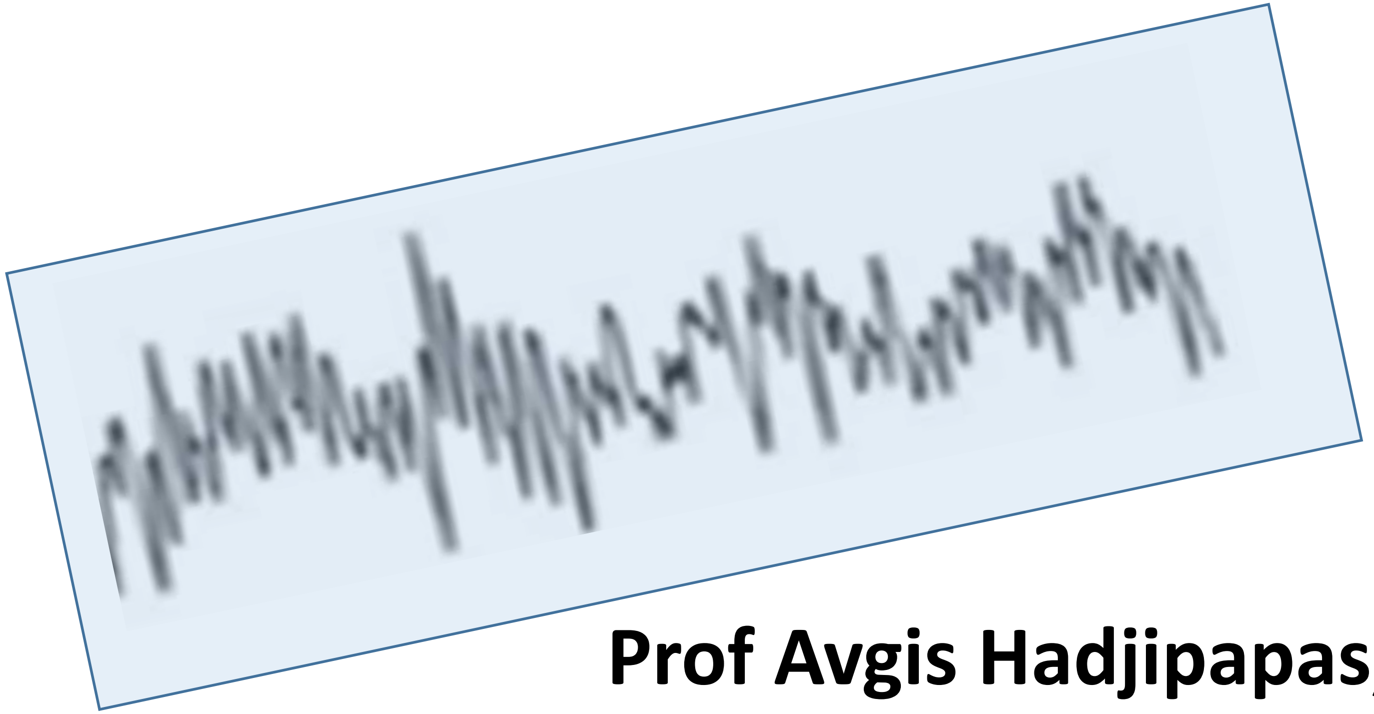
Neuronal oscillations: a window on the workings of the human brain



Prof Avgis Hadjipapas, MD, MSc, PhD

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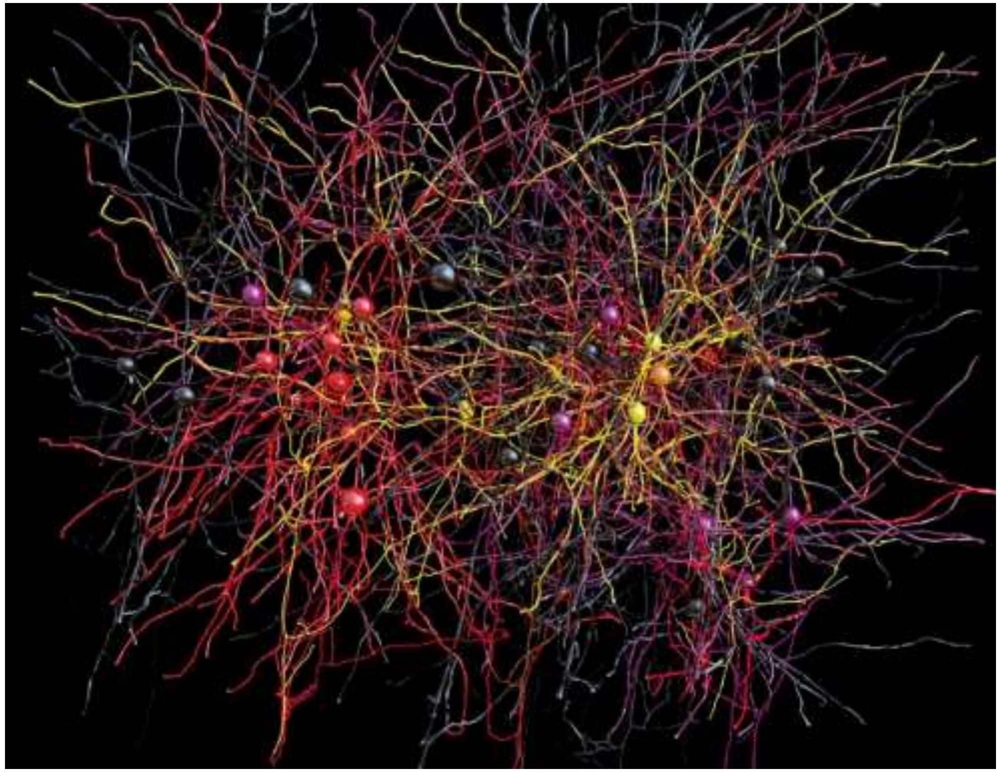
Overview

- The brain as a network
- Oscillations as a bridge between different spatial scales and between animal models and man (gamma)
- Oscillations as a means to understand how networks work (gamma)
- Oscillations, once formed, have (functional) consequences
  - Synchronization and gamma oscillations in monkey visual area V1
  - Excitability modulations: circadian rhythms modulate EEG and seizure timing
- Conclusions

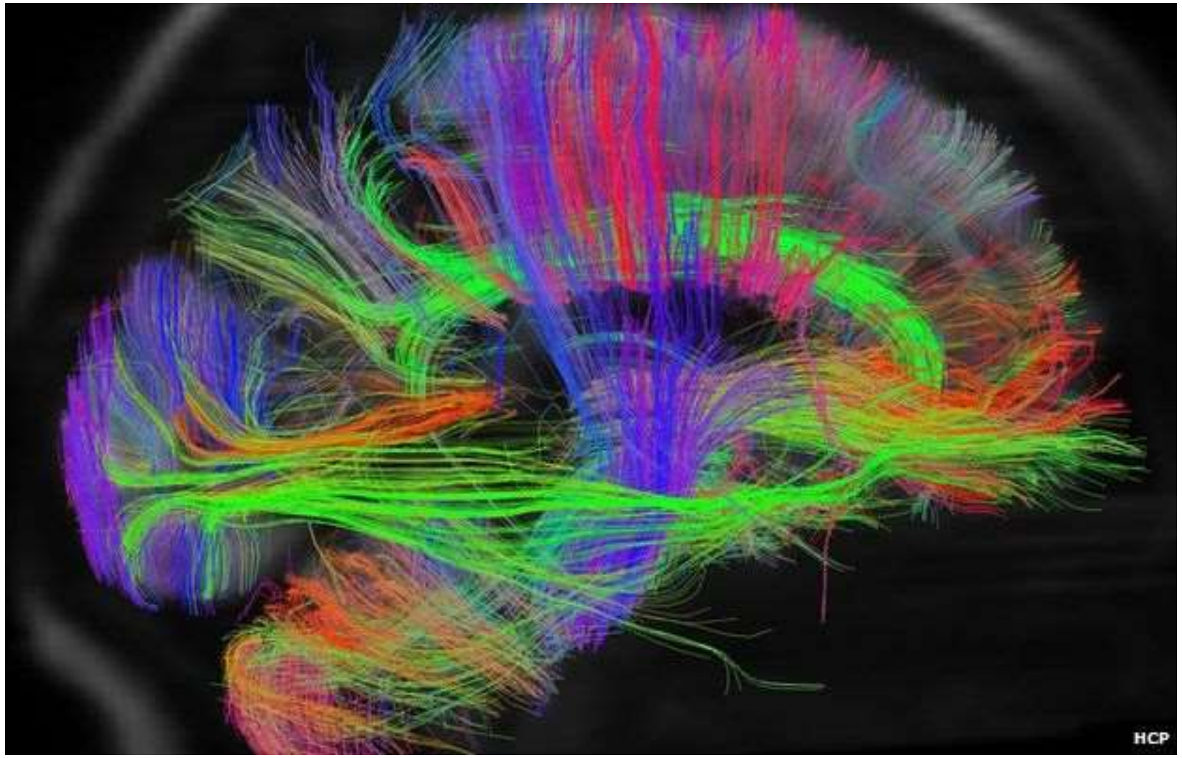
Brain: a vast network of units interconnected in complex fashion

