE-mTL output and interpretation

The left and right mTL seizure detectors evaluate each data point (i.e., feature vector for a 2-s window) independently, without regard to the preceding or subsequent time windows. We created a graphical output for the SCOPE-mTL analysis, to visualize the temporal evolution of the detector outputs for each seizure. Each seizure had 3 graphs, one for each learning algorithm (Fig. 2D). Fig. 2E shows a representative graphical output. The top plot displayed overall seizure probability for the 90 s preceding the scalp EEG ictal onset. The bottom plot displayed the raw outputs of the left and right mTL seizure detectors, i.e., the probability that an occult seizure occurred in the left or right mTL, respectively.

Staff epileptologists (DM, SFZ, AJC, and SSC) independently reviewed the SCOPE-mTL graphical outputs for each seizure, without EEG data and without any knowledge of the seizure. None of the epileptologists had prior experience with these graphical outputs. Prior to review of the graphical outputs, they received a brief tutorial on what the plots represented and a general framework of how to interpret them. The graphical outputs for all 3 algorithms were displayed simultaneously for each seizure reviewed, with each algorithm output representing an independent "vote" on seizure probability. The reviewers were first asked to decide whether there was occult mTL seizure activity prior to scalp EEG ictal onset. If yes, the reviewer estimated the mTL seizure onset time and lateralization (left, right, or indeterminate). Group consensus on whether occult mTL seizure activity preceded the scalp EEG ictal onset was reached when at least 3 reviewers were in agreement. Group consensus for mTL seizure onset time was the average mTL seizure onset time predicted across all reviewers who predicted an occult mTL onset. Consensus for mTL seizure lateralization was reached if at least 3 reviewers were in agreement.

2.9. Statistics

Statistics are reported as the mean ± standard deviation. Pearson's correlation coefficient, linear regression, and Cohen's kappa calculations were performed in MATLAB.

3. Results

3.1. Patient demographics

We located seizure recordings for 29 patients who met our inclusion and exclusion criteria and who underwent pre-surgical evaluation at our institution with simultaneous FO electrodes and scalp EEG recordings between 2005 and 2016. Data from two patients was excluded due to EEG records being too active (abundant interictal activity or clustering seizures), and data from three patients was excluded due to excessive electrode artifact. Altogether, 89 seizures from 24 patients were evaluated further. Table 1 shows the demographics of the patients included in this study.

3.2. Seizure characteristics

On visual interpretation of the seizure recordings, consensus on all four measures of scalp EEG ictal onset time, scalp EEG ictal lateralization, FO ictal onset time, and FO ictal lateralization was reached for 84 of 89 seizures. Failure to reach consensus for scalp EEG ictal onset time resulted in two seizures being discarded from further analysis. An additional seizure was discarded from further analysis due to a consensus that the FO ictal onset was non-lateralized. Failure to reach consensus on scalp ictal lateralization occurred for three seizures, which we included in further analysis. Altogether, 86 of the 89 seizures were used for further analysis. Consensus seizure onset times and lateralization were used as the "gold standard" for gauging performance of the SCOPE-mTL algorithm.

Of the 86 mTL seizures analyzed, 44 were left mTL seizures, and 42 were right mTL seizures. On average, mTL seizure onset (i.e., seizure onset on the FO electrodes) preceded the scalp EEG ictal pattern by 14.3 ± 10.4 s (median: 13 s, maximum: 42 s).

3.3. Example graphical outputs and interpretation

Graphical outputs of the SCOPE-mTL algorithm varied considerably from seizure to seizure. Supplementary Fig. S1 shows representative graphical outputs in which no occult mTL onset could be identified, either due to lack of detection, noisy baseline, or artifact obscuring the pre-ictal recording. Fig. 3 shows representative graphical outputs for seizures in which group consensus identified an occult mTL seizure onset. Some occult seizures were easily lateralized (Fig. 3A, B), whereas others could not be lateralized (Fig. 3C). Fig. 3D shows the graphical output for the representative seizure in Fig. 1. Occult mTL seizure onset and lateralization are identifiable, even prior to the development of myogenic artifact on the scalp EEG. Confidence in predicting occult seizure onset and lateralization was bolstered by the similar trends between the 3 machine learning algorithms, with lasso regression being most convincing in this case.

