Functional connectivity estimated through virtual implantation predicts surgical outcome in children with epilepsy

Ludovica Corona[1,2], Eleonora Tamilia[3], M Scott Perry[1], Joseph R. Madsen[4], Steven M. Stufflebeam[5], Phillip L. Pearl[6], Christos Papadelis[1,2,7]

1. Jane and John Justin Neurosciences Center, Cook Children's Health Care System, Fort Worth, TX, USA; 2. Department of Bioengineering, University of Texas at Arlington, Arlington, TX, USA.
3. Fetal-Neonatal Neuroimaging and Developmental Science Center, Boston Children's Hospital, Harvard Medical School, Boston, MA,USA. 4. Division of Epilepsy Surgery, Department of Neurosurgery, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA.
5. Athinoula Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. 6. Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA.
7. School of Medicine, Texas Christian University and University of North Texas Health Science Center, Fort Worth, TX, USA.

Background & Rationale

- Functional Connectivity (FC) is an **epilepsy biomarker** that describes how different brain areas are functionally connected.
- FC networks may help to identify pathological **hubs** that facilitate the spread of the epileptogenic activity to the rest of the brain.
- Our **aim** is to map noninvasively the epileptogenic network in children with drug resistant epilepsy undergoing surgery through "implantation" of virtual sensors and to assess the prognostic value of resecting the noninvasively localized pathological hubs.
- We **hypothesize** that pathological hubs (i.e., brain areas with high interictal connectivity) can be noninvasively identified with high-density EEG (HD-EEG) and MEG, and that their surgical resection leads to favorable outcome.

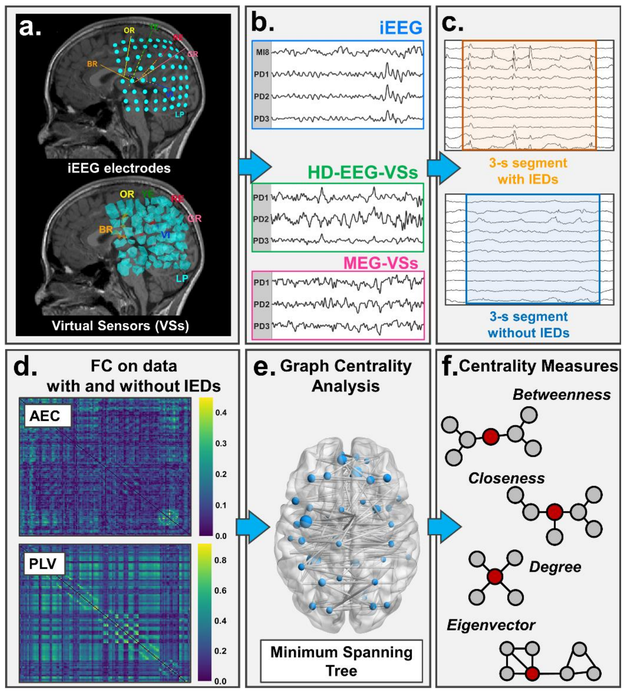

Fig. 1. Flow chart of methods. **a)** Virtual sensors (VSs) at iEEG locations; **b)** iEEG and VSs time-series filtered at (1-50) Hz; **c)** Selection of data with and without IEDs; **d)** AEC and PLV matrices, for each frequency band, type of activity (with and without IEDs) and signal (iEEG, HD-EEG-VSs, MEG-VSs); **e)** General representation of MST to generate sub-graphs; and **f)** MST's centrality measures.

Methods

- We analyzed iEEG, MEG, and HD-EEG data from **37 patients** (17 females, 12.62 ± 4.93 years) who underwent surgery.
- We performed electric and magnetic source imaging (ESI/MSI) to reconstruct **source activity at VSs locations**, equal to iEEG electrodes (**Fig. 1a, b**).
- We identified segments with and without interictal epileptiform discharges (IEDs), 1-minute for each type of activity (**Fig. 1c**).

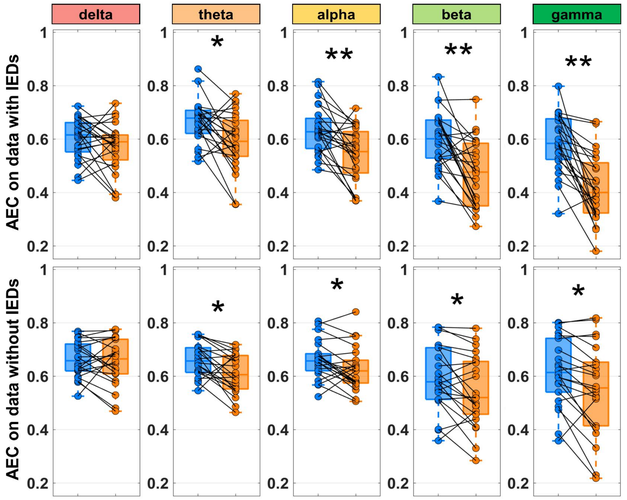

Fig. 2. FC measure for iEEG Analysis across all frequency bands. AEC for iEEG showed significant increases of FC inside (blue) resection compared to outside (orange), in good outcome patients, both on data with and without IEDs. No differences were seen in poor outcome patients (except for AEC gamma IEDs).

