Introduction and Clinical use of HFO (High Frequency Oscillation)

홍 승 봉
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Lecture contents

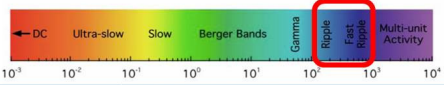
- Brain Oscillations?
- Physiology of High Frequency Oscillation (HFO)
- Physiologic vs pathologic HFO?
- HFO in temporal lobe epilepsy
- HFO in neocortical epilepsy
- Future study

Brain Oscillations?

- Rhythmic neural activity in the central nervous system
- First EEG pattern described: 8-12 Hz alpha waves by Hans Berger
- By-product of neuronal activity vs. Essential part of brain function?
- Functions
  1) Input selection and plasticity
  2) Binding cell assemblies
  3) Consolidation and combination of learned information
  4) Control of single neuron activity by phase info
  5) many more…

Frequency Spectrum of EEG waves

High Frequency Oscillation (HFO)



Oscillations	Representative Function
Ultra-slow / Slow (DC~1 Hz)	Cyclic Modulation of Gross Excitability
Delta (1~4 Hz)	Slow-wave Sleep
Theta (4~8 Hz)	Learning and Memory (especially in MTL)
Alpha (8~12 Hz)	Synchronous, coherent activity of thalamic pacemaker cells (predominantly in occipital lobe)
Beta (12~30 Hz)	Movement control, Long-range Synchrony
Gamma (30~80 Hz)	Perception, Memory, Consciousness (?)
Ripple (80~200 Hz)	Memory consolidation
Fast ripple (200-500Hz)	Epileptic, ??

Classification and Terminology of HFO

- Short-term synchronization of neuronal activity
- Fast oscillations (>80 Hz) described since early 1990s
- Also called fast activity, high frequency activity, very fast oscillations
- Further attempts to sub-classify HFO in different frequency bands
  1) Ripple (80-200 Hz): physiological activity in hippocampus (Buzsaki et al, 1992)
  2) Fast Ripple (200-500 Hz): in epileptic tissue (Bragin et al, 1999, 2004)
- Distinction not so clear → pathological ripples, HFOs above 600 Hz in normal somatosensory cortex

Big Question in Physiology of HFO

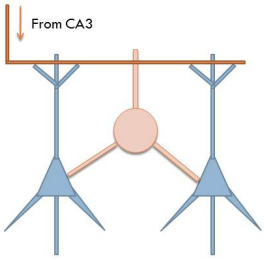
How can groups of neurons achieve coordinated and synchronized firing in such a high frequency?

General Mechanisms of HFO Generation

1) Interneuron Theory
2) Synchronous Action Potential Firing of a Group of Principal Cells (pyramidal cell or granule cells)
   i. Excitatory Coupling between Pyramidal Cells
   ii. Electrotonic Coupling (gap junctions)
   iii. Ephaptic Interactions (field effect)

Interneuron Theory

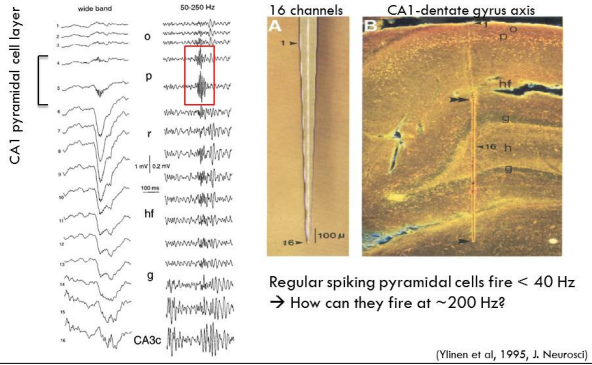
- HFOs can result from summation of IPSPs on pyramidal neurons
- Interaction between Fast Spiking Interneurons and Regular Spiking Pyramidal Cells
- Extensively studied in Rat Hippocampus



CA1 in Hippocampus,
Blue: Pyramidal Neuron,
Red: Interneuron

Interneuron Theory

Voltage depth profile analysis

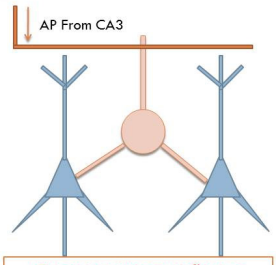


Regular spiking pyramidal cells fire < 40 Hz
→ How can they fire at ~200 Hz?

