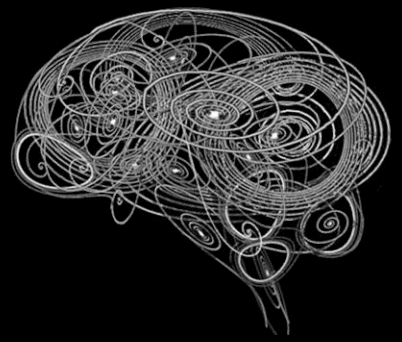
The brain is not a passive receiver: State-Dependent Control of Oscillatory Brain Dynamics

Jérémie Lefebvre
Krembil Research Institute
Department of Mathematics, University of Toronto



Neural Dynamics and Statistics, BIRS-Banff, Feb 26th – March 3rd 2017

Krembil Relentless.

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

SYNC LAB COMPUTATIONAL NEUROSCIENCE | NONLINEAR DYNAMICS

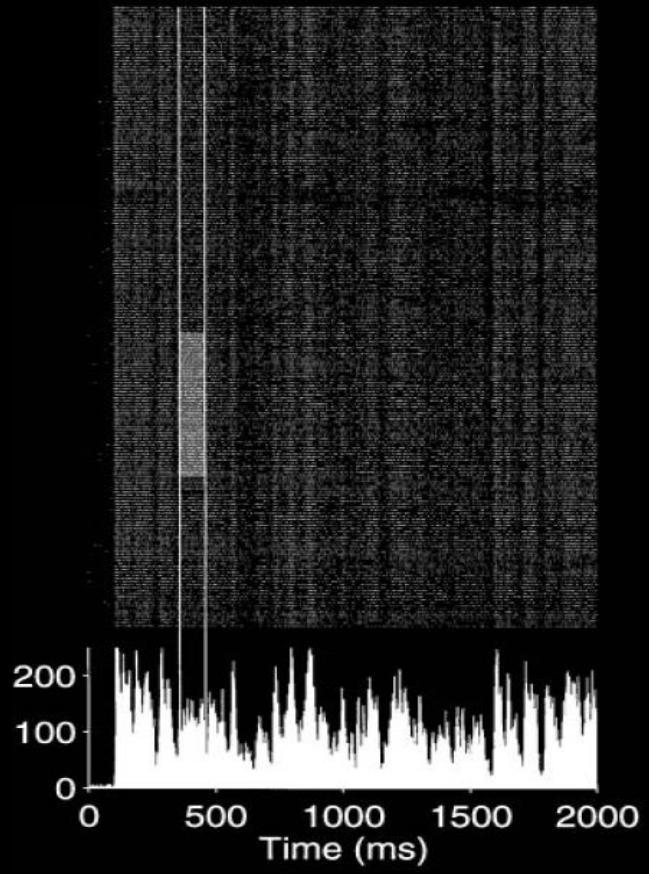
UNIVERSITY OF TORONTO

Short Story

- Neural variability plays an important role in gauging controllability of cortical circuits and remains a real challenge for brain stimulation;
- How can we compensate for this variability to guide oscillatory brain activity for therapeutic interventions? (assuming oscillations have a functional role!)
- Our results reveal that in presence of rhythmic stimulation, non-linear noise-induced effects combine to resonance and entrainment to shape synchronous activity in cortical networks;
- When such networks are embedded within a thalamo-cortical loop, “state-dependence” of stimulation corresponds to fluctuations in cortical susceptibility to entrainment, mediated by sub-cortical populations
- These results open new perspectives on the optimal control of brain oscillations for basic and clinical research.

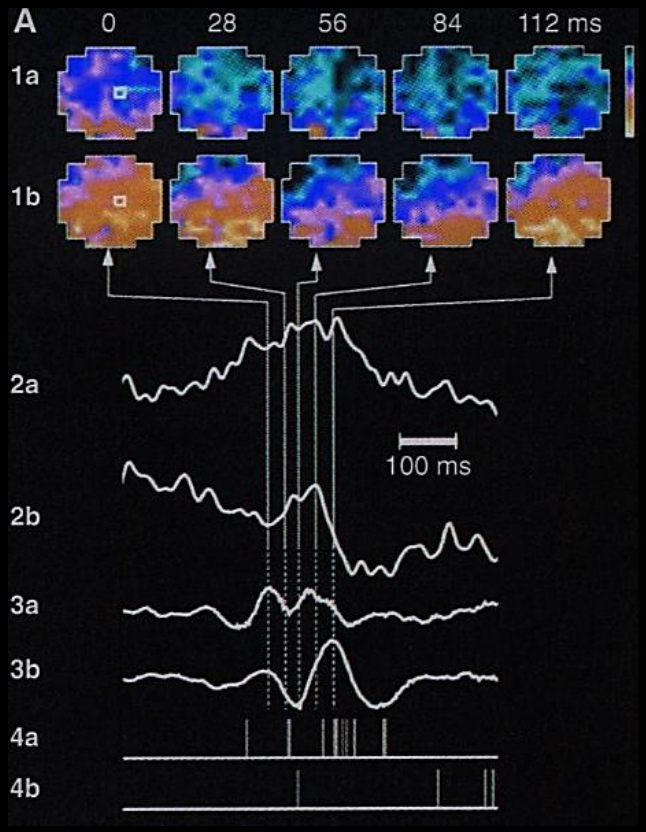
Variability across scales

Shadlen & Newsome 1998



Response variability of a neuron recorded from area MT of an alert monkey. Raster plot depicting response for 210 presentations of an identical random dot motion stimulus.

Arieli et al. 1996



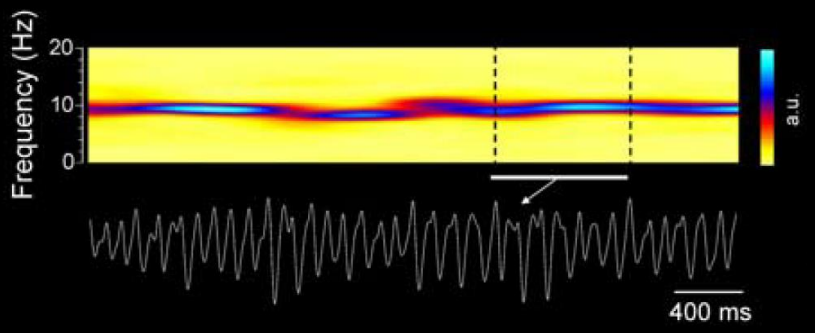
Two individual responses (a and b) to a repeated visual stimulus. The images (1a,b) show the activity in a 2 mm by 2 mm area of cortex, taken at different times from response onset.

Variability in oscillatory activity (in time)

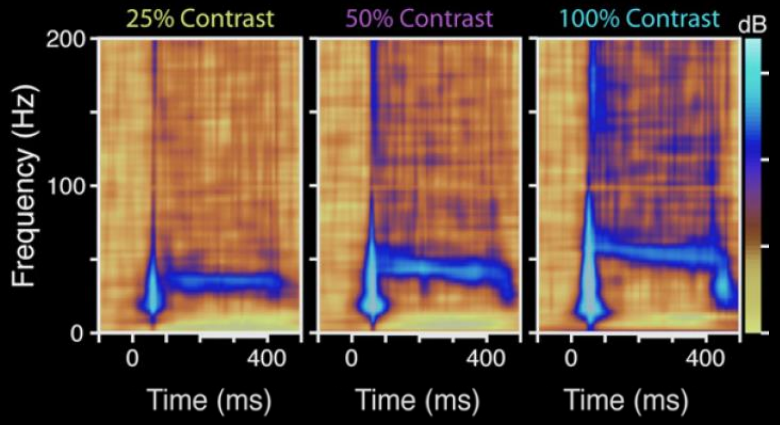
Statistics of oscillatory regimes are NOT stationary.

