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Background & Rationale

- Resting-state **functional connectivity (FC)** can help identify hubs (i.e., highly connected regions) in **epileptogenic brain networks** whose resection may lead patients with drug resistant epilepsy (DRE) to seizure freedom.
- Our **aim** is to construct normative FC maps from typically developing (TD) children and examine whether FC deviations from these maps can identify the epileptogenic zone (EZ).
- We **hypothesize** that increased FC is associated with the epilepsy condition and that regions with increased FC deviating from normative maps are more likely to be epileptogenic.

- We compared **regional FC** estimated from EZ and non-EZ regions across patients with focal DRE, and from healthy ones of TD. We also compared FC between EZ and non-EZ regions in patients with focal DRE.
- We compared **global FC** (mean across 166 VSs) between populations and FC between epileptogenic and non-epileptogenic hemispheres (mean across VSs of one hemisphere) of patients with focal DRE.

- Patients with focal DRE had increased FC in EZ vs. non-EZ regions ($p < 0.05$, *Wilcoxon rank-sum test*) (**Fig. 3C**).

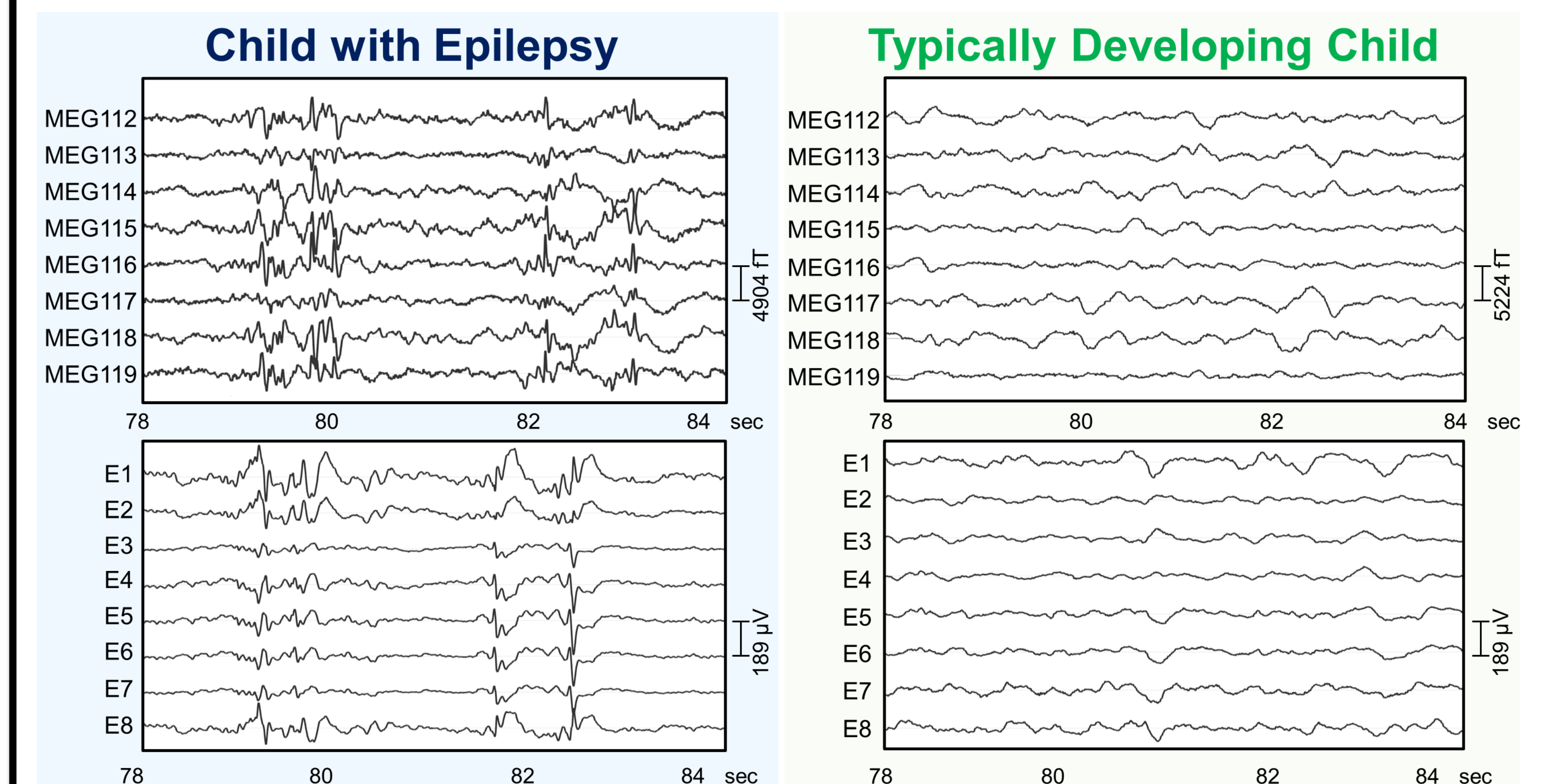


