Neural Engineering

* Modeling * Signal processing
* Micro technology * Neurotronics
* Neural prostheses (peripheral, brain, auditory, visual).

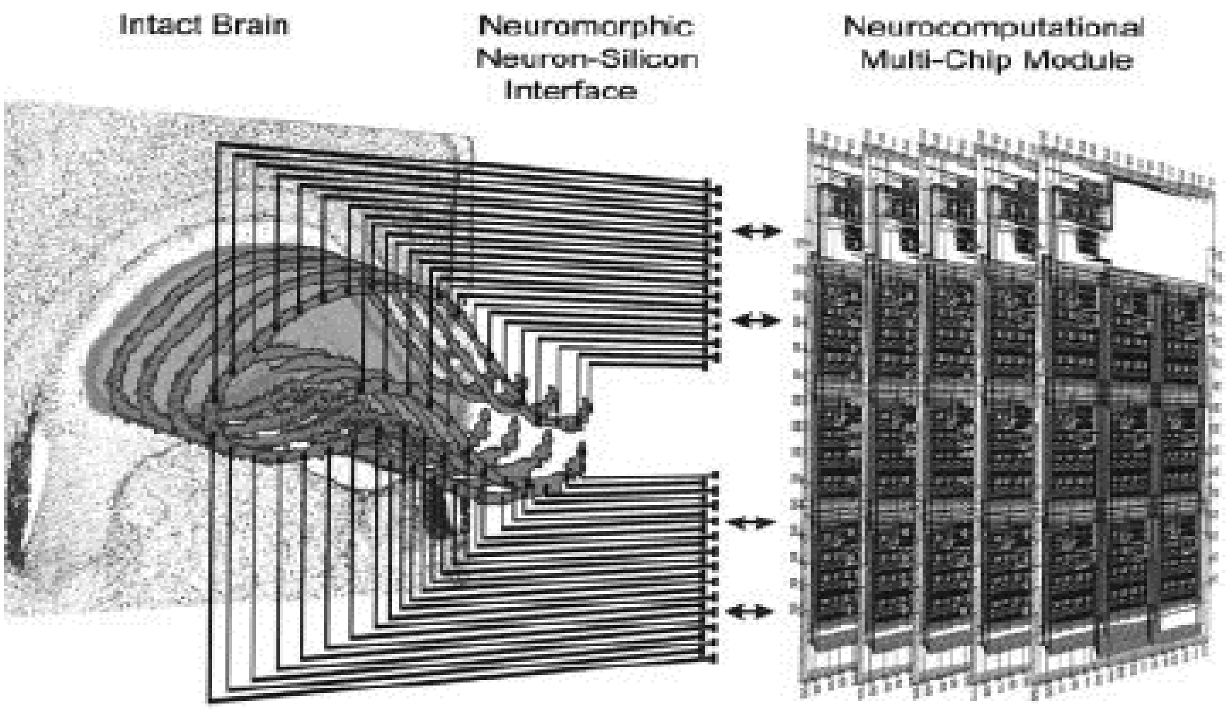
* Artificial Neural Networks.
* Biological Neural Networks.

Machine Intelligence

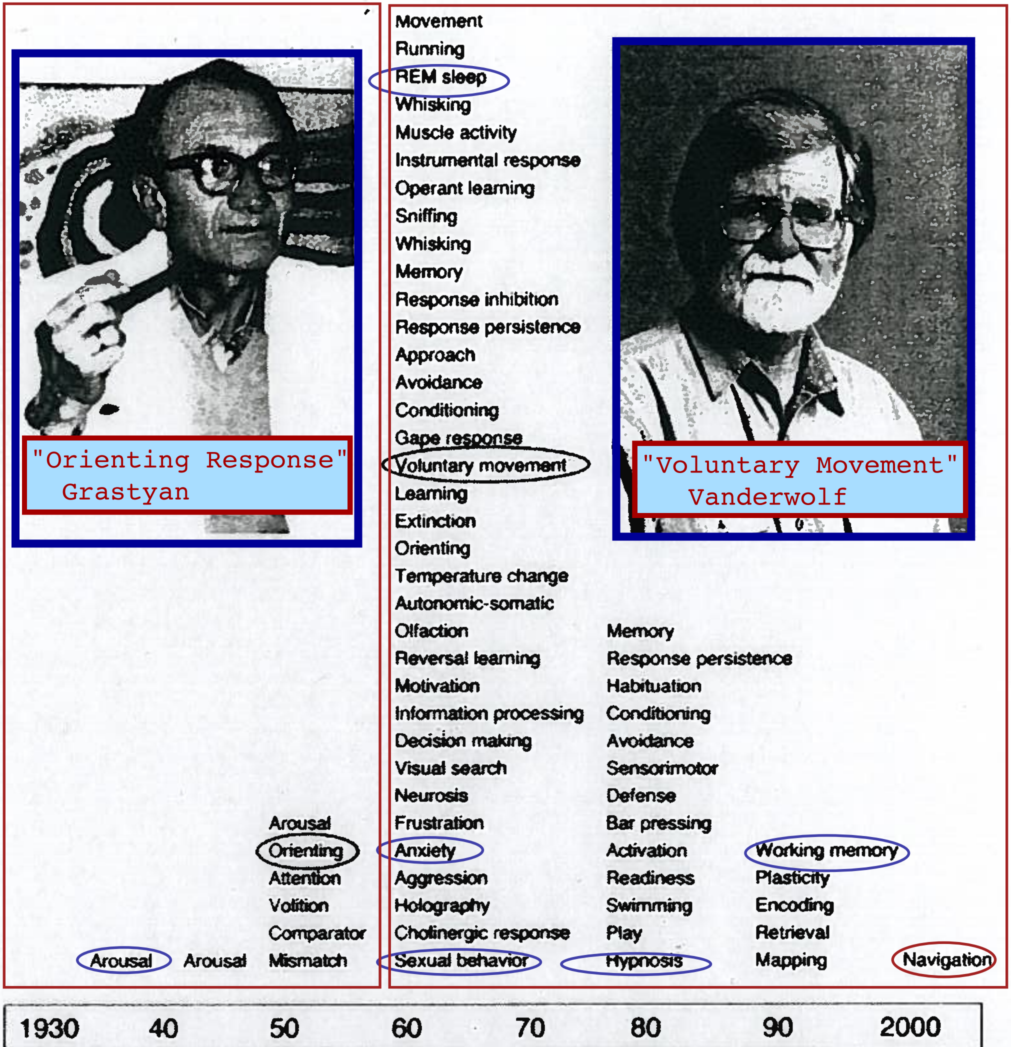
* Cultured neuroprobes * cell adhesion
* Protein interactions * Nerve guidance
* Implantable microsystems
* Neural signaling.

In silico Tissue Engineering

Implantable brain prosthesis on the horizon?



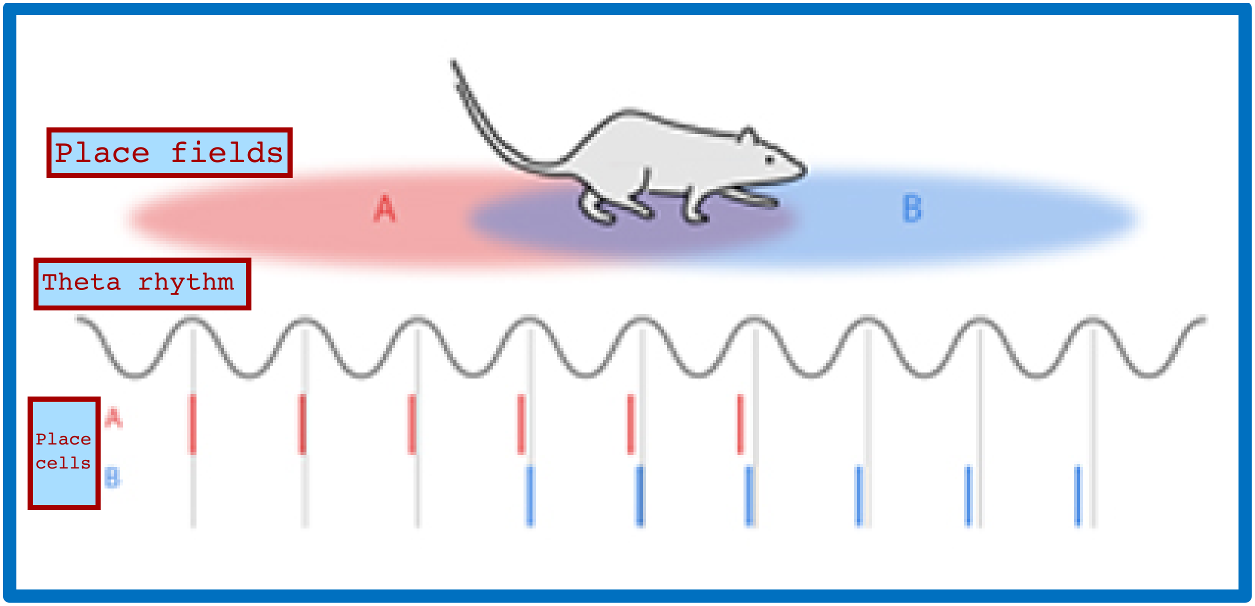
The Theta Electrical Rhythm Of The Brain



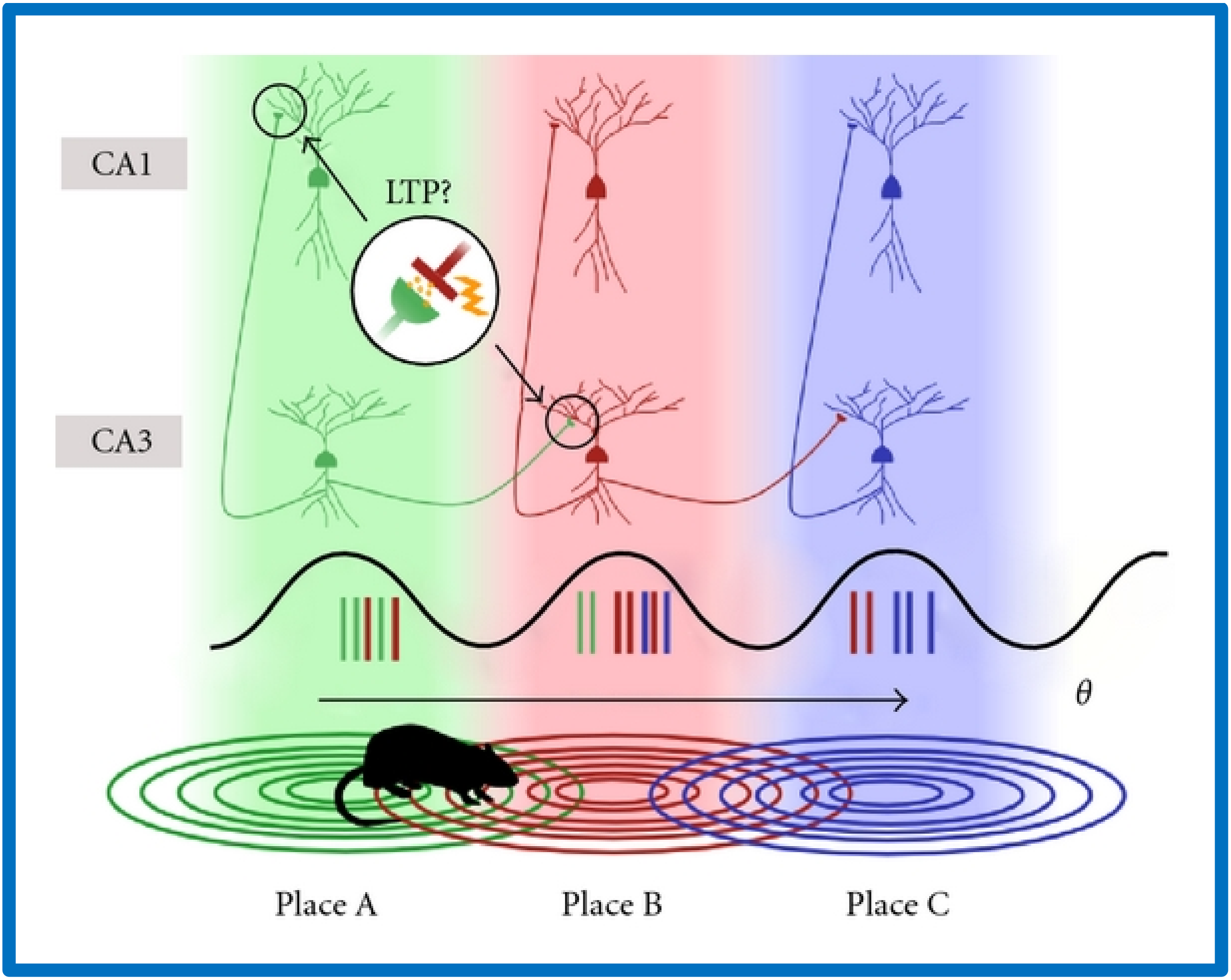
Time line of Hypotheses for

the behavioral correlates of hippocampal theta oscillations. Most ideas can be lumped as reflecting an "input function," such as Grastyán's (left) "orienting response" hypothesis. The most influential "output" hypothesis of theta oscillation has remained the "voluntary movement" correlate by Cornelius (Case) H. Vanderwolf (right).

