

Background and Aim

- Children with **drug refractory epilepsy (DRE)** require resective neurosurgery to achieve seizure freedom, whose success strongly depends on the **accurate delineation** of the epileptogenic zone (EZ).
- Spikes, ripples** and **fast ripples** have been proposed as **biomarkers to delineate the EZ** in children with DRE.
- Spikes and ripples** suffer from **low specificity**, but they can be seen in almost all patients with epilepsy.
- Fast ripples** are more focal and specific to the EZ but are highly restricted both spatially and temporally¹ and thus may not be sampled with conventional intracranial EEG (iEEG) macroelectrodes².
- Previous studies have shown that **spikes and ripples propagate** across large brain areas, and that the onsets of these propagations are more specific biomarkers of epilepsy than areas of spread³.
- Here, we tested the hypothesis that the **overlapping onset of spike and ripple propagations (OSR) is a more specific epilepsy biomarker than fast ripples**, and that this biomarker can be seen in several patients with DRE in contrast to fast ripples.

Methods

- We analyzed iEEG recordings from **29 pediatric patients** with successful epilepsy surgery (Engel 1; more than one year follow-up).
- For each patient, we detected **spatiotemporal propagations** of interictal spikes (SP) (1-70 Hz), ripples (RP) (80-250 Hz), and fast ripples (FRP) (250-500 Hz) using an in-house automated algorithm.
- We then **ranked the iEEG electrodes and sorted them according to their timing occurrence** in each propagation category. The first 25% of rank-sorted electrodes were considered as onset.
- We estimated the **sensitivity** and **specificity** of onset, spread, and entire zone of propagation for each category in predicting resection, and compared them to overlapping onset of spike and ripple (OSR).
- We also compared the **sensitivity** and **specificity** of the onset of fast ripple propagations, all fast ripples, and the OSR among all patients.

Conclusion

- We show for the first time that the **overlapping onset of spikes and ripples is a highly specific interictal predictor** of the EZ compared to other biomarkers.
- This biomarker **was seen in all patients** in contrast to fast ripples, which were seen in only one out of four patients in our cohort.
- Such a biomarker may **augment presurgical evaluation** of children with DRE by delineating the EZ without the need to record ictal events.

