Interictal High Frequency Oscillations as Neurophysiologic Biomarkers of Epileptogenicity

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Joyce Y. Wu, MD
Associate Professor
Division of Pediatric Neurology
David Geffen School of Medicine at UCLA
<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
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<tr>
<td>Tuberous Sclerosis Alliance</td>
<td>PI</td>
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<td>Today’s and Tomorrow’s Children Fund</td>
<td>PI</td>
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<td>Novartis – RAD001M2301, RAD001M2304</td>
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<td>NIH – K23 NS051637, R34 MH089299, P20 NS080199, U01 NS082320, R01 NS082649</td>
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Learning Objectives

• To gain better understanding of a neurophysiologic/EEG biomarker

• To evaluate the role of a neurophysiologic/EEG biomarker
High Frequency Oscillations
High Frequency Oscillations

Ripples  
100-250 Hz

Fast Ripples  
250-500 Hz
High Frequency Oscillations

- 100-250 Hz
  - Ripples
    - Ictal
    - Interictal

- 250-500 Hz
  - Fast Ripples
    - Ictal
    - Interictal
Normal vs Pathologic HFO

• Physiologic HFO
  • Sensory stimulation
  • Electrical stimulation

• Pathologic R and FR
  • Spontaneously occurring
  • 100-250 Hz and 250-500 Hz
  • At least 4 oscillations
  • < 1 second in duration
Fast Ripples as Surrogate Marker in Animal Models

- 1st described in a rat model in 1999
- Found only in epileptic rats, before seizure onset, absent in control rats
- Localizing to the epileptogenic zone (mesial temporal structures)

Bragin et al 1999 Epilepsia
Spatially Localizing

Temporally Predictive
Micro- or macroelectrodes?

Interictal High-Frequency Oscillations (80–500Hz) in the Human Epileptic Brain: Entorhinal Cortex

Anatol Bragin, PhD,1,2 Charles L. Wilson, PhD,1,2 Richard J. Staba, PhD,3 Mark Reddick, MS,3 Itzhak Fried, MD, PhD,4,5 and Jerome Engel, Jr., MD, PhD1,2,3

• First human HFO study
• Utilized depth microelectrodes
• Implanted in mesial temporal lobe/entorhinal cortex
• Ripples (100-200 Hz) and FR (250-500 Hz)
• Seen in 12 of 19 patients
Micro- or macroelectrodes?

**Interictal high-frequency oscillations (100–500 Hz) in the intracerebral EEG of epileptic patients**

Elena Urrestarazu,* Rahul Chander, François Dubeau and Jean Gotman

- Depth *macro*electrodes
- Ripples in all 7 patients (80-200 Hz)
- FR in 5 of 7 patients (250-500 Hz)
Correlate with neuroimaging?

High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type

Julia Jacobs, Pierre LeVan, Claude-Édouard Châtillon, André Olivier, François Dubeau and Jean Gotman

- Depth *macro*electrodes
- Mesial temporal atrophy, focal cortical dysplasia, nodular heterotopia – no etiology-dependent HFO findings
- Ripples (80-250 Hz) and FR (250-500 Hz) were present outside of the lesion
- Lesion alone does not necessarily correlate with HFO
• Ripples and FR can be used to localize the seizure onset zone in non-lesional epilepsy patients
• Ripples and FR are more specific and accurate than spikes in delineating the seizure onset zone

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<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
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<tr>
<td>Spikes</td>
<td>91%</td>
<td>30%</td>
<td>44%</td>
</tr>
<tr>
<td>Ripples</td>
<td>91%</td>
<td>40%</td>
<td>54%</td>
</tr>
<tr>
<td>Fast Ripples</td>
<td>66%</td>
<td>80%</td>
<td>76%</td>
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• Rate of spikes, ripples, and FR were assessed 1) before and after seizures without medication changes, and 2) before and after medication reduction without intervening seizures
• After seizures, spikes increased, but ripples and FR stayed at similar rates
• After medication reduction, ripples and FR rate and duration both increased, similar to seizures
Localizing to seizure onset zone?

- HFO often occurred independently of spikes
- HFO prominent in the seizure onset zone
- Seizure onset zone can be identified with high specificity with only 10 minutes of HFO

*Interictal high-frequency oscillations (80–500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain*

Julia Jacobs, Pierre LeVan, Rahul Chander, Jeffery Hall, François Dubeau, and Jean Gotman

*Epilepsia, 49(11):1893–1907, 2008*
Localizing to the epileptogenic zone?