Short time scale

α Lorincz et al. 2008

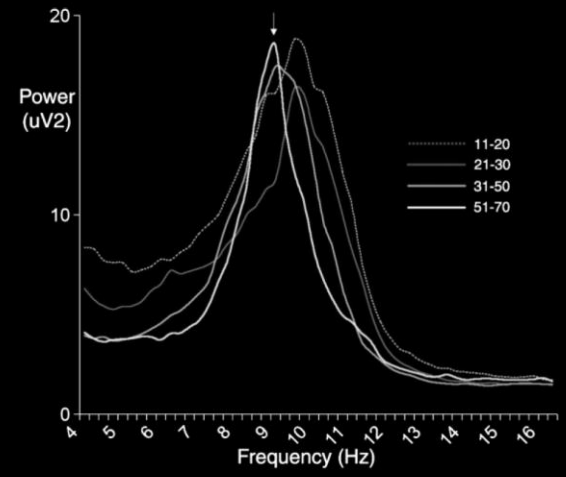


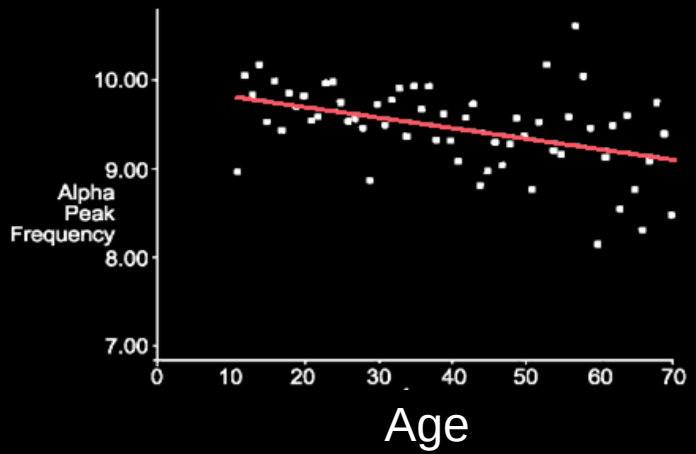
γ Ray & Maunsell 2010



Long time scale

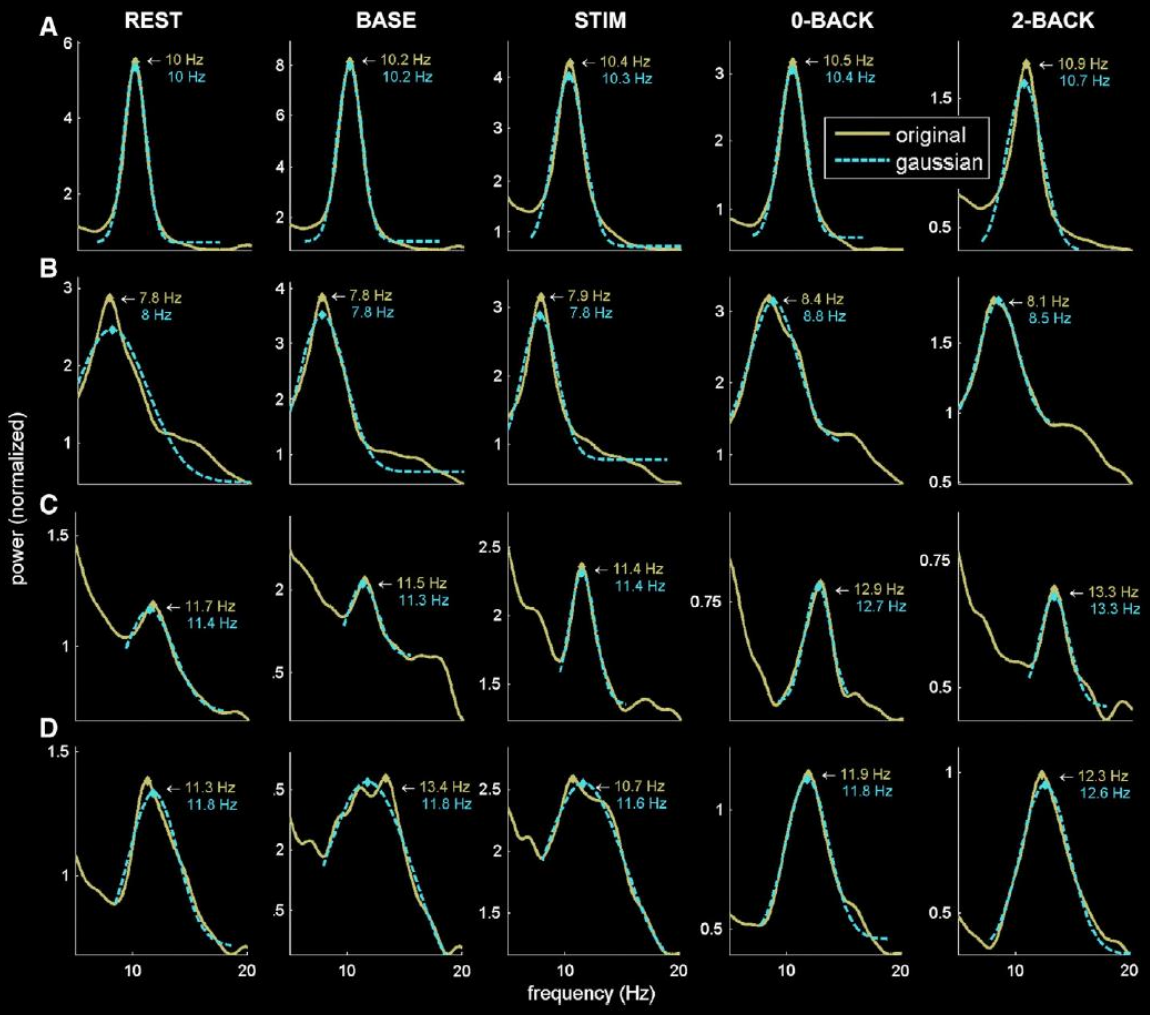
α Clark et al. 2003





Variability in oscillatory activity (between subjects)

α



Heagens et al. 2014

How do we control such systems?

Variability in dynamics put severe constraints on “controllability”

Manipulating oscillatory dynamics

We are interested in understanding the different mechanisms by which oscillatory activity can be controlled/altered:

1. Internal sources: changes in oscillatory features (power, frequency) as a function of changes in internal “state” (attention, etc)

2. Pharmaceutical sources: Changes in oscillatory features induced by a drug (anesthesia, etc)

3. External sources: Oscillatory fluctuations triggered by stimulation (“neuromodulation”).

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Internal sources

Using mean-field analysis, we have used a large-scale network to understand the effect of internal fluctuations (change in noise statistics) on alpha (10Hz) activity.

$$X_i \rightarrow Poisson(f[u_i])$$

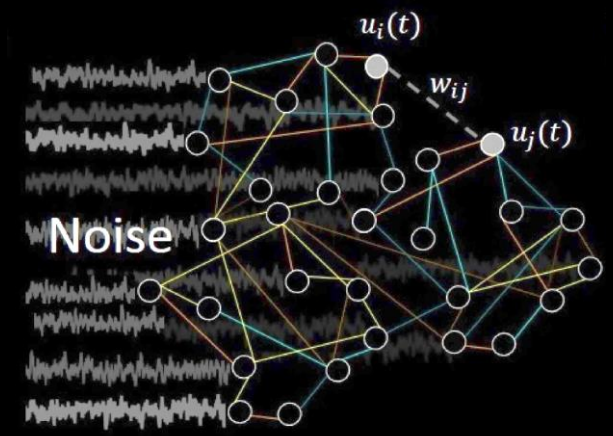
$$\alpha^{-1}\frac{d}{dt}u_i(t) = -u_i(t) + N^{-1}\sum_{j=1}^{N} w_{ij}X_j(t-\tau) + \sqrt{2D}\xi_i(t)$$

mean field analysis

$$\frac{d}{dt}\bar{u}(t) = -\bar{u}(t) + \ll f[\bar{u}(t)] \gg_N$$

Stochastic stability analysis

$$\omega \approx G(\tau, \bar{w}, D)$$



Hutt et al. 2016, Lefebvre et al. 2015

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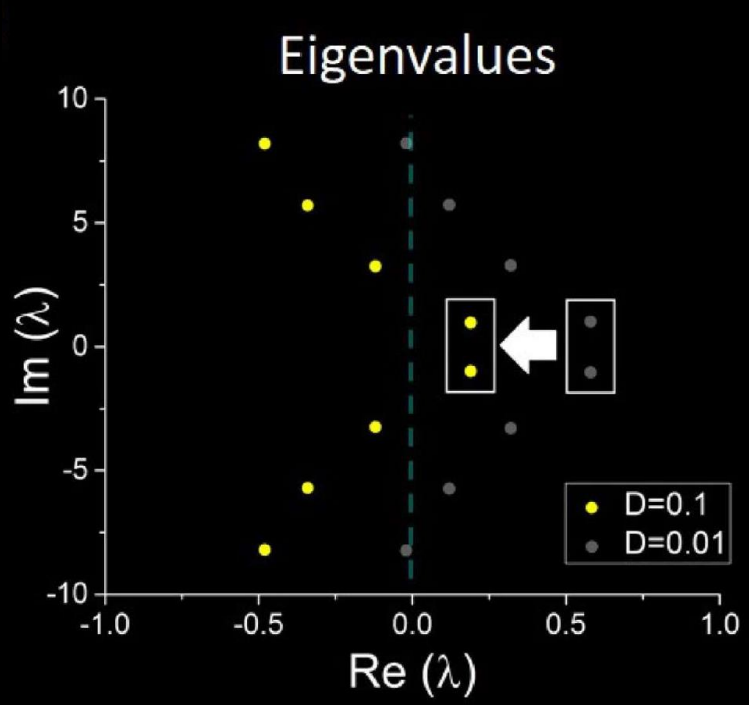

