High Frequency Oscillations in Temporal Lobe Epilepsy

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Learning Objectives

• Understand the difference between physiological and pathological HFOs

• Understand the mechanisms underlying HFOs

• Understand the association of HFOs with disease activity in patients

• Understand the association of HFOs with seizure outcome

• Understand how to record and detect HFOs
Disclosure Statement

Dr. Federico has received speaker fees from UCB.
Background

- Identifying epileptogenic zone is critical in surgical treatment of refractory focal epilepsy
- Ictal EEG is very useful for diagnosing and classifying seizures and epilepsy
- Epileptiform discharges are highly specific for the epileptic brain, but
  - Not always concordant with ictal onset zone
  - Only loosely related to disease activity
- HFOs may be a new biomarker for epilepsy
## EEG frequency bands

### EEG-MEG bands

<table>
<thead>
<tr>
<th>Berger's bands</th>
<th>&quot;high-frequency&quot; bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>near-DC</td>
<td>δ δ δ δ α β γ ω ω ω ω ρ σ</td>
</tr>
</tbody>
</table>

- **Ripples**: (80-250 Hz)
- **Fast ripples**: (250 – 600 Hz)
High frequency oscillations (HFOs)

- **Definition:**
  
  Events with at least 4 consecutive oscillations between 80-500 Hz that clearly rise above baseline.

- Recorded in humans and animals
- Most studies recorded HFOs from mesial temporal structures
- Best seen during slow-wave sleep
- Seen with interictal discharges, seizures, and in between
Mechanisms underlying epileptic HFOs

- Co-firing of small groups of pathologically-interconnected principal cells
  - Ephaptic interactions
  - Gap junctions
  - Fast synaptic transmission
- Out-of-phase firing of neuronal populations
  - Structural, molecular, functional changes
  - Increased synaptic noise
  - Acquired channelopathy
- Synaptic inhibition limits spatial extent of HFOs
Physiological HFOs

• Ripples (≈ 200 Hz) first described in area CA1 and entorhinal cortex of freely behaving rats
  – Memory formation and reactivation of previous experiences

• Extratemporal neocortex
  – Related to information processing functions
Pathological HFOs – animal model

• Fast ripples (> 250 Hz) first recorded in the hippocampus in a rat model of epilepsy, but not control animals (Bragin et al. Epilepsia 1999;40:127)
  – Physiological ripples decreased in epileptic hippocampus
HFOs & Susceptibility

Kainic acid model of status epilepticus in rats

Post-status, all animals that exhibited HFOs (in DG) went on to develop spontaneous seizures

The sooner HFOs appeared the sooner the spontaneous seizures appeared

Bragin et al. Epilepsia 2004; 45:1017
Fast ripples in rat

HFOs in humans

A  patient 309

REC
RmHip
LEC
LmHip

B
LmHip  unfiltered

hp 200 Hz

~80 Hz

~400 Hz


HFOs and the seizure onset zone

• HFOs are reliable markers of the seizure onset zone
  – Occur in regions of spontaneous seizures, more reliably than interictal discharges
  – Occur in regions where the afterdischarge threshold is low for cortical stimulation
• HFOs increase prior to seizures and AED withdrawal
• HFOs occur independently of the location and type of lesion
• HFOs can be found in non-lesional epilepsy
Identifying the Epileptogenic Zone

- Pathological HFOs may be useful for presurgical evaluation

- Ripples and fast ripples more abundant at seizure onset zone.