Micro and meso scale



From: Allen Institute

Macro scale

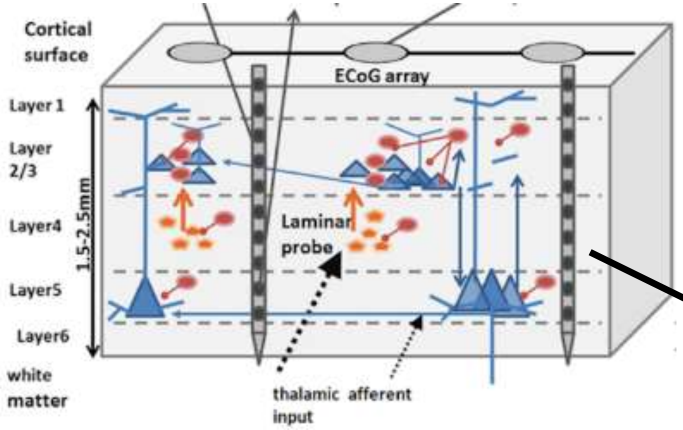


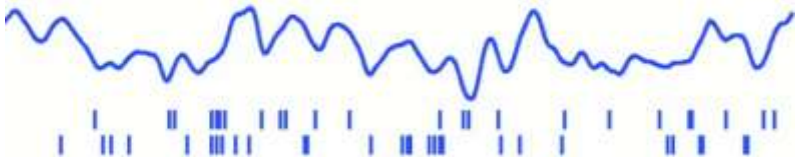
From: Human Connectome project

- **100 X 10^9 units, 10^{15} connections →**
- **No unit can be studied in isolation- <u>interactions</u>** are important
- Collective activity: **<u>interaction</u>** between network units- **<u>oscillations prime example of this</u>**

Want to study collective network activity in vivo, … but what can we measure?

In the animal





Extracellular slow field potential : Local Field Potential (**LFP**): aggregated membrane potential and synaptic activity **(µm-mm)**; **laminar specificity possible**

Extracellular multi unit activity (MUA): action potentials (spikes) fired by neurons;
- **Single unit activity** can be obtained by spike sorting algorithms

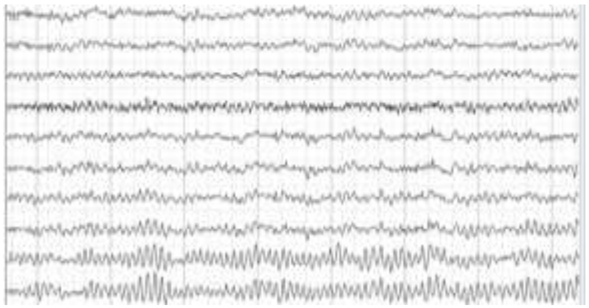
With **laminar probes** we can estimate activity in **different cortical layers**

In the human

Neuroimaging: using **non-invasive recordings** (magnetoencephalography (**MEG)/** high-density **EEG**) and mathematical source localization models/algorithms - we can **estimate/localize** highly-aggregated network activity (**mm-cm**)

MEG

EEG



What type of network activity shall we study?

Activity that

1) … can be experimentally controlled/ is highly reproducible
2) … can be observed in both animal models and humans
3) … depends on interactions within neuronal networks
4) ... has a functional role or consequence

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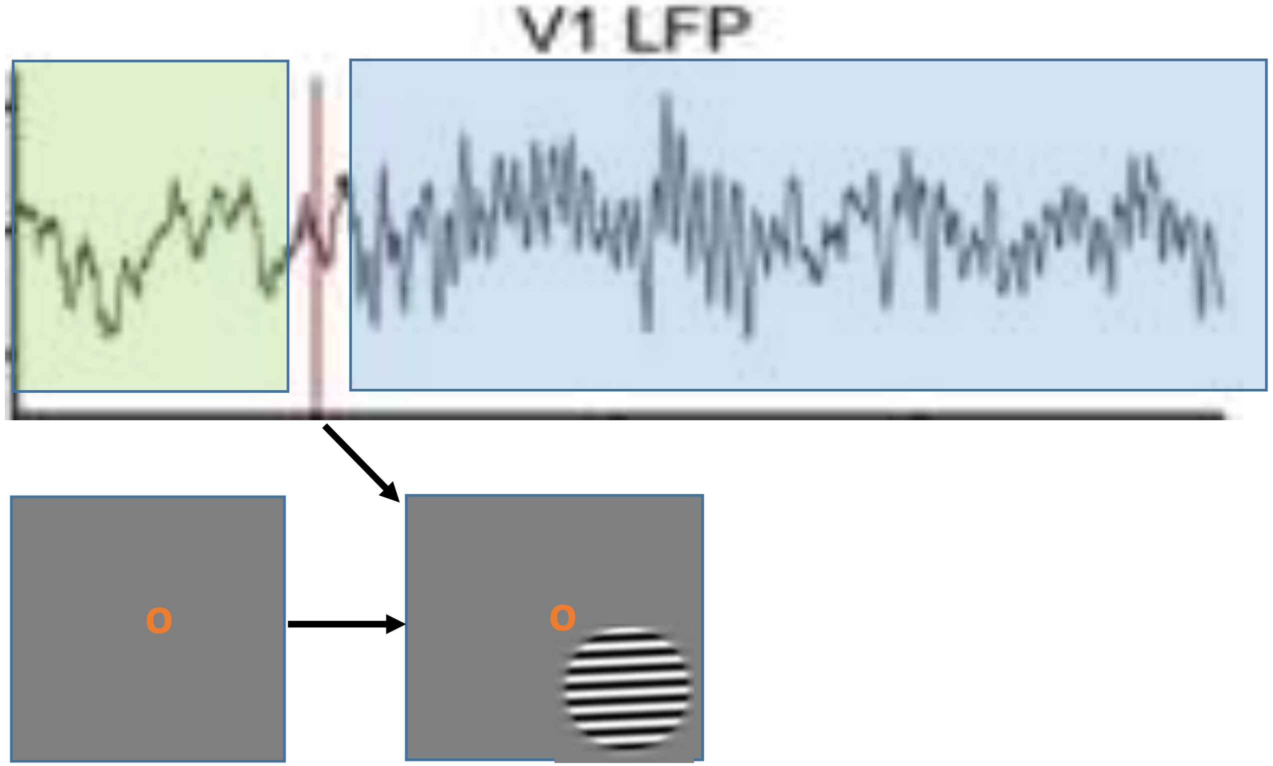
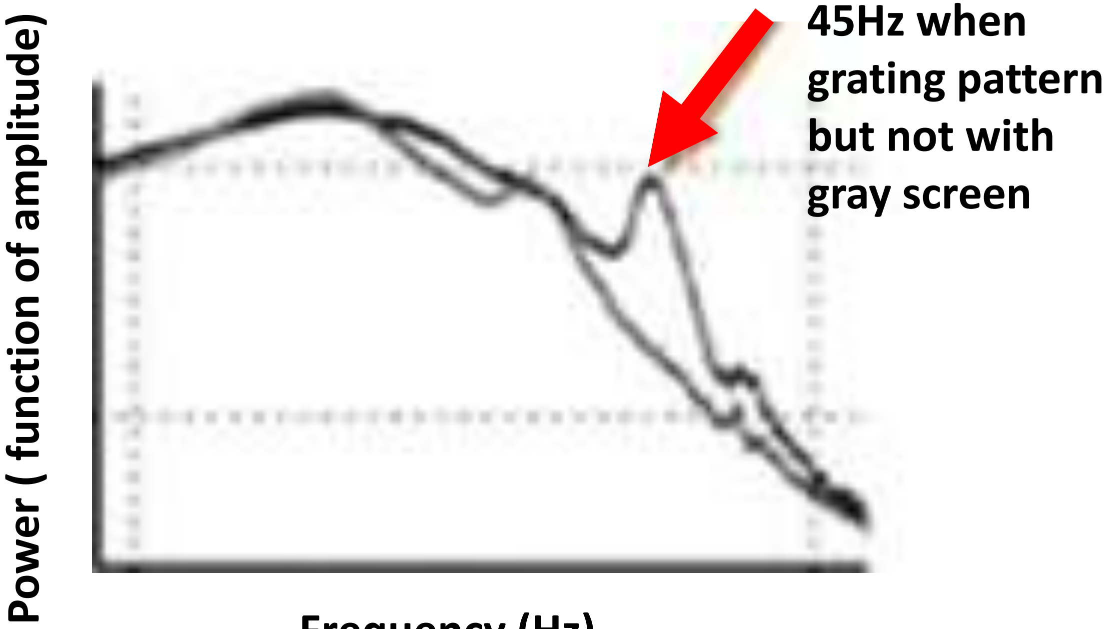
Stimulus- induced high frequency (20-90 Hz) gamma oscillations: noninvasive experimental control

From: Hadjipapas, A., Lowet, E., Roberts, M.J., Peter, A., De Weerd, P., 2015. Neuroimage 112, 327–34