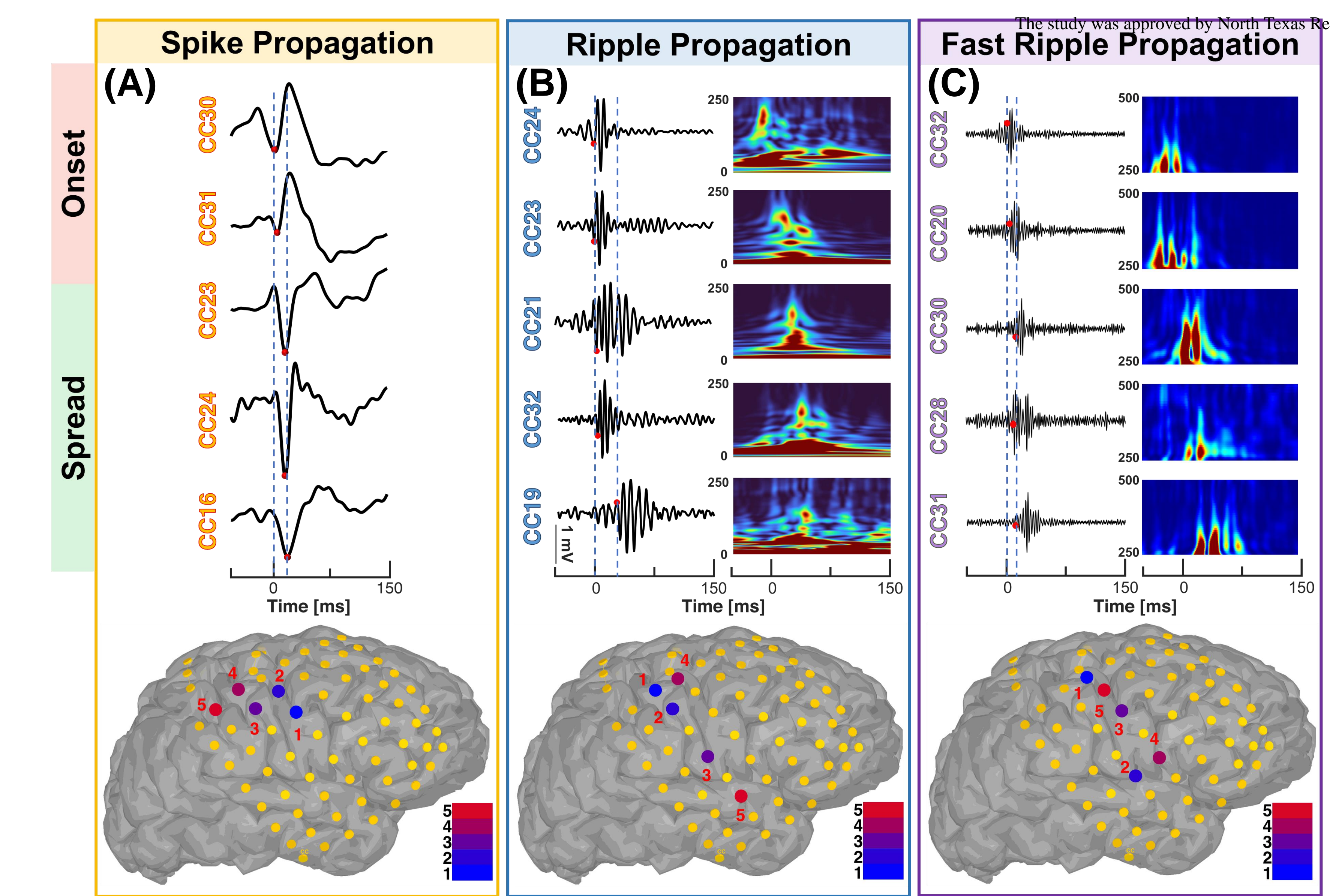


Figure 1. Sequences of spikes, ripples and fast ripples propagations for a patient with DRE, amplitudes are normalized. (A) Propagation of interictal spikes across time from an onset area to areas of spread and their corresponding spatiotemporal path on the patient's cortical surface. (B) Propagation of ripples across time, the corresponding time-frequency analysis plots (from 0 to 250 Hz) and spatiotemporal path on patient's cortical surface. (C) Propagation of fast ripples (same display as in (B)).

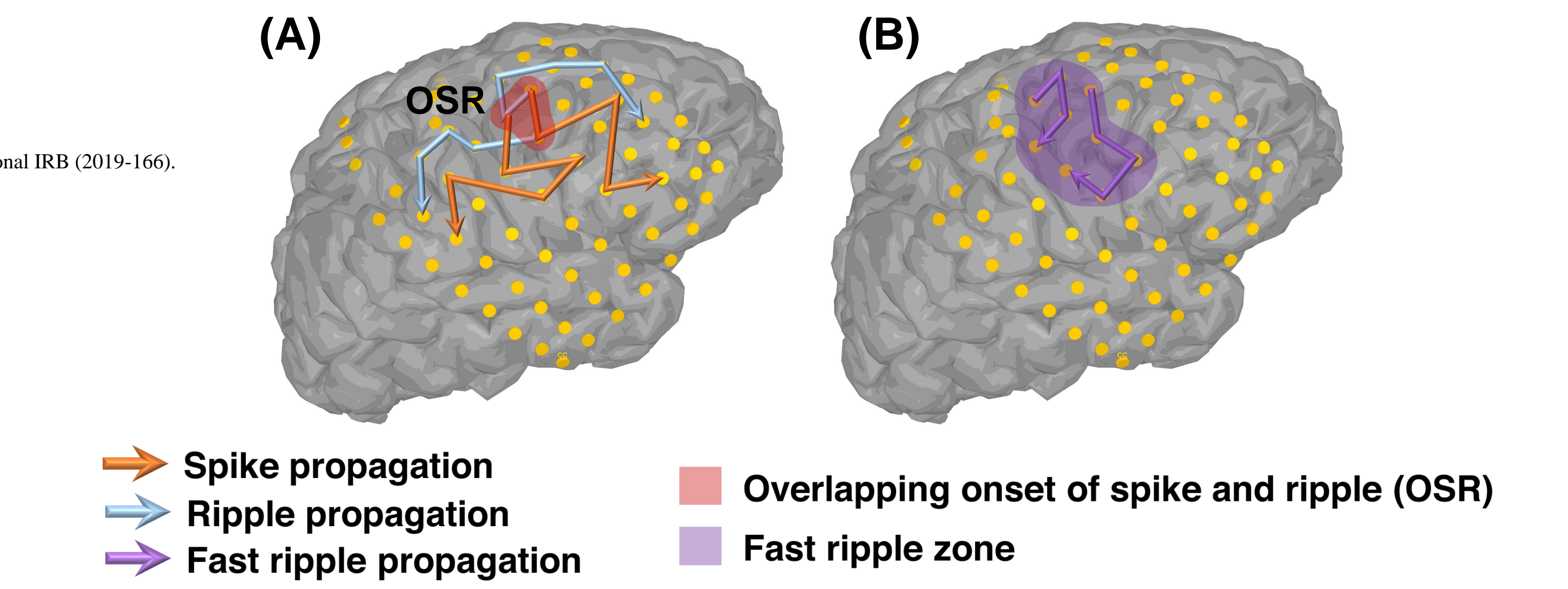


Figure 2. Overlapping propagation sequences of spikes and ripples vs. fast ripple area. (A) Spike and ripple propagation sequences and overlapping onset of spike and ripple propagations (red area) (B) The entire area containing fast ripple propagations (violet area).

