High Frequency Brain Signal :

Methodology and Application

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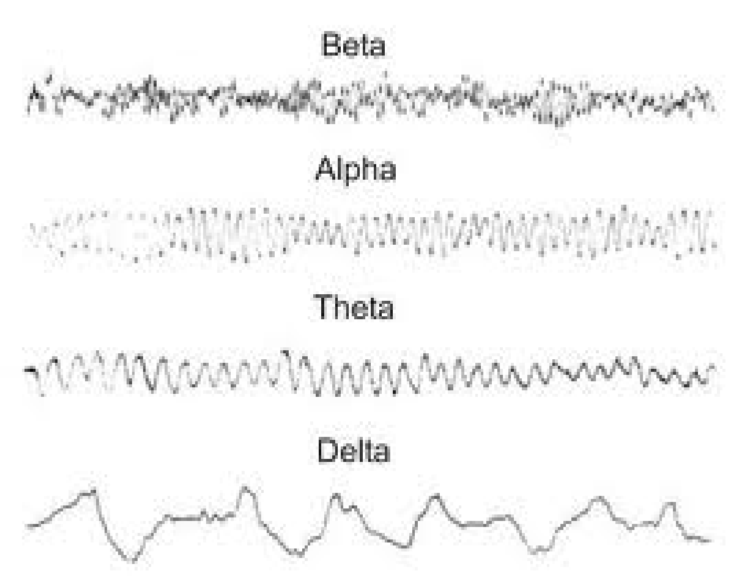
Content

- High Frequency Brain Signals (HFBS)
- Hardware development for detecting HFBS
- Software development for analyzing HFBS
- Clinical Applications of HFBS
  - Epilepsy
  - Migraine
  - Functional mapping and others
- Discussion

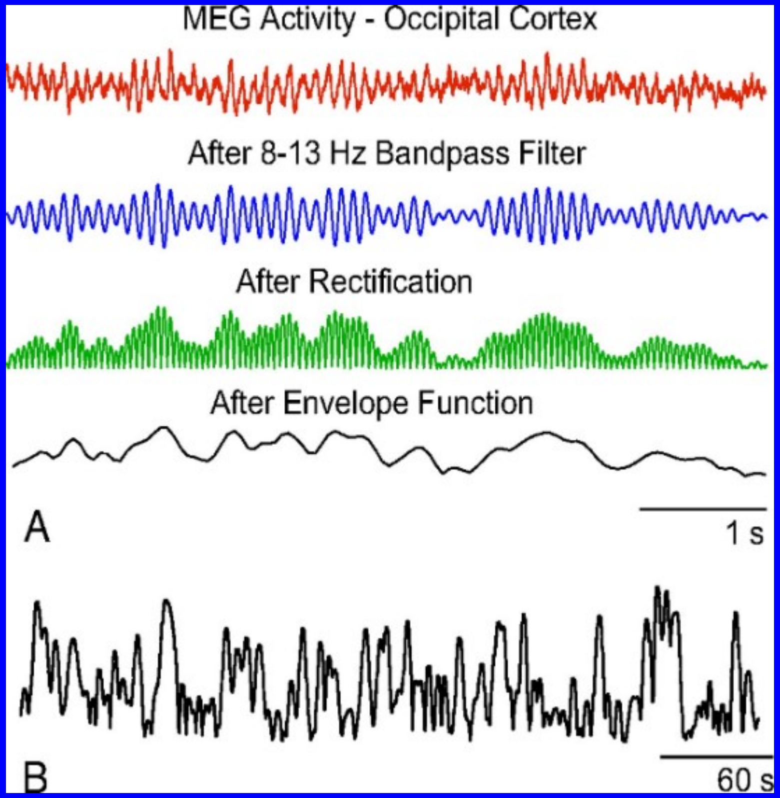
Background (1)

- The brain generate electric/magnetic signals in a set of frequency bands.
  - Delta wave – (0.1–4 Hz)
  - Theta wave – (4–7 Hz)
  - Alpha wave – (8–12 Hz, Mu: 8-13 Hz)
  - Beta wave – (13–30 Hz)
  - Gamma wave – (30–100 Hz, 30-120 Hz, 40 Hz)
  - High-frequency oscillations (HFOs): brain activity (signals) in a high-frequency range. (e.g. > 30 Hz, 70 Hz or 80 Hz)



Brain Signals in Frequency Domain

- Nomenclature for bandwidths and upper and lower bounds of each bandwidth of interest still evolving
  - Spike: 14-70 Hz
  - Gamma
    - Low 30-70 Hz
    - High 70-150 Hz
  - Ripples 80/100 – 200/250 Hz
  - Fast ripples > 200/250 Hz (250-600 Hz)
  - HFOs: 30-600 Hz
  - Very HFOs (VHFOs): 1000 – 2500 Hz (> 600 Hz)
- No standardized names or terms
- HFBS includes HFOs in the presentation

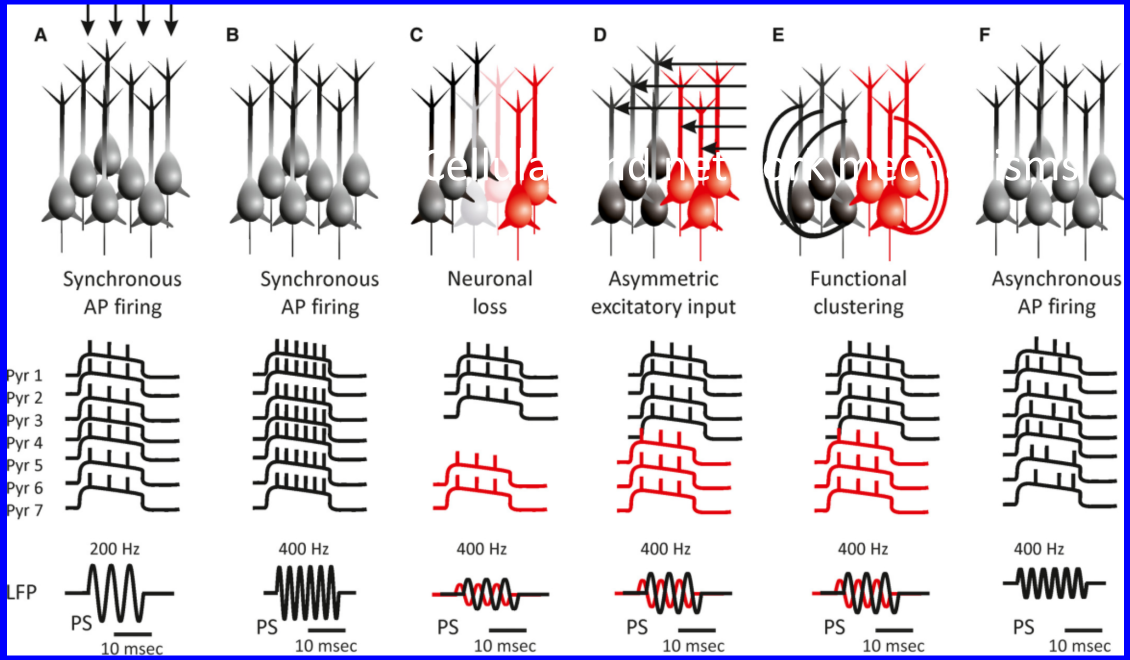


Classification of HFBS

- Physiological High Frequency Brain Signals
  - Elicited/Evoked Functional Activation (Gamma)
    - Low 30-70 Hz
    - High 70-150 Hz
  - Spontaneous/Intrinsic/Endogenous Brain Activity (HFOs)
    - Ripples
    - High 70-150 Hz
- Pathological High Frequency Brain Signals
  - Oscillatory HFOs
    - Ripples (80-250 Hz)
    - Fast ripples (250-600 Hz)
  - High frequency spikes (HFSs)
    - Spikelets (80-250 Hz)
    - Fast spikelets (250-600 Hz)

Cerebral Mechanisms (1)

- The exact mechanisms underlying the generation of HFOs remain unclear.
  - "Out of phase" activity : discharges of groups of neuronal populations.
  - "Axon-axon gap" junctions: generate coherent population oscillations higher than 100 Hz.



Cellular and network mechanisms of HFOs

Jiruska et al. Epilepsia 2017; 58:8; 1330

The burst discharge by pyramidal cells may be detectable with MEG and EEG when 10,000–50,000 cells are synchronously active.

Murakami, et al. J Physiol 575.3 (2006) pp 925–936

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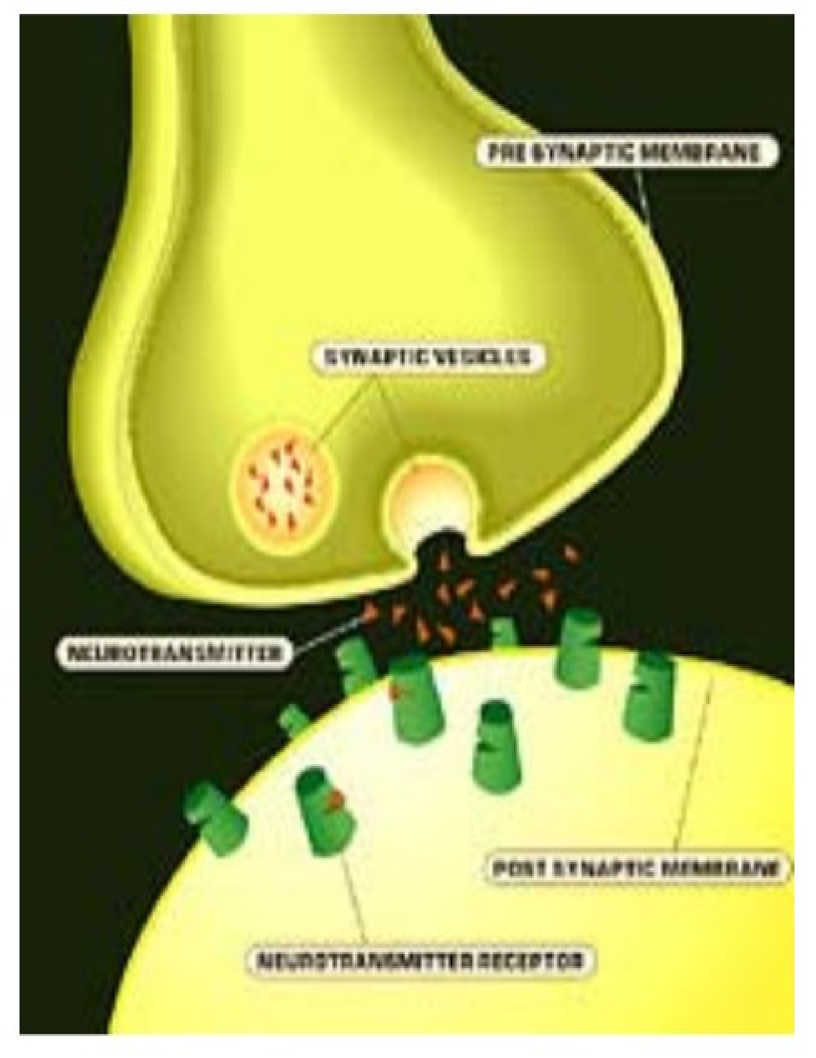
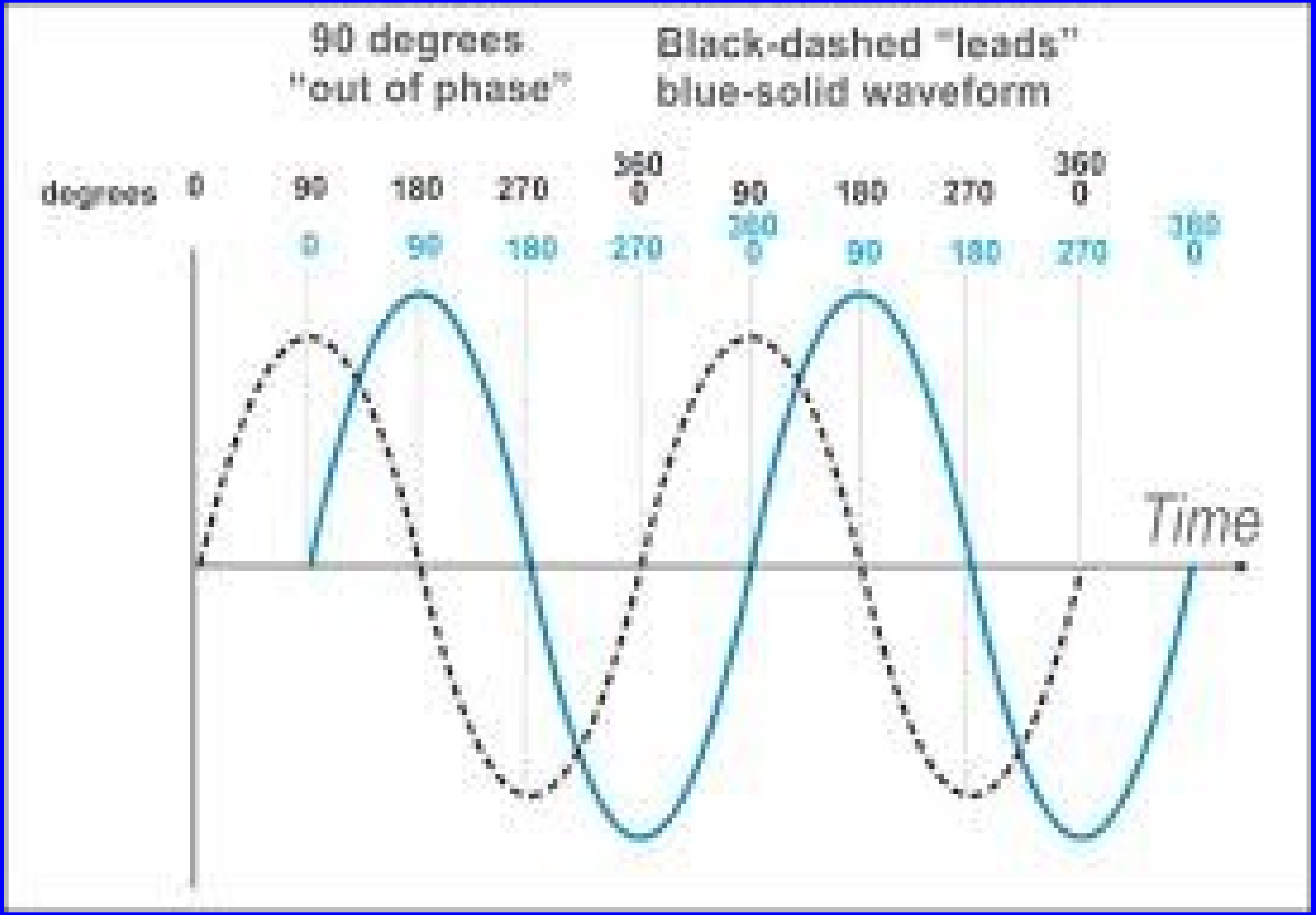
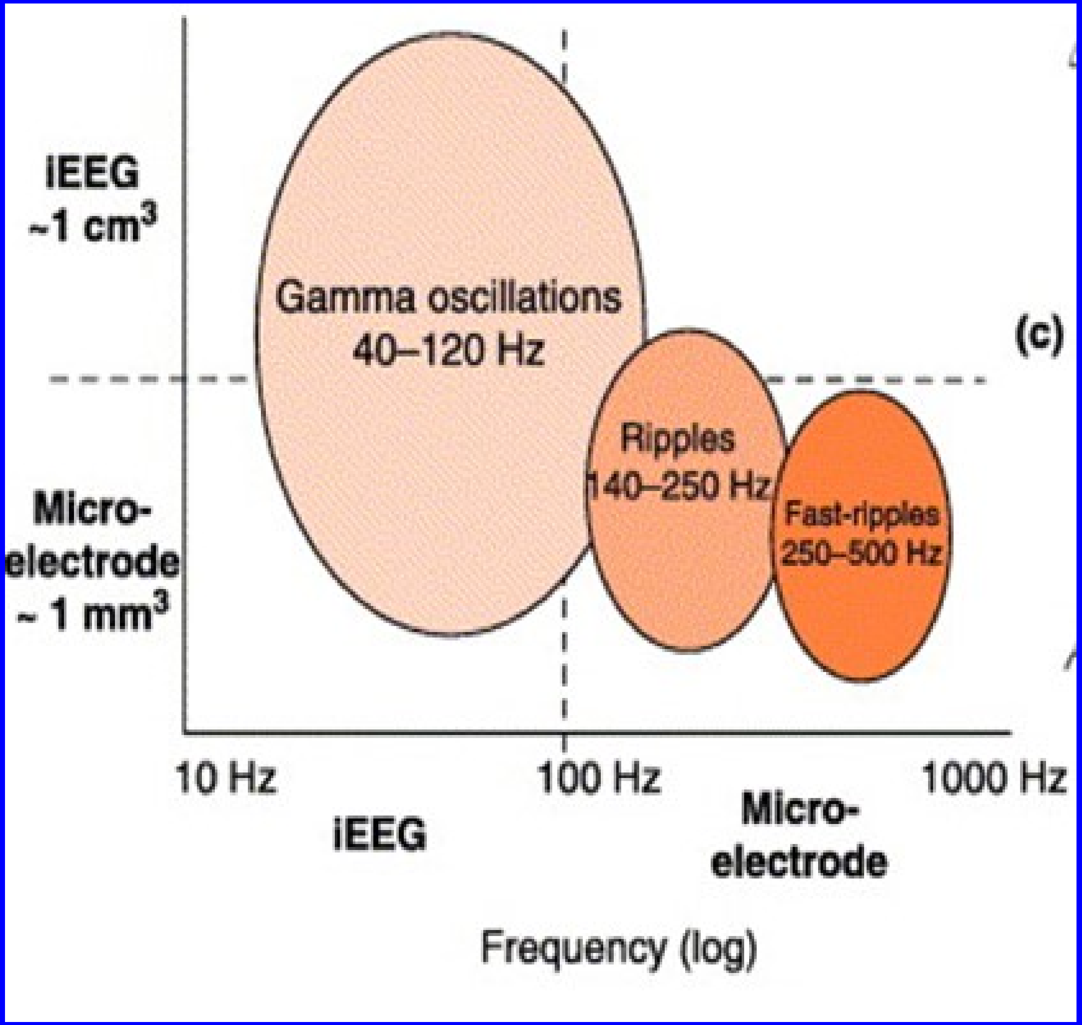
Cerebral Mechanism (2)





Cerebral Mechanisms of HFOs

- Different generator:
  - Low frequency: post-synaptic potentials
  - High frequency: gap junction and/or "out of phase"
- Brain HFOs ≠ Neural HFOs
- Frequency signatures of MEG/EEG signals
  - Spatiotemporal overlaps of ~50,000 neurons
- Frequency-spatial relation:
  - Low frequency : large area
  - High frequency: small area



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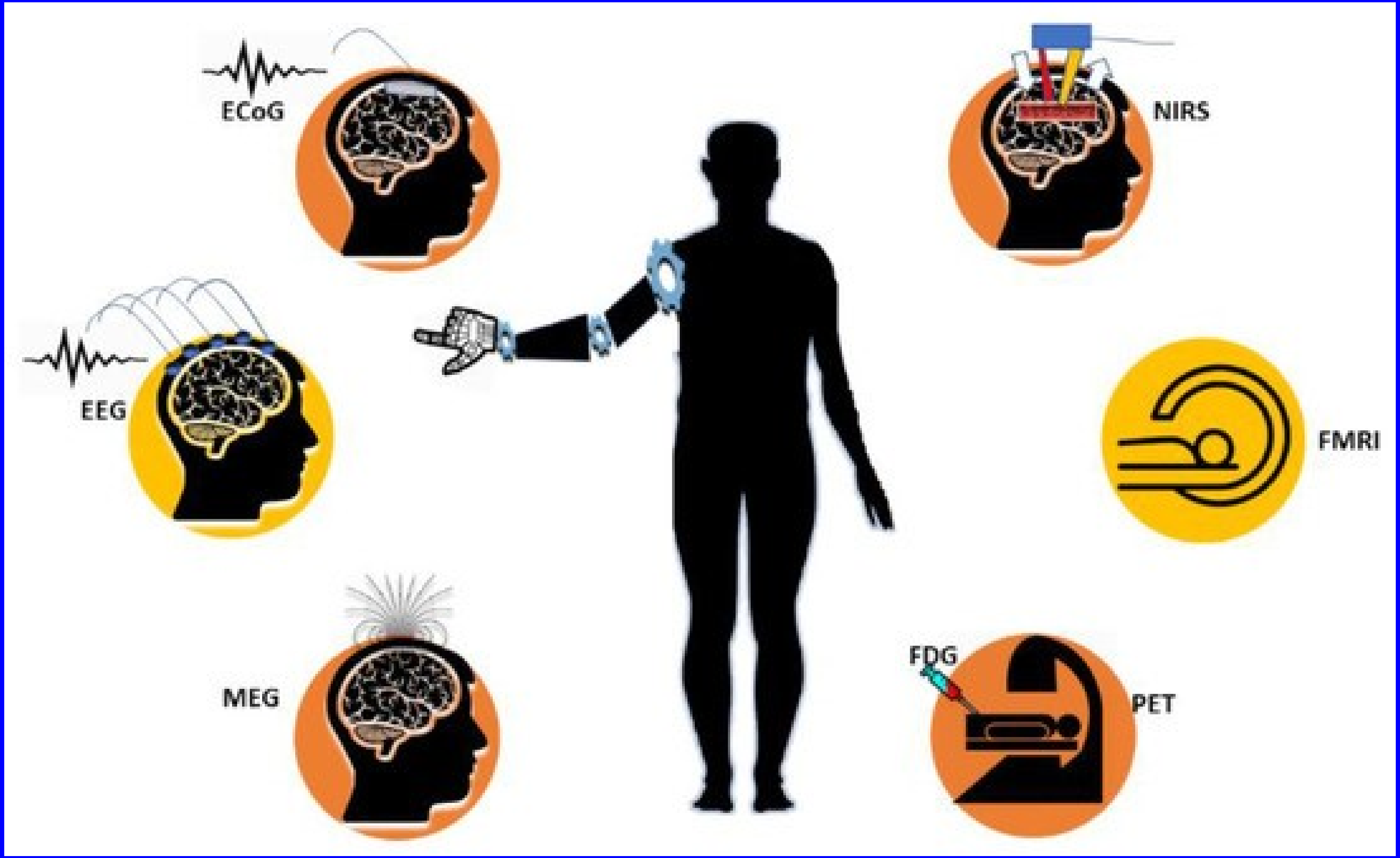
Neuroimaging Techniques for Detecting HFBS



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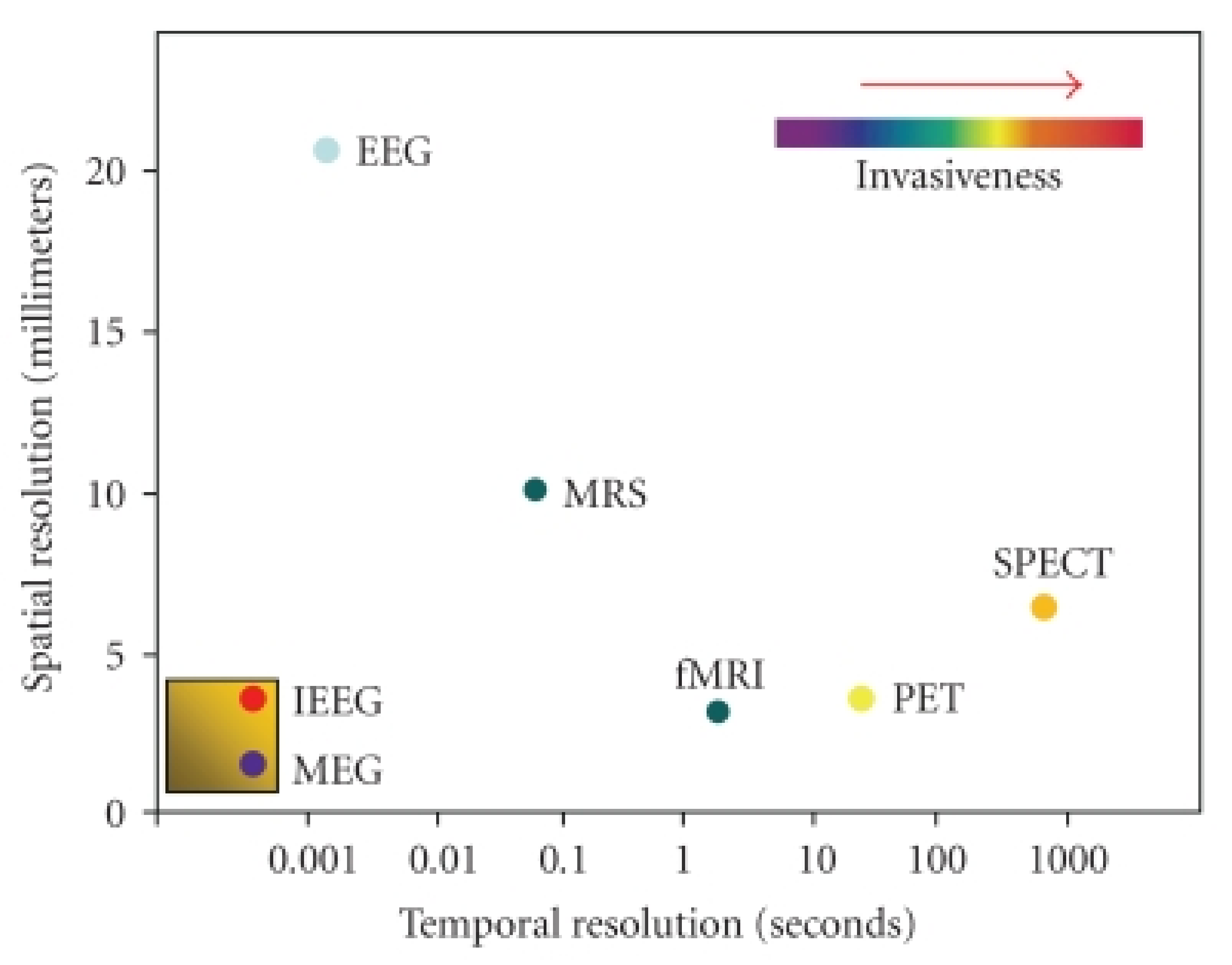
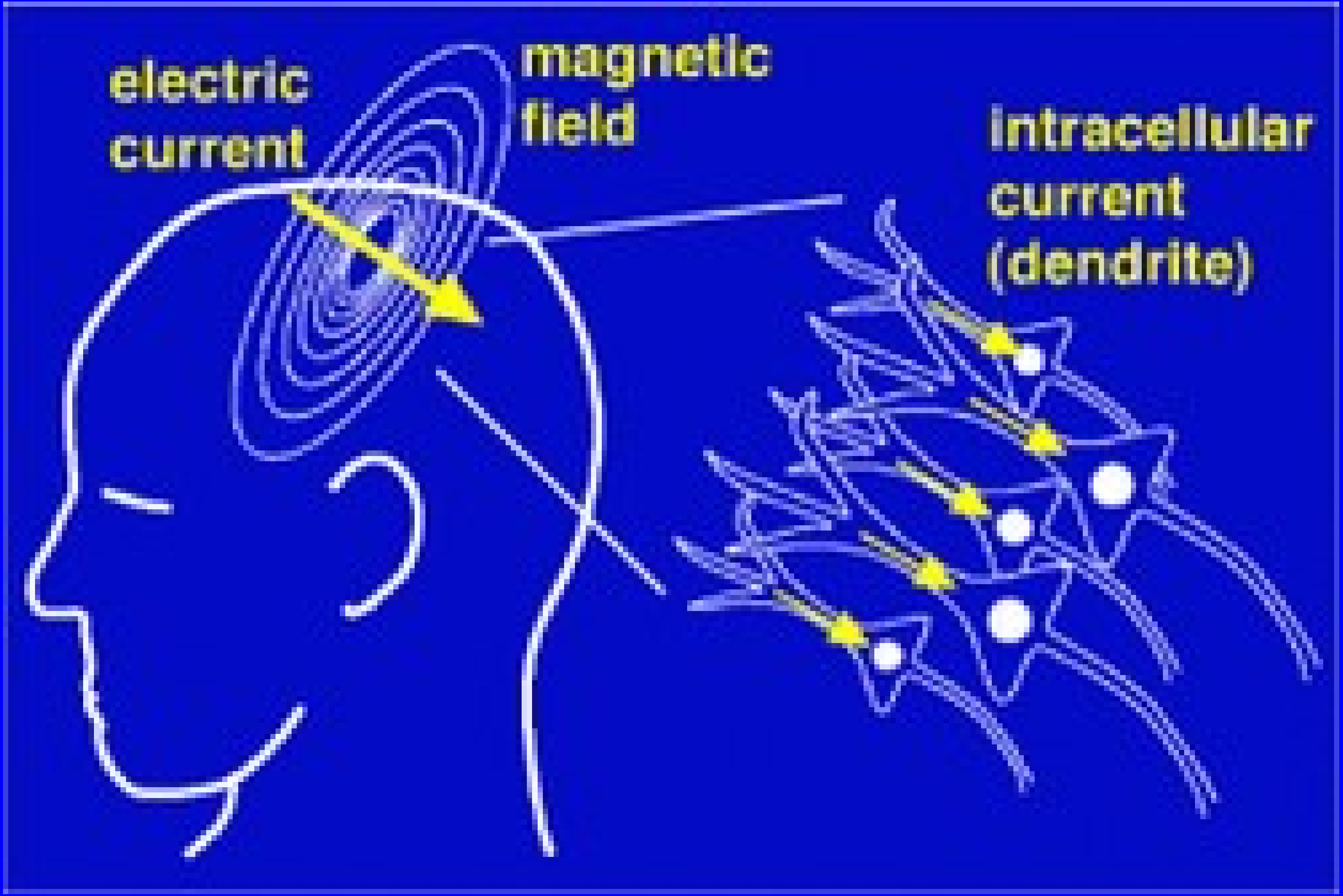
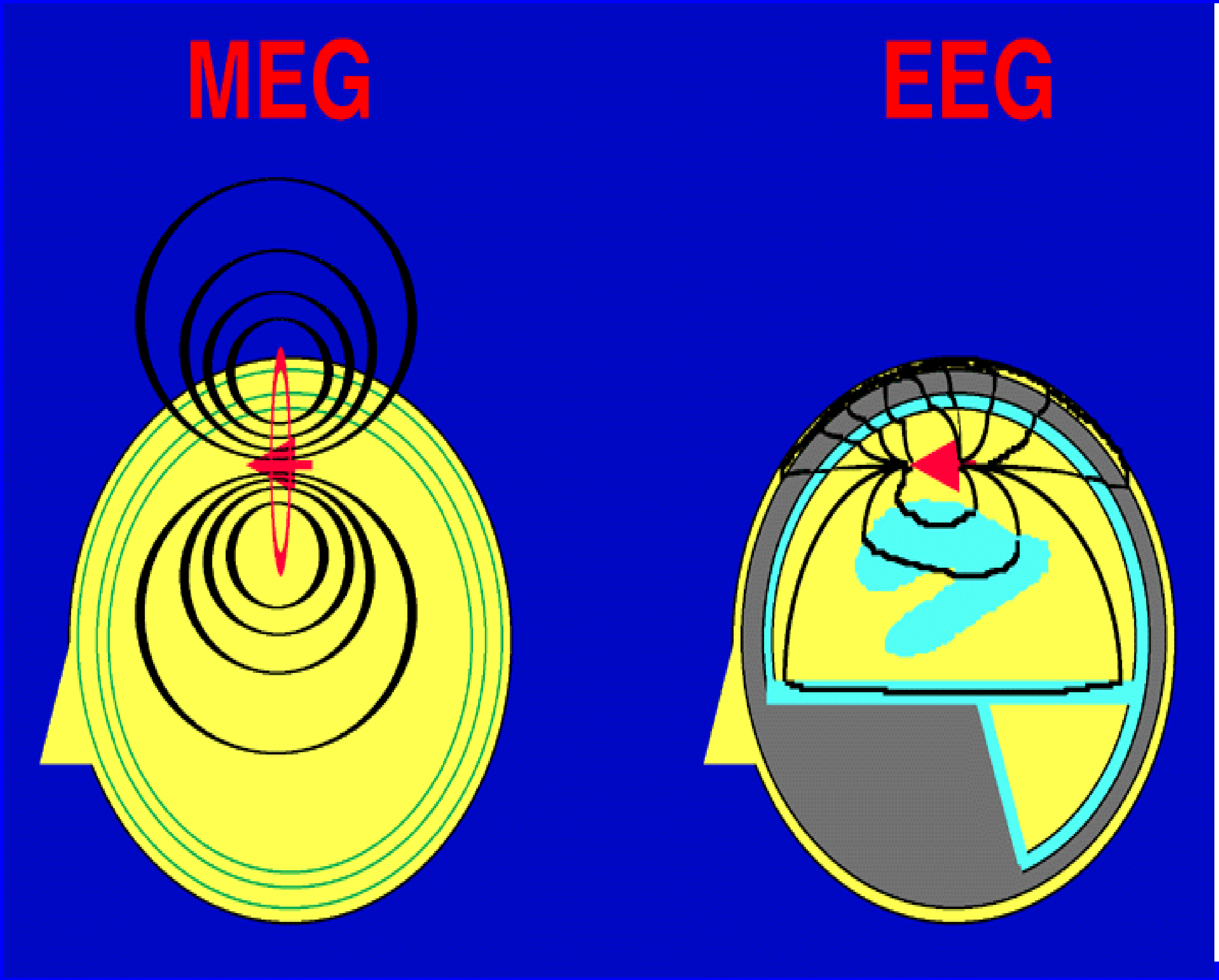
Neuroimaging Techniques for Recording HFBS

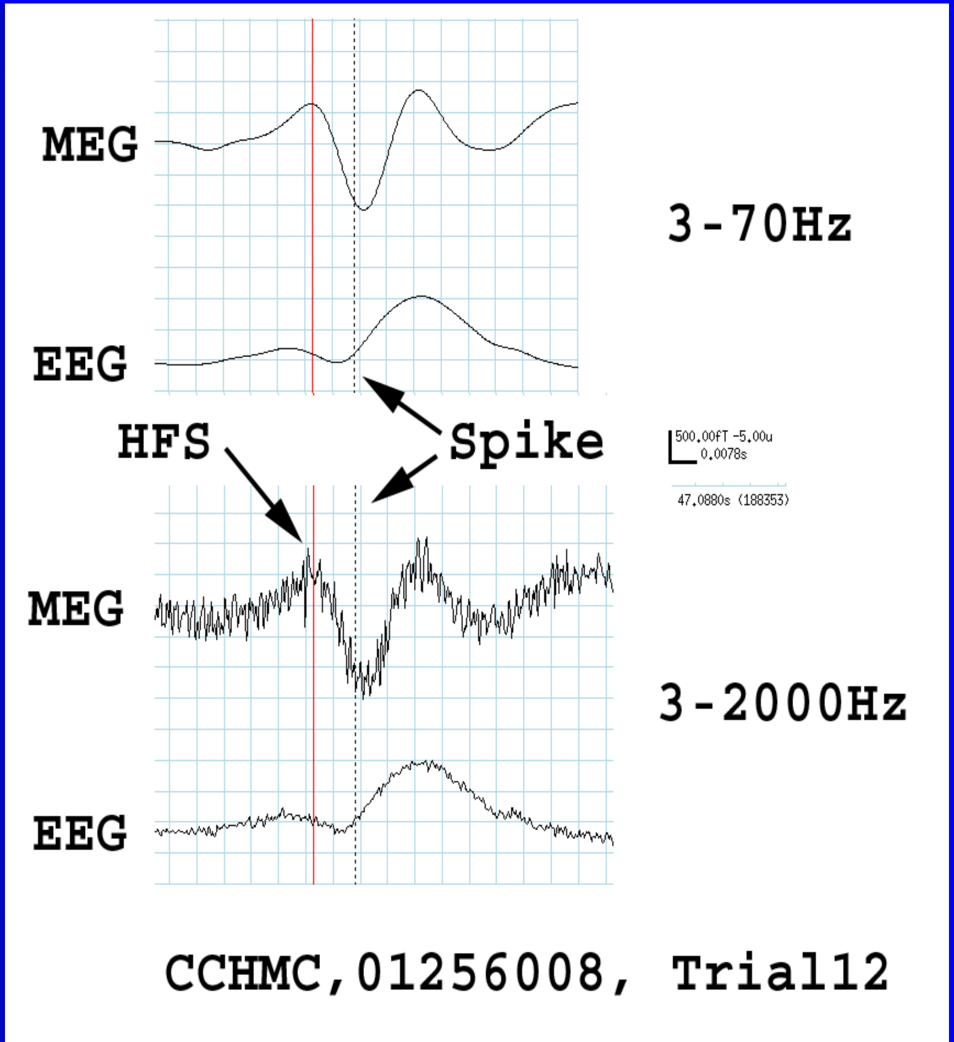


MEG <-> EEG


electric current
magnetic field
intracellular current (dendrite)

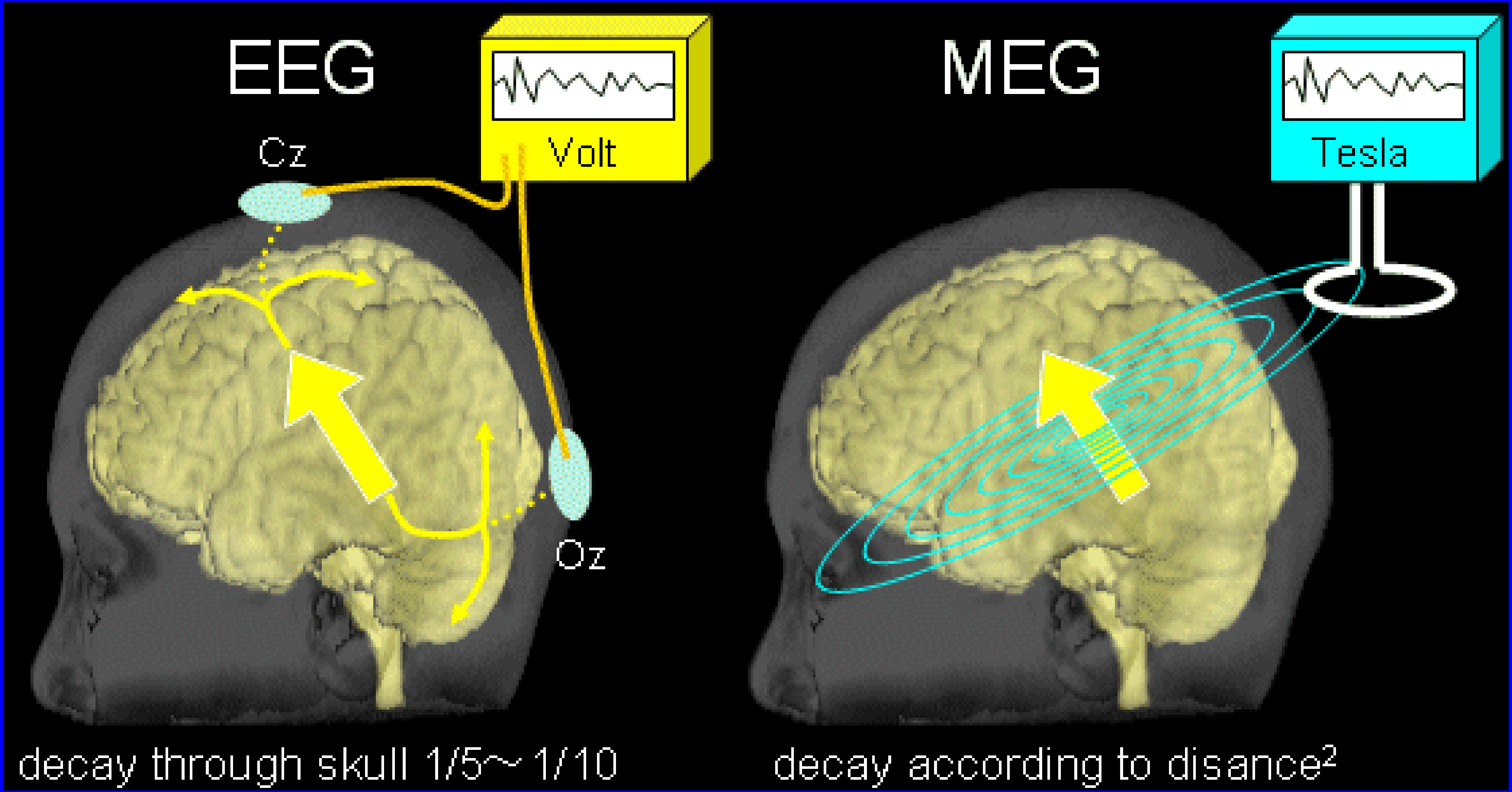
HFOs and MEG/EEG





- Skull and skin blocks much of the EEG high frequency signal. MEG passes through skull and skin unchanged.

MEG and EEG



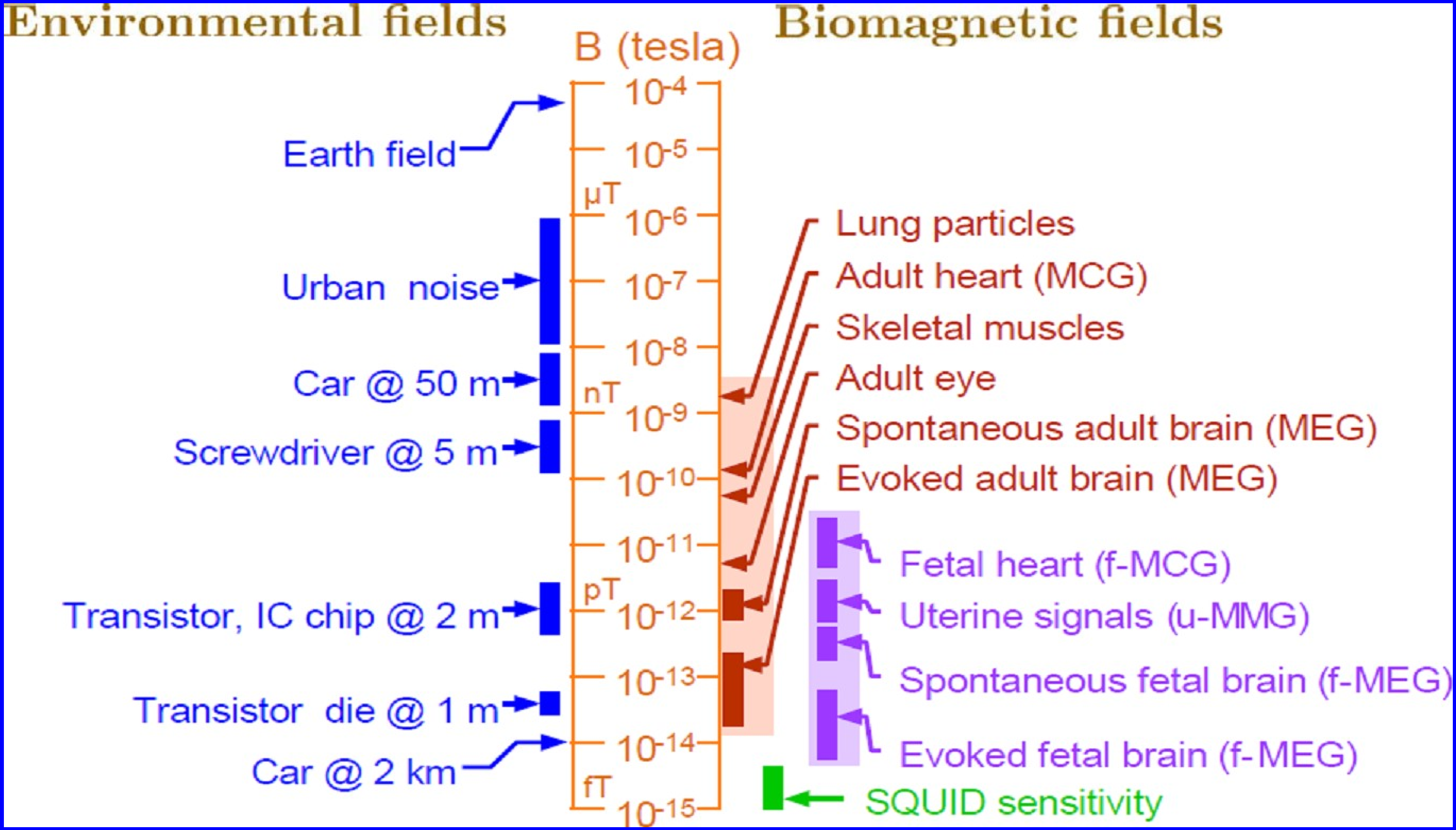
EEG
Volt
Cz
Oz
MEG
Tesla
decay through skull 1/5~ 1/10
decay according to disance²

Parameters	MEG (Magnetic flux)	EEG (Electric current)
Original	intracellular	extracellular
direction	Perpendicular to current	Parallel to current
distortion	Not distorted as they pass through the brain tissue	Significantly distorted by brain tissue
resistance	Biological tissues offer practically No resistance to magnetic signals	Biological tissues offer resistance to magnetic signals
Generators	Tangential pyramidal neurons	Radial pyramidal neurons
formation	At least 50,000 neurons firing	At least 10,000 neurons firing
Spatial characteristics	Very close spatial neighboring Neurons firing	Spatial neighboring Neurons firing
Frequency effect	No low pass filter effect	Low pass filter effect
Spatial resolution	High spatial resolution	Low spatial resolution
Sensitivity to spikes	70% spikes similar to EEG, 20-30 different	70% spikes similar to EEG, 20-30 different
References	Practically no.	Yes, a set of montages
Record sensor direction	Magnetometers (coils, has direction)	Electrodes, no direction
Magnetometers are placed across the head surface	The shape of a brain activity source can be determined (in theory)	The shape of a brain activity source cannot be determined (in theory)
Source and distribution of magnetic flux	The depth of sources is well proportional to the distance between the extrema	The depth of sources may not be well proportional to the distance
Distance and source strength	Greatly affects the strength	affect the strength
Orientation and source strength	Greatly affects the strength	affect the strength
Orientation and sensitivity	Tangential sources	Radial (and tangential) sources
Brain structural and sensitivity	Sensitive parallel to surface of skull (e.g. along the sides of sulci)	Sensitive perpendicular to surface of skull (e.g. tops of gyri or at bottoms of sulci)
Spatial resolution	3-4 mm (or 1-2 mm in surface) at good condition	7-8 mm or worse
Price	Very expensive	Cheap

MEG and EEG

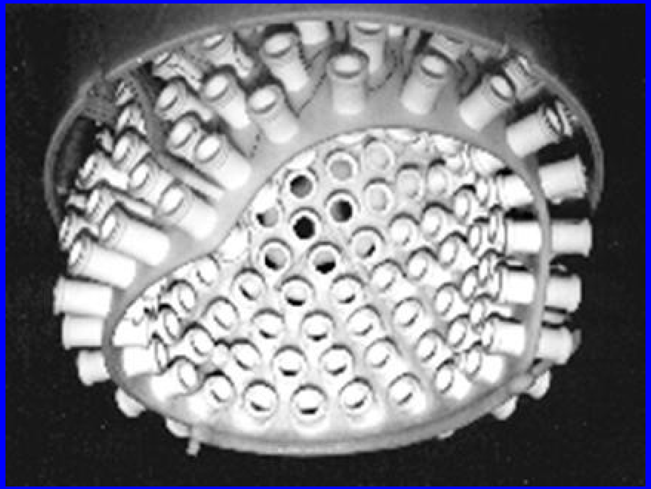
Frequency Effect	**No low pass filter effect (Skull, skin and other tissues)**	**Low pass filter effect (Skull, skin and other tissues)**
Spatial resolution	High spatial resolution Decay with distance significantly	Low spatial resolution Decay with distance slightly
Sensitivity to spikes	Tangential spikes/HFOs (MEG vs. EEG: 70% same)	Radial spikes/HFOs (MEG vs. EEG: 20-30 different)

Biomagnetic Signals are Very Weak

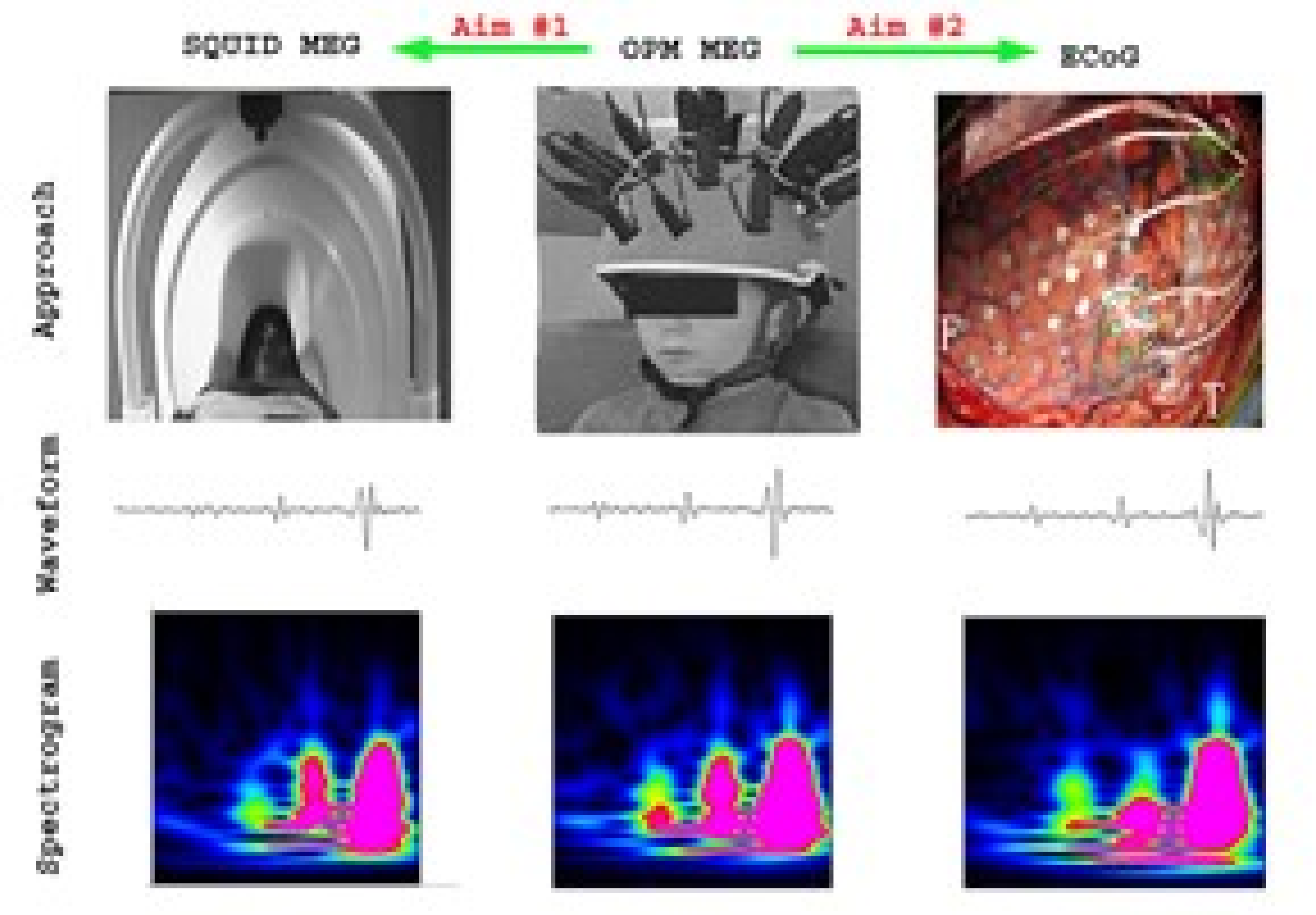


MEG System (Hardware)

- 275 MEG channels and 128 EEG electrodes
- Sampling rate is 12 ,000 Hz per channel.