Power spectrum of signal

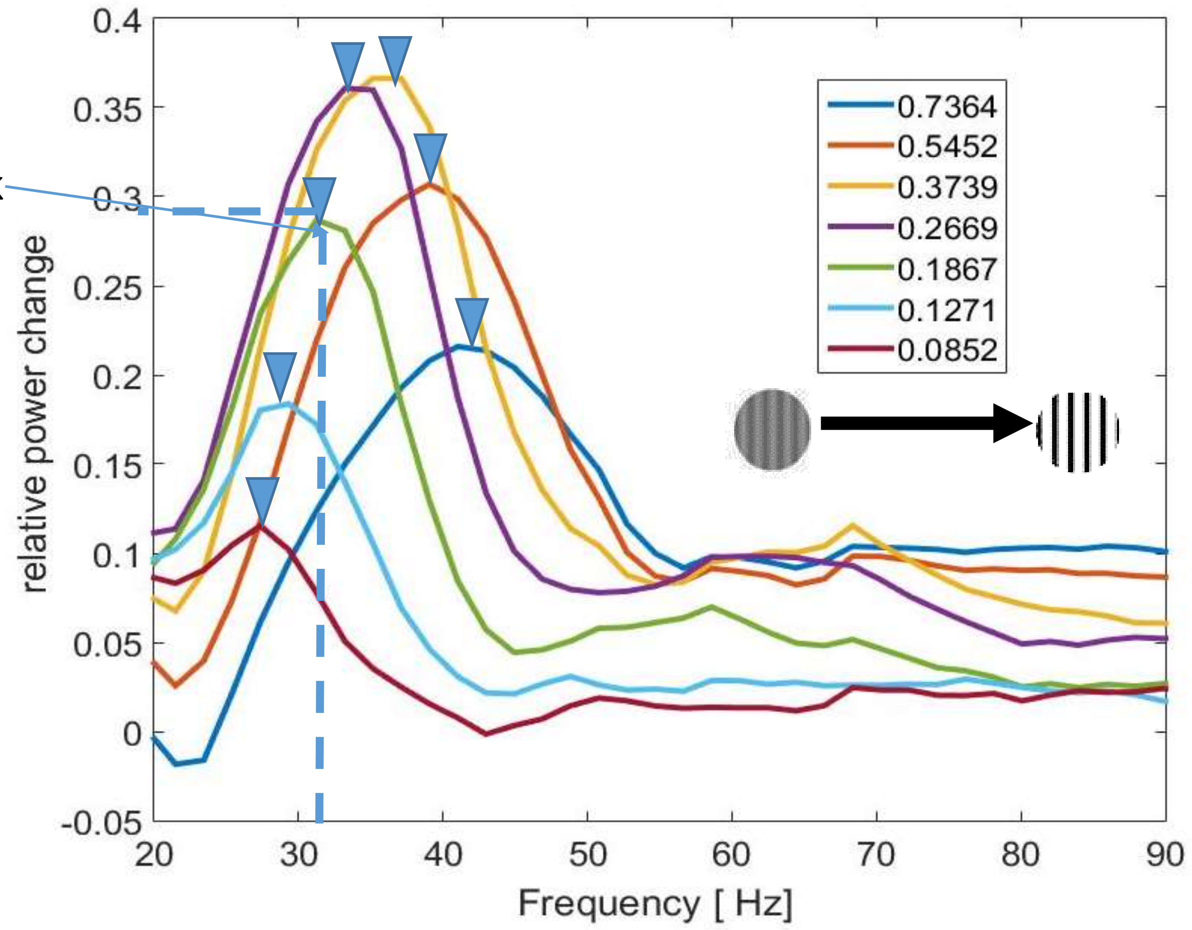


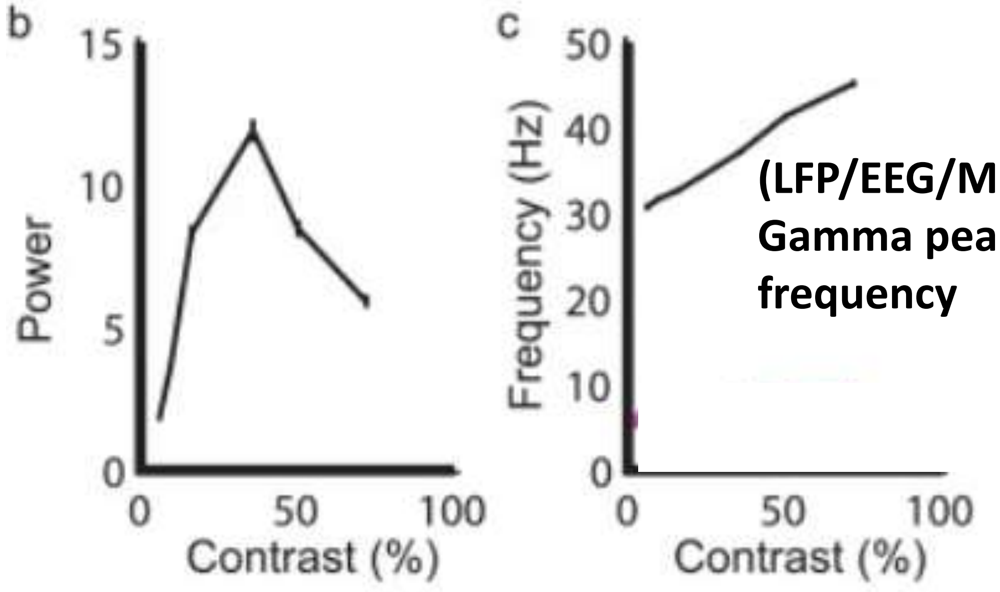
- **Oscillations: highly stimulus specific**: shading of black & white bars (luminance **contrast**), spacing between bars (spatial frequency, SF), orientation of bars etc → **Crucial oscillation parameters can be controlled with visual stimuli (NONINVASIVE CONTROL of gamma activity→ experiments/recordings in HUMAN participants possible)**
- **Early MEG studies when I was at Aston, Birmingham:** SF, Contrast, Colour & SF decoding, orientation decoding from spectral information **+ much work from many other groups including monkey work**!

Main effects of stimulus luminance contrast on gamma oscillations in primary visual cortex of the monkey

Relative V1 LFP spectrum as function of contrast

Extract peak **frequency** and peak **power**





(LFP/EEG/MEG) Gamma peak frequency

- **Robust, parametric effects on network activity:** frequency & power parametric modulation with variation of a **single stimulus parameter (contrast)**
- **Reproducible in HUMANS? Needed direct comparison…**

Roberts et al, 2013, Hadjipapas et al, 2015, Zachariou et al, 2021

What type of network activity shall we study?

Activity that

1) … can be experimentally controlled/ is highly reproducible
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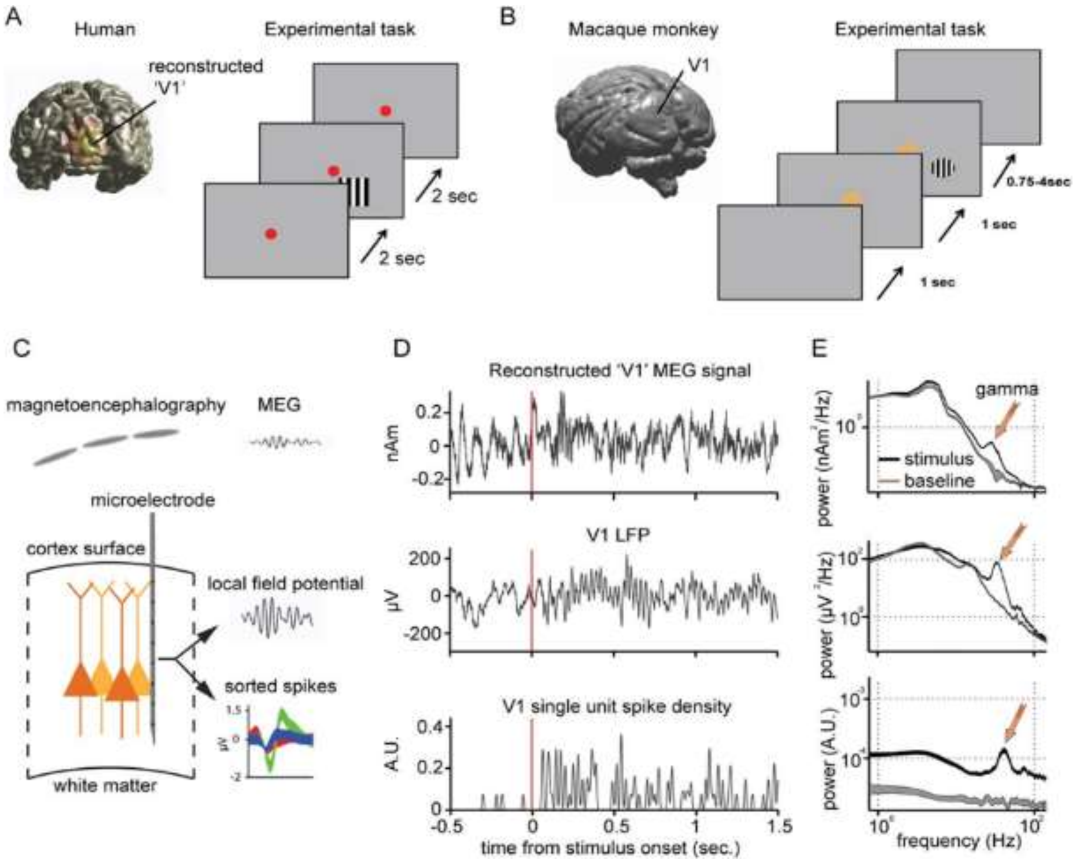
3) … depends on interactions within neuronal networks
4) ... has a functional role or consequence

