Pathological and Physiological Scalp High-Frequency Oscillations in Children with Drug Resistant Epilepsy and Healthy Controls

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Background & Rationale

- **High-frequency oscillations** (HFOs) are promising **interictal biomarkers** of the **epileptogenic zone (EZ)** in **drug-resistant epilepsy (DRE)**.
- Their clinical value is questionable since the HFO-generating area is often relatively large and not specific to the EZ, so its complete resection is often unnecessary for seizure freedom.
- Previous **intracranial EEG (iEEG)** studies discriminated **physiological** from **pathological HFOs** but were limited by the inherent inability of iEEG to obtain whole-head coverage and record data from healthy controls.
- Here, we use whole-head **noninvasive techniques**, such as **magnetoencephalography (MEG)** and **high-density EEG (HD-EEG)**, to detect HFOs from both children with DRE and healthy controls and to identify features that differentiate pathological from physiological HFOs.

Methods

- **Patients: 55 children with DRE** (age: 12.9 ± 3.5 years; 33 females) and **48 healthy controls** (age: 11.4 ± 3.7 years; 25 females). Children with DRE were categorized as having **focal or generalized/diffuse DRE**. In the focal DRE group, the epileptogenic zone (EZ) was defined based on presurgical evaluation.
- **Recordings:** We analyzed simultaneous magnetoencephalography (MEG; 306 sensors) and high-density EEG (HD-EEG; 256 channels) data sampled at ≥ 1000 Hz.
- **HFOs:** We detected HFOs (ripples: 80-160 Hz) on MEG and HD-EEG separately using an automated detection algorithm followed by visual review and localized their cortical sources using electric and magnetic source imaging **(Fig 1A).** For each HFO, we extracted a set of temporal, spatial, morphological, and spectral features **(Fig 1B).** HFOs were then grouped in four classes (**Fig 1C**) based on whether they were generated by: (1) the controls' healthy brain **(HFOs-controls)**; (2) the EZ in focal DRE **(HFOs-EZ)**; (3) the non-EZ in focal DRE **(HFOs-nonEZ)**; and (4) the generalized/diffuse DRE brain **(HFOs-Gen)**. HFO features were compared between these four groups (Kruskal-Wallis).
- For all statistical tests, we used a significance level of 0.05.

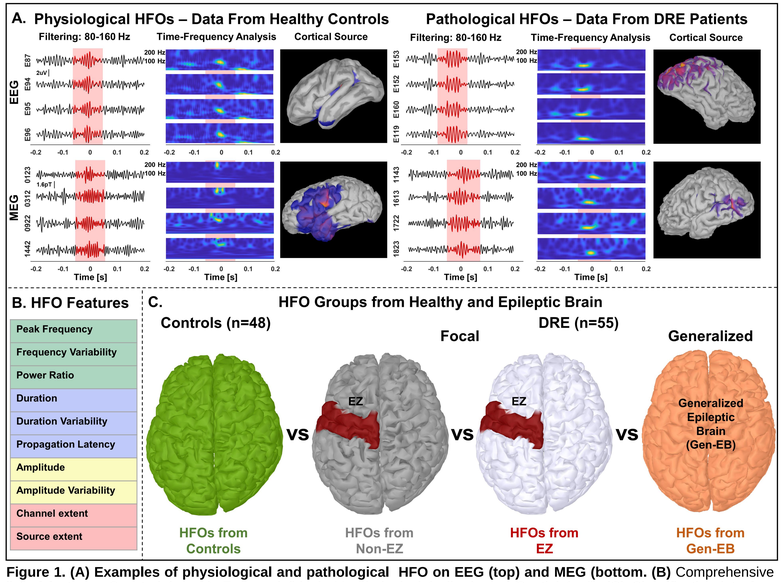

Figure 1. (A) Examples of physiological and pathological HFO on EEG (top) and MEG (bottom. (B) Comprehensive list of features. Spectral (green), Temporal (blue), Morphological (yellow), and Spatial (red). **(C)** Classification into four groups of HFOs (HFOs from Healthy Controls, HFOs from DRE-focal from non-EZ, HFOs from DRE-focal from EZ, and HFOs from RDE-generalized). DRE = Drug-Resistant Epilepsy; EZ = epileptogenic zone

Results

- We found more HFOs on HD-EEG than MEG in both healthy controls (1.27 vs 0.12 HFOs/min, p < 0.001) and children with DRE (0.94 vs 0.30 HFOs/min, p < 0.001).
- For HD-EEG, various HFO features differed between four classes: HFO-controls showed lower frequency, duration and duration variability than HFOs-EH, as well as longer propagation latency, smaller amplitude, amplitude variability and smaller spatial extent (**Fig 2A**).
- Looking at the HFO groups from DRE, HFOs-nonEH and HFOs-Gen often differed from HFOs-EH, with the latter being the most different from controls.
- We generated the cortical distribution maps of physiological HFOs (HFOs-controls) for HD-EEG and MEG, which showed high rates in somatosensory (0.3 HFOs/min) and temporal areas (0.03 HFOs/min) (**Fig 3A**).
- We also generated the cortical distribution of features from HFO-Controls, demonstrating differences among the lobes in frequency, amplitude, and source extent (**Fig 3B**).
- HFO-controls did not differ between dominant and non-dominant hemispheres for both HD-EEG and MEG, but their frequency and amplitude on HD-EEG positively and negatively correlated with age (**Fig 3C**, R=0.47, R = -0.50), respectively.