(Ylinen et al, 1995, J. Neurosci)

Interneuron Theory

- Role of Interneurons



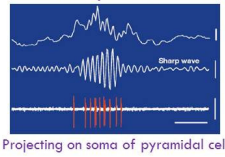
One interneuron can influence several pyramidal cells
→ synchronous firing of pyramidal cells

1) CA3 input excites Interneurons in CA1
2) Rhythmic Firing of Interneurons (transient firing at ~200 Hz)
3) Rhythmic IPSP (Inhibitory Post-Synaptic Potentials) on CA1 Pyramidal Cells
4) Temporal Window during which Pyramidal Cells are able to fire Action Potentials
5) Resulting Summation of IPSPs on Pyramidal Cells generates low-amplitude high-frequency field oscillations

Interneuron Theory

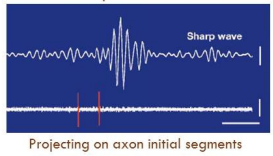
- Diverse Interneurons come into play for the generation of HFOs

Palvalbumin-positive Basket Cell



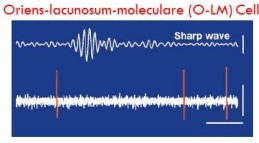
Projecting on soma of pyramidal cell

Palvalbumin-positive Axo-axonic Cell



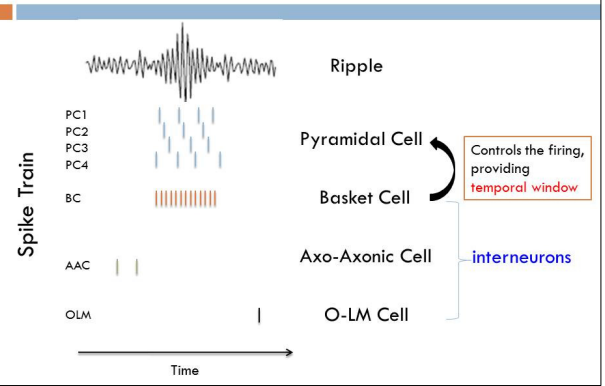
Projecting on axon initial segments

Oriens-lacunosum-moleculare (O-LM) Cell



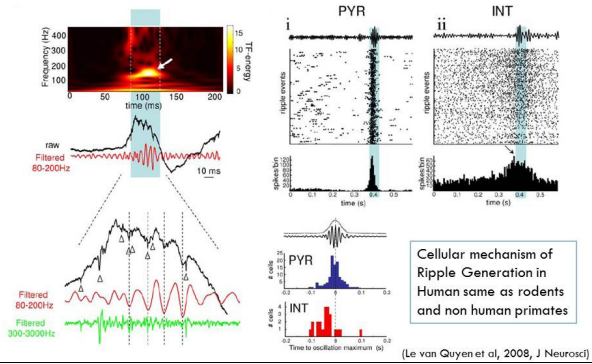
(Klausberger et al, 2003, Nature)

Interneuron Theory



Interneuron Theory

Depth microelectrodes in human hippocampus to record ripples



(Le van Quyen et al, 2008, J Neurosci)

General Mechanisms of HFO Generation

1) Interneuron Theory
2) Synchronous Action Potential Firing of a Group of Principal Cells (pyramidal cell or granule cells)
   - i. Excitatory Coupling between Pyramidal Cells
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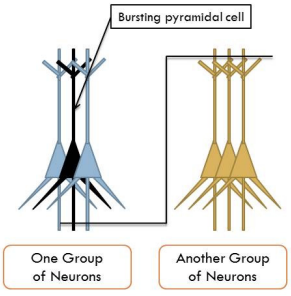
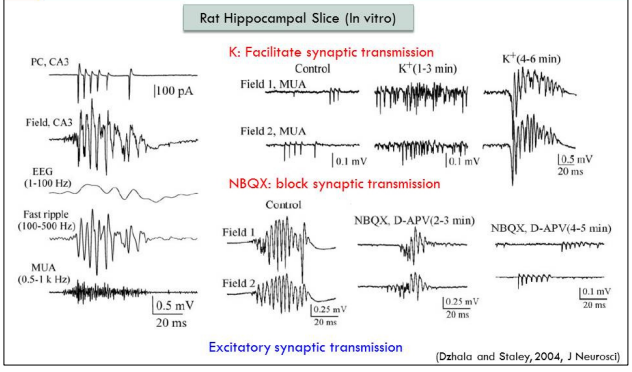
Excitatory Coupling between Pyramidal Neurons



1) Activation of one pyramidal neuron (bursting pyramidal cell) would result in EPSP (Excitatory Post-Synaptic Potential)
2) EPSP causes subsequent depolarization at post-synaptic pyramidal neurons
3) Synchronous Firing of Synaptically Coupled Neurons

Excitatory Coupling between Pyramidal Neurons



(Dzhala and Staley, 2004, J Neurosci)

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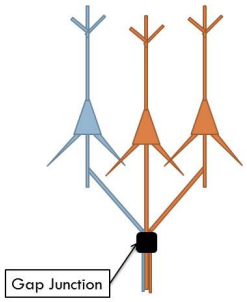
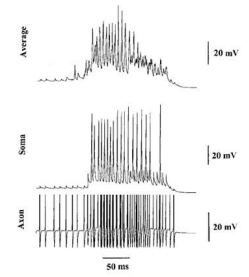
Electrotonic Coupling