Place Cells

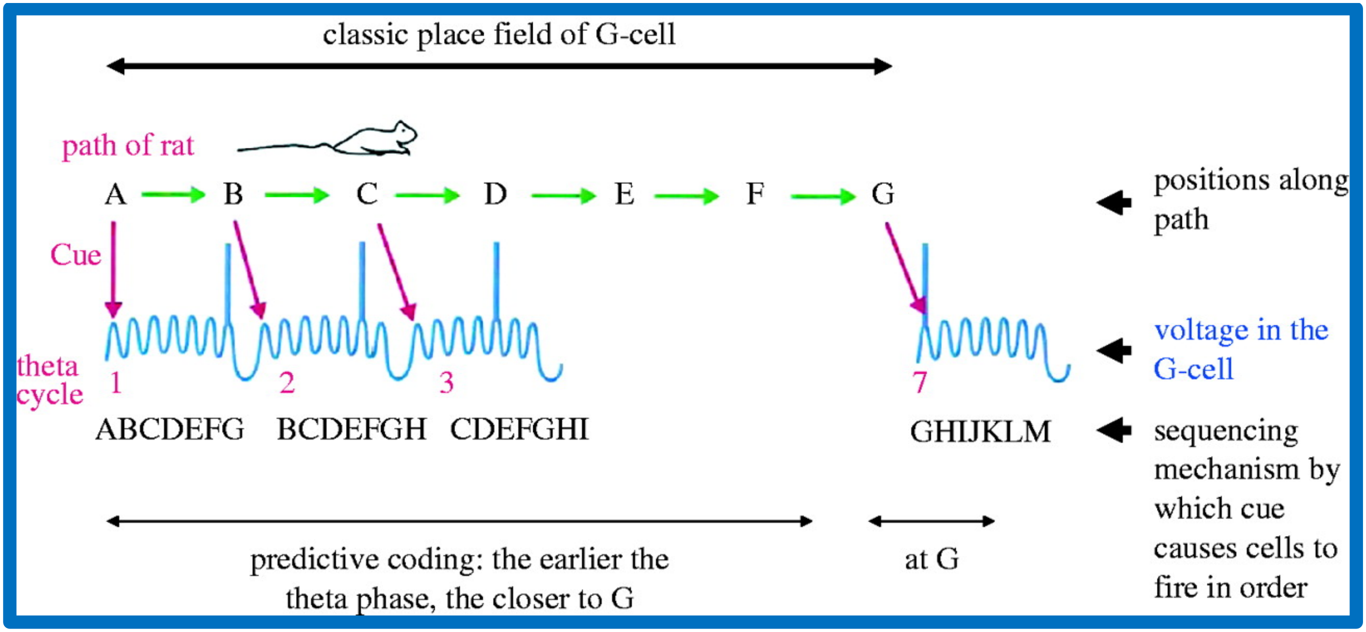


Place cells in the brain are thought to be essential for navigation in space. When one walks through a defined area in a room, the corresponding place cells are activated. The place fields of different place cells may very well overlap. If a rat, for example, crosses the place fields A and B, first the place cell A, then the cells A and B, and finally the place cell B will be activated. This sequence of events will take place in a time frame of seconds. For neurons, though, several seconds almost seem like eternity as many cellular processes take place at much shorter time scales. For connections between two cells to be strengthened, they must be activated within milliseconds. Only if cell A "fires" a few milliseconds before cell B, the brain may be able to memorize the sequence "AB".

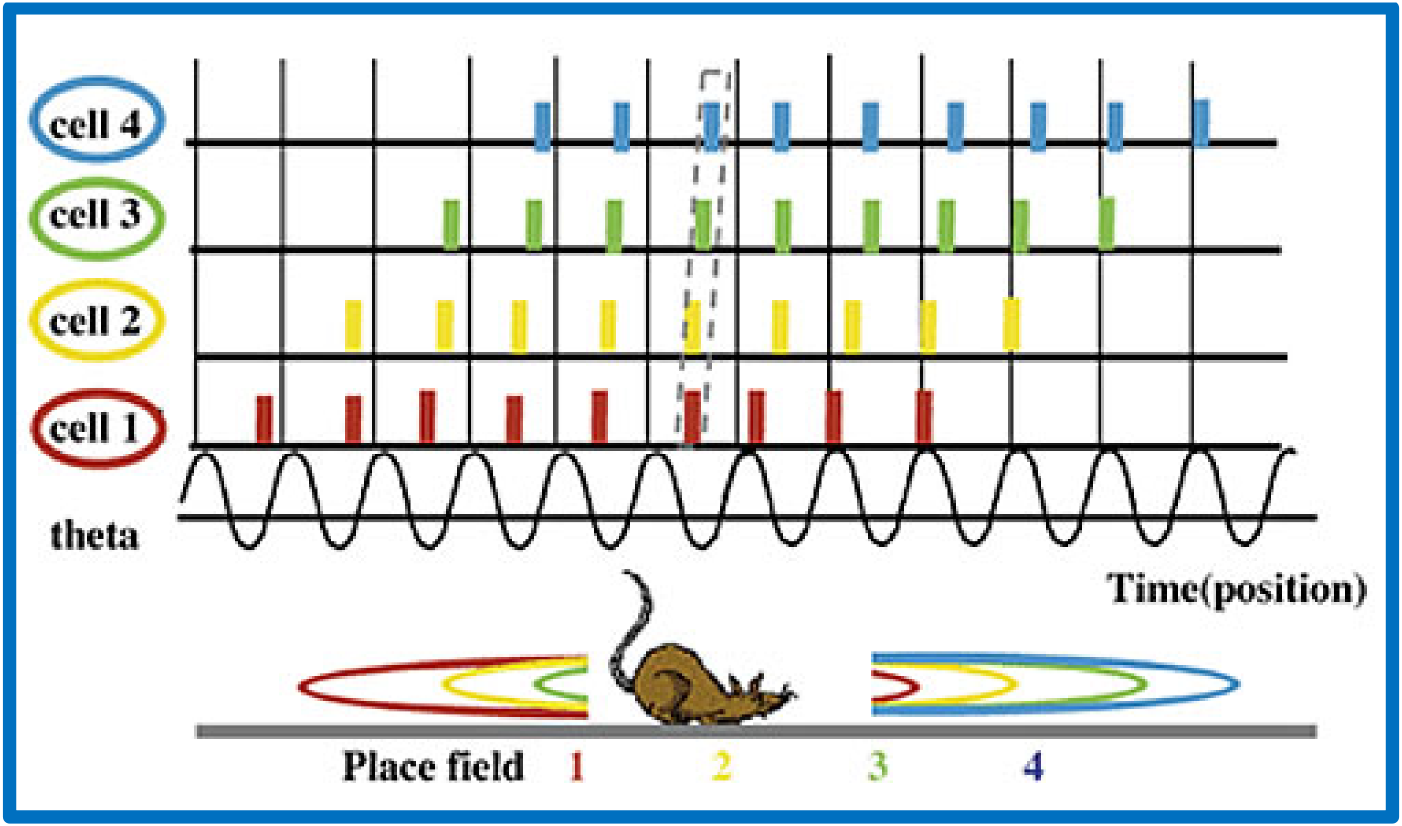


Place cells in CA3 and CA1 exhibit partial or entire place field overlap. During exploration, hippocampal networks undergo strong 4–7 Hz theta modulation. Overlapping CA3 place cells fire sequentially within the same theta cycle, establishing the conditions necessary for synaptic plasticity to occur between CA3 cell assemblies associated in time and space. Synaptic plasticity could also take place between CA3 and CA1 place cells with the same receptive field as both would fire near simultaneously and are anatomically coupled via the Schaffer collateral to CA1 pathway.

Theta Phase Precession



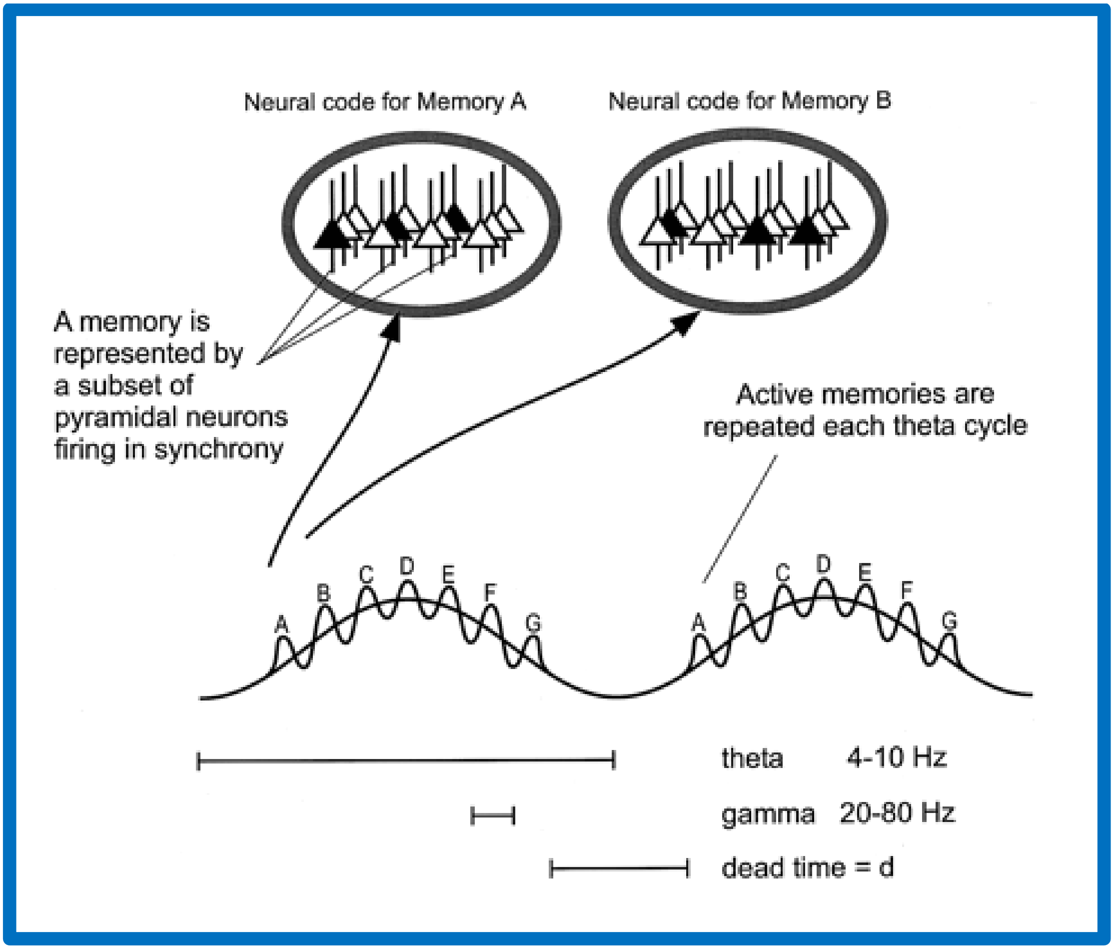
The place field of the illustrated cell covers a small part of a path; this part is labelled by successive letters of the alphabet—the firing starts at A and stops when the rat moves past G. Voltage (intracellular) traces show successive theta cycles (nos. 1–7) each of which has seven gamma subcycles. Firing occurs near the peak of a gamma cycle and with earlier and earlier theta phase as the rat runs from left to right. This is termed phase precession. The precession process can be understood as resulting from a sequencing (chaining) mechanism within each theta cycle in which the cue (current position) triggers sequential readout from different cells representing successive positions (e.g. A–G) along the path. This is termed a sweep. The cell illustrated represents the position G. Firing at positions A–F is predictive of the rat being at G.



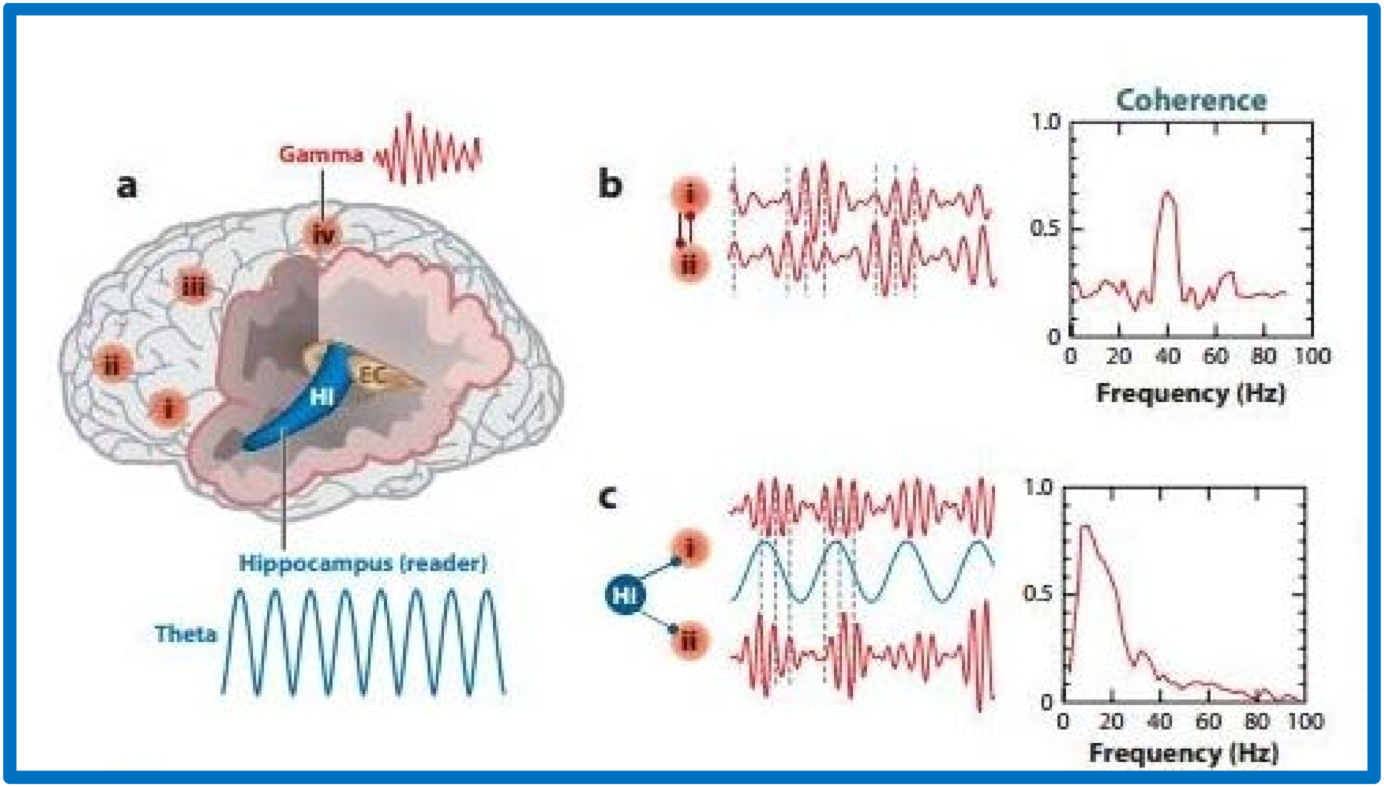
Theta phase precession observed in the place cells of the rat hippocampus. When the rat runs to the right, the phase shift in firing within each theta rhythm cycle occurs in place cells 1 to 4, which are activated sequentially. The phase is arranged in order of firing within one phase cycle (an example is represented by gray lines). The rat running environment is expressed in compressed form in each theta cycle.