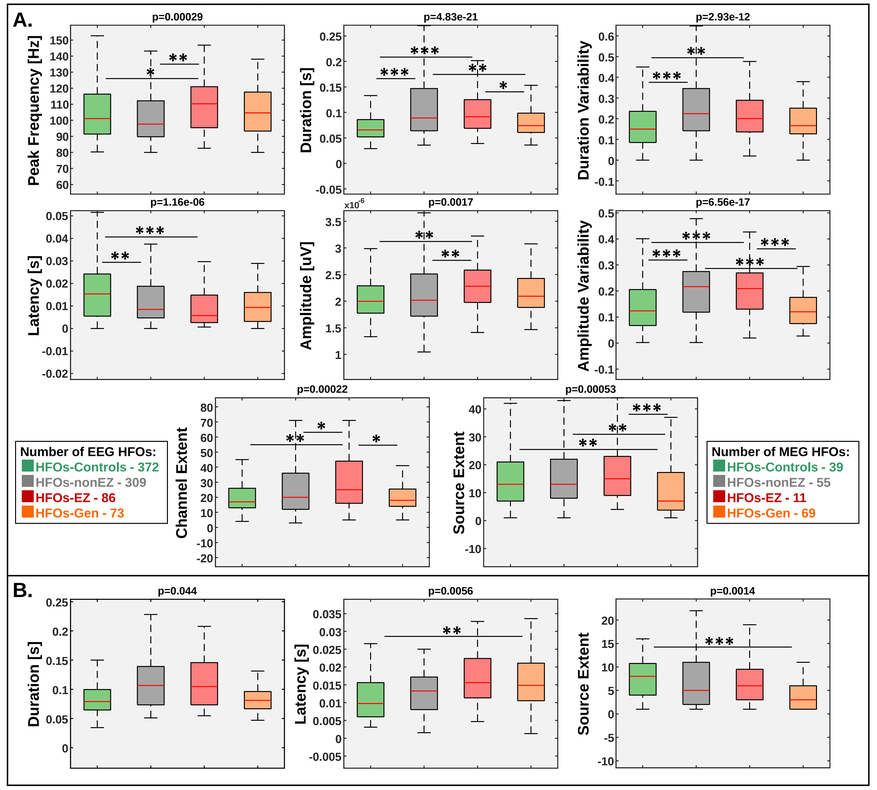

Figure 2. (A) HD-EEG results: boxplots of the comparison between HFOs-Controls (green), HFOs-nonEZ (grey), HFOs-EZ (red) and HFOs-Gen (orange). **(B) MEG results** (* p value ≤ 0.05; ** ≤ 0.01; *** ≤ 0.001).

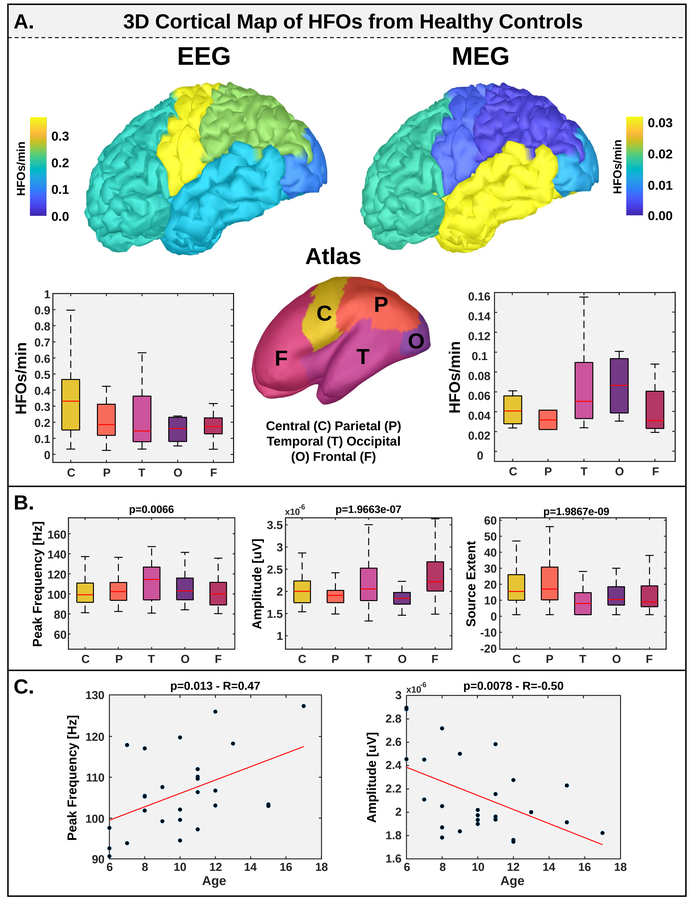

Figure 3. (A) Anatomical Distribution of Physiological EEG and MEG HFOs represented on inflated cortex. HFOs were assigned to a lobar region based on the Desikan-Killiany atlas (5 lobes) and their rates averaged across the whole cohort (38 subjects for EEG and 41 for MEG). Results for HD-EEG are presented on the left and for MEG on the right. **(B) EEG Feature Distribution from HFOs-Controls. (C) Correlation with age for HD-EEG.**

Conclusions

We present here the first cortical distribution map of physiological HFOs from healthy controls estimated non-invasively with HD-EEG and MEG. We report a comprehensive set of features that can distinguish physiological from pathological HFOs.

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