Fig. 1 Simultaneous MEG and HD-EEG. Data from simultaneous MEG (306 channels) and HD-EEG (256 channels) recordings of a child with DRE and a TD performed in a supine position while sleeping.

Methods

- Simultaneous high-density EEG (HD-EEG) and magnetoencephalography (MEG) data were analyzed from **20 children with DRE** (14 females, median age: 14 years) and **20 TD children** (11 females, median age: 10 years) (**Fig.1**).
- We performed **electromagnetic source imaging (EMSI)** on merged artifact-free portions and reconstructed virtual sensors (VSs) time-series in 166 regions of interest of a cortical atlas (AAL3) (**Fig.2**).
- We computed undirected FC [Amplitude Envelope Correlation (**AEC**) and corrected imaginary Phase Locking Value (**ciPLV**)] at the source-level from overlapping epochs (3-sec each) for different bands (**Fig. 2**) and selected their top 10% across time.
- The minimum spanning tree was used to generate a graph with *nodes* equal to VSs and *edges* equal to inverted FC values, and its centrality metrics (i.e., *betweenness*, *closeness*, *degree*, and *eigenvector*) to assess each node's importance (**Fig. 2**).
- For patients with DRE, FC z-scores were computed using controls as baseline.
- For patients with focal DRE, we defined “**epileptogenic (EZ)**” regions based on the presurgical evaluation and as **non-EZ** those in the contralateral hemisphere.