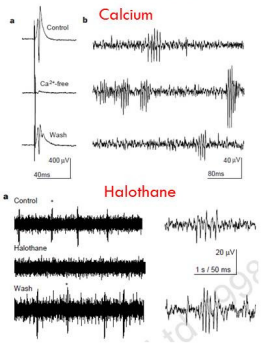


1) An action potential in one pyramidal cell (blue) may propagate through axons
2) Action potentials "jumps" into adjacent neurons (orange) through gap junctions
3) If depolarization is sufficient to trigger action potentials in neighboring neurons, then these fire in synchrony

Electrotonic Coupling

Computer simulation | Gap junction blocker





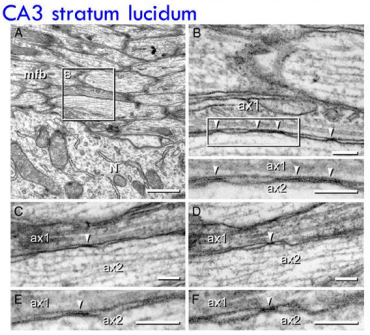
Computer simulation predicts gap junctions are located in axon-axon junction to effectively generate HFOs

(Traub et al, 1999, Neuroscience), (Draguhn et al, 1998, Nature)

Electrotonic Coupling

Mossy fiber axons in rat dorsal hippocampus

CA3 stratum lucidum



- Existence of Gap Junctions in axo-axonic junction has been postulated based on electrophysiological, modeling and dye-coupling study
- First evidence for existence of axo-axonic gap junction in dentate granule cells
- Important for the generation of HFO

(Hamzei-Sichani et al, 2007, PNAS)

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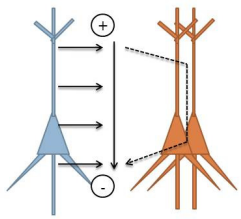
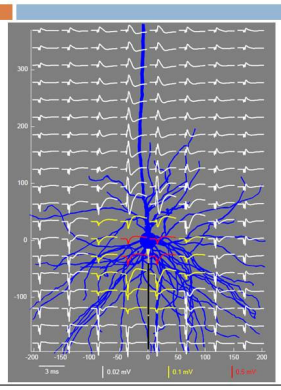
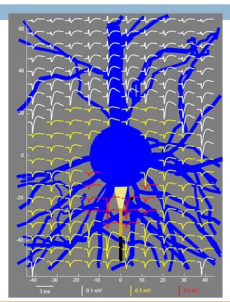
Ephaptic Interaction (Field Effect)



1) One neuron (blue) generates action potential
2) Depolarizing currents underlying the action potential flow in the extracellular space can generate electric fields
3) This electric field can depolarize adjacent neurons (orange)
4) If the field effect is sufficiently strong, it can trigger action potential firing in the neighboring neurons.

Ephaptic Interaction (Field Effect)





Field Potentials near Axon Hillock are strong enough to evoke action potentials in neighboring neurons
→ Closely located cells can be influenced

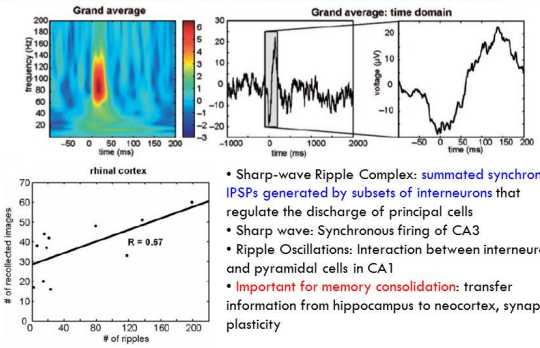
(Holt and Koch, 1999, J Comp. Neurosci)

Physiological vs. Pathological HFOs

- Physiological High Frequency Oscillations
  1) Sharp-wave associated Ripples in MTL
  2) Somatosensory evoked High Frequency Oscillations
- Pathological High Frequency Oscillations
  - Characteristics of pHFOs
  - Epileptic Process and Emergence of pHFOs
  - pHFOs as a variant of normal HFOs?
  - Relationship with pHFOs and Interictal Spikes
- HFO in mesial TLE and neocortical epilepsy
- Future Questions and Directions for HFO research

Physiologic HFO
Sharp-wave Ripple Complex

HFO recordings in depth electrodes during cognitive tasking in human

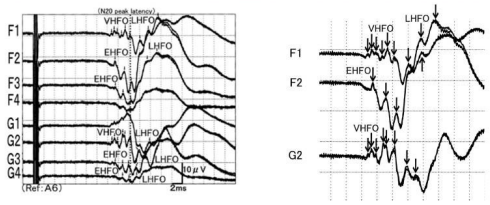


- Sharp-wave Ripple Complex: summated synchronous IPSPs generated by subsets of interneurons that regulate the discharge of principal cells
- Sharp wave: Synchronous firing of CA3
- Ripple Oscillations: Interaction between interneuron and pyramidal cells in CA1
- Important for memory consolidation: transfer information from hippocampus to neocortex, synaptic plasticity

(Axmacher et al, 2008, Brain)