# TABLE: Studies Comparing Interictal Ripples and FRs to the Potential Epileptogenic Region

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Site</th>
<th>Electrodes</th>
<th>Epileptogenicity Parameter</th>
<th>Study Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bragin and colleagues (1999)(^5,9)</td>
<td>Rats (KA) and human</td>
<td>MT</td>
<td>Micro</td>
<td>Epileptic individuals and seizure onset side</td>
<td>FRs</td>
</tr>
<tr>
<td>Bragin and colleagues (2002)(^35)</td>
<td>Human</td>
<td>MT</td>
<td>Micro</td>
<td>Multiunit neuronal synchronization</td>
<td>FRs</td>
</tr>
<tr>
<td>Bragin and colleagues (2004)(^29)</td>
<td>Rats (KA)</td>
<td>MT</td>
<td>Micro</td>
<td>Side of KA injection, having seizures</td>
<td>Both</td>
</tr>
<tr>
<td>Urrestarazu and colleagues (2006)(^49)</td>
<td>Human</td>
<td>MT/F</td>
<td>Macro</td>
<td>Seizure onset zone</td>
<td>FRs</td>
</tr>
<tr>
<td>Jacobs and colleagues (2008)(^43)</td>
<td>Human</td>
<td>MT/F</td>
<td>Macro</td>
<td>Seizure onset zone</td>
<td>FRs &gt; ripples</td>
</tr>
<tr>
<td>Worrell and colleagues (2008)(^42)</td>
<td>Human</td>
<td>MT</td>
<td>Micro and macro</td>
<td>Seizure onset zone</td>
<td>Both</td>
</tr>
<tr>
<td>Jacobs and colleagues (2010/2009)(^50,56;); Zijlmans and colleagues (2011)(^48)</td>
<td>Human</td>
<td>MT/F/P/O</td>
<td>Macro</td>
<td>After discharges and seizure onset zone</td>
<td>Both</td>
</tr>
<tr>
<td>Ogren and colleagues (2009)(^79)</td>
<td>Human</td>
<td>MT</td>
<td>Micro</td>
<td>Hippocampal atrophy</td>
<td>FRs</td>
</tr>
<tr>
<td>Jiruska and colleagues (2010)(^30)</td>
<td>Rats (TT)</td>
<td>MT</td>
<td>Micro</td>
<td>Side of injection</td>
<td>FRs &gt; ripples</td>
</tr>
<tr>
<td>Jacobs and colleagues (2010)(^8)</td>
<td>Human</td>
<td>MT/F/O</td>
<td>Macro</td>
<td>Surgical outcome</td>
<td>Ripples &gt; FRs</td>
</tr>
</tbody>
</table>

The conclusion describes whether fast ripples or ripples were more specific for the presumed epileptogenic area or whether no clear difference was found.

F = frontal; FR = fast ripple; KA = kainic acid; MT = mesiotemporal; O = occipital; P = parietal; TT = tetanus toxin.
HFOs & post-surgical outcome

- Better post surgical outcome has been related more with the amount of fast ripples removed from brain tissue

Interictal to ictal transition

N = 7 animals, N = 14 slices
Wistar rats p21-24

5 successive pre-seizure to seizure transitions were recorded for 7 animals, N = 35

Pre-ictal HFO power changes

Pre-ictal HFO changes in humans

Electrodes used to record HFOs in humans

• Depth electrode – microelectrode *(UCLA)*
  – 1.25 mm & 0.04 mm diameter
• Custom made depth macroelectrode *(MNI)*
  – 0.85 mm² surface area
• Commercial subdural grid/strip and depth electrodes *(Ad-tech, U of Calgary, Toronto Sick Kids)*
  – 50 mm² surface area (grid/strip)
  – 16 mm² surface area (depth)
Detection of HFOs

- Fast sampling rate, at least 4 x upper frequency of interest (2000 Hz)
- High pass filter – may not be available in all commercial EEG systems
- Increase EEG amplitude and time base
- Beware of filtering artefact
Practical considerations

- High sampling rates produce large volumes of data
- 10 min recording is all that is needed
- Bipolar montages have less artefact
- Beware of artefacts
  - electrical (60 or 50 Hz)
  - muscle artefact – looks less smooth than HFOs
- Do not over-interpret very sporadic HFOs
Other methods of detecting HFOs

- Frequency power spectrum, using a Fourier or wavelet transform
HFOs in scalp EEG and MEG

• HFOs been recorded in relation to epileptiform discharges in scalp EEG & MEG

• This may represent a new biomarker
  – Epileptogenesis (e.g., following CNS insult)
  – AED effectiveness
Muscle artefact and ripple oscillations

Summary

• HFOs (> 80 Hz) can be recorded with commercially available intracranial electrodes and scalp electrodes
• HFOs may be a biomarker of the epileptogenic zone
  – Fast ripples more localized to the ictal onset zone
  – Better post surgical outcome is associated with removal of tissue producing fast ripples
• Recording HFOs is possible with most clinical EEG systems,
  – However, fast sampling rate (> 2000 Hz), ample data storage, and expertise in identifying HFOs (in setting of artefact) is required
• Automated detection of HFOs is a currently active field of investigation
Thank you