3.4. SCOPE-mTL allows early and accurate detection of mTL seizure onsets

We first analyzed the specificity of SCOPE-mTL in predicting occult mTL seizure onsets prior to the appearance of a scalp EEG ictal pattern. A histogram of the number of seconds between mTL seizure onset and scalp EEG ictal onset for all 86 seizures is shown in Fig. 4A.

18 seizures in our dataset had seizure onsets on FO electrodes and scalp EEG that were near-simultaneous (occurring within 5 s of one another). Based on the SCOPE-mTL graphical outputs, the group consensus was that 16 of these 18 seizures had no detectable occult mTL seizure onset, and that the remaining 2 seizures had mTL seizure onsets occurring within 5 s of scalp ictal onset. Our SCOPE-mTL approach thus has high specificity, in that none of the seizures with near-simultaneous mTL and scalp EEG ictal onset were classified as having significant (>5 s) occult mTL seizure activity.

We next analyzed results for the 68 remaining seizures, in which occult mTL seizure onset preceded scalp EEG ictal onset by more than 5 s. For 50 of these seizures, the group consensus on the SCOPE-mTL graphical outputs correctly predicted that the mTL seizure onset preceded the scalp ictal onset by over 5 s. For 5 seizures, the group failed to reach consensus on whether there was an occult mTL seizure onset. For 13 seizures, the group

Table 1
Patient demographics.

Patient	Age (y)	Sex	# Seizures used	Seizure onset lateralization	Surgery	Surgical pathology	Outcome
1	49	M	1	Left			
2	44	M	1	Left	Left ATL	HC sclerosis	Lost to follow up
3	20	M	2	Left	Left ATL	HC sclerosis	Engel Class 1
4	16	M	3	Right	Right ATL	HC sclerosis	Engel Class 1
5	42	F	6	Left			
6	57	M	3	Right	Right ATL	HC sclerosis	Engel Class 1
7	40	F	5	Bitemporal	Palliative Right ATL	HC sclerosis	Engel Class 1
8	27	F	9	Bitemporal			
9	33	M	6	Left	Left ATL	Subependymal gliosis	Engel Class 3
10	65	M	3	Bitemporal			
11	50	M	6	Bitemporal			
12	57	F	1	Bitemporal	Palliative Left ATL	HC sclerosis	Engel Class 1
13	67	M	1	Bitemporal			
14	37	F	3	Bitemporal	Bilateral HC RNS		
15	36	M	1	Left	Left HC RNS		
16	23	F	9	Right	Right ATL	Reactive gliosis	Engel Class 1
17	65	M	1	Bitemporal			
18	20	M	4	Bitemporal	Bilateral HC RNS		
19	59	M	7	Bitemporal	Palliative Right ATL	HC sclerosis	Engel Class 4
20	30	M	2	Bitemporal	Palliative Right ATL	HC sclerosis	Engel Class 1
21	42	F	5	Bitemporal	Palliative Left ATL	HC sclerosis	Engel Class 3
22	53	F	5	Left			
23	53	M	1	Left	Left ATL	Focal cortical dysplasia	Engel Class 1
24	35	M	1	Bitemporal			

Abbreviations: ATL = anterior temporal lobectomy; HC = hippocampal; RNS = responsive neural stimulator.