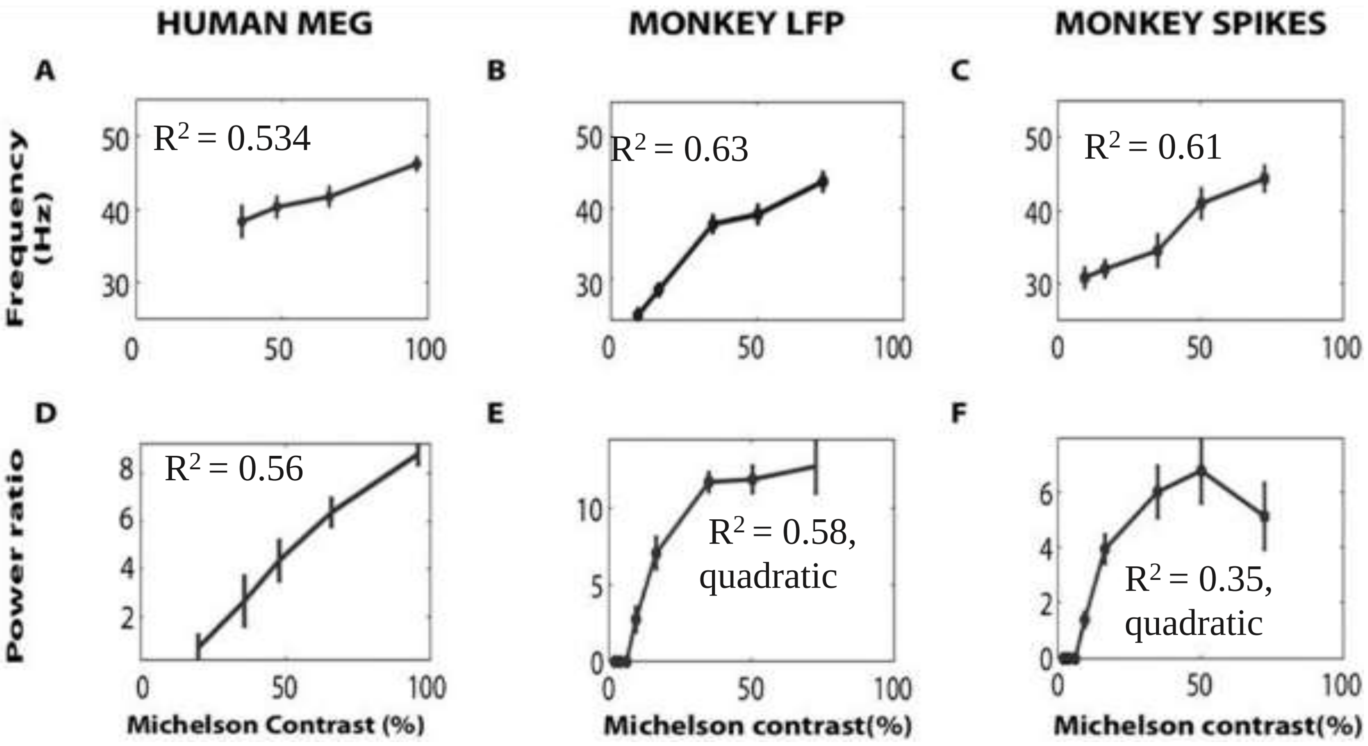
Human Brain Project
University of Nicosia Medical School
Maastricht University

Margarita Zachariou (postdoctoral Research Fellow)

Mark Roberts, Peter De Weerd, Eric Lowet (postdoctoral Research Felllow)

Comparing effects of contrast across monkey single units, LFP , and human magnetoencephalogram (MEG)





- **Frequency effect similar across both species and all spatial scales! but power effect different** (why? … different talk…)
- **Similarities & differences btw species & scales highly informative**

Hadjipapas et al, 2015. *NeuroImage* 112, 327–34

Comparative study- importance

- Aggregate signals measured noninvasively in humans (MEG, EEG): **biased** towards **synchronous activity**
- **Oscillations comprise such activity, hence often very 'visible' in signals →**
- Phenomena observed in **humans** explained by powerful **theoretical frameworks** derived from **animal experiments** and **computational models**
- **Oscillations can thus provide a window on network function in humans**

Comparative study- importance

- But how are these oscillations generated?
- previous study: only a few individual neurons showing oscillations; most neurons **no periodic activity in the gamma range!**

- **… HOW DO SINGLE UNITS PRODUCE THESE OSCILLATIONS?**

What type of network activity shall we study?

Activity that

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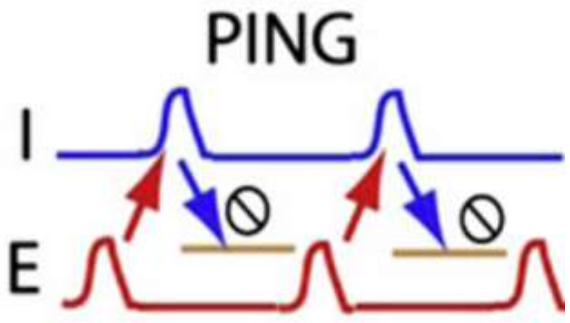
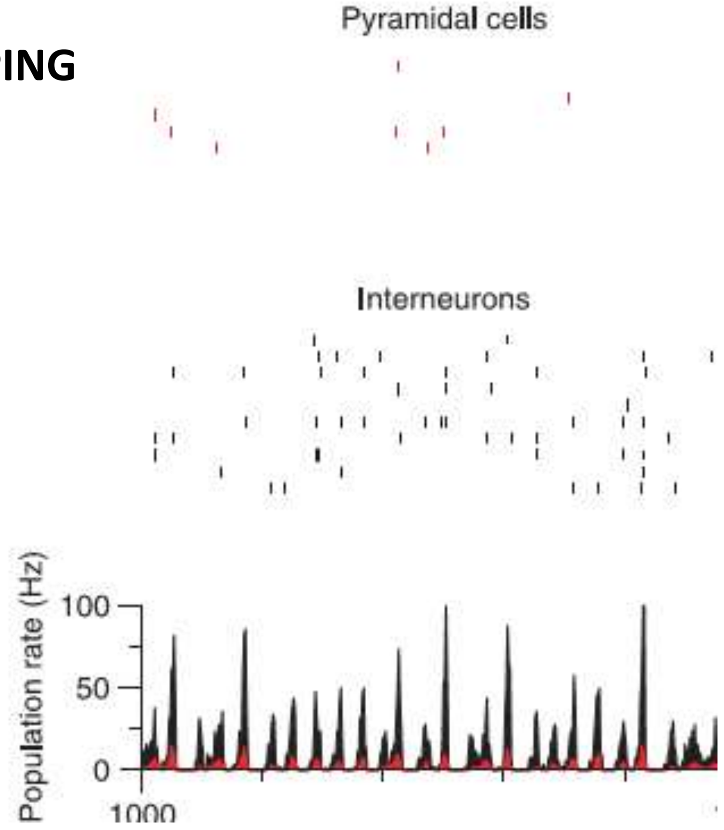
Models of gamma oscillation generation: Pyramidal Interneuron Gamma (PING) and weak PING



Tiesinga and Sejnowski, Neuron, 2009, 24;63(6):727-32.

- Pyramidal/Excitatory neurons (E)
- Inhibitory Interneurons: (I)

weak PING



Brunel and Wang, J Neurophysiology, 2003 Jul;90(1):415-30.

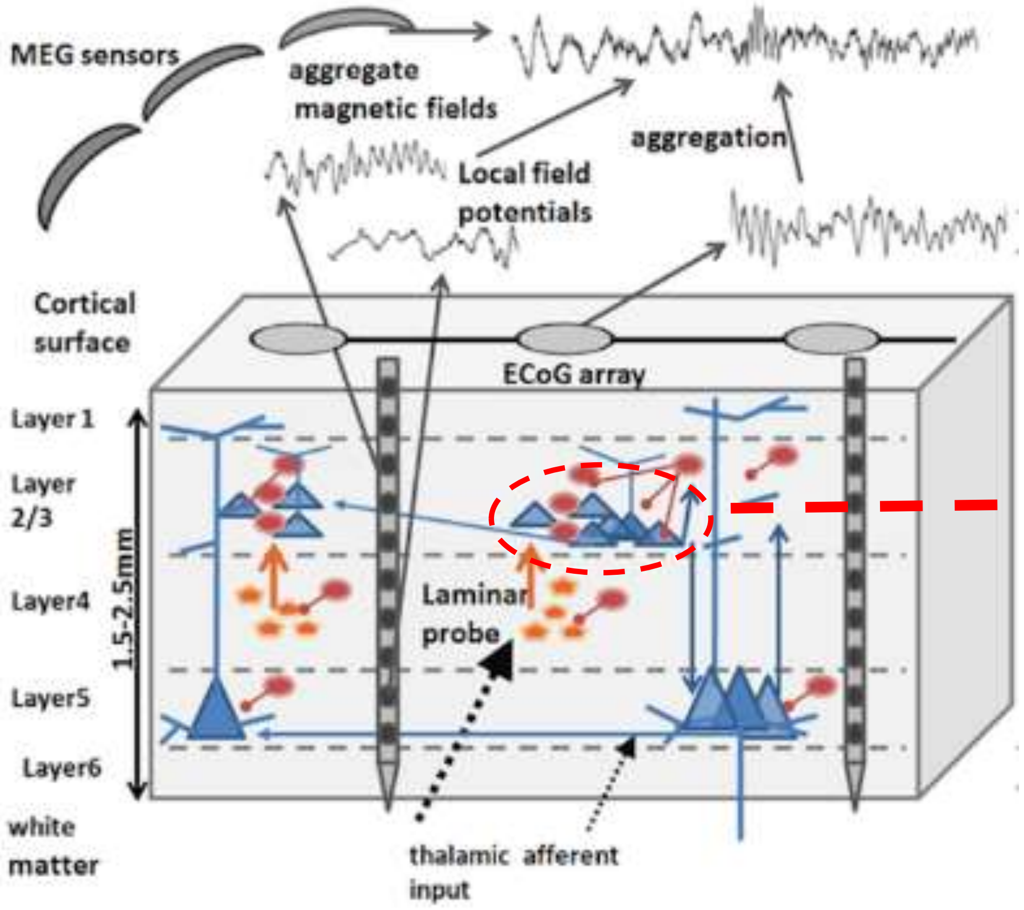
- **PING depends on E and I neurons firing synchronously… BUT …**
- **Empirical data: individual neurons fire irregularly and not that synchronously …**
- **How come oscillations if single units irregular?**

- **I fire on most cycles and synchronize network**
- **individual E do not; they skip cycles**
- **… BUT, a few E fire almost on every cycle**
- **PING or weak PING model better fits monkey V1 data?**

Cortical neuronal network?