Results

- We detected **spikes and ripples in all patients**, and fast ripples in only 7 patients.
- Spikes and ripples were propagating in all patients.** Fast ripples were propagating in 6 patients. Spike and ripple onset was overlapping in all 29 patients.
- Spike, ripple, and fast ripple propagations had **significantly different** ($p < 0.01$) average durations of 28.3 ± 24.3 , 38.7 ± 37 , and 25 ± 14 ms, respectively.
- The onset of spike and ripple propagations (but not fast ripples) showed **higher specificity** to the EZ compared to the corresponding areas of spread ($p < 0.05$).
- The OSR showed **higher specificity to predict resection** compared to the onset (or spread) of spikes or ripples (but not fast ripple) propagations ($p < 0.01$).
- The OSR was **more specific** in predicting resection compared to fast ripples ($p < 0.01$).

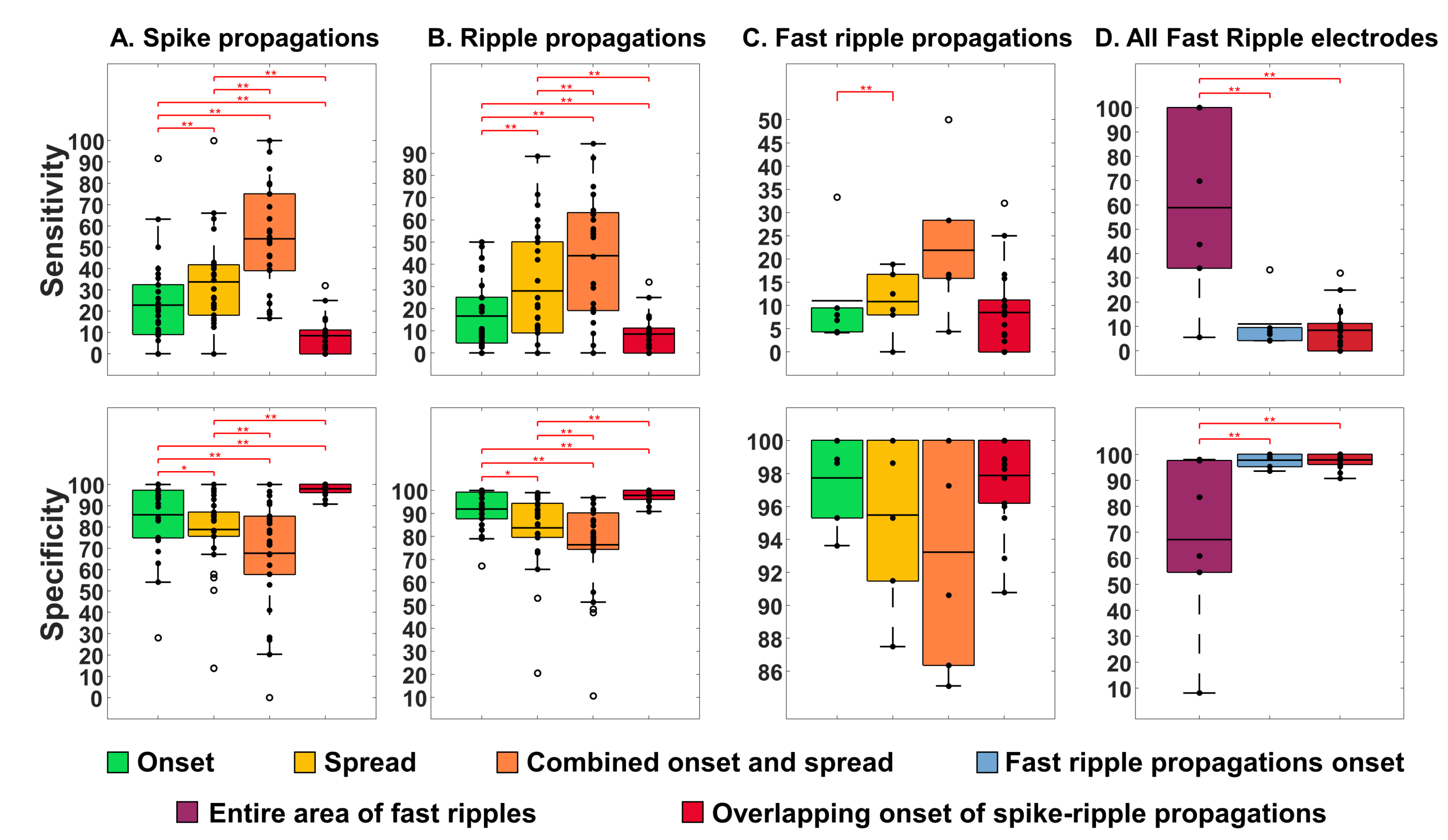


Figure 3. Sensitivity and Specificity of the EZ for the different biomarkers: Sensitivity and specificity for delineating the EZ for the overlapping onset of spikes and ripples propagations in comparison to the onset, spread, and entire areas of spikes, ripples, and fast ripples. The overlapping onset of spikes and ripples propagations compared to onset, spread, and entire area of (A) spike propagations, (B) ripple propagations, and (C) fast ripple propagations. (D) The overlapping onset of spikes and ripples propagations compared to onset of fast ripple propagations and the entire area of fast ripples. (*) indicates $p < 0.05$; (**) indicates $p < 0.01$.

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References

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