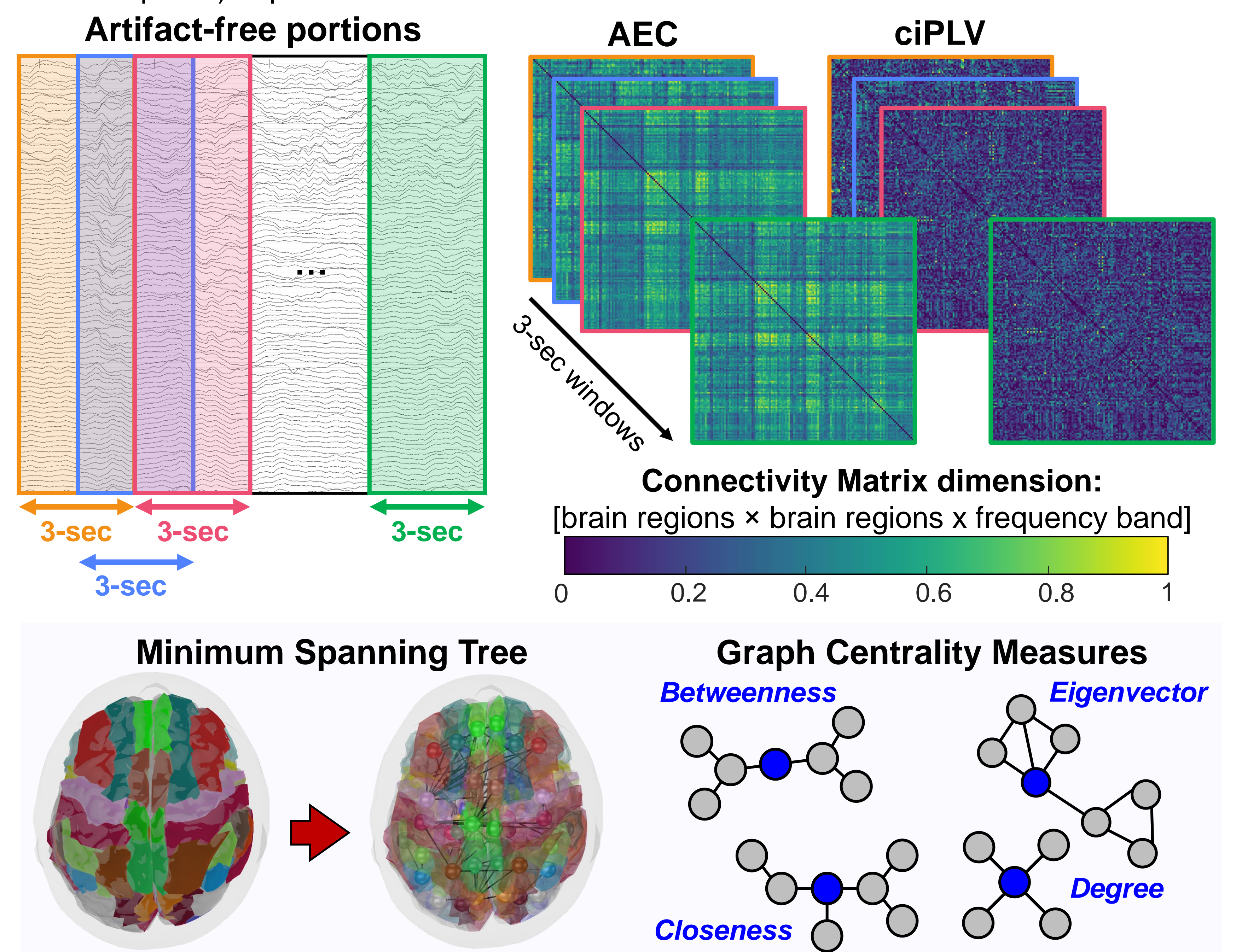


Fig. 2 Pipeline Data Analysis: **Top:** FC performed at the source-level on 3-sec epochs (50% overlap) across merged artifact-free portions for different bands (*delta*: 1-4 Hz; *theta*: 4-8 Hz; *alpha*: 8-12 Hz; *beta*: 12-30 Hz; *low-gamma*: 30-70 Hz; *high-gamma*: 70-100 Hz; *gamma*: 30-100 Hz; and *broad*: 1-100 Hz). Strongest FC values (top 10%) between ROIs were extracted across time windows. **Bottom:** Undirected brain-graph generated via the Minimum Spanning Tree (MST) and estimation of centrality measures of the MST.

Results

- We found higher global FC in children with DRE than controls in all frequency bands ($p < 0.05$, *Wilcoxon rank-sum test*) (**Fig. 3A**), as well as high AEC betweenness for low-gamma band ($p = 0.006$).
- We found increased ciPLV betweenness and degree (gamma band) in the epileptogenic vs. non-epileptogenic hemisphere of children with focal DRE ($p < 0.05$, *Wilcoxon signed-rank test*) (**Fig. 3B**).
- We observed differences ($p < 0.001$, *Kruskal-Wallis test*) when comparing FC between EZ, non-EZ, and healthy regions (**Fig. 3C**).