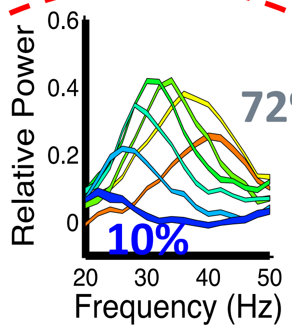
System Identification challenge→ Use data, Use models, Use both together …

Inputs to the network :
Visual stimuli/ (Luminance) Contrast modulation

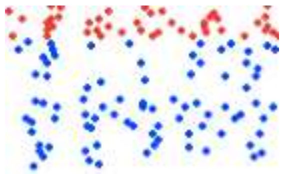


Outputs of the network: **Stimulus-induced gamma oscillations in spikes, LFP, ECoG, MEG**

LFP



SINGLE UNITS



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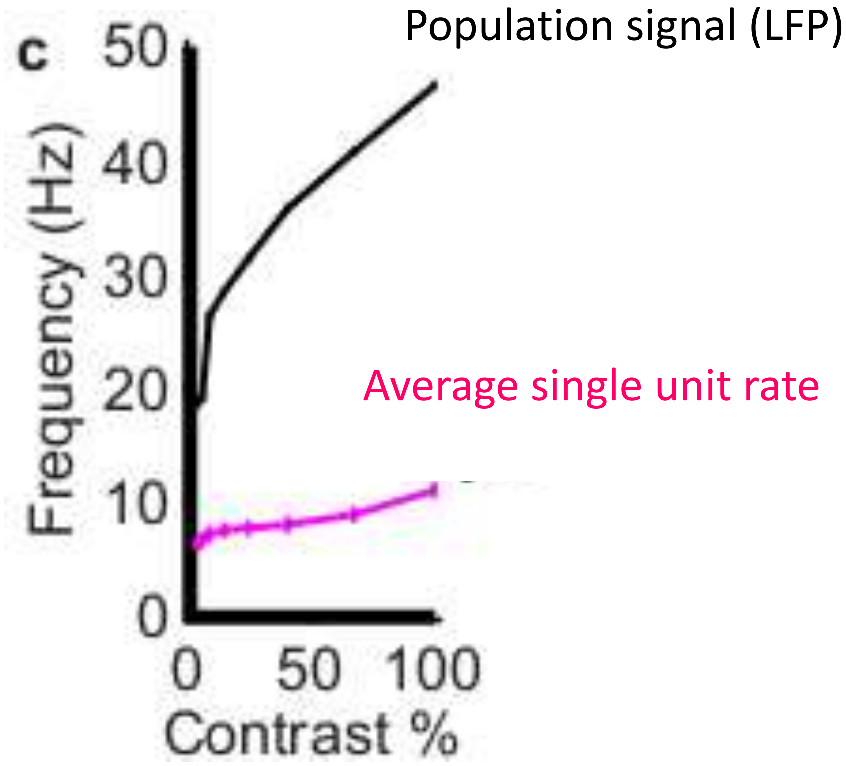
Monkey data consistent with weak PING (sparse oscillation)

Experimental monkey data



Zachariou, M., Roberts, M., Lowet, E., De Weerd, P., Hadjipapas, A. 2021. ***NeuroImage 229***, 117748.

- Optimal would be (to be able) to separate single units in **E and I**
- Were unable to do this (so far) (why?.. yet another different talk …)
- … However, used average (mixed **E and I**) population statistics to address our hypothesis:

1. Most **individual units** (average dominated by **E**) do **NOT** fire in **gamma**
2. **Population frequency always higher than single unit rate**→ most units do not fire on every oscillation cycle but instead **skip cycles**

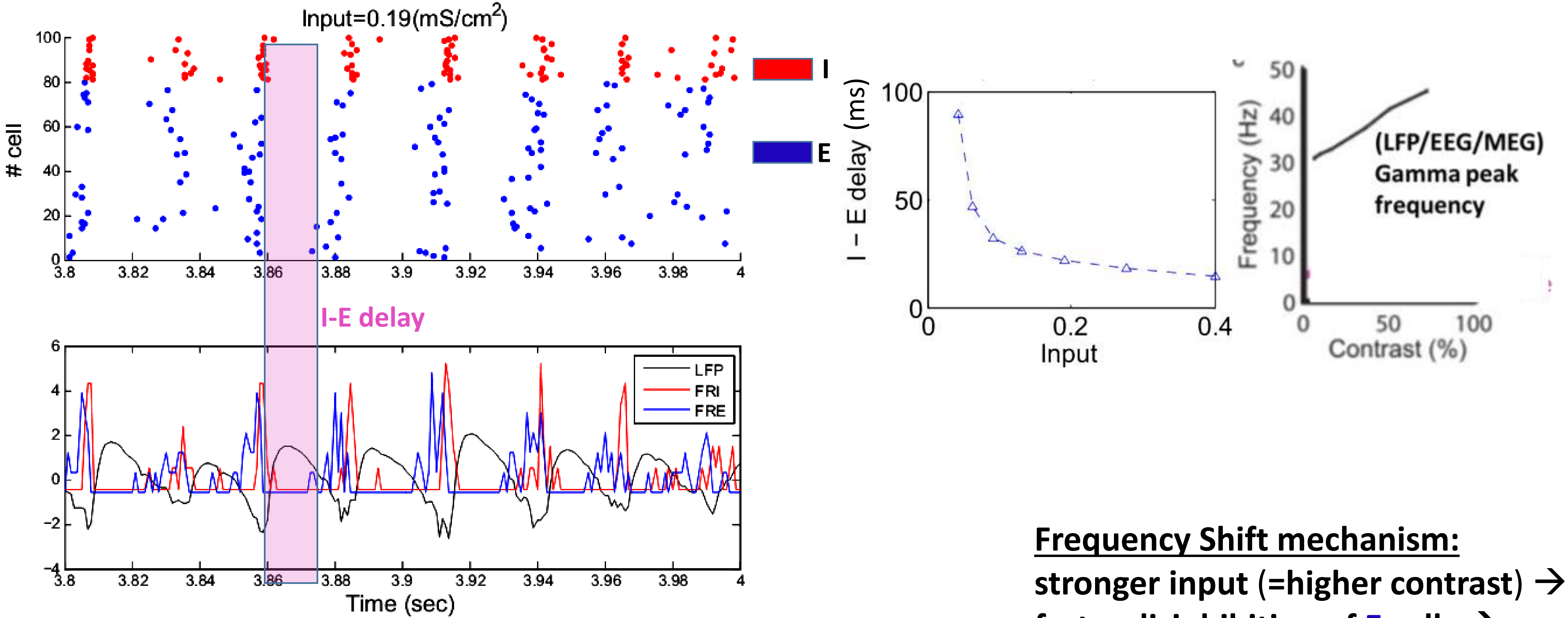
- → Data indicates a **sparse oscillation: model seems to be weak PING (rather than (strong) PING)**

Empirically-constrained, neuronal network model of gamma

- We built a computational, conductance-based (HH) model of gamma oscillations
- Luminance Contrast as proxy for input from retina and thalamus
- Validated model by experimental data: model had to simultaneously satisfy several statistically robust behaviours observed in experimental data
- … this allowed us to understand exact role of E and I in shaping oscillation frequency and power as function of contrast

Zachariou, M., Roberts, M., Lowet, E., De Weerd, P., Hadjipapas, A. 2021.
NeuroImage 229, 117748.

