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.

$$z_t = A_t \cdot e^{i\varphi_t} \quad (1) \qquad MVLmi = \left| \frac{1}{N_c} \sum_{t=1}^{T} z_t \right| \quad (2)$$

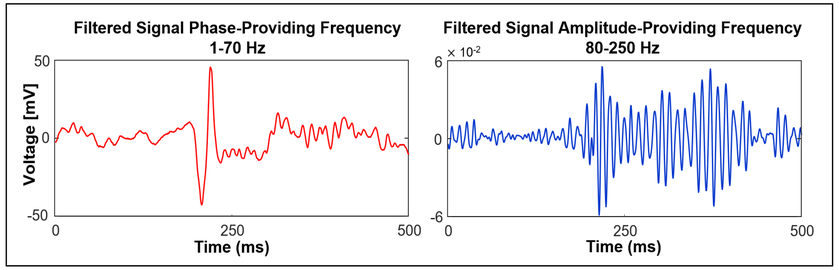

Figure 1. This icEEG signal is band pass filtered to extract the slow phase-providing frequency (here 1–70 Hz, red line) and the fast amplitude-providing frequency (here 80–250 Hz, blue line).

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 ≥ 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,5h**).
- HFOs in resected electrodes exhibited **strong phase locking with spikes** (p<0.001, **Fig. 4e**) at a mean phase angle of 345 ± 79°. HFOs in non-resected electrodes also showed strong phase locking (p<0.001, **Fig. 4f**) but at a mean phase angle of 14 ± 78°.

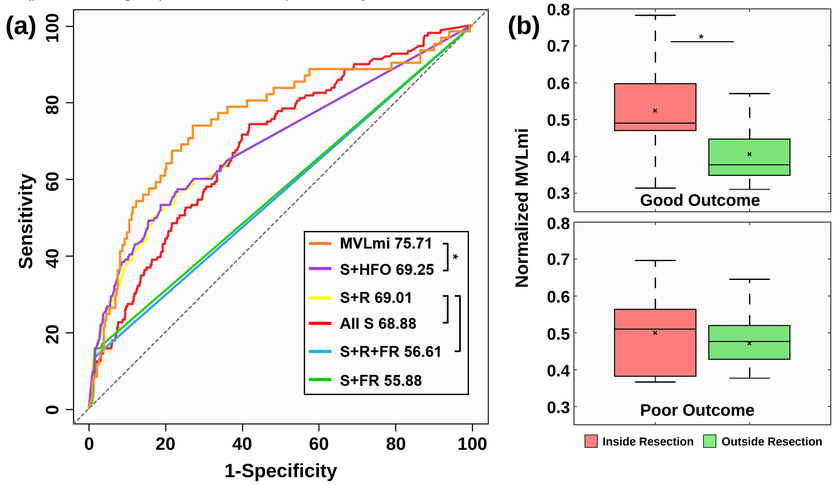

Figure 2. Biomarkers' ROC curves and MVLmi values. (a) ROC curves for 6 out of 11 total biomarkers (All S, S+R, S+FR, S+HFOs, S+R+FR, and MI(1-70 Hz)&(80-250 Hz); **(b)** Boxplot of Normalized MVLmi for electrodes located inside vs outside resection for good and poor outcome patients.

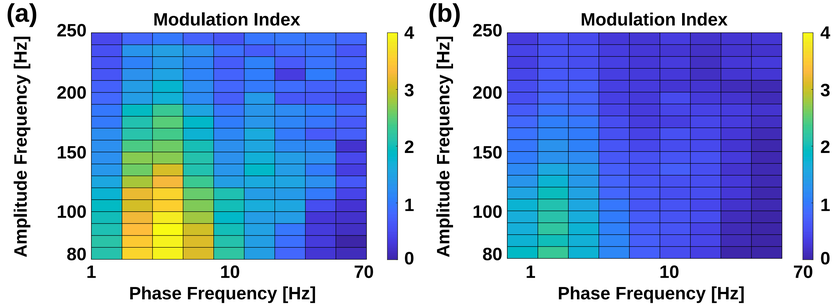

Figure 3. Average comodulogram representations of phase-amplitude coupling between spikes (1-70 Hz) and ripples (80-250 Hz) inside (**a**) and outside resection (**b**) for good outcome patients.

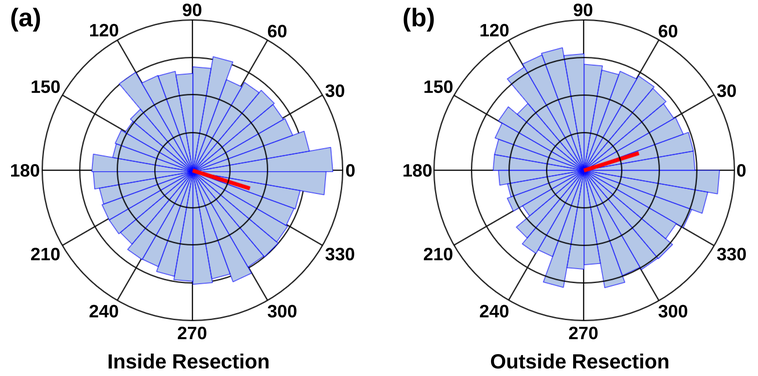

Figure 4. Probability density function of ripples preferred phase angle of coupling with respect to spikes inside (**a**) and outside resection (**b**) for patients with good outcome.

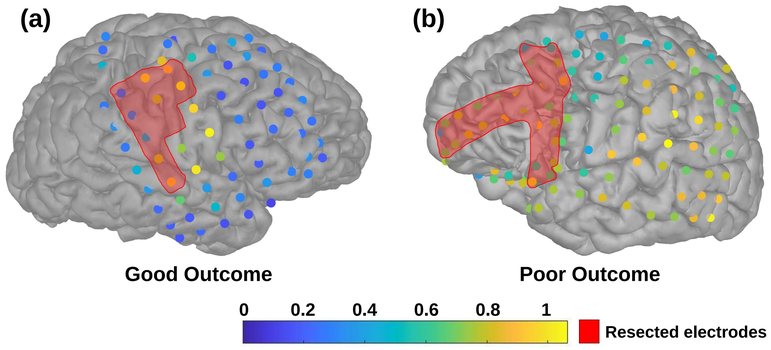

Figure 5. Normalized MVLmi displayed on the cortical surface of a **good outcome** patient (**a**) and a **poor outcome** patient (**b**) showing the resected electrodes (within red area).

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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