

Phase Amplitude Coupling between Spikes and Ripples Identifies the Epileptogenic Zone in Children with Drug Resistant Epilepsy

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Background & Rationale

- For children with **drug-resistant epilepsy (DRE)**, surgery is the best available treatment to achieve seizure freedom. Success of epilepsy surgery depends on the precise delineation of the **epileptogenic zone (EZ)**, the brain area that is indispensable for the generation of seizures.
- Several epilepsy biomarkers are currently used for the delineation of the EZ. Among them, **spikes** are well established but suffer from **low specificity** since they can also be found in **non-epileptogenic brain areas**.
- High frequency oscillations (HFOs)**, categorized into **ripples (80-250 Hz)** and **fast ripples (250-500 Hz)**, have been proposed as alternative promising biomarkers of epilepsy, but their performance at the patient's level is weakened by the presence of strong physiological HFO generators.
- Here, we aim to **distinguish between more and less epileptogenic spikes in intracranial EEG (icEEG)** by assessing the temporal and cross-frequency coupling features between spikes and HFOs.

Methods

- Patients:** 28 patients (age: 11 ± 6 years; 12 females) who underwent epilepsy surgery after extraoperative icEEG.
- We dichotomized our patients into **good (Engel 1; 17 patients, ≥ 1 -year follow-up)** and **poor outcome (Engel ≥ 2 ; 11 patients)**.
- Spikes and HFOs:** In an automated fashion, we identified **Spikes (S)** (1-70 Hz), **Ripples (R)**, and **Fast Ripples (FR)**, and sorted them into **10 groups**: All S, All R, All FR, S only, R only, FR only, S+R, S+FR, S+HFOs (S+R or S+FR), and S+R+FR.
- For each icEEG channel, we estimated the **rate of these events** and computed the **Mean Vector Length Modulation Index (MVLmi)** reflecting the strength of coupling between **amplitude of HFOs (80-250 Hz)** and **phase of Spikes (1-70 Hz)** (Fig. 1) using Eq. 1 and 2.
- Using **Receiver Operating characteristic (ROC)**, we evaluated the **predictive accuracy** of each biomarker to **localize the clinically defined Seizure Onset Zone (SOZ) and Resection**.
- We compared **ROC curves** with DeLong test between all biomarkers.
- MVLmi values** and **coupling angles** between Spikes and Ripples were **compared between SOZ and non-SOZ** and **resected and non-resected electrodes** (Mann-Whitney U, Rayleigh's, Watson's test).
- For all statistical tests, we considered significance at the level of $p < 0.05$.

$$z_t = A_t \cdot e^{i\varphi_t} \quad (1)$$

$$MVLmi = \left| \frac{1}{N_c} \sum_{t=1}^T z_t \right| \quad (2)$$

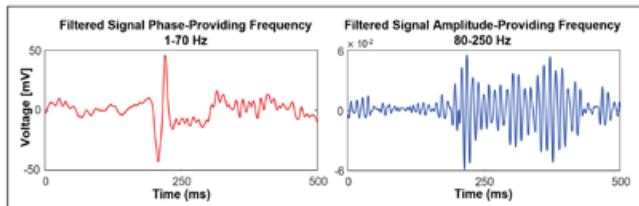


Figure 1. This icEEG signal is band pass filtered to extract the slow phase-providing frequency (here 1-70 Hz, red line) and the fast amplitude-providing frequency (here 80-250 Hz, blue line).

Results

- S+HFOs, S+R, and All S **performed better than the other S/HFOs combinations** ($p < 0.01$) for localizing both the SOZ and resection, but no difference was observed among them ($p > 0.05$, Fig. 2a).
- The MVLmi, rather, outperformed all other biomarkers for prediction of resection ($p < 0.01$, Fig. 2a). MVLmi, S+R and S+HFOs showed higher sensitivity (for specificity values $\geq 85\%$) (Fig. 2a).
- We observed a **higher MVLmi values inside** (normalized mean: 0.53 ± 0.12) **compared to outside resection** (normalized mean: 0.41 ± 0.08) for good outcome patients ($p = 0.0024$, Fig. 2b, 3a, 5a), while the same was not true for poor outcome patients ($p = 0.31$, Fig. 2b, 3d, 5b).
- HFOs in resected electrodes exhibited **strong phase locking with spikes** ($p < 0.001$, Fig. 4e) at a mean phase angle of $345 \pm 79^\circ$. HFOs in non-resected electrodes also showed strong phase locking ($p < 0.001$, Fig. 4f) but at a mean phase angle of $14 \pm 78^\circ$.

