Overlap of spike and ripple propagation onset predicts surgical outcome in drug resistant epilepsy

Saeed Jahromi[1,2], Margherita A.G. Matarrese[1,2,3], Lorenzo Fabbri[1,2], Eleonora Tamilia[4,5], M Scott Perry[1], Joseph R. Madsen[6], Jeffrey Bolton[5], Scellig S.D. Stone[6], Phillip L. Pearl[5], Christos Papadelis[1,2,7]

1. Neuroscience Research, Jane and John Justin Institute for Mind Health, Neurosciences Center, Cook Children's Health Care System, Fort Worth, TX, USA 2. Department of Bioengineering, The University of Texas at Arlington, Arlington, TX 76010, USA
3. Research Unit of Nonlinear Physics and Mathematical Modeling, Department of Engineering, Università Campus Bio-Medico di Roma, Rome, Italy 4. Fetal-Neonatal Neuroimaging and Developmental Science Center, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
5. Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA 6. Division of Epilepsy Surgery, Department of Neurosurgery, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
7. School of Medicine, Texas Christian University, Fort Worth, TX, USA

Background and Aim

- Children with **drug resistant epilepsy** (DRE) require resective neurosurgery to achieve seizure freedom.
- The success of the surgery strongly depends on the **accurate delineation** of the **epileptogenic zone (EZ)**.
- **Interictal spikes and ripples** are **sensitive** interictal biomarkers of the EZ, but often occur in large areas of the brain whose resection is unnecessary for seizure freedom.
- **Interictal fast ripples** are more **specific** to the EZ but are difficult to record with macroelectrodes due to their low amplitude and high frequency and are less often present in intracranial electroencephalography (iEEG) recordings.
- Previous studies have shown that **spikes and ripples propagate** across large brain areas; the onset of this propagating activity is a more specific biomarker of epilepsy than areas of spread.
- Here, we examined whether the **spike-ripple onset overlap zone (SRO)** serves as a **highly specific and accurate** biomarker of the **EZ**. We hypothesize that this biomarker can be seen in **most** children with drug resistant epilepsy (DRE) and its resection **predicts surgical outcome**.

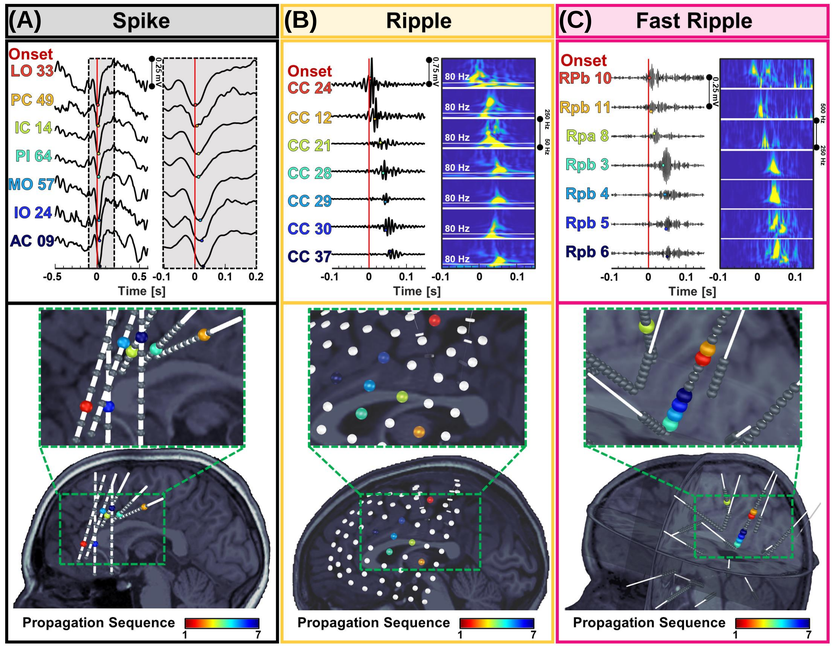

Figure 1. Sequences of spike, ripple, and fast ripple propagations in patients with DRE. (A) Temporal propagation of interictal spikes from onset to spread and its corresponding spatiotemporal path on depth electrodes (12-year-old female). **(B)** Temporal propagation of ripples, the corresponding time-frequency analysis plots (from 50 to 250 Hz) and spatiotemporal path on patient's cortical surface (11-year-old male). **(C)** Propagation of fast ripples (from 250 to 500 Hz, 6-year-old female).

Methods

- We analyzed iEEG recordings from **41 pediatric patients** [25 good outcome (Engel≤1), 16 poor outcome(Engel>1)].
- For each patient, we detected **spatiotemporal propagations** of interictal spikes (1-70 Hz), ripples (80-250 Hz), and fast ripples (250-500 Hz) using an in-house algorithm.
- We then **assigned normalized ranks to the iEEG electrodes** according to their **temporal occurrence** in each type of propagation and found the best threshold to define onset and spread electrodes.
- We estimated the **prognostic value** of the **SRO** in **predicting outcome** and compared it to propagation onset and spread, and entire zones of spikes, ripples, and fast ripples, as well as to the clinically defined seizure onset zone (SOZ).
- We estimated the **statistics** of propagation onset and spread, and entire zones of spikes, ripples, and fast ripples in predicting resection of good outcomes and compared them to statistics for **SRO**.

