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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