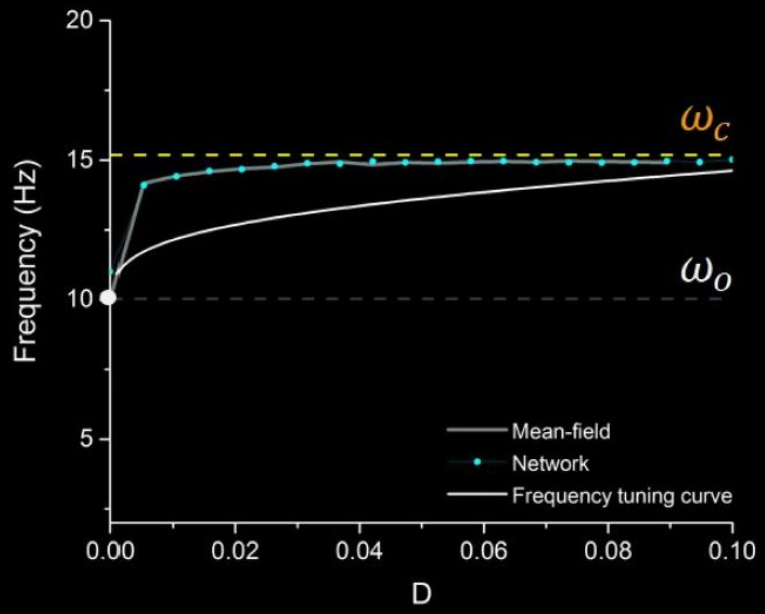

Hutt et al. 2016, Lefebvre et al. 2015

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1. Internal sources: changes in oscillatory features (power, frequency) as a function of changes in internal “state” (attention, etc)

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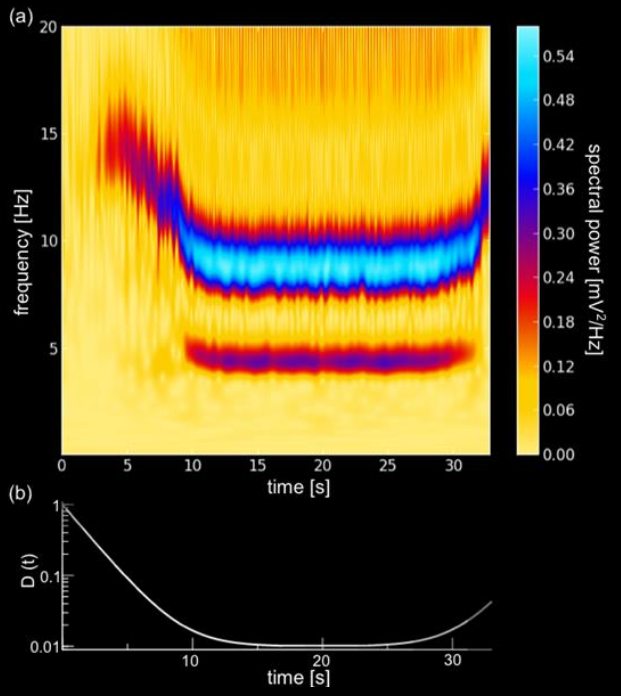
3. External sources: Oscillatory fluctuations triggered by stimulation (“neuromodulation”).

Pharmaceutical sources

Using a thalamocortical system, we have used mean-field and stochastic approaches to understand the peculiar spectral signatures observed at the onset of loss of consciousness in Propofol-induced anesthesia…

Full story on Friday!



Axel Hutt

Hutt & Lefebvre, submitted

Manipulating oscillatory dynamics

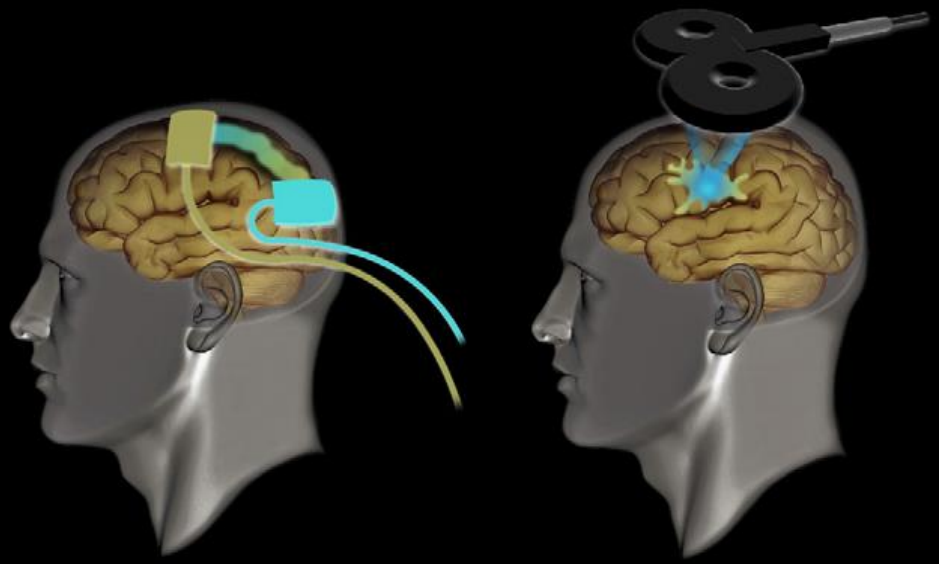
We are interested in understanding the different mechanisms by which oscillatory activity can be controlled/altered:

1. Internal sources: changes in oscillatory features (power, frequency) as a function of changes in internal “state” (attention, etc)

2. Pharmaceutical sources: changes in oscillatory features induced by a drug (anesthesia, Parkinson, epilepsy)

3. External sources: Oscillatory fluctuations triggered by stimulation (“neuromodulation”).

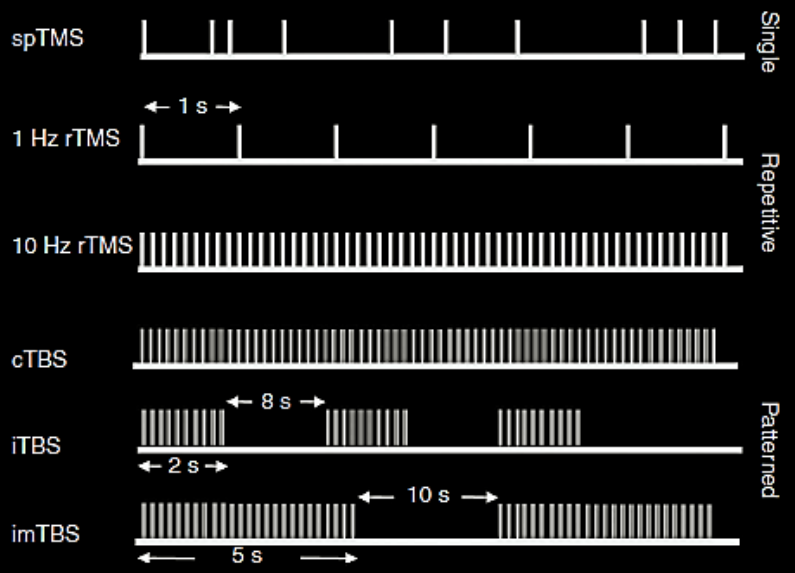
Variability is a challenge for brain stimulation