- We computed Amplitude Envelope Correlation (**AEC**), and Phase Locking Value (**PLV**) in delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (30-50 Hz) bands (**Fig. 1d**).
- From each FC matrix, we generated a brain network using the Minimum Spanning Tree (**MST**) (**Fig. 1e**).
- For each node, we computed four **centrality measures**: *betweenness*, *closeness*, *degree*, and *eigenvector* (**Fig. 1f**).
- We validated the **relationship between FC** and **centrality measures with the epileptogenic zone** (**EZ**) by comparing FC values inside vs. outside resection.
- We estimated **predictive values of surgical outcome** for each FC measure (*Fisher's exact* test).

Results

- We found higher FC inside than outside resection ($p < 0.05$) in good outcome patients for the following metrics:

  iEEG: AEC (theta, alpha, beta, and gamma) and PLV (alpha) on data with IEDs, and AEC (theta, alpha, beta, and gamma) on data without IEDs (**Fig. 2**);

  ESI: AEC (theta) on data with IEDs, AEC (alpha, beta, and gamma) and PLV (gamma) on data without IEDs;

  MSI: PLV (theta, alpha, beta, and gamma) on data with IEDs, and PLV (delta, alpha, beta, and gamma) on data without IEDs.

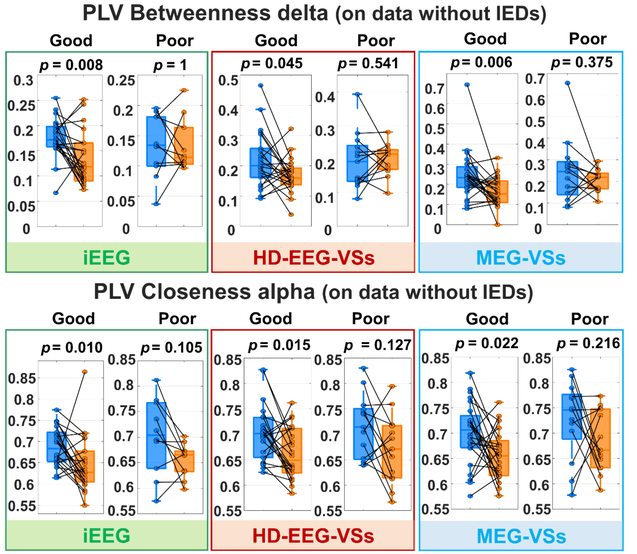

Fig. 3. FC measures for iEEG and VSs analyses. PLV *betweenness* delta and PLV *closeness* alpha for iEEG, HD-EEG-VSs, and MEG-VSs analyses, on data without IEDs, inside (blue) vs. outside (orange) resection for patients with good and poor outcome.

- PLV *betweenness* delta and PLV *closeness* alpha showed differences ($p < 0.05$) inside vs. outside resection in good outcome patients on all data without IEDs (**Fig. 3**) .
- PLV *closeness* in alpha was mapped at the patient's level to show changes of FC values based on surgical outcome (**Fig. 4**).
- PLV *betweenness* delta, estimated on data without IEDs was predictive ($p < 0.05$) at the patient-level for all modalities (**Fig.5**).

Conclusions

- We showed that **FC estimated noninvasively with VSs** can **overcome iEEG limitations** and **help the presurgical evaluation** of children with drug resistant epilepsy**,** by identifying pathological hubs (brain regions with high FC) .
- **Such a method** can **predict surgical outcome from noninvasive data**, even in the absence of interictal activity.

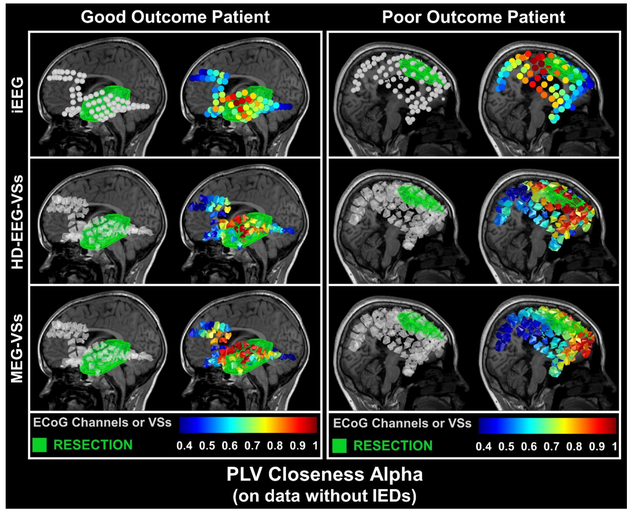

Fig. 4. FC analysis at patient's level. Heat map of PLV *closeness* estimated on data without IEDs in alpha frequency band for a 12-year-old male patient with good (left) and a 14-year-old male patient with poor (right) outcome.

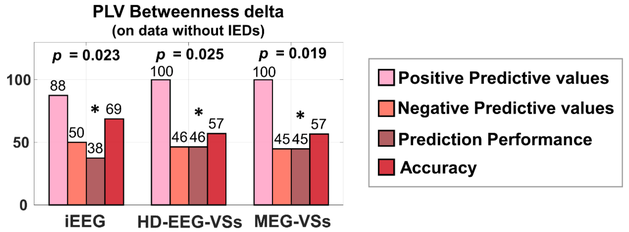

Fig. 5. Surgical predictive measure. PLV *betweenness* delta for iEEG, HD-EEG-VSs, and MEG-VSs analyses was predictive of the surgical outcome. Significant differences are displayed with asterisk (*) for $p < 0.05$.

Funding: RO1NS104116-01A1 and R21NS101373-01A1 by NINDS.