Somatosensory Evoked HFOs

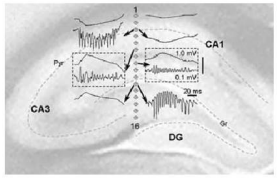
Somatosensory evoked potentials recorded in grid electrodes in epilepsy patients



- Physiological HFOs in rat barrel cortex during vibrissae or thalamic stimulation
- Similar oscillations found in Human during sensory peripheral nerve stimulation
- ➔Rapid temporal integration of tactile sensory information
- Mechanism unclear: may involve synchronous discharges from interneurons and pyramidal cells that fire at preferred latencies corresponding to individual cycles of the field oscillation
- Only occurs when evoked, no spontaneous form reported

(Sakura et al, 2009, J Clin Neurophysiol)

Pathologic HFOs (pHFOs):
Burst of Population Spikes



- Pathological HFOs, especially Fast Ripples, represent field potentials of population spikes from clusters of abnormally synchronous bursting neurons
- Synchronous bursting neurons postulated to play an important role in epilepsy

Abnormally Bursting Neurons + Fast Synchronization Mechanisms = Fast Ripple!

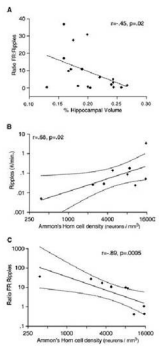
(Bragin et al, 2007, Epilepsia), (Su et al, 2002, J Neurosci)

Epileptic Process and Emergence of pHFOs

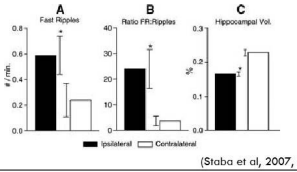
Factors that can contribute to the generation of pHFOs

- Neuronal Cell Loss (e.g. Hippocampal Sclerosis)
  - pHFOs in non-lesional TLE?
- Bursting Neurons
- Axonal Sprouting
- Gap Junctions

Neuronal Cell Loss and pHFOs

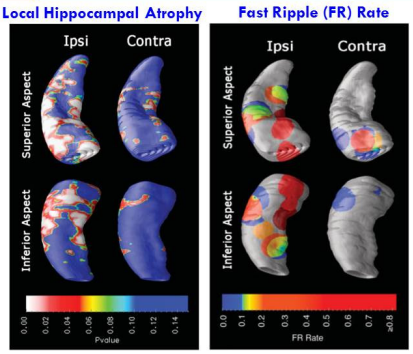


- Significant Inverse Relationship between FR/R ratio and Hippocampus Volume (FR:150~500 Hz, R:80~150 Hz)
- Hippocampal Sclerosis: extensive cell loss
- FR mostly concentrated in epileptic hippocampus that shows significant sclerosis
- Significant correlation between Neuronal Cell Loss and Emergence of pHFOs



(Staba et al, 2007, Epilepsia)

Local Hippocampal Atrophy and pHFOs



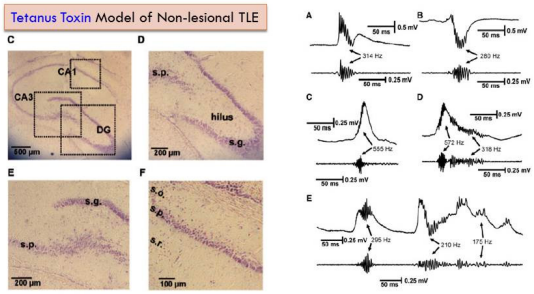
- Rate of FR (150-500 Hz) discharge 3 times higher in area of significant local HA than non-atrophic areas
- Positive correlation between FR occurrence and severity of damage in local HA region
- Neuronal cell loss and subsequent synaptic reorganization contributes to generation of FR

(Ogren et al, 2009, Ann Neurol)

Cell Loss not Pre-requisite for pHFOs

Almost all animal studies used Kainic Acid or Pilocarpine, which induces status epilepticus and significant neuronal cell loss → Is neuronal cell loss required to generate FRs?

Tetanus Toxin Model of Non-lesional TLE



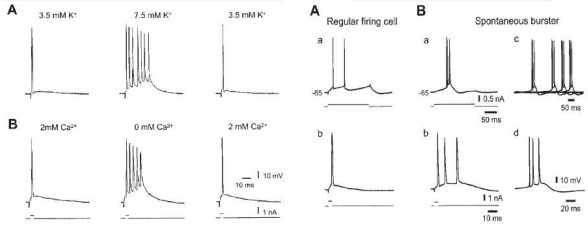
(Jiruska et al, 2010, Brain)

Bursting Neurons and pHFOs

Brief depolarzing current pulse

Acute Models of Epilepsy (High K, Low Ca)

Pilocarpine Model of Epilepsy

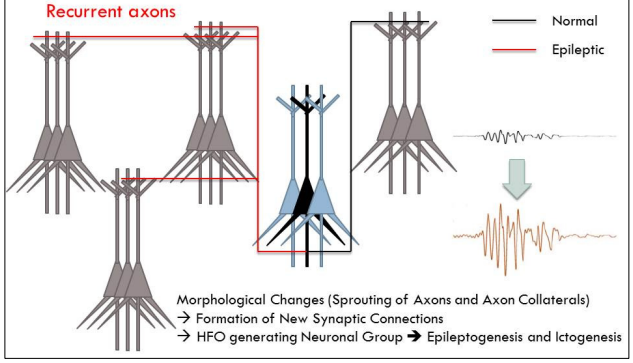


- "Epileptic Neuron": Transformation from regular spiking neuron to spontaneously bursting neuron after epileptic insult (dysfunction of Ca channel implicated)
- Bursting neurons play important role in initiating abnormal population bursts (fast ripples!)