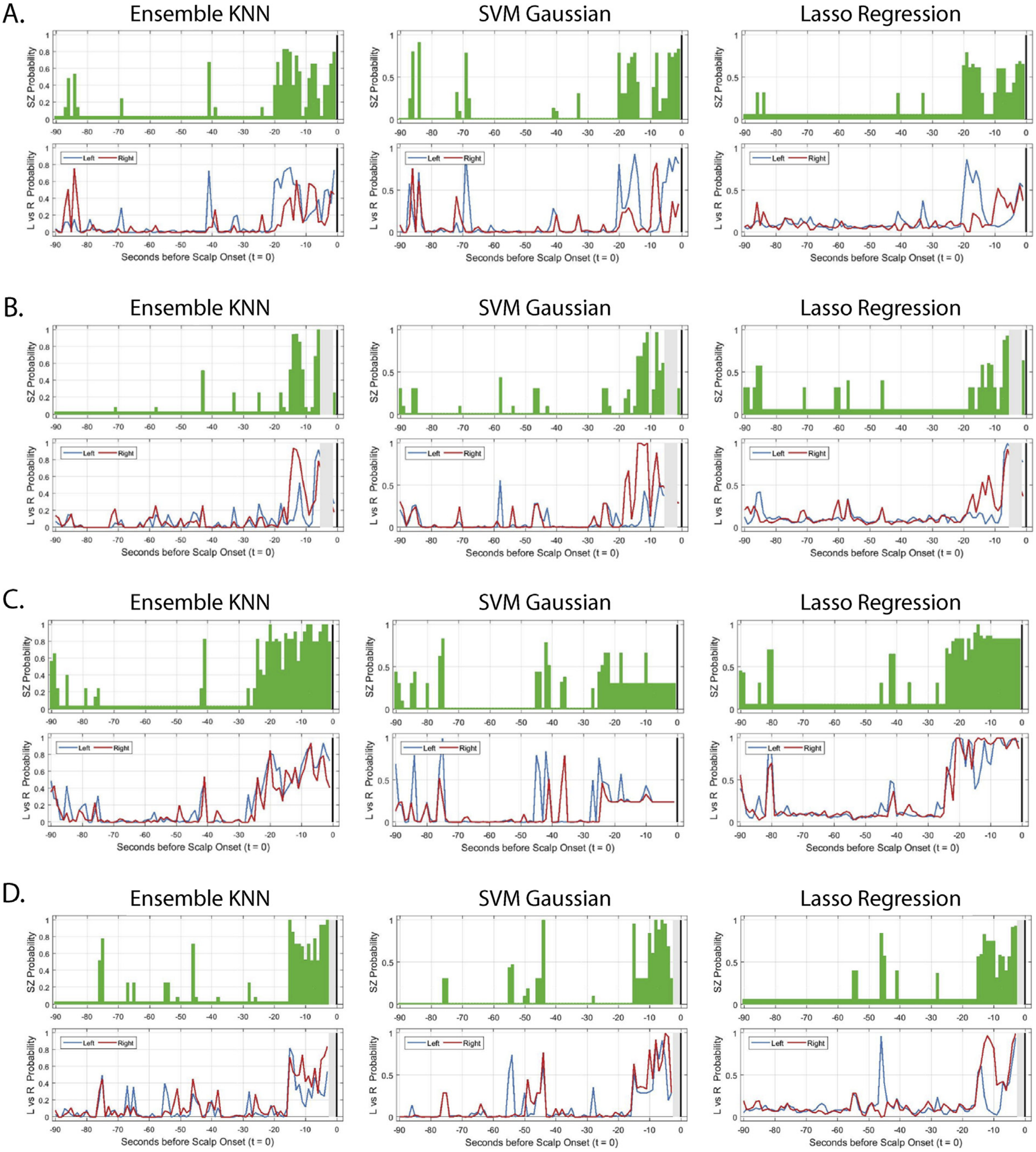

Fig. 3. SCOPE-mTL graphical outputs for representative seizures with detectable early mTL seizure onsets. (A) Graphical output for a seizure in which left mTL ictal activity precedes scalp EEG ictal onset by 20 s. (B) Graphical output for a seizure in which right mTL ictal activity precedes scalp EEG ictal onset by 14 s. (C) Graphical output for a left mTL seizure where mTL ictal onset precedes scalp EEG ictal onset by 24 s. This seizure cannot be lateralized based on the graphical output (left and right detector outputs largely overlap in the bottom plots). (D) Graphical output for the seizure shown in Fig. 1, a right mTL seizure starting 14 s before scalp EEG ictal onset. Group consensus based on the SCOPE-mTL analysis predicted that mTL seizure onset occurred 15 s prior to scalp EEG ictal onset, with lateralization to the right. See Fig. 2 for description of the components of the graphical output. Light gray vertical bars in the graphical output represent artifactual epochs that were excluded from analysis.

consensus failed to predict an early, occult mTL onset. SCOPE-mTL thus has a sensitivity of ~73% (50 out of 68) for identifying seizures in which occult mTL seizure activity precedes the scalp EEG ictal onset by more than 5 s.