The Theta-Gamma Neural Code

Theta and gamma frequency oscillations occur in the same brain regions and interact with each other, a process called ***cross-frequency coupling***. The dual oscillations form a code for representing multiple items in an ordered way. This form of coding has been most clearly demonstrated in the hippocampus, where different spatial information is represented in different gamma subcycles of a theta cycle. Experimental evidence demonstrated the correlation of oscillatory properties with memory states, correlation with memory performance, and effects of disrupting oscillations on memory. This coding scheme coordinates communication between brain regions and is involved in sensory as well as memory processes.



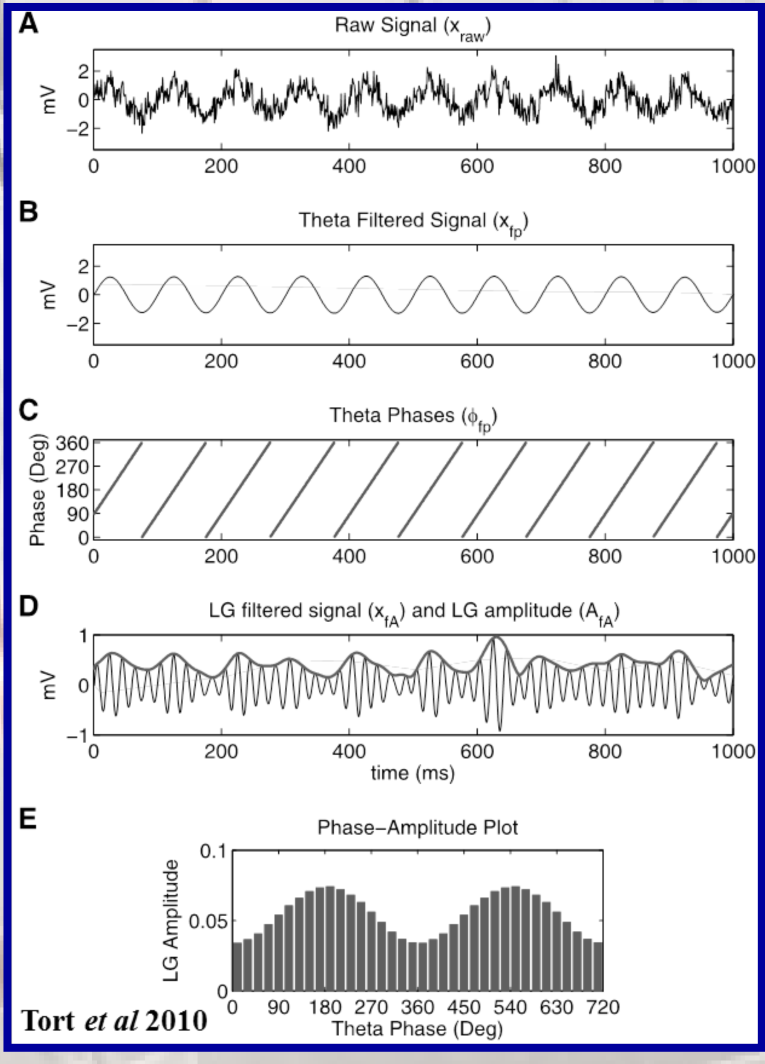
Schematic of the theta-gamma neural code. The ovals at top represent states of the same network during two gamma cycles (active cells are black and constitute the ensemble that codes for a particular item). Different ensembles are active in different gamma cycles.



Oscillatory coupling mechanisms. (a) Schematic view of the human brain showing hot spots of transient gamma oscillations (i–iv) and theta oscillation in the hippocampus (HI); entorhinal cortex (EC). Oscillators of the same and different kind (e.g., theta, gamma) can influence each other in the same and different structures, thereby modulating the phase, amplitude, or both. (b) Phase-phase coupling of gamma oscillations between two areas. Synthetic data used for illustration purposes. Coherence spectrum between the two signals can determine the strength of phase coupling. (c) Cross-frequency phase-amplitude coupling. Although phase coupling between gamma waves is absent, the envelope of gamma waves at the two cortical sites is modulated by the common theta rhythm.

Modulation Index (MI) or

Cross Frequency Coupling Index (I_{CFC})



Analytic Functions and the Hilbert Transform

In mathematics and signal processing, an analytic signal is a complex-valued function that has no negative frequency components. The real and imaginary parts of an analytic signal are real-valued functions related to each other by the Hilbert transform.

The analytic representation of a real-valued function is an *analytic signal*, comprising the original function and its Hilbert transform. This representation facilitates many mathematical manipulations.

Consider a real valued signal s(t), then

$$\boxed{s_a(t) = s(t) + j\,\mathcal{H}\{s(t)\} = A(t)e^{j\Phi(t)}}$$

where

$s_a(t)$ ≡ analytic representation of s(t).

$\mathcal{H}\{s(t)\}$ ≡ Hilbert transform of s(t) ≡ convolution of s(t) with $h(t) = \frac{1}{\pi t}$

$A(t)$ ≡ envelope of s(t).

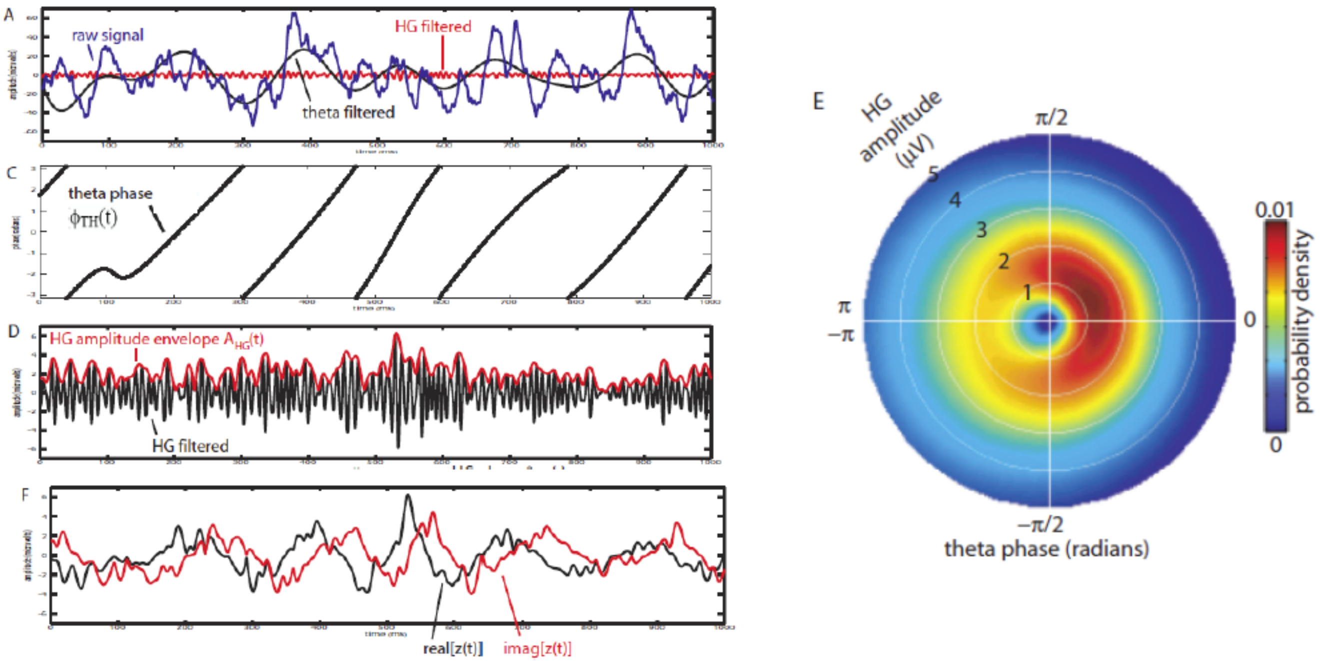
$\Phi(t)$ ≡ instantaneous phase of s(t).

Modulation Index (MI)

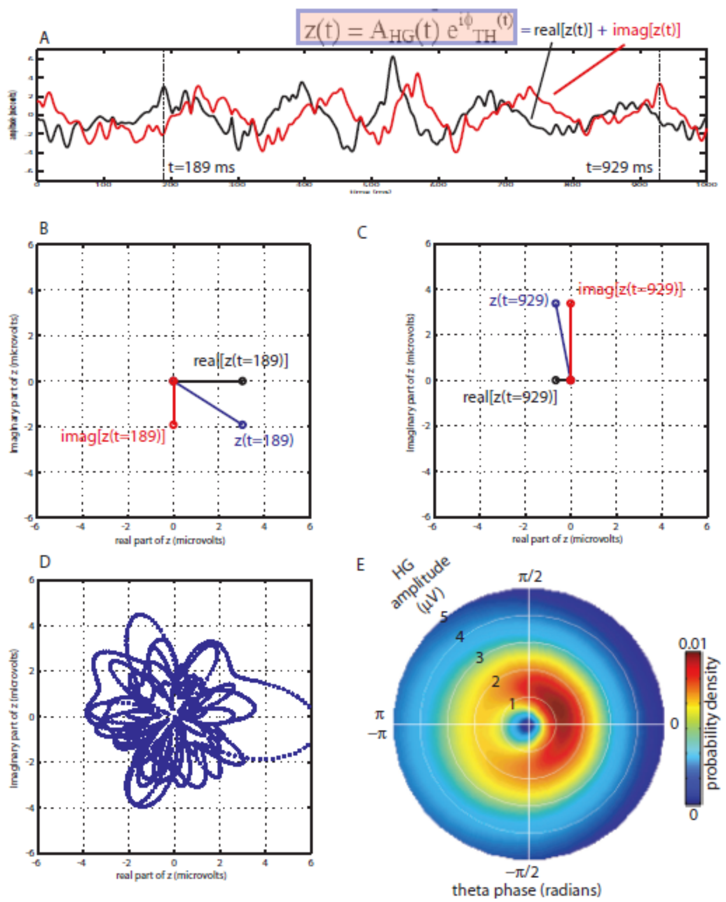
MI involves the construction of a composite complex-valued signal, created from the combination of the amplitude time series of one frequency with the phase time series of a second frequency:

$$z(t) = A_{f_1}(t)e^{i\phi_{f_2}(t)}$$

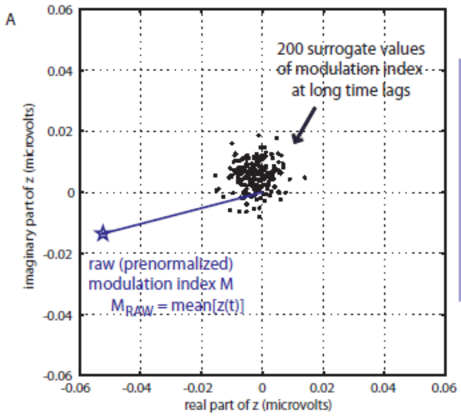
where f_1 represents the frequency of the amplitude time series and f_2 the frequency of the phase time series signal.



R. T. Canolty, *et al.*
Science **313**, 1626 (2006);

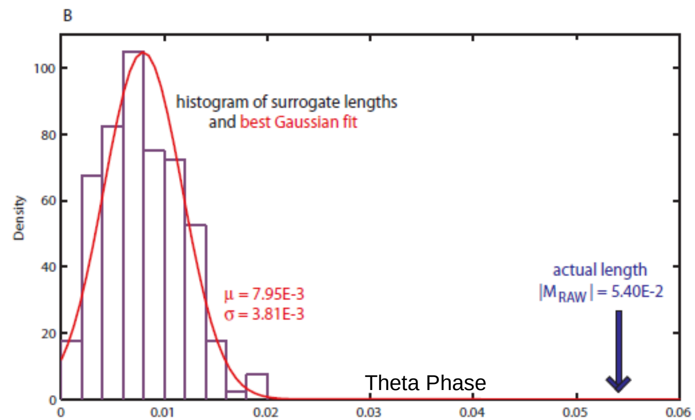


MODULATION INDEX EXAMPLE A) The real (black) and imaginary (red) parts of z(t) with two time points marked at t = 189 ms and t = 929 ms. B) The value of the composite signal z(t) at t = 189 ms in the complex plane (blue), together with the values of the real (black) and imaginary (red) parts. C) As in B, for t = 929 ms. D) The values of z(t) for all sample points over the one second interval examined. E) The estimated joint probability density function (PDF) for z(t), which can be thought of as a normalized histogram of values assumed by z in the complex plane. Note that if the distribution of theta phase is uniform and the HG amplitude time series and the theta phase time series are statistically independent, then this PDF will be radially symmetric. Since the phase distribution is uniform (data not shown), then any the observed asymmetry must be due to statistical dependence between the two time series.