tDCS/TACS

TMS

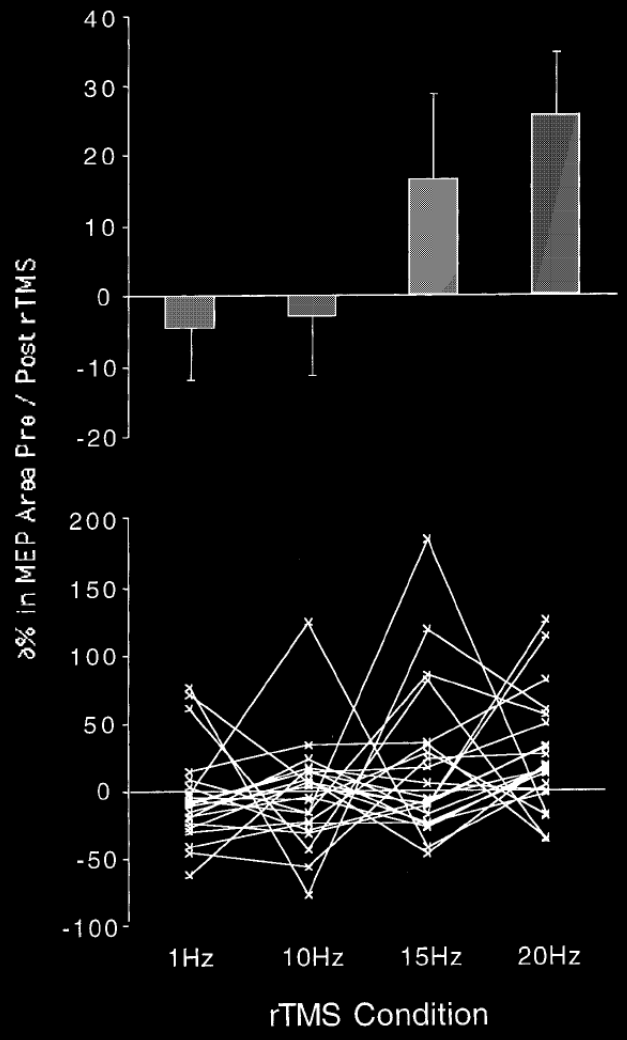
Common stimulation patterns



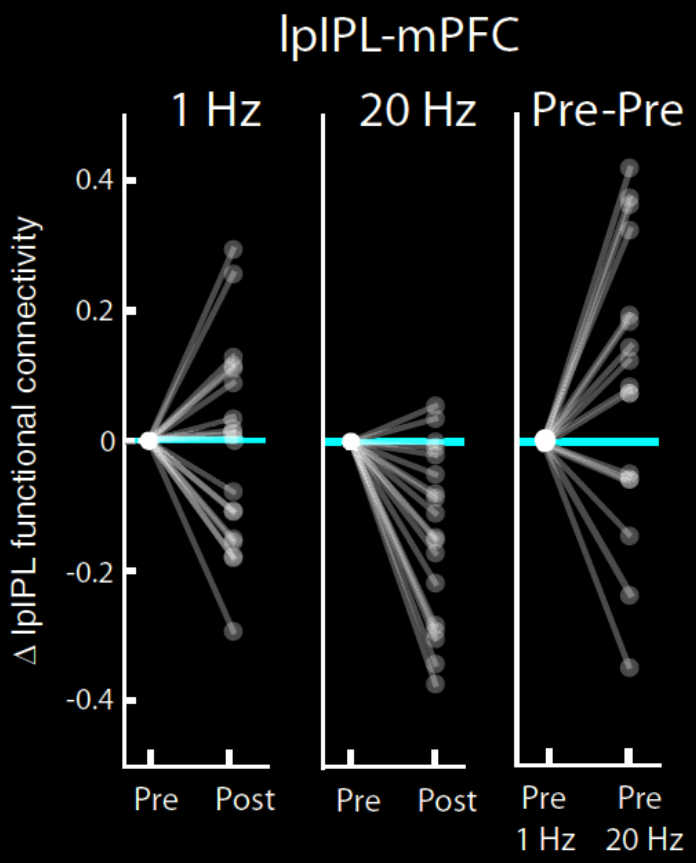
Questions *:* *What is the impact of stimulation on EEG?*
What is the optimal signal to use?

(Dayan et al. 2013 , Thut & Minuissi 2009, Huesta & Volpe 2009)

Effects on functional connectivity are variable



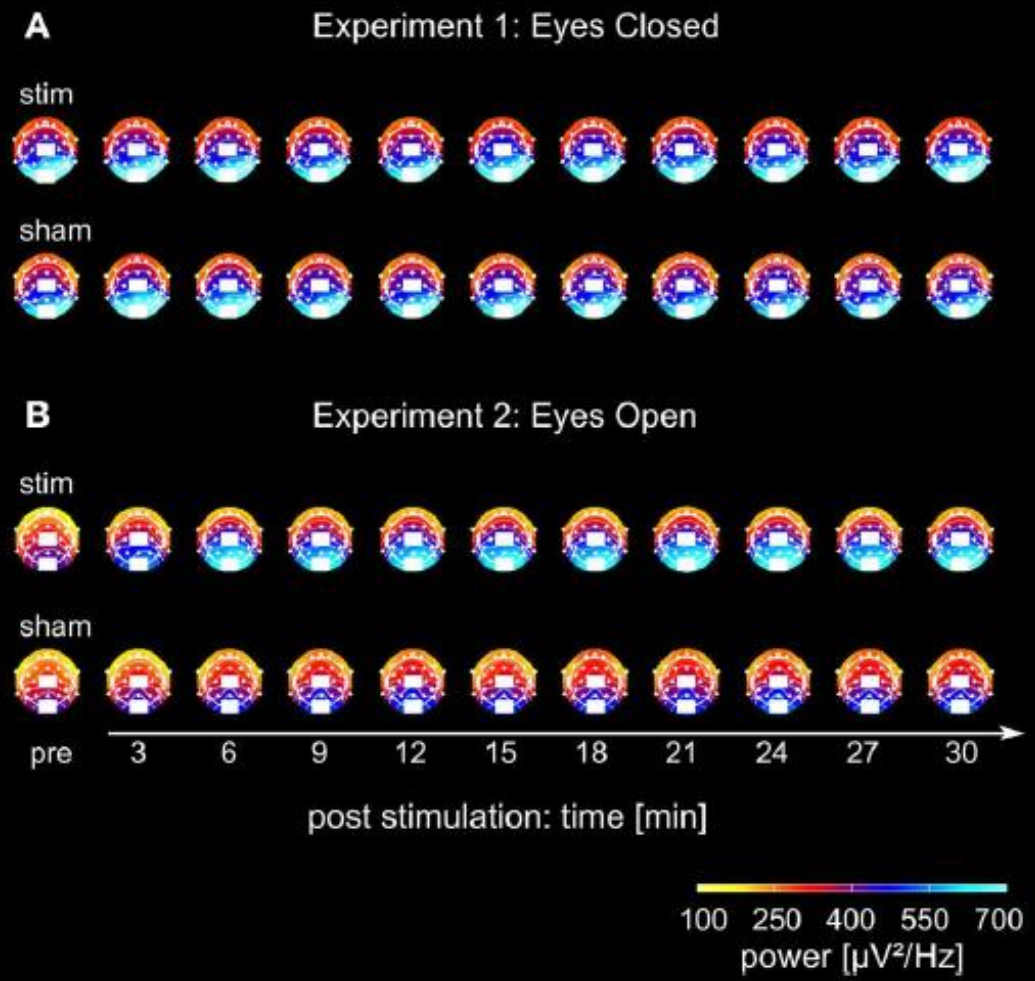
Maeda et al 2000



Eldaief et al. 2011

Effects on neural oscillations are variable

Many studies have shown that stimulation efficacy is state-dependent i.e. outcomes depend on ongoing neural activity.

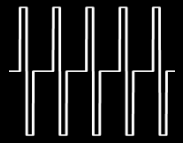


Neuling et al. 2013

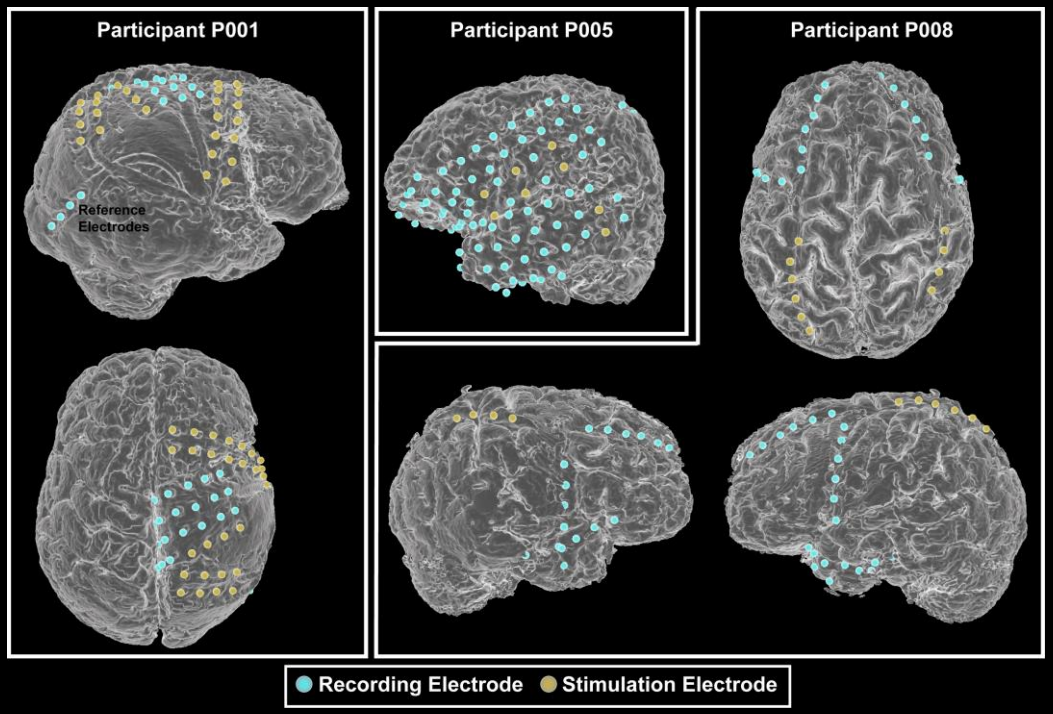
Case study: Human periodic DCS

In this experiment, we tried to quantify this state dependence by trying to entrain endogenous resting state “alpha” oscillations in different conditions.