… An example. Oscillation frequency shift with contrast/input…



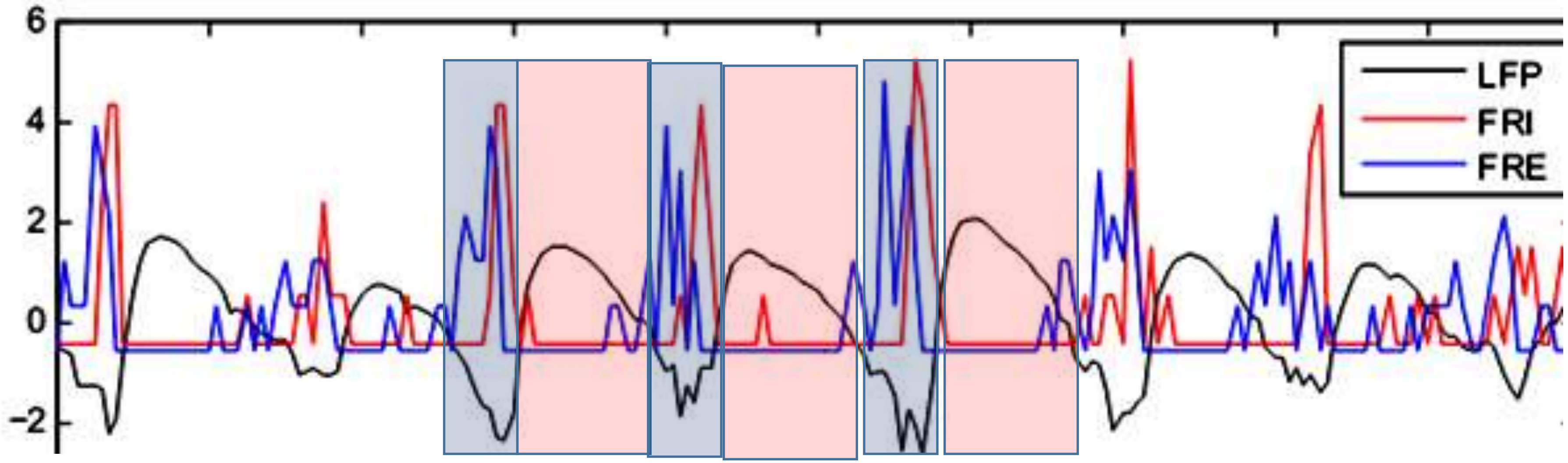
-Note some **irregular firing** while (some) **periodicity especially in I**

-Oscillation Mechanism: E prompt I, these fire and silence network for some time (**I-E delay**) before some **E** are released from inhibition, fire again, and start new oscillation cycle

Frequency Shift mechanism:

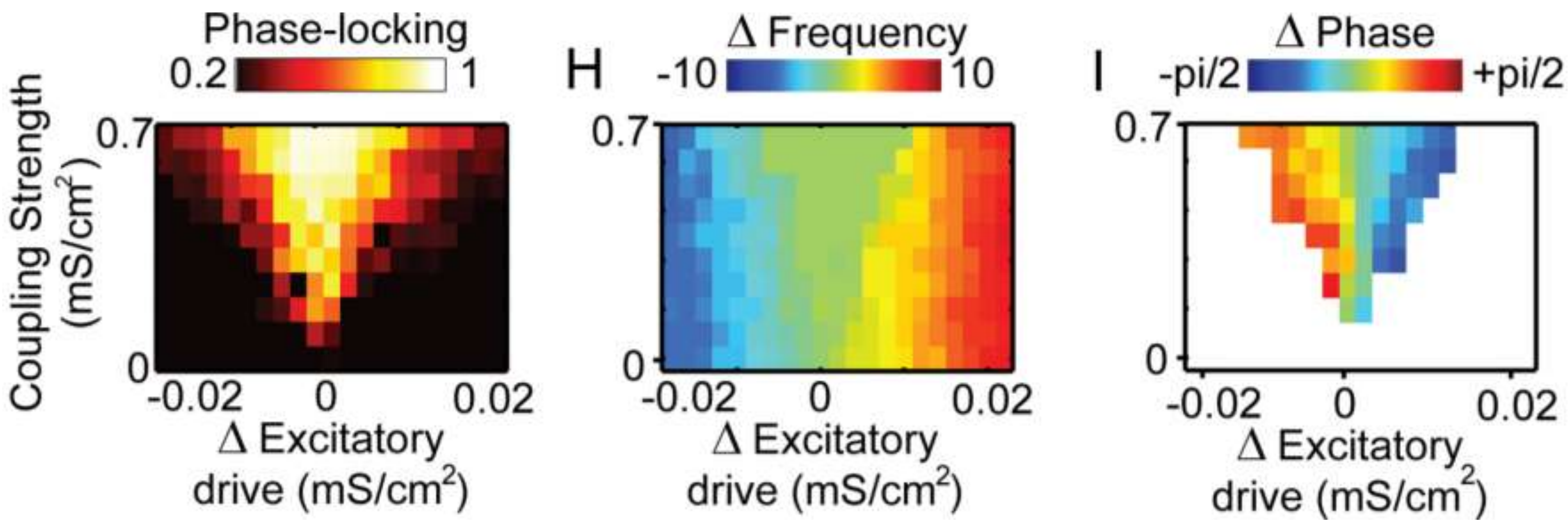
stronger input (=higher contrast) → faster disinhibition of E cells → shorter IE delay → higher oscillation frequency

Oscillations represent modulations of excitability: define windows of opportunity for neurons to fire



- Cortical networks constantly under **strong barrage of INHIBITION**…
- Neurons fire mostly when **INHIBITION** is low (**EXCITABILITY** is high)
- … fire at certain **PHASES** of oscillation and not others → **WINDOWS OF OPPORTUNITY** for neurons to fire
- **OSCILLATION FREQUENCY AS CENTRAL PARAMETER:** determines size & spacing of these windows
- Oscillation frequency is also of paramount importance for synchronization **between networks** (and individual neurons)

Oscillation frequency is crucial for synchronization



Lowet E, Roberts M, Hadjipapas A, Peter A, van der Eerden J, De Weerd P. *PLoS Comput Biol.*2015;11(2):e1004072.

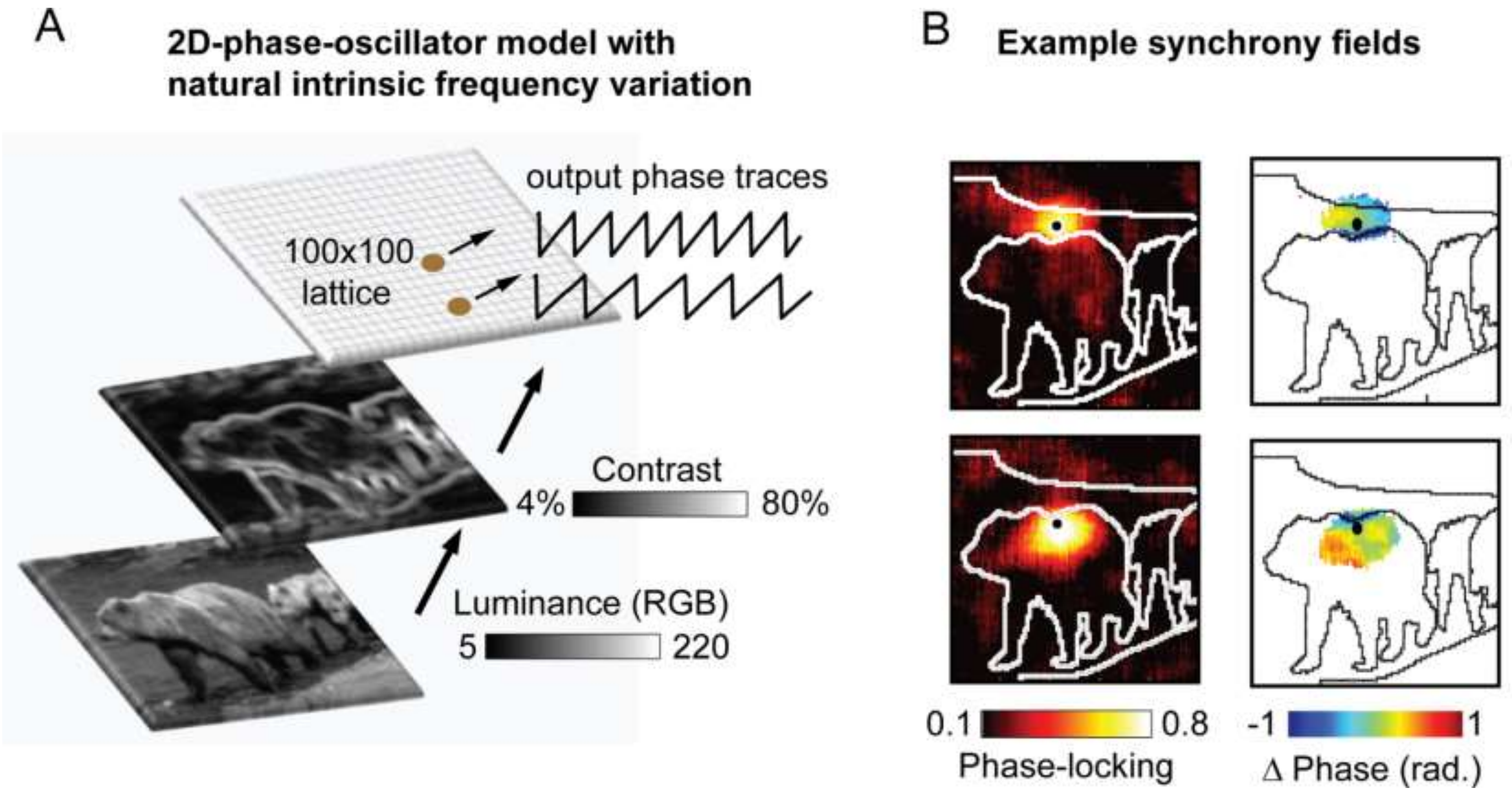
Hadjipapas A, Charalambous CC, Roberts MJ. *Front Syst Neurosci.* 2023 Jan 4;16:1121438. doi: 10.3389/fnsys.2022.1121438.

Lowet E, De Weerd P, Roberts MJ, Hadjipapas A. *Front Syst Neurosci*. 2022 Jul 8;16:908665. doi: 10.3389/fnsys.2022.908665.