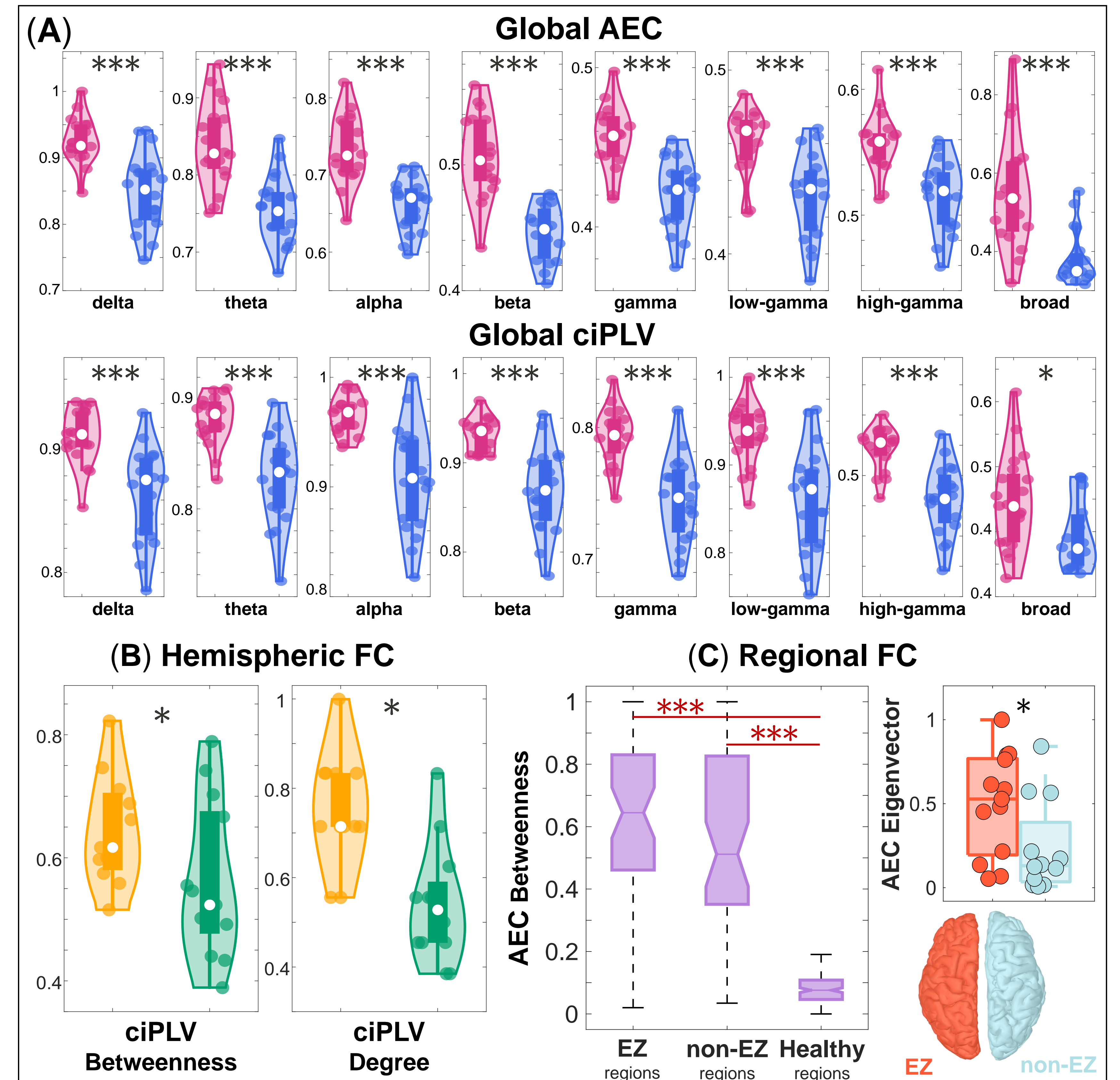


Fig. 3 Source FC results. (A) Global ciPLV and AEC closeness was significant higher in children with DRE (pink-colored) vs. TD (blue-colored) in gamma and broad bands. (B) ciPLV betweenness and degree (gamma band) computed across ROIs of either epileptogenic (yellow-colored) or non-epileptogenic (green-colored) hemisphere for patients with focal DRE. (C) *Left:* AEC betweenness (gamma band) estimated for those regions deviating from normative maps (z -score ≥ 1.96) classified as EZ, non-EZ, and healthy (i.e., regions of TD). *Right:* AEC eigenvector (gamma band) estimated for EZ (orange-colored) and non-EZ (blue-colored) regions of patients with focal DRE. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Conclusions

- Our findings indicate that **FC deviations from normative maps**, constructed from noninvasive electrophysiological data, **can identify epileptogenic regions** in the brain of children with DRE facilitating their presurgical evaluation process.

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