(Yaari and Beck, Brain Pathology, 2002)

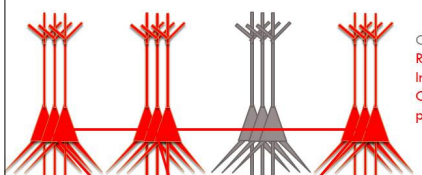
Increased Excitatory Coupling in Epilepsy

Recurrent axons



Morphological Changes (Sprouting of Axons and Axon Collaterals)
→ Formation of New Synaptic Connections
→ HFO generating Neuronal Group → Epileptogenesis and Ictogenesis

Hypothesis: Pathologically Interconnected Neuronal (PIN) Clusters



Gray: Normal Neuronal Group
Red: Pathologically Interconnected Neuronal Clusters, Capable of generating pathological HFOs

Characteristics of PIN clusters

- Spontaneously bursting neurons
- Excessive Excitatory Coupling
- Increased Axo-axonic Gap Junctions
- Neuronal Cell Loss
- Increased Random Synaptic Activity
- maybe more

(Bragin et al, 2000, Epilepsia)

Clinical Use of HFO in patients with epilepsy

HFO as Biomarker of Epileptic Brain

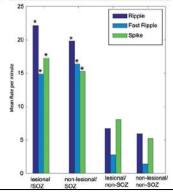
- **Interictal HFO better indicator of SOZ than spikes (Jacobs et al., 2008)**

Table 3. Rates of the different types of events, comparing seizure onset channels (SOZ) with channels outside the seizure onset zone (NSOZ)

Event type	Rate SOZ	Rate NSOZ	Rate threshold	Sensitivity	Specificity
Spikes	20.4 ± 15.1	5.2 ± 9.1	24.4	33.4%	95%
Spikes with ripples	9.6 ± 7.5	1.8 ± 4.7	13.3	30.2%	95%
Spikes with fast ripples	7.3 ± 7.7	0.5 ± 1.9	3.9	54.5%	95%
Ripples	25.8 ± 21.5	5.8 ± 10.5	27.6	37.5%	95%
Fast ripples	24.3 ± 32.4	1.9 ± 4.7	11.4	52.5%	95%

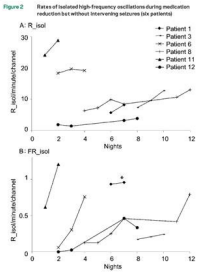
The threshold rate indicates above which rate channels could be placed in the SOZ with 95% specificity. The best sensitivity was found for the rate of spikes with fast ripples and fast ripples alone.

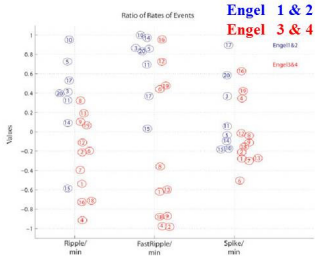
- **HFO marks epileptogenicity rather than specific lesion type (Jacobs et al., 2009)**



HFO as Biomarker of Epileptic Brain

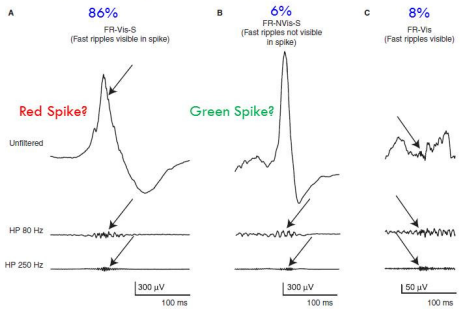
- **HFO behaves similarly to seizures →** medication reduction leads to increase in HFO rate, but not for spikes (Zelman et al., 2009)
- Resection of HFO-generating areas leads to better surgical outcome than resection of irritative zone and SOZ itself (Jacobs et al., 2010)





Interictal Spikes and pHFOs

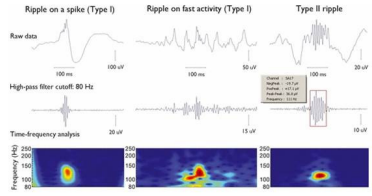
Depth electrode recording in 7 focal epilepsy patients



(Urrestarazu et al, 2007, Brain)

Type 1 vs Type 2 ripples: pHFO?