ECOG



Biphasic pulse stimulus
2 mA ; 200 µs in duration at 10Hz

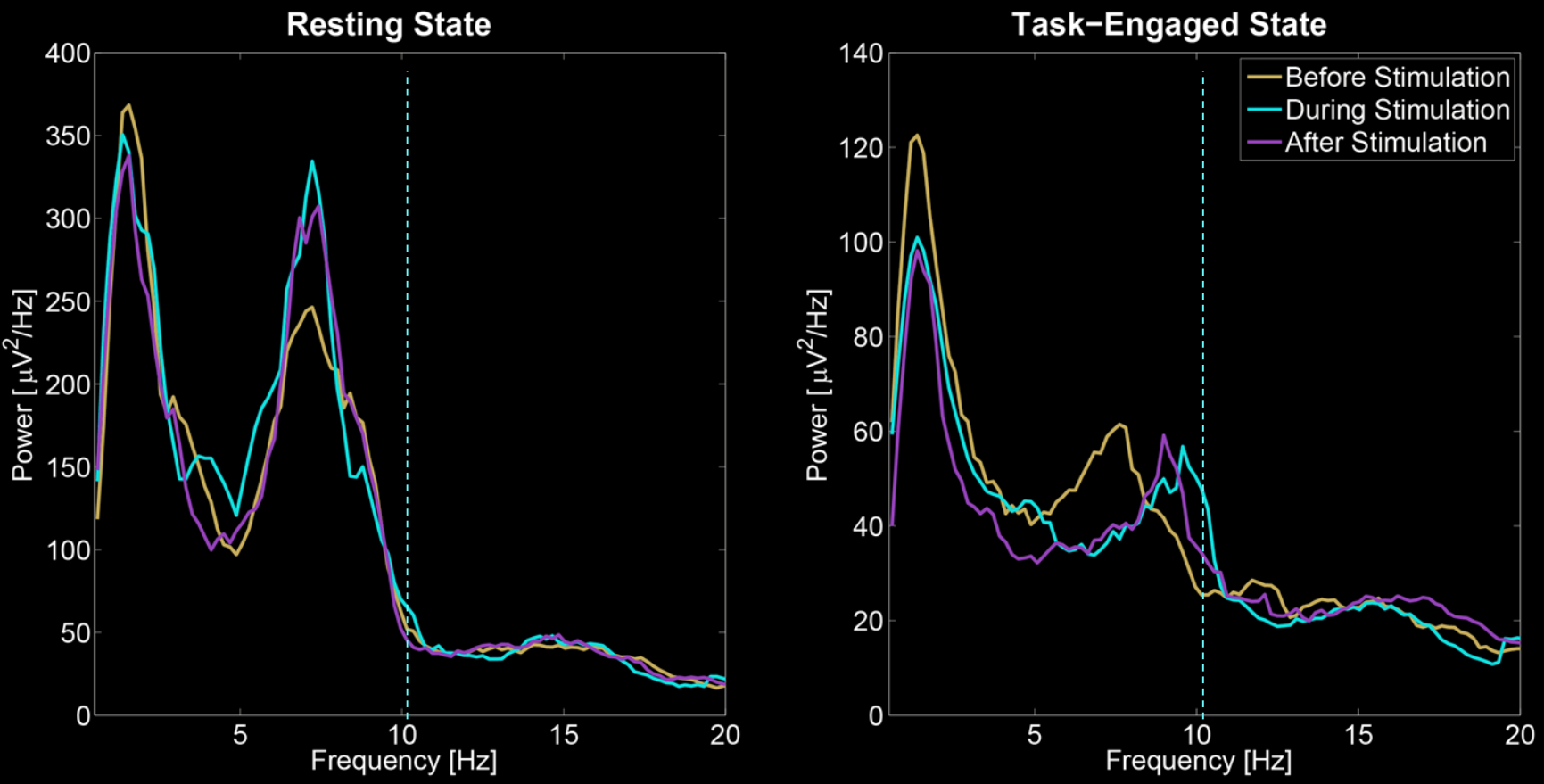


Flavio Frohlich

Alagapan et al. 2016

Case study: Human periodic DCS

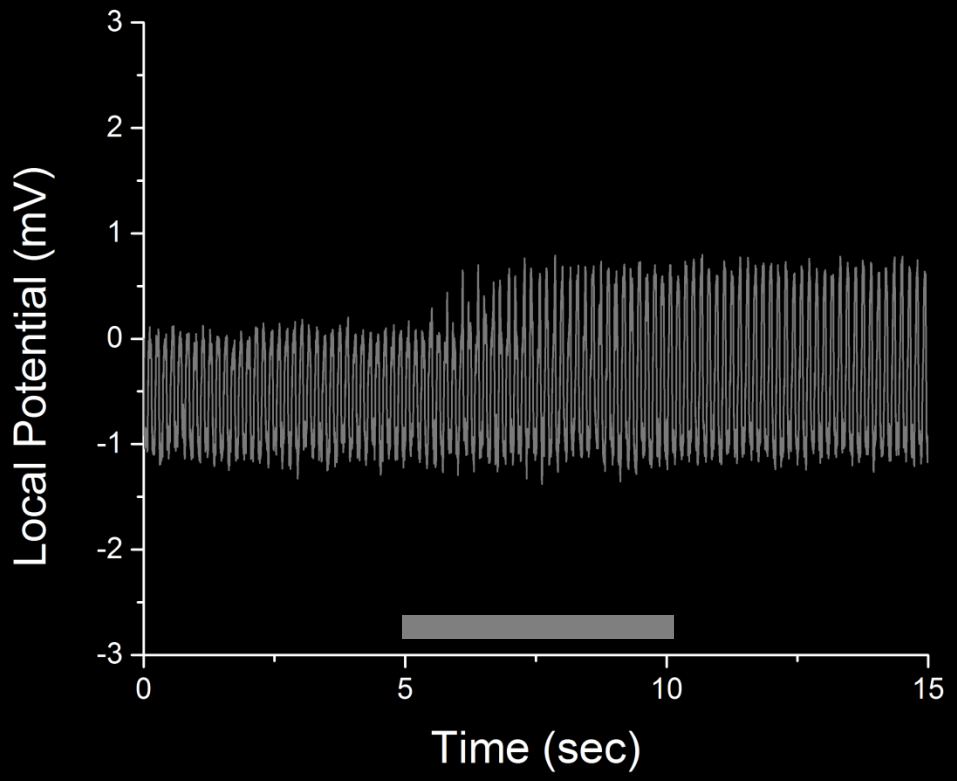
Entrainment of neural activity was only possible in the task-engaged state.



Alagapan et al. 2016

Case study: Human periodic DCS

Using a conceptual model with feedback we could qualitatively reproduce the observed state-dependent responses.



Rest – 7.5Hz

Alagapan et al. 2016

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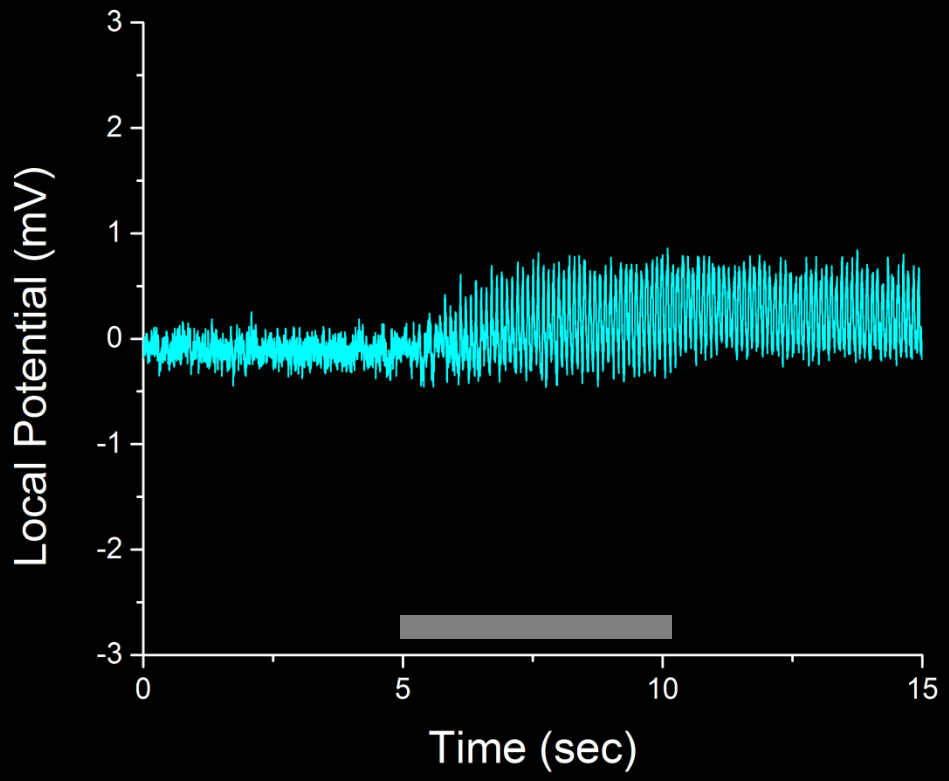