Seizure outcome?
• Removal of HFO-generating area correlated with good surgical outcome
• HFO could be used as a marker of epileptogenicity
• HFO may be more accurate than spikes or seizure onset
• Patients in whom the majority of HFO-generating areas remained had poor surgical outcome
• FR present in neocortex
• All subdural macroelectrodes
• First study in children

• All intraoperative electrocorticography, avg nearly 12 minutes
• FR present in 80%, 24/30 consecutive electrocorticographies
• All 19 children with complete resection of FR-generating area are seizure-free, avg 27 months postop follow-up
• Remaining 5 children with incomplete resection of FR-generating area all continued with seizures postop
• FR found outside of MRI lesions and outside of FDG-PET hypometabolic areas
16 yo M with intractable epilepsy for 4 yr (visual blurring and distortion)
Prospective HFO

• Next 30 consecutive ECoGs reviewed prospectively for FR, within 1 week of surgery, often within 24 hours

• Surgical follow up, median 36 months

• FR detected in 80%, in 24 patients

• 20 seizure free patients had complete FR resection; 3 with TSC had remote seizure foci, and 1 had contralateral seizure focus

Hussain et al (Submitted)
“Live” Intraoperative HFO

• In the same study, 11/30 ECoGs were interpreted “live” in the operating room, immediately after recording ended and after surgical decisions were made
• “live” read did not alter or delay surgery
• No significant difference between “live” read and an unrushed second read

Hussain et al (Submitted)
How do FR compare to other ECoG findings?

- Combining retrospective and prospective series, total 60 patients, among FR, paroxysmal fast activity (PFA), spikes, continuous epileptiform discharges (CEDs), and focal slowing, FR fared the best
  - Highest specificity (100%)
  - Highest positive predictive value (100%)
  - Highest Accuracy (87.5%)

Hussain et al (Submitted)
FR Resection & Postop Sz Freedom
(all 60 children)

Hazard Ratio 31.9, p < 0.001

Hussain et al (Submitted)
Spatially Localizing

Temporally Predictive

Clinical Trial?

Spatially Localizing

Non-Invasive

Temporally Predictive?
Interictal scalp fast oscillations as a marker of the seizure onset zone

Ripples (80-200 Hz)

Gamma (40-80 Hz)
Scalp Fast Ripples

Conventional Setting
30 mm/sec
1 Hz / 70 Hz / 60 Hz notch

Fast Ripple Setting
300 mm/sec
250 Hz / 500 Hz
Scalp Fast Ripples

- Tuberous Sclerosis Complex
- Before Seizure Onset – Family History, Skin Findings, or Cardiac Rhabdomyoma
- Prospective serial scalp EEGs
- Can HFO be a predictive temporal marker?
Epilepsy and Autism Biomarker Studies in Infants

UCLA Tuberous Sclerosis Complex (TSC) Center

NIH TSC Clinical Trial - Potential EEG Biomarkers and Antiepileptogenic Strategies for Epilepsy in TSC

NEEDED: Newborns to 6 months old infants with TSC with NO history of seizures

Epilepsy in Tuberous Sclerosis Complex (TSC) Research Study... change the outcome

What:
The purpose of this research study is to look for early signs of autism in children with Tuberous Sclerosis Complex (TSC), a genetic disorder where autism is common.

Who:
Infants 3 to 9 months old who are diagnosed with TSC may be eligible to participate.

We are looking for children with Tuberous Sclerosis Complex (TSC) between the ages of 0 months and 2 years!
In summary…

• HFO first seen in rat models as potential surrogate marker of the epileptogenic zone
• First recorded in epilepsy patients with depth microelectrodes, then depth macroelectrodes, and subdural macroelectrodes
• First in mesial temporal structures, now also neocortex
• First in adults, now also children
• First hours of implanted recording, now minutes of implanted/intraoperative ECoG
In summary…

- FR localization independent of neuroimaging
- FR independent of etiology
- FR reflects seizure frequency, disease course
- FR localizes to the seizure onset zone
- FR localizes to the epileptogenic zone, with complete FR excision leading to sz freedom
- can be seen “live” in the OR
- detectable non-invasively on scalp EEG

Interictal HFO a good spatial marker of epileptogenicity and the epileptogenic zone
Future Directions

• Surgical Clinical Trial?
• Temporally Predictive?

Thank You