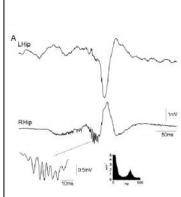
- Type I : HFO superimposed on epileptiform discharges such as paroxysmal fast, spike, or sharp wave
- Type II : HFO independent of epileptiform discharges
- Type I ripples : detected almost exclusively in the seizure onset zone or primary propagation area



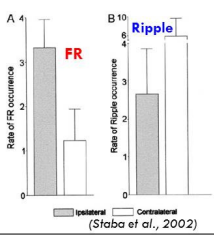
(Wang S et al, 2013, Epilepsia)

HFO in Mesial Temporal Lobe Epilepsy

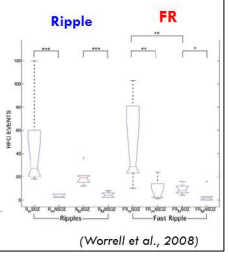
- HFO first identified in rodent models of MTLE and human patients with MTLE using microwires (UCLA group)
- Most papers, using intracerebral depth electrodes, report that interictal HFOs mark epileptic MTL, especially fast ripple → controversy about ripple exists in MTLE



(Staba et al., 2004)

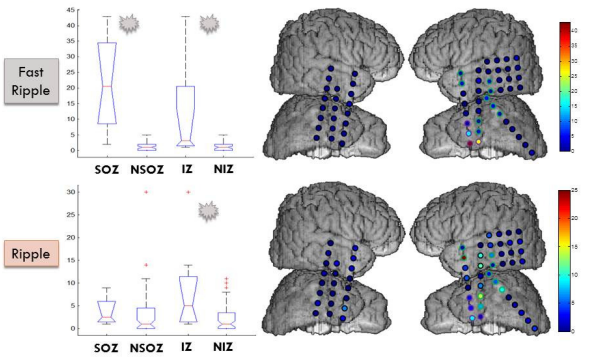


(Staba et al., 2002)



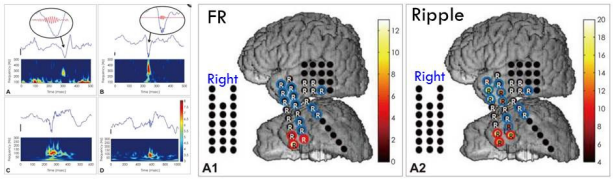
(Worrell et al., 2008)

Our Observation: mesial TLE cases (bilateral strip electrodes)



HFO in Temporal Lobe Epilepsy

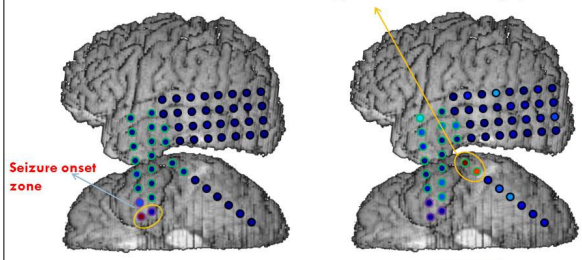
- Subdural electrodes were able to detect ripple and fast ripple.
- Both Ripple and Fast Ripple: lateralized to epileptic side
- Fast ripple: more focal to mesial-basal temporal cortex



(Cho, Hong et al, 2012, J Clin Neurol)

Our Observation: MTLE cases

Pathology showed cortical dysplasia

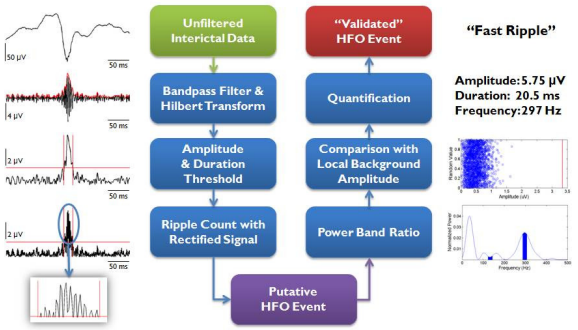


Fast Ripple | Ripple

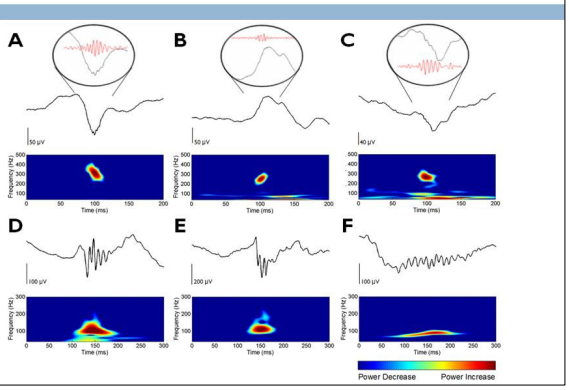
Our study in Neocortical Epilepsy

- 15 patients with neocortical epilepsy
- subdural grids, strips and depth electrodes
- Signal acquisition: Neuroscan SynAmps 2 system, 2kHz sampling rate with 0.05 ~ 500 Hz bandpass filter setting, at least >6 hours of interictal data
- 6 of 10-minute interictal segments
- Seizure onset zone (SOZ):
- Irritative zone (IZ): SOZ + electrodes with interictal spikes
- Statistical analyses: comparison of event rate in SOZ versus NSOZ and IZ versus NIZ in each patient → Wilcoxon test with Bonferroni correction to account for multiple comparisons