Task – 10.0Hz

Alagapan et al. 2016

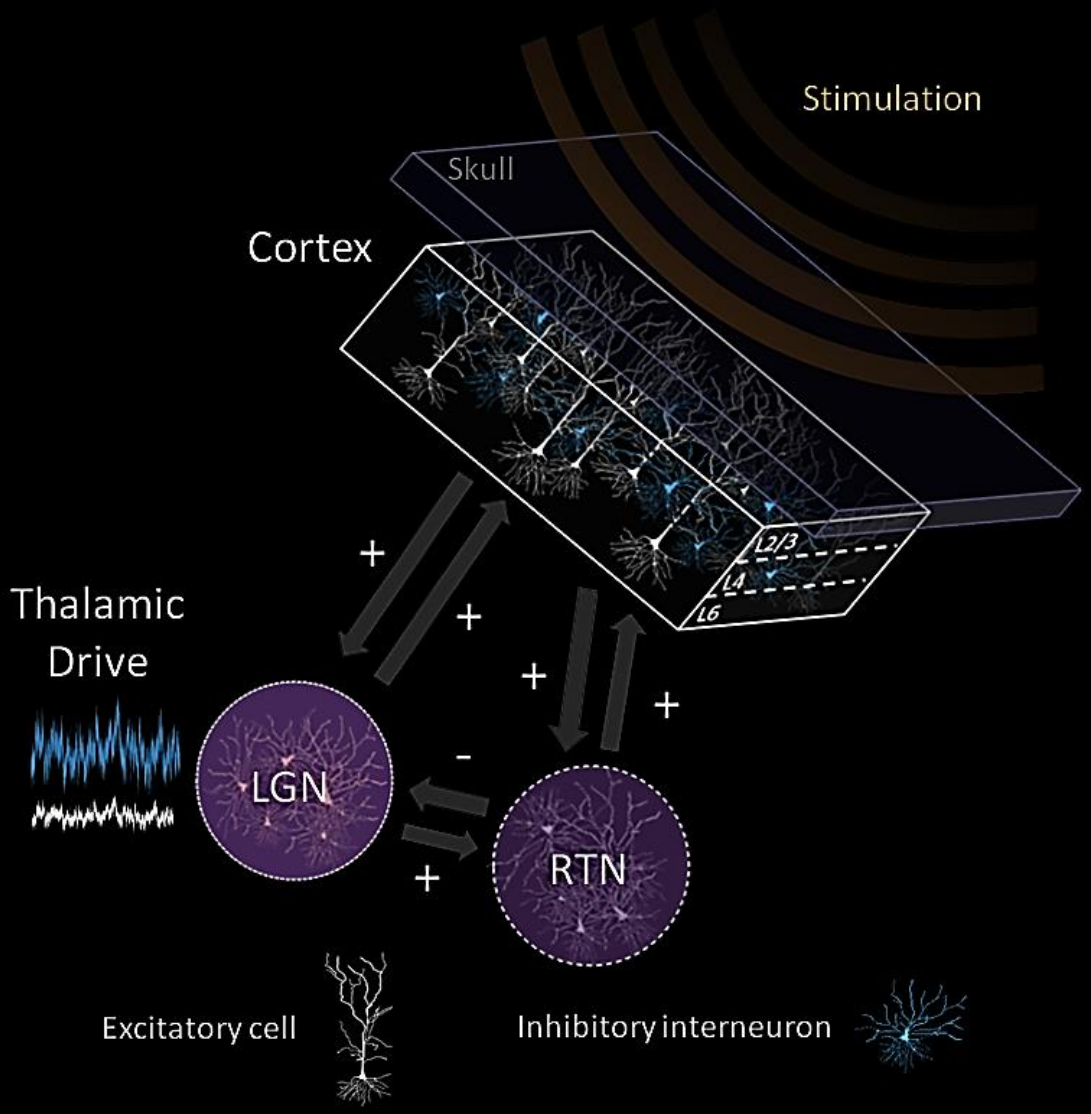
Main Goal

We want understand the underpinnings of this phenomenon by looking at a neural oscillator model of the cortex. The goal is to study both intrinsic oscillatory features of this network but also how emerging synchronous oscillations interact with external perturbations (stimulation) in a state-dependent way*.

Step 1: characterize response of cortical networks to stimulation of various amplitudes and frequencies

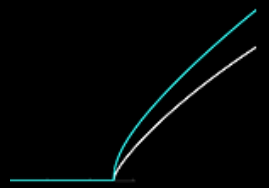
Step 2: See how the results change as a function of state

Thalamocortical network



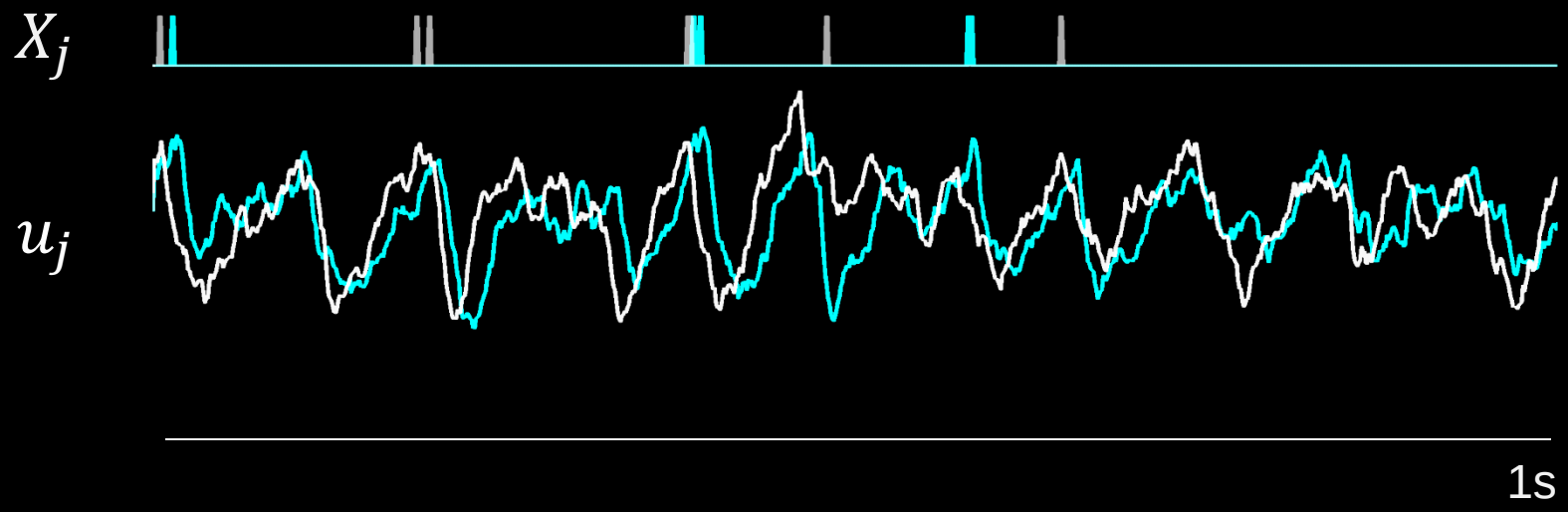
Frohllich, Lefebvre (In Preparation)

Thalamocortical network



Network of Poisson neurons $X_j^n \rightarrow Poisson\left(f\left[u_j^n(t)\right]\right)$

$n = \{e, i, LGN, RTN\}$



Thalamocortical network

Network of Poisson neurons o $X_j^n \rightarrow Poisson\left(f\left[u_j^n(t)\right]\right)$

Membrane Leak Recurrent connections Adaptation Noise+Stim

$$\frac{du_j^n(t)}{dt} = -u_j^n(t) + \sum_m \sum_k W_{jk}^{nm}(c) \cdot E_k^m\left(t - \tau_{jk}\right) + v_j^n(t) + \sqrt{2D}\,\varphi_j^n + I(t)$$

$$\alpha^{-1} \frac{dv_j^n(t)}{dt} = -v_j^n(t) + u_j^n(t)$$

with post-synaptic potentials $E_k^m(t) = \eta \circ X_k^m$.

Neuroelectric (“EEG”) output:

$$A(t) = \frac{1}{N_e} \sum_{k=1}^{N_e} \phi_e^k u_e^k(t) + \frac{1}{N_i} \sum_{k=1}^{N_i} \phi_i^k u_i^k(t)$$

Main Goal

We want understand the underpinnings of this phenomenon by looking at a neural oscillator model of the cortex. The goal is to study both intrinsic oscillatory features of this network but also how emerging synchronous oscillations interact with external perturbations (stimulation) in a state-dependent way*.