New MEG Technology Detect HFOs



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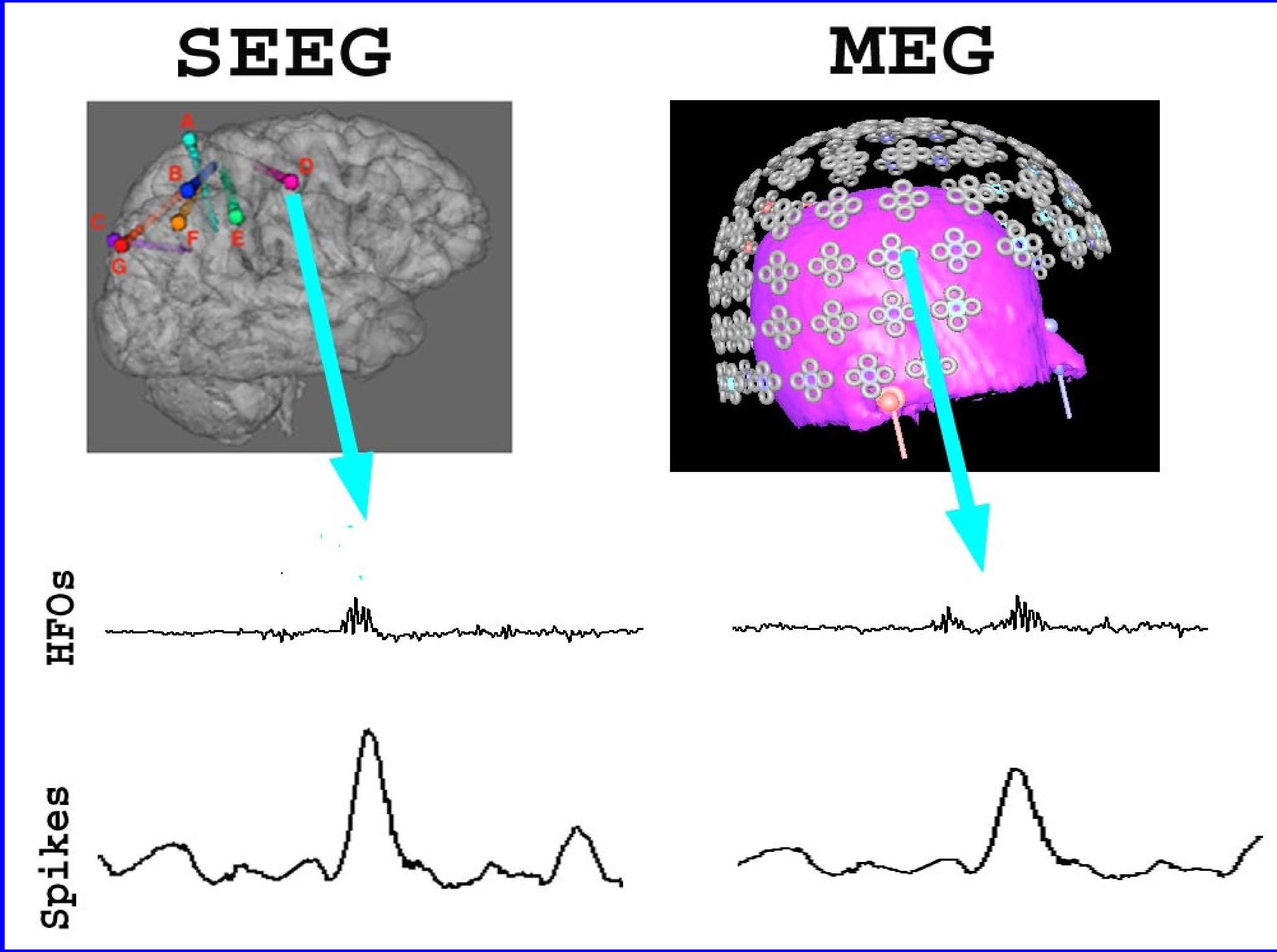
Methods (1)

- A Set of manual or automatic methods have been developed for detecting HFOs
- Visual identification is the widely used method
  - one band-pass filter
  - Multiple band-pass filters
- Sensor levels:
  - Waveforms
  - Accumulated spectrogram (spontaneous)
  - Real-time Spectrogram (elicited)

HFOs at Sensor and Source Levels



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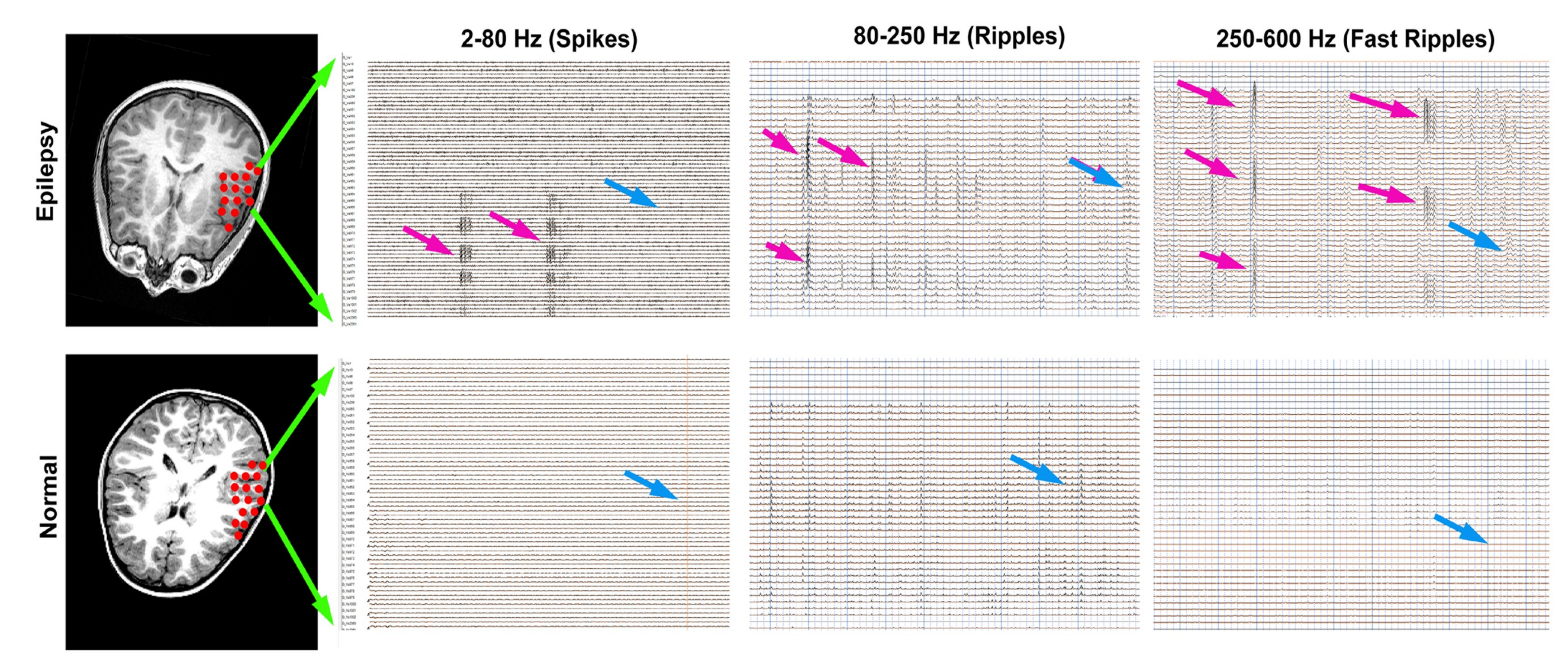
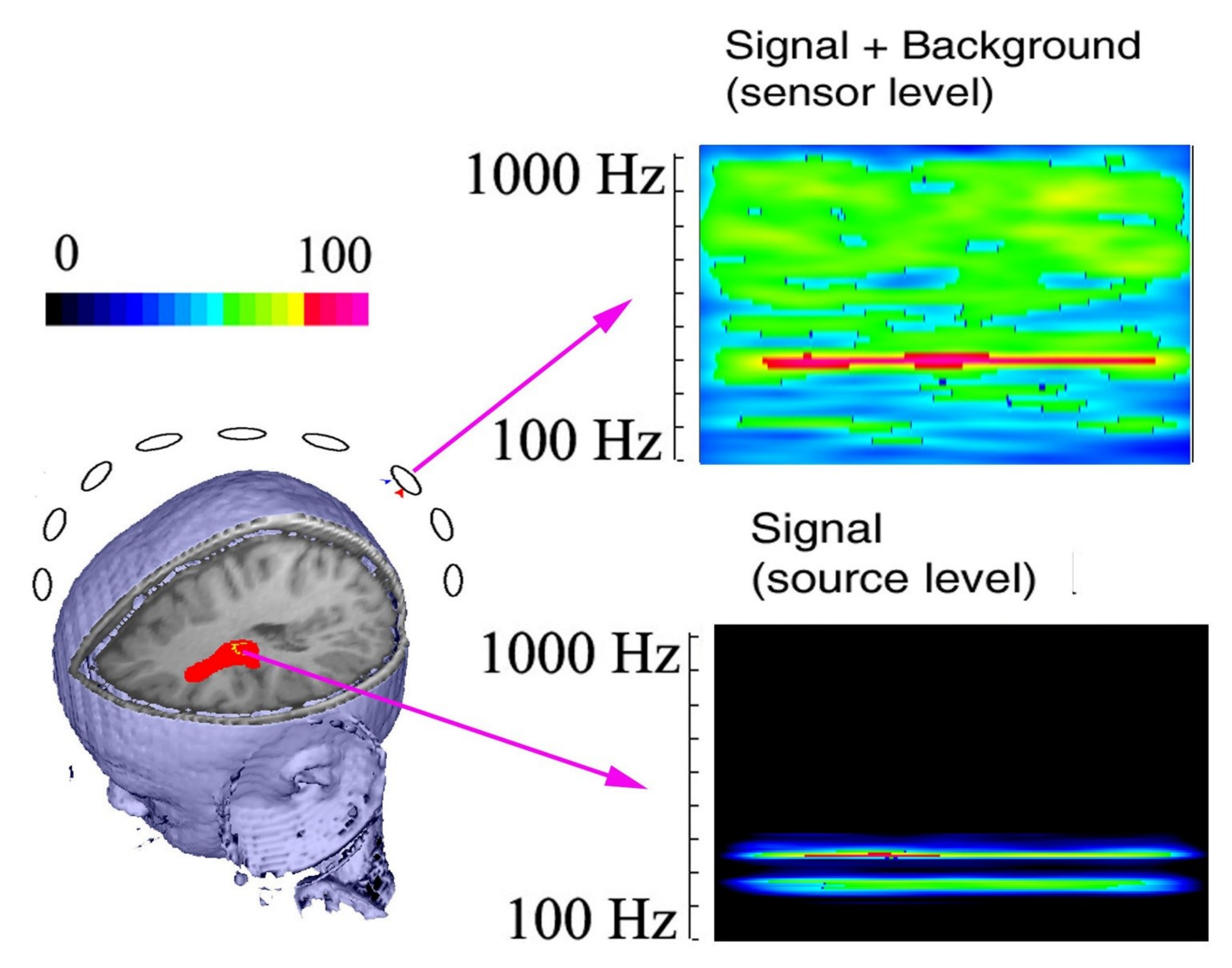
Methods (2)

- Detect HFOs at source levels
  - Precise spatial information
  - High signal-to-noise ratio
- Virtual Sensor
  - MEG virtual sensor waveform -> iEEG
  - MEG virtual sensor waveform->SEEG
- Source Imaging
  - MEG HFO source imaging ->iEEG sources
  - MEG HFO source imaging->SEEG sources

HFOs at Source Levels (Virtual Sensor) (waveforms)



HFOs at Source Levels (Virtual Sensor) (spectrograms)



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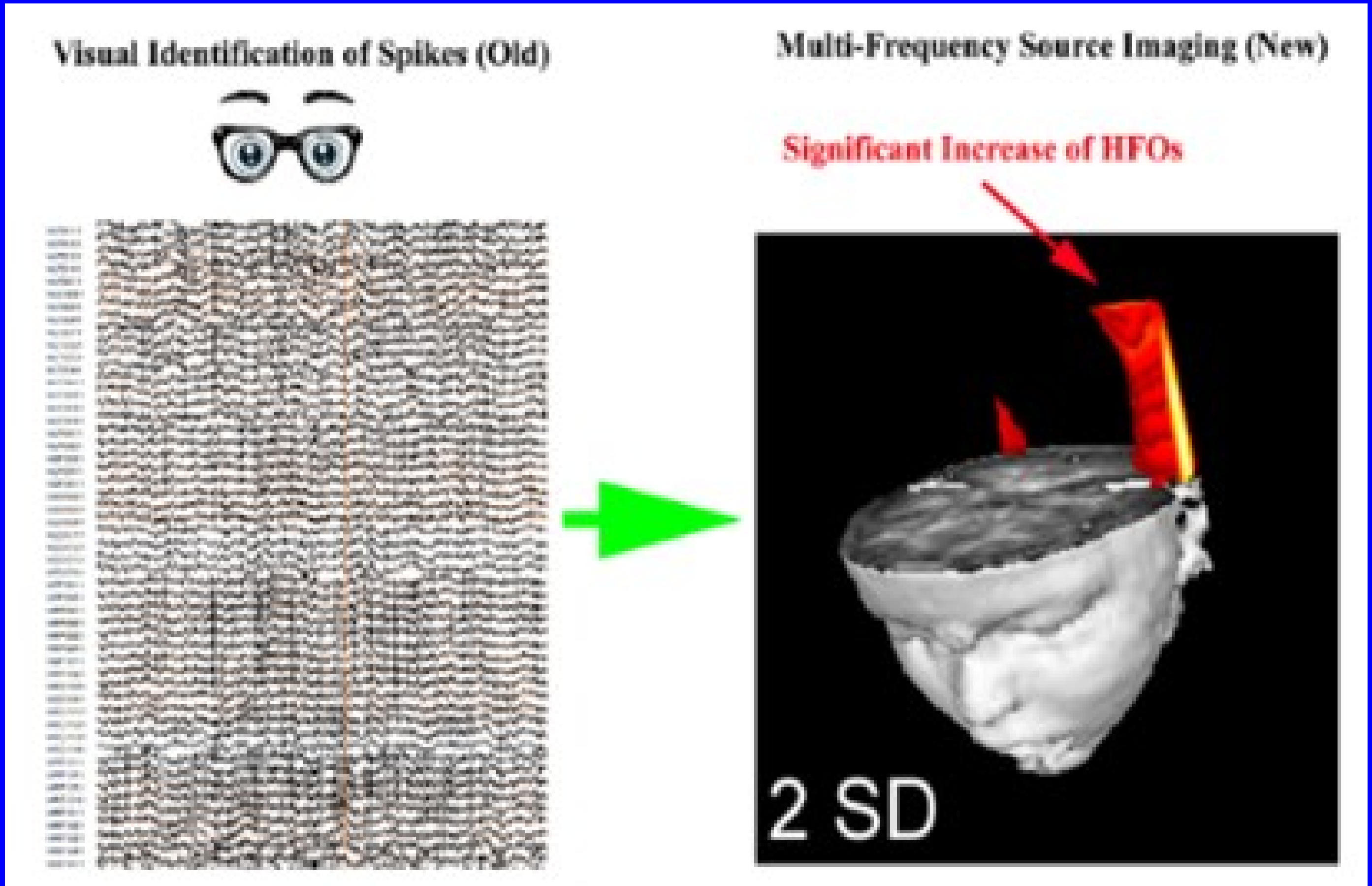
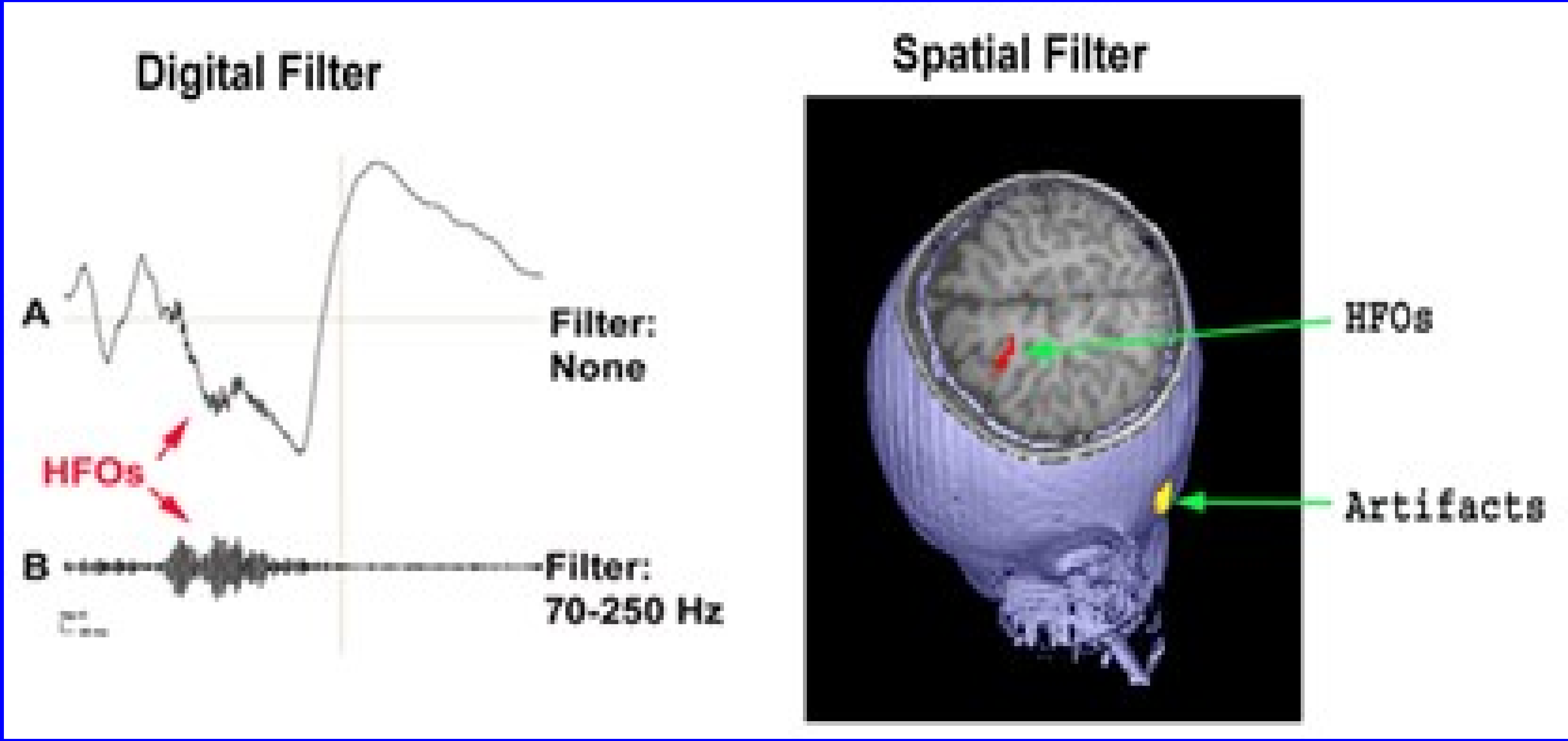
Detect and Localize HFOs with AI

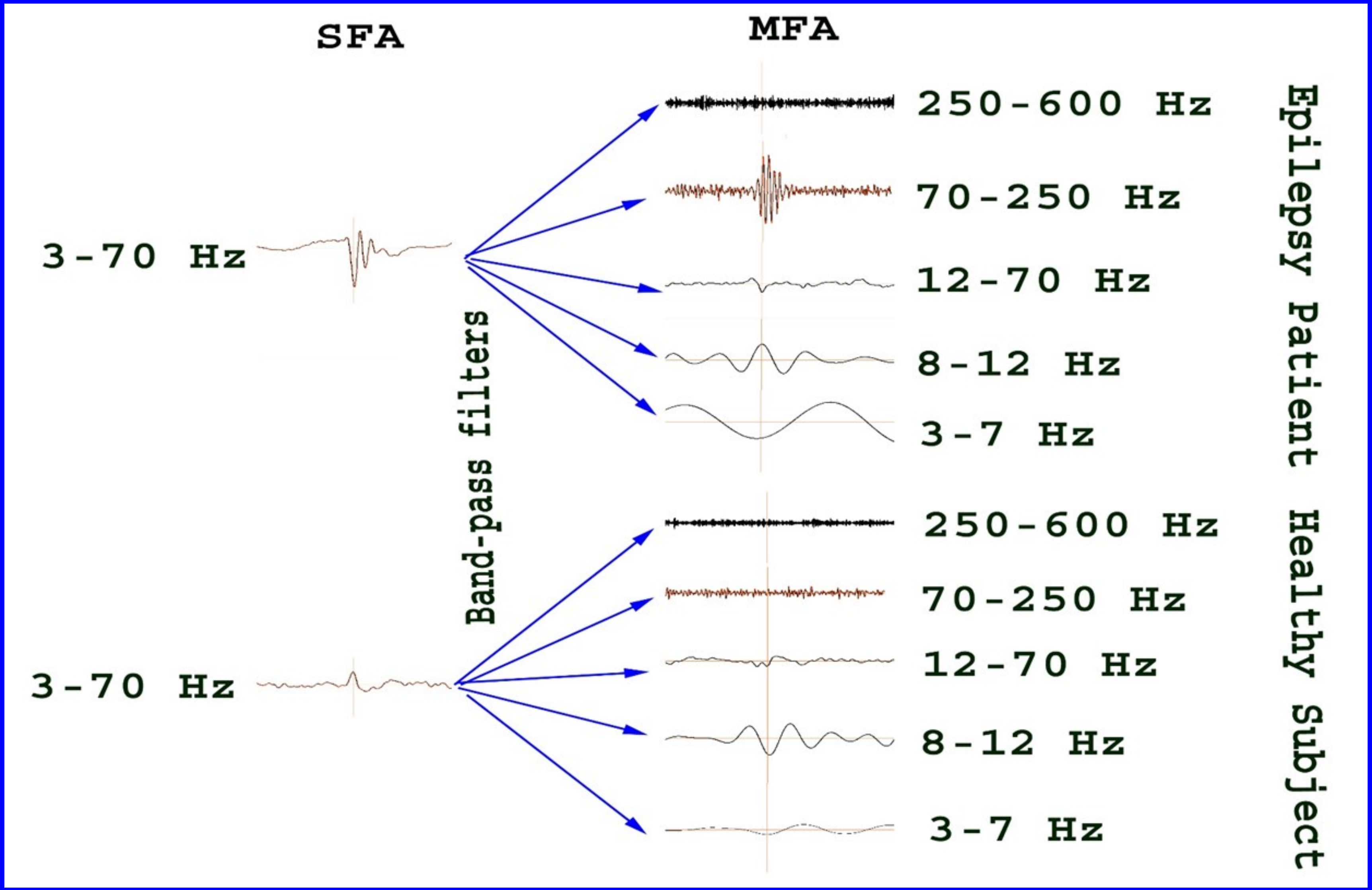


AI mark HFOs -> Volumetric Source Imaging

Separate HFOs from Muscle Artifacts



HFOs at Sensor Levels (Multi-Filters)



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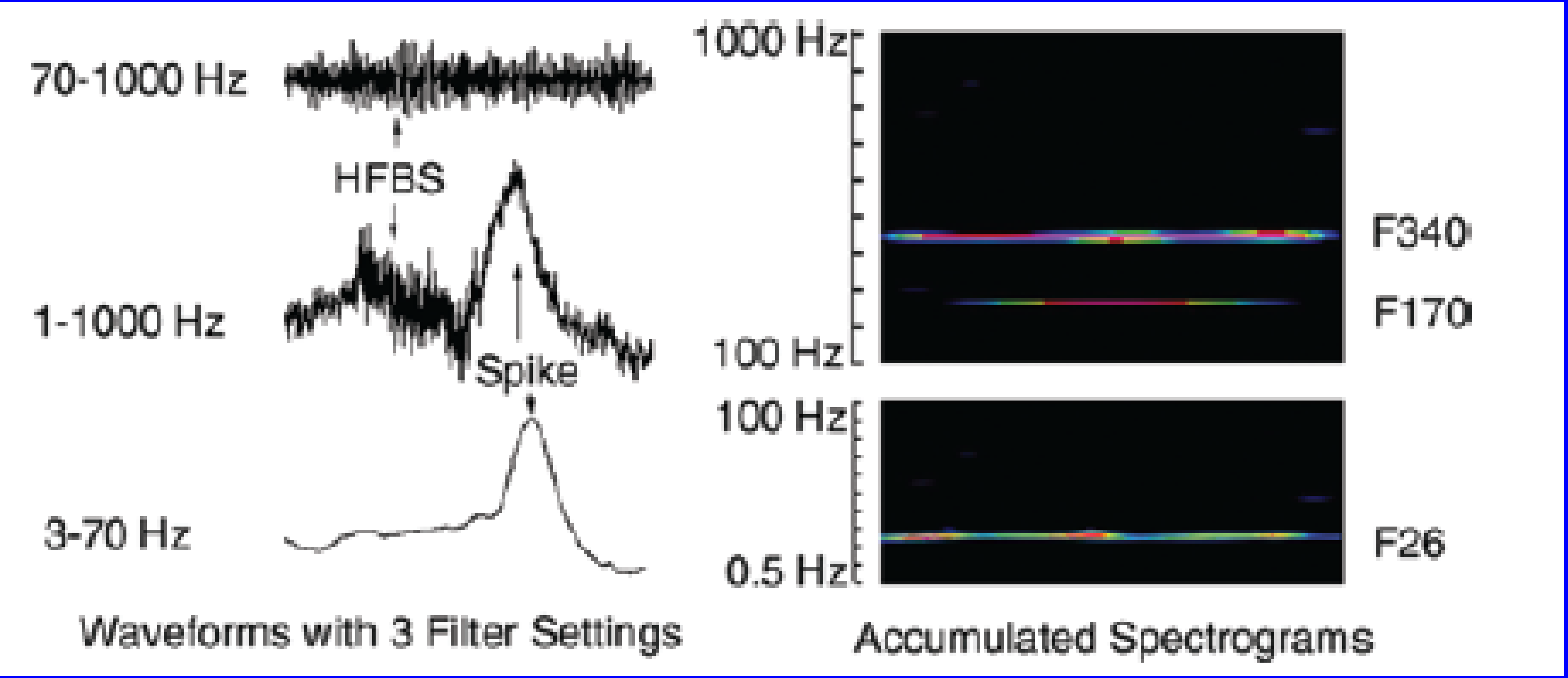
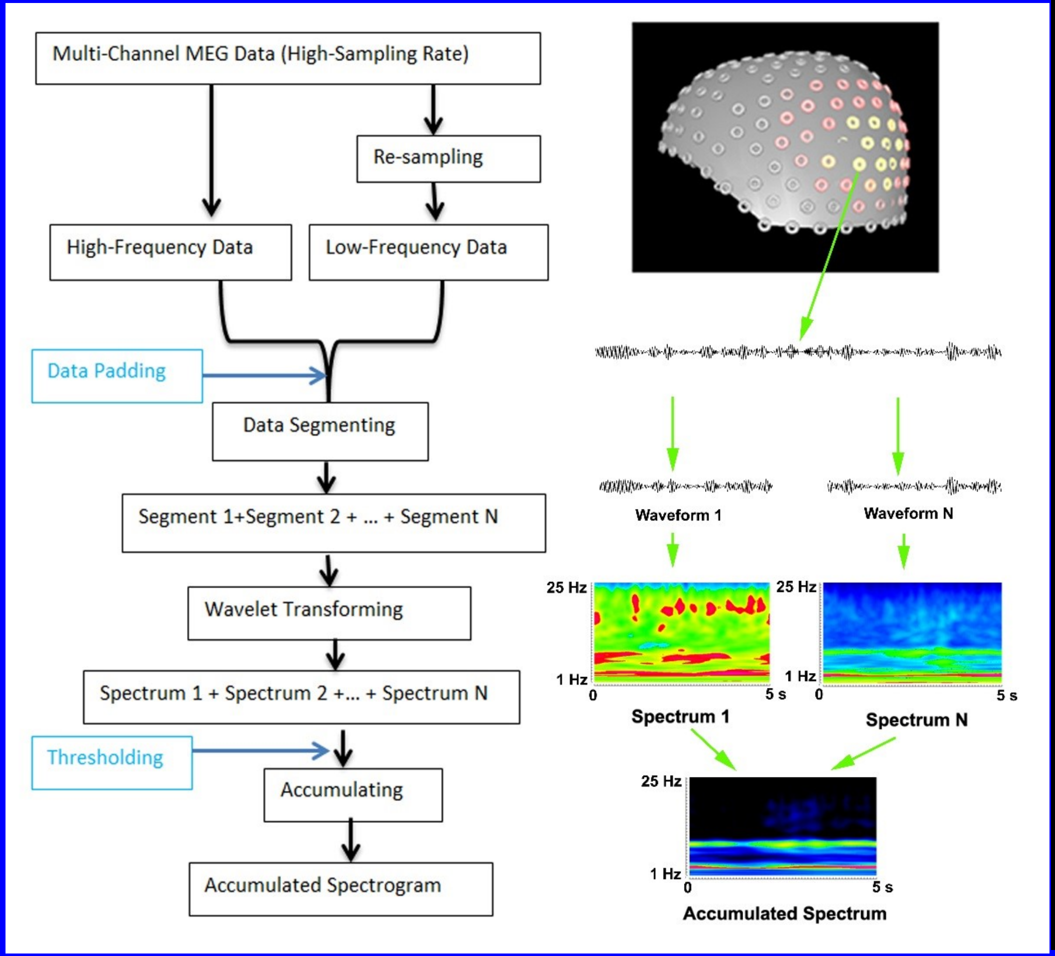
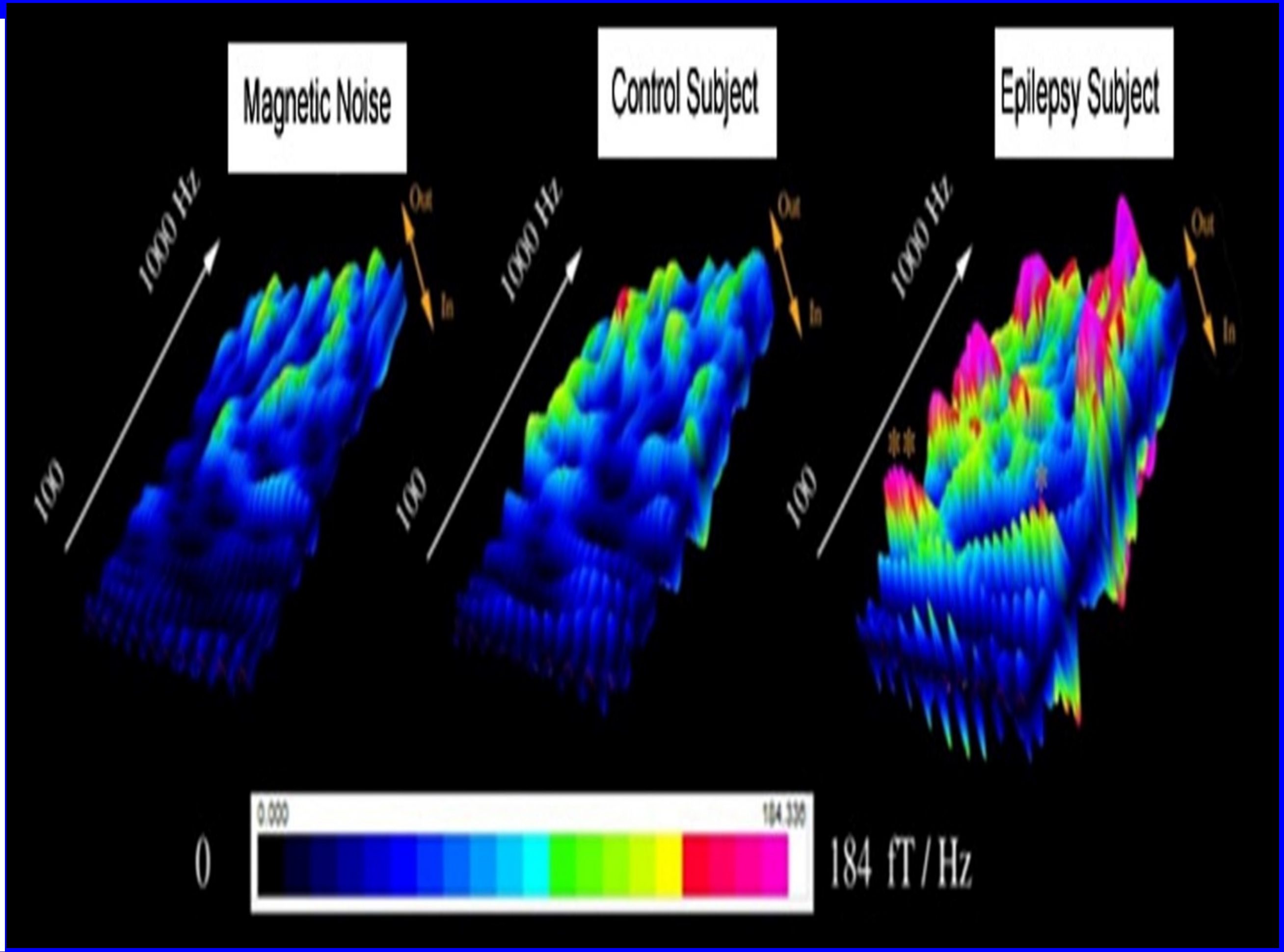
HFOs in Spectrograms (Precise Frequency)



Accumulated Spectrogram (Effective)





Visual Identification: subjective and time-consuming, Accumulated Spectrogram: objective and efficient (fast)

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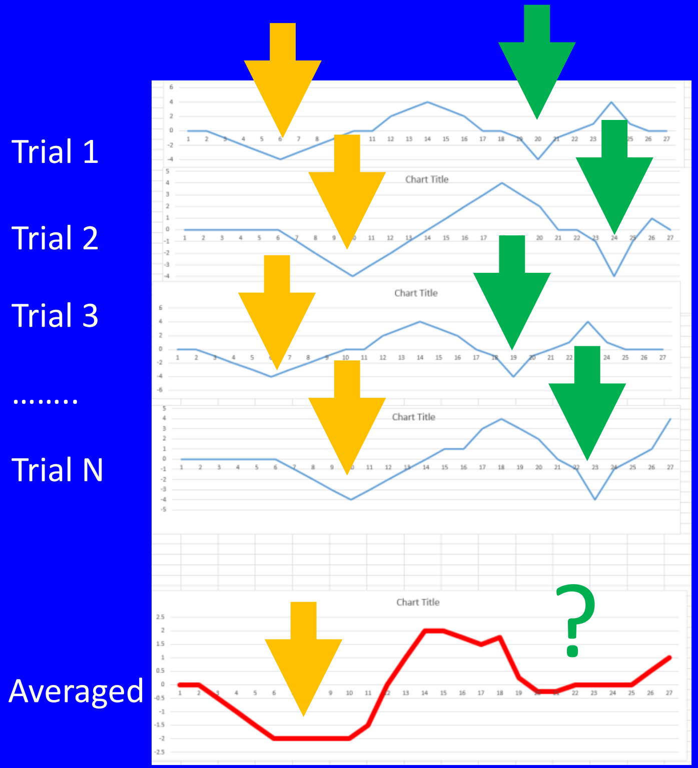
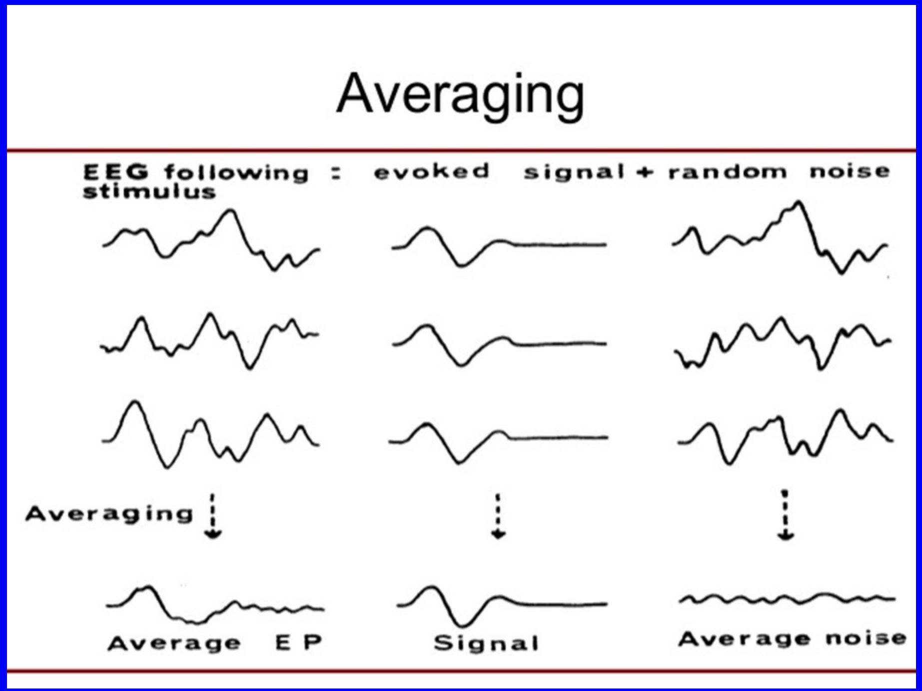
Functional/evoked HFOs

(average vs. accumulation)

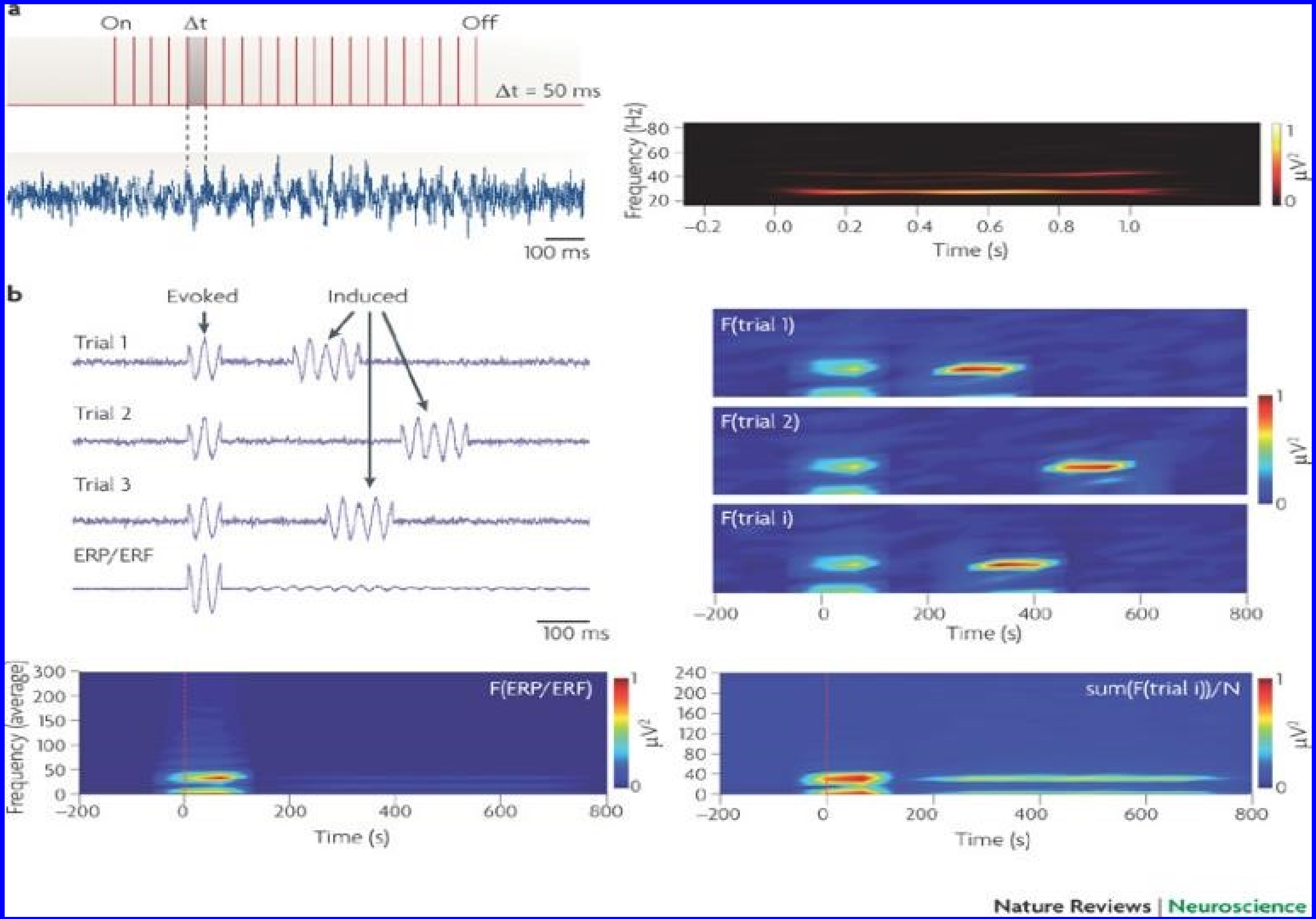




Latency variation of brain responses significantly affect s high frequency signals :
Low frequency components remain,
High frequency components disappeared

Functional/Elicited HFOs

(accumulation)



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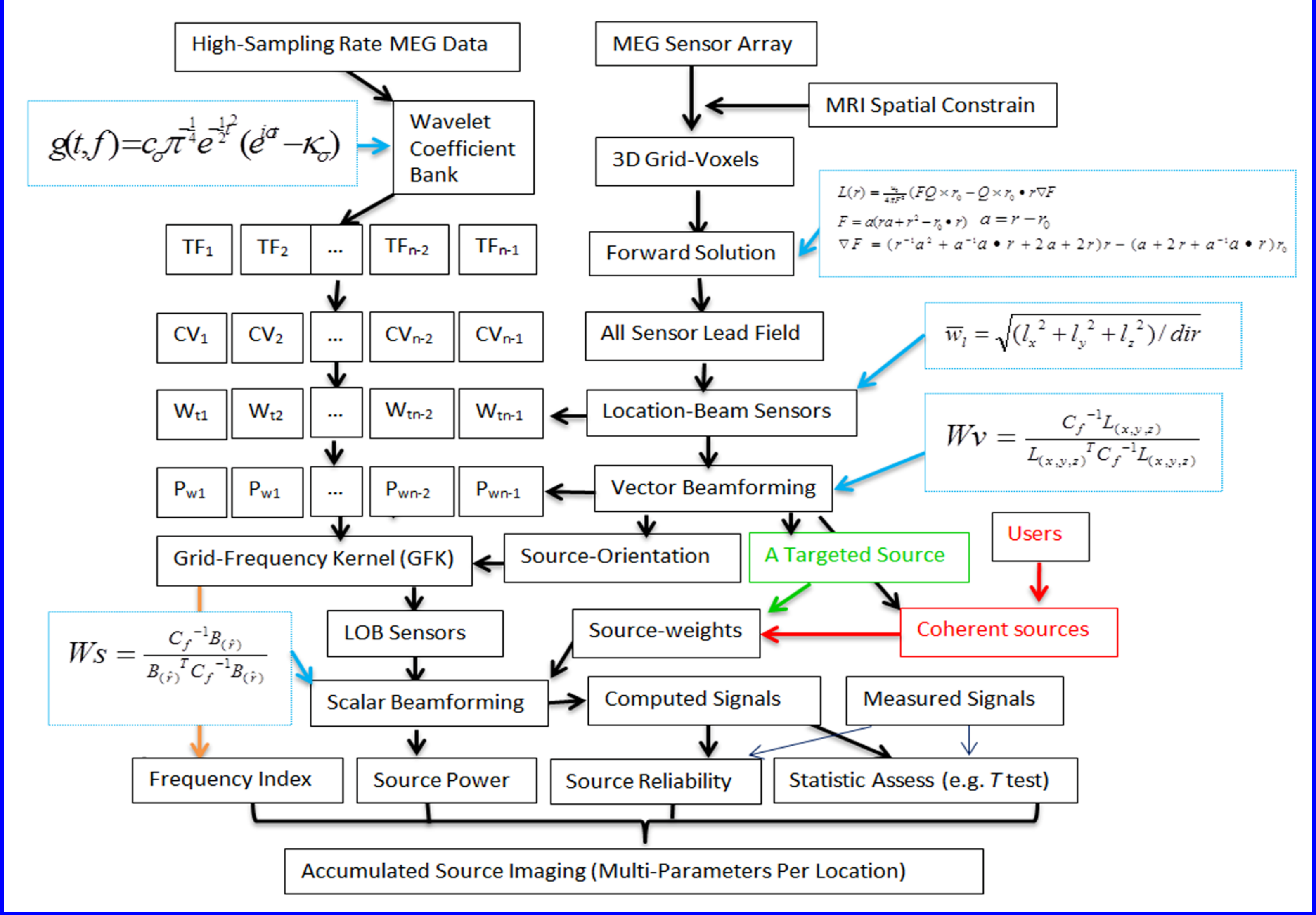
Accumulated Source Imaging (ASI)



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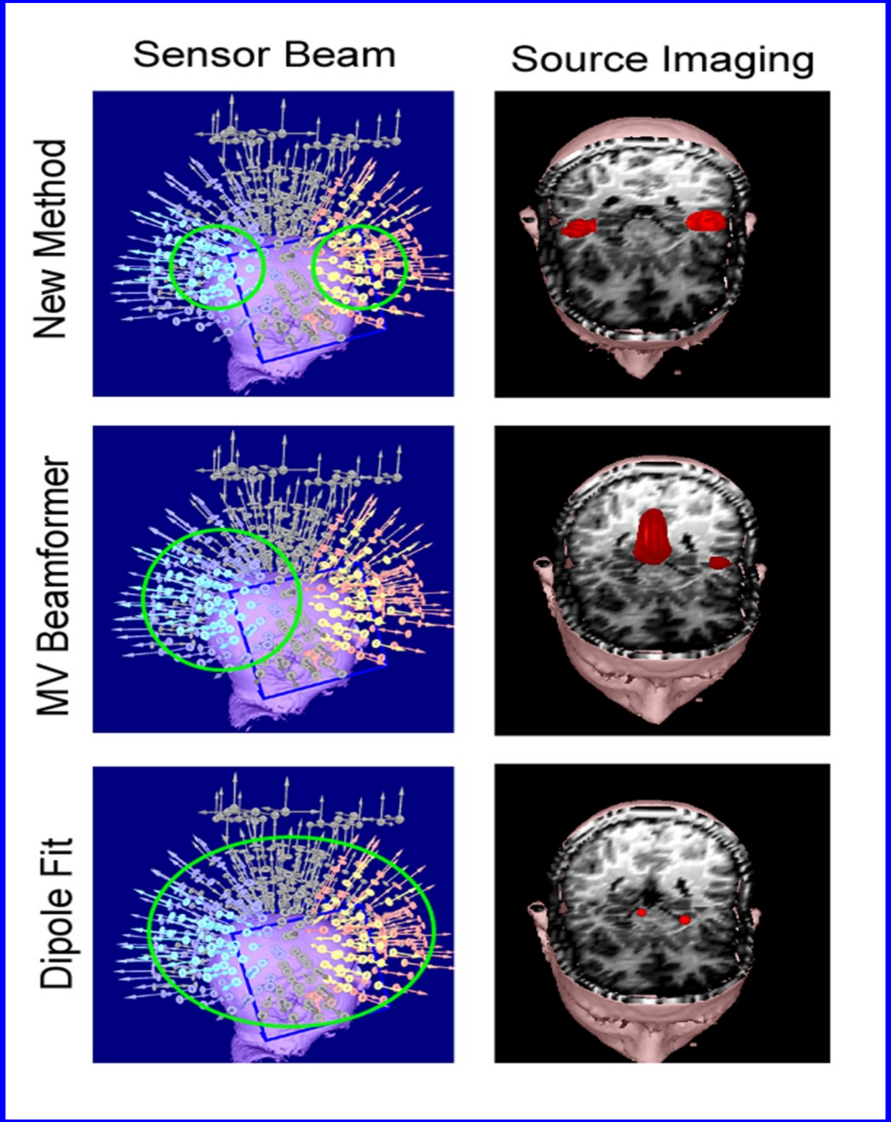
Accumulated Source Imaging (2)

1. Increase the reliability by combining spatial filtering and accumulating.
2. Increase the accuracy by using two-step beamforming



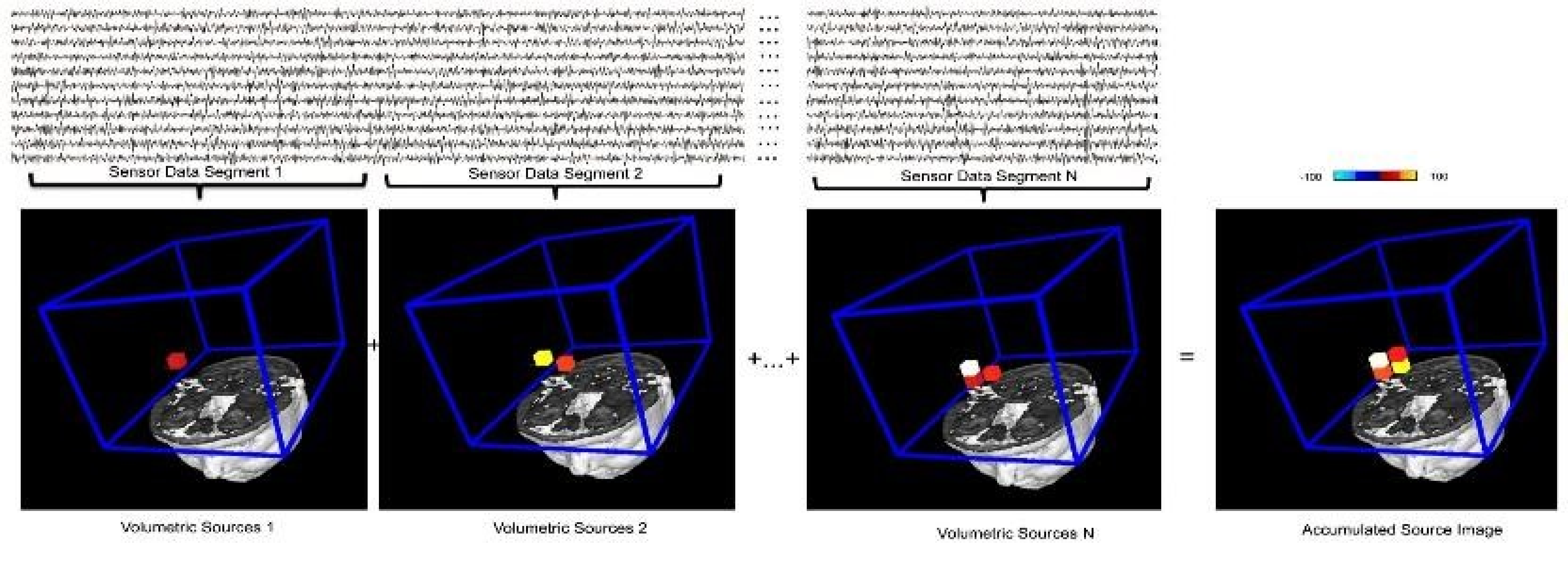
MEG Processor (One of the Best?)

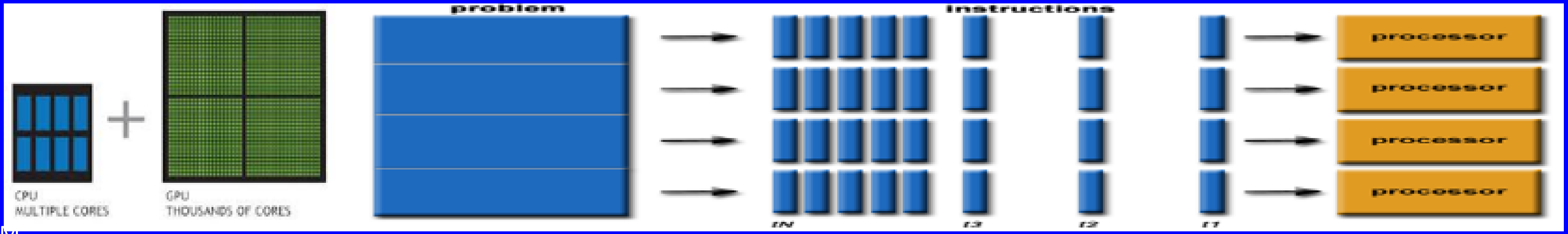
Table . Differences between accumulated source imaging (ASI) and similar methods.