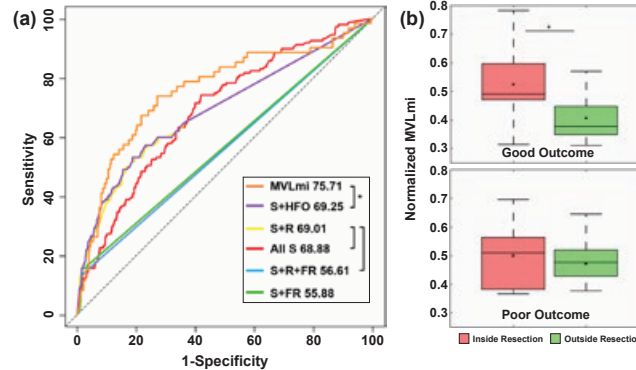


Figure 2. Biomarkers' ROC curves and MVLmi values. (a) ROC curves for 6 out of 11 total biomarkers (All S, S+R, S+FR, S+HFOs, S+R+FR, and MI(1-70 Hz)&(80-250 Hz)); (b) Boxplot of Normalized MVLmi for electrodes located inside vs outside resection for good and poor outcome patients.

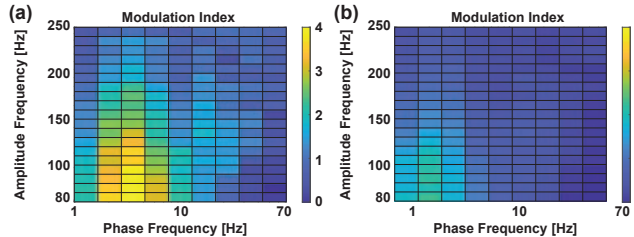


Figure 3. Average comodulogram representations of phase-amplitude coupling between spikes (1-70 Hz) and ripples (80-250 Hz) inside (a) and outside resection (b) for good outcome patients.

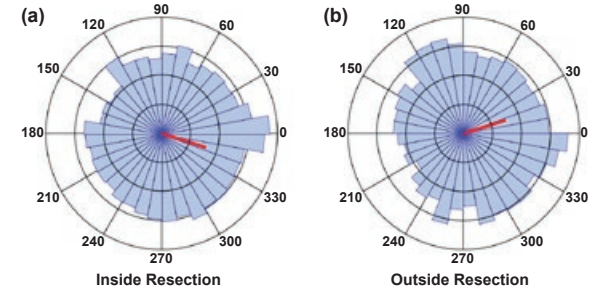


Figure 4. Probability density function of ripples preferred phase angle of coupling with respect to spikes inside (a) and outside resection (b) for patients with good outcome.

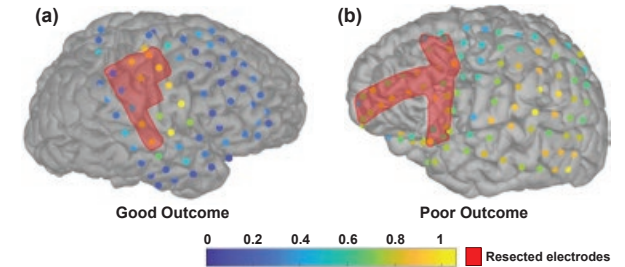


Figure 5. Normalized MVLmi displayed on the cortical surface of a good outcome patient (a) and a poor outcome patient (b) showing the resected electrodes (within red area).

Conclusions

- Our study showed that **HFOs overlapping on spikes are not better biomarkers of the EZ than spikes alone**.
- Rather than their temporal co-occurrence, **features of cross-frequency coupling**, such as the MVLmi and phase angle, between spikes and ripples **can distinguish between more and less epileptogenic spikes**.

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