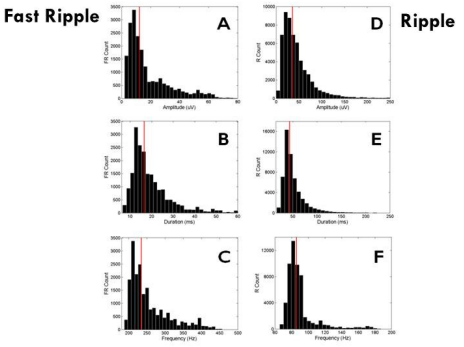
Automated HFO Detection



Examples of Neocortical HFOs



Quantification of Detected HFOs



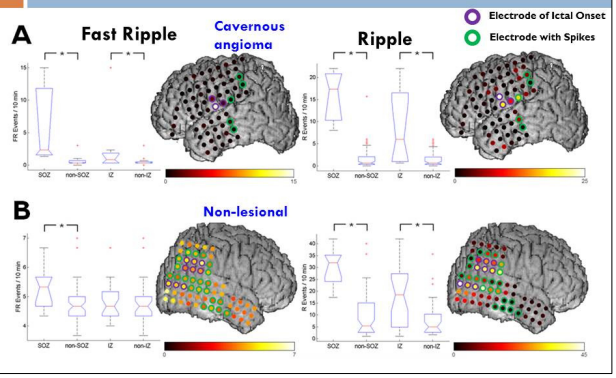
Individual Statistics

$p < 0.05$
$p < 0.1$

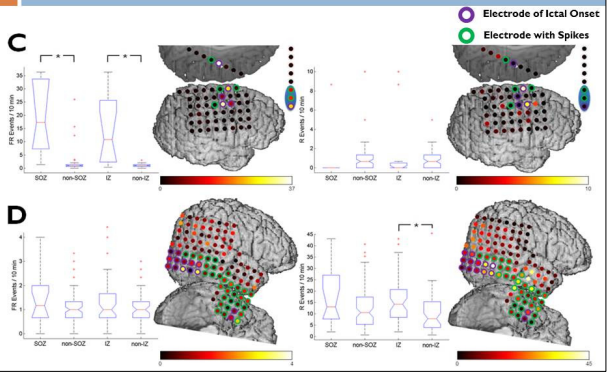
	Channel Count		Fast Ripple				Ripple			
Patient #	SOZ vs non-SOZ	IZ vs non-IZ	SOZ	non-SOZ	IZ	non-IZ	SOZ	non-SOZ	IZ	non-IZ
1	3 vs 61	8 vs 56	2.33 (7.62)	0.33 (0.44)	0.83 (5.03)	0.33 (0.45)	17.33 (7.13)	0.67 (2.51)	6.00 (8.49)	0.67 (1.77)
2	6 vs 84	17 vs 73	0.67 (0.54)	0.67 (1.03)	0.67 (0.96)	0.33 (1.01)	1.67 (2.13)	1.33 (1.21)	1.67 (1.79)	1.33 (1.13)
3	3 vs 57	25 vs 35	2.33 (3.29)	0 (7.26)	0.67 (8.93)	0 (0.42)	6.17 (6.84)	1.83 (5.18)	4.00 (5.74)	0.33 (1.57)
4	9 vs 53	28 vs 34	5.33 (0.71)	4.67 (0.64)	4.67 (0.63)	4.67 (0.73)	32.00 (7.99)	5.33 (9.17)	18.50 (13.07)	5.00 (7.80)
5	9 vs 93	13 vs 89	0 (1.62)	0.33 (1.16)	0.33 (2.43)	0.33 (0.77)	3.67 (5.69)	0.67 (4.12)	2.67 (5.37)	0.67 (4.19)
6	8 vs 76	54 vs 30	1.00 (1.78)	1.00 (9.22)	1.33 (10.50)	0.67 (0.49)	11.33 (11.35)	8.00 (9.79)	9.50 (11.11)	7.33 (6.37)
7	2 vs 62	13 vs 51	2.67 (3.30)	0.33 (0.62)	0.33 (1.32)	0.33 (0.67)	8.00 (2.83)	1.00 (1.15)	1.33 (3.22)	1.00 (0.80)
8	10 vs 96	30 vs 76	3.50 (6.89)	2.00 (1.25)	2.00 (4.47)	2.00 (1.28)	33.50 (16.87)	9.00 (9.33)	19.50 (13.19)	7.00 (8.38)
9	14 vs 90	46 vs 58	1.17 (1.24)	1.00 (0.68)	1.00 (0.87)	1.00 (0.68)	13.00 (12.41)	10.50 (8.80)	14.17 (10.47)	7.83 (6.94)
10	5 vs 59	13 vs 51	31.00 (22.16)	1.00 (16.29)	2.17 (27.50)	0.67 (6.74)	14.00 (31.29)	17.00 (9.82)	19.17 (18.99)	16.50 (8.71)
11	3 vs 61	9 vs 55	3.33 (1.12)	1.67 (0.94)	1.67 (1.89)	1.33 (2.03)	12.50 (10.21)	4.00 (7.21)	12.00 (11.21)	3.33 (7.11)
12	9 vs 54	20 vs 43	1.67 (3.41)	0.33 (2.15)	1.67 (3.17)	0 (1.77)	10.67 (13.98)	14.67 (16.01)	12.67 (14.10)	14.67 (16.41)
13	6 vs 88	12 vs 82	17.33 (14.81	1.00 (3.35)	10.83 (12.99	1.00 (0.61)	0 (3.54)	0.67 (1.29)	0 (3.60)	0.67 (0.87)
14	3 vs 61	8 vs 56	0.33 (0.91)	0.17 (1.12)	0.33 (0.93)	0.17 (0.97)	9.00 (2.12)	4.00 (4.56)	10.33 (3.12)	2.50 (3.43)
15	7 vs 121	22 vs 106	4.33 (3.07)	2.00 (1.60)	3.67 (2.78)	2.00 (2.78)	52.67 (13.70)	2.00 (9.8)	28.17 (19.43)	1.67 (5.20)