To determine how accurately mTL seizure onset times could be predicted using the SCOPE-mTL approach, we analyzed all seizures with significant (>5 s) occult mTL seizure activity. Fig. 4B and C shows the consensus predicted mTL seizure onset times based on SCOPE-mTL, plotted against the actual mTL seizure onset times, for all patients, and broken down by individual patient. There was a strong linear relationship between the predictions and the actual data, with a Pearson's correlation coefficient of 0.69 ($p < 0.001$). A linear fit of the data with intercept at the origin yielded a slope of 0.95 (95% CI: [0.86, 1.03]). SCOPE-mTL thus allows exceptionally high accuracy in predicting occult mTL seizure onset times.

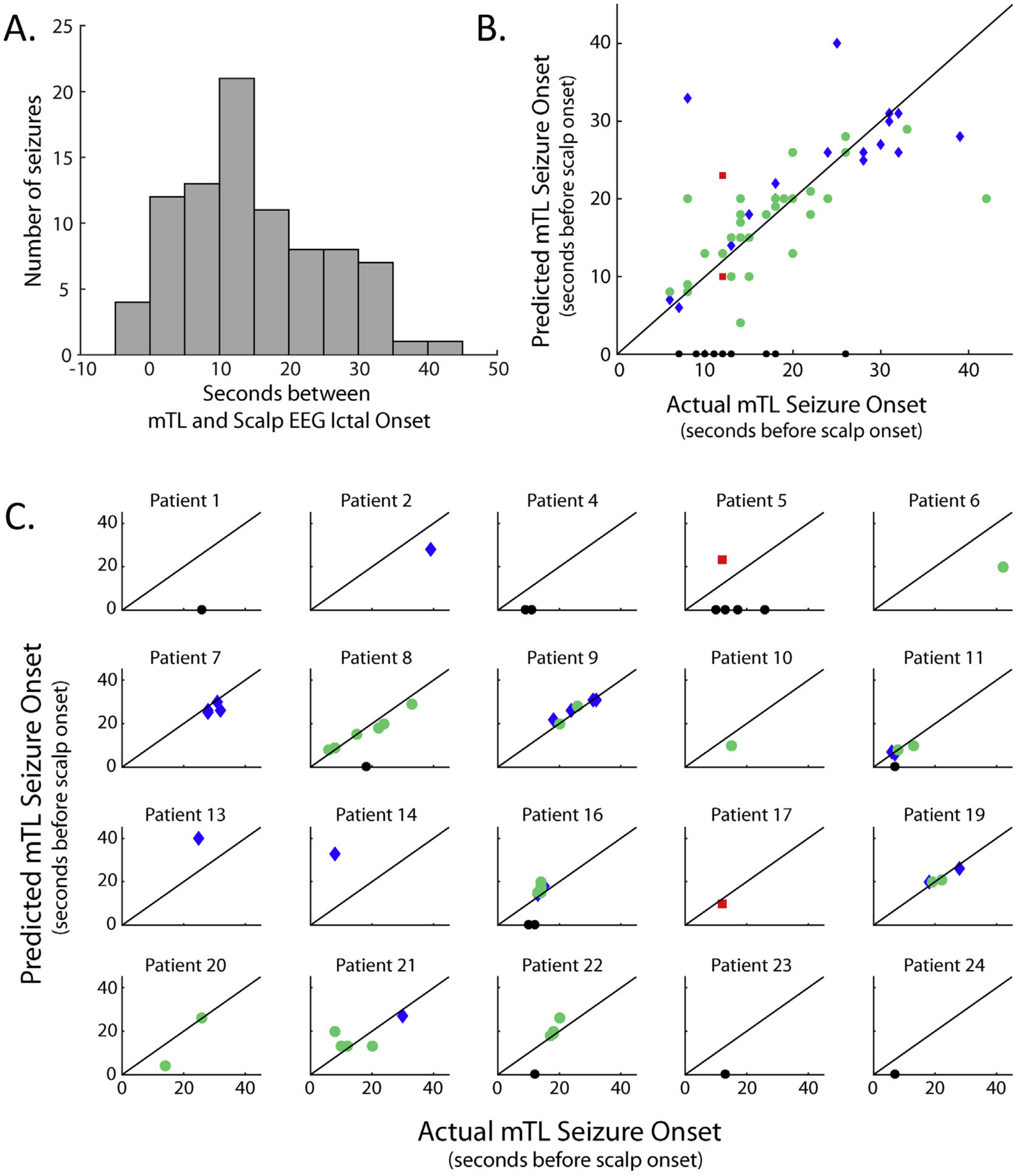

Fig. 4. Accuracy of predicted mTL seizure onset time and lateralization using SCOPE-mTL. (A) Histogram showing the distribution of time between mTL seizure onset and scalp EEG ictal onset, for all 86 seizures in our dataset. (B) Scatter plot showing actual mTL seizure onset times (based on FO seizure onset) vs predicted mTL seizure onset times (based on SCOPE-mTL consensus interpretation) for all seizures with occult mTL activity lasting >5 s. Green filled circles represent occult seizures that were correctly lateralized, red squares represent occult seizures that were incorrectly lateralized, blue diamonds represent occult seizures that were detected but not lateralizable, and black circles represent occult seizures that went undetected. The black line shown has a slope of 1 and represents the ideal case, in which the predicted times are the same as the actual times. (C) Similar to (B), but broken down by individual patient. Data from 20 patients are shown; the remaining 4 patients had only seizures in which occult mTL activity lasted ≤5 s.

3.5. SCOPE-mTL allows accurate prediction of occult mTL seizure lateralization