	ASI	DM	SAM	SAM(g2)	BF	MN	MUSIC
Optimized for Localizing HFOs	Yes	No	No	No	No	No	No
Handle Large dataset	Yes	No	No	No	No	No	No
Handle multi-frequency signals	Yes	No	No	No	No	No	No
Multi-parameter per location	Yes	No	No	No	No	No	No
Volumetric source scan	Yes	No	Yes	Yes	Maybe	Yes	Yes
Detect dynamic sources	Yes	Yes	No	No	No	Yes	Yes
Detect stationary sources	Yes	No	Yes	Yes	Yes	No	No
Detect correlated sources	Yes	Yes	No	No	No	Yes	Yes
Noise suppression	Yes	No	Yes	Yes	Yes	No	Yes

ASI: accumulated source imaging; DM: dipole modeling (dipole fitting); SAM: synthetic aperture magnetometry; SAM (g2): SAM excess kurtosis (g2); BM: conventional beamforming; MN: minimum-norm; MUSIC: multiple signal classification

Accumulated Source Imaging





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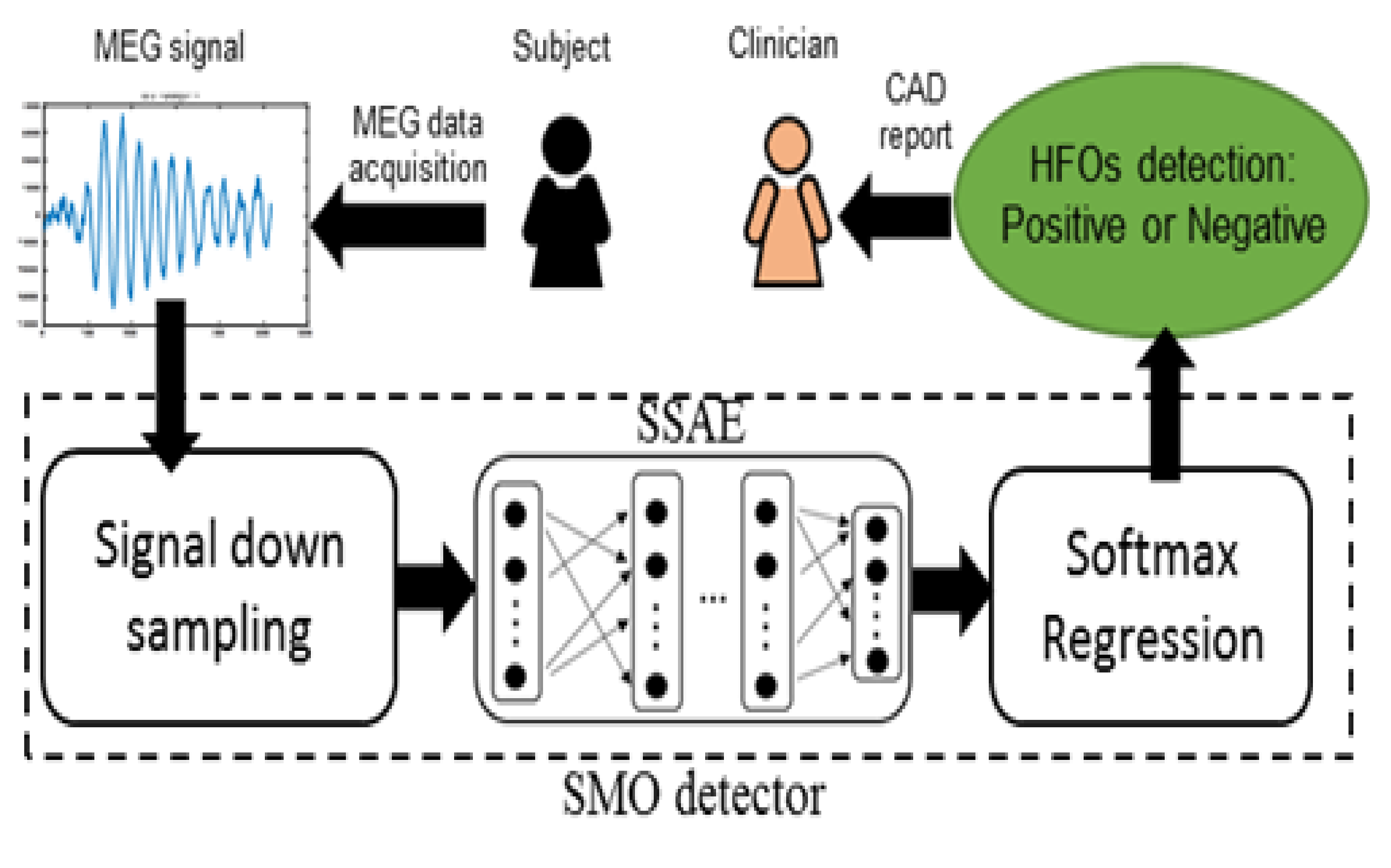
Methods (3)

- Artificial Intelligence (AI):
  - Deep learning
  - Machine learning
  - stacked sparse autoencoder
- Other methods
  - Pattern recognition
  - Wavelets, Spectral power,
  - stationarity, and others

Automatically Detect HFOs with AI



stacked sparse autoencoder (SSAE)-> SSAE MEG Oscillation (SMO) Detector

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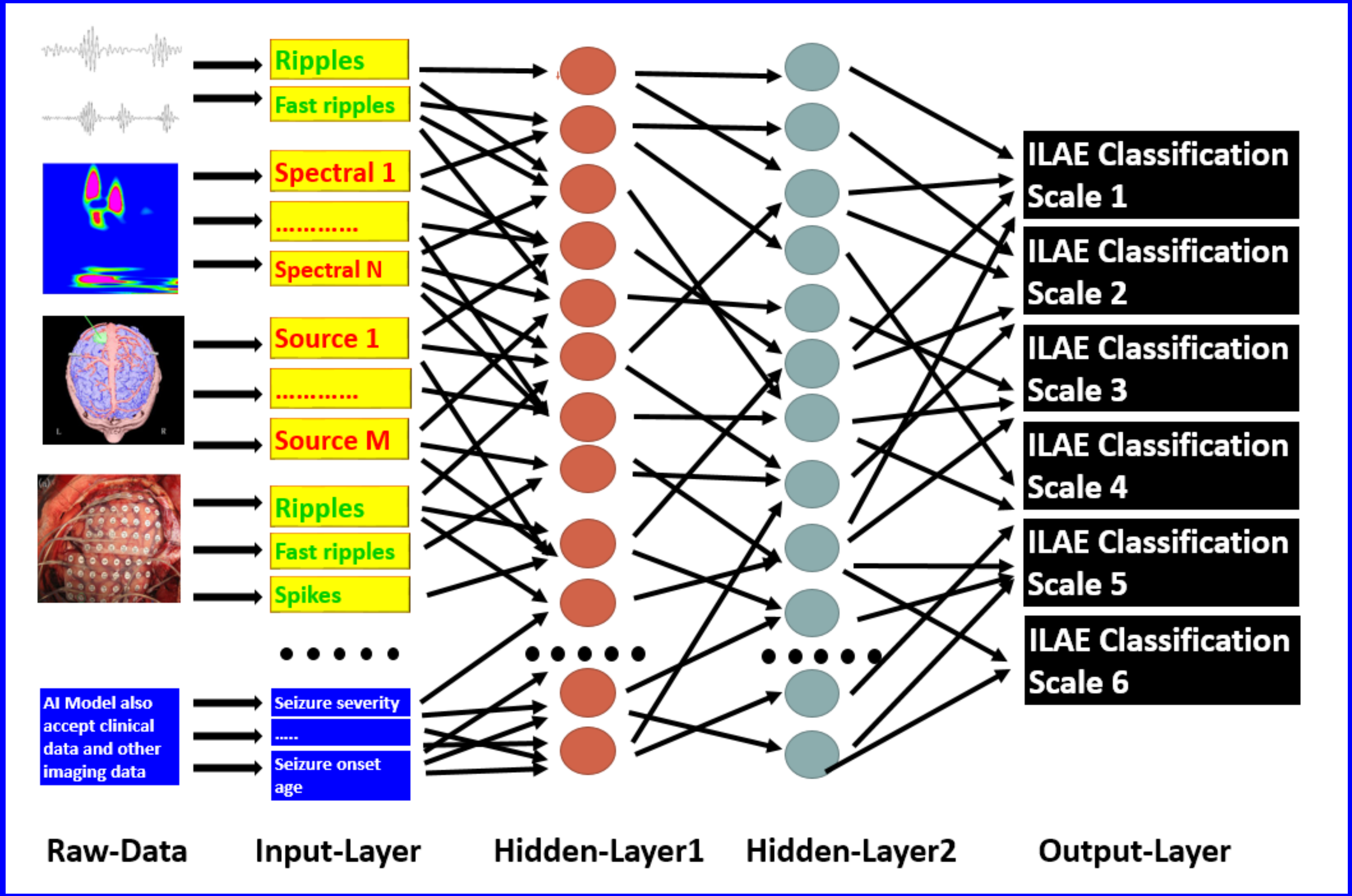
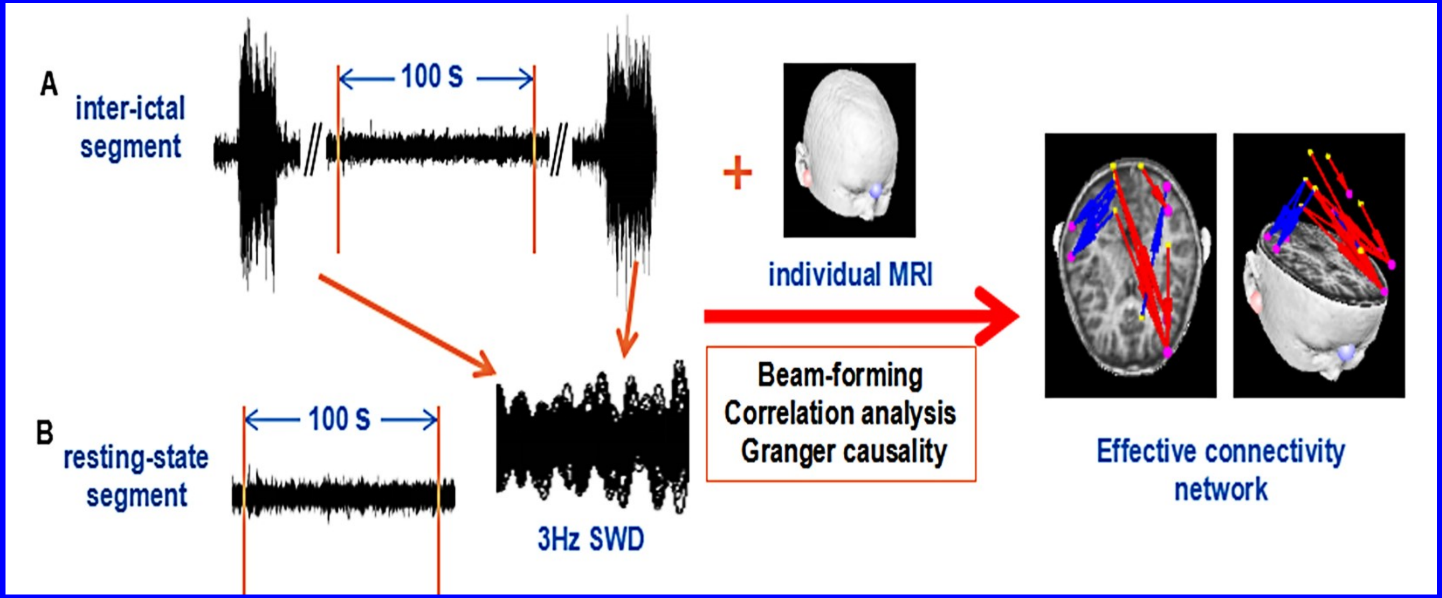
Automatically Detect HFOs with AI



Methods (4)

- Advanced HFO technology
  - Frequency Encoded Source Imaging
  - Epileptogenicity Index
  - Frequency coupling
  - Frequency dependent networks
  - Others
-

Neural Network Analysis



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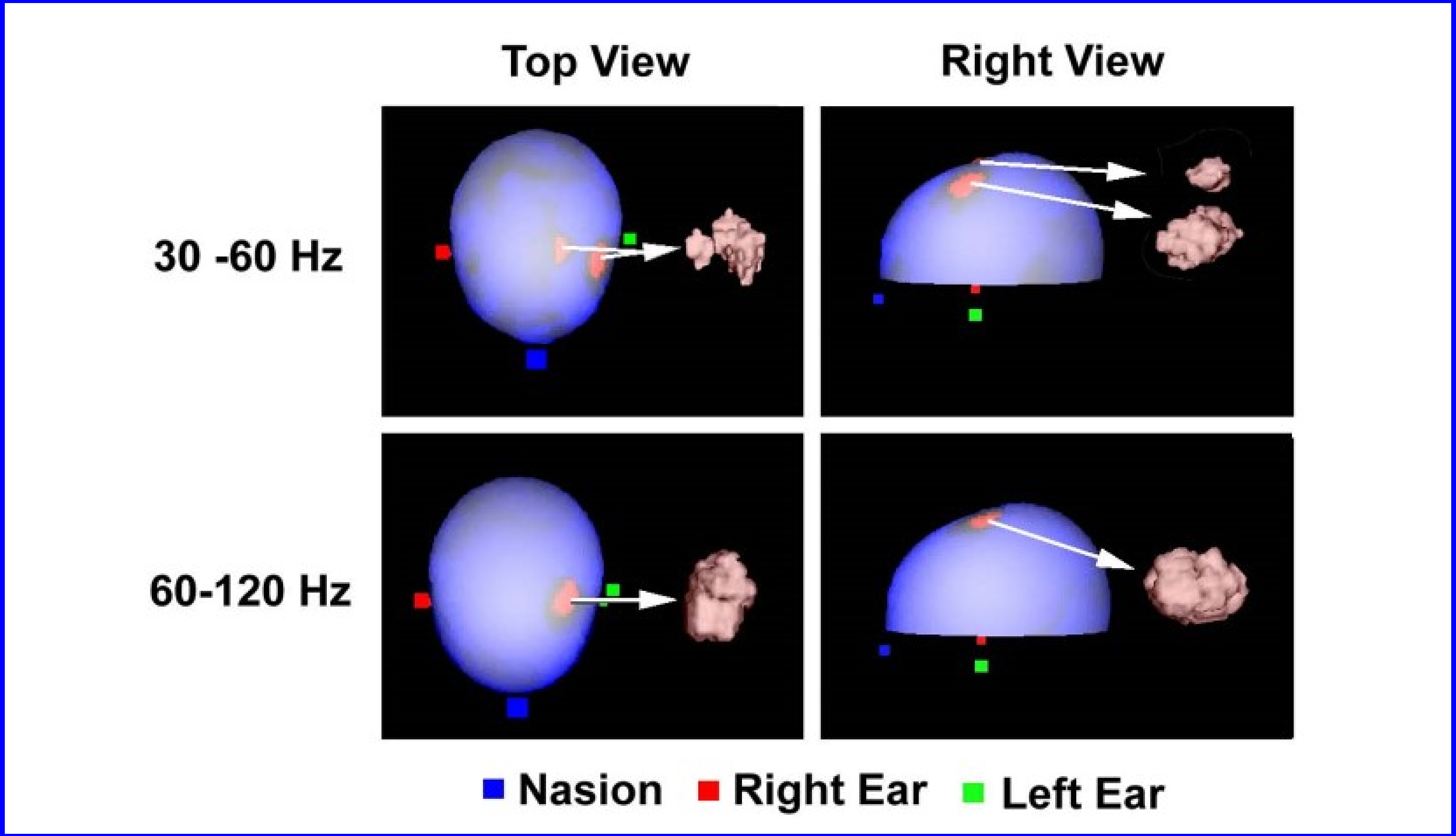
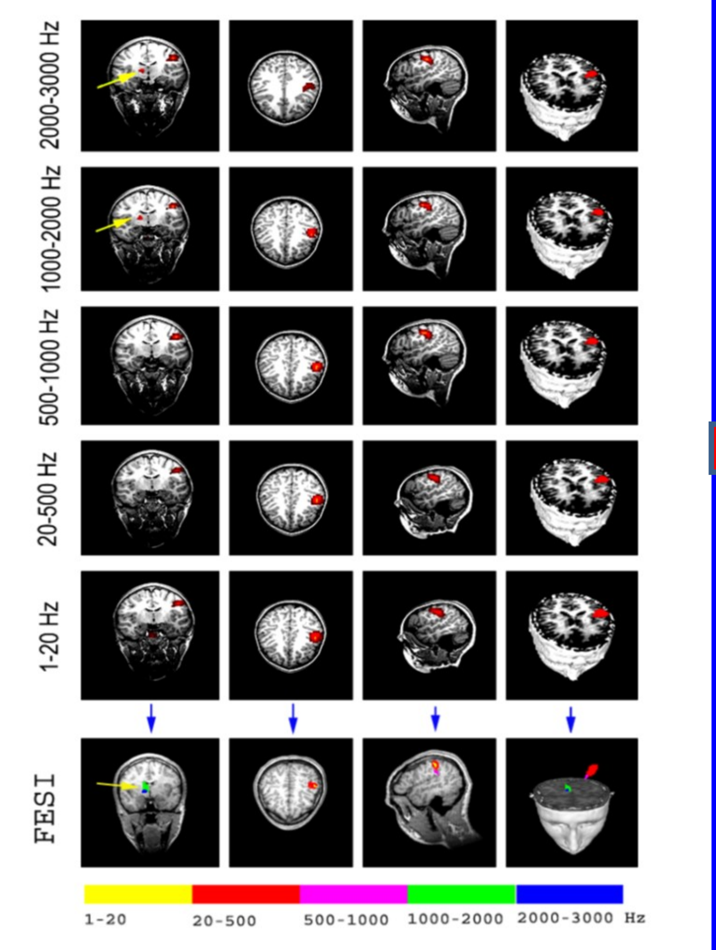
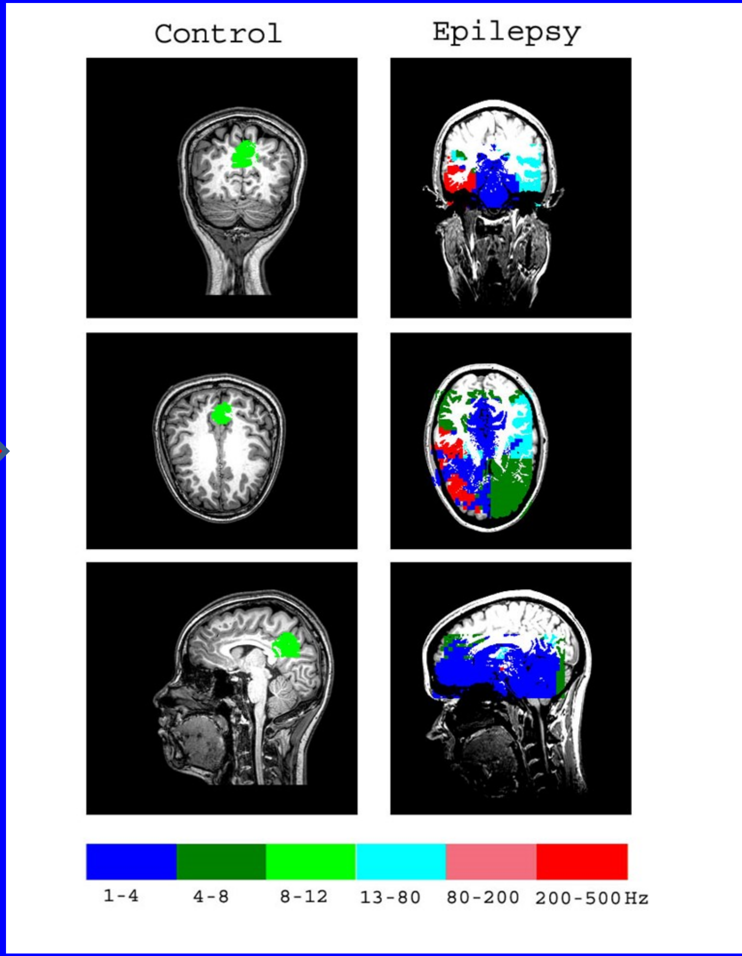
Volumetric Source Estimation



Frequency-Encoded Source Imaging(1)





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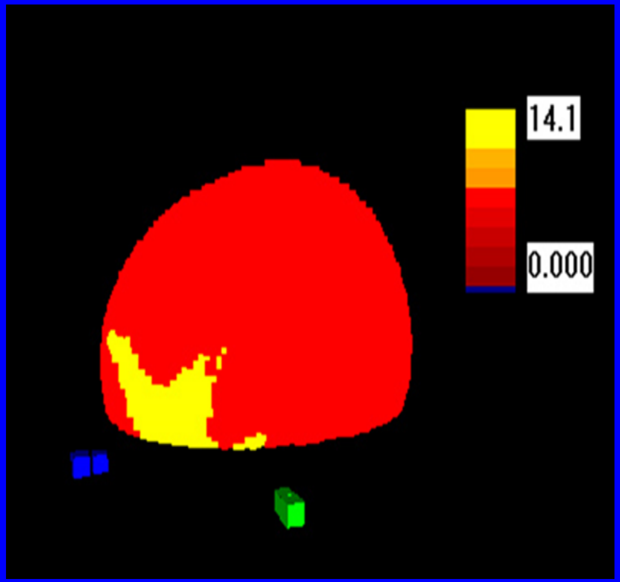
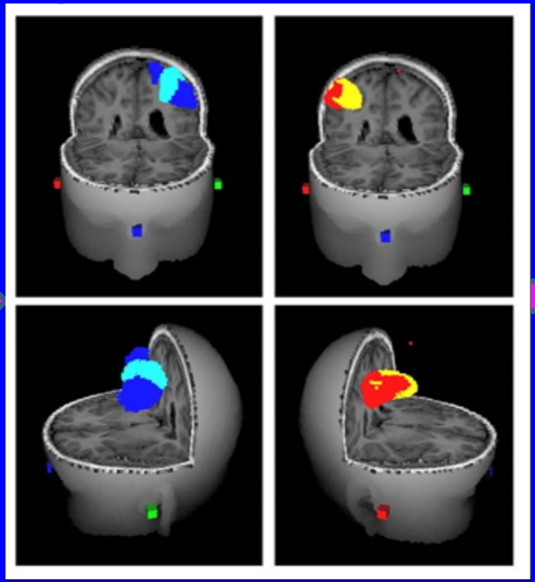
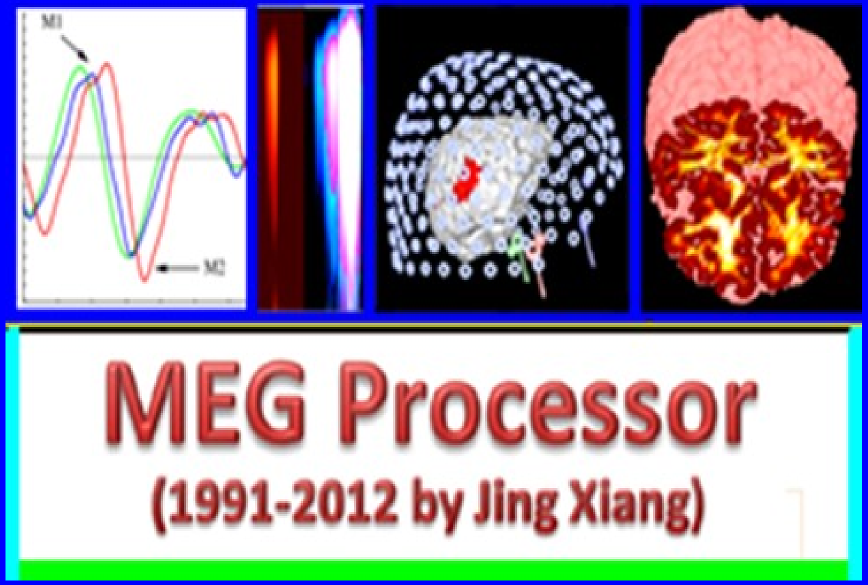
Goal : Using All HFBS to Solve Clinical Problems







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Clinical Applications(Focus on 3)

Epilepsy (~800)

- Spike searching
- Presurgical planning
  - Epileptic foci: HFOs
  - Functional mapping: high gamma
- Generalized epilepsy
- Cortical organization
  - consequence of seizures
  - consequence of medication
  - relationship to co-morbidities
- Post-traumatic epileptogenesis
- Withdrawal of treatment
- Pharmacoresistance
- more...

Psychiatry (~275)

- Schizophrenia: high gamma
- Depression
- Anxiety
- OCD
- PTSD
- Drug effects: new drug targeted at HFOs

Other Neurological Diseases (~450)

- Migraine
  - Acute : HFOs
  - Chronic: HFOs
- Normal Aging
- Mild cognitive impairment
- Alzheimer’s
- Cerebrovascular disease
- Functional reorganization
- Multiple sclerosis
- Tinnitus
- Migraine and Headache
- Traumatic Brain Injury
- Brain Tumor: HFOs

Neurodevelopment (~200)

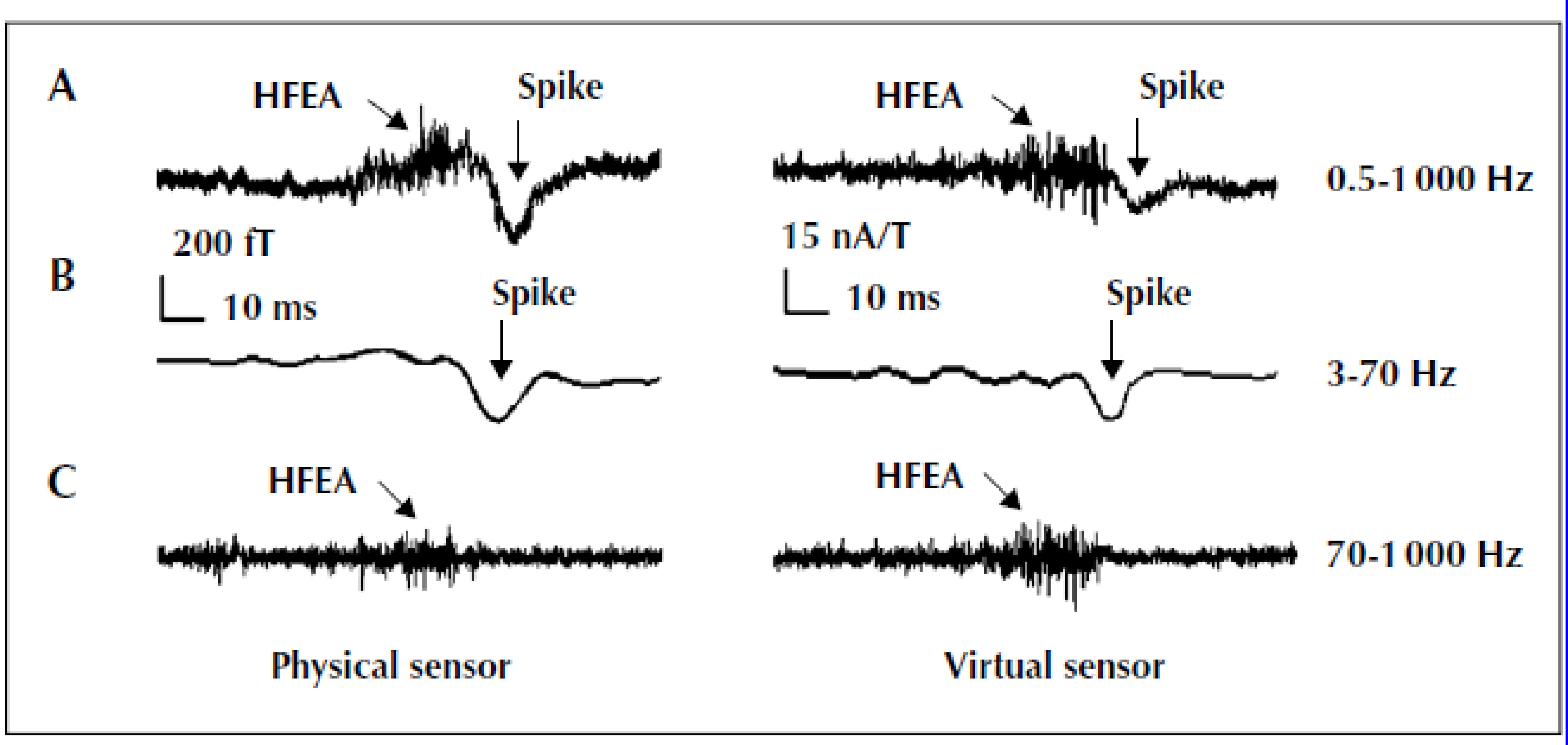
- Fetal
- Neonatal
- Autism: high gamma
- ADHD
- Functional (re)organization
- Brain Tumors

		Epileptic HFOs	Physiological HFOs	Artificial HFOs#
Waveforms	Oscillations	>4	>4	any
	Amplitudes	>1.5 SD of baseline§	<1.5 SD of baseline*	>10 SD of baseline
	Overlap on spikes	Yes§	No	No
	Ride on slow wave	Yes§	No	No
	Visible in both raw and filtered data	Yes§	Yes	No
	Inter-event interval	>25 ms	> 25 ms	
Spectrograms	Time	irregular burst: 5-30 ms	Rhythmic, ~70 ms	Random/constant
	Frequency	80-250 Hz (ripples); 250-600Hz (fast ripples) 600-2500 Hz (VHFOs)	Elicited: 70-150 Hz Endogenous: 102 Hz	< 100 Hz >2500 Hz 60 Hz or 50 Hz
	Pattern	Isolate island or horizontal	Connected or vertical	Straight lines
	Power	Very high power > 3 uV	Low-median power ~0.95 uV	Fixed
	Ratio (HFOs/alpha)	>0.38§	<0.27*	>4.0#
		Energy > 95%background	Energy > 85% background	undefined
Source Imaging	Location	Within the brain (cortex, gray matter)	Within the brain (cortex, gray matter)	Out of the brain (around neck, eyes)
	Source strength	>3 SD of the global mean	> 1 SD of the global mean	> 10 SD of global mean
	Pattern	Peak with propagated activation	Activation without clear peaks	Typically irregular
	Relation to MRI/CT	Mimic anatomical shape	Mimic anatomical shape	No relation
Networks	Hub Location	Within the brain	Within the brain	Out of the brain
	strength	Increased*	Normal*	No connection
	Clustering index	Increased*	Normal*	Not available
	Path	Shortened*	Normal*	Not available
Modulation	NREM Sleep	Decrease*	No change*	No change
	REM Sleep	No change*	Ripple increase*	No change
	Sleep stage	Large extent (NREM)*	Small extent (REM)*	No change
	Sleep cycle	High rate in first cycle*	Low rate in first cycle*	No change
	Task induced	No*	Yes*	No
	Sleep time	Decrease with time during NREM	Increase with time during REM	
Clinical correlates	High rates in SOZ	Yes*	No*	No relationship
	Increase with Seizure frequency	Yes*	No*	No relationship
	Anti-epileptic drug	Reduce HFOs	No	No relationship
	Removal HFO tissues	Good surgical outcomes	No	No relationship
	Hyperventilation	Elicit HFOs (absence epilepsy)	No	No relationship

SD: standard deviation; SOZ: seizure onset zone; AED: antiepileptic drug
*Compared to normative database: ~160 healthy children
§Compared to pediatric epilepsy database: ~ 390 pediatric epilepsy patients
#Artificial HFOs: power-line noise, cardiac signals, muscle activity, eye movement, Gibbs filter artifact

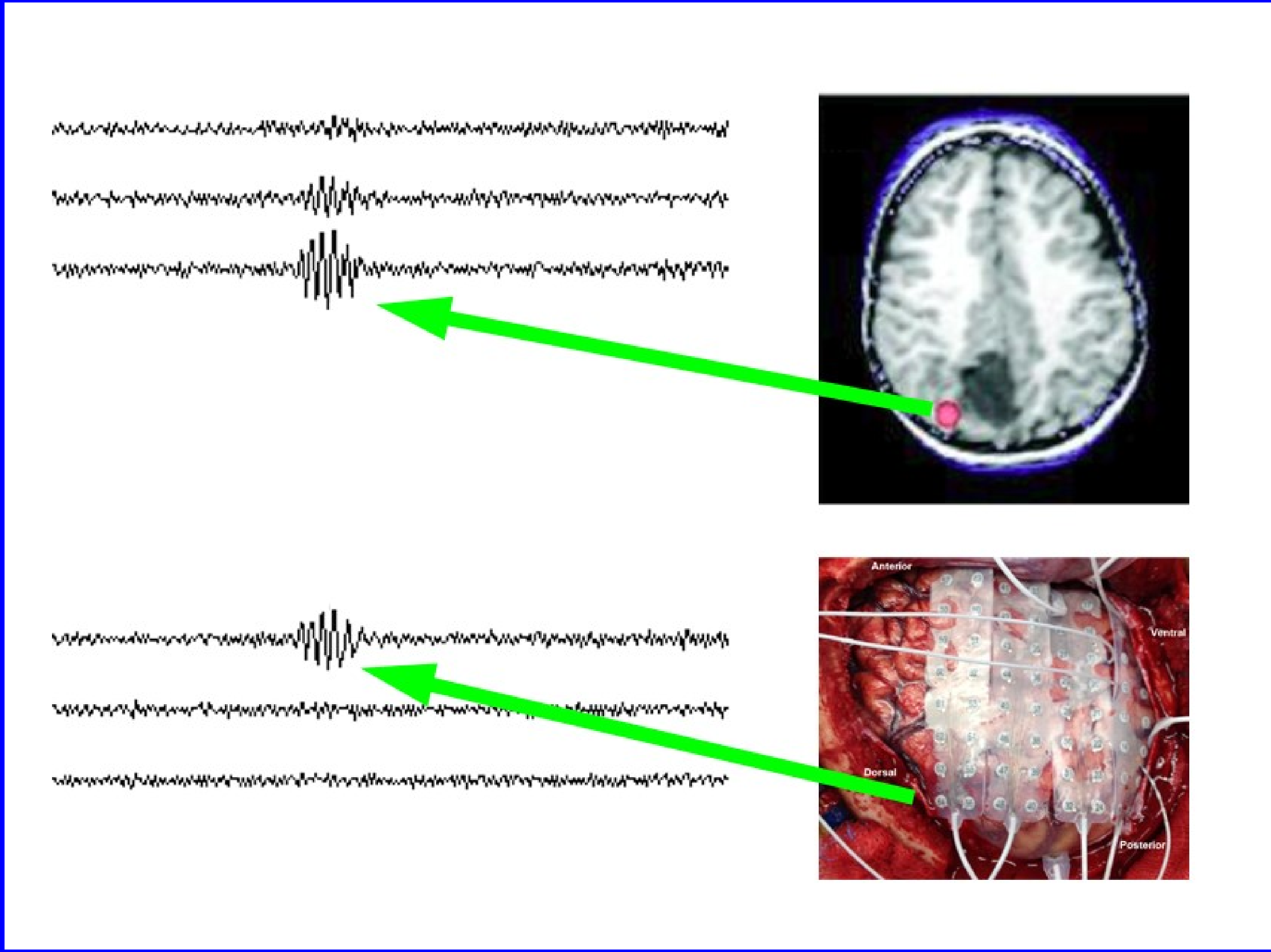
HFOs in Epilepsy

(Detectable at both sensor and source levels)

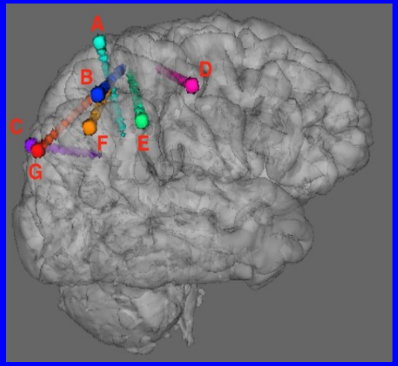


11:54 AM

HFOs on Virtual Sensors and ECoG

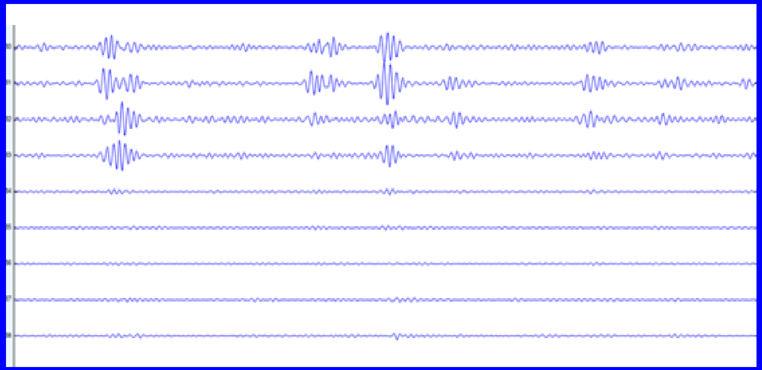


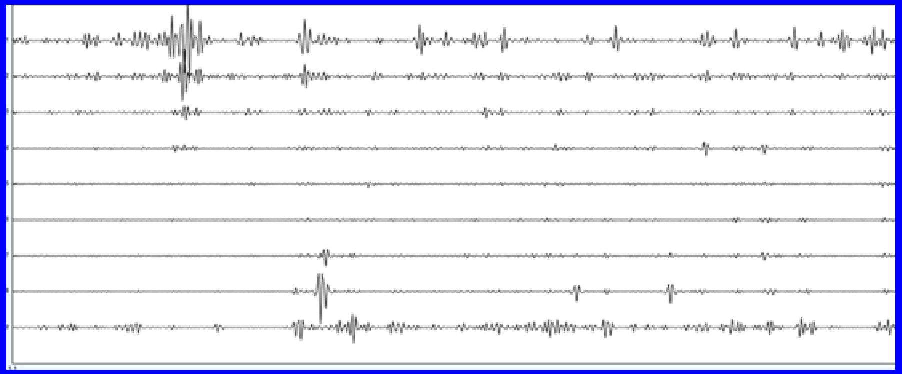
HFOs on Virtual Sensors vs. SEEG (250-500 Hz)



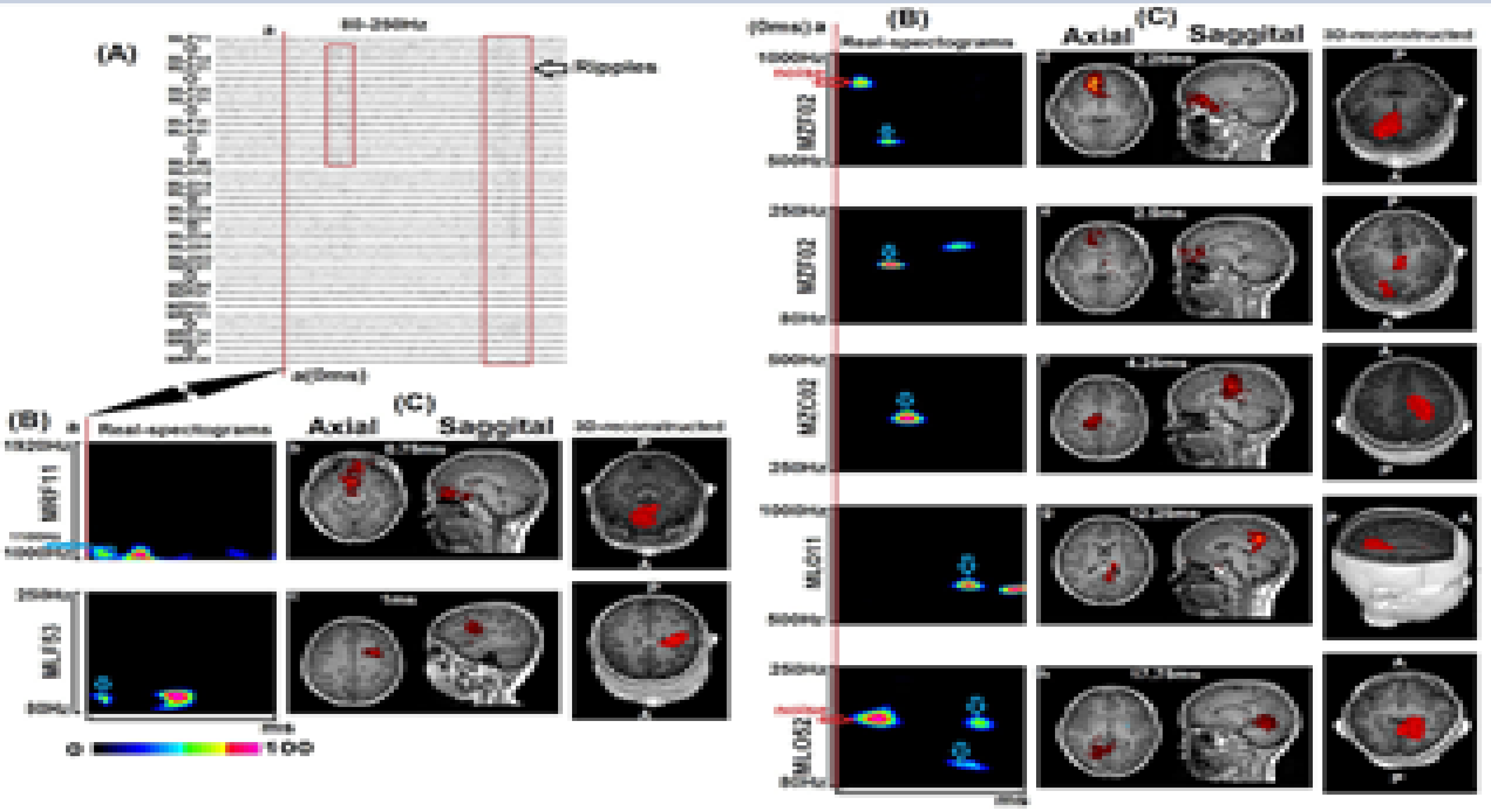
SEEG

MEG Virtual Sensor





HFOs Appear Before, During and After Seizures



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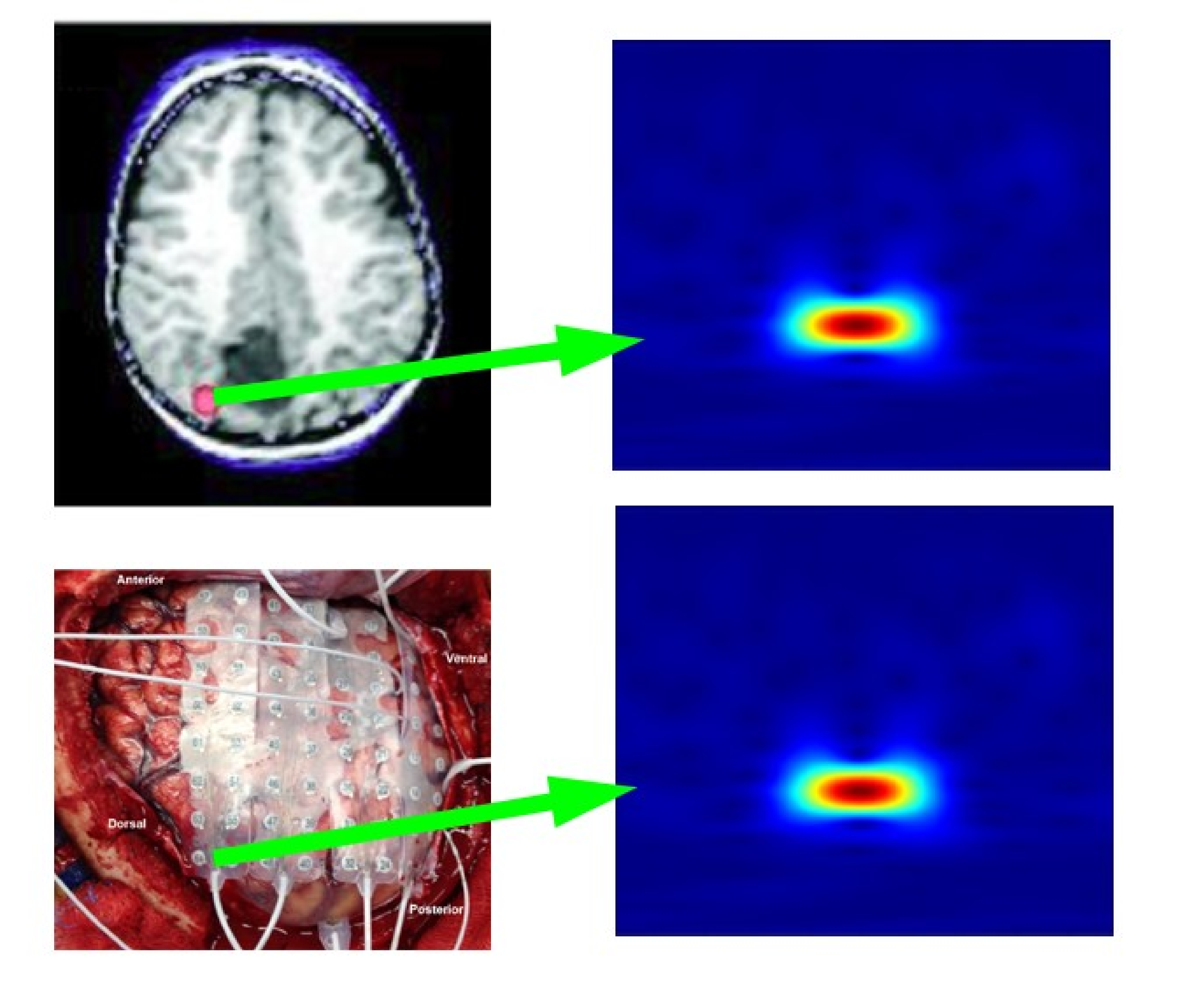
Virtual Sensor Spectrogram



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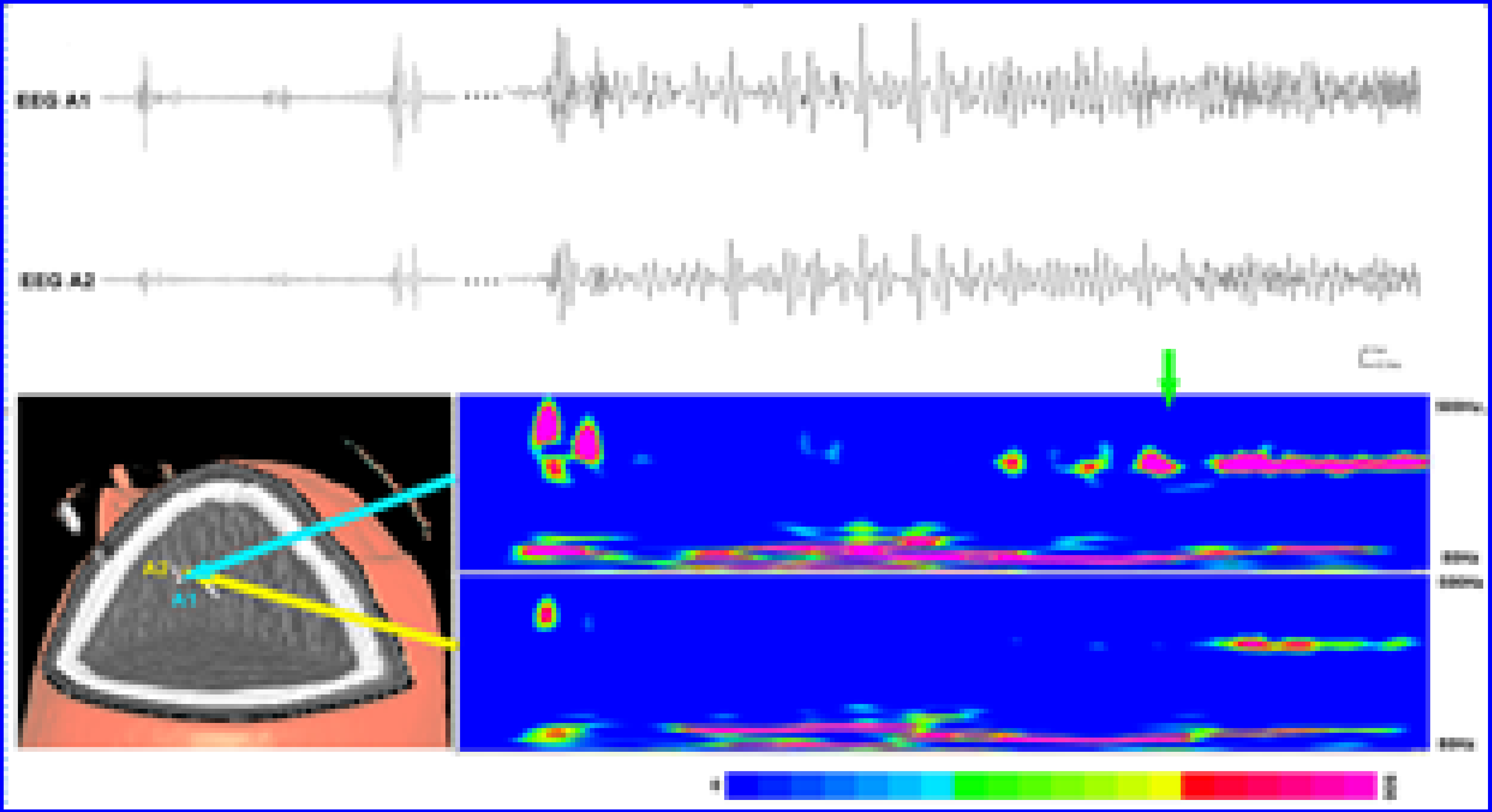
HFOs in Waveform and Spectrograms



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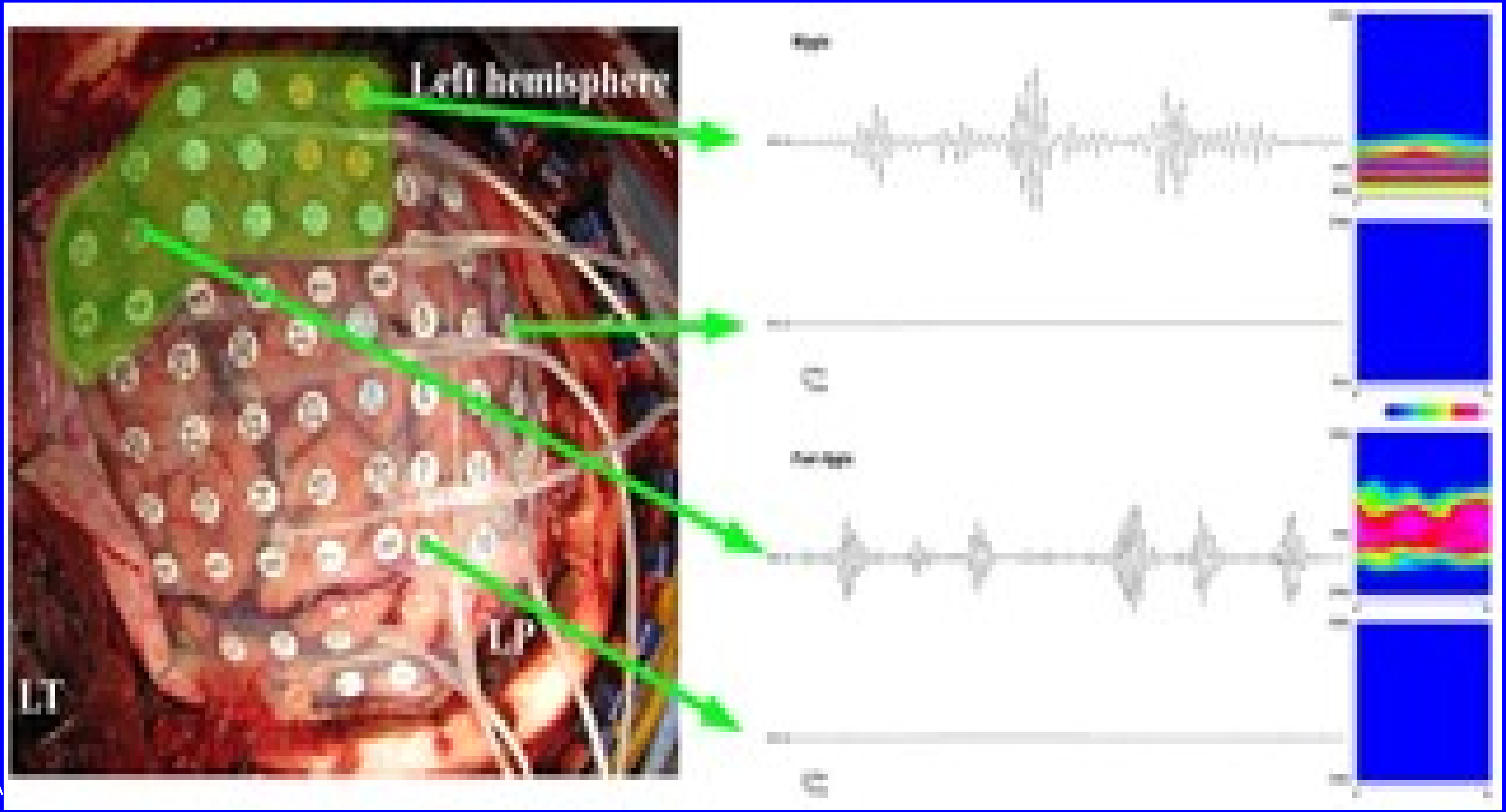
HFO Propagation