- At **given (rather weak)** anatomical connectivity **(coupling strength):**
  - oscillations with small **frequency differences** (**detuning**) **synchronize**
  - oscillations with **large detuning remain independent**
- ***Within* synchronization regions**, the **phase difference** of the oscillations encodes the original detuning present
- **Universality**: Implications for **synchronization** between neurons, layers, cortical columns, brain areas.. and also implications for **neural computation/neural coding…**

Oscillation frequency & resultant synchronization patterns crucial for neural computation

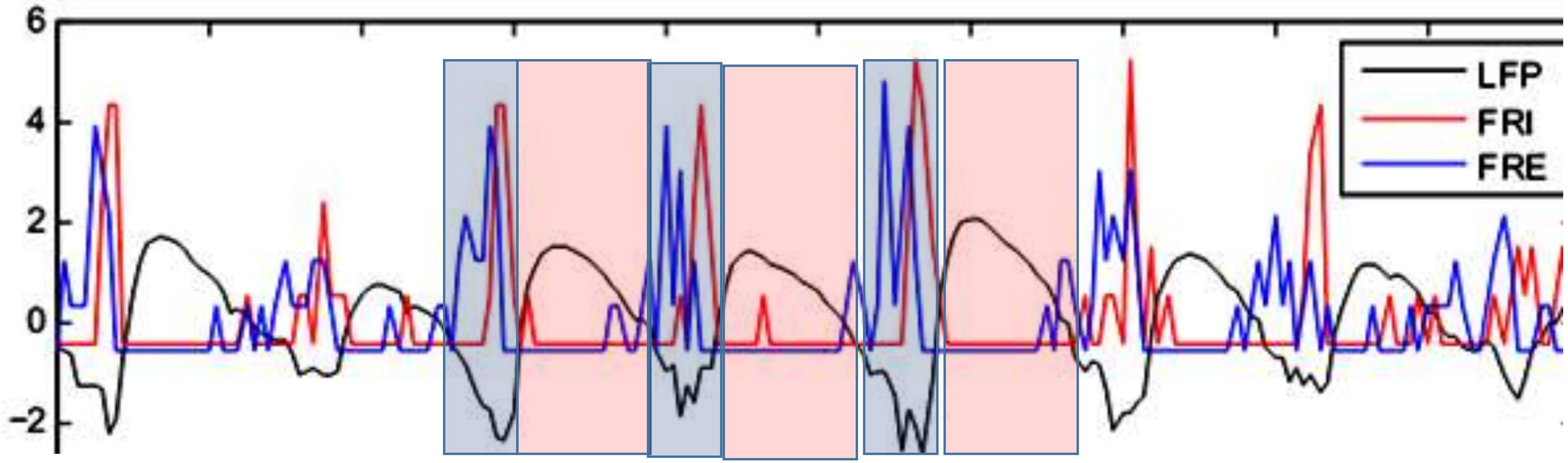
In visual cortex network **intrinsic frequency**: **contrast-dependent** **as we saw previously: implications …**



Synchronization as **neural code** for **EMERGENT local feature grouping/image segmentation**

Lowet E, Roberts M, Hadjipapas A, Peter A, van der Eerden J, De Weerd P. *PLoS Comput Biol.* 2015;11(2):e1004072.

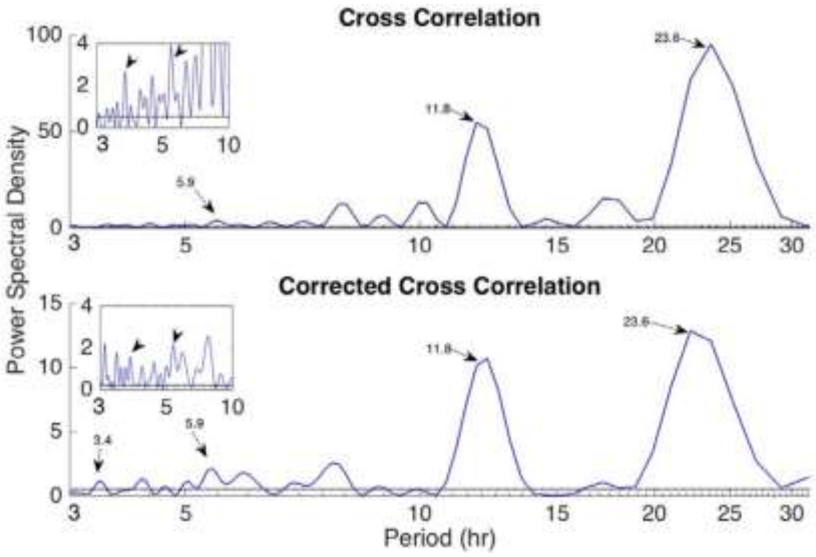
Oscillations and excitability revisited: seizure occurrence & timing



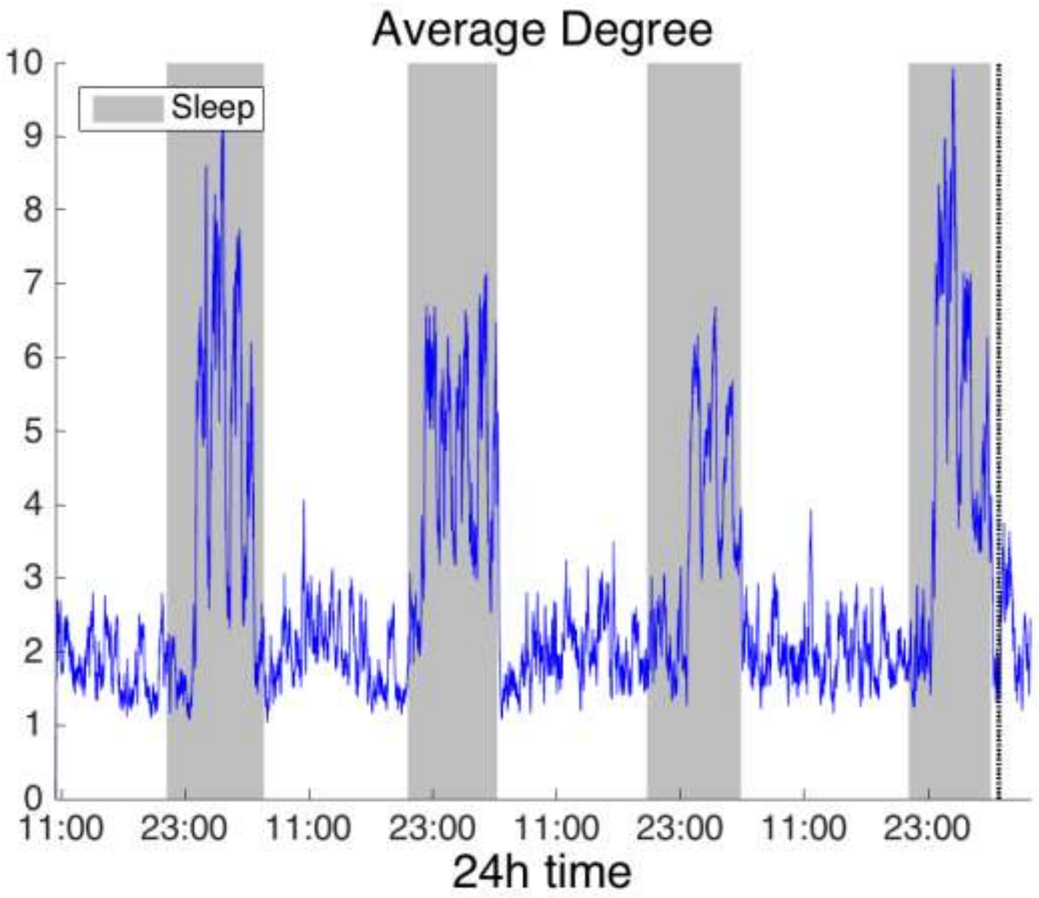
- Networks under strong barrage of **INHIBITION**…
- Neurons fire mostly when **INHIBITION** is low (**EXCITABILITY** is high)
- … fire at certain **PHASES** of oscillation and not others → define **WINDOWS OF OPPORTUNITY**
- **excitability variations** at multiple time scales important for the **surfacing (timing)** of **SEIZURES**
- **→ slow, circadian rhythms (excitability modulation) and timing of seizures (next slides)**

Circadian rhythm in long term recordings EEG of patients with epilepsy

- Seizure prediction algorithms based on EEG usually look for short-term changes just before seizure
- So called **interictal** state assumed to be **stable/constant**
- Very few studies had looked at **continuous, long-term EEG recordings**
- Did this here in 9 patients, **Cyprus Institute Neurology and Genetics (CING)** (patient mix: both more focal and generalized seizures, recording duration 21–94 hr))