Using SCOPE-mTL, group consensus on mTL seizure lateralization was reached for 34 seizures (40% of all seizures; 50% of seizures in which mTL seizure onset preceded scalp onset by >5 s). When the group was in consensus, lateralization predictions based on the graphical outputs were exceptionally accurate, with 32 of the 34 predictions (94%) being correct (kappa = 0.88; 95% CI: [0.72, 1.04]). 19 seizures with correct lateralization were right-sided, and 13 were left-sided. Seizures with correct and incorrect consensus lateralizations are depicted by the green circles and red squares, respectively, in Fig. 4B and C. Lateralization accuracy for individual reviewers was also high. Individual reviewers predicted lateralization for 32–39 seizures, with individual lateralization accuracy ranging from 85 to 91%. Examples of scalp EEG and FO recordings for 10 representative seizures that were correctly lateralized on group consensus can be found in the Supplementary Information.

3.6. Scalp EEG spectral features important for early mTL seizure onset detection

Analysis of the SCOPE-mTL algorithm can provide information on how activity on specific scalp EEG channels and frequencies changes during occult mTL seizures. We analyzed coefficients from the lasso regression model of SCOPE-mTL, to determine which spectral features were most important for classification of occult mTL seizure activity. (Other learning algorithms were not assessed, as the non-linearity of the Gaussian SVM model makes interpretation of coefficients difficult, and the *K*-nearest neighbors algorithm does not yield a suitable model). The 20 most important spectral features for the lasso regression model were designated as those whose coefficients had the largest absolute values. Table 2 lists these spectral features and their coefficients, for the left mTL seizure detector. All features involved the theta, alpha, or beta frequency bands. 14 of the 20 features involved alpha or beta frequencies, which could often be missed or confounded by arousal or myogenic artifact. Channel locations for these features were widespread, with 10 in the left hemisphere, 6 in the right hemisphere, 1 in the midline, and 3 with bitemporal location (i.e., *T*1–*T*2). Of note, important spectral features for the right mTL detector were analogous (same frequencies, though mirror image channels) to those for the left mTL detector.