(higher frequency -> onset)



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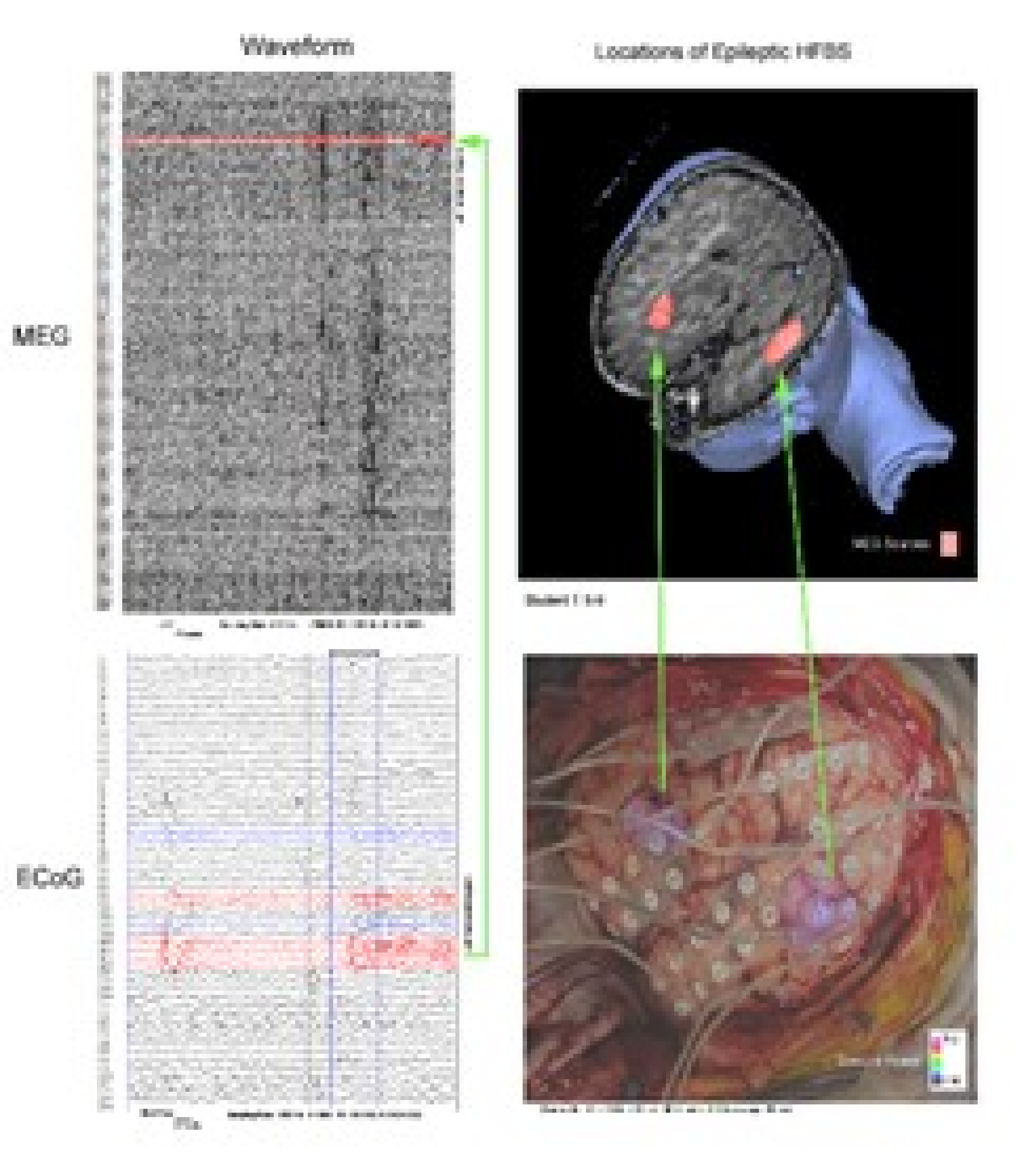

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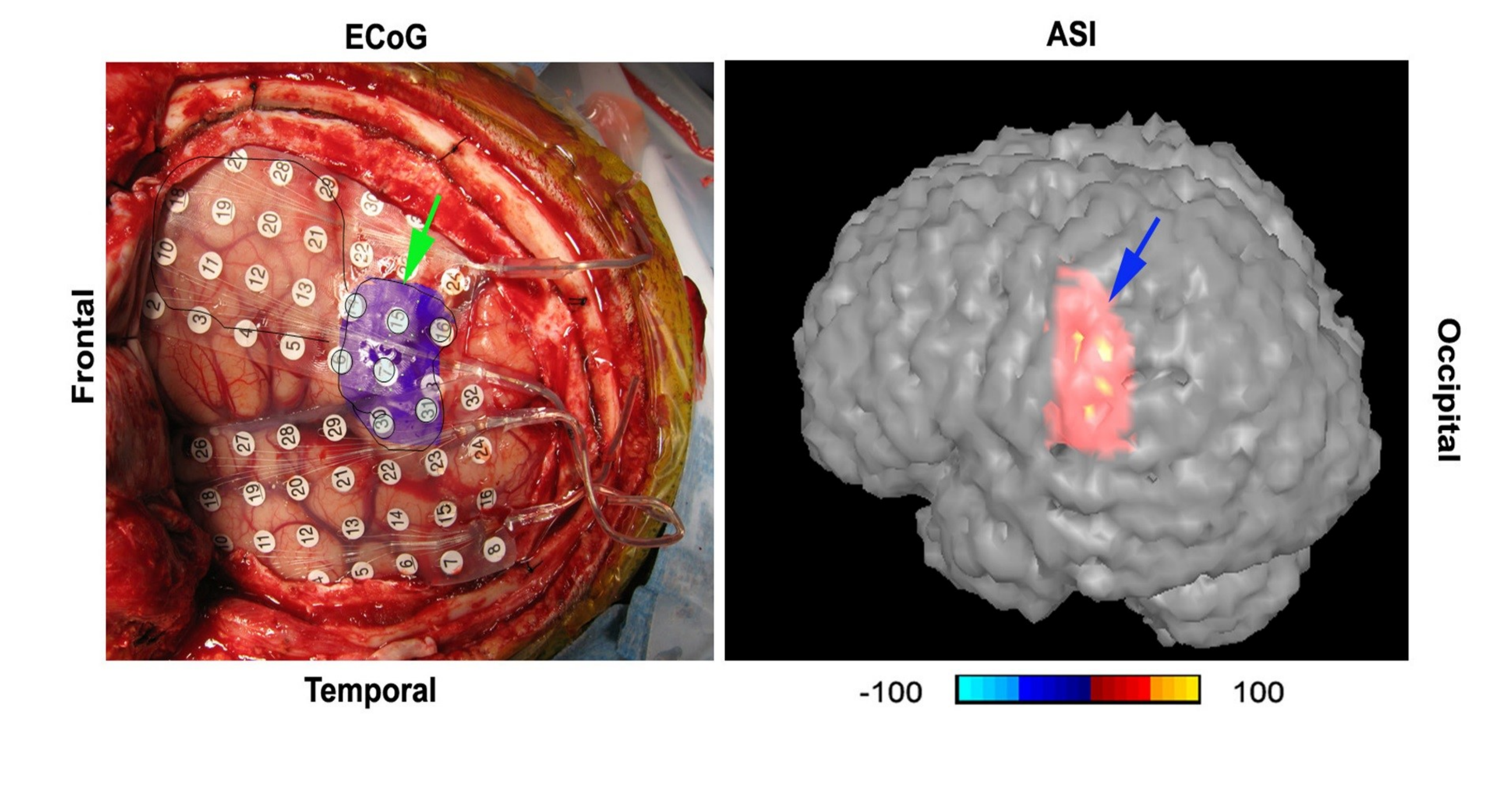
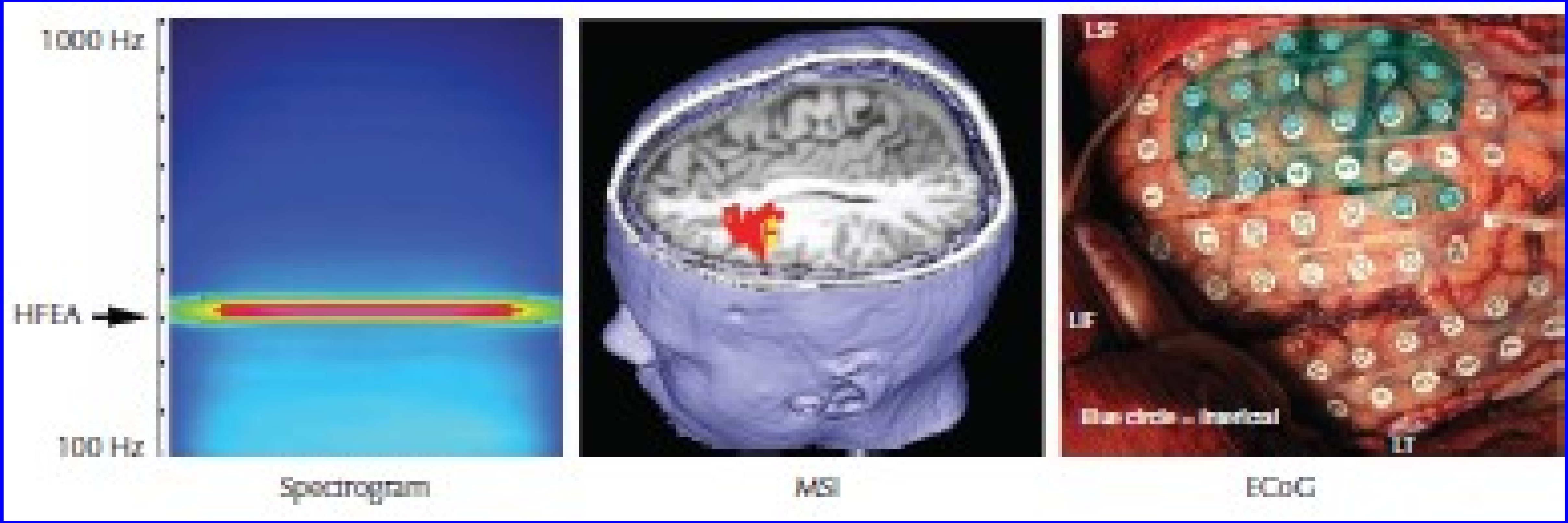
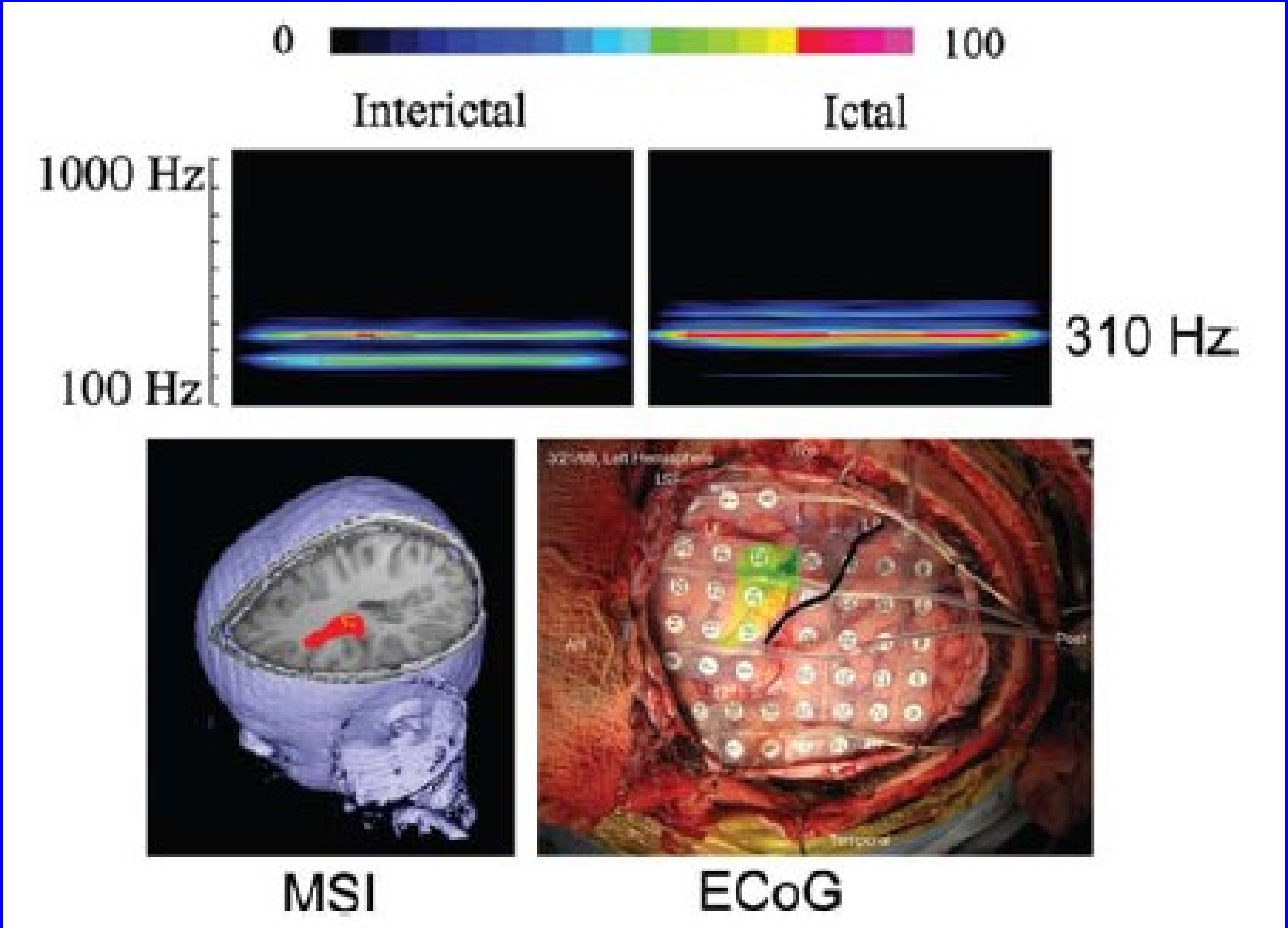
MEG Can Localize HFOs Noninvasively



Identify and Localize HFOs for ECoG

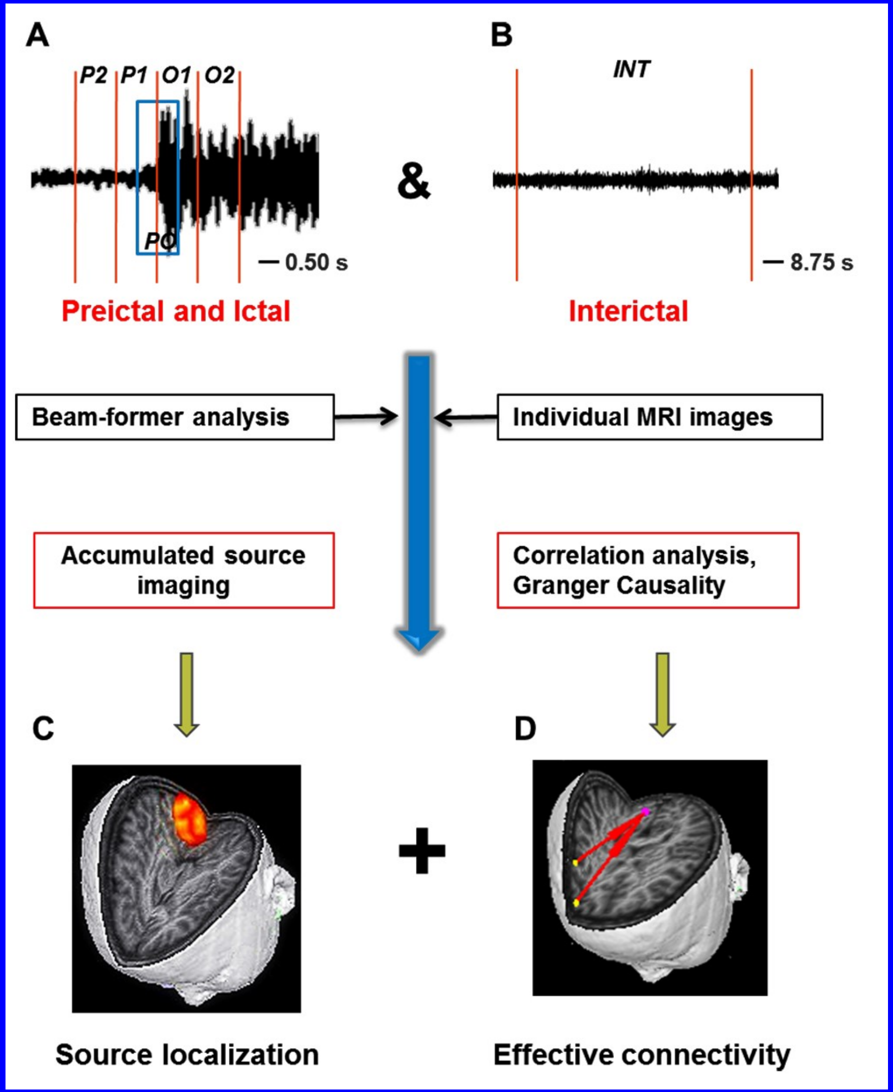
(MEG-Guided ECoG)





11:54 AM

HFBS and Network (Connection)



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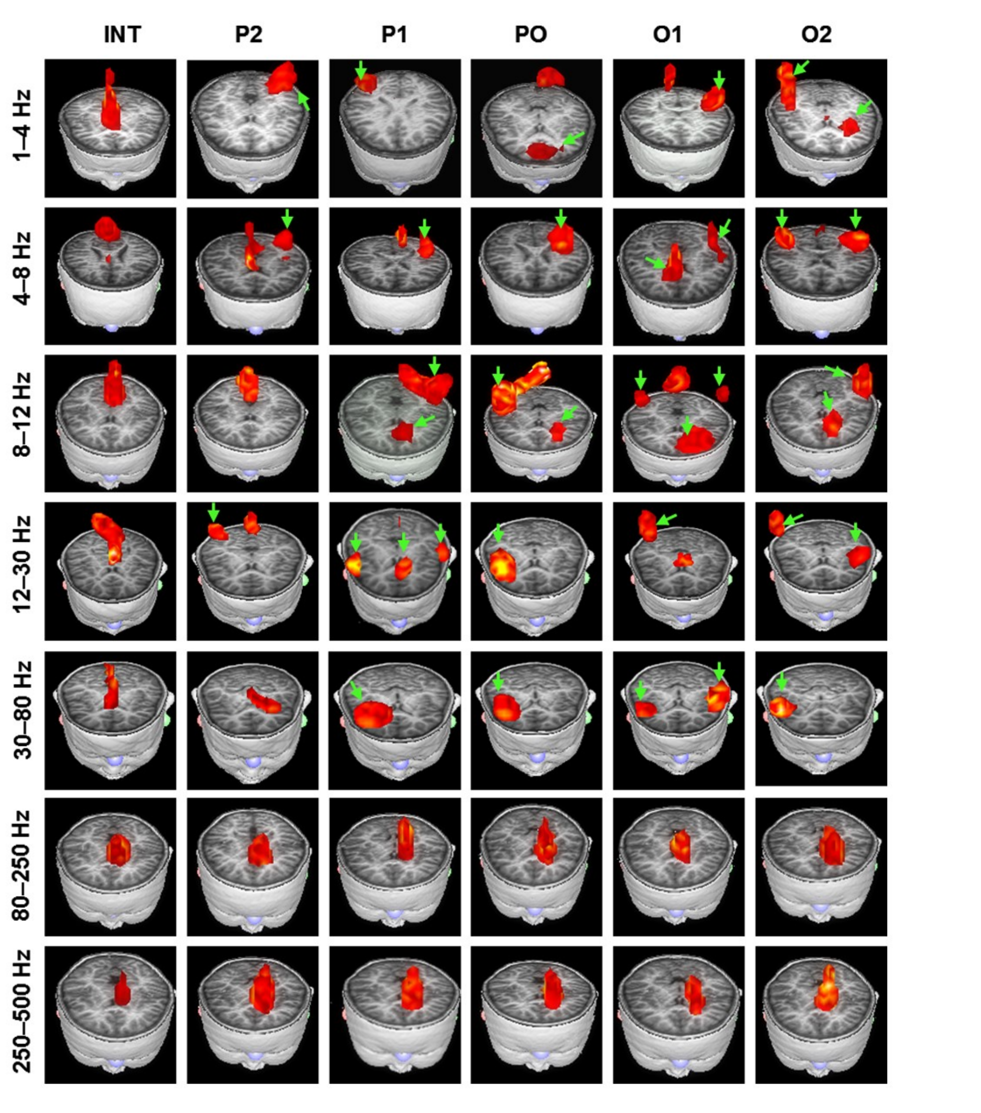
Source Imaging of Low-High Frequency Signals



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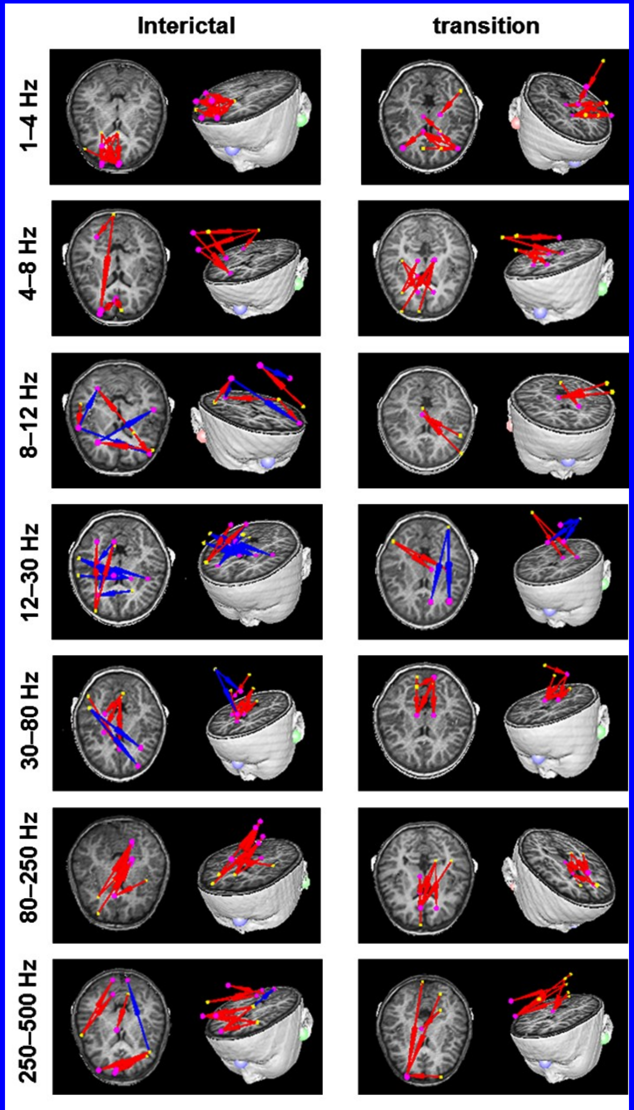
Source Networks of Low and High Frequency Signals



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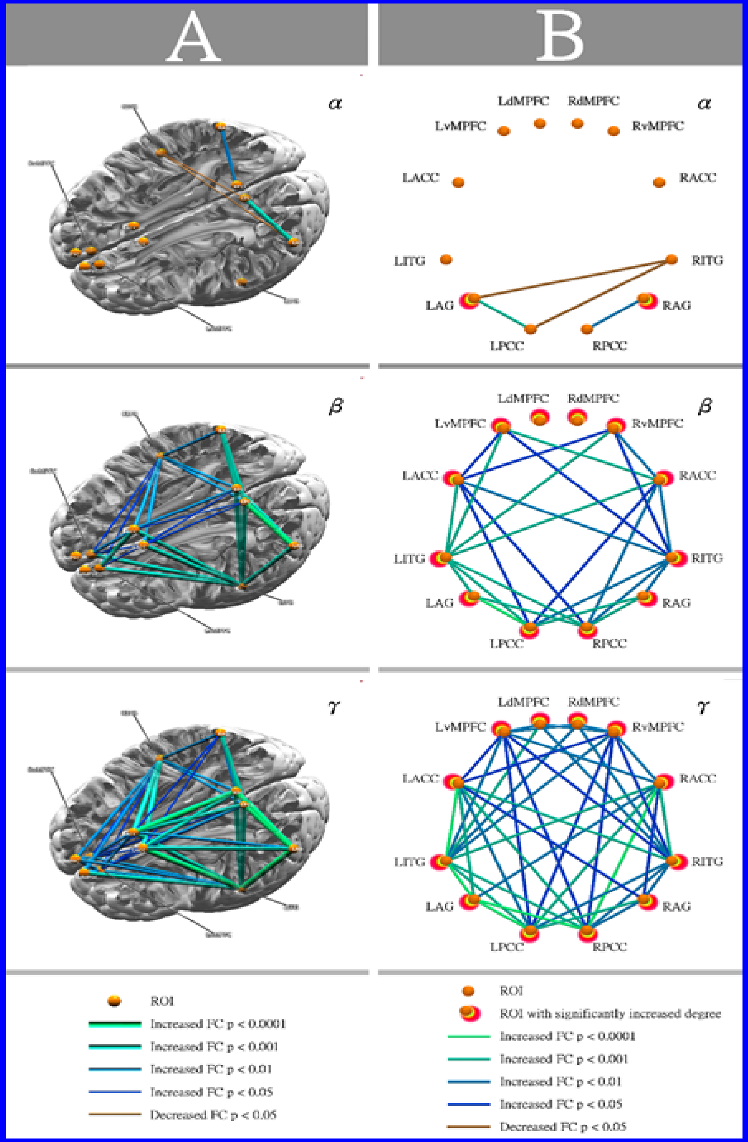
Network of HFBS



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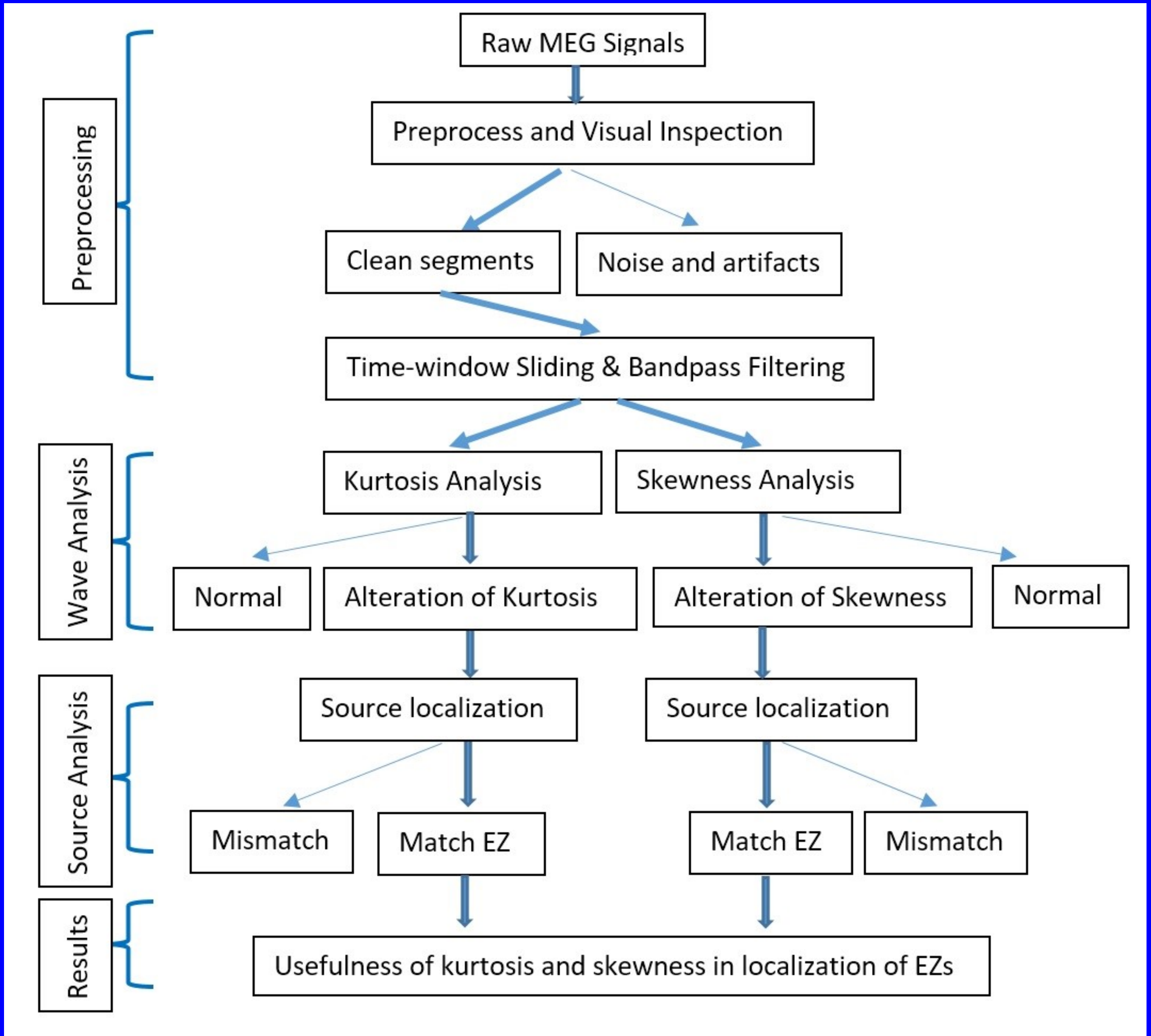
Kurtosis/skewness Based Source Imaging



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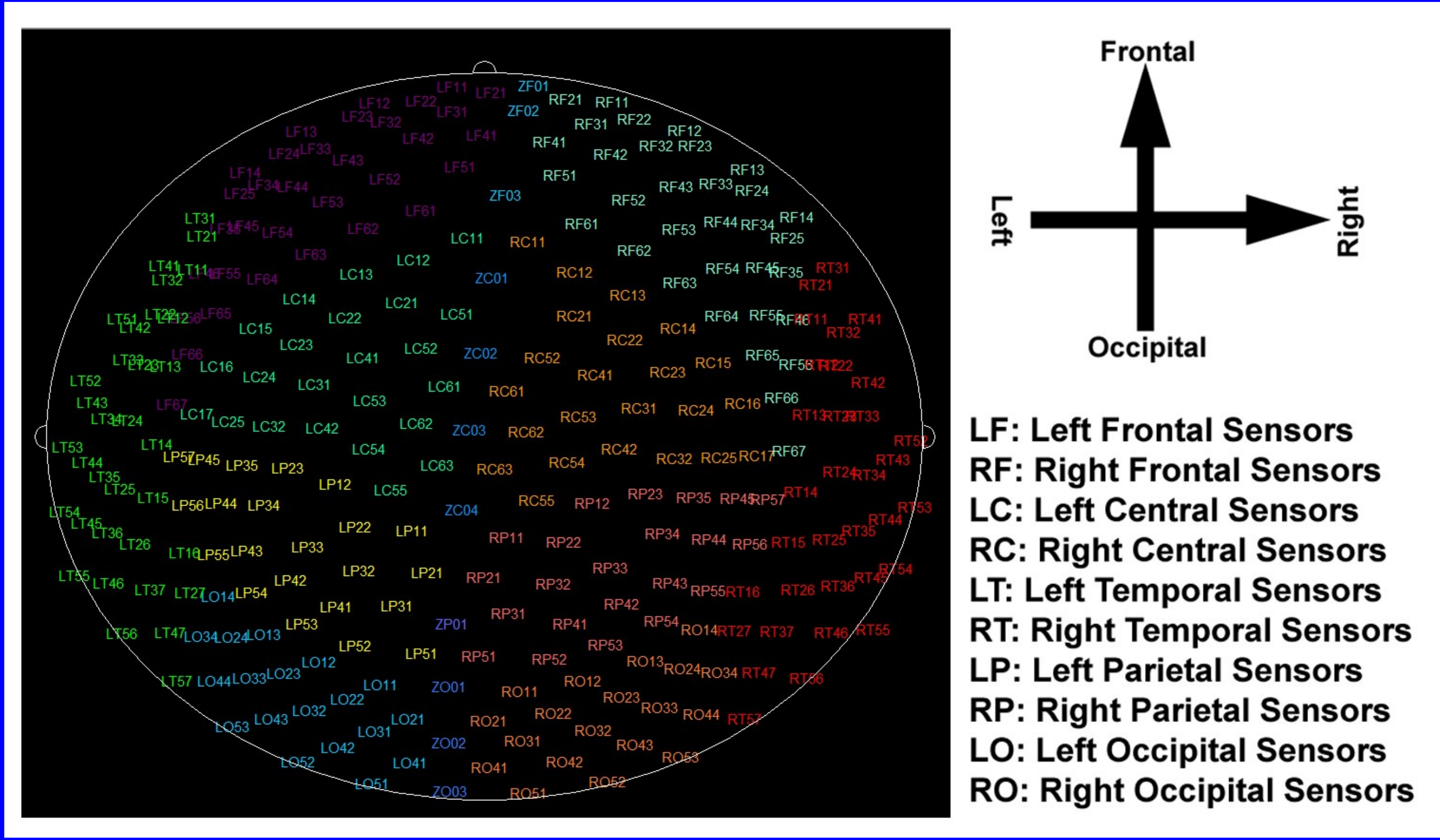
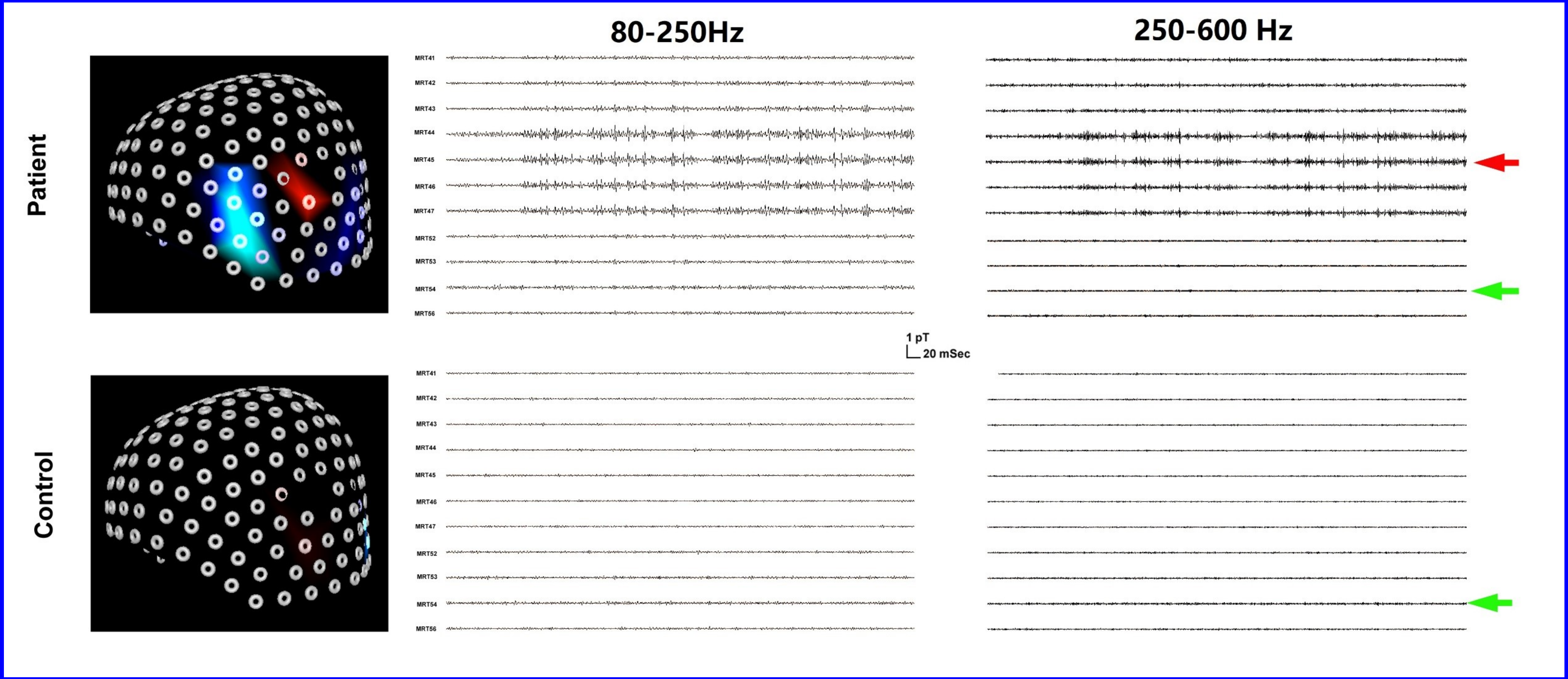
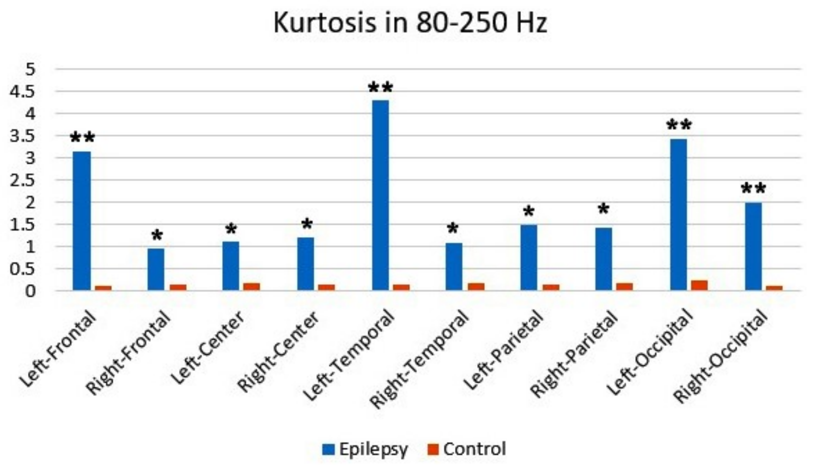
Kurtosis/Skewness at Sensor Levels

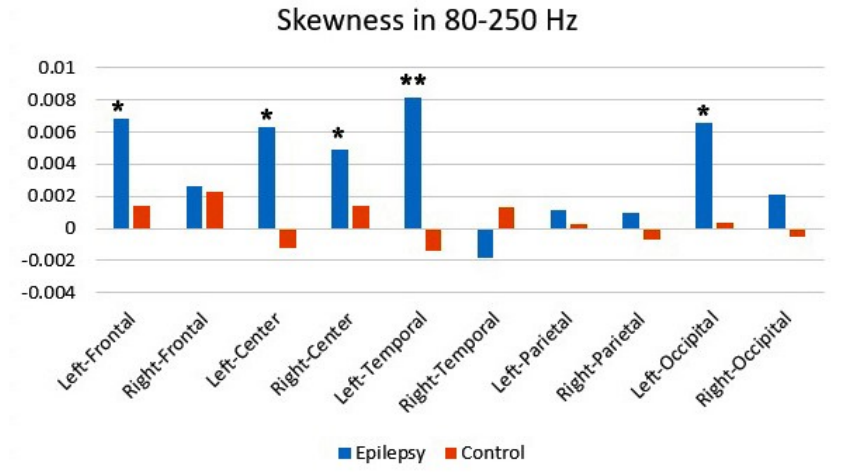


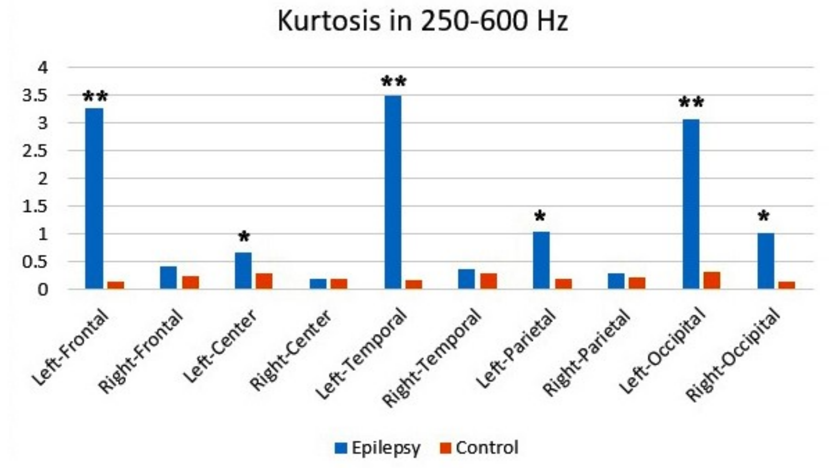
HFOs (Ripples and Fast Ripples)

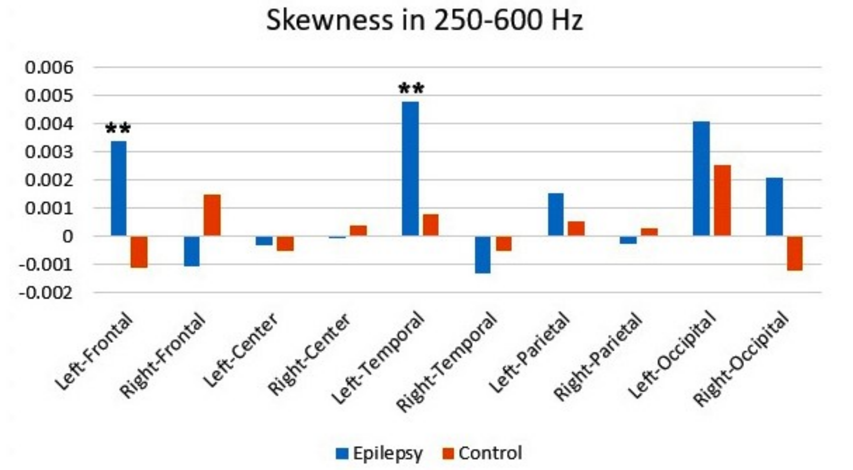


Measurements of Kurtosis

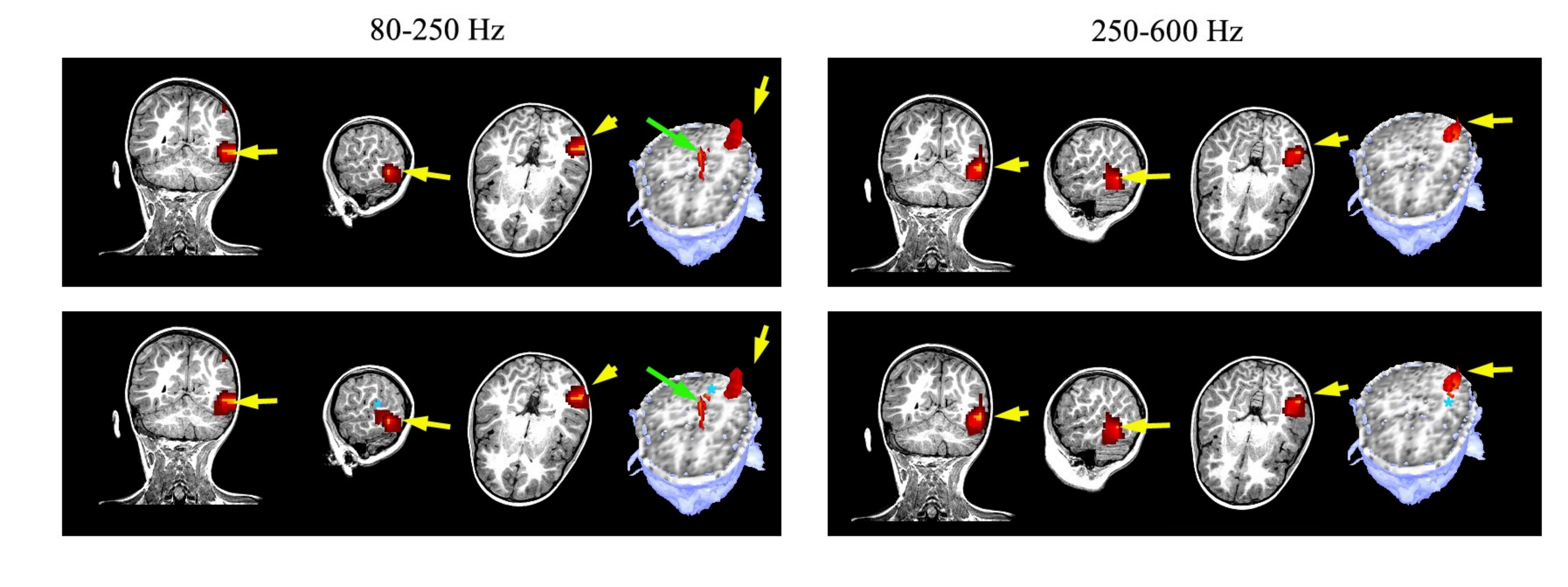








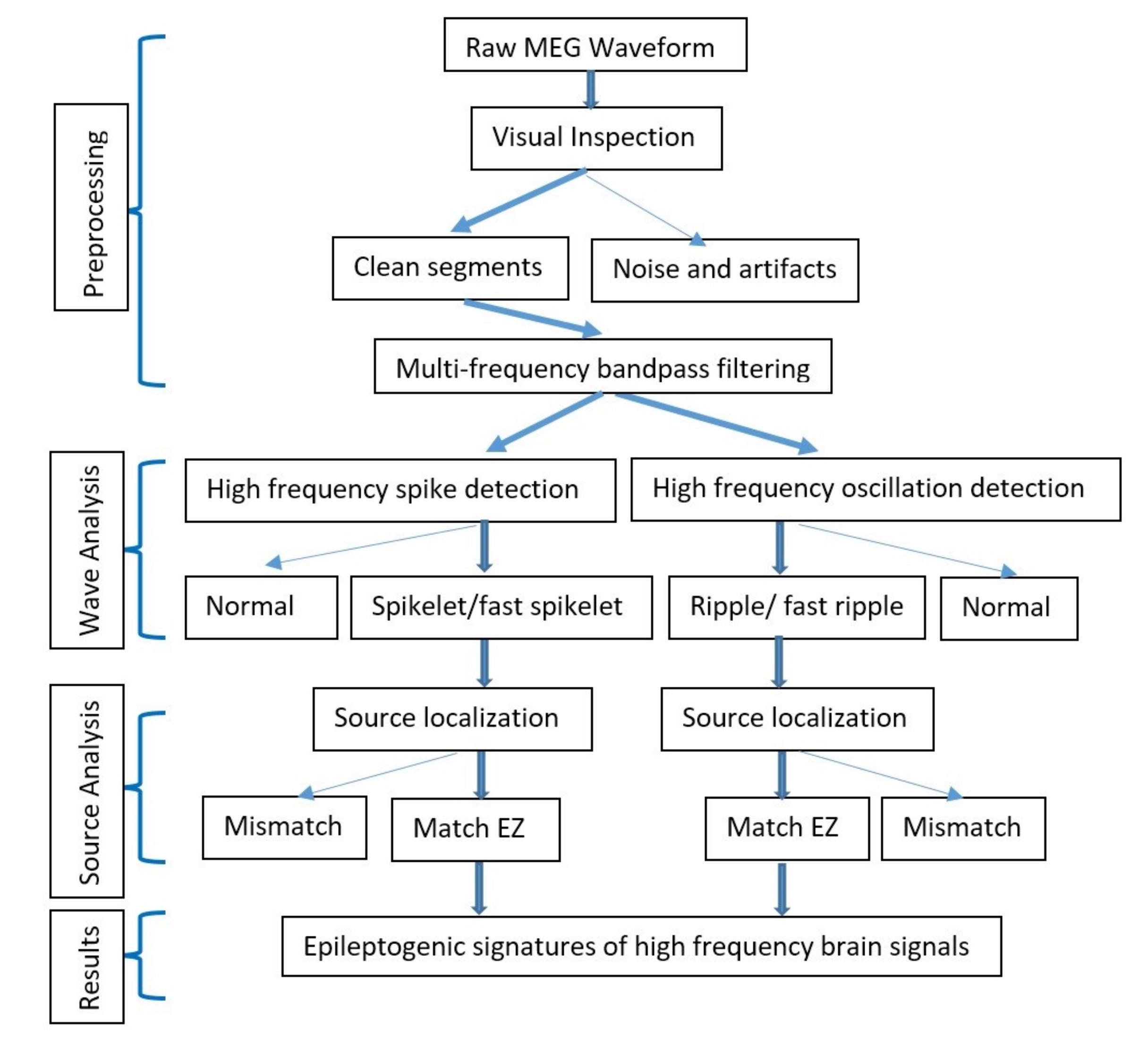
Kurtosis/Skewness Source Imaging



MEG HFBS and Kurtosis/Skewness

- ❑ Epileptic HFBS have significantly elevated kurtosis and skewness.
- ❑ Kurtosis and skewness based source imaging can localize EZs
- ❑ Kurtosis and skewness of HFBS provide quantitative indication of epileptic activity
- ❑ MEG HFBS kurtosis/skewness is novel approach
  - ❖ Better than visual identification (time-consuming and subjective)
  - ❖ Better than invasive recordings (risky and costly)

Neuromagnetic High Frequency Spikes



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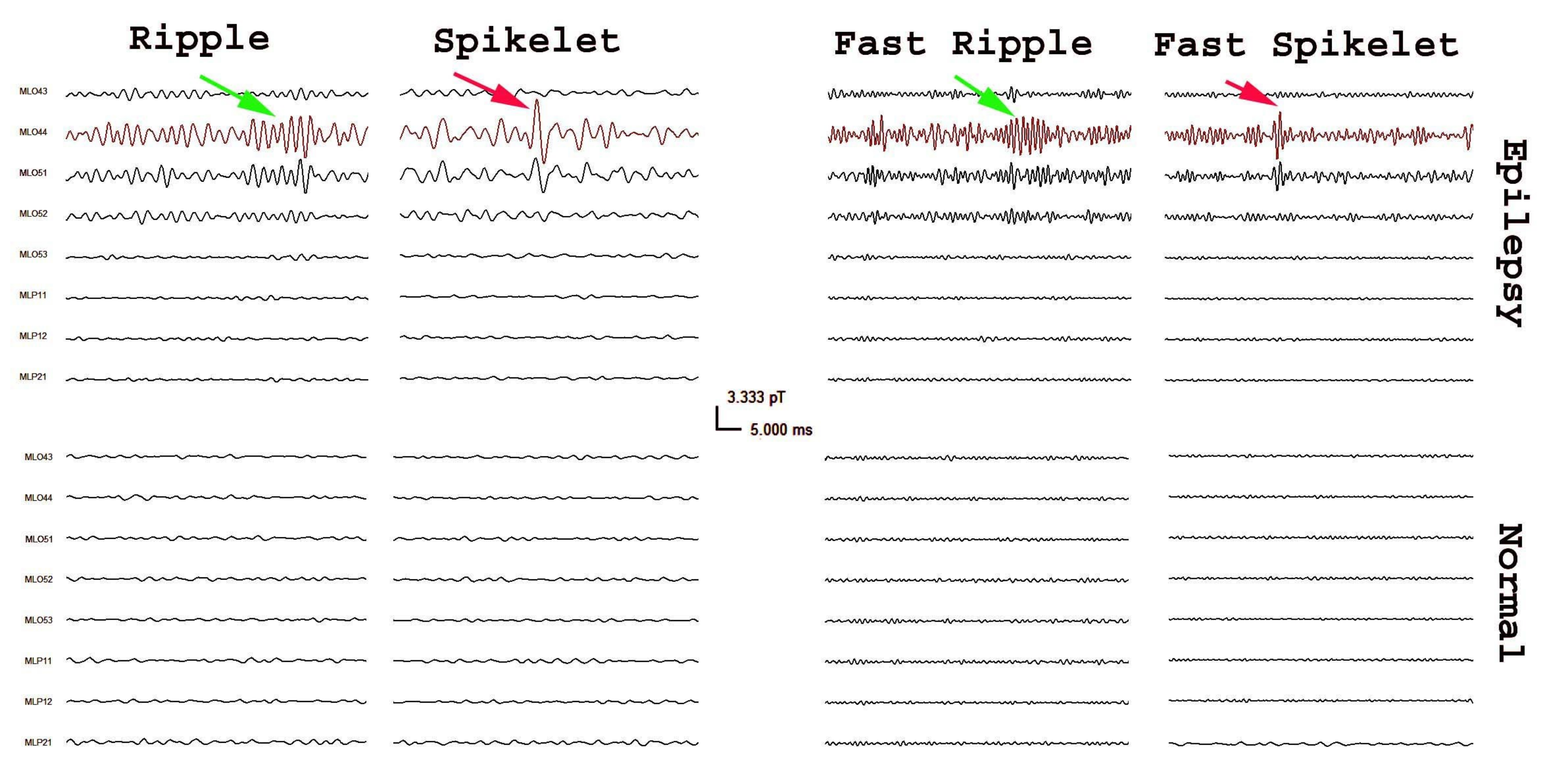
Ripples/Fast Ripples vs. Spike/Fast Spikelets