Note harmonics at 12, ~6 and ~ 3 hours. Very consistent across patients

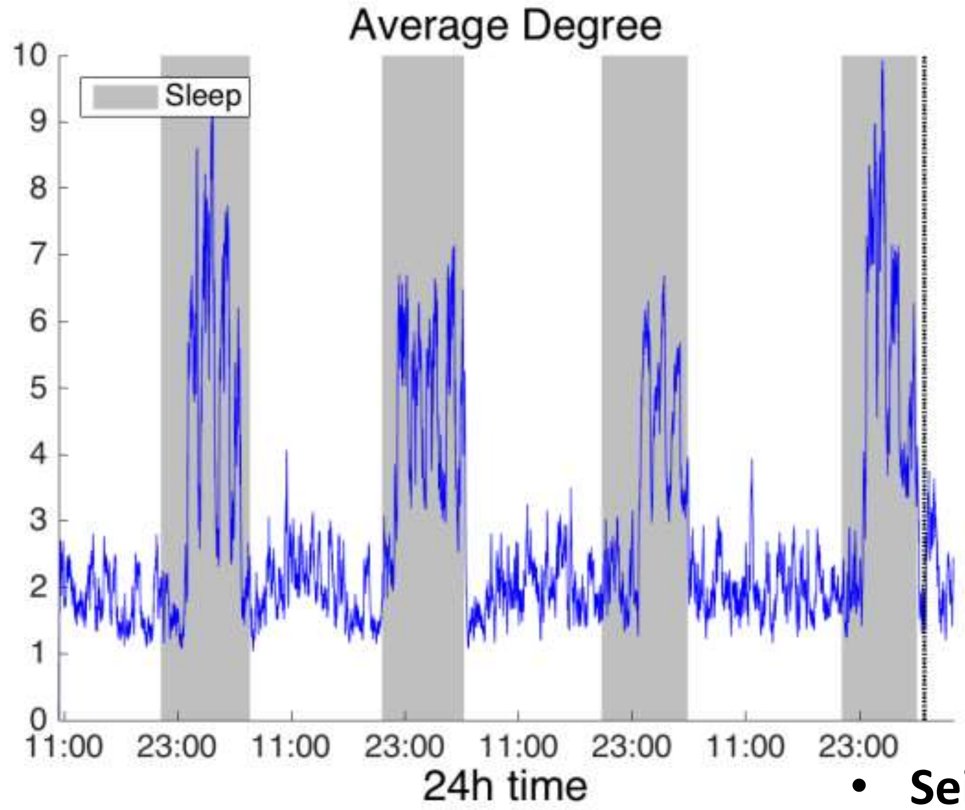


Circadian modulation of EEG connectivity fluctuation (over time)

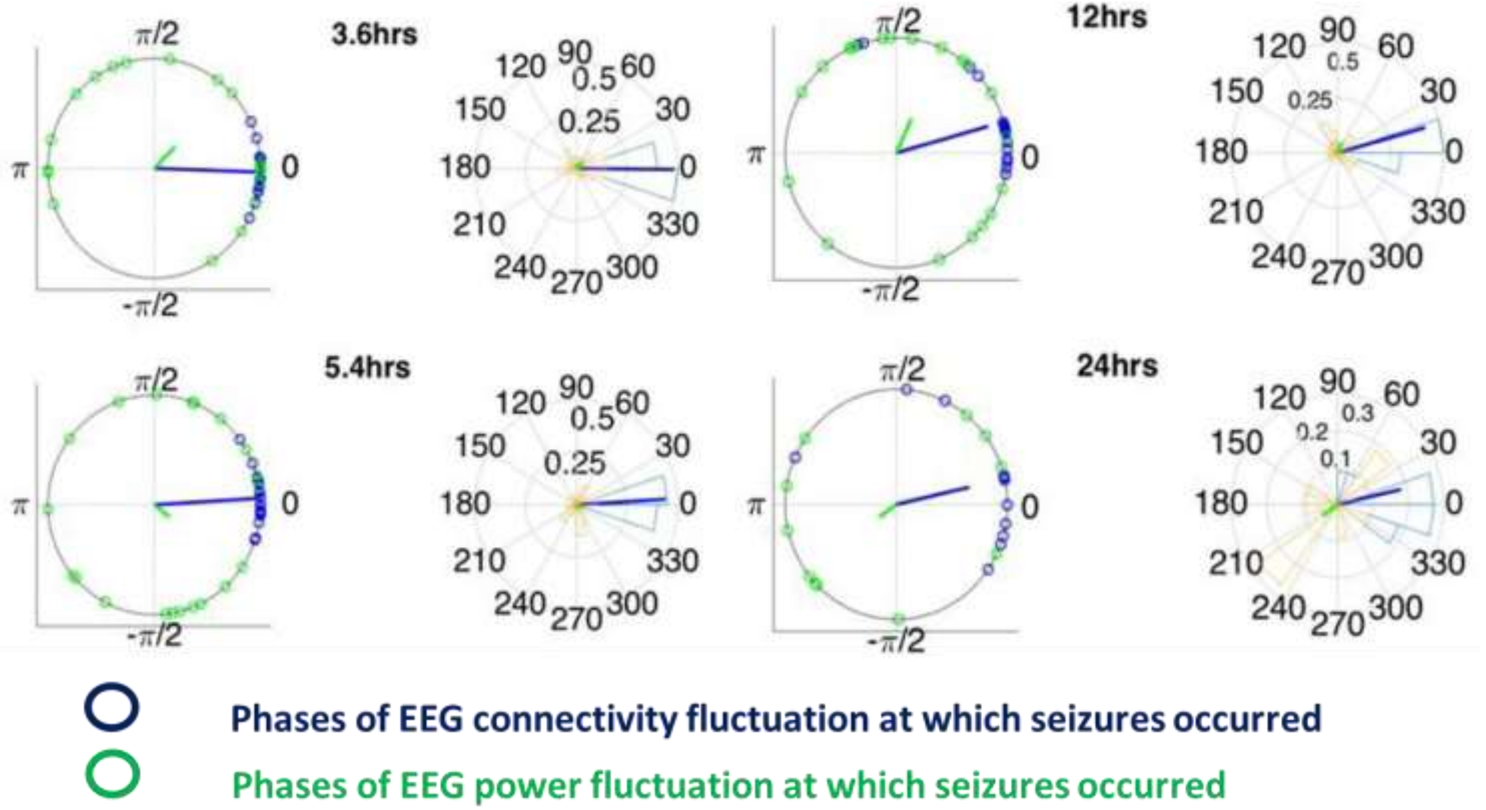
Anastasiadou MN, Christodoulakis M, Papathanasiou ES, Papacostas SS, Hadjipapas A, Mitsis GD. *Front Neurosci. 2019 Mar 20;13:221.*

Mitsis GD., Anastasiadou M., Christodoulakis M, Papathanasiou SE., Papacostas SS. and Hadjipapas A. *Human Brain Mapping, 2020*

Seizures occur at preferred phases of EEG-derived, circadian functional connectivity and NOT elsewhere



Circadian (and ultradian) modulation of EEG connectivity patterns



- **Seizure pathophysiology: Global EEG state (connectivity)** more important for seizure occurrence than **local EEG signal (local signal power)**
- **Automated seizure prediction:** interictal state not constant: circadian variation must be considered.
- **Future:** (**BUT** more studies/data needed!) **seizure forecasting** in individual patients and **closed loop system**

Mitsis GD, Anastasiadou MN, Christodoulakis M, Papathanasiou ES, Papacostas SS, Hadjipapas A. *Hum Brain Mapp*. 2020;41(8):2059-2076.

Conclusions

- The brain is a vast, complex network of interacting units and oscillations are a prime example of activity that depends on network interactions
- Studying mechanisms of oscillation generation can teach us lessons on how neurons cooperate to produce collective network states
- Oscillations can form a bridge between different spatial scales and between animal models and human brain function
- Oscillations, once formed, have important functional consequences:
  - They shape/constrain synchronization→ communication between neurons, layers and brain areas!
  - They control excitability → global brain state and departures from this normal state as in epileptic seizures; can use oscillation theoretical framework for understanding better WHEN seizures occur (seizure forecasting)

Acknowledgements

Gamma oscillations/Human Brain Project

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Human Brain Project

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Prof Peter De Weerd,
Dr Eric Lowet, Current address: Boston University

Epilepsy & circadian rhythms

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30 Years 1990-2020 THE CYPRUS INSTITUTE OF NEUROLOGY & GENETICS

University of Cyprus

Maastricht UMC+

Maastricht University

Prof Georgios Mitsis

Dr Eleftherios Papathanasiou
Prof Savvas Papacostas

Dr Maria Anastasiadou
Dr Manolis Christodoulakis

Dr Rob Rouhl
Dr Mark Roberts

THANK YOU!

Questions?

My papers that were mentioned in this talk …

• Human Brain Project: Comparative analysis of monkey and human gamma oscillations and neuronal network model constrained by empirical data

- **Hadjipapas, A.**, Lowet, E., Roberts, M.J., Peter, A., De Weerd, P., 2015. ***NeuroImage*** 112, 327–34
- Zachariou, M., Roberts, M., Lowet, E., De Weerd, P., Hadjipapas, A. 2021. ***NeuroImage*** 229, 117748.

• Oscillation frequency and role in neuronal synchronization and neural coding

- Lowet E, De Weerd P, Roberts MJ, **Hadjipapas A.** ***Front Syst Neurosci*.** 2022 Jul 8;16:908665. doi: 10.3389/fnsys.2022.908665.
- Lowet E, Roberts M, **Hadjipapas A**, Peter A, van der Eerden J, De Weerd P. ***PLoS Comput Biol***.2015;11(2):e1004072.
- **Hadjipapas A**, Charalambous CC, Roberts MJ. ***Front Syst Neurosci***. 2023 Jan 4;16:1121438. doi: 10.3389/fnsys.2022.1121438.

• Circadian rhythms and epileptic seizures

- Anastasiadou MN, Christodoulakis M, Papathanasiou ES, Papacostas SS, **Hadjipapas A**, Mitsis GD. ***Front Neurosci***. 2019 Mar 20;13:221.
- Mitsis GD., Anastasiadou M., Christodoulakis M, Papathanasiou SE., Papacostas SS. and **Hadjipapas A. *Hum Brain Mapp*.** 2020;41(8):2059-2076.

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