4. Discussion

Lateralization and localization of scalp EEG seizure recordings are often limited by extracerebral artifacts, poor sensitivity for deep ictal activity, and significant seizure propagation by the time of scalp EEG ictal onset. These limitations are often reason to pursue invasive studies with intracranial electrodes. Yet, visual analysis of scalp EEGs is quite limited, and many complex features of the EEG cannot be discerned on visual inspection alone. Computational approaches provide a complementary method to extract additional information from scalp EEG seizure recordings to augment interpretation and better guide epilepsy surgical decision making.

Here, we focused on mTL seizures, which often start in the mTL many seconds before a scalp EEG ictal correlate becomes visible. We asked whether quantitative analysis of pre-ictal scalp EEG recordings could be used to detect and lateralize this early, occult mTL seizure activity, prior to the appearance of a definitive scalp EEG ictal pattern. The SCOPE-mTL approach developed here detected occult mTL seizure activity with high sensitivity and excellent specificity. 73% of mTL seizures with early occult onsets were identified as such. None of the mTL seizures with near-simultaneous mTL and scalp EEG seizure onsets were identified as having an occult mTL onset. Predicted mTL seizure onset times were highly correlated with actual mTL seizure onset times. Lateralization of occult mTL seizure activity was possible for 50% of these seizures, with an accuracy of 94%. Importantly, SCOPE-mTL can be applied to Phase 1 presurgical data acquired from most epilepsy monitoring units, as the scalp EEG electrode configuration required is employed in most epilepsy monitoring units.

Table 2
20 most important spectral features (Lasso regression).

Rank	Channel	Frequency	Coefficient
1	T1-T3	Theta	0.2337
2	T1-T2	Alpha	0.2315
3	Fz-Cz	Beta	−0.223
4	C3-P3	Beta	0.2058
5	F8-T4	Alpha	−0.206
6	T1-T3	Alpha	0.2014
7	T1-T2	Beta	0.1834
8	P4-O2	Theta	−0.174
9	T1-T3	Beta	0.1713
10	T4-T2	Theta	−0.165
11	T3-T5	Beta	0.1566
12	T6-O2	Beta	0.1462
13	T3-C3	Beta	−0.136
14	T1-T2	Theta	0.1303
15	F3-C3	Alpha	−0.111
16	T6-O2	Alpha	0.1104
17	T3-T5	Alpha	0.1064
18	P3-O1	Beta	0.1059
19	Cz-C4	Theta	−0.085
20	T3-C3	Theta	0.0849

The utility of computational approaches such as SCOPE-mTL lies in complementing, rather than replacing, traditional visual interpretation of the scalp EEG. Clinicians typically use multiple features from the scalp EEG, for instance, the location of focal slowing, interictal discharges, and visible seizure onsets, to determine the epileptogenic zone. Concordance among these features increases the clinician's confidence that lateralization and/or localization of the epileptogenic zone is correct. The clinical implications down the line, whether it be implantation of intracranial electrodes or resection of brain tissue, holds significant risk for the patient, and it is the clinician's responsibility to ensure that the potential benefits of these procedures justify the risks. As such, any additional, independent, and accurate information that can increase the clinician's confidence in determination of the epileptogenic zone is almost always desirable. SCOPE-mTL adds a new facet to the interpretation of the scalp EEG, drawing on the subtle scalp EEG changes that precede the definitive ictal onset, and transforming this information into a read-out that is clinically meaningful. Because the subtle pre-ictal changes on scalp EEG are separate from the visible ictal pattern that is traditionally interpreted, SCOPE-mTL can thus provide an independent assessment of seizure lateralization, to complement the interpretation of the visible ictal pattern.