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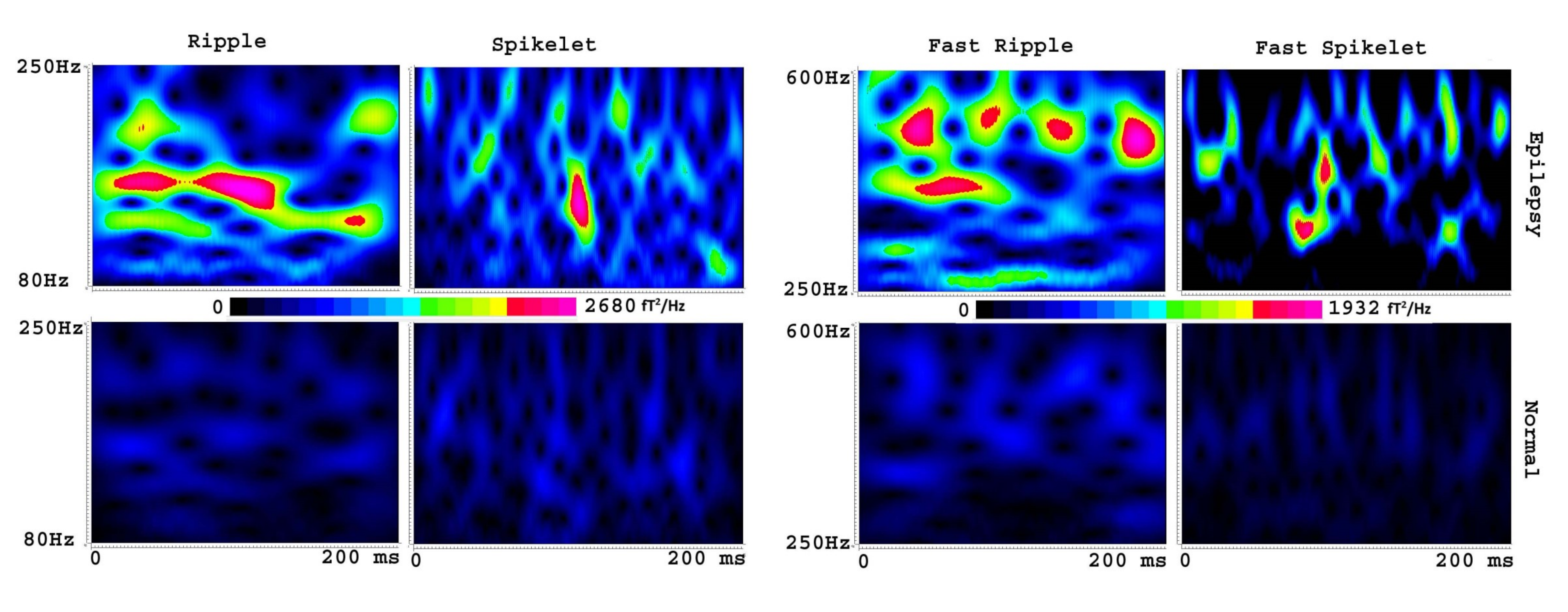
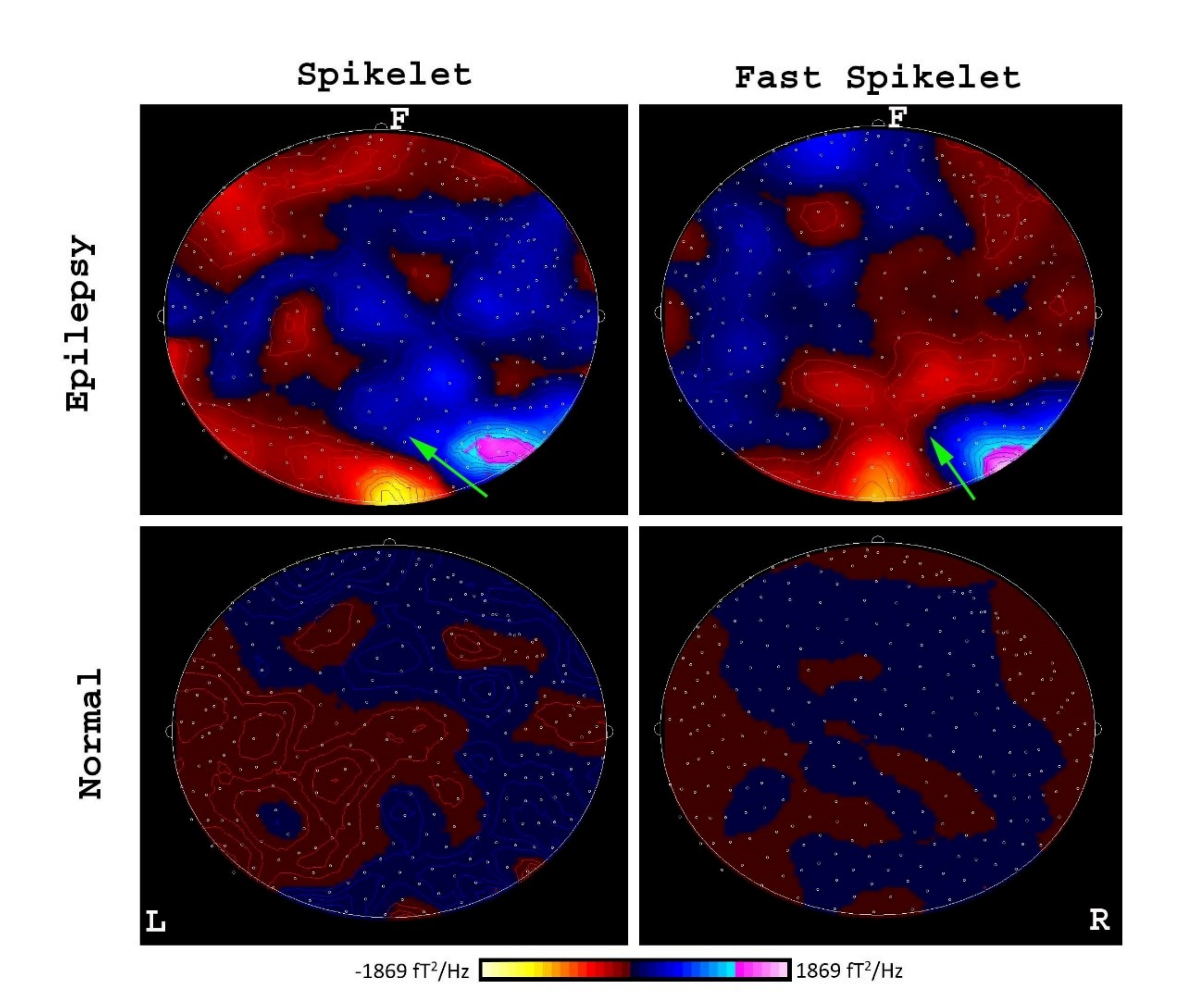
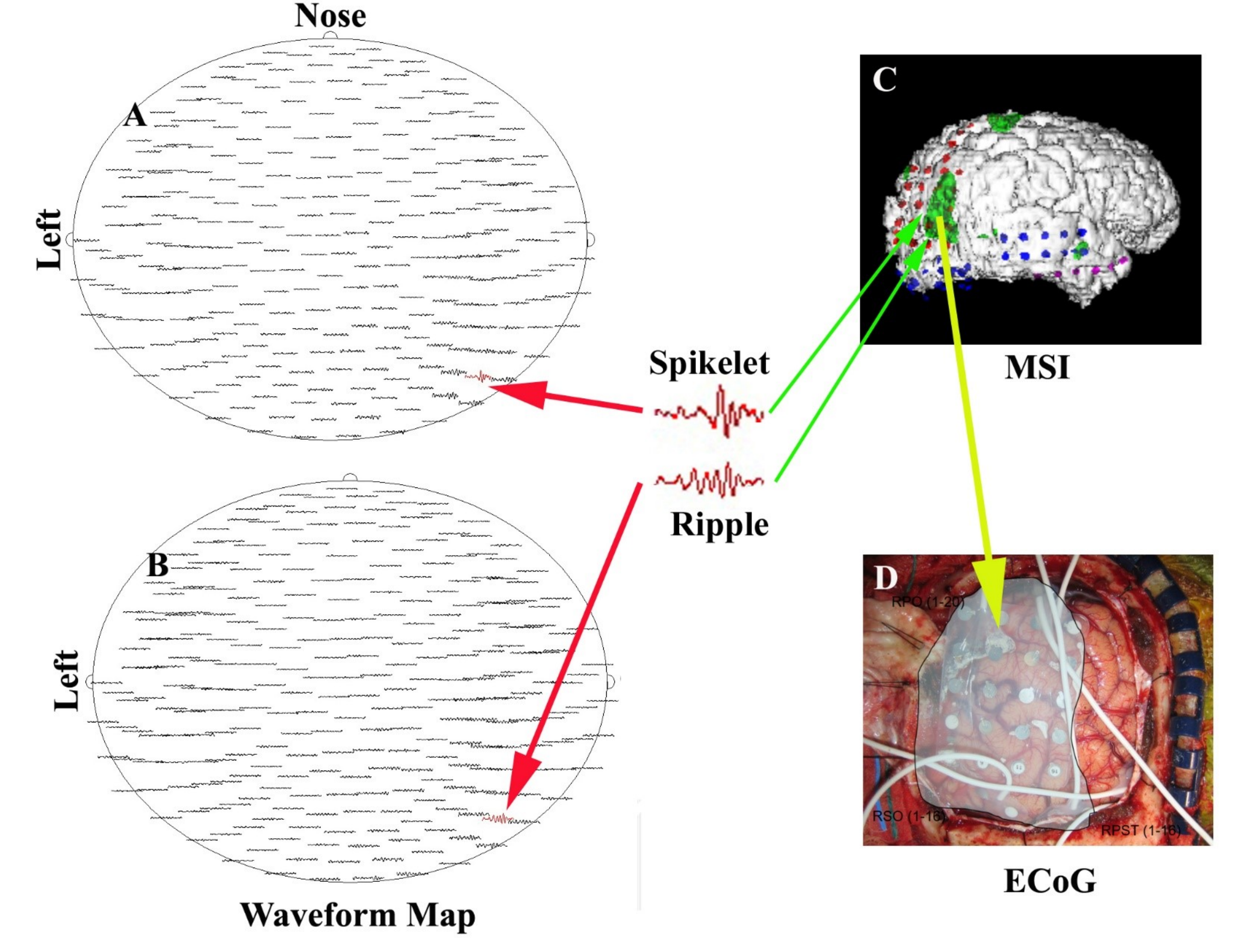
Spectrograms of HFOs and HFSs



Spectral Map of HFSs



MEG HFSs and ECoG HFSs



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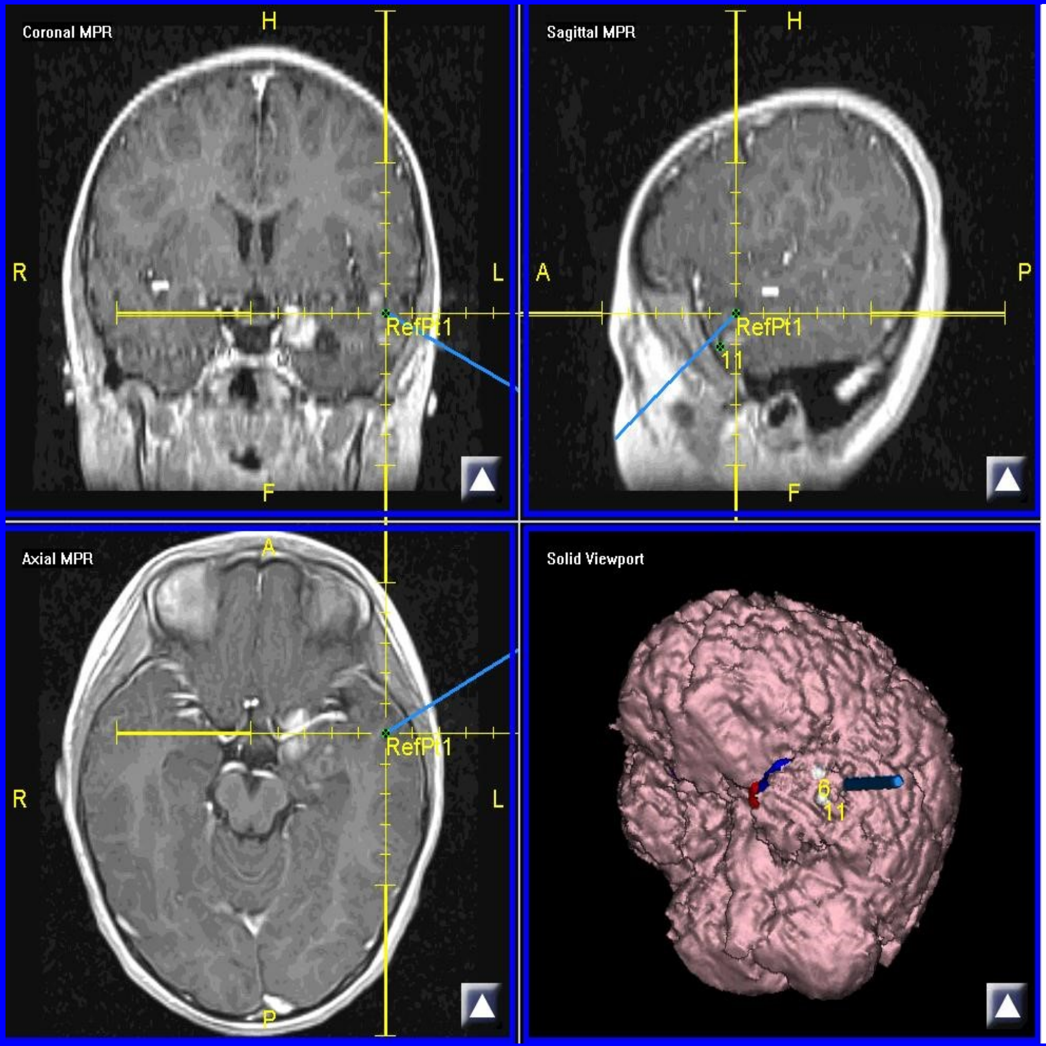
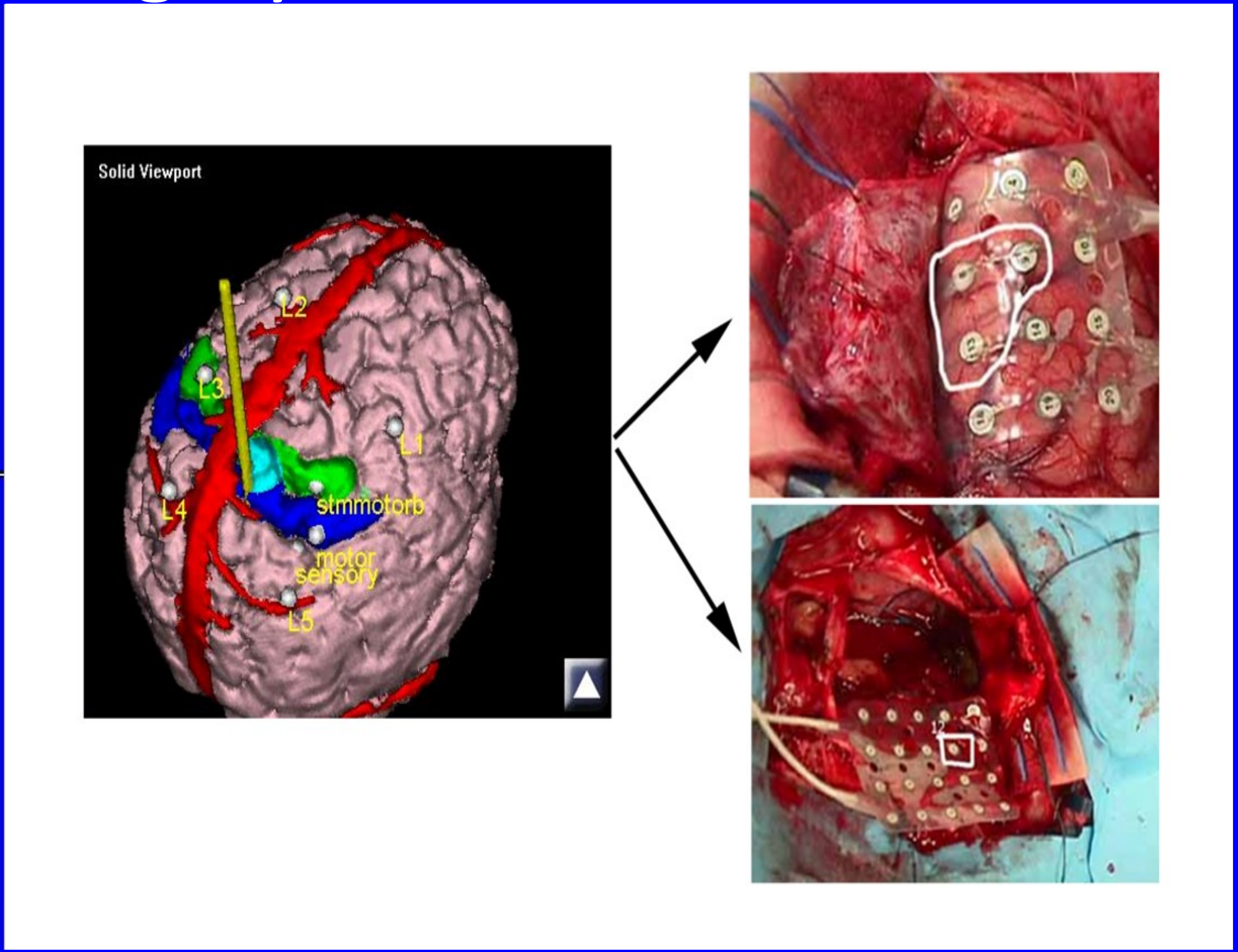
MEG Detection of Epileptic HFSs

- Epileptic brain generates high frequency spikes (HFSs) in 80-600 Hz
- HFSs include spikelets (80-250 Hz) and fast spikelets (250-600 Hz)
- HFSs are a new epileptogenic biomarker for localizing epileptogenic zones
- HFSs can be noninvasively detected by MEG

Magnetic Source Imaging Guided Surgery





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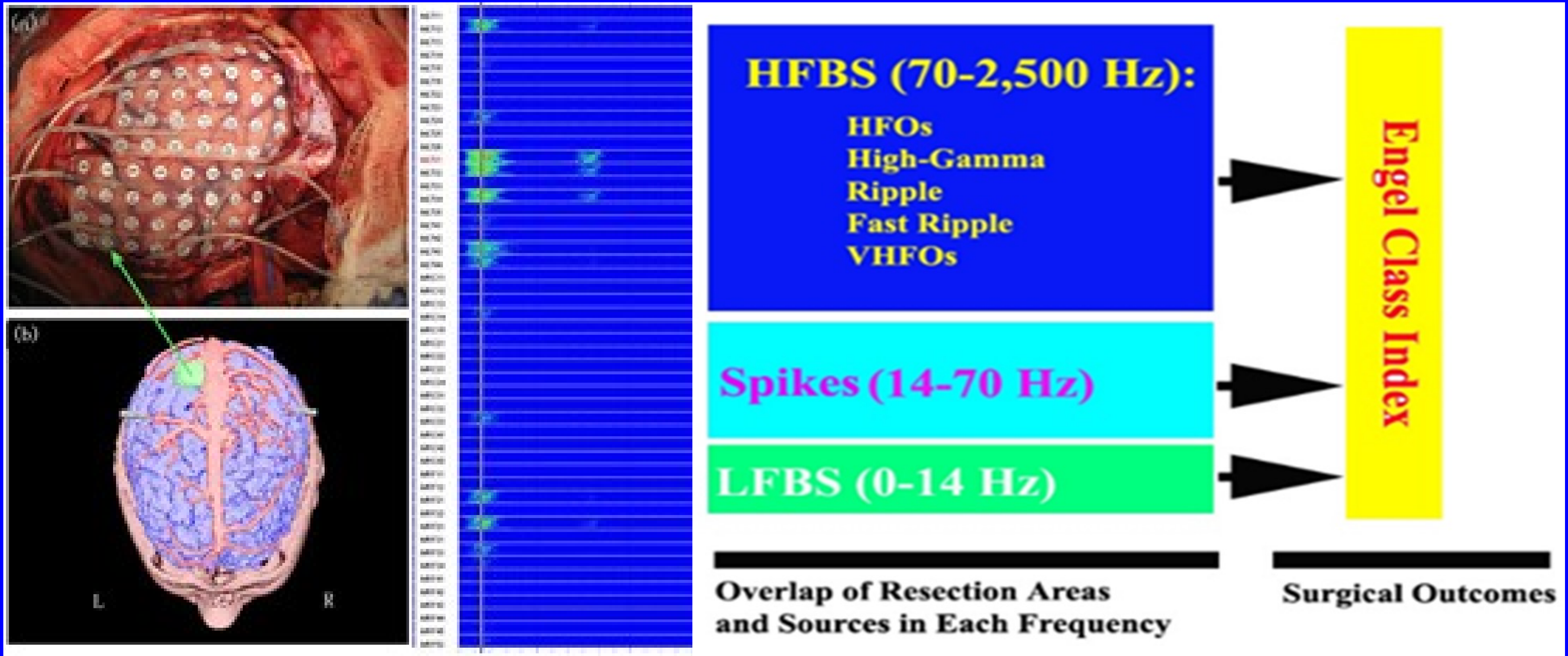
Resection Brain Areas Generating HFBS Predicts Favorable Outcomes



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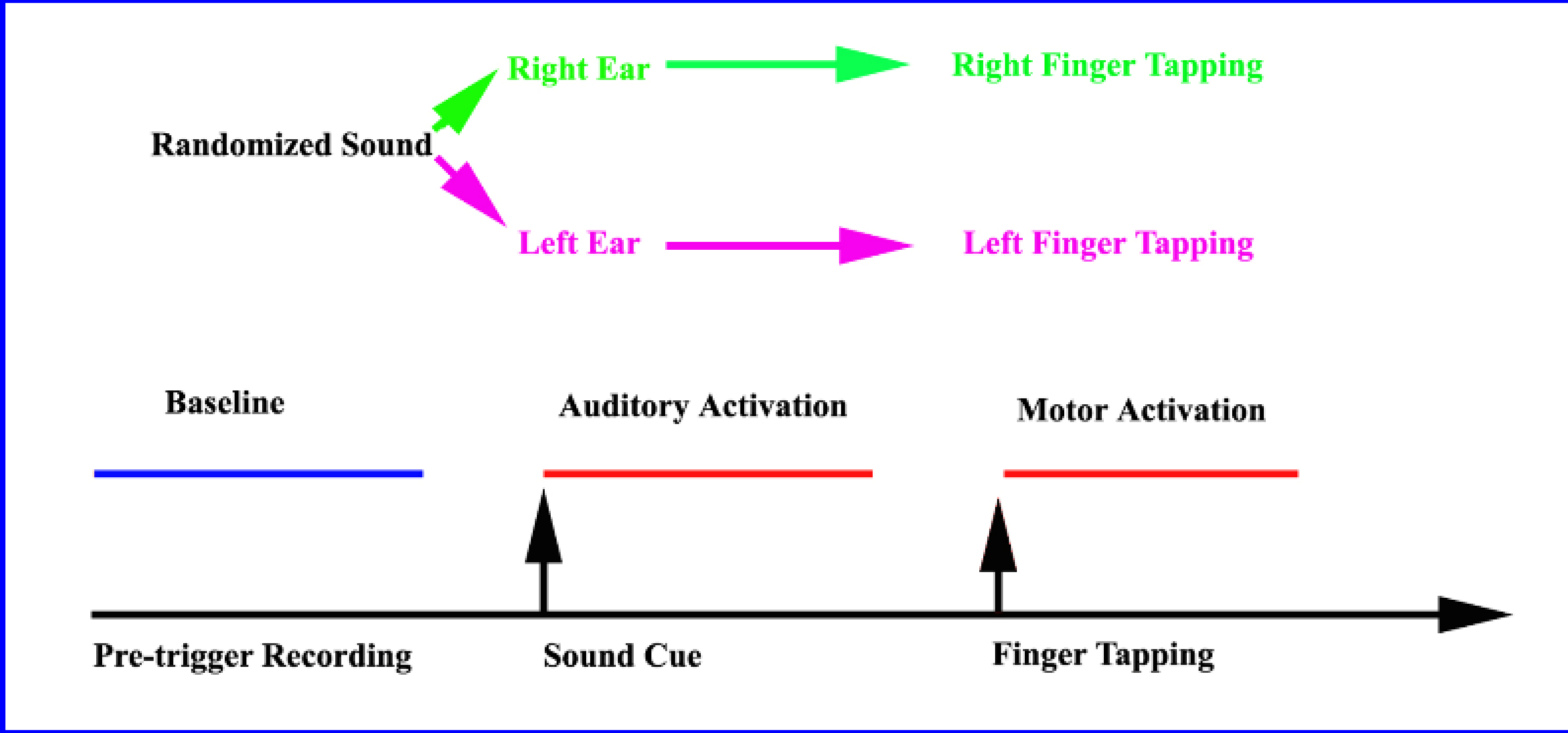
Content

- High Frequency Brain Signals (HFBS)
- Hardware development for detecting HFBS
- Software development for analyzing HFBS
- Clinical Applications of HFBS
  - Epilepsy
  - Migraine
  - Functional mapping and others
- Discussion

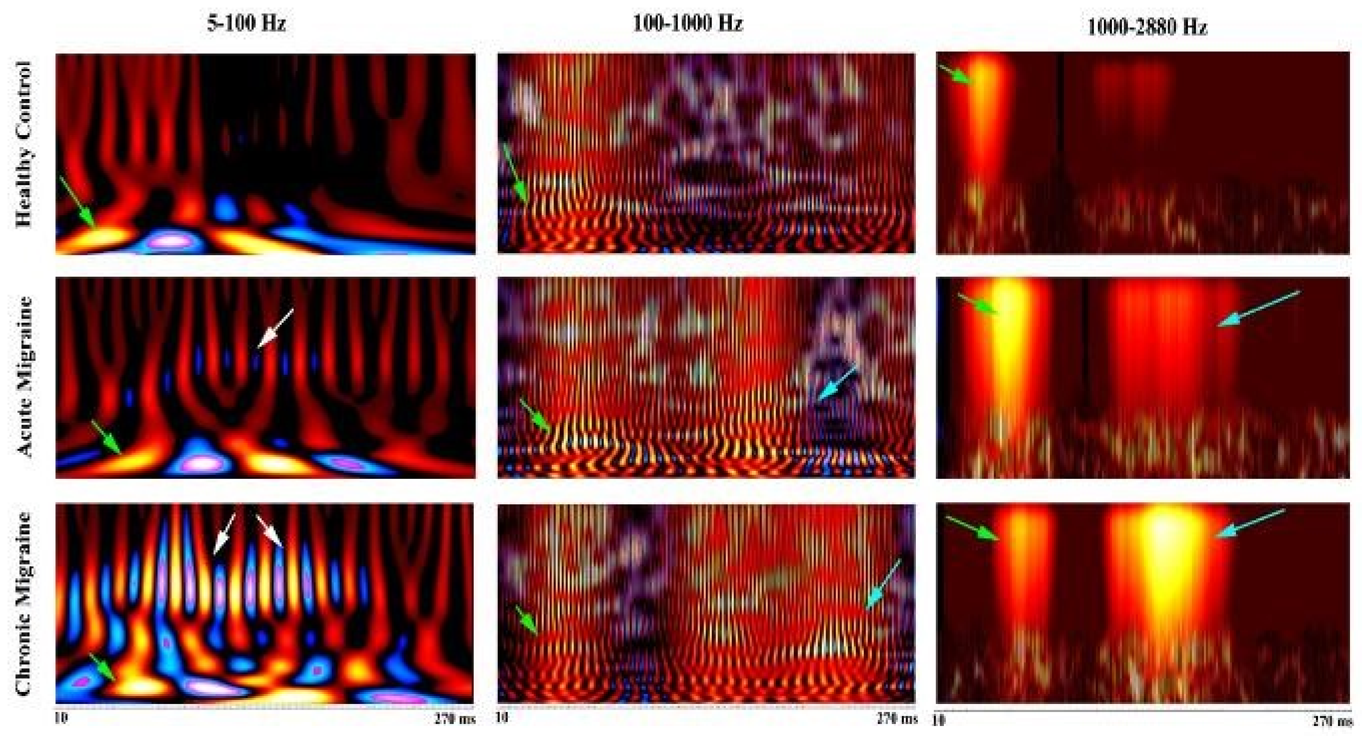
MEG Study of Acute Migraine

(Subjects and Methods)

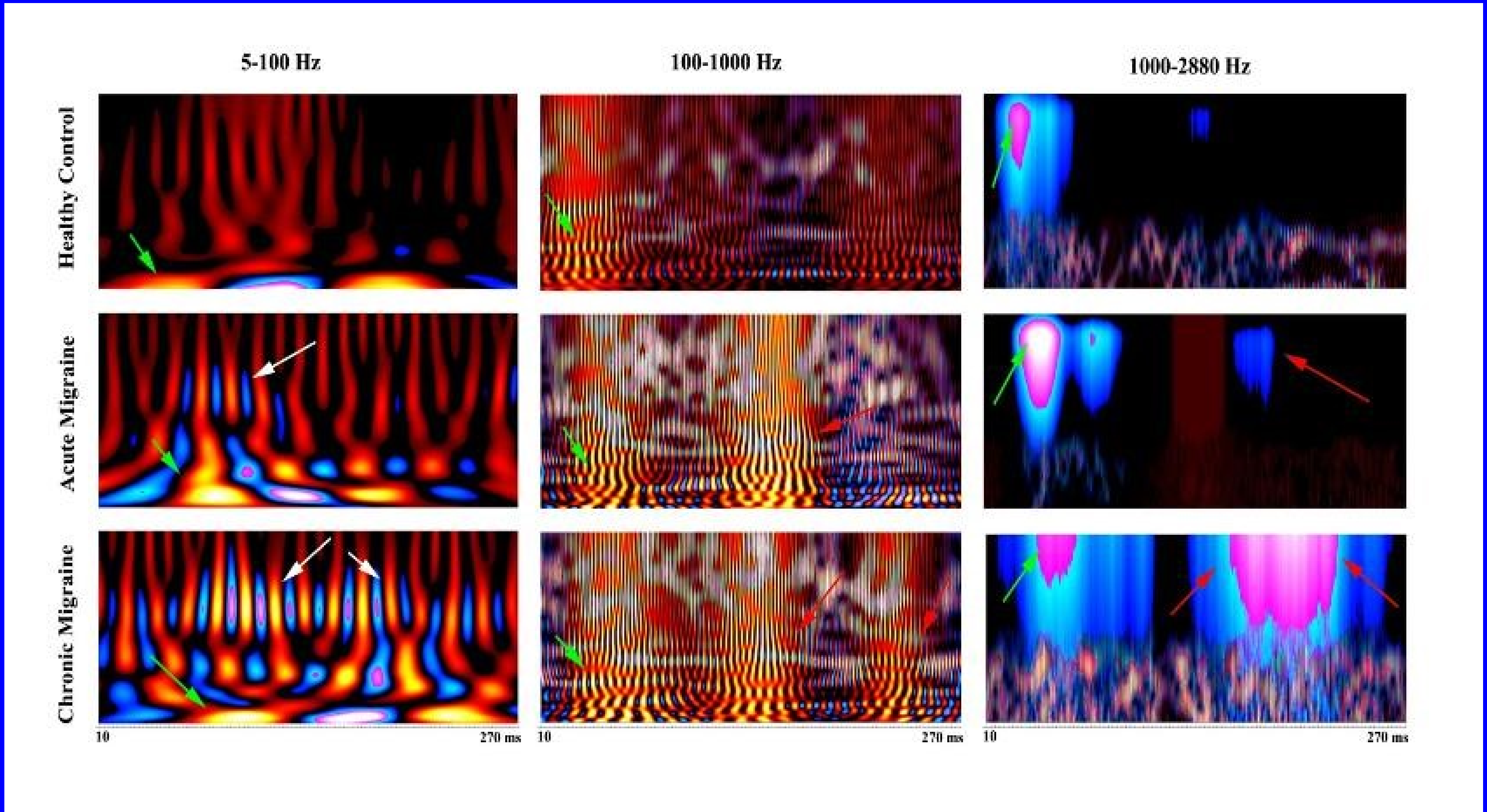
- **Auditory-motor paradigm:** Participants performed a brisk finger tapping task with both the right and the left index finger immediately after hearing a cue.



Average-> Time locked Signals
Accumulation->Elicited Signals



Average-> Time locked Signals
Accumulation->Elicited Signals



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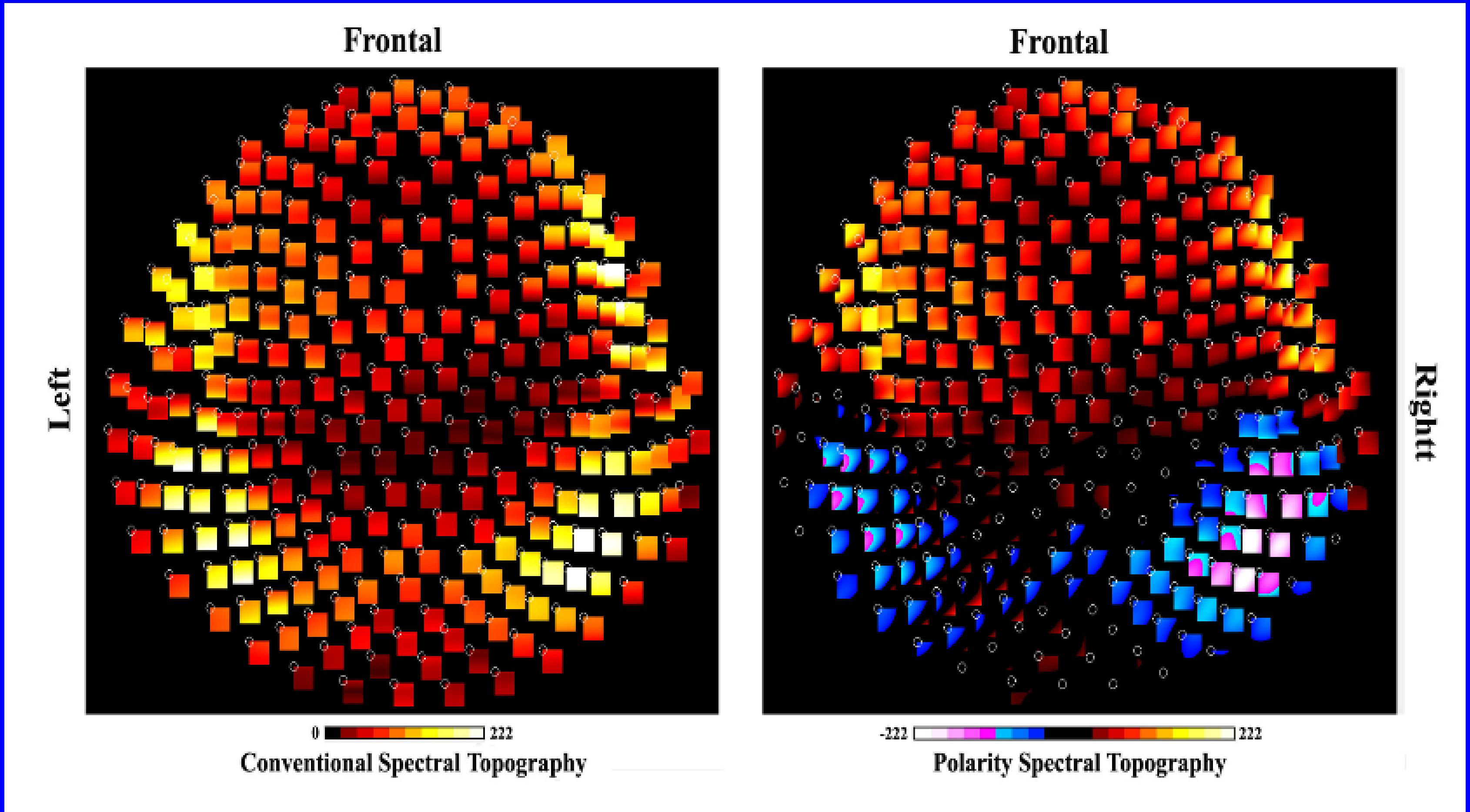
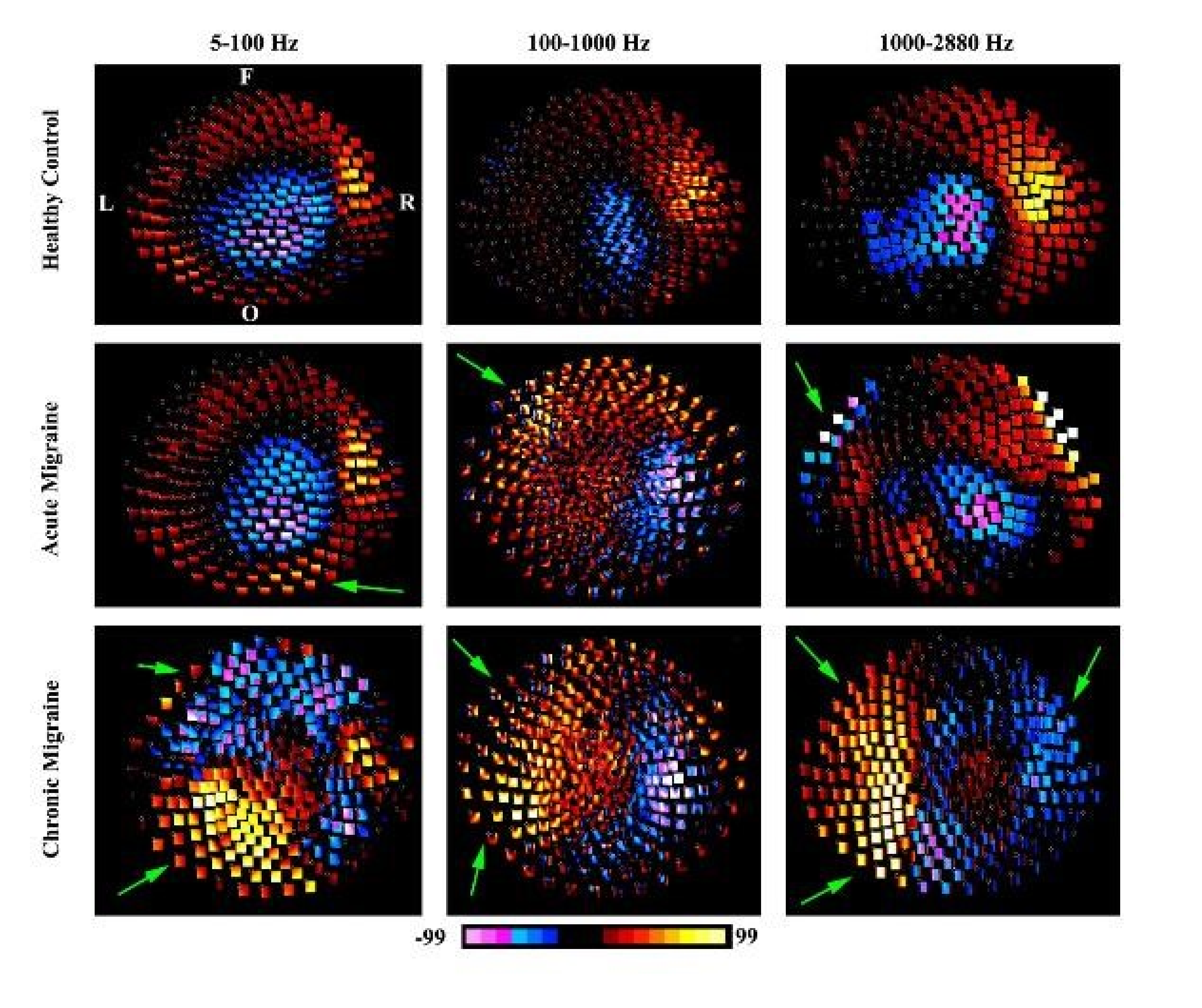
Spectrogram vs. Polarity Spectrogram



HFOs in Migraine



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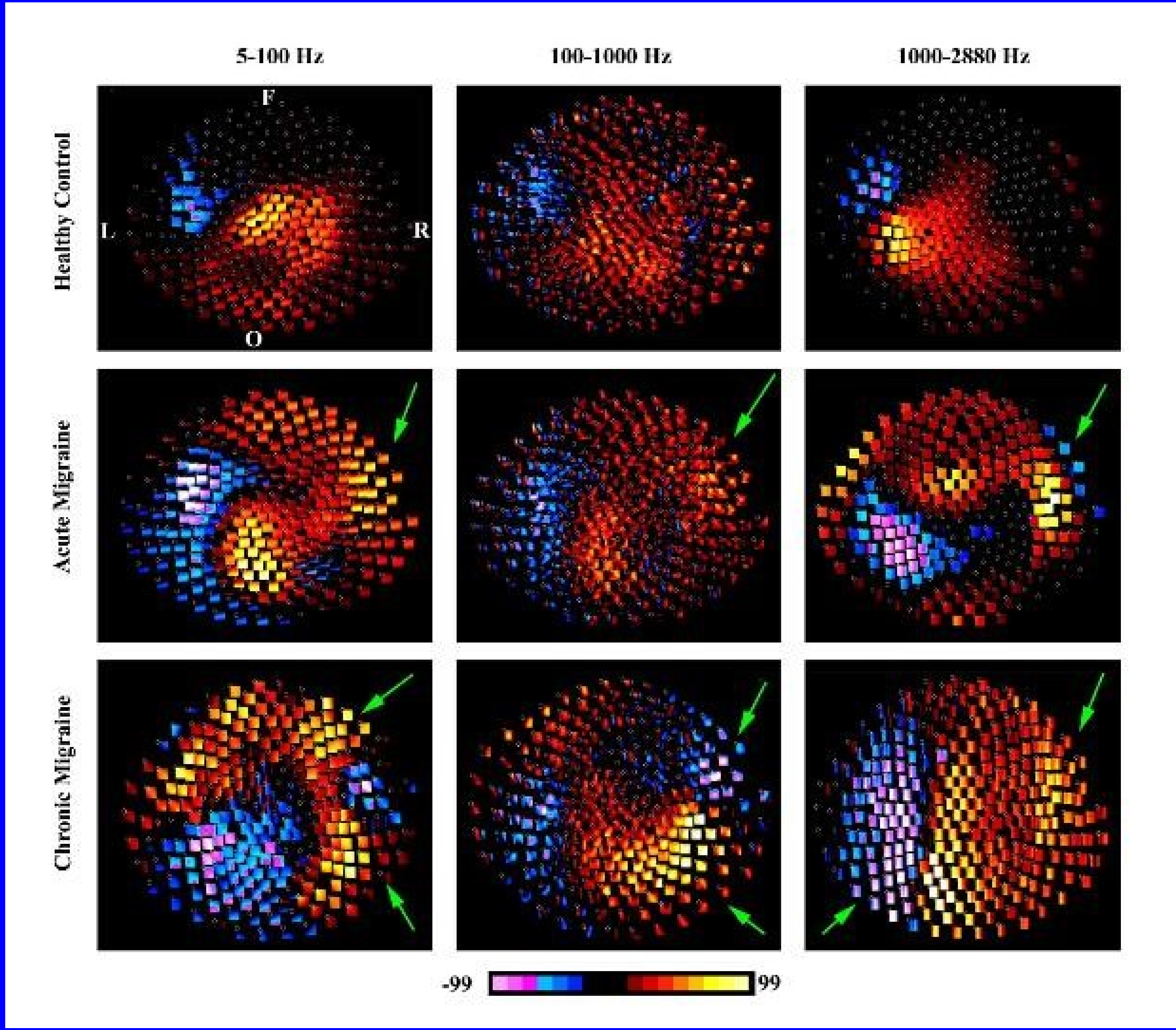
HFOs in Migraine



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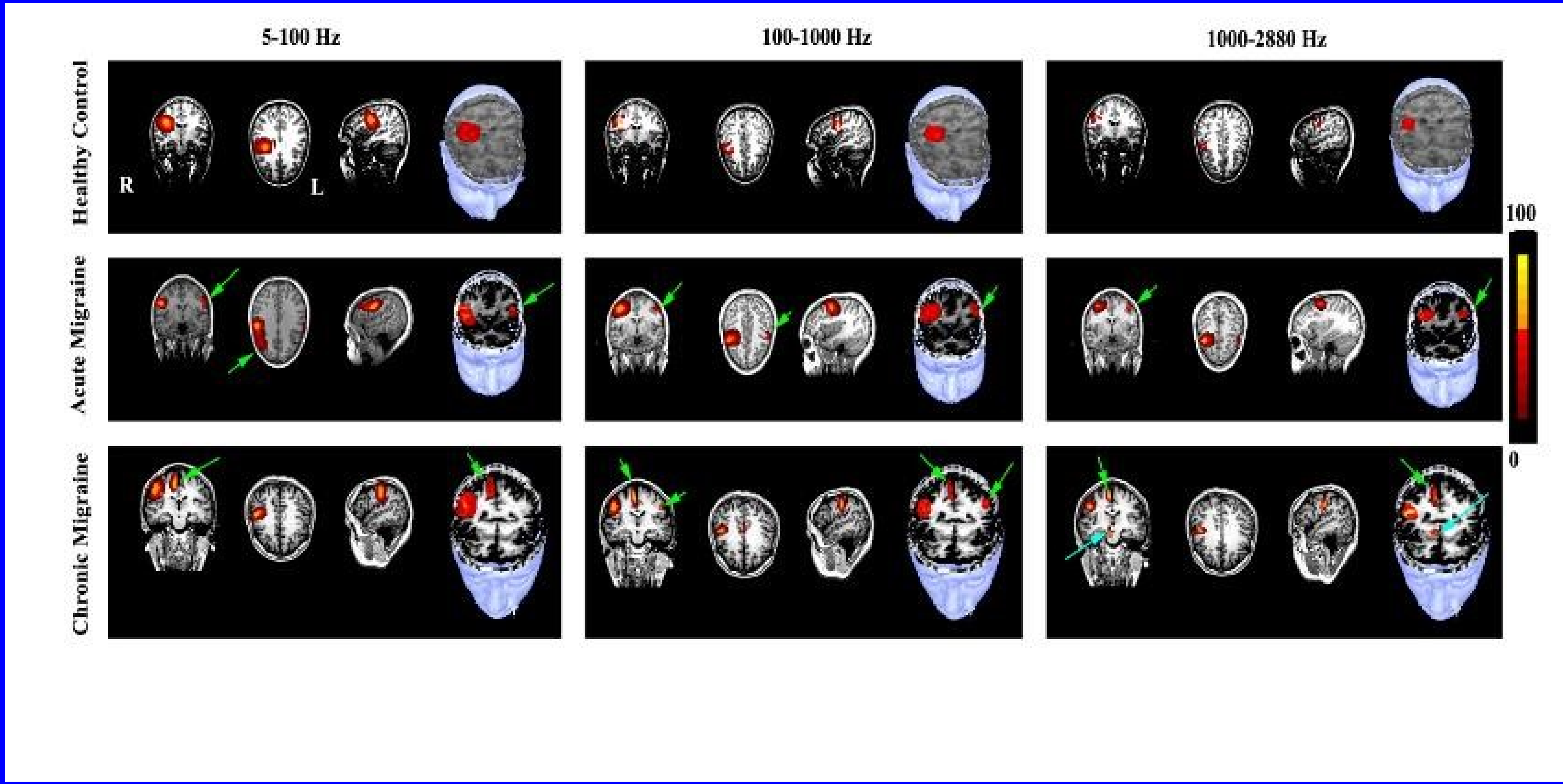
HFOs in Migraine