Results

- We detected **spikes and ripples in all patients**, and fast ripples in **only 16** patients.
- **Spikes and ripples were propagating in 39 and 40 patients,** respectively. **Fast ripples** were propagating in **10 patients**. **Spike and ripple onset were overlapping** in **34 (83%) patients**.
- **Spikes propagated the fastest** [5.2 (4.0-7.0) m/s] **followed by fast ripples** [3.3 (1.7-3.7) m/s] (P<0.001 for spike vs. ripple, and P<0.01 for spike vs. fast ripple propagations).
- **Ripples propagated at the lowest velocity** [1.7 (1.2-2.6) m/s] (P=0.02 for ripple vs. fast ripple propagations).
- The **SRO** had the **shortest distance to resection** (7±4 mm) and **highest overlap with resection** (82±21%) in good outcome patients compared to individual onsets of spike and ripple propagations.
- The **SRO** showed the maximum area under the curve for predicting outcome compared to propagation onset and spread and the entire area of spikes, ripples, and fast ripples.

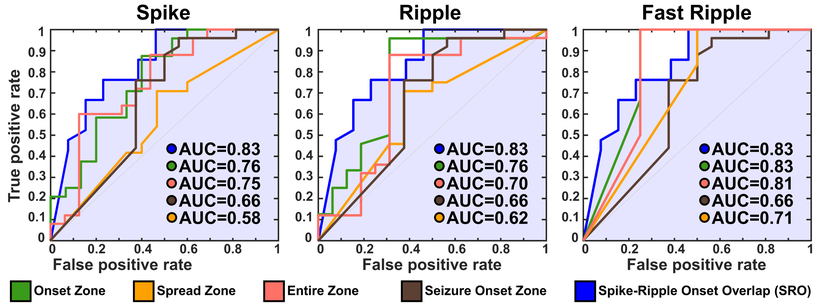

Figure 2. Statistics for prediction of surgical outcome. Receiver Operating Characteristic (ROC) curves and their area under the curve (AUC) for propagation onset and spread, and entire zones of spikes, ripples, and fast ripples, the SRO, and the SOZ as predictors of post-surgical outcome.

Results (Continued)

- The SRO showed **higher specificity** and **precision** in predicting the resection of good outcome patients compared to propagation onset and spread, and entire zones of spikes, ripples, and fast ripples.

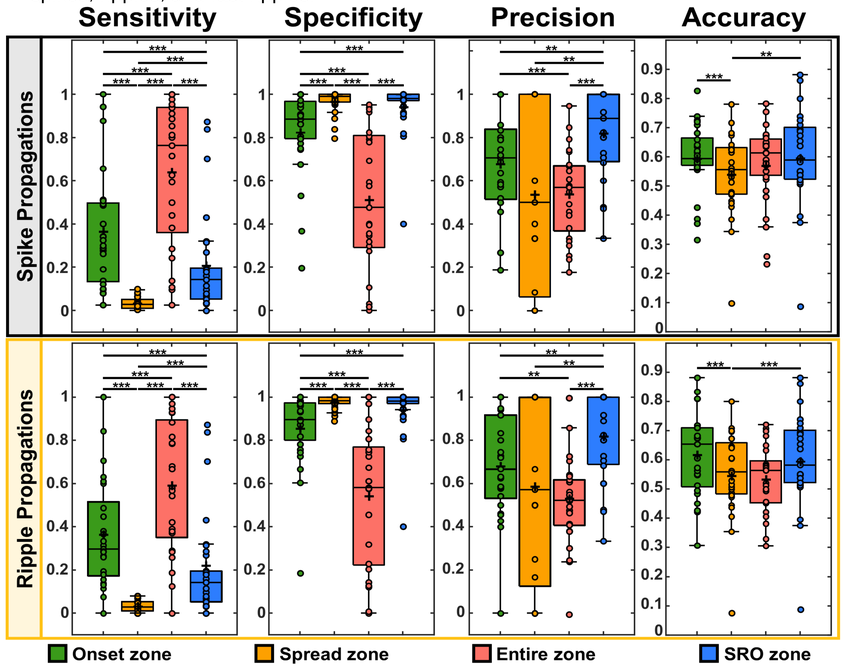

Figure 3. Statistics for prediction of resection in good outcome patients. Sensitivity, specificity, precision, and accuracy of the SRO, propagation onset and spread, and entire zones of **(A)** spike and **(B)** ripple propagations in predicting the resection zone of good outcome patients. The multiple comparisons issue was accounted for using the FDR correction. Significant differences are indicated by asterisks: *P<0.05, **P<0.01, and *** P<0.001.

Conclusion

- We show for the first time that the **overlapping onset of spike and ripple propagations is a highly specific and precise interictal biomarker** of the EZ compared to other biomarkers.
- A complete resection of the **overlapping onset of spikes and ripples** is related to seizure freedom.
- Such a biomarker may **augment presurgical evaluation** of children with DRE by delineating the EZ without the need to record ictal seizures.

Funding

This study was supported by the National Institute of Neurological Disorders & Stroke (RO1NS104116-01A1, PI: C. Papadelis; and R21NS101373-01A1, PIs: C. Papadelis and S. Stufflebeam).