Step 1: characterize the responses of cortical networks to stimulation in presence of stationary oscillatory properties

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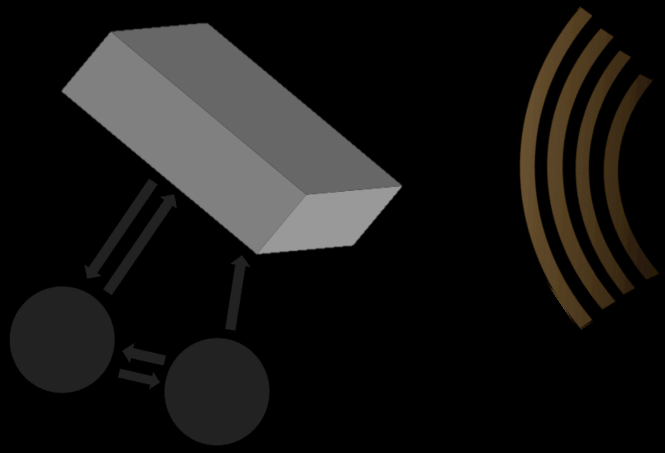
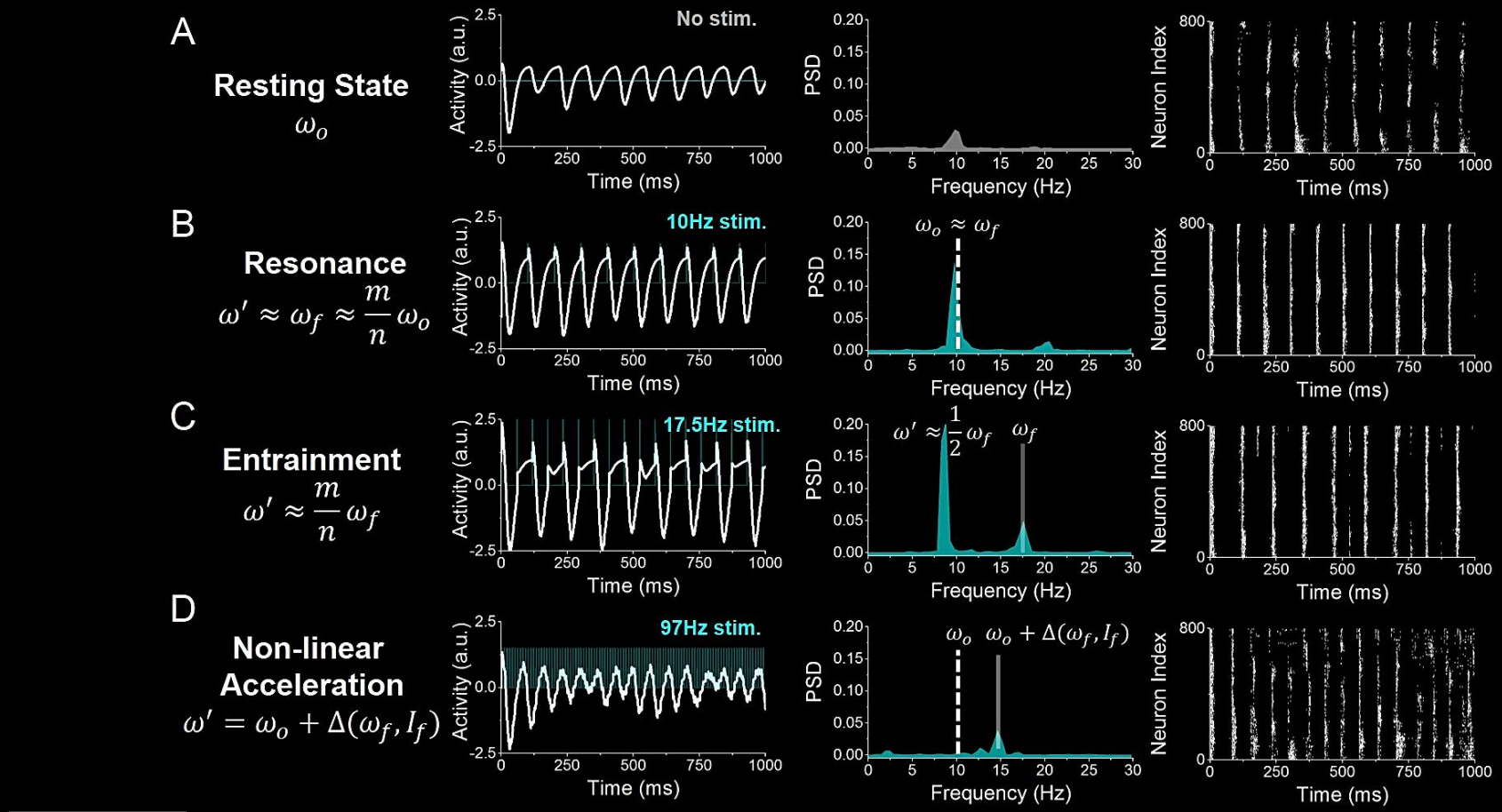
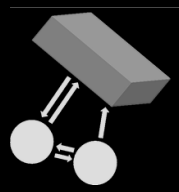