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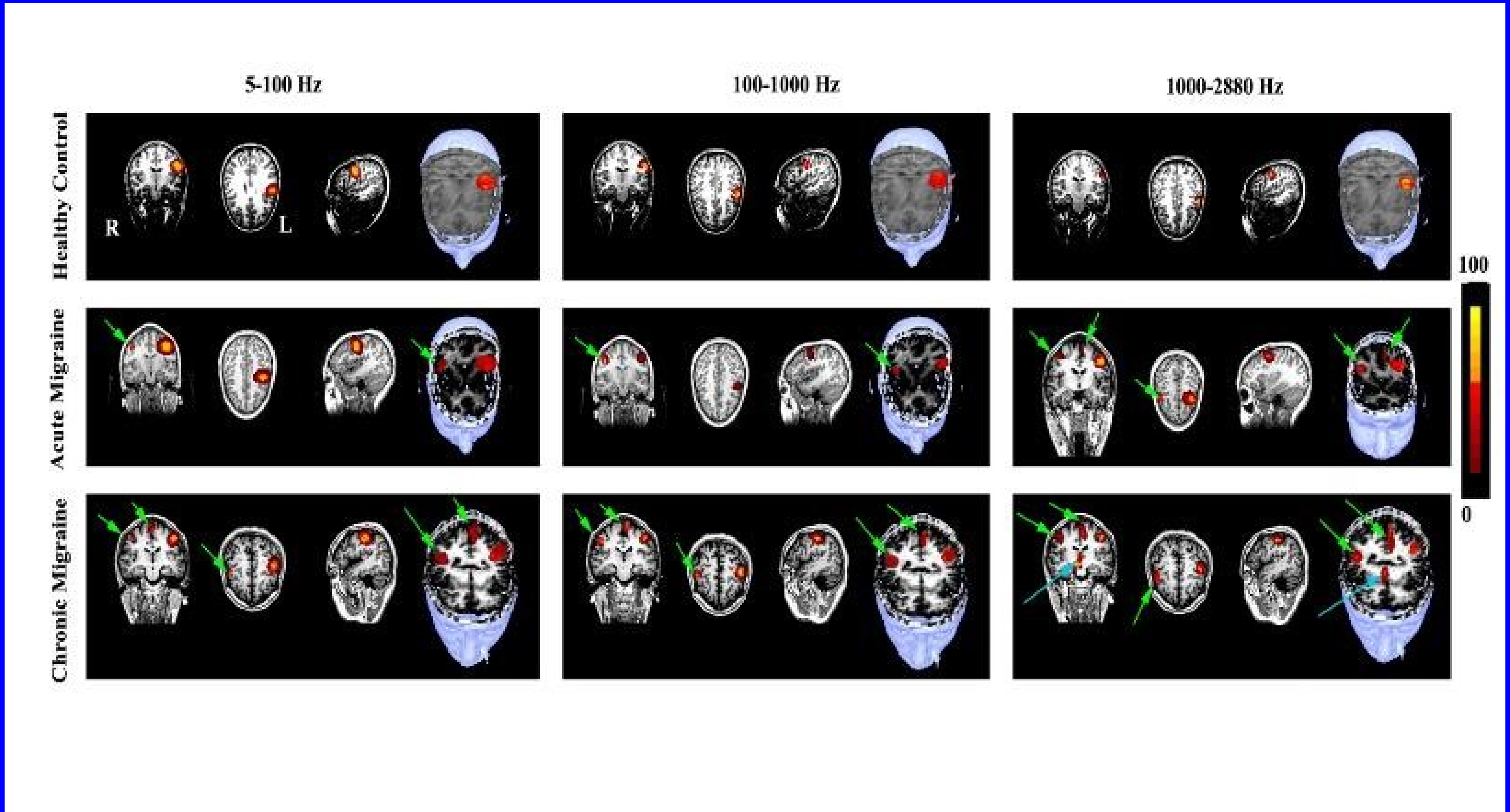
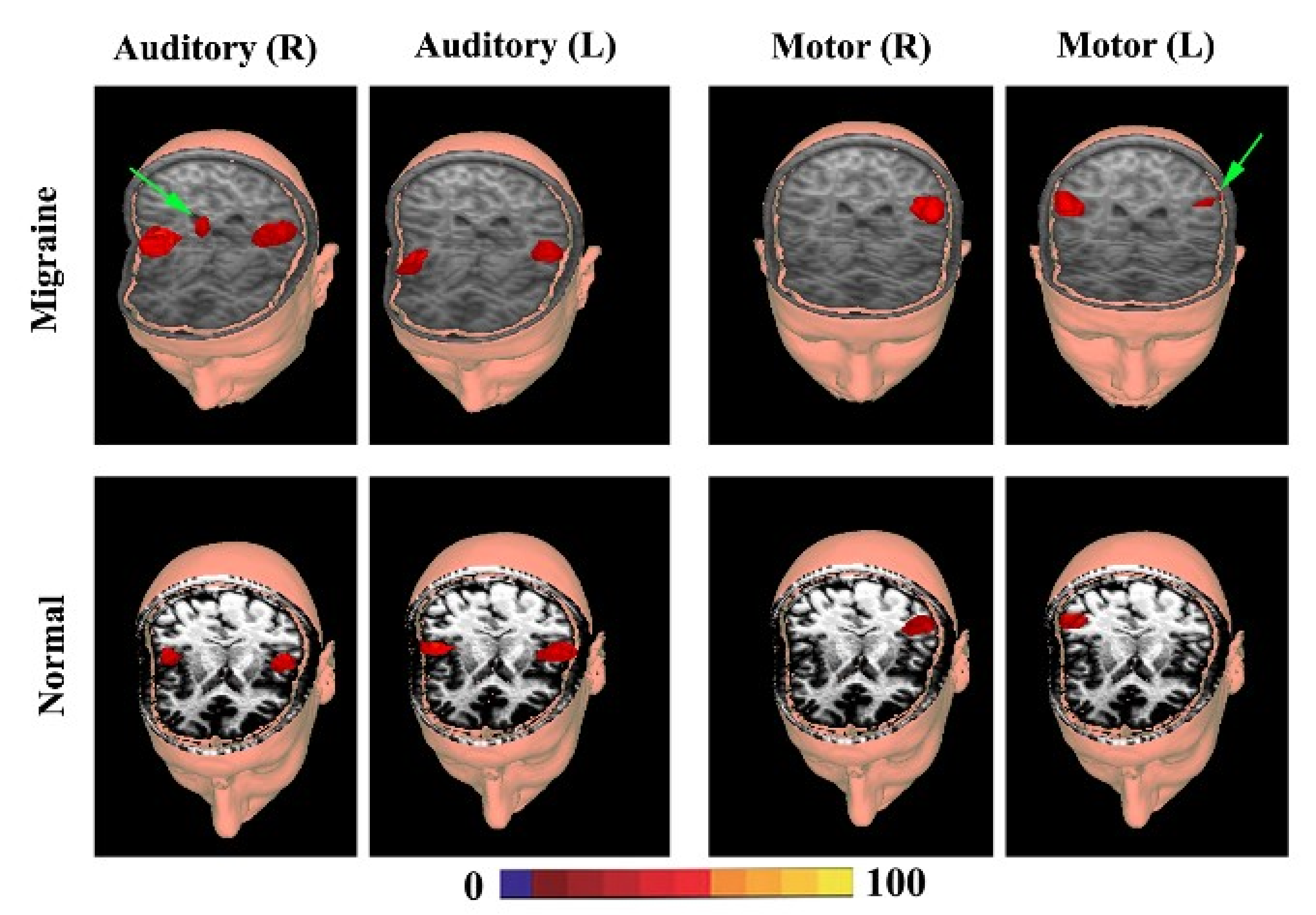
HFOs in Migraine



MEG Study of Acute Migraine

(Results-magnetic sources 100-1000 Hz)



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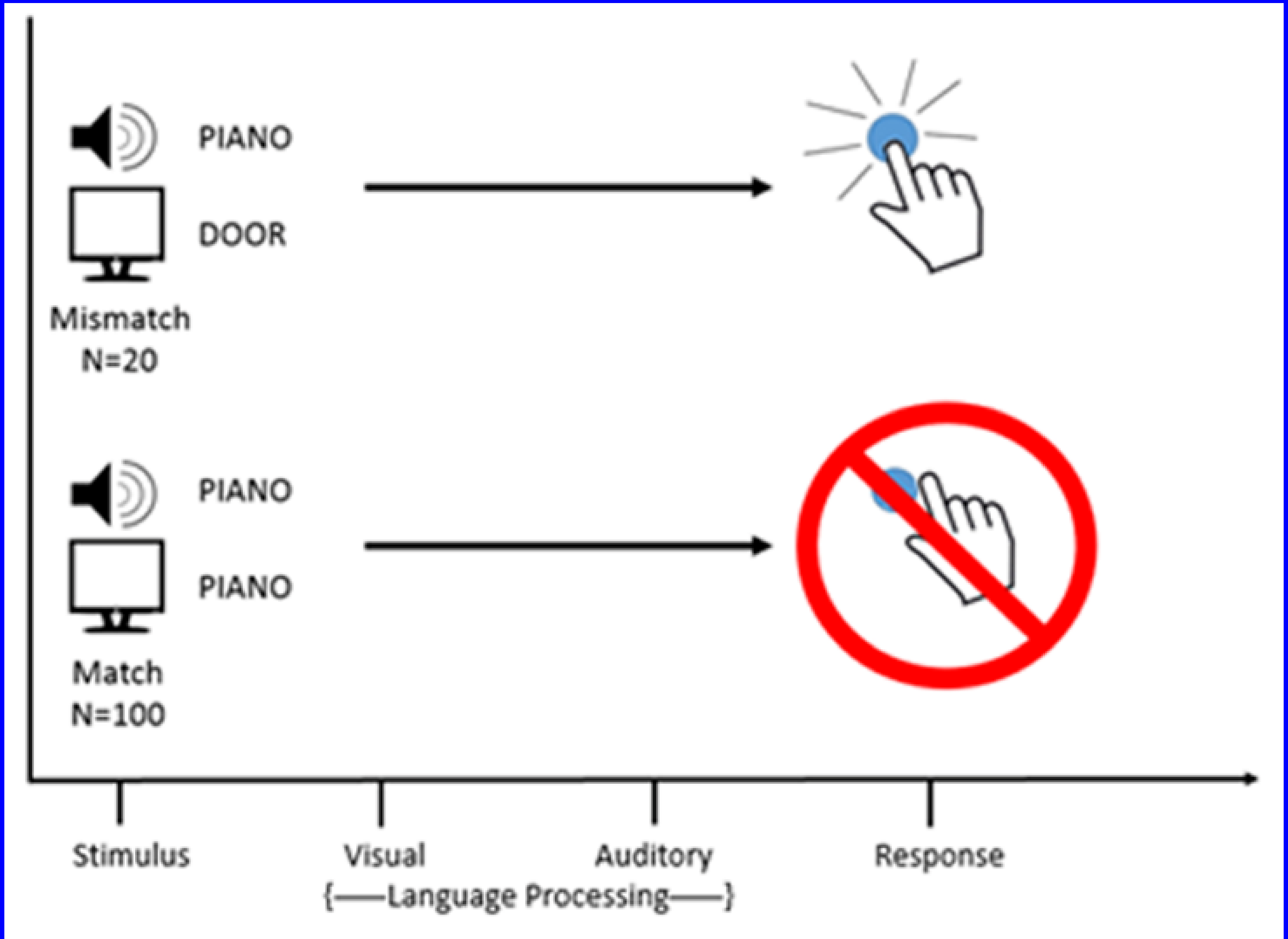
Word Comparison Task



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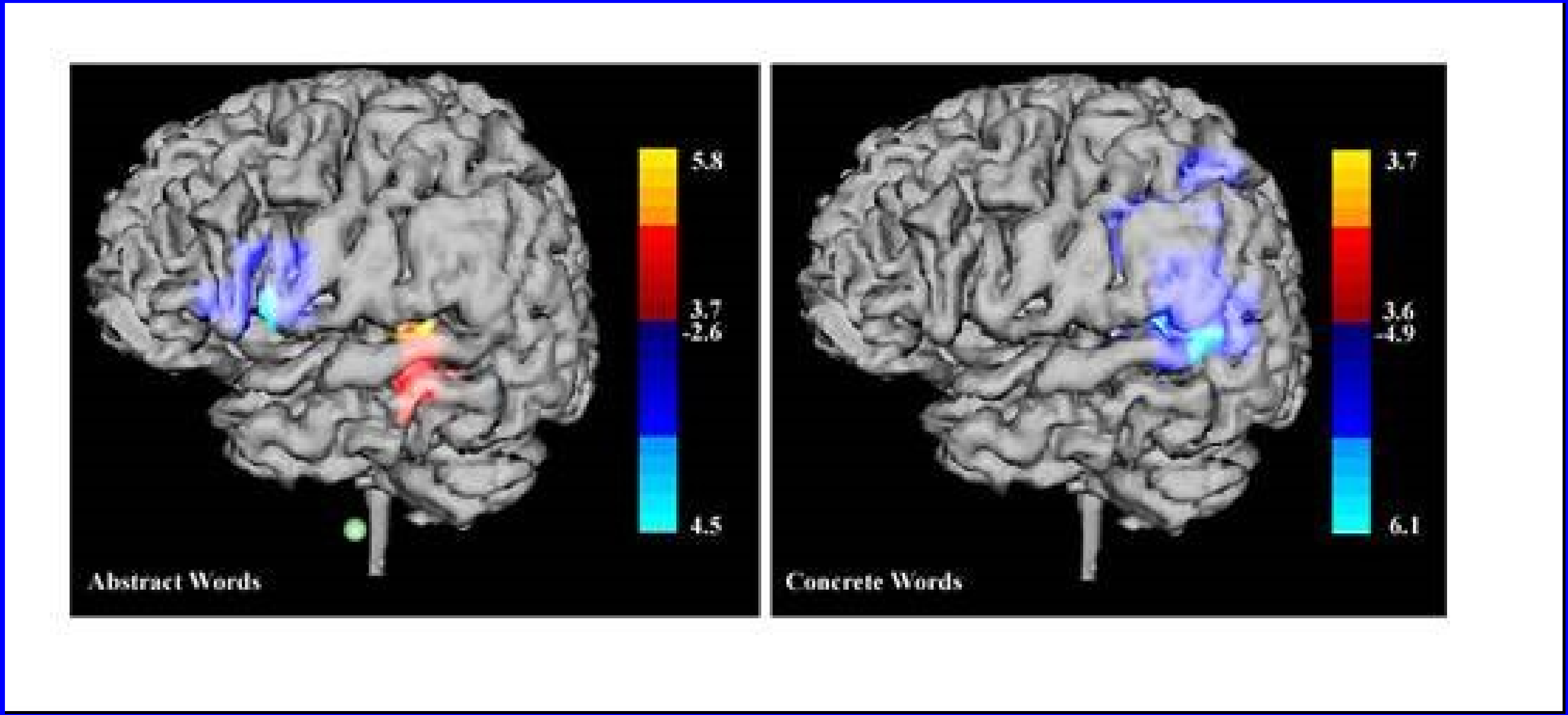
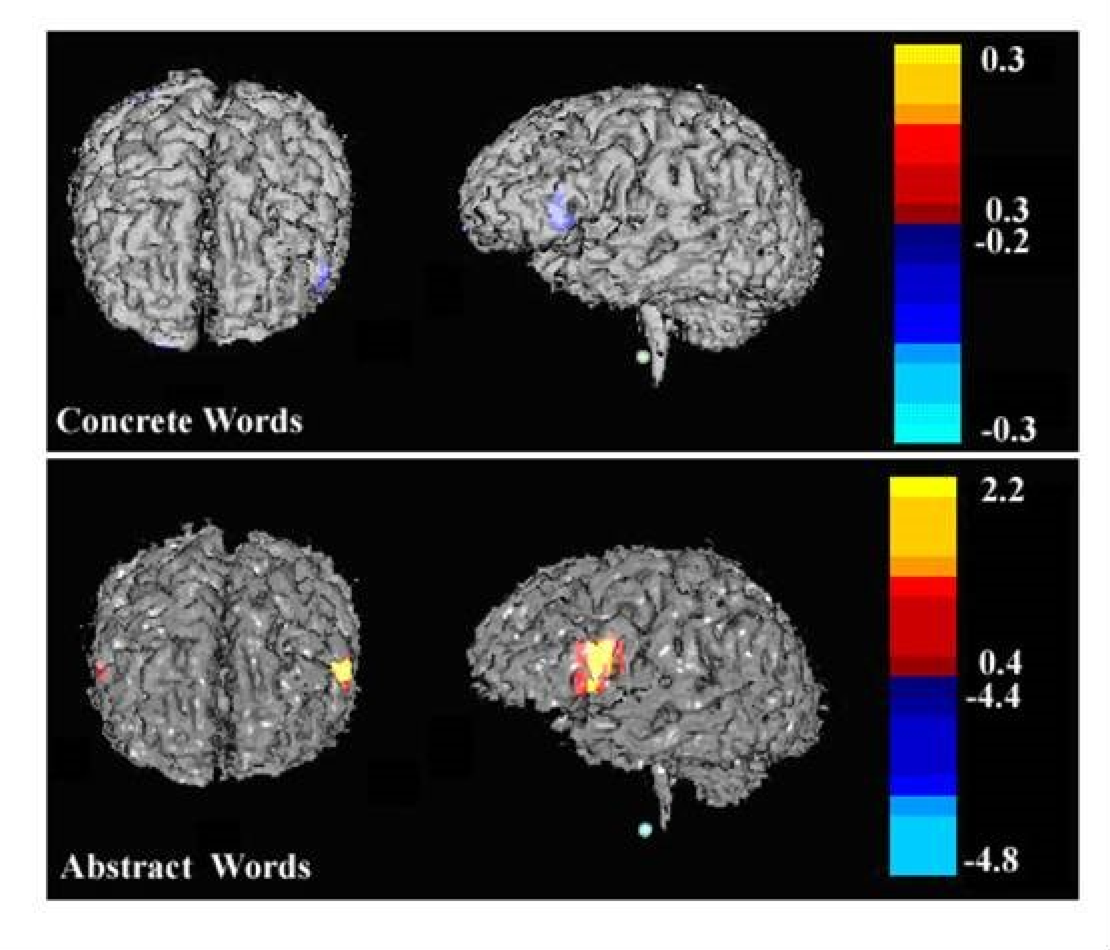
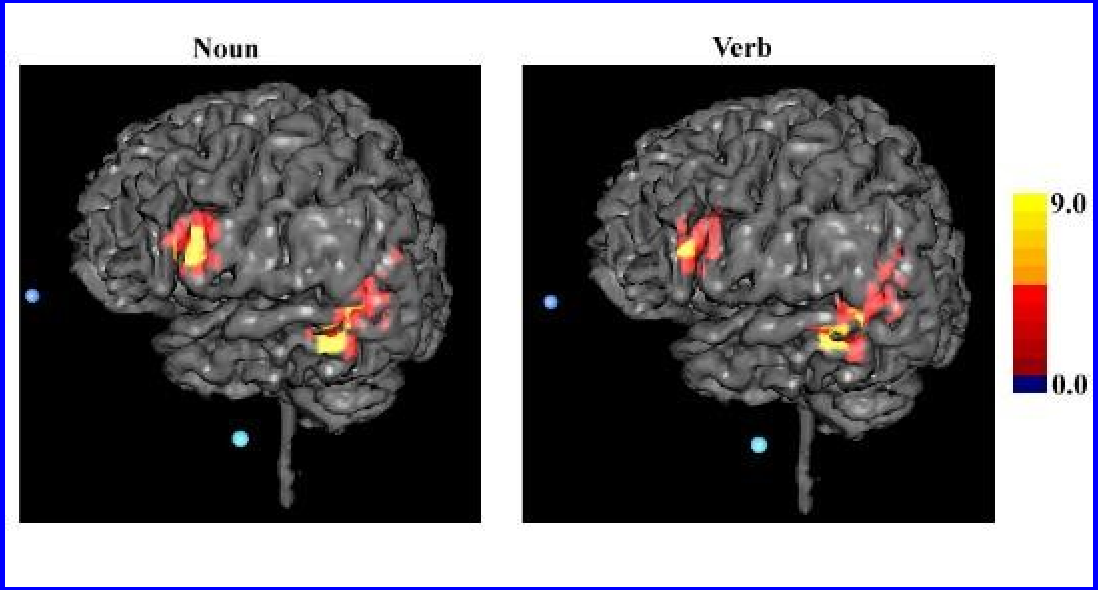
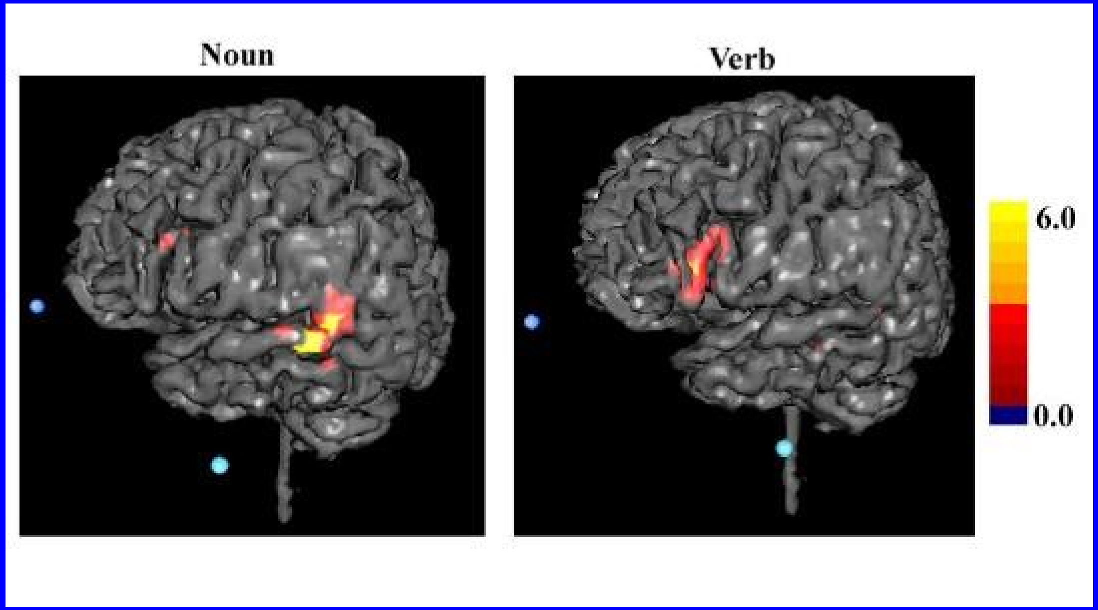
Results



Results







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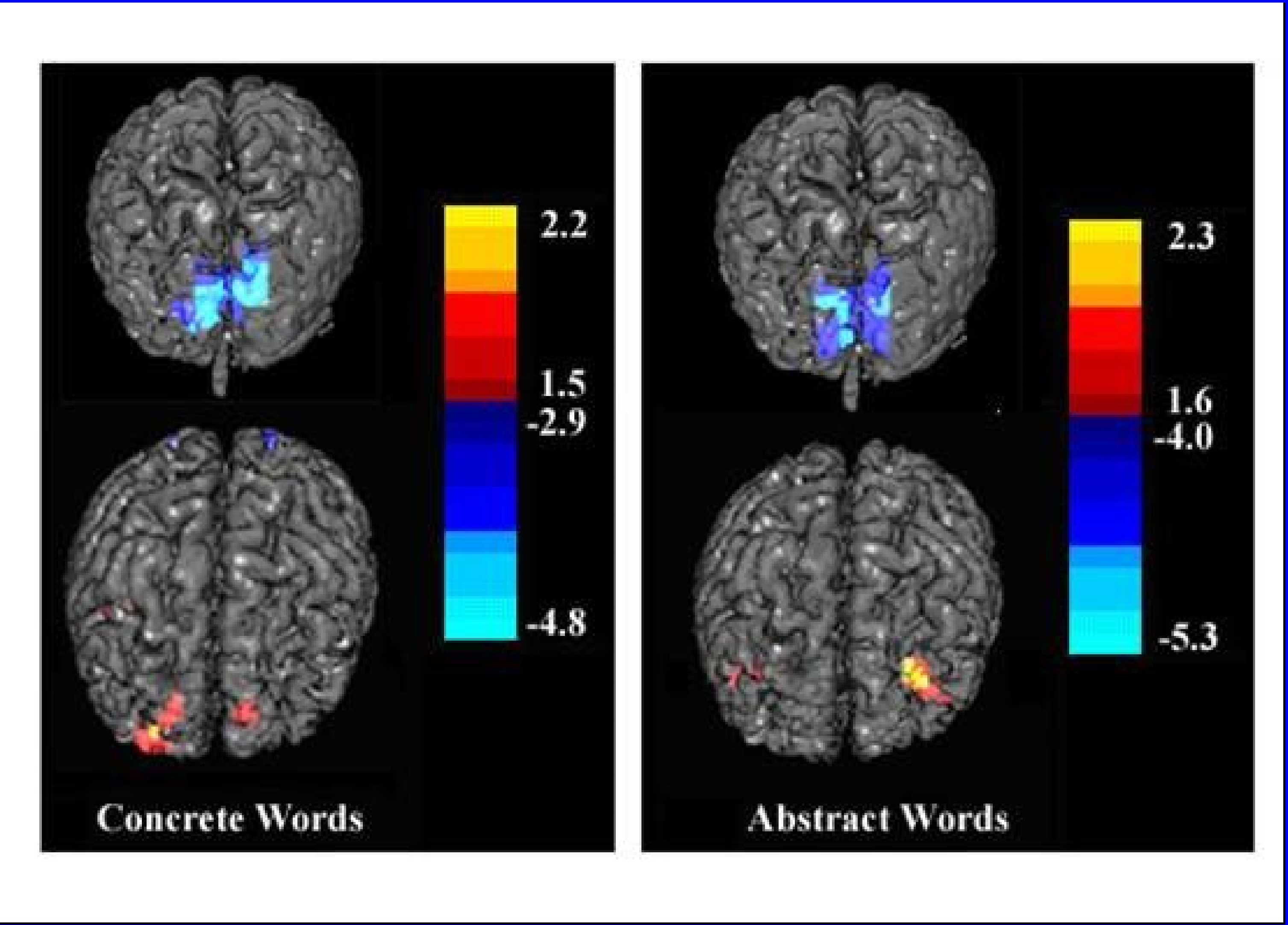
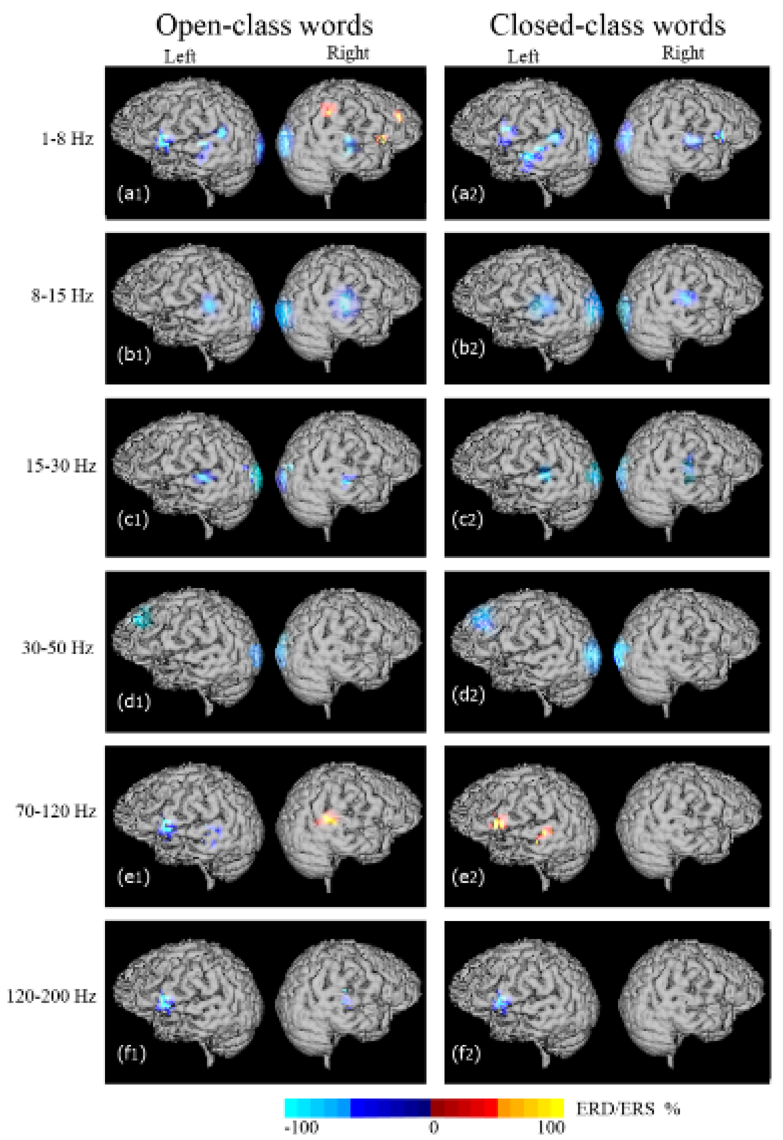
Results



HFOs in Language Mapping



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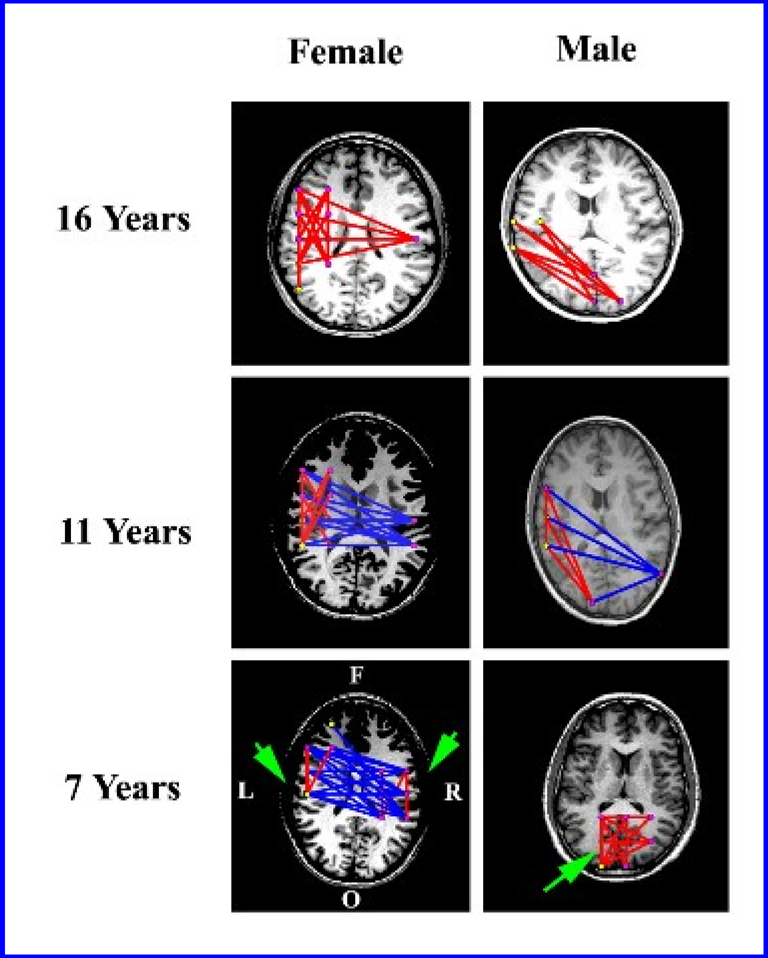
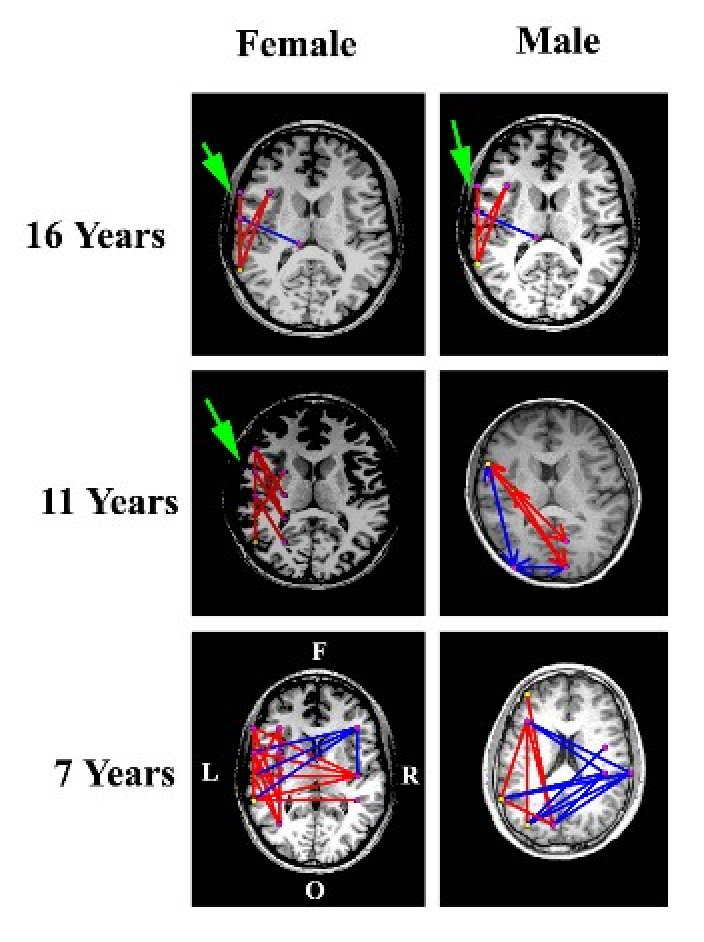
Development of Language Network





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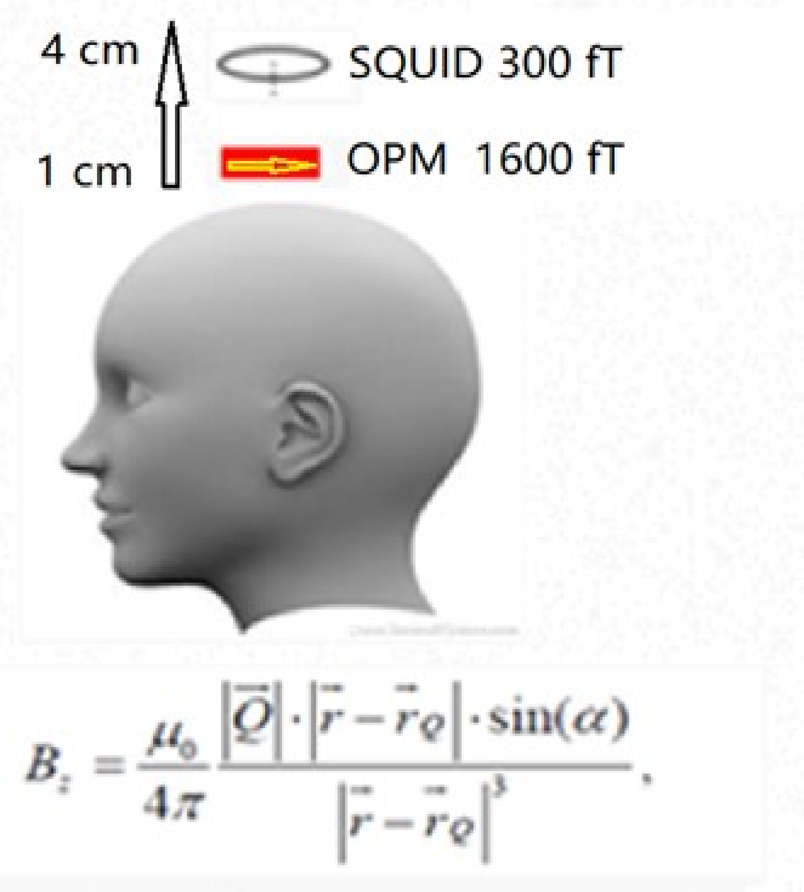
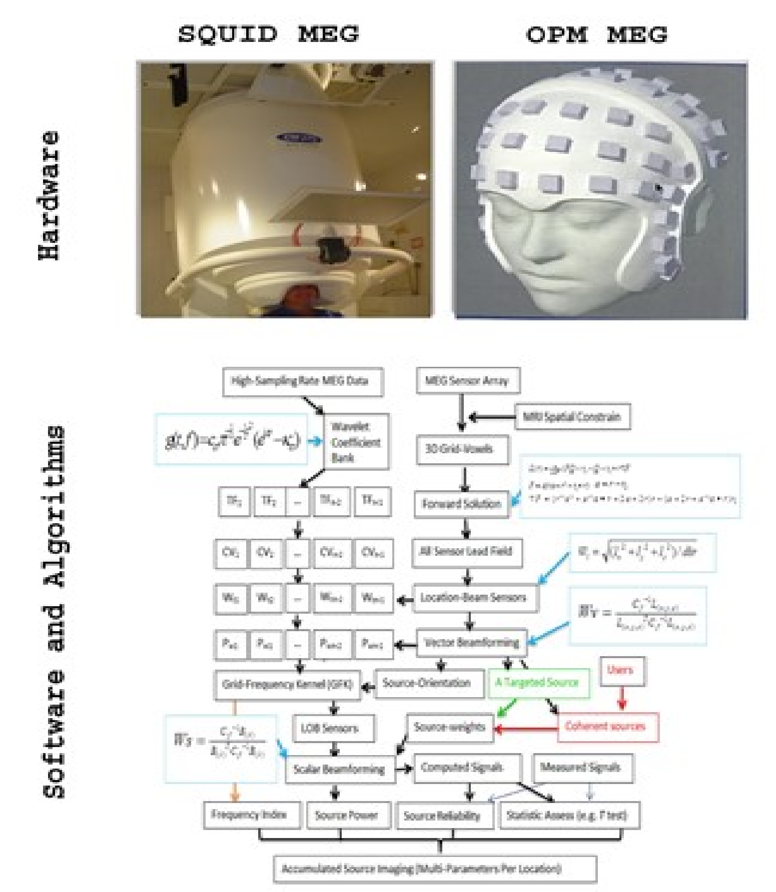
New Technology for Brain Research
Processing Algorithms, Software, Hardware

SQUID OPM/AM Wearable





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The Brain Generates HFBS
A New Frontier,   Solve Clinical Problems

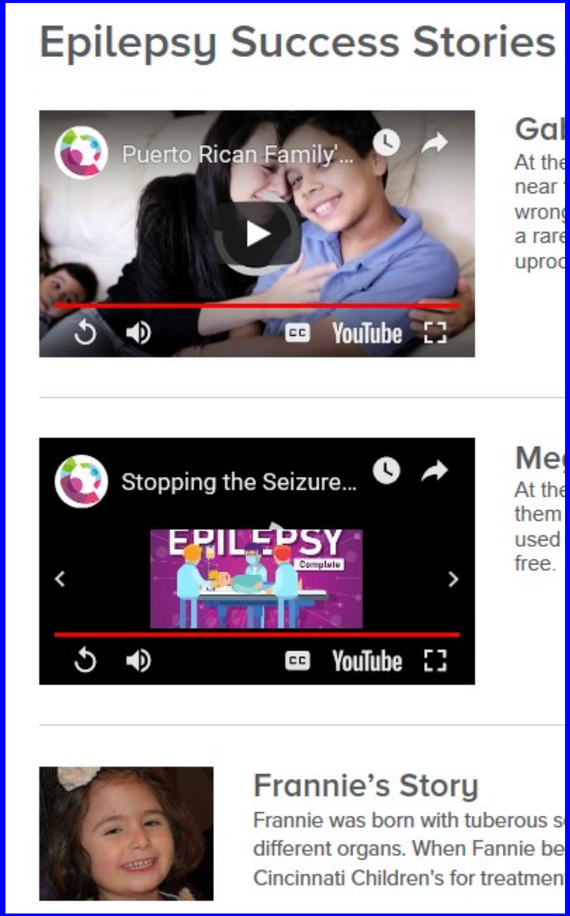
Spikes → HFOs → DC-HFOs →

New Dimensions for Source Scan (275 -> 275 x 10)

Dipole → ASI → FESI →

Increase Post-operative Seizure Freedom (spikes~30%; no spike~85%)

~50% → ~75% → ~90 →



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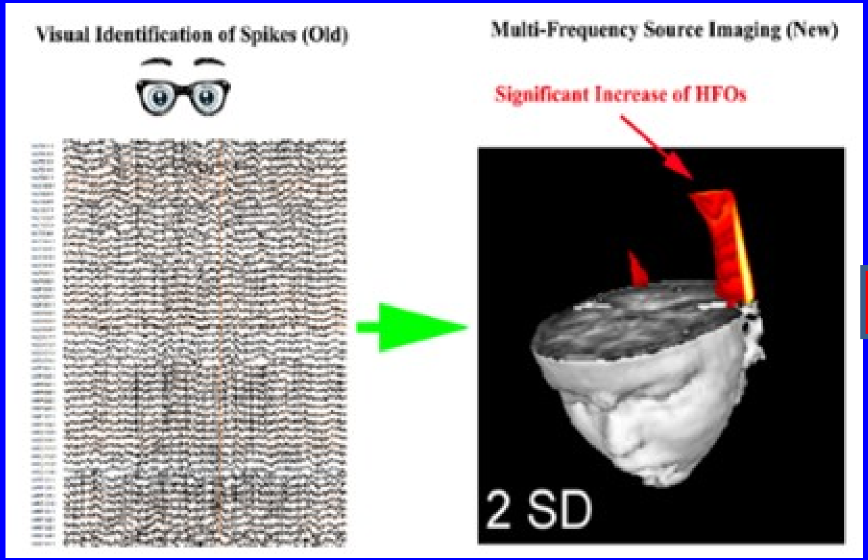
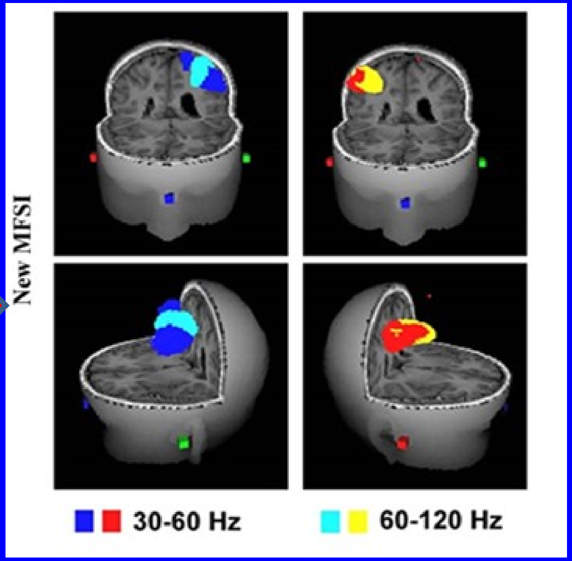
The Future of MEG Research

LFBS
Waveform

HFBS
MSI

MFA
FESI





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High Frequency MEG/EEG Database

clinicaltrials.gov/ct2/show/NCT00600717

Apps Measurement Com... Windows-classic-sa... Mail - Xiang, Jing -... https://covidscreen....

Brief Summary:

The objective of this study is to use high-frequency brain signals (HFBS) to localize functional brain areas and to characterize HFBS epilepsy, migraine and other brain disorders. We hope to build the world's first high-frequency MEG/MEG/ECoG/SEEG database for the developing brain. HFBS include high-gamma activation/oscillations, high-frequency oscillations (HFOs), ripples, fast ripples, and very high frequency oscillations (VHFOs) in the brain.

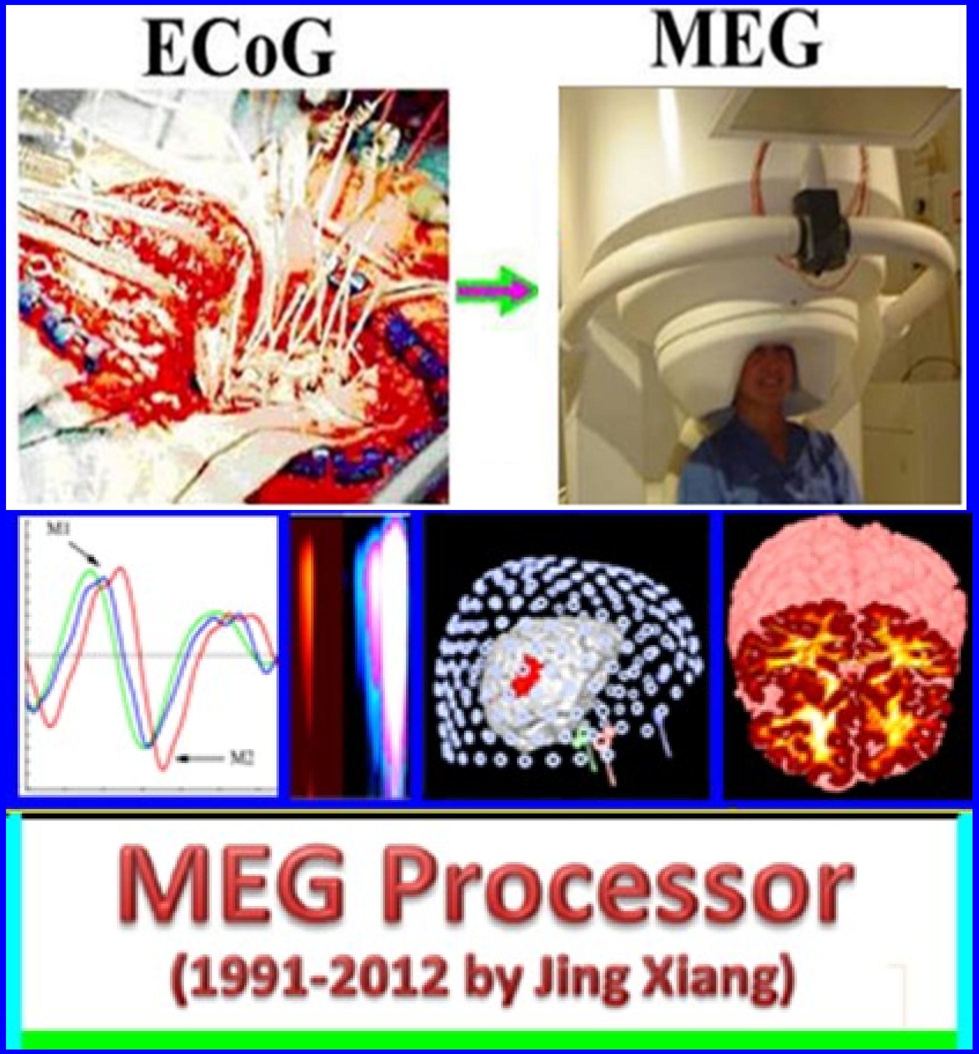
To reach the goals, we have developed several new MEG/EEG methods: (1) accumulated spectrogram; (2) accumulated source imaging; (3)frequency encoded source imaging; (4) multi-frequency analysis; (5)artificial intelligence detection of HFOs; (6) Neural network analysis (Graph Theory); and (7) others (e.g. ICA, virtual sensors).

Condition or disease
Healthy
Epilepsy
Migraine
Headache
Pain
Autism
Cerebral Palsy

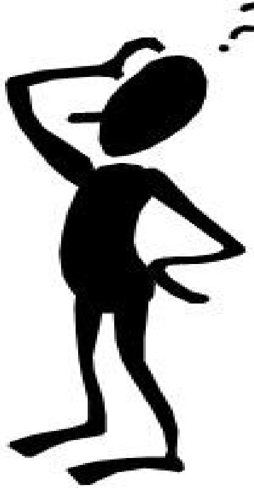
https://clinicaltrials.gov/ct2/show/NCT00600717

Acknowledgements

NIH R21 NS 104459
Ohio Third Frontier TECG20170361
CCHMC Innovation Fund
NIH R21 NS081420-01A1
NIH R21 NS072817
NIH R01 HD38578
NIH K23 MH100640-01A1
NIH 1K23MH108603-01
Shared Facility Discovery Award (SFDA)
Arnold Strauss Fellow Award
BRIMS Scholar
Trustee Grants CCHMC

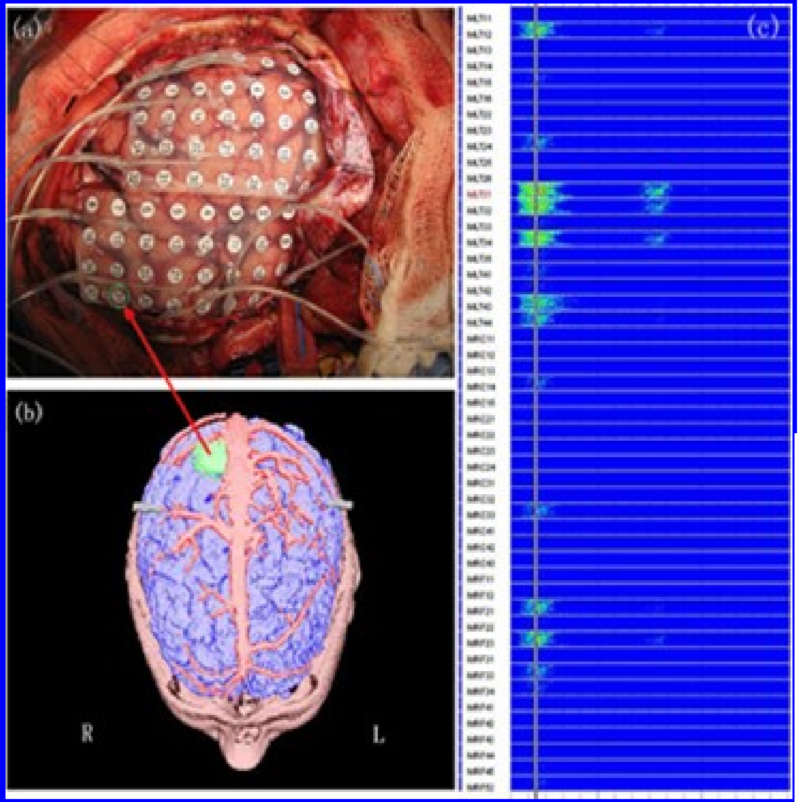


Thank you ☺



Discussion (New Area, Bright)

(Biomag, USA Clinical MEG, ASCMA)



The New MEG Frontier?