- Number in each cell indicates median rate (/10 min) with standard deviation in parenthesis
- IZ (Irritative Zone) = SOZ + Spike-generating Region
- Either fast ripple or ripple are increased at least in IZ compared to non-epileptogenic region in all patients (Note that some did not reach statistical significance, only showing trend)

Specific Examples - 1

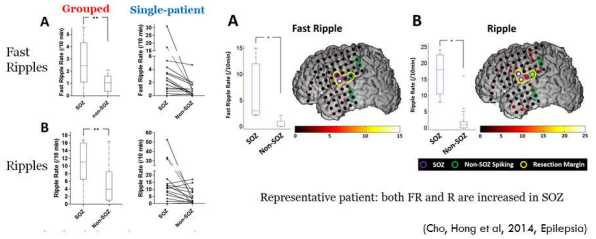


Specific Examples - 2



HFO in Neocortical Epilepsy

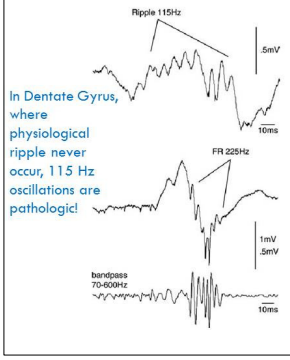
- Both ripple (R) and fast ripple (FR) : well detected in neocortical epilepsy with subdural electrodes
- Both R and FR : significantly more detected in SOZ than non-SOZ, but FR was more localized to SOZ than R.
- Higher resection rate of HFO : better surgical outcome



Representative patient: both FR and R are increased in SOZ

(Cho, Hong et al, 2014, Epilepsia)

Problems to be Solved



In Dentate Gyrus, where physiological ripple never occur, 115 Hz oscillations are pathologic!

- Distinction between physiological versus pathological HFOs:

→need more than frequency range, maybe spatial profile, morphology, relationship with other interictal activity etc.

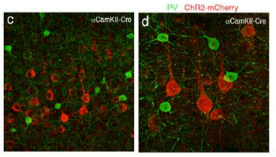
FR: abnormally synchronous bursting of population spikes

R: summation of IPSPs on pyramidal neurons

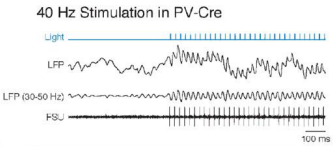
Problems to be solved

- Cellular mechanism
- Role of individual neuronal subtype

➔ Optogenetics may be a solution



Cell-type specific expression of light-sensitive ion channels (Channelrhodopsin-2) Green: PV interneuron, Red: Pyramidal Cell

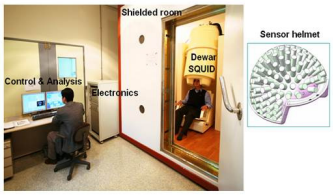


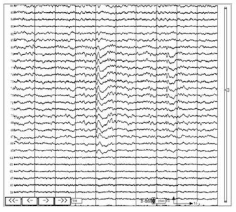
Driving PV-positive interneurons generates gamma oscillations → causal role of PV interneuron in fast oscillations

(Cardin et al, 2009, Nature)

Problems to be solved

- Non-invasive detection (MEG) of pHFOs





(KRISS in Korea)

New Treatment

- Pharmacology of HFOs
  - Can pHFOs be modified by existing AED or SSRI ?
    - Levetiracetam, lacosamide, citalopram ?
  - Can pHFOs be selectively modulated by new drugs or other interventions? (e.g. specific axo-axonic gap junction blocker?)
    - Carbenoxolone and quinine ?
  - Understand mechanism of pHFOs further, and develop new AEDs or other methods of intervention