We envision a number of different scenarios in which SCOPE-mTL and approaches like it could be particularly useful in Phase 1 presurgical evaluations. First, in the case where seizure onset is obscured by significant myogenic artifact, the "clean" segment of scalp EEG preceding the myogenic artifact could be analyzed to assess for earlier occult mTL seizure onset and to assist with lateralization. In the case of a seizure that occurs with significant electroclinical delay, analysis of pre-ictal scalp EEG data could be used to increase confidence in localization and lateralization predictions. Finally, in the case where scalp EEG ictal onset is diffuse or non-lateralizable due to significant propagation of seizure activity, analysis of the pre-ictal scalp EEG could be used to detect focal seizure onset and to gauge laterality before the seizure has propagated significantly.

It is notable that, on close examination of the combined scalp EEG and FO seizure recordings (Fig. 1 and Supplementary Information), there are often subtle visible changes on the "pre-ictal" scalp EEG that appear to correlate with and lateralize correctly with ongoing ictal activity on the FO electrodes. However, without the *a priori* knowledge that there is an ongoing seizure, these scalp EEG changes on their own are often deemed too small or too visually subtle to be considered definitively ictal and to contribute to interpretation of the seizure. For instance, onset of low amplitude fast activity may easily be confounded with a state change (e.g., arousal from sleep) or with onset of myogenic artifact. Similarly, onset of intermittent slowing may be confounded with interictal background abnormalities. We suspect that this situation is a common occurrence with traditional visual interpretation of the scalp EEG. Yet, the consistent accuracy of these pre-ictal findings suggests that perhaps traditional visual interpretation of seizures could integrate some of these subtle but lateralized pre-ictal findings with more confidence. Importantly, computational tools such as SCOPE-mTL can be trained to recognize these subtle but specific changes and to attach a clinical significance to them that would not otherwise have been appreciated based on traditional visual interpretation.

Our study does have several potential caveats that should be noted. First, our data set was relatively small, with only 24 patients and 86 seizures. Validation of our approach using a much larger dataset is warranted. Second, there is a potential bias associated with our dataset, based on the fact that all patients in our dataset were selected to undergo investigation with FO electrodes, rather than with intracranial depth electrodes. Implantation with FO electrodes at our institution typically implies a strong suspicion for mesial temporal epilepsy, whereas in more ambiguous cases (often depending on the appearance of seizures on scalp EEG), patients undergo recordings with depth electrodes. Whether there are differences in the pre-ictal and ictal scalp EEG patterns between these groups is unclear, though one could argue that regardless of which monitoring approach was chosen, in the end, patients with mTL epilepsy should ultimately share similar patterns of ictal onset and propagation. Last, we analyzed only mTL seizures in this study. Whether our algorithm is specific to mTL seizures or would also be of use for lateralization of seizures of extra-temporal origin is not yet known.

From a scientific standpoint, it is interesting that SCOPE-mTL uses scalp EEG spectral features to detect focal mTL seizure activity, in the absence of a clear scalp EEG ictal pattern. Importantly, we found that channel locations in both hemispheres were important for detection of seizure activity that was presumed to be focal, or at the least, unilateral. These findings provide further evidence that what we consider to be "focal" seizures nevertheless involve brain regions that extend far more broadly than just the area of visible ictal activity. Our study adds to a growing number of studies which demonstrate that even the most focal of seizures are likely network processes associated with widespread changes in brain activity (Fahoum et al., 2012; Haneef et al., 2014; Kramer and Cash, 2012; Lam et al., 2016; Laufs, 2012; Zaveri et al., 2009).

5. Conclusions

Our study provides a clear proof-of-principle that quantitative analysis of pre-ictal scalp EEG can provide accurate information regarding seizure onset and lateralization in mTL epilepsy. As we analyzed only mTL seizures in this study, it is unclear how accurately SCOPE-mTL would perform on seizures that do not originate in the mTL. Future studies will test this approach with other seizure types and develop new algorithms to detect seizures arising from other brain regions, including the mesial frontal lobes. Such work will be instrumental for improving seizure lateralization and localization on scalp EEG recordings.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2017.06.040.

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