Current Literature
In Clinical Science

Sensing the Body Electric: Biomarkers of Epileptic Brain

Removing Interictal Fast Ripples on Electrocorticography Linked With Seizure Freedom in Children.

Wu JY, Sankar R, Lerner JT, Matsumoto JH, Vinters HV, Mathern GW. *Neurology* 2010;75:1686–1694.

BACKGROUND: Fast ripples (FR, 250–500 Hz) detected with chronic intracranial electrodes are proposed biomarkers of epileptogenesis. This study determined whether resection of FR-containing neocortex recorded during intraoperative electrocorticography (ECoG) was associated with postoperative seizure freedom in pediatric patients with mostly extratemporal lesions. METHODS: FRs were retrospectively reviewed in 30 consecutive pediatric cases. ECoGs were recorded at 2,000 Hz sampling rate and visually inspected for FR, with reviewer blinded to the resection and outcome. RESULTS: Average age at surgery was 9.1 ± 6.7 years, ECoG duration was 11.8 ± 8.1 minutes, and postoperative follow-up was 27 ± 4 months. FRs were undetected in 6 ECoGs with remote or extensive lesions. FR episodes (n = 273) were identified in ECoGs from 24 patients, and in 64% FRs were independent of spikes, sharp waves, voltage attenuation, and paroxysmal fast activity. Of these 24 children, FR-containing cortex was removed in 19 and all became seizure-free, including 1 child after a second surgery. The remaining 5 children had incomplete FR resection and all continued with seizures postoperatively. In 2 ECoGs, the location of electrographic seizures matched FR location. FR-containing cortex was found outside of MRI and FDG-PET abnormalities in 6 children. CONCLUSION: FRs were detected during intraoperative ECoG in 80% of pediatric epilepsy cases, and complete resection of FR cortex correlated with postoperative seizure freedom. These findings support the view that interictal FRs are excellent surrogate markers of epileptogenesis, can be recorded during brief ECoG, and could be used to guide future surgical resections in children.

Commentary

Localization of epileptic brain is the cornerstone of successful epilepsy surgery. In the final decades of the 20th century, advances in neuroimaging led to significant improvements in epilepsy surgery efficacy (1). Unfortunately, the gains in epilepsy surgery efficacy have reached a plateau. In particular, patients with normal MRI, diffuse or multifocal imaging abnormalities remain a significant challenge. There is an intense effort to better localize epileptic brain for epilepsy surgery.

Electrophysiology was the breakthrough that drove the initial development of epilepsy surgery (1). While not the first to utilize intraoperative electrocorticography to map epileptic brain, Penfield and Jasper at the Montreal Neurological Institute are notable for demonstrating the benefits of close collaboration between neurosurgeon and electrophysiologist (2). They recorded epileptiform spikes from the neocortex to map the epileptogenic brain and guide focal resection (2). The current conceptual approach to epilepsy surgery defines the epileptogenic zone (EZ) as the brain region which must be resected for seizure freedom (3). The brain region generating interictal spikes, called the irritative zone (IZ), provides an interictal map of epileptic brain but is generally more widespread than the region generating spontaneous seizures, the ictal onset zone (IOZ). The relationship between the IZ, IOZ, and EZ remains poorly defined in practice. For this reason, chronic intracranial EEG recording (iEEG) to capture habitual seizures remains the gold standard for localizing epileptic brain and guiding surgery.

Unfortunately, iEEG extending over days is associated with significant cost, morbidity, and patient discomfort. In addition, the need for iEEG is unclear in many patients. Patients with a clear epileptogenic structural lesion on MRI may not require iEEG (4) but still benefit from limited duration intraoperative electrocorticography recordings (ECoG) to guide surgery. Many epilepsy centers, particularly in pediatric epilepsy surgery, utilize ECoG rather than chronic iEEG recordings, but the data are still limited (5, 6). A robust interictal signature of the EZ could potentially eliminate the need for multi-day iEEG in a wider spectrum of patients. Thus, the search for electrophysiological biomarkers of the EZ remains an active and potentially high impact area of clinical research. Perhaps the most promising candidate for interictal EZ localization is the use of pathological high frequency oscillations (pHFO) (7, 8).

The study highlighted here is important because they use intraoperative ECoG to localize epileptic brain using interictal pHFO (9). This is motivated by over a decade of accumulating evidence that pHFO are useful electrophysi-

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ological signatures of epileptic brain and seizure generation (10). The current paper does have weaknesses, however, that may limit its immediate impact. In particular, the study is a retrospective review of pediatric patients who underwent large resective surgeries, and whether the result can be generalized to focal epilepsy is unclear. In addition, the volume of EEG data is remarkably small, and the analysis is limited to visual review. While positive findings from visual review of small retrospective data sets likely reflect a robust signal, decades of clinical EEGs have illuminated the remarkable variability of human electrophysiology, which can be obscured by limited data sampling (11). Here, the average amount of data analyzed was only 11.8 minutes. From this limited data set, a total of 273 fast ripples were visualized in 24 patients, and in 17 patients fewer than 10 fast ripple events were visualized. Nonetheless, 19 patients had resection of channels generating fast ripple pHFO, and all were seizure free; whereas none of the 5 without resection of fast ripple pHFO were seizure free. The limited selection of data, small number of events, and the fact that the majority of patients had either hemispherectomy or lobar resections leave unclear how well the results will generalize to focal cortical resections.

In summary, the paper discussed here represents a potentially important direction for improving the localization of epileptic brain and efficacy of epilepsy surgery. Future prospective studies evaluating large intraoperative data streams will hopefully follow.

by Gregory A. Worrell, MD, PhD

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