Organizer: Jing Xiang

Room: # 104

Time: 13:30-14:30

Biomag2016

Symposium Summary

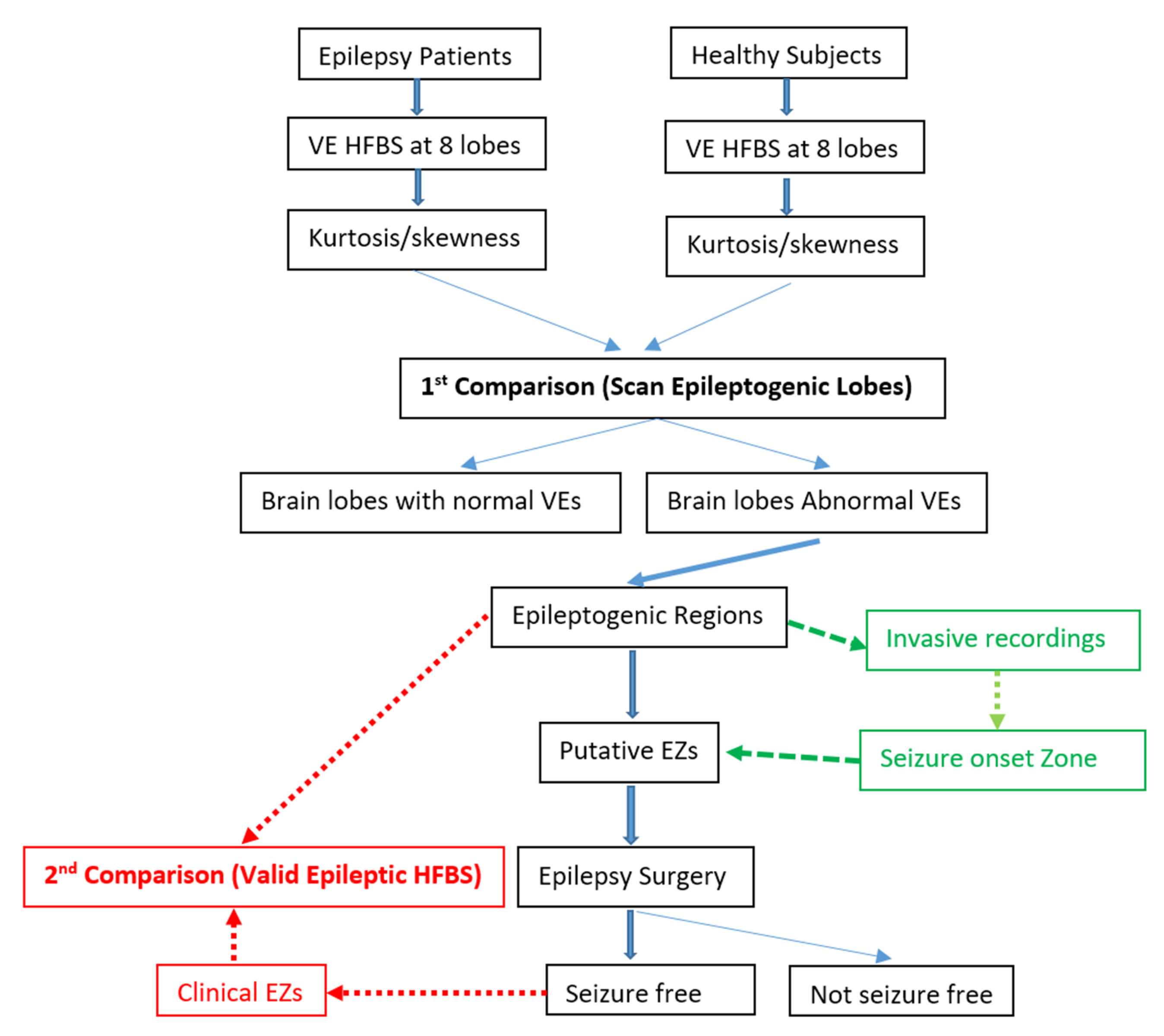
MEG Detection of Low to High Frequency Neuromagnetic Activity

Recent success in localizing low- (LFBS, 0-14 Hz) and high-frequency brain signals (HFBS, 70-2,8
of epilepsy, migraine and potentially many other disorders using magnetoencephalography
interesting because both clinicians and basic researchers can benefit from it. For example: (
effectiveness of epilepsy surgery by approximately 30%. By promoting the applications of HF
intractable epilepsy patients being seizure free. (2) By using LFBS and HFBS, MEG has reve
excitability and that medications normalizing cortical excitability can reduce the incidence of m
and HFBS can advance our understanding of the cerebral mechanisms of multi-frequency brai
software developers may use LFBS and HFBS to create novel solutions for diagnosis and treatme

Speakers:

- **Milena Korostenskaja** (Florida Hospital for Children, USA)
  "High Gamma Functional Mapping for epilepsy surgery"
- **Kimberly A. Leiken** (Cincinnati Children's Hospital Medical Center, USA)
  "Assessment of Cortical Excitability in Migraine with Neuromagnetic High-frequency Signals"

Detect HFBS with VE and Kurtosis/Skewness



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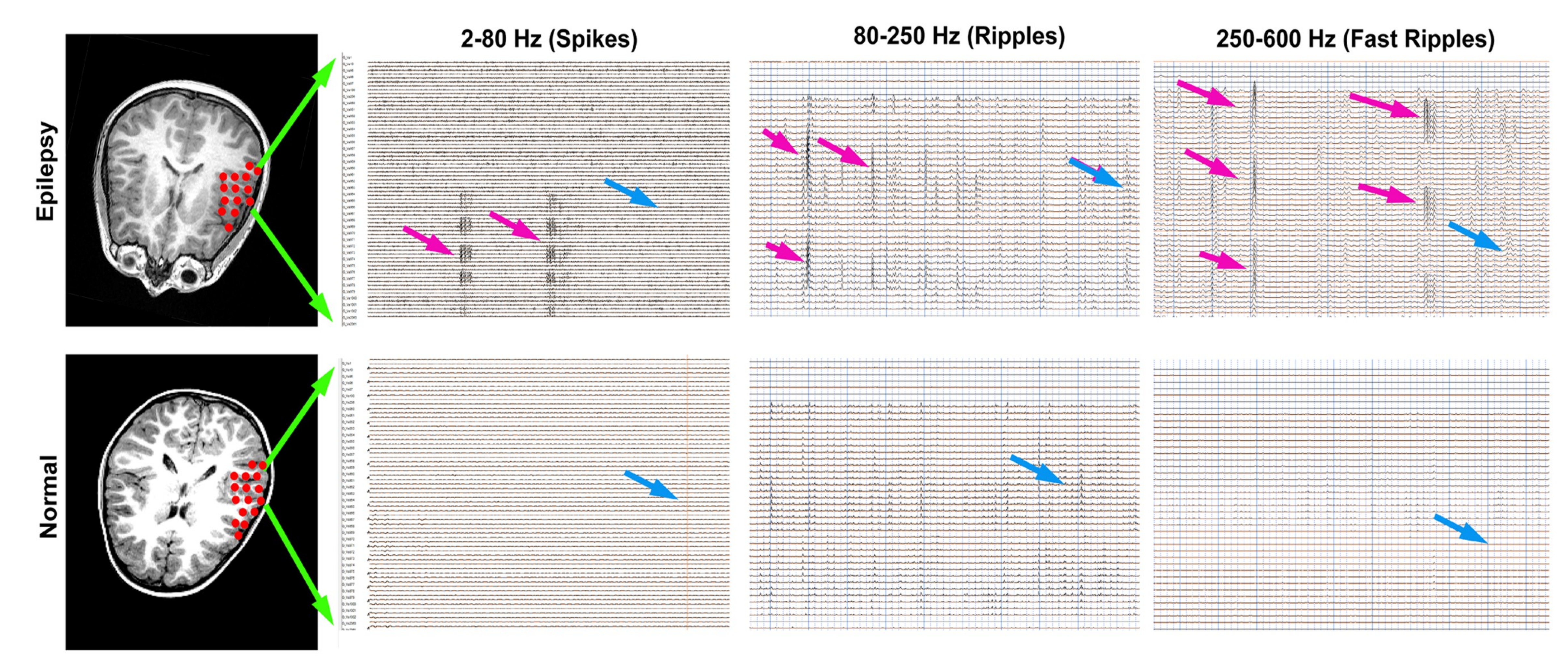
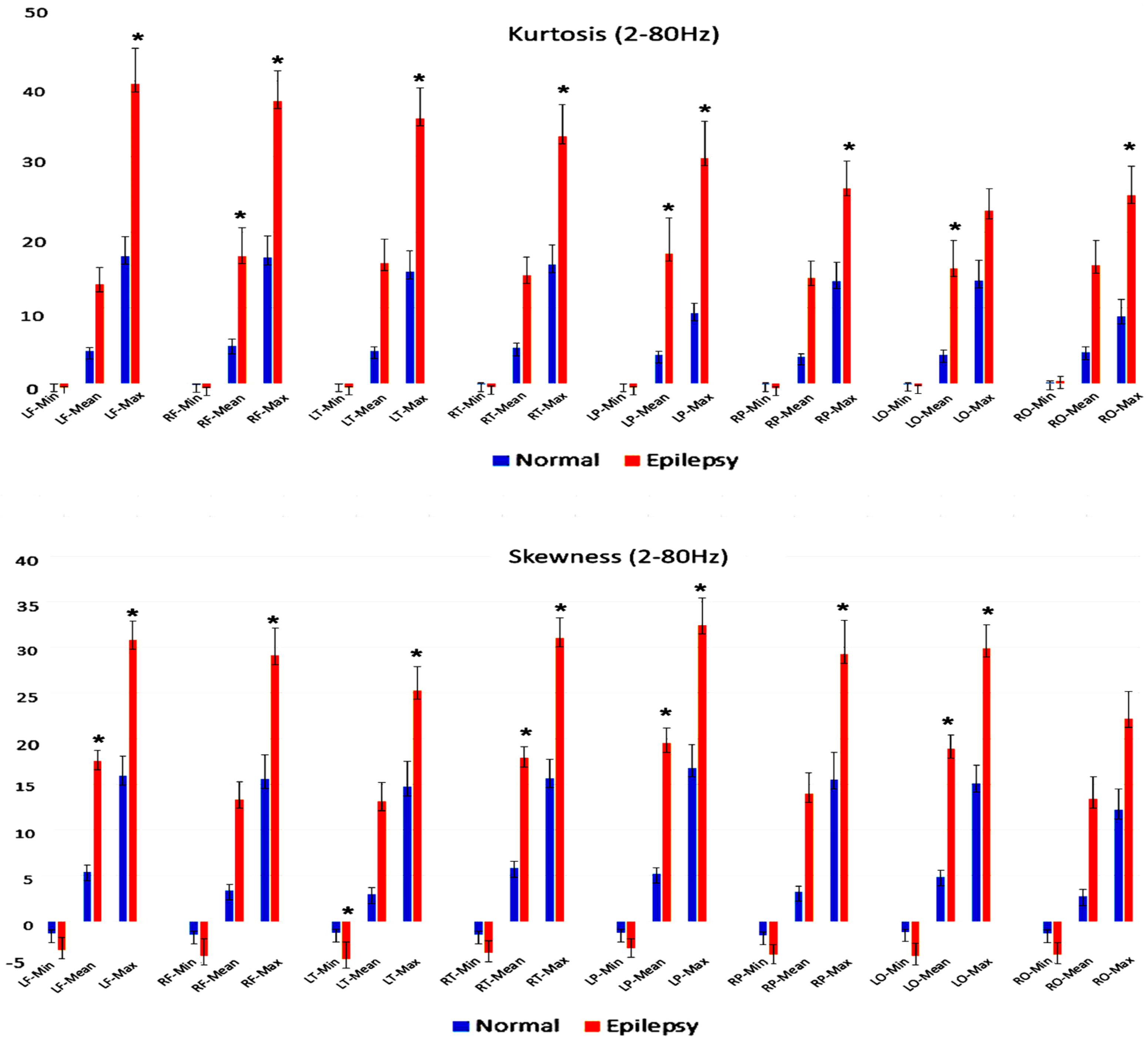
Virtual Sensor + Kurtosis/Skewness





Kurtosis (2-80Hz)
50
40
30
20
10
0
LF-Min
LF-Mean
LF-Max
RF-Min
RF-Mean
RF-Max
LT-Min
LT-Mean
LT-Max
RT-Min
RT-Mean
RT-Max
LP-Min
LP-Mean
LP-Max
RP-Min
RP-Mean
RP-Max
LO-Min
LO-Mean
LO-Max
RO-Min
RO-Mean
RO-Max
Normal
Epilepsy
Skewness (2-80Hz)
40
35
30
25
20
15
10
5
0
-5
LF-Min
LF-Mean
LF-Max
RF-Min
RF-Mean
RF-Max
LT-Min
LT-Mean
LT-Max
RT-Min
RT-Mean
RT-Max
LP-Min
LP-Mean
LP-Max
RP-Min
RP-Mean
RP-Max
LO-Min
LO-Mean
LO-Max
RO-Min
RO-Mean
RO-Max
Normal
Epilepsy

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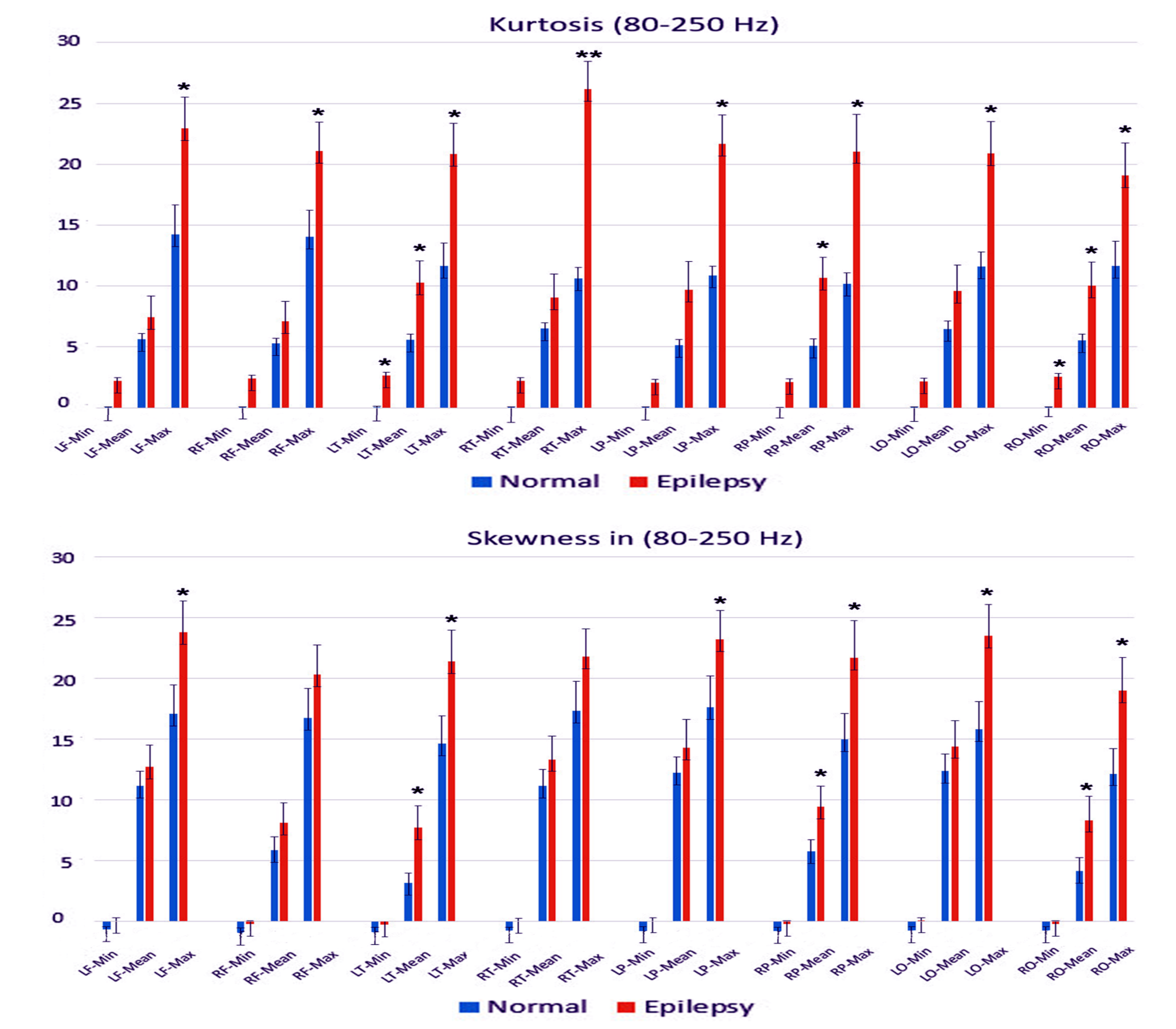
Kurtosis (80-250 Hz)
30
25
20
15
10
5
0
LF-Min LF-Mean LF-Max RF-Min RF-Mean RF-Max LT-Min LT-Mean LT-Max RT-Min RT-Mean RT-Max LP-Min LP-Mean LP-Max RP-Min RP-Mean RP-Max LO-Min LO-Mean LO-Max RO-Min RO-Mean RO-Max
Normal
Epilepsy
Skewness in (80-250 Hz)
30
25
20
15
10
5
0
LF-Min LF-Mean LF-Max RF-Min RF-Mean RF-Max LT-Min LT-Mean LT-Max RT-Min RT-Mean RT-Max LP-Min LP-Mean LP-Max RP-Min RP-Mean RP-Max LO-Min LO-Mean LO-Max RO-Min RO-Mean RO-Max
Normal
Epilepsy

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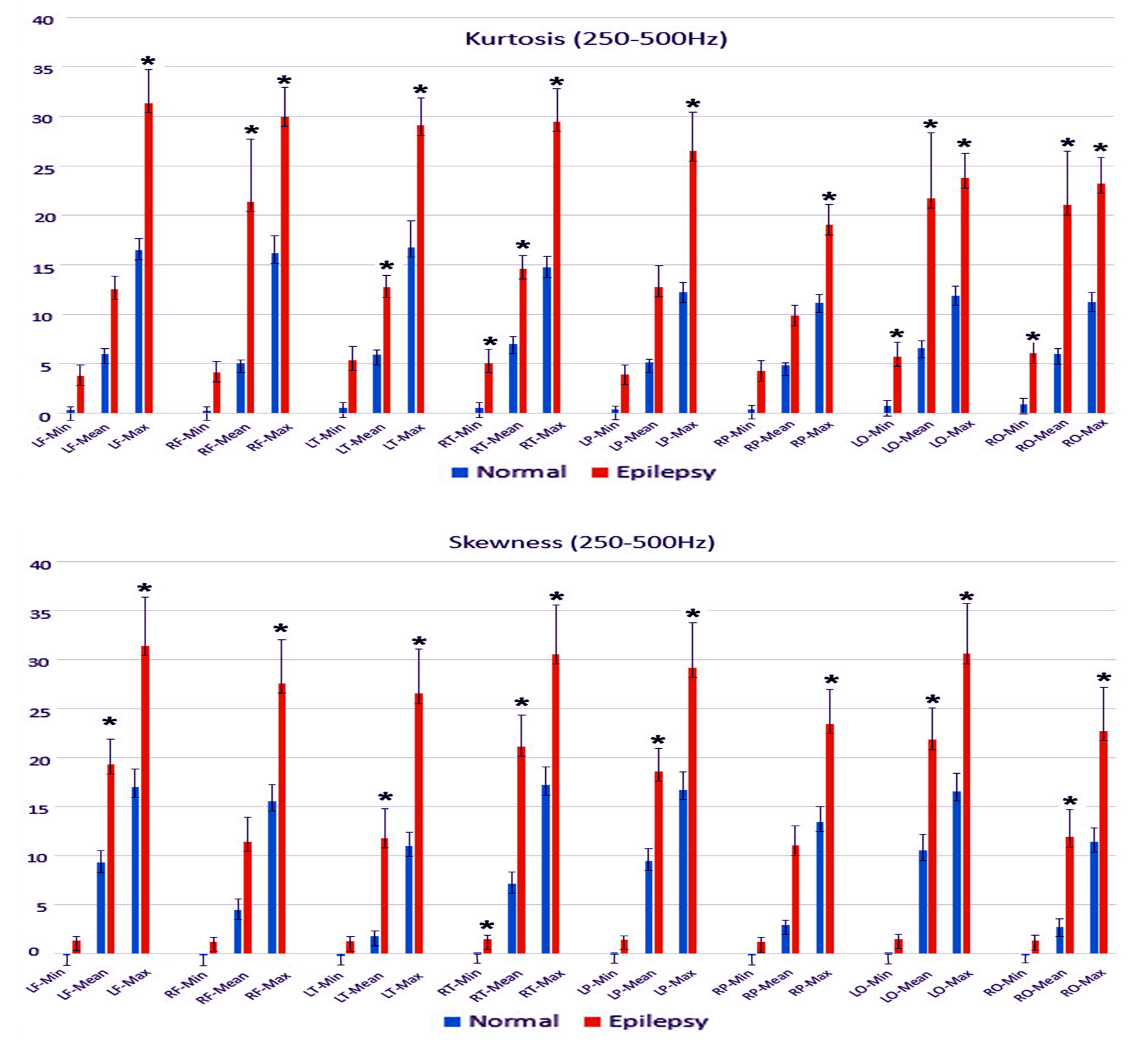
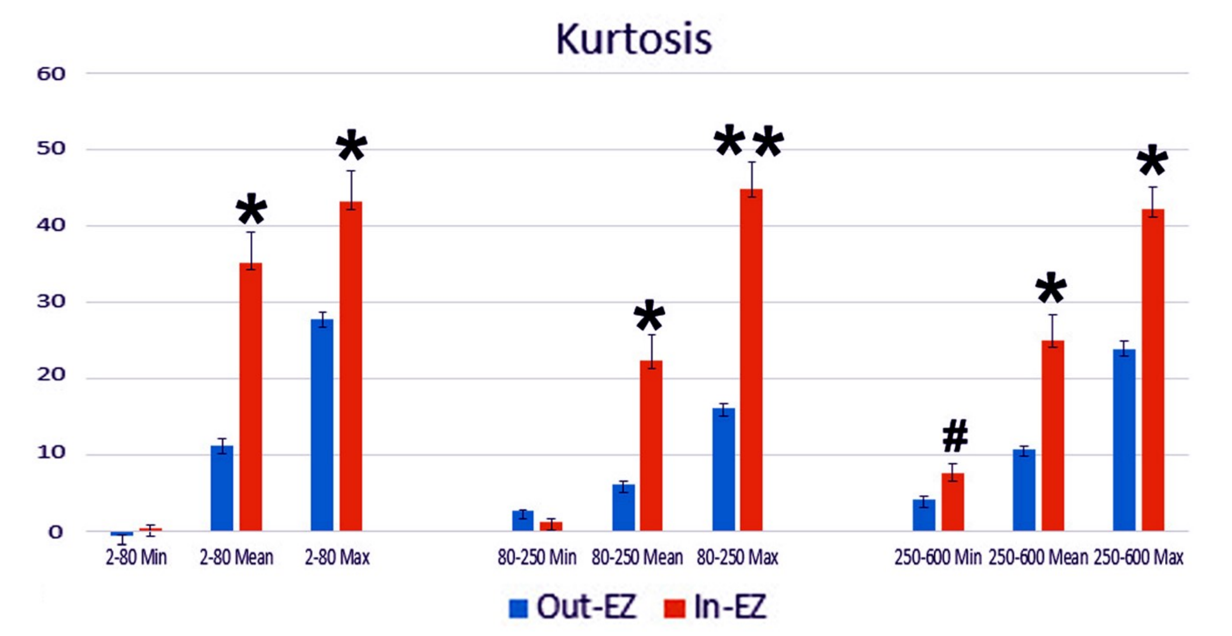
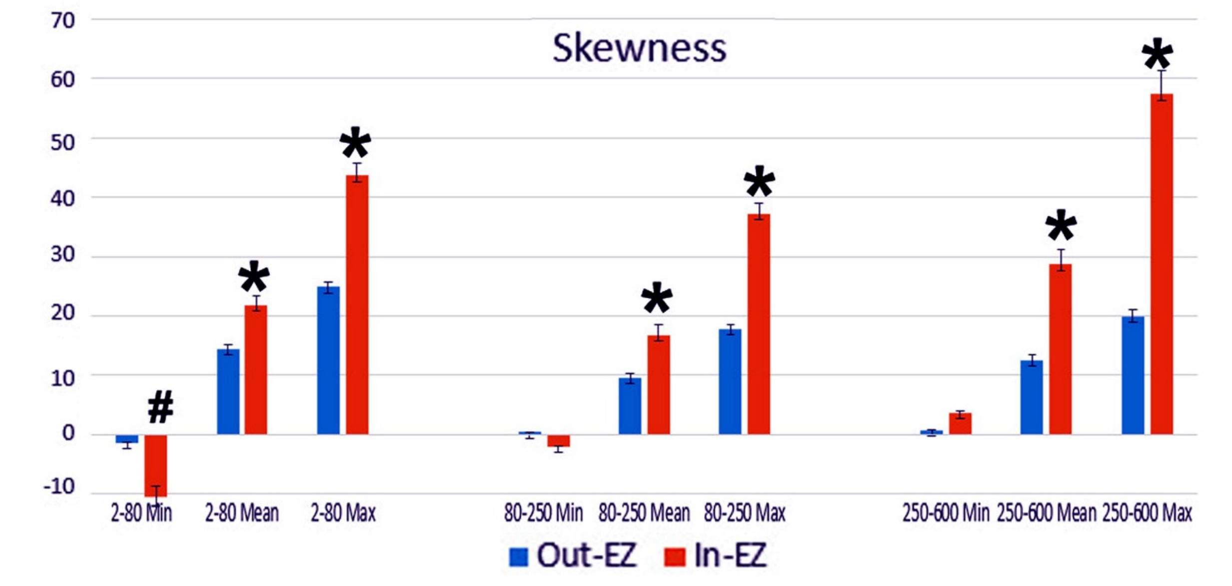
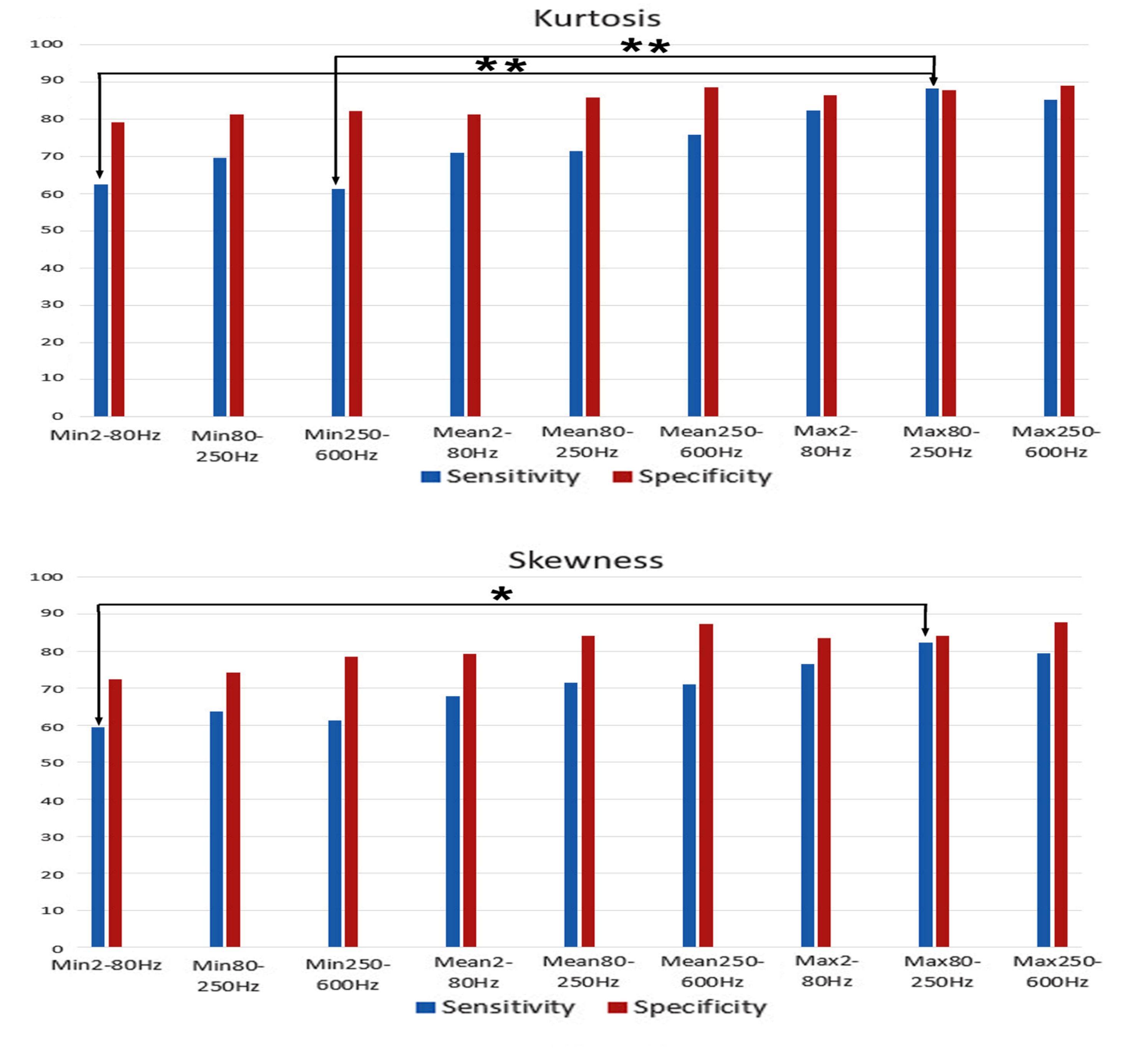

Kurtosis (250-500Hz)
0
5
10
15
20
25
30
35
40
LF-Min
LF-Mean
LF-Max
RF-Min
RF-Mean
RF-Max
LT-Min
LT-Mean
LT-Max
RT-Min
RT-Mean
RT-Max
LP-Min
LP-Mean
LP-Max
RP-Min
RP-Mean
RP-Max
LO-Min
LO-Mean
LO-Max
RO-Min
RO-Mean
RO-Max
Normal
Epilepsy
Skewness (250-500Hz)
0
5
10
15
20
25
30
35
40
LF-Min
LF-Mean
LF-Max
RF-Min
RF-Mean
RF-Max
LT-Min
LT-Mean
LT-Max
RT-Min
RT-Mean
RT-Max
LP-Min
LP-Mean
LP-Max
RP-Min
RP-Mean
RP-Max
LO-Min
LO-Mean
LO-Max
RO-Min
RO-Mean
RO-Max
Normal
Epilepsy

11:54 AM


Kurtosis
60
50
40
30
20
10
0
2-80 Min
2-80 Mean
2-80 Max
80-250 Min
80-250 Mean
80-250 Max
250-600 Min
250-600 Mean
250-600 Max
Out-EZ
In-EZ


Skewness
70
60
50
40
30
20
10
0
-10
2-80 Min
2-80 Mean
2-80 Max
80-250 Min
80-250 Mean
80-250 Max
250-600 Min
250-600 Mean
250-600 Max
Out-EZ
In-EZ

11:54 AM

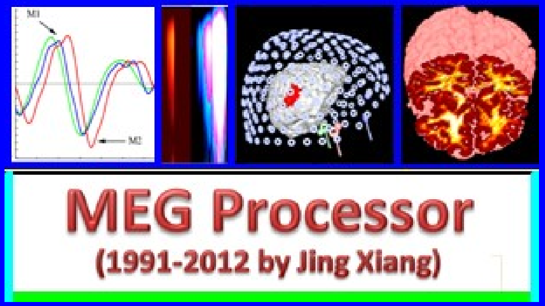

Kurtosis
100
90
80
70
60
50
40
30
20
10
0
**
**
Min2-80Hz
Min80-250Hz
Min250-600Hz
Mean2-80Hz
Mean80-250Hz
Mean250-600Hz
Max2-80Hz
Max80-250Hz
Max250-600Hz
Sensitivity
Specificity
Skewness
100
90
80
70
60
50
40
30
20
10
0
*
Min2-80Hz
Min80-250Hz
Min250-600Hz
Mean2-80Hz
Mean80-250Hz
Mean250-600Hz
Max2-80Hz
Max80-250Hz
Max250-600Hz
Sensitivity
Specificity

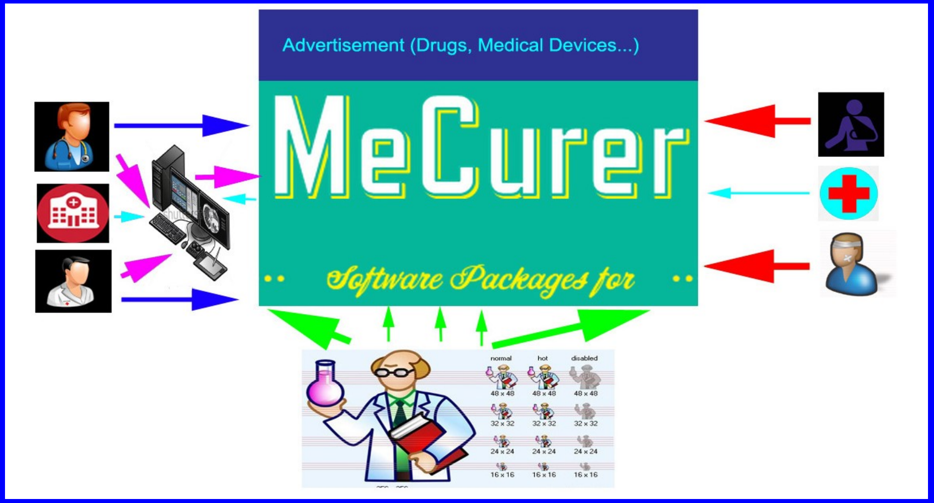
11:54 AM

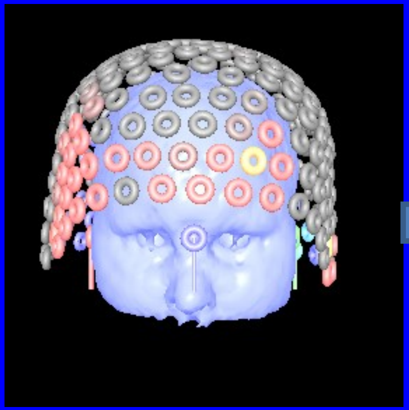
Virtual Sensor Kurtosis and Skewness

- Epilepsy: Altered kurtosis and skewness in VE HFBS.
- Kurtosis of VE signals in 80-250 Hz are the most sensitive
- Kurtosis of VE signals in 250-600 Hz are the most specific
- Propose to use VE HFBS in kurtosis/skewness:
  - Maximum kurtosis in 80-250 Hz for phase I
  - Maximum kurtosis in 250-600 Hz for phase II

High Sampling Multi-channel MEG/EEG →Big Data



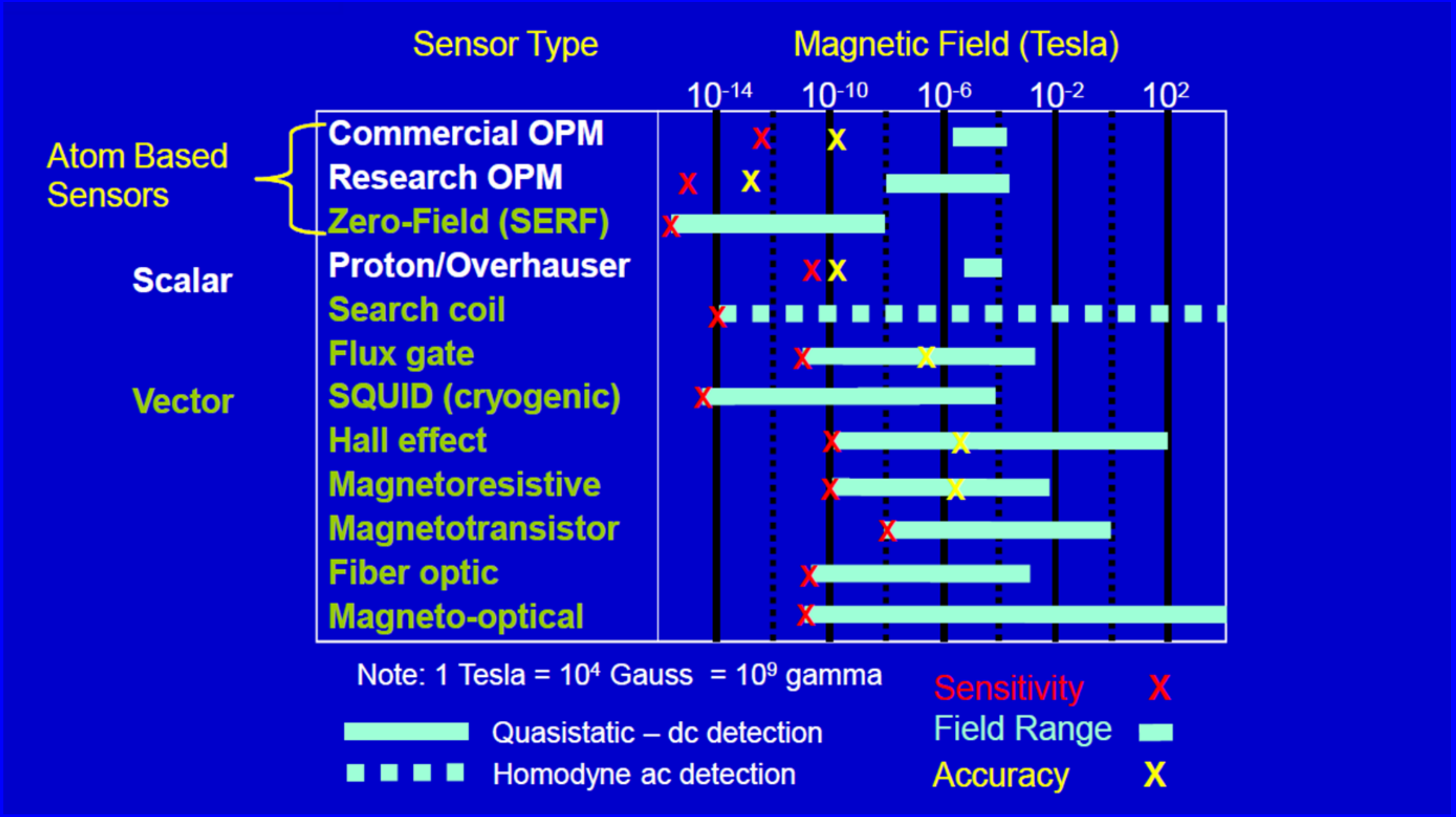




- Big Data
- Cloud

- Multi-channel and high-sampling MEG/EEG -> Big Data
- 275 x 12000-> 1 GB/1 Minute --→ 1 TB/1 Hour

New Next Generation of MEG Sensor



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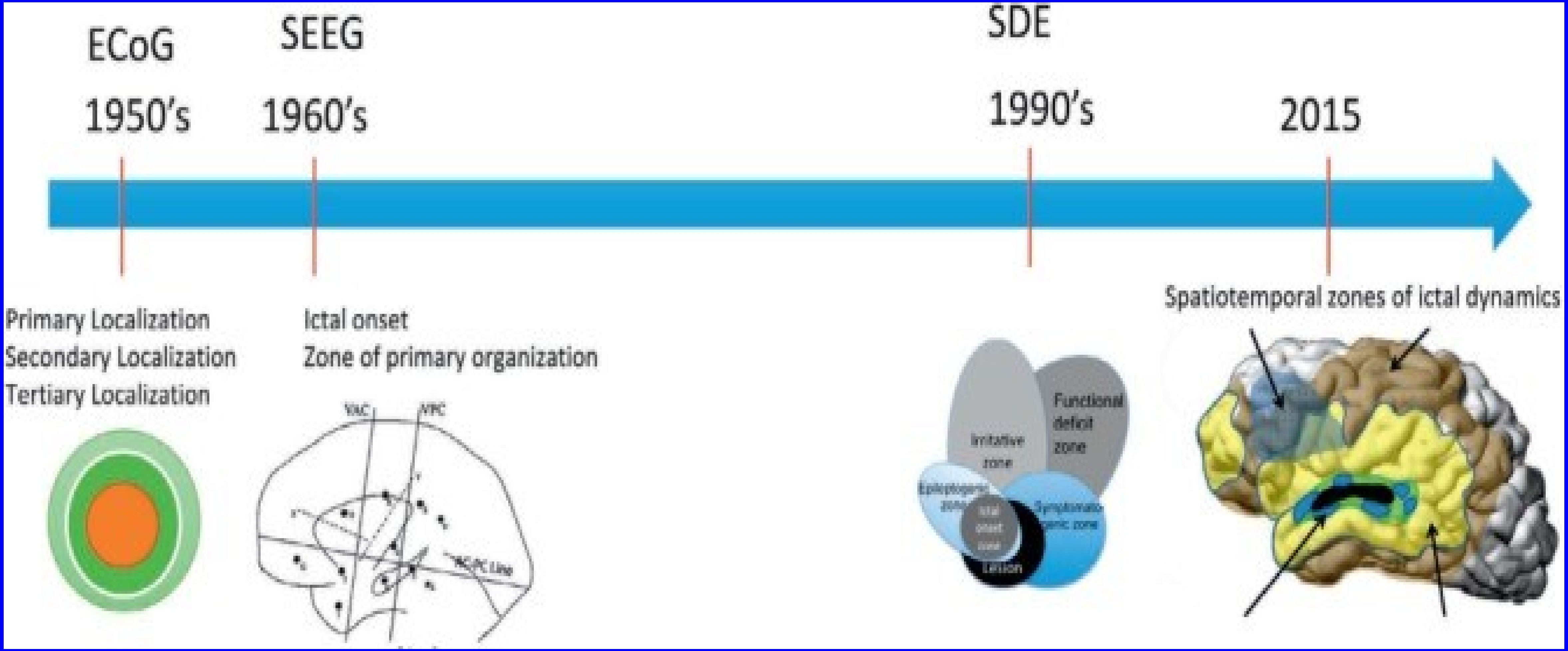
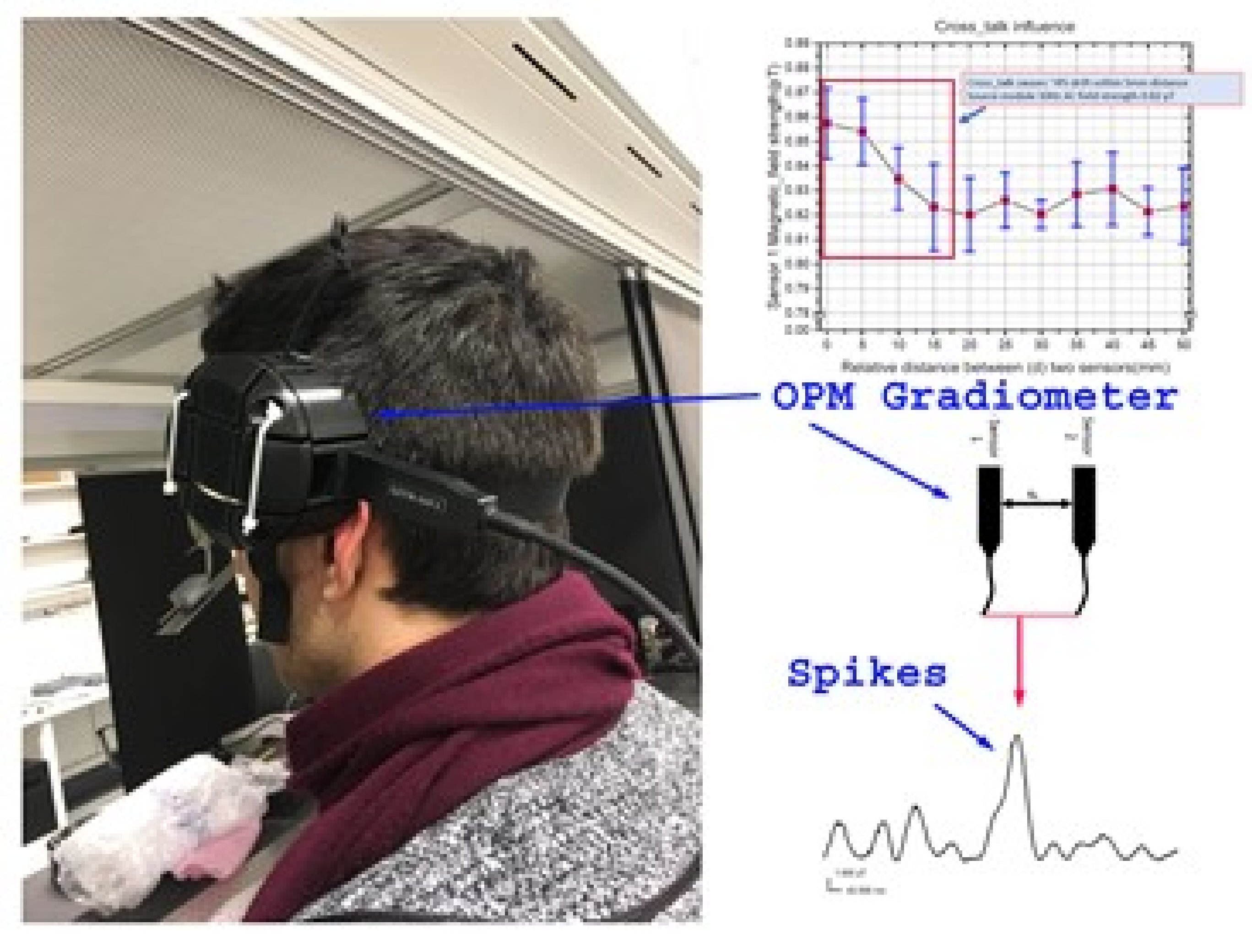
Epilepsy Surgery




Cross_talk influence
Relative distance between (d) two sensors(mm)
OPM Gradiometer
Spikes

11:54 AM

Epileptic vs Physiological HFOs

		Epileptic HFOs	Physiological HFOs	Artificial HFOs[c]
Waveforms	Oscillations	>4	>4	any
	Amplitudes	>1.5 SD of baseline[b]	<1.5 SD of baseline[a]	>10 SD of baseline
	Overlap on spikes	Yes[b]	No	No
	Ride on slow wave	Yes[b]	No	No
	Visible in both raw and filtered data	Yes[b]	Yes	No
	Inter-event interval	>25 ms	> 25 ms	
Spectrograms	Time	irregular burst: 5-30 ms	Rhythmic, ~70 ms	Random/constant
	Frequency	80-250 Hz (ripples); 250-600Hz (fast ripples) 600-2500 Hz (VHFOs)	Elicited: 70-150 Hz Endogenous: 102 Hz	< 100 Hz >2500 Hz 60 Hz or 50 Hz.
	Pattern	Isolate island or horizontal	Connected or vertical	Straight lines
	Power	Very high power > 3 uV	Low-median power ~0.95 uV	Fixed.
	Ratio (HFOs/alpha)	>0.38[b]	<0.27[a]	>4.0[a]
		Energy > 95%background	Energy > 85% background	undefined
Source Imaging	Location	Within the brain (cortex, gray matter)	Within the brain (cortex, gray matter)	Out of the brain (around neck, eyes)
	Source strength	>3 SD of the global mean	> 1 SD of the global mean	> 10 SD of global mean
	Pattern	Peak with propagated activation	Activation without clear peaks	Typically irregular
	Relation to MRI/CT	Mimic anatomical shape	Mimic anatomical shape	No relation
Networks	Hub Location	Within the brain	Within the brain	Out of the brain
	strength	Increased[a]	Normal[a]	No connection
	Clustering index	Increased[a]	Normal[a]	Not available
	Path	Shortened[a]	Normal[a]	Not available
Modulation	NREM Sleep	Decrease[a]	No change[a]	No change
	REM Sleep	No change[a]	Ripple increase[a]	No change
	Sleep stage	Large extent (NREM)[a]	Small extent (REM)[a]	No change
	Sleep cycle	High rate in first cycle[a]	Low rate in first cycle[a]	No change
	Task induced	No[a]	Yes[a]	No
	Sleep time	Decrease with time during NREM	Increase with time during REM	
Clinical correlates	High rates in SOZ	Yes[a]	No[a]	No relationship
	Increase with Seizure frequency	Yes[a]	No[a]	No relationship
	Anti-epileptic drug	Reduce HFOs	No	No relationship
	Removal HFO tissues	Good surgical outcomes	No	No relationship
	Hyperventilation	Elicit HFOs (absence epilepsy)	No	No relationship

SD: standard deviation; SOZ: seizure onset zone; AED: antiepileptic drug

[a]Compared to normative database: ~160 healthy children

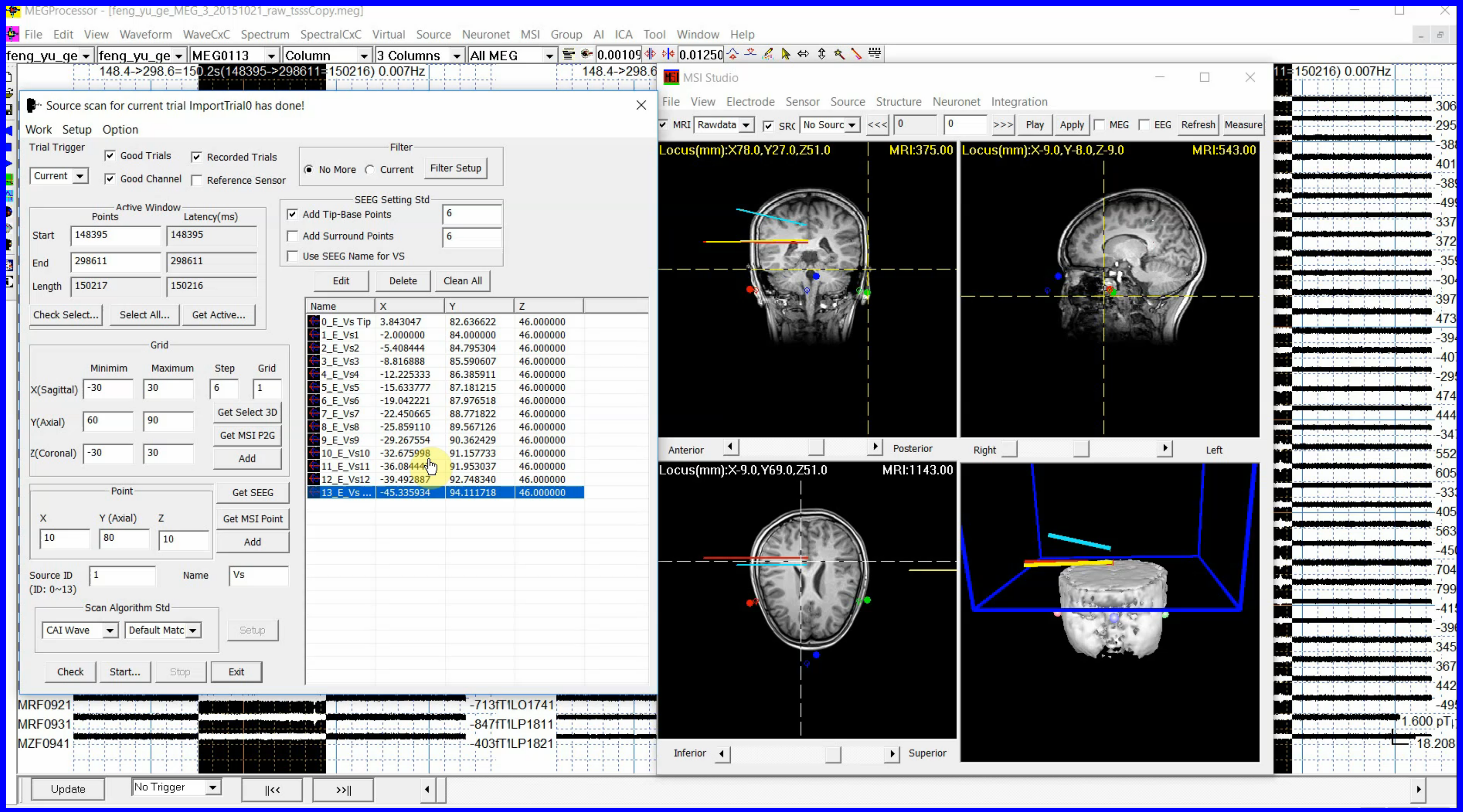
[b]Compared to pediatric epilepsy database: ~ 390 pediatric epilepsy patients

[c]Artificial HFOs: power-line noise, cardiac signals, muscle activity, eye movement, Gibbs filter artifact

Demo (SEEG/iEEG to MRI/CT)

11:54 AM

Demo (3, HFO burst)



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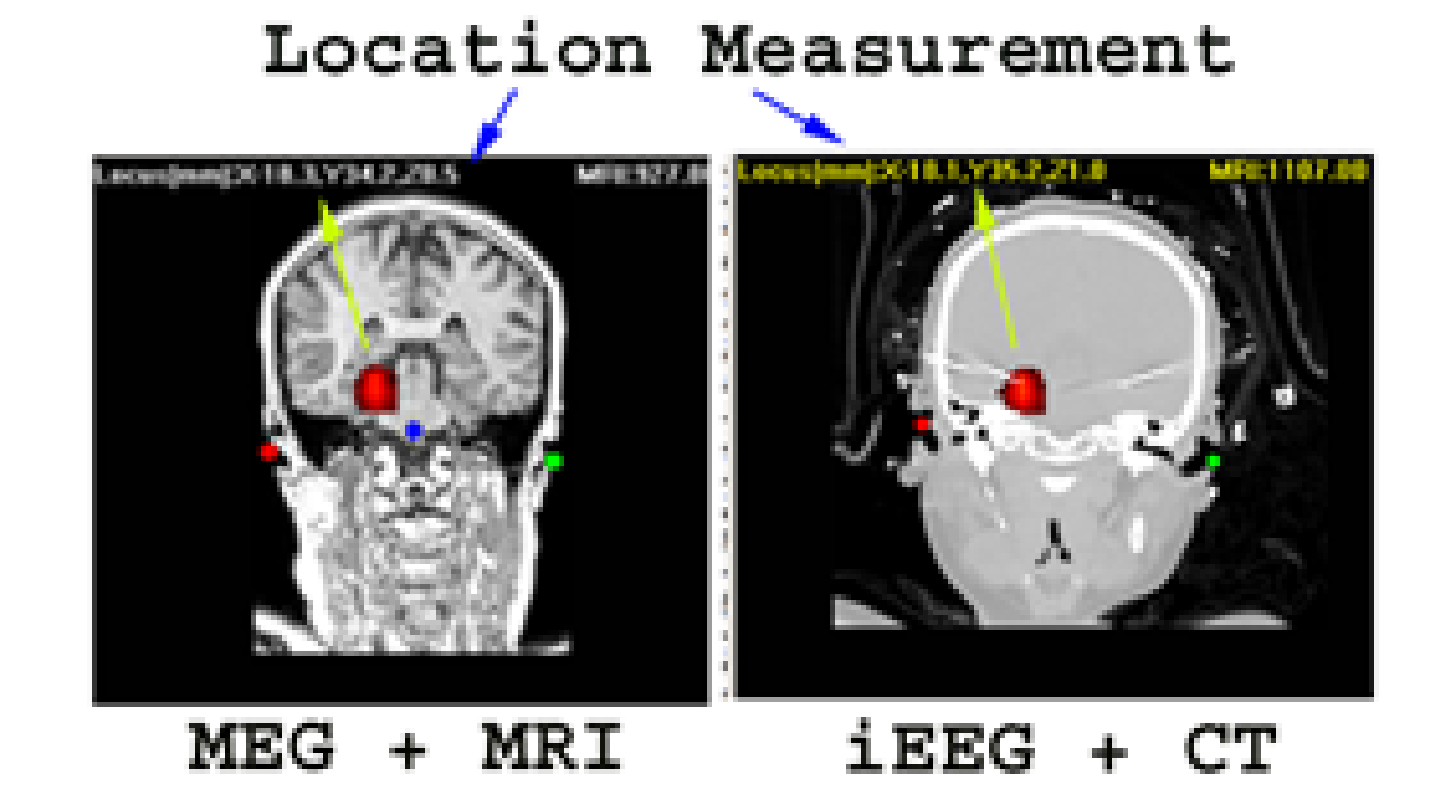
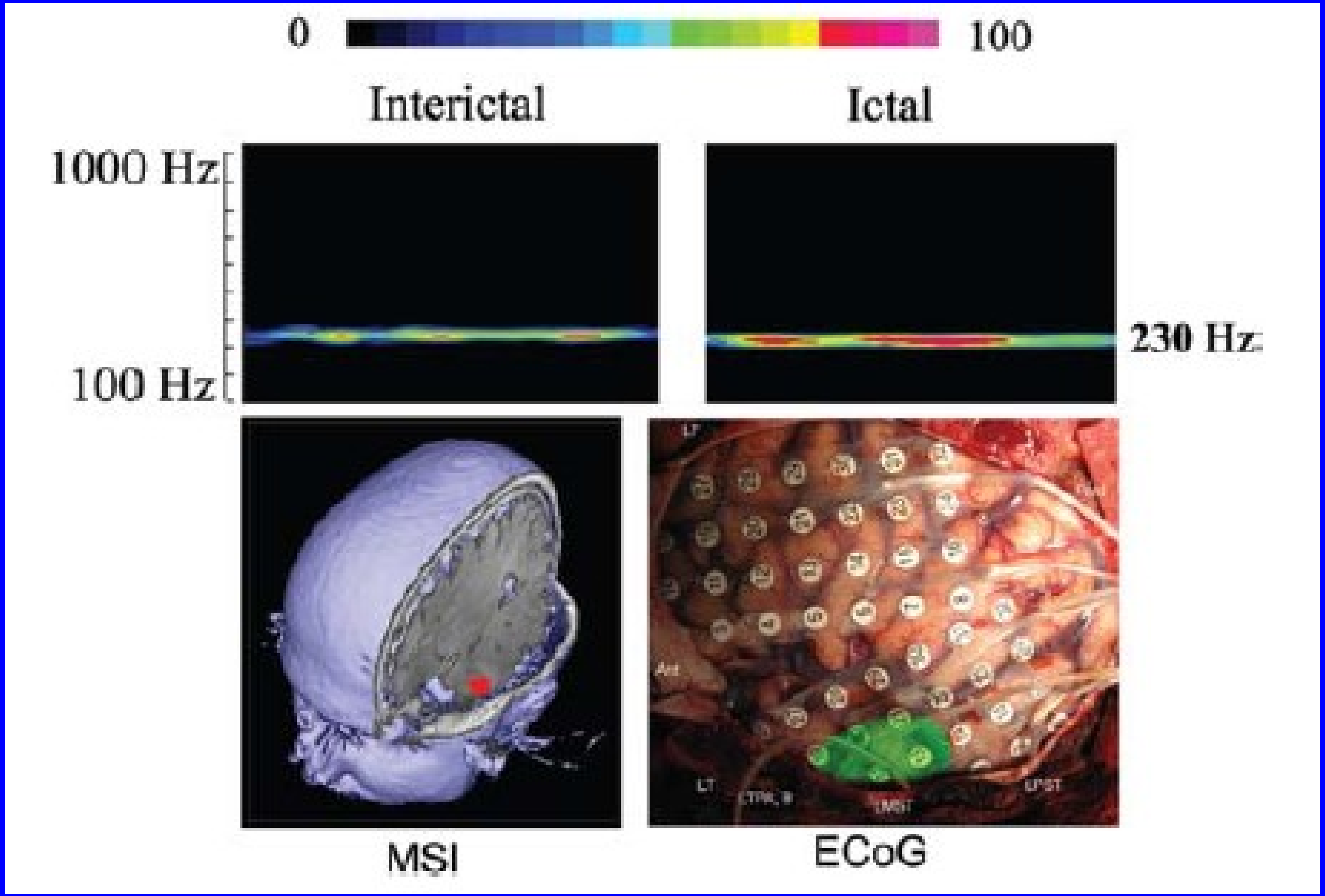
HFO Source Imaging
(Noninvasive vs. Invasive)





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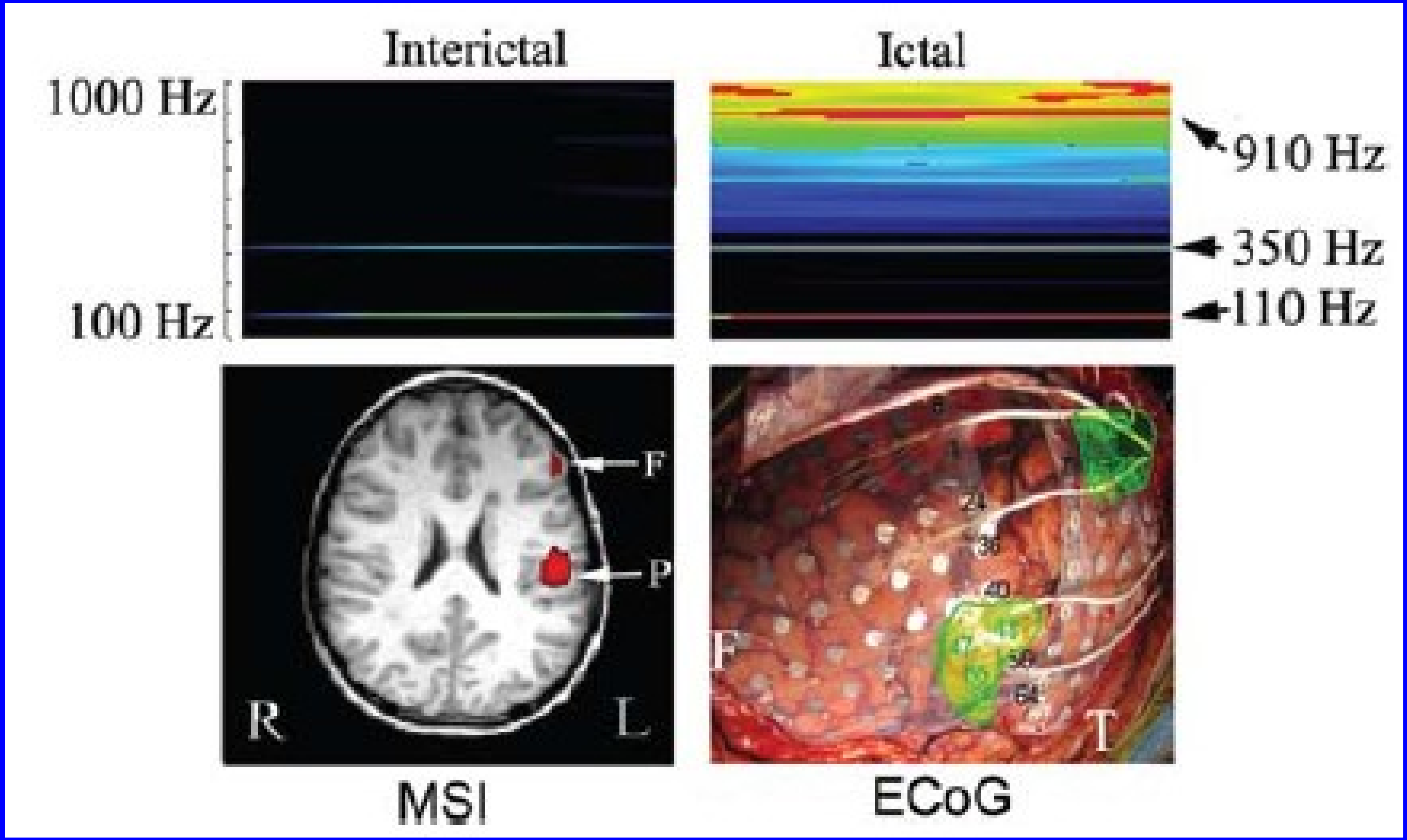
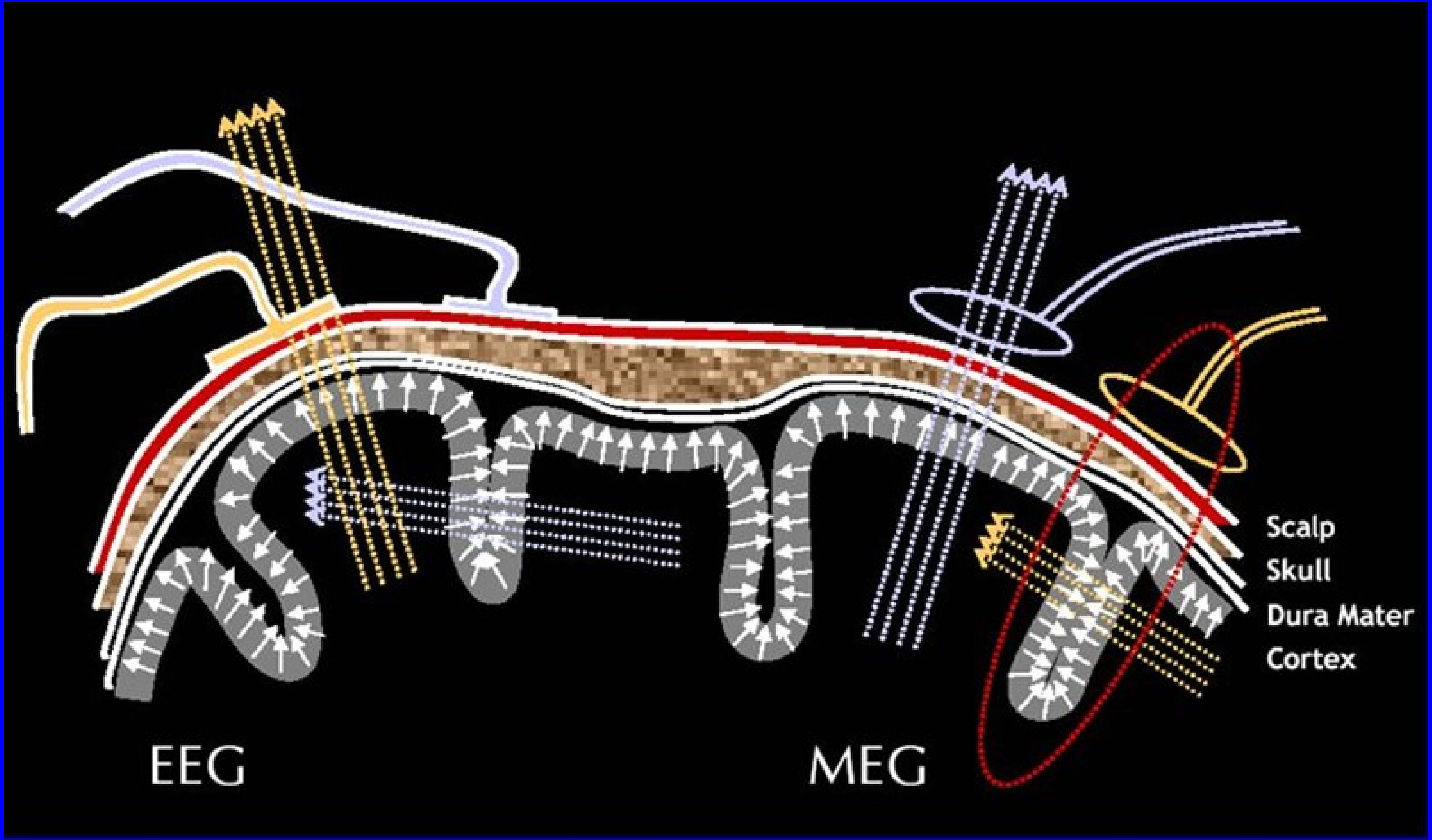
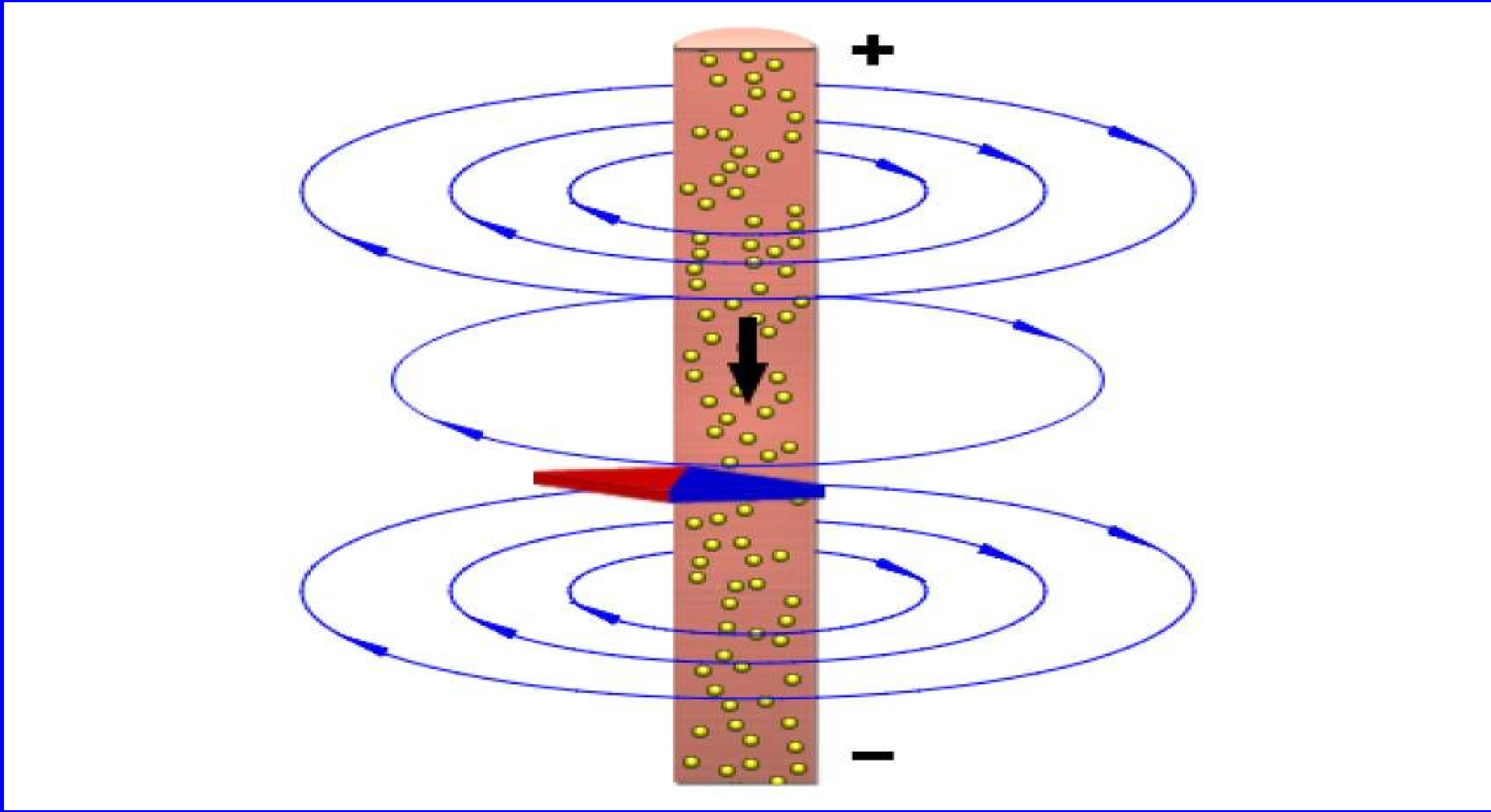

Interictal
Ictal
1000 Hz
100 Hz
910 Hz
350 Hz
110 Hz
F
P
R
L
F
T
MSI
ECoG

11:54 AM

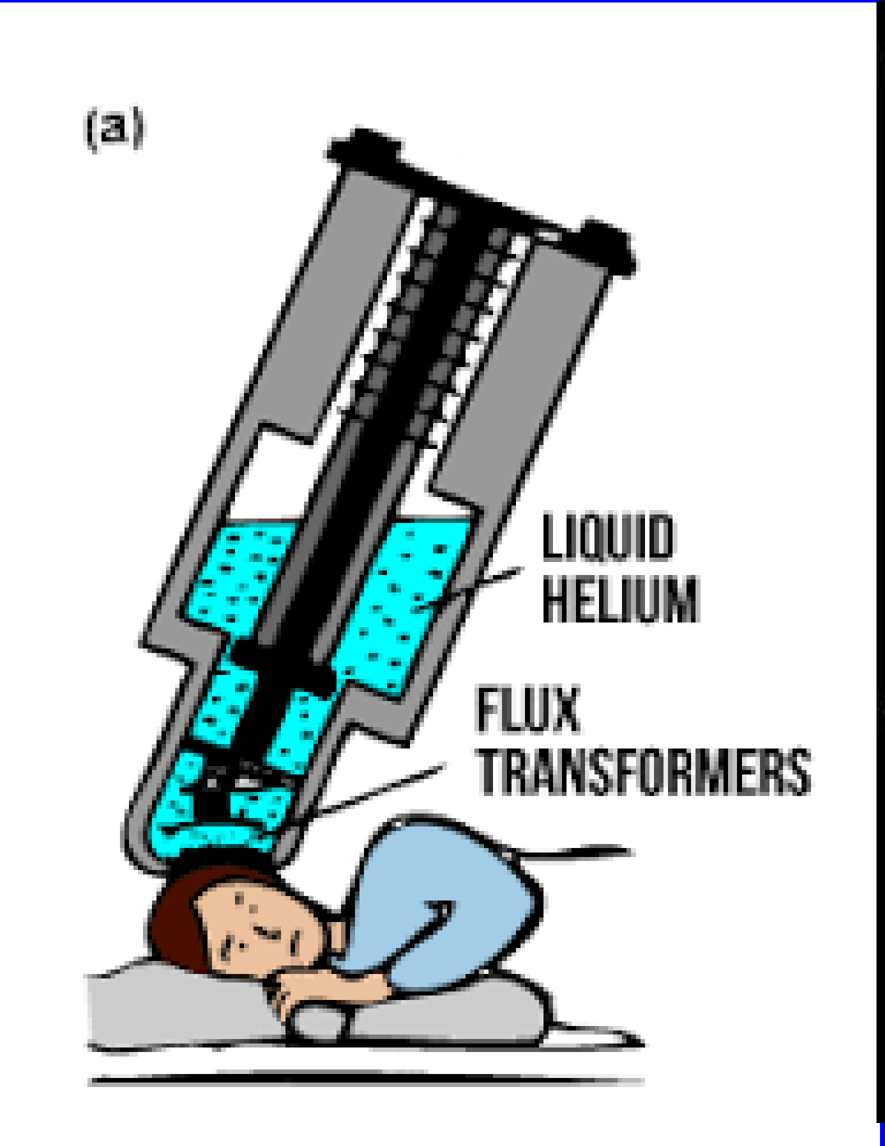
MEG and EEG

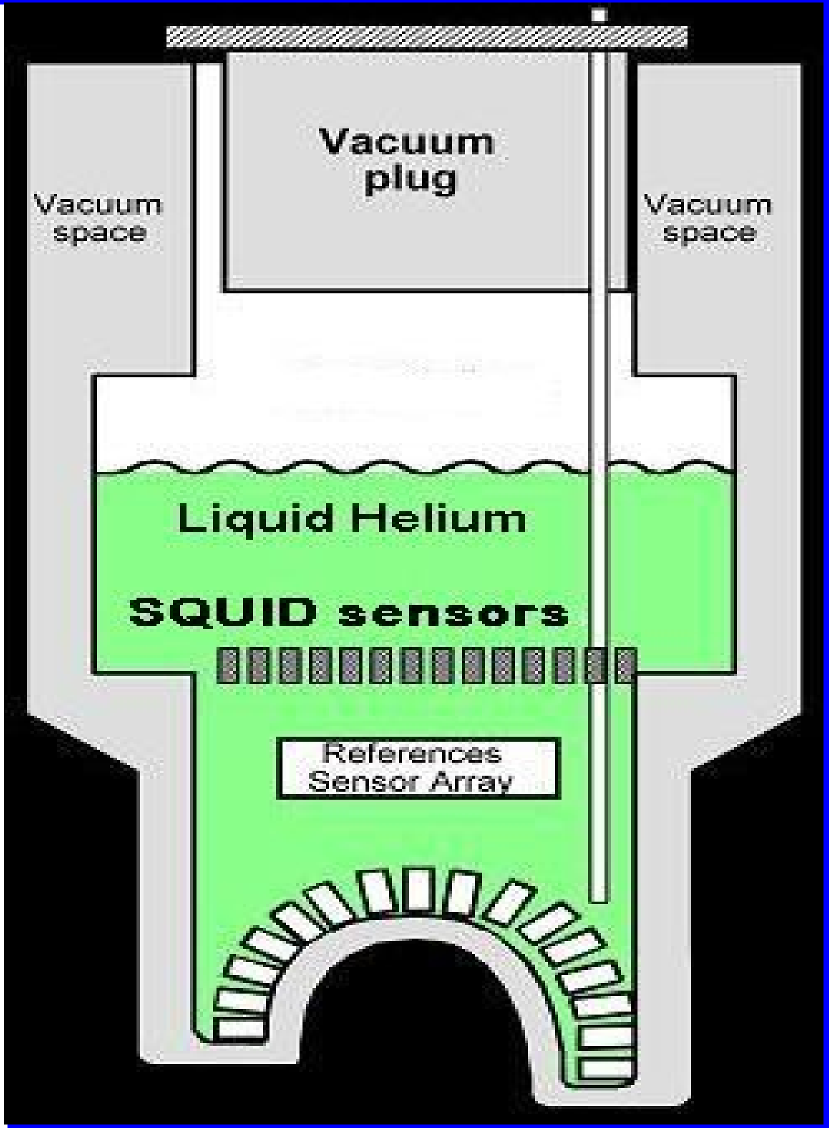


Electrical vs. Magnetic Signals



SQUID Based MEG





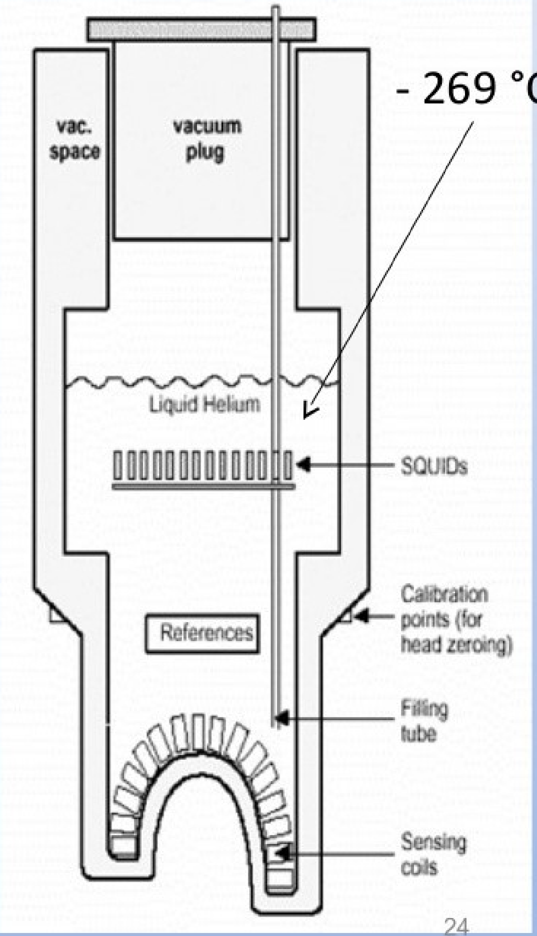
Superconducting Quantum Interference Device (SQUID)

The EEG & MEG instrumentation

MEG

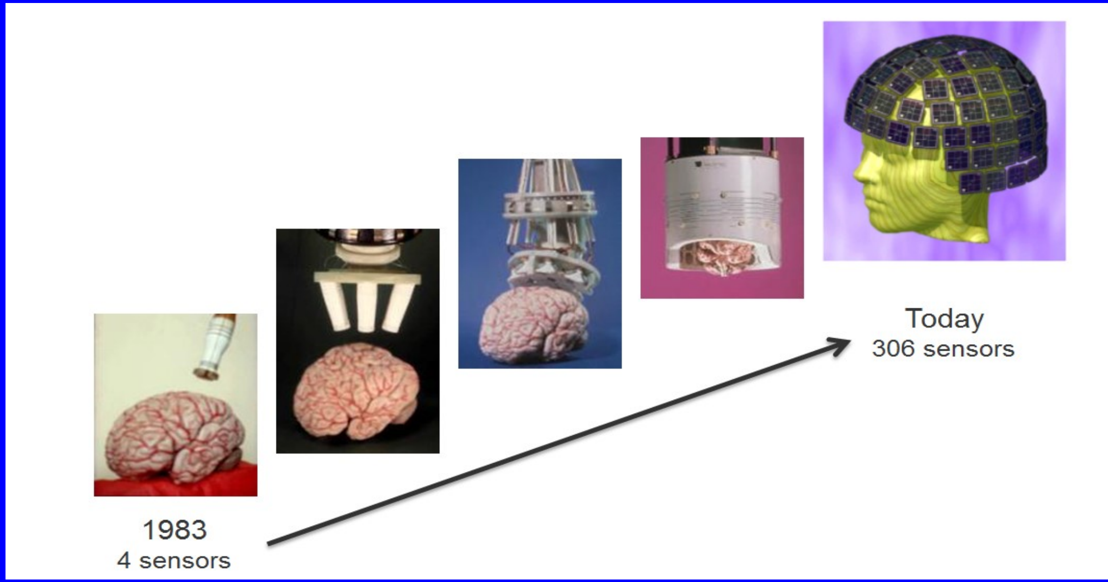
SQUIDs

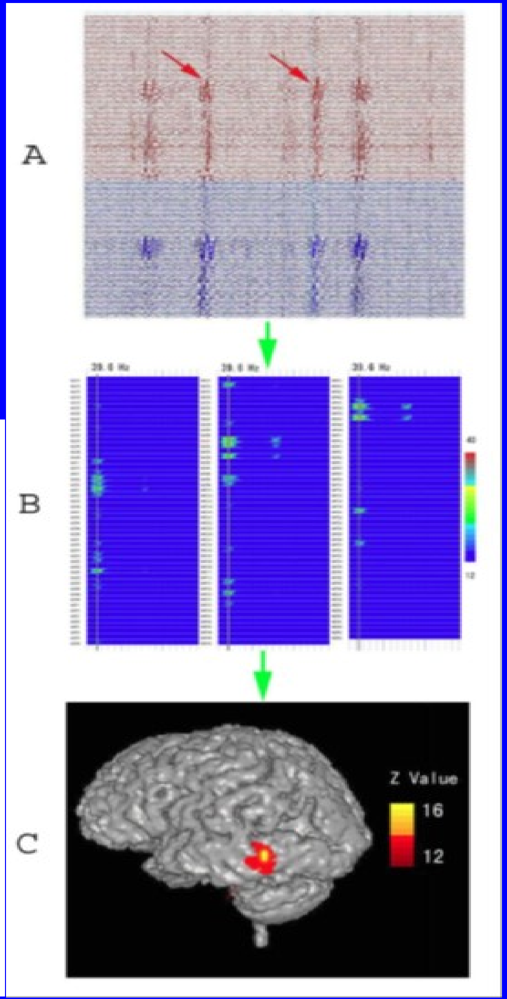
Sensors (Pick up coil)



Development of Magnetoencephalography (MEG)

- High sampling rate hardware
- HFOs are highly localized and can be utilize for developing better MEG/EEG source localization methods (e.g. wavelet-based beamformer).



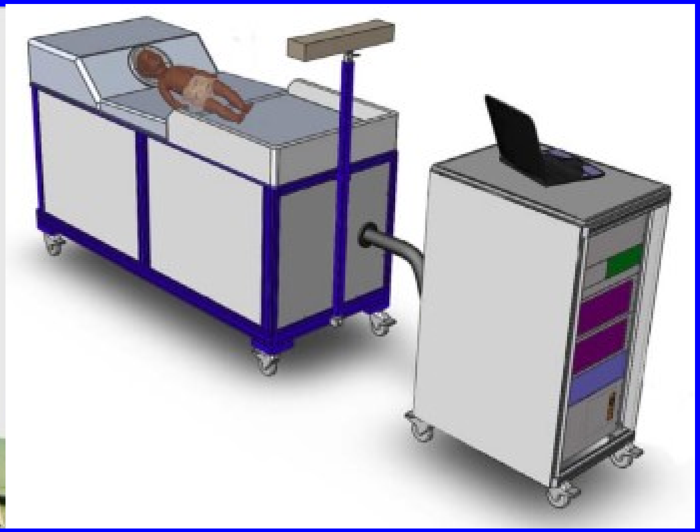


Development of Biomagnetism

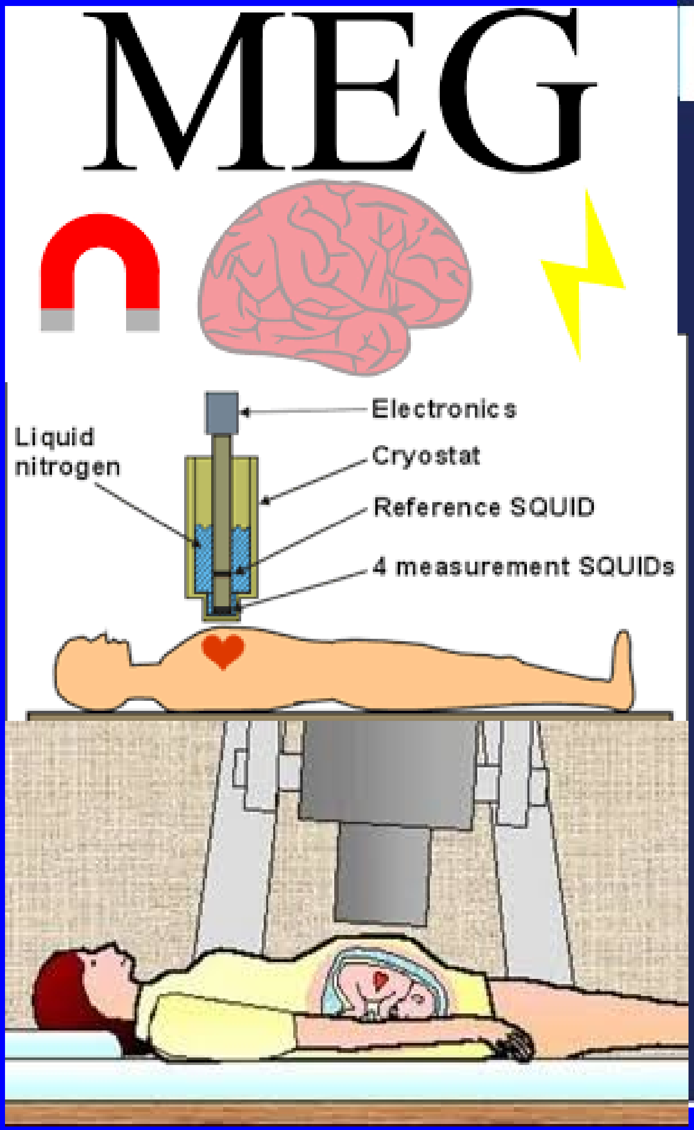
See
Hear
Touch

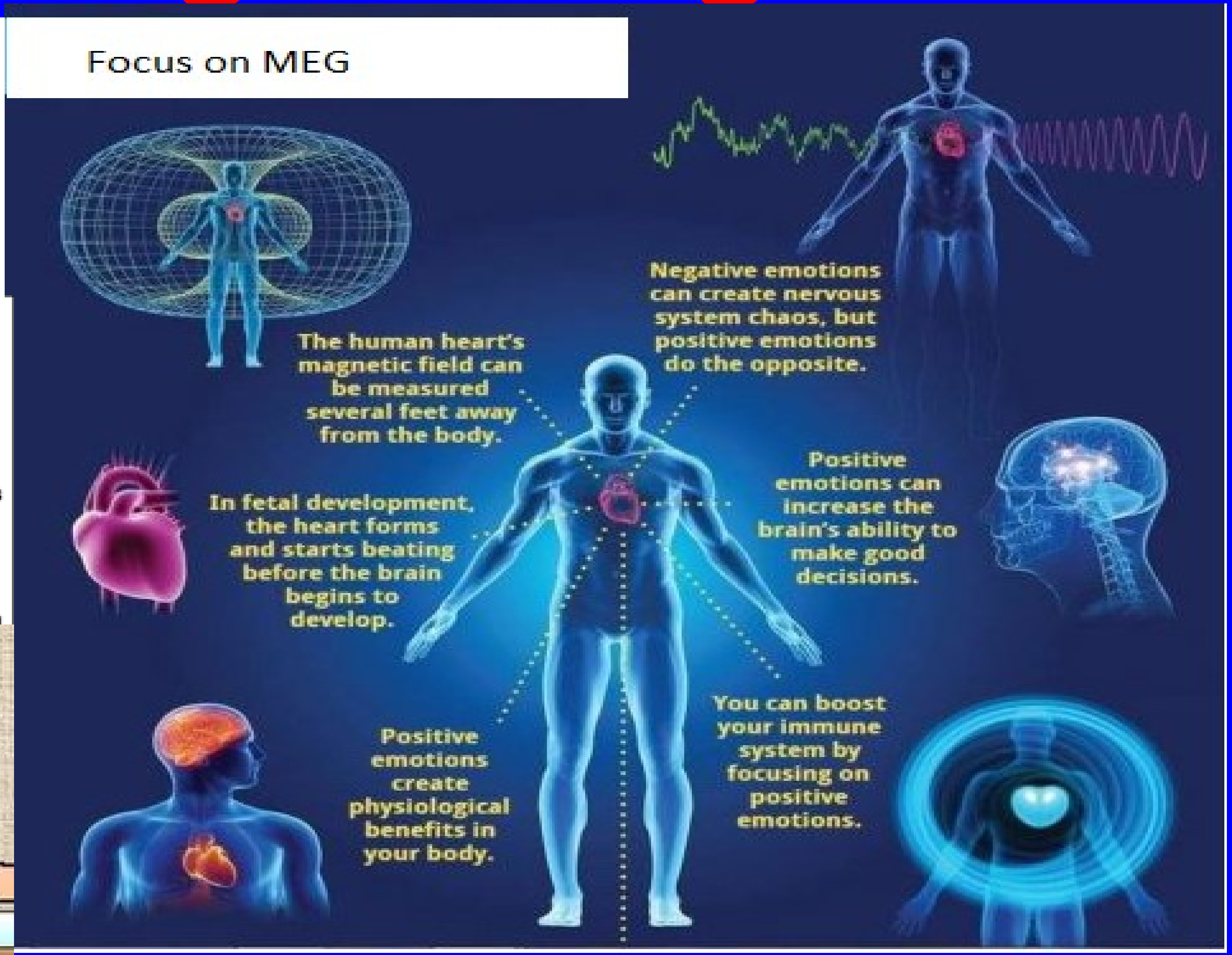
EEG
ECG
EMG
....

MEG
MCG
MMG
....



Biomagnetic Signals





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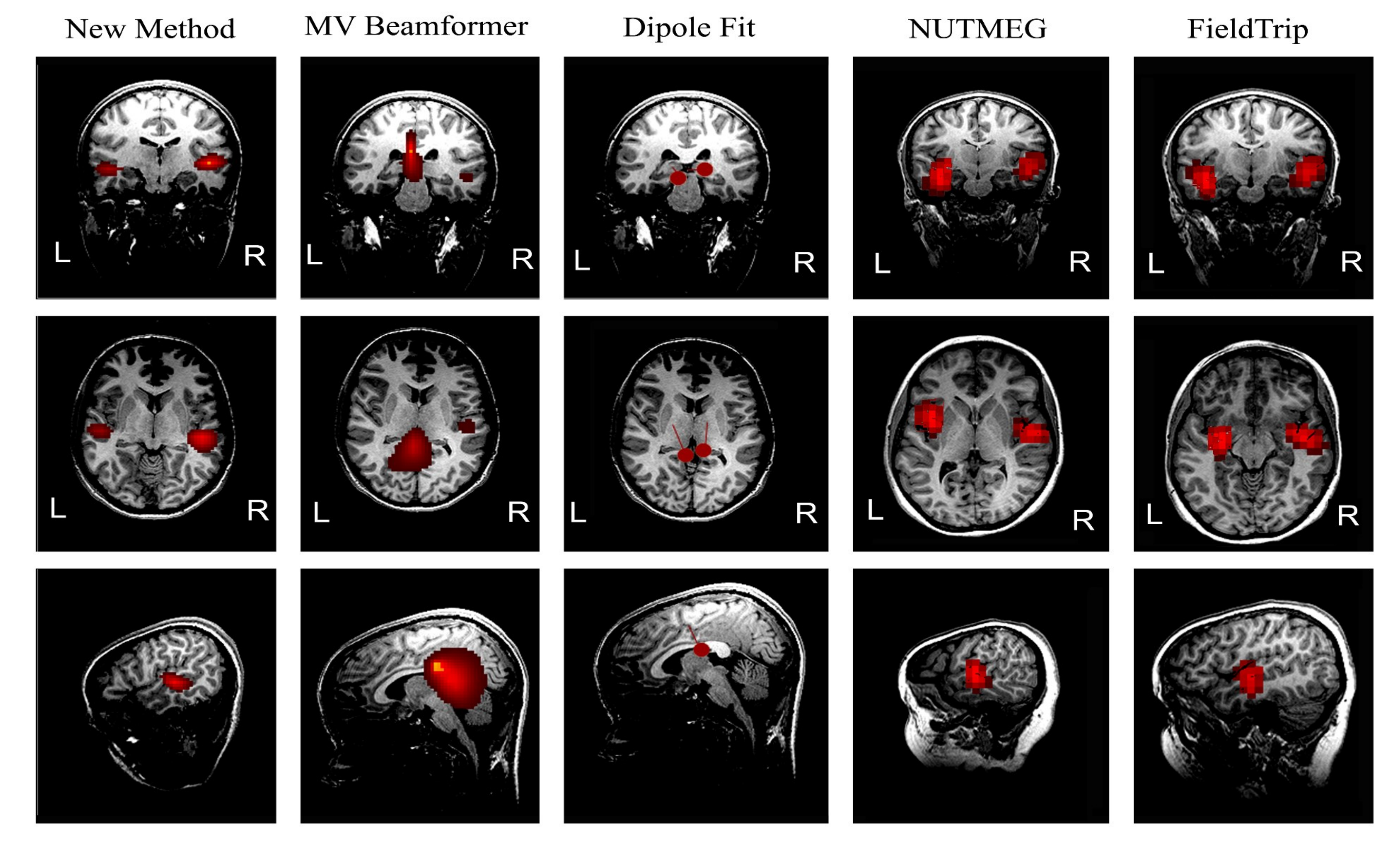
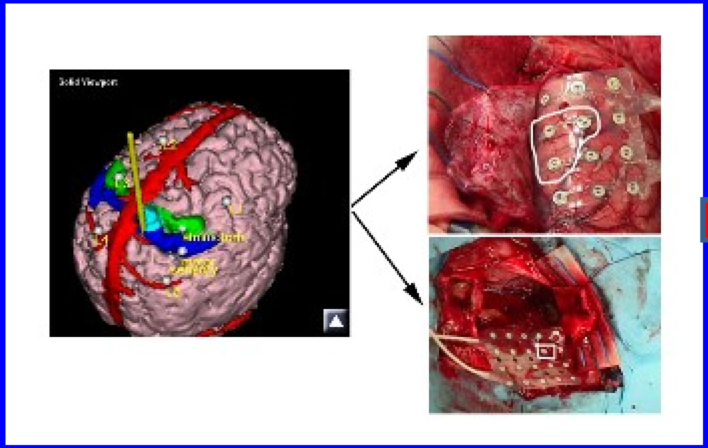
Source Analysis Methods

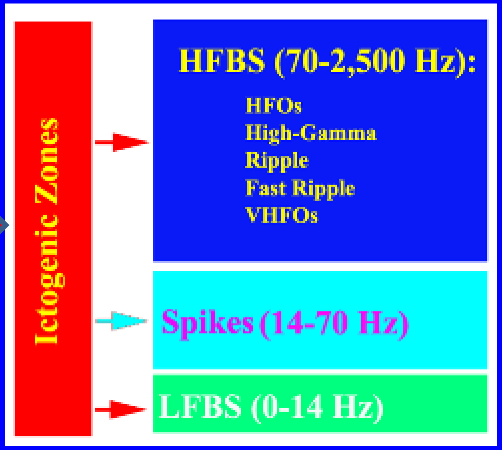


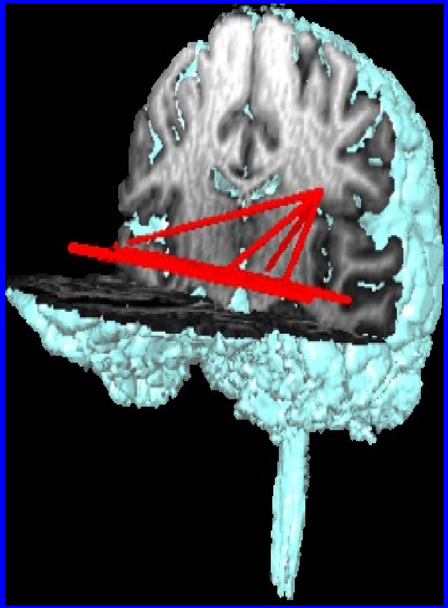
Other Applications of HFBS

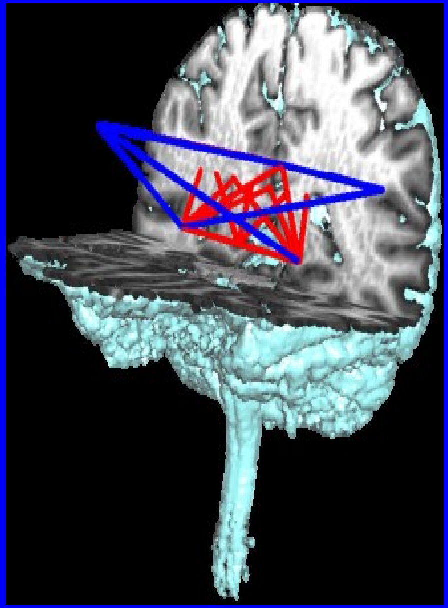
HFOs Are Noninvasively Detectable

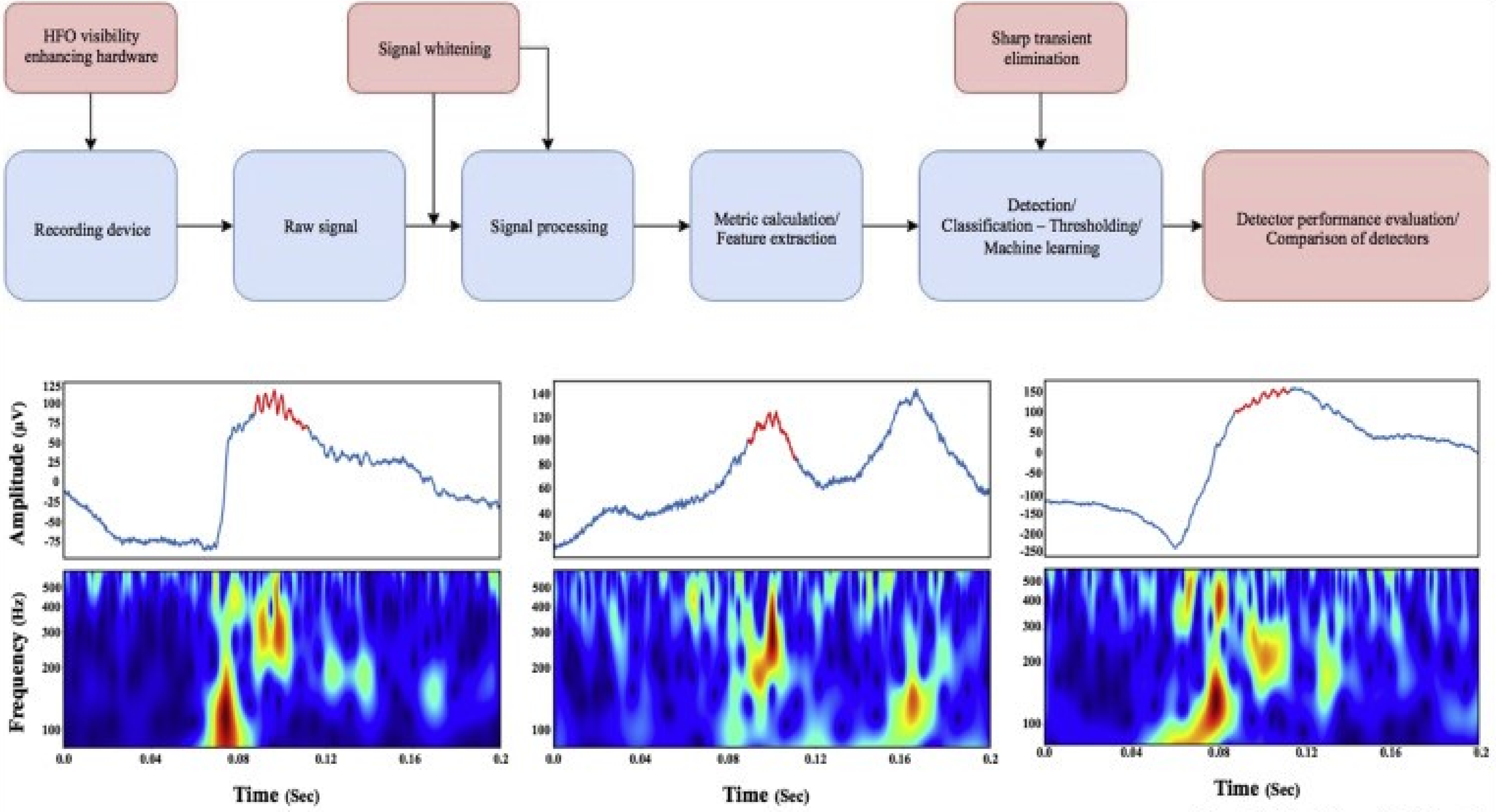
(Change outcomes in Epilepsy and Migraine)



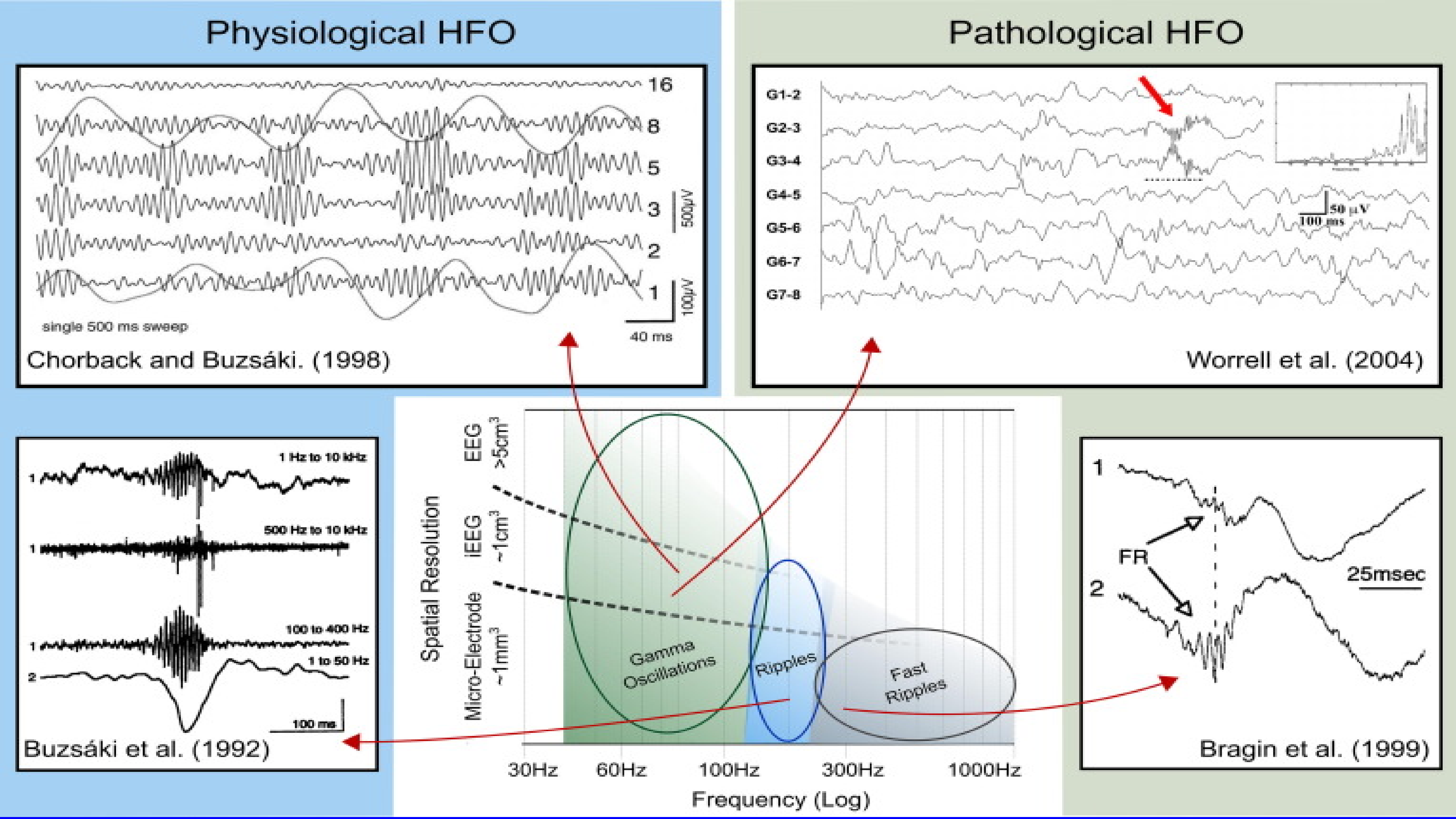








Current Opinion in Biomedical Engineering



Physiological HFO
Pathological HFO
16
8
5
3
2
1
500µV
100µV
single 500 ms sweep
40 ms
Chorback and Buzsáki. (1998)
G1-2
G2-3
G3-4
G4-5
G5-6
G6-7
G7-8
50 µV
100 ms
Worrell et al. (2004)
1 Hz to 10 kHz
500 Hz to 10 kHz
100 to 400 Hz
1 to 50 Hz
100 ms
Buzsáki et al. (1992)
EEG
>5cm³
iEEG
~1cm³
Micro-Electrode
~1mm³
Spatial Resolution
Gamma Oscillations
Ripples
Fast Ripples
30Hz
60Hz
100Hz
300Hz
1000Hz
Frequency (Log)
1
2
FR
25msec
Bragin et al. (1999)

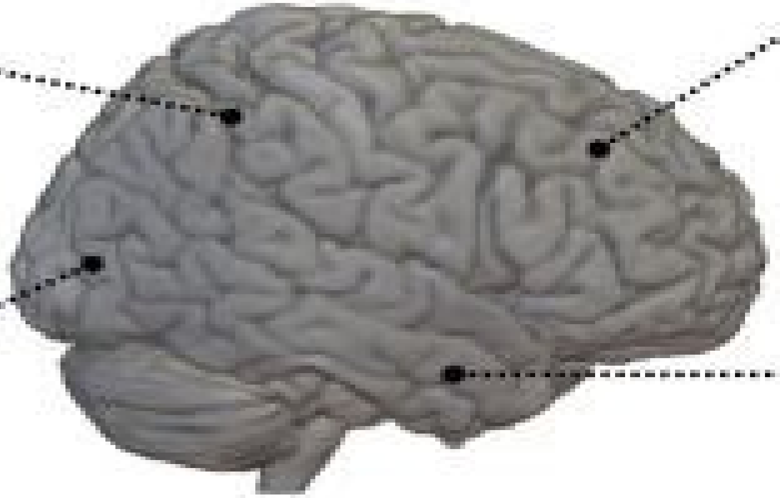
Brain Oscillations during Mental Preparation and Resting-State Activity

-Right hemisphere
-Left hemisphere
-Both

Studies:
(7) Kounios et al. 2006 (mental preparation - CRA)
(8) Kounios et al. 2008 (resting-state - anagrams)

Frontal lobe:
↓α power [7]
↑α power (8-9,75Hz) [8]
↓α power (8-9,75 Hz) [8]
↑β2 power [8]
↑β3 power [8, EC]
↑γ power [8, EC]

Parietal lobe:
↓α power [7]
↓β2 power [8]
↑γ power [8, EO]
↓β3 power [8, EC]
↑β3 power [8, EO]
↓γ power [8, EC]



Occipital lobe:
↓α (10-12,75Hz) power [8]
↑α power [7]
↓β1 power [8]
↑β3 power [8, EO]
↓β2 power [8]

Temporal lobe:
↓α power [7]
↑α power (8-9Hz) [8]
↑β2 power [8]
↑β3 power [8, EO]
↑γ power [8, EC]
↑β3 power [8, EC]

High Insight subjects show widespread greater RH activity [11]