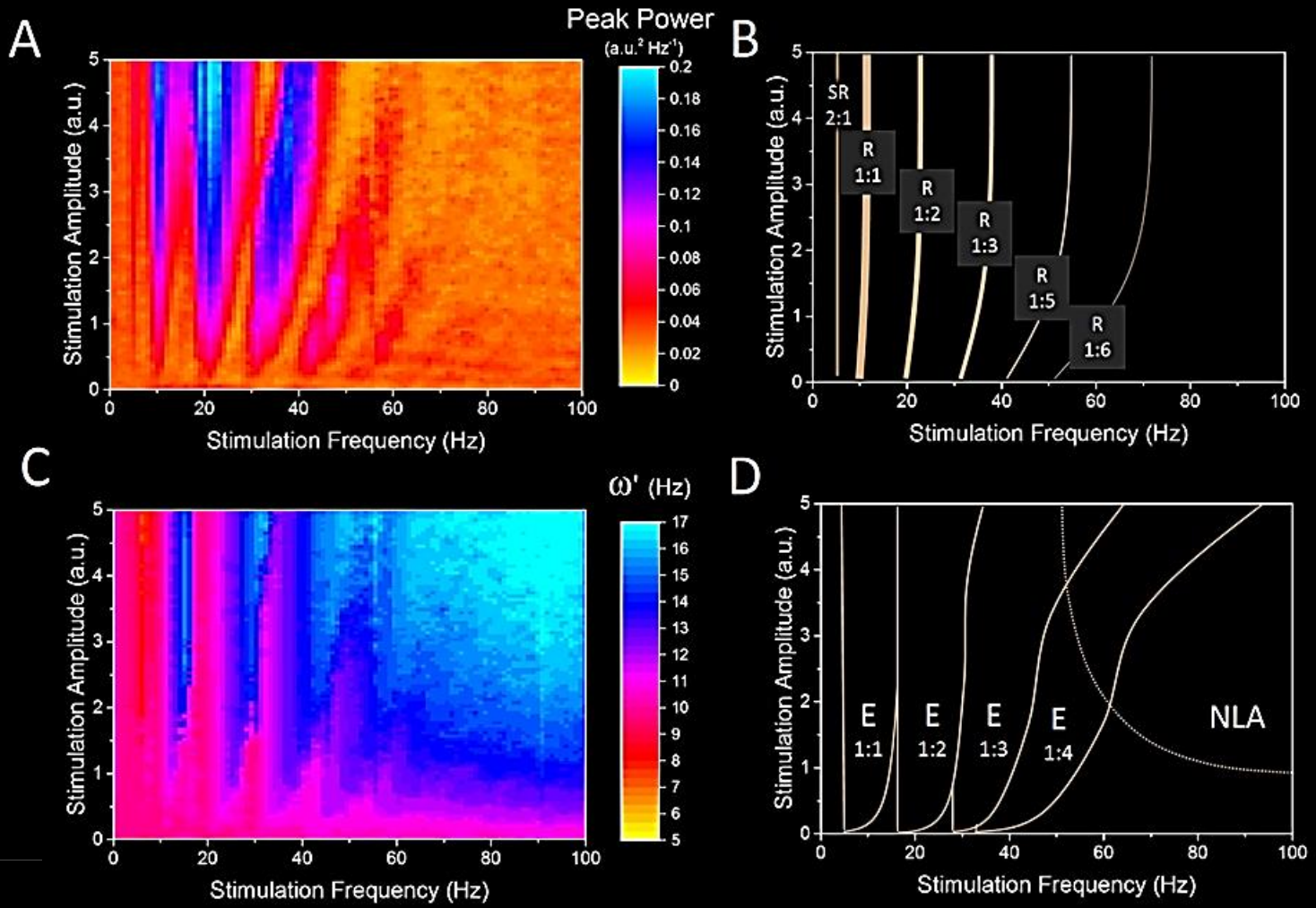
1. Responses of cortical networks

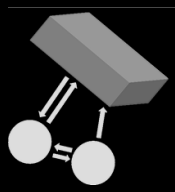




Herrmann et al. 2016

1. Resonance Peaks and Arnold Tongues





Herrmann et al. 2016

Main Goal

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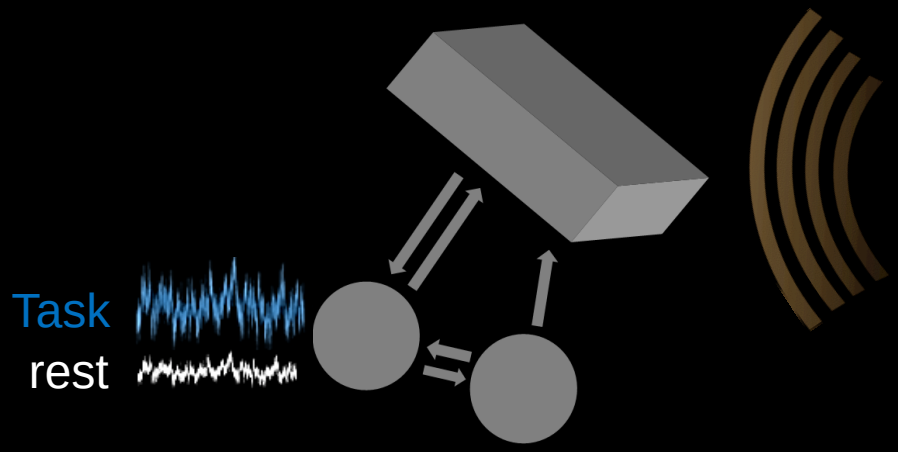
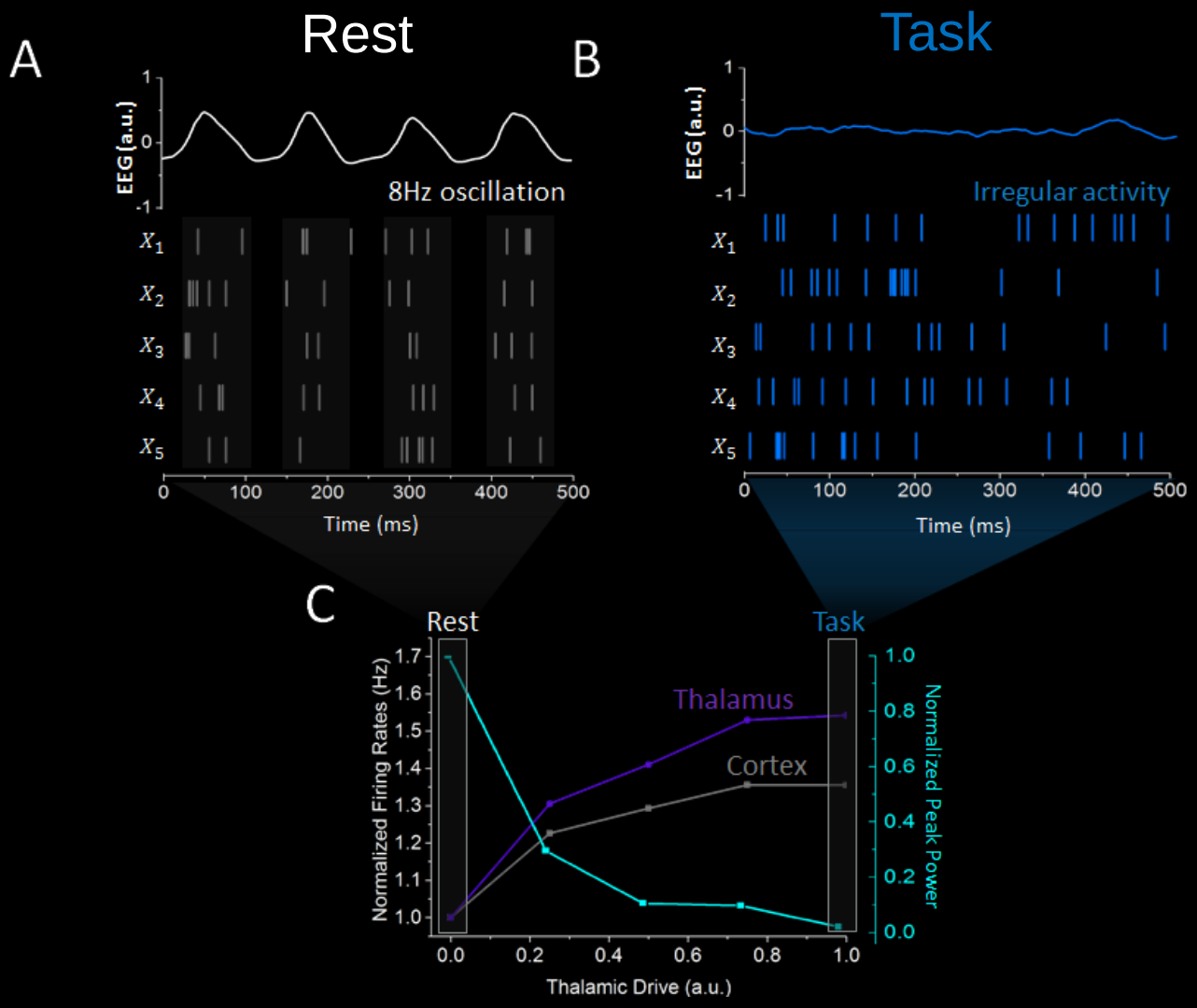


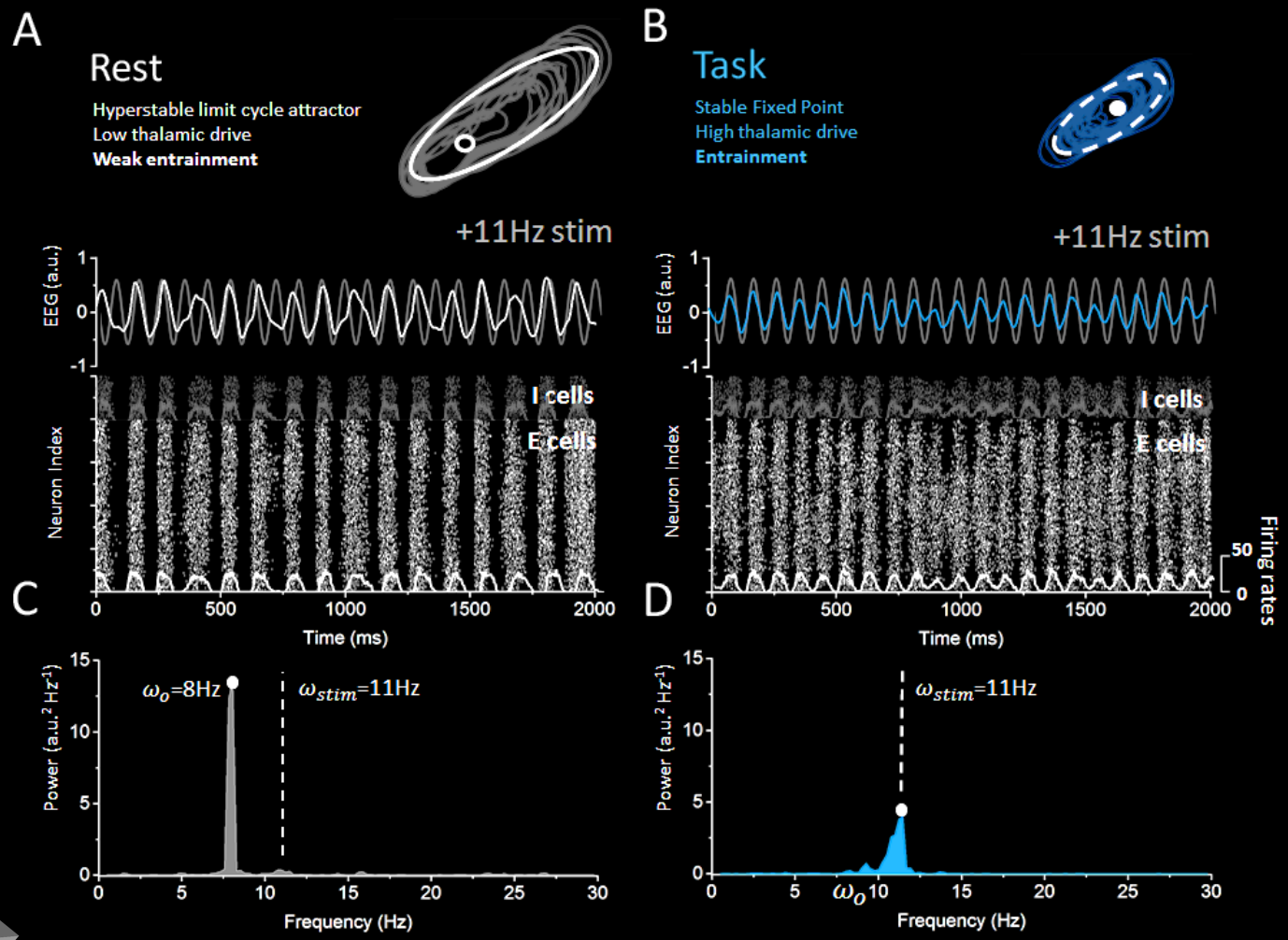
2. Transition from synchronous to irregular activity



Frohllich, Lefebvre (In Preparation)

2. State-Dependent Entrainment

(See Poster!)