Compare the actual mean M (call it M_{RAW}) to a set of surrogate means $\{M_{sur}\}$ created by offsetting A_{HG} and φ_{TH} by some large time lag. That is, we introduce a time lag τ between A_{HG} and φ_{TH} such that the composite signal is a function of both time and lag:

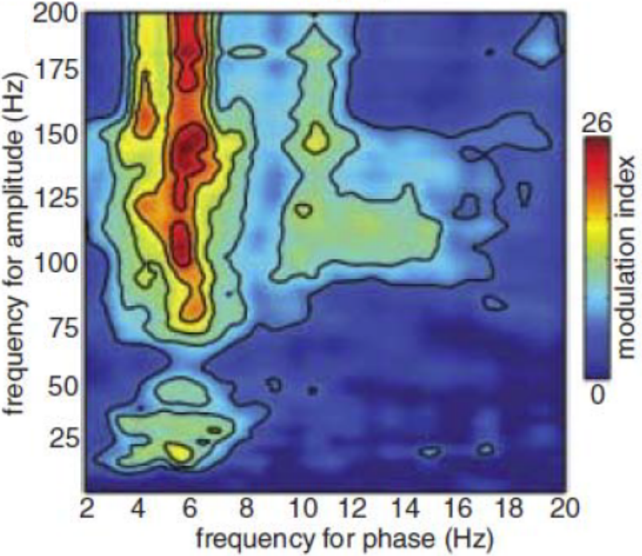
$$z(t, \tau) = A_{HG}(t + \tau)\, e^{i\varphi_{TH}(t)}$$



Normalized modulation index $|M| = (|M_{RAW}| - \mu)/\sigma = 12.1$

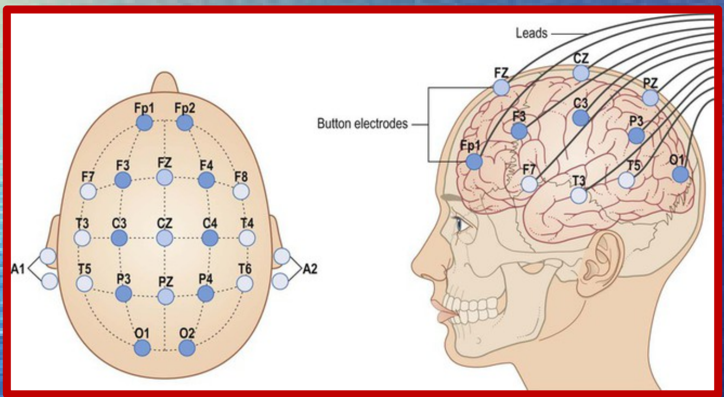
MODULATION INDEX EXAMPLE A) The raw modulation index value in the complex plane (blue), which is the temporal mean of z(t), or the first moment of the PDF Also shown are 200 surrogate values aquired by computing the modulation index after first shifting the HG amplitude time series and the theta phase time series by some large lag. In this way the statistics of the individual time series are maintained, and only the pairing of sample points between the two time series is changed. Each actual and surrogate modulation index value has a modulus or length (which is used to determine the strength of coupling) and a phase, which indicates where in the low freuqency waveform large analytic amplitudes of the high frequency band tend to occur. All relevant independent statistical biases of the two time series will be reflected by the modulus and phase of the surrogate values. B) The histogram of surrogate lengths (black) and the best fit Gaussian (red). Normalizing the raw modulation index values by the surrogate fits isolates the effect of interest, the statistical dependence between the two time series.

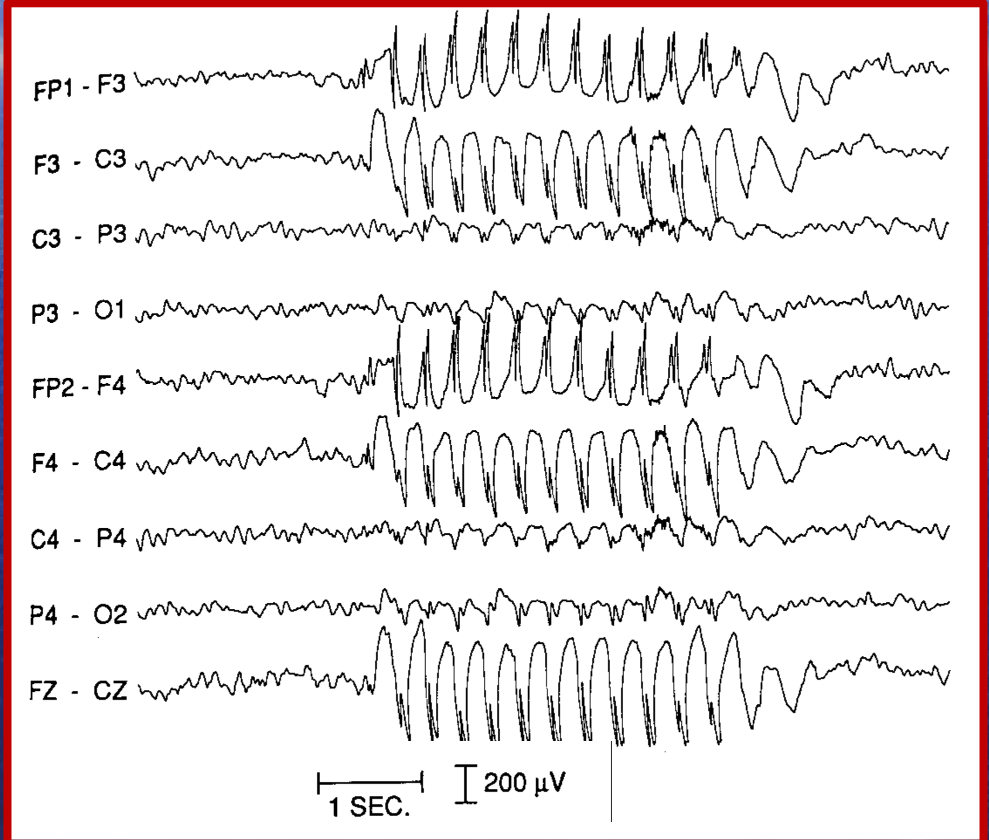
Comodulogram




Electrical Rhythms
of the Brain in
Epilepsy

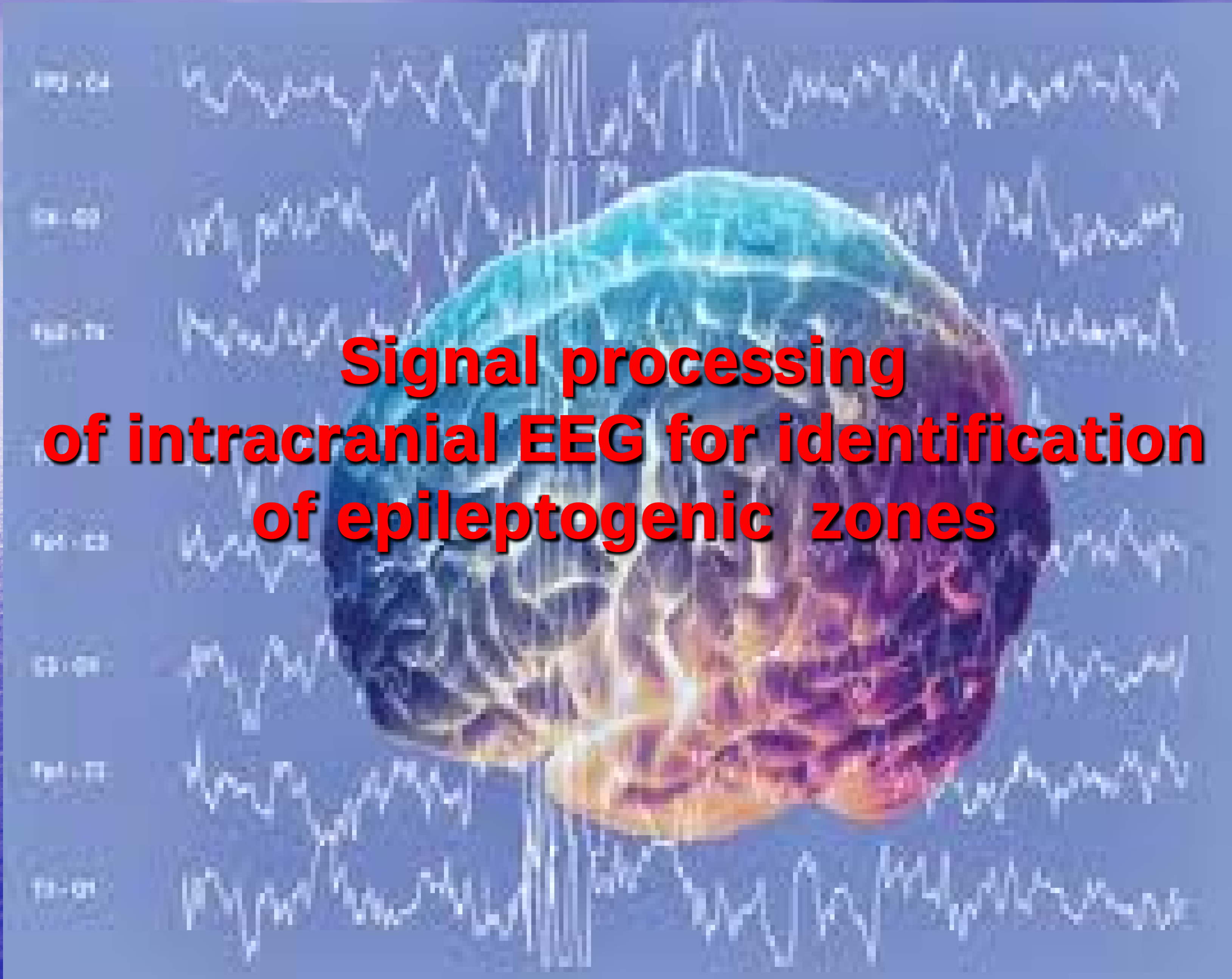
Epilepsy is a neurological disorder in which normal brain functions are disrupted by abnormal spontaneous, rhythmic, coordinated neuronal electrical discharges (known as **seizures**). There are many different types with varying dynamics.





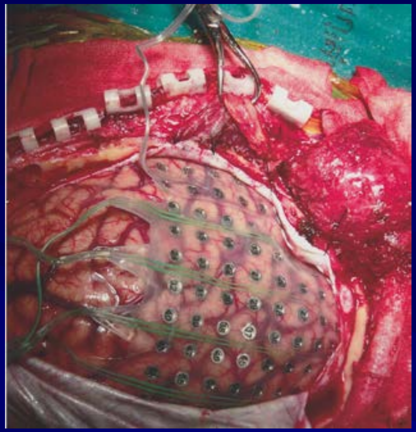
An example of EEG recording during epileptic seizure of the absence type in a human patient.

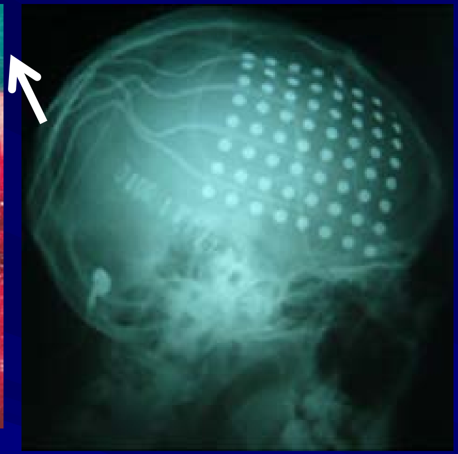
Signal processing of intracranial EEG for identification of epileptogenic zones

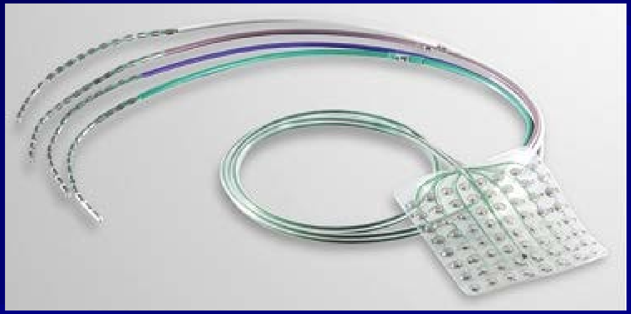


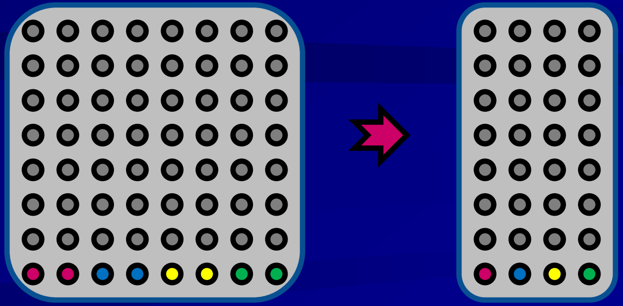
iEEG Patient Data Acquisition

Dr Chinvarun: Thailand Comprehensive Epilepsy Program, Phramongkutklao Hospital



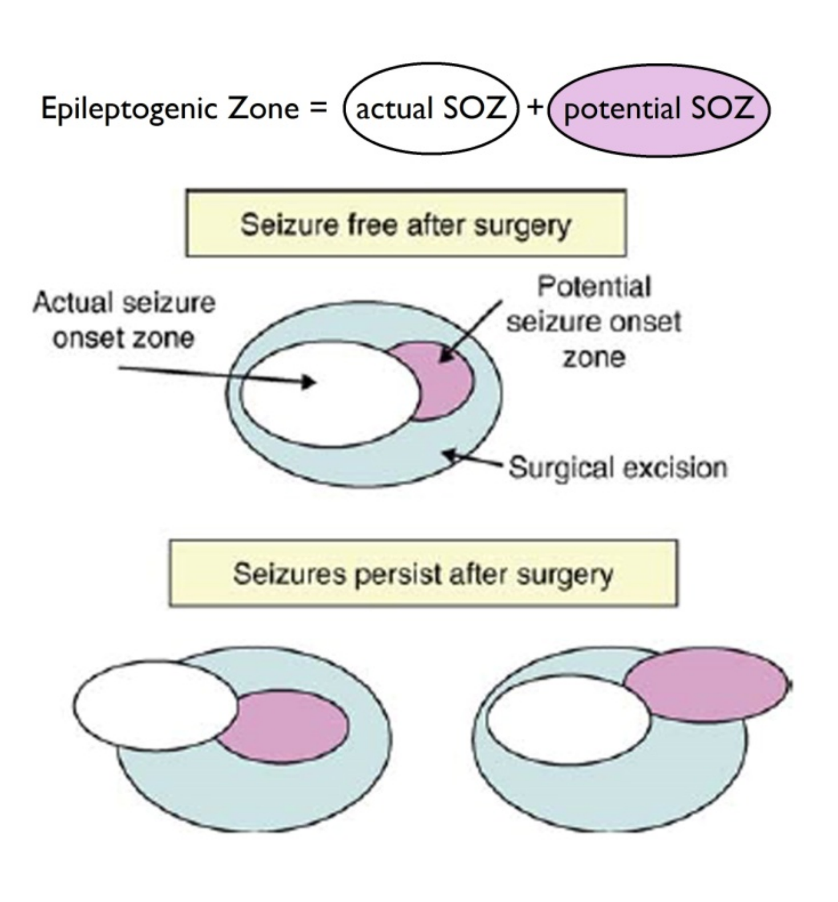




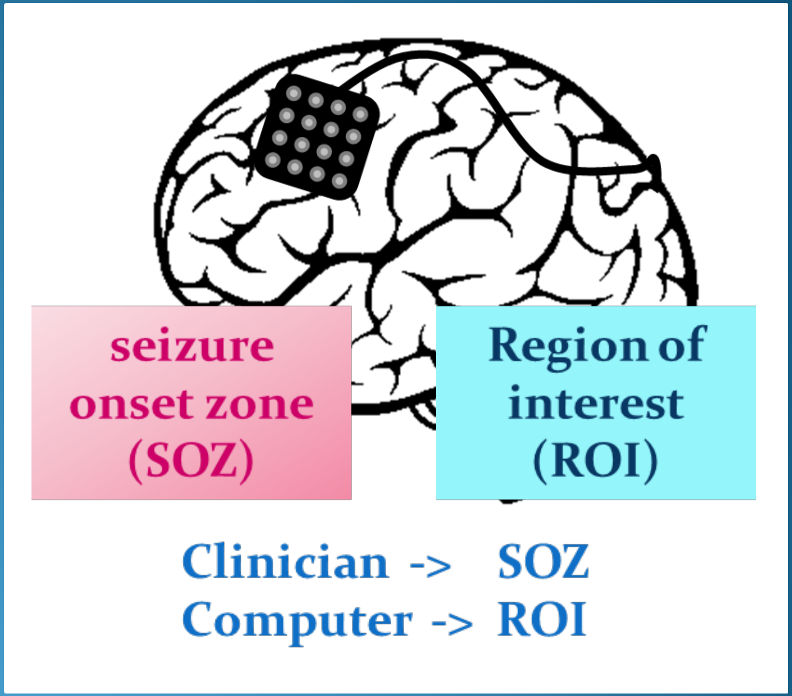


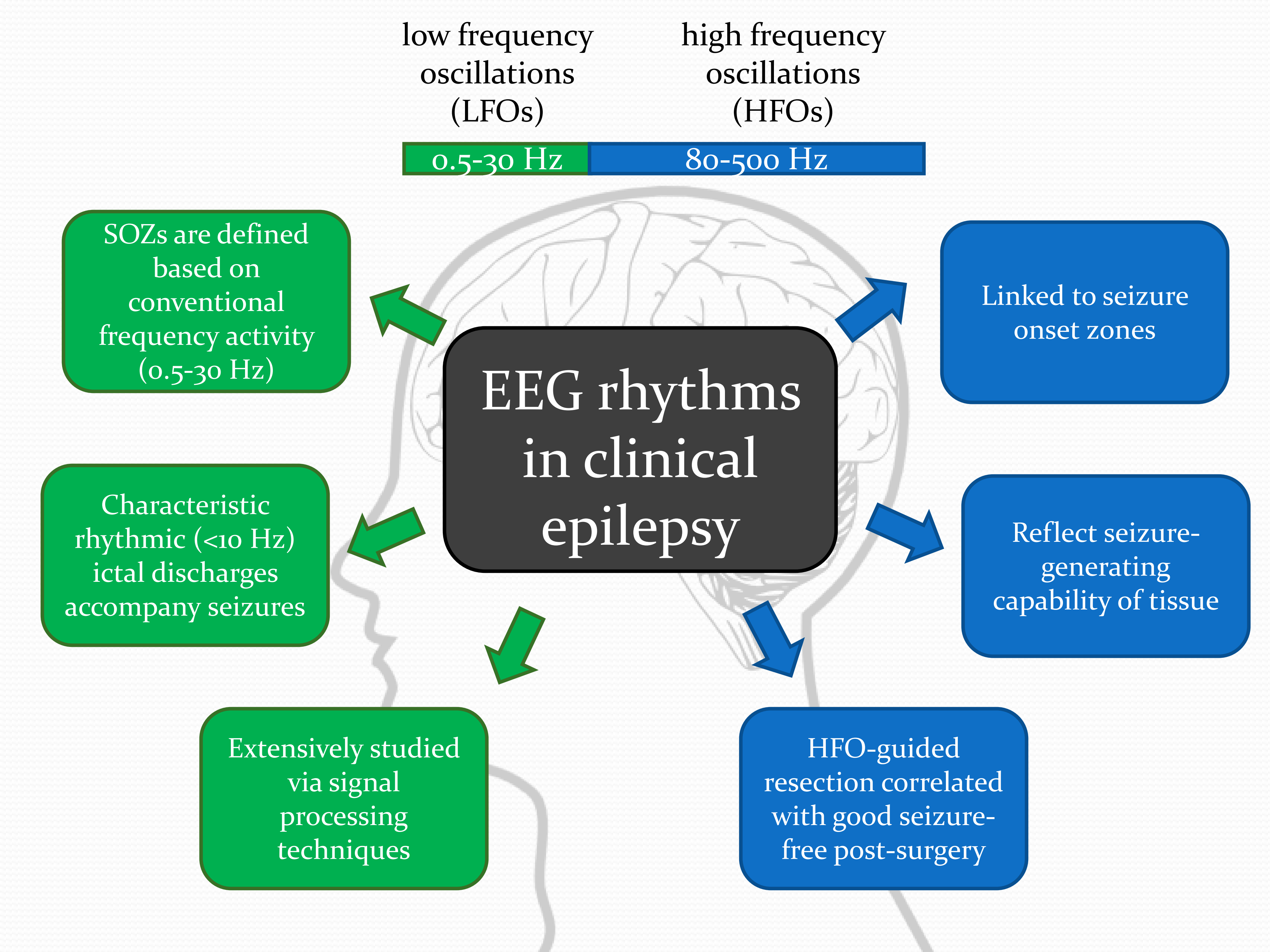
- Subdural grid electrodes
  - 64 contact (8x8)
  - platinum/stainless steel contacts
  - Diameter: 3 mm
  - Interelectrode distance: 10mm (c.c)
- iEEG recording
  - Stellate HARMONIE digital system (Montreal, QC)
  - Sampling rate: 2000 Hz
  - Reference electrode: behind ears
  - Ground electrode: forehead
  - Hardware filter: HP @ 0.05 Hz
- Offline Processing
  - Bipolar Montage as Channels
  - FIR notch filtering (50 Hz + harmonics)

Epileptogenic Zone (EZ)



Wieser and Zumsteg, 2009




low frequency oscillations (LFOs)
high frequency oscillations (HFOs)
0.5-30 Hz
80-500 Hz
EEG rhythms in clinical epilepsy
SOZs are defined based on conventional frequency activity (0.5-30 Hz)
Characteristic rhythmic (<10 Hz) ictal discharges accompany seizures
Extensively studied via signal processing techniques
Linked to seizure onset zones
Reflect seizure-generating capability of tissue
HFO-guided resection correlated with good seizure-free post-surgery

Methods

Electrical Rhythm Extraction:

- **Empirical Mode Decomposition (EMD)**

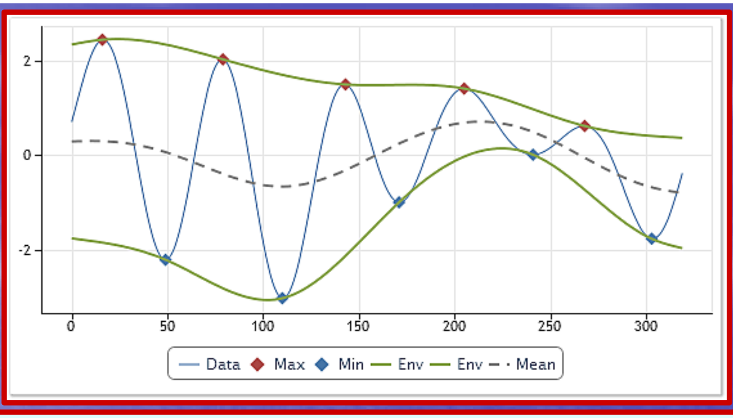
Frequency-Time Distributions:

- **Wavelet Transform (WT)**
- **Frequency Normalized Wavelet Transform (NWT)**
- **Wavelet Phase Coherence (WPC)**
- **Modulation Index (MI)** `(Cross Frequency Coupling Index)`

Machine Learning:

- **Support Vector Machines (SVMs)**

Empirical Mode Decomposition (EMD)



Process

•The EMD will break down a signal into its component Intrinsic Mode Functions (IMFs).
•An IMF is a function that has:

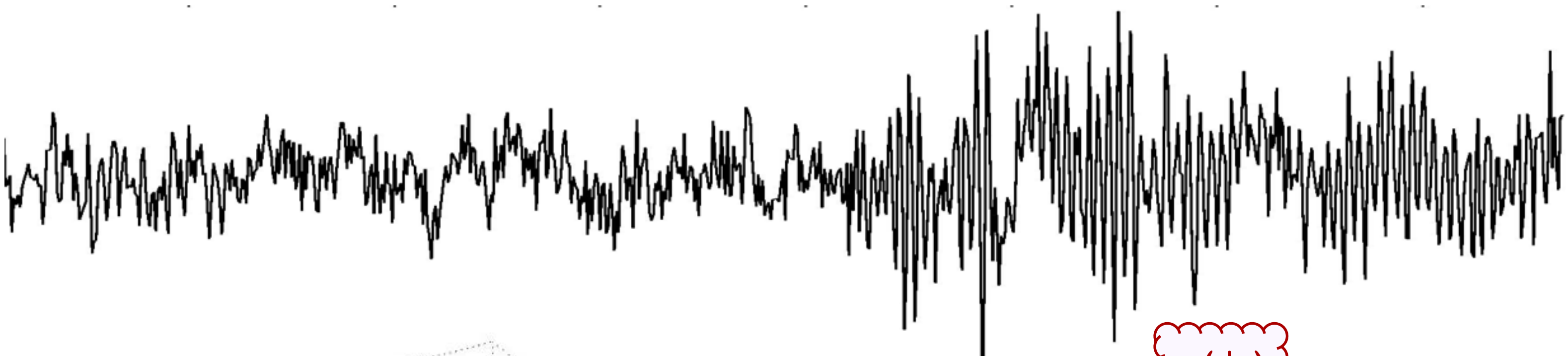
1. Only one extreme between zero crossings, and
2. A mean value of zero.

For a signal X(t), let m_1 be the mean of its upper and lower envelopes as determined from a cubic-spline interpolation of local maxima and minima.
• The first component h_1 is computed:
$h_1=X(t)-m_1$
• In the second sifting process, h1 is treated as the data, and m_{11} is the mean of its upper and lower envelopes:
$h_{11}=h_1-m_{11}$
•This sifting procedure is repeated k times, until h_{1k} is an IMF, that is:
$h_{1(k-1)}-m_{1k}=h_{1k}$
•Then it is designated as $c_1=h_{1k}$, the first IMF component from the data, which contains the shortest period component of the signal.

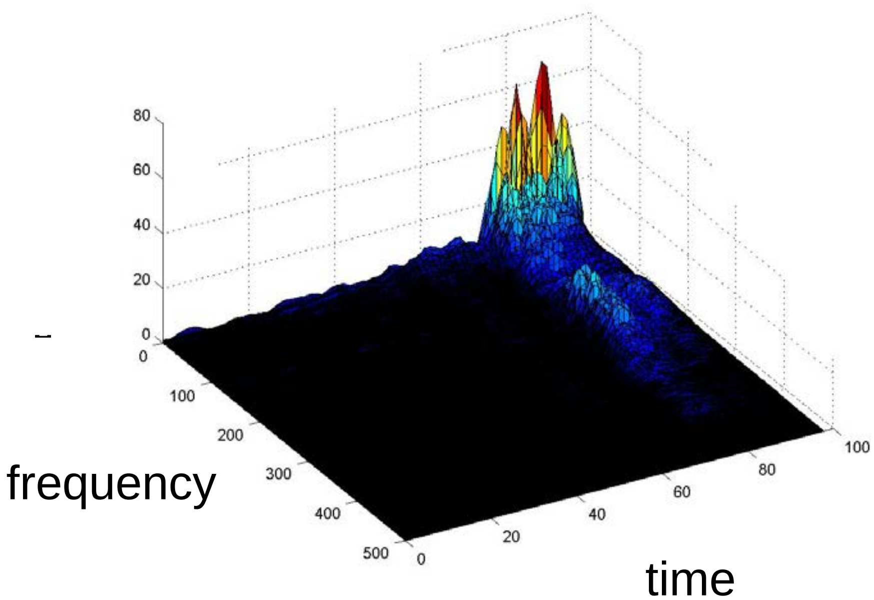
•Separate it from the rest of the data: $X(t)-c_1 = r_1$

•The procedure is repeated on r_j: $r_1-c_2 = r_2,\dots,r_{n-1} - c_n = r_n$

Wavelet Transforms



x(t)



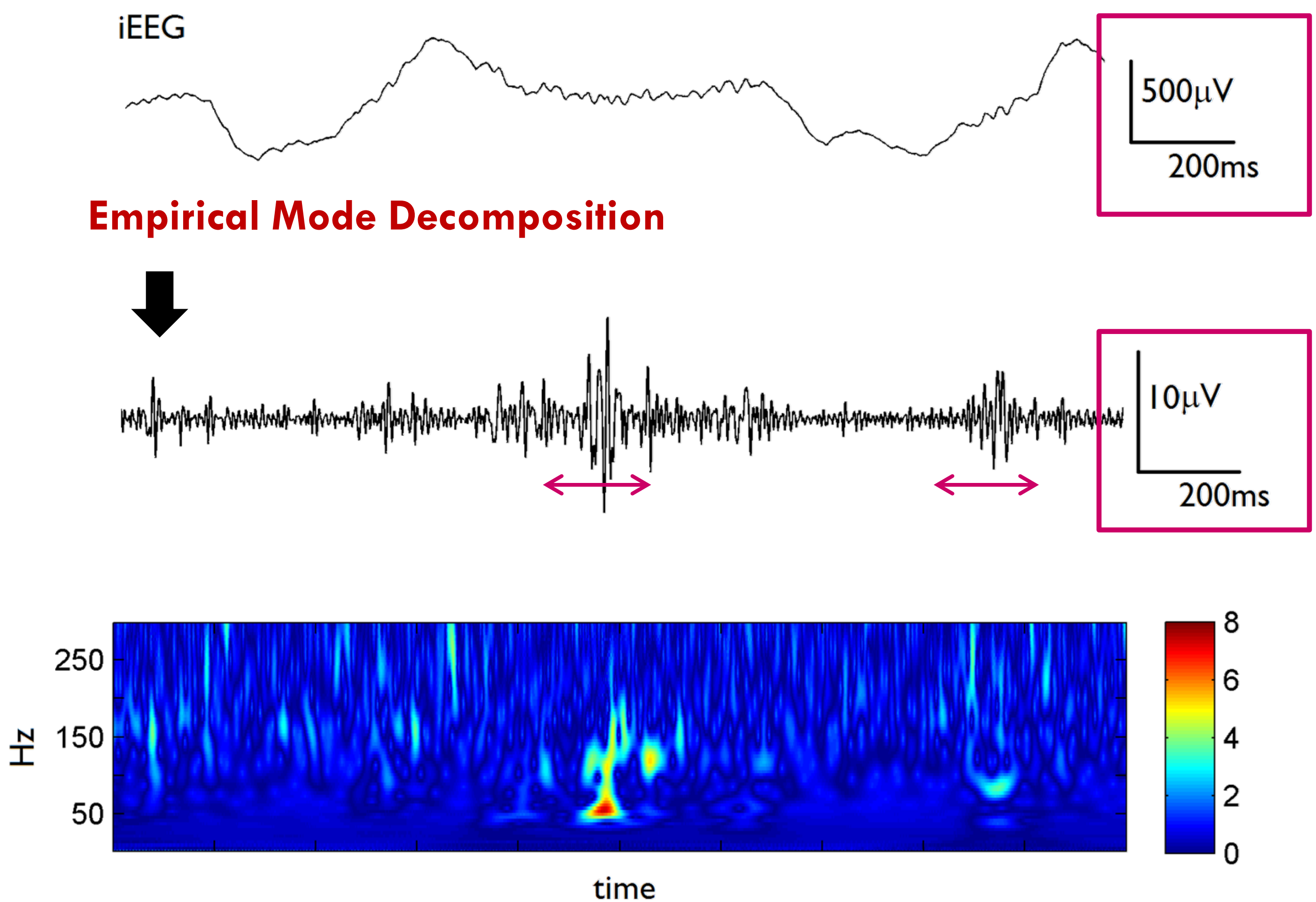
$$\psi_{a,b}(t) = \frac{1}{\sqrt{a}}\psi\left(\frac{t-b}{a}\right)$$

Wavelet

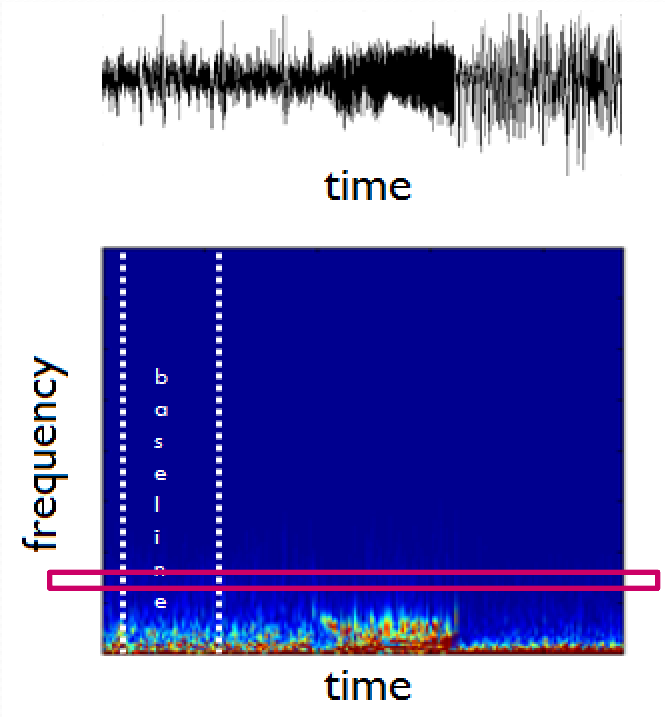
Coefficient in the time-frequency distribution

$$c_{j,k} = \int_{-\infty}^{+\infty} x(t)\psi_{j,k}(t)dt$$

iEEG Signal Characteristics

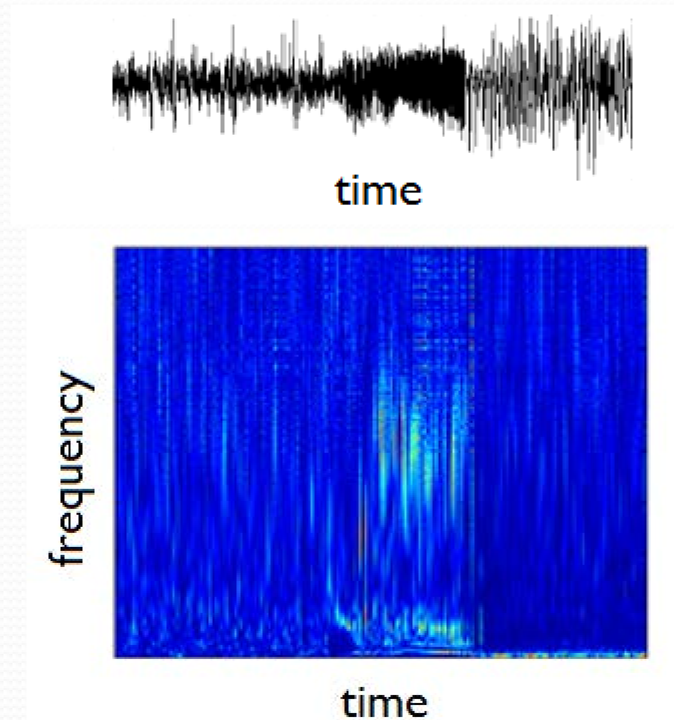


Frequency Normalized Wavelet Transform (NWT)

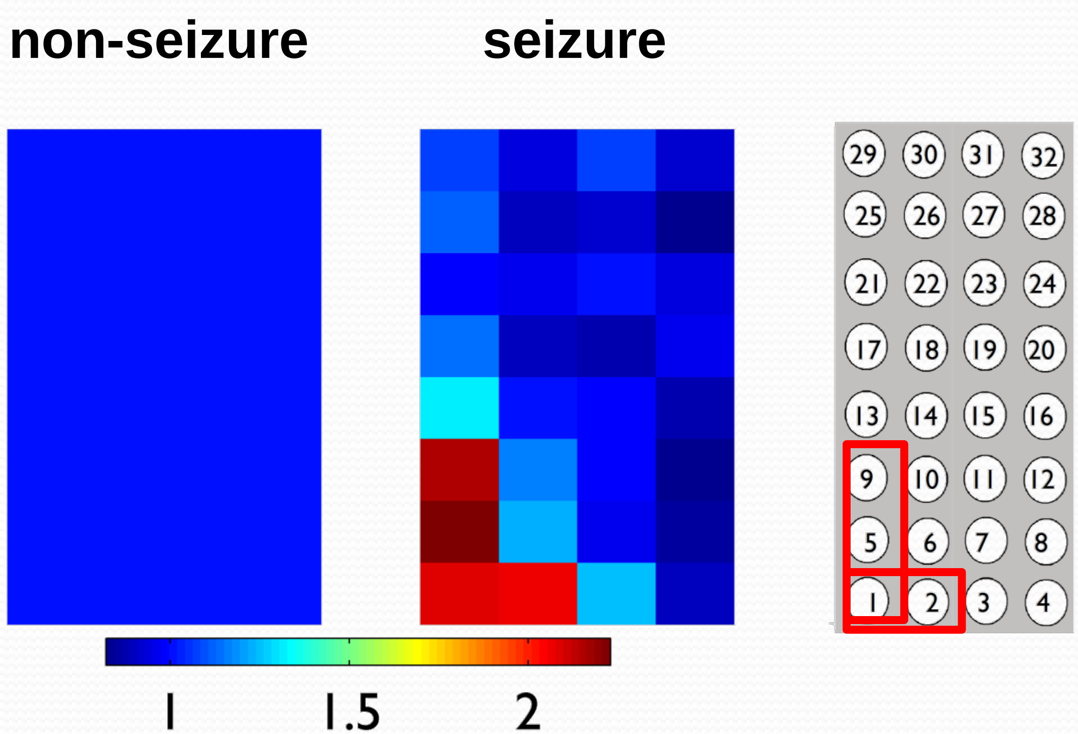


$$W_{norm}(f,t) = \frac{|W(f,t)| - \mu(f)\,|_{t1}^{t2}}{\sigma(f)\,|_{t1}^{t2}}$$

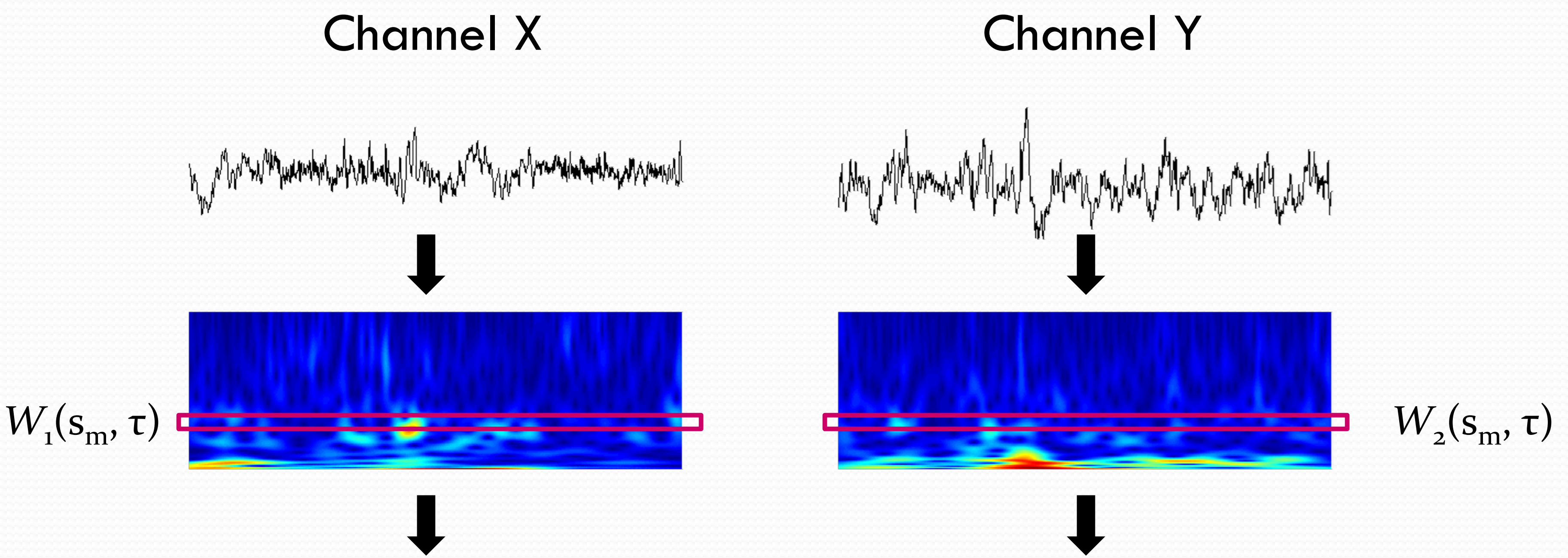
normalization



Selective Grid Marking using HFO Spectral Power during iEEG ictal activity



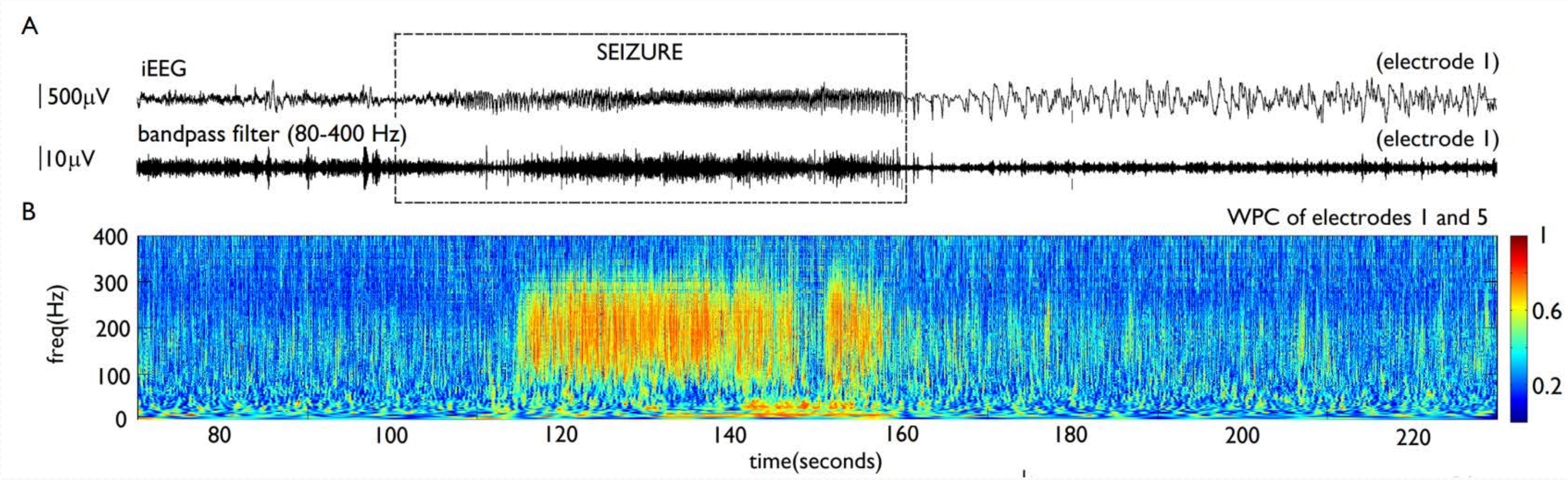
Wavelet Phase Coherence

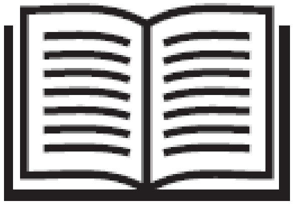


$$\Delta\phi(s_m,\tau) = \arctan \frac{\tilde{w}_1(s_m,\tau)w_2(s_m,\tau) - w_1(s_m,\tau)\tilde{w}_2(s_m,\tau)}{w_1(s_m,\tau)w_2(s_m,\tau) + \tilde{w}_1(s_m,\tau)\tilde{w}_2(s_m,\tau)}$$

$$\rho(s_m,\Delta\tau_n) = \left|\left\langle \exp(i\Delta\phi(s_{m,}\Delta\tau_n))\right\rangle\right|$$

Wavelet Phase Coherence (WPC)





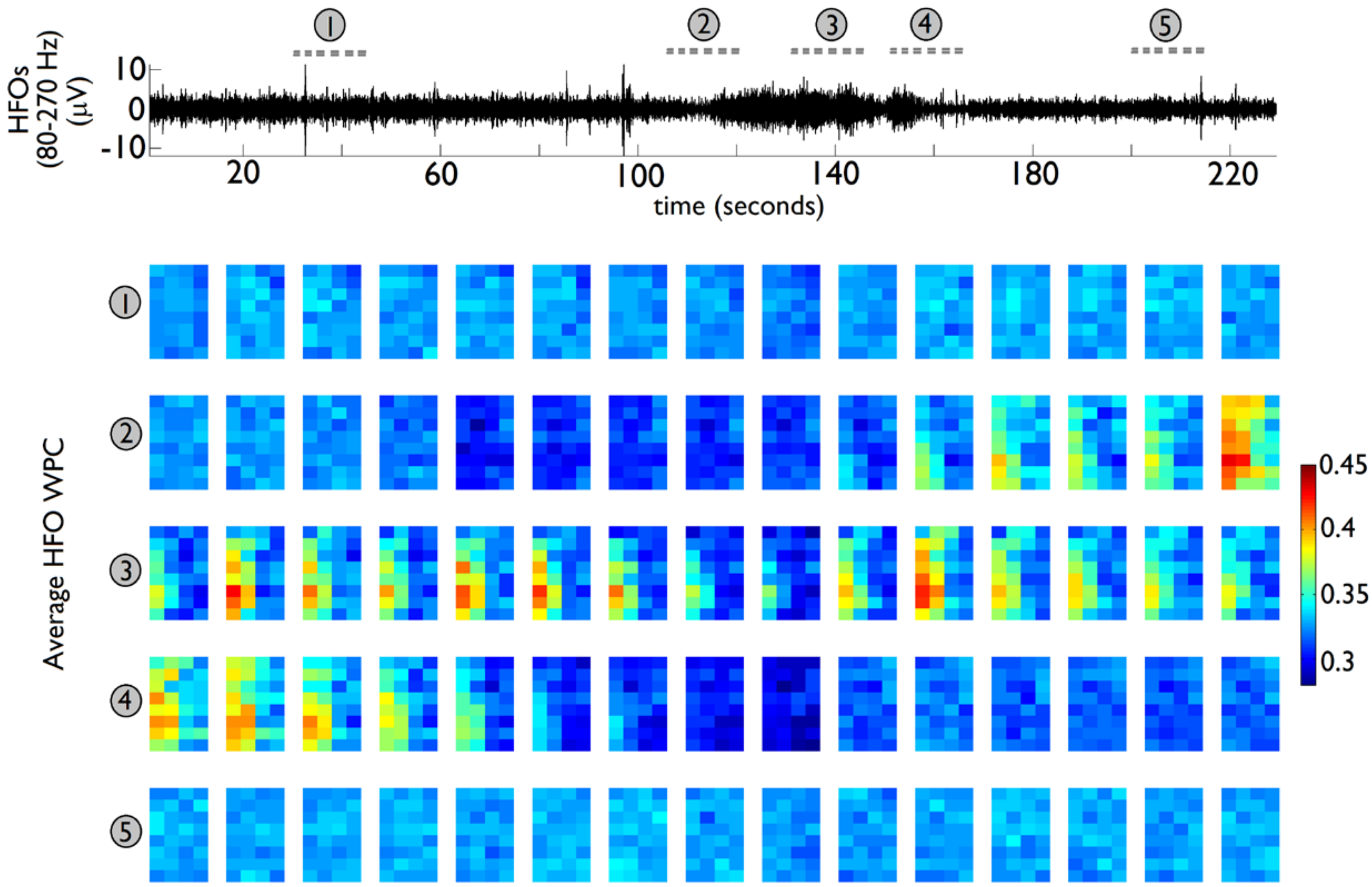
FULL-LENGTH ORIGINAL RESEARCH

Mapping the coherence of ictal high frequency oscillations in human extratemporal lobe epilepsy

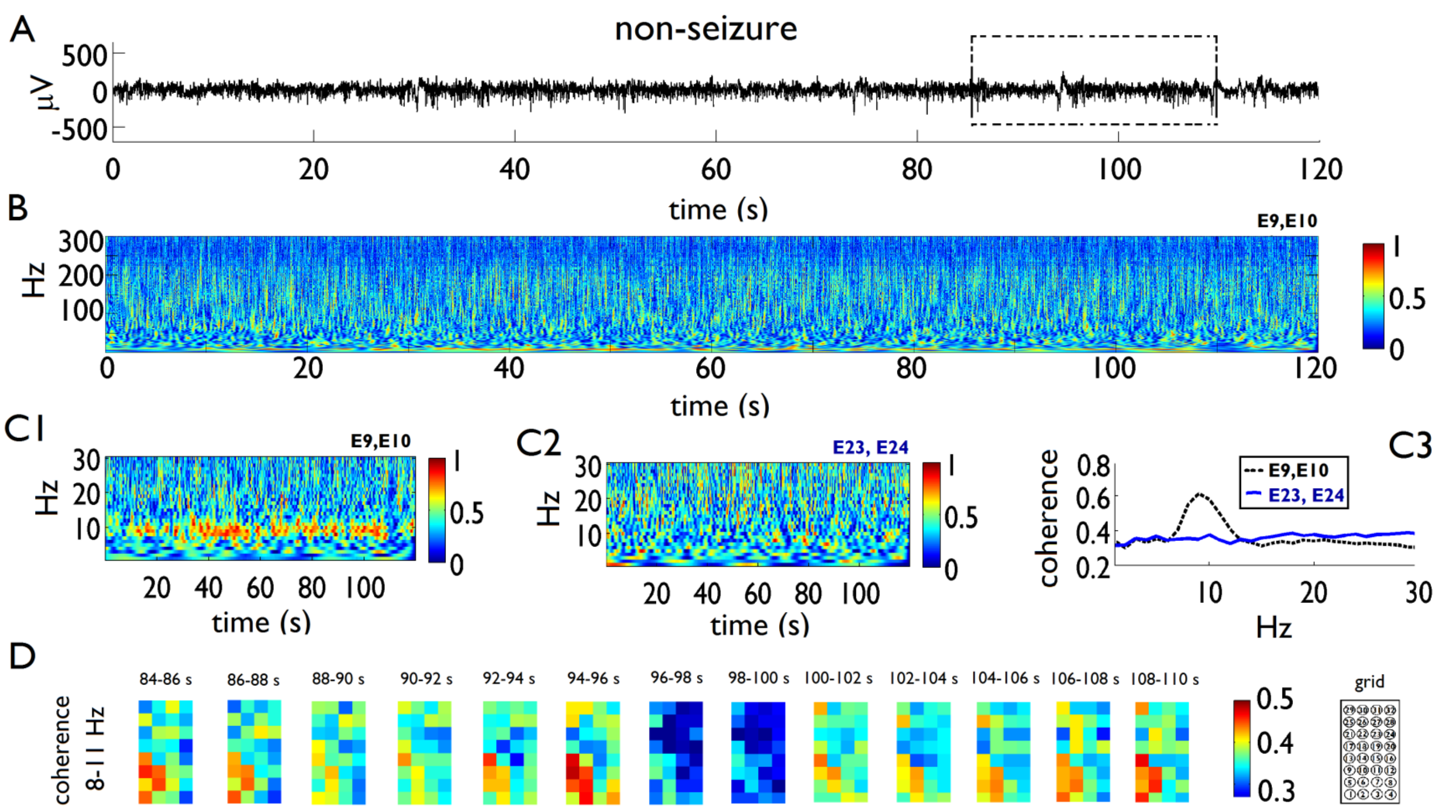
*Marija Cotic, *Osbert C. Zalay, †Yotin Chinvarun, ‡Martin del Campo, ‡§¶Peter L. Carlen, and *#Berj L. Bardakjian

Epilepsia, 56(3):393–402, 2015
doi: 10.1111/epi.12918

Wavelet Phase Coherence: Ictal HFOs



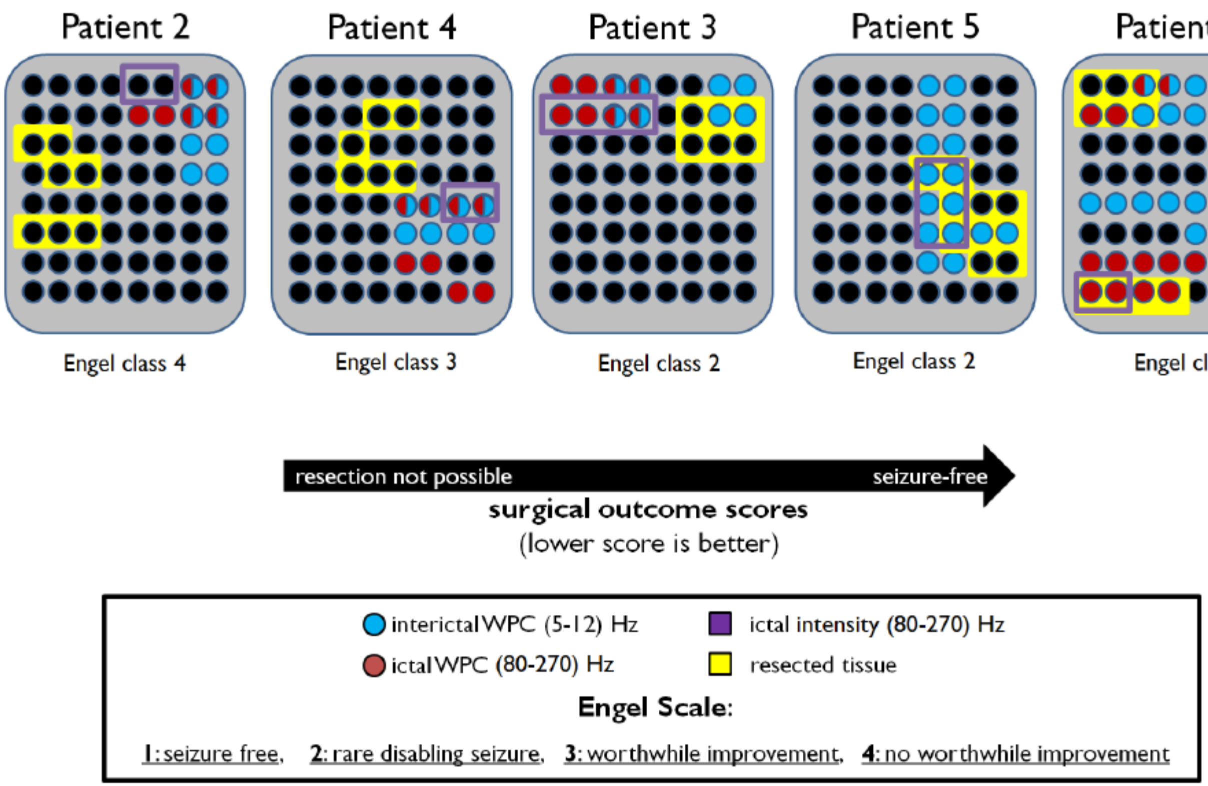
Wavelet Phase Coherence: Interictal LFOs



Tissue Resection Areas and LFO/HFO defined ROIs

Number of LFO/HFO electrodes coinciding with resected electrodes:

0/7 0/6 2/6 6/10 8/10



HFO/LFO ROIs map to Epileptogenic Cortex

Summary

- HFO (80-300 Hz) coherence and intensity were both elevated during seizures in select electrodes on the patient subdural grids.

- LFO (5-12 Hz) coherence was elevated during interictal activity in select electrodes on the patient subdural grids.

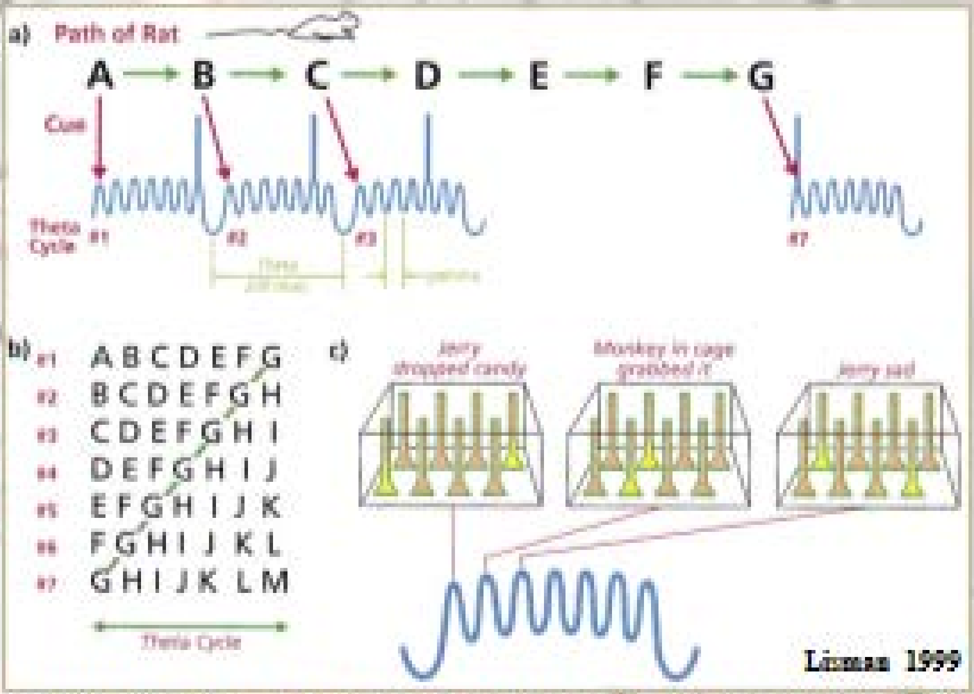
- Elevated LFO/HFO coherence identified coinciding regions of interest (ROIs) on the patient subdural grids.

- A good surgical outcome was observed for patients in whom the clinically marked SOZ(s) was in close proximity to LFO/HFO defined ROIs.

LFO-HFO Coupling

Normal

- Theta-gamma code



Lisman 1999

Pathological

- Modulationin children with TLE found to **correlate spatiotemporally** with the **seizure onset** Ibrahim, Valiante, et al 2014
- Ictal **ripples** are **tightly locked** to the phase of the slow-wave at **≤ 1 Hz** and **loosely locked** to that of **≥ 3 Hz** Nariai et al 2011
  - Locking reversed during interictal activity

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doi:10.1088/1741-2560/12/2/026011

Defining regions of interest using cross-frequency coupling in extratemporal lobe epilepsy patients

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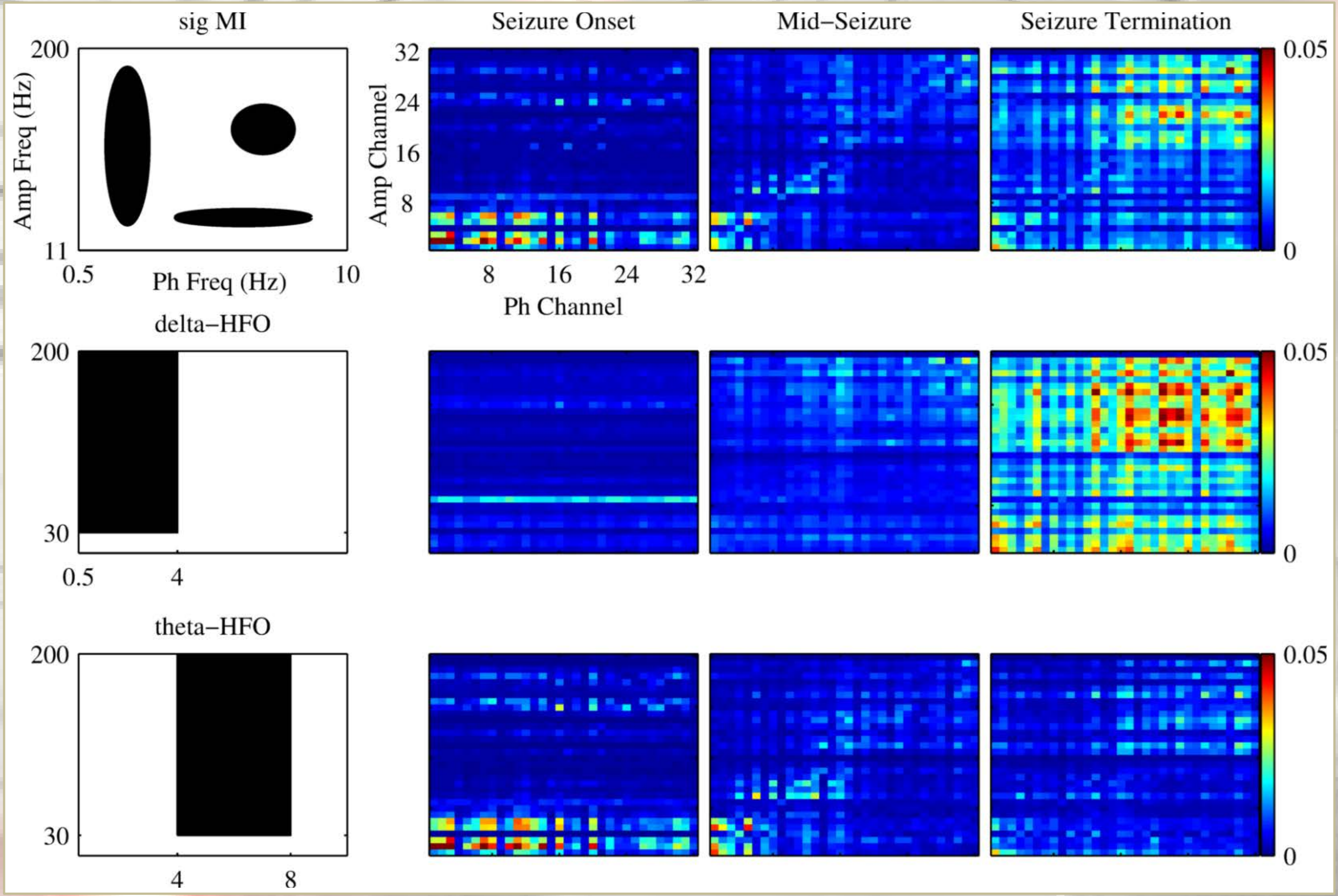
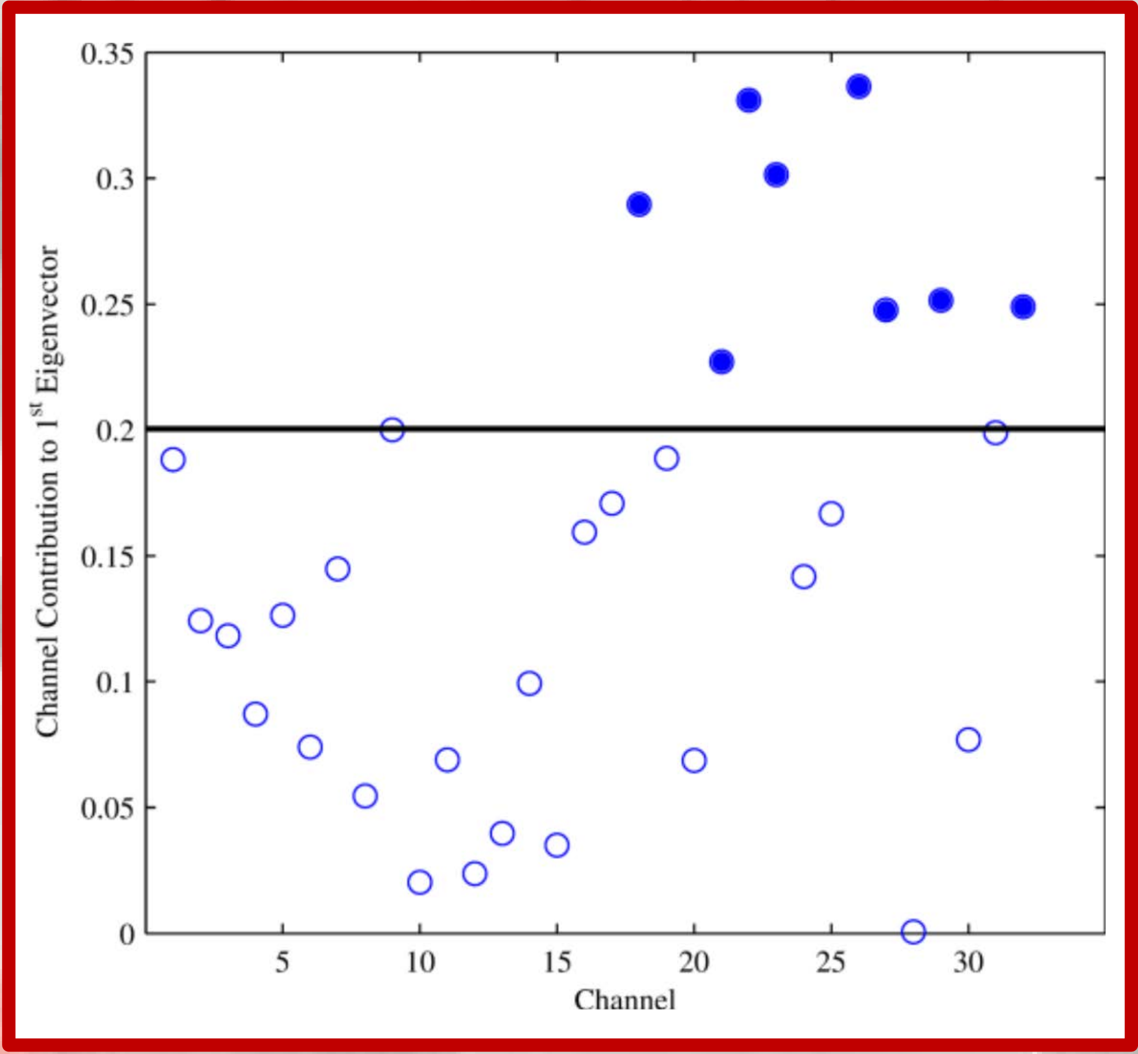
[5] Department of Electrical and Computer Engineering, University of Toronto, Toronto, M5S 3G4, Canada

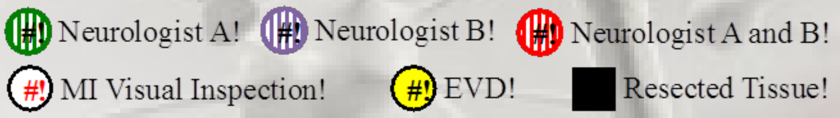
MI-Based Matrices for Eigen Value Decomposition (EVD)



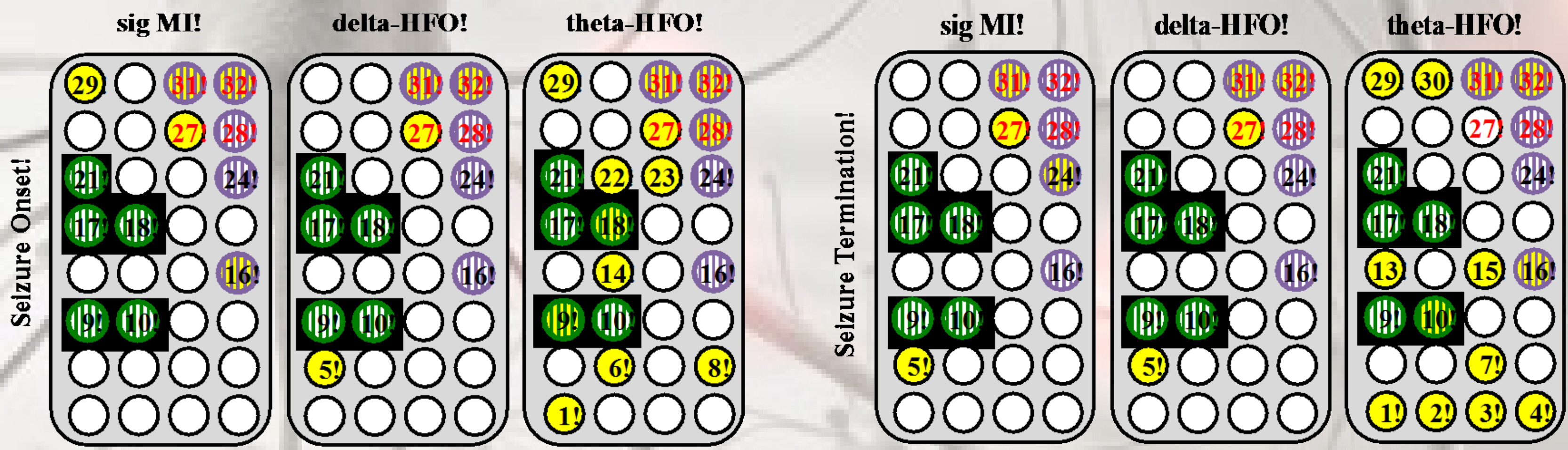
EVD-Based Channel Selection



EVD-based ROI



Patient B (EC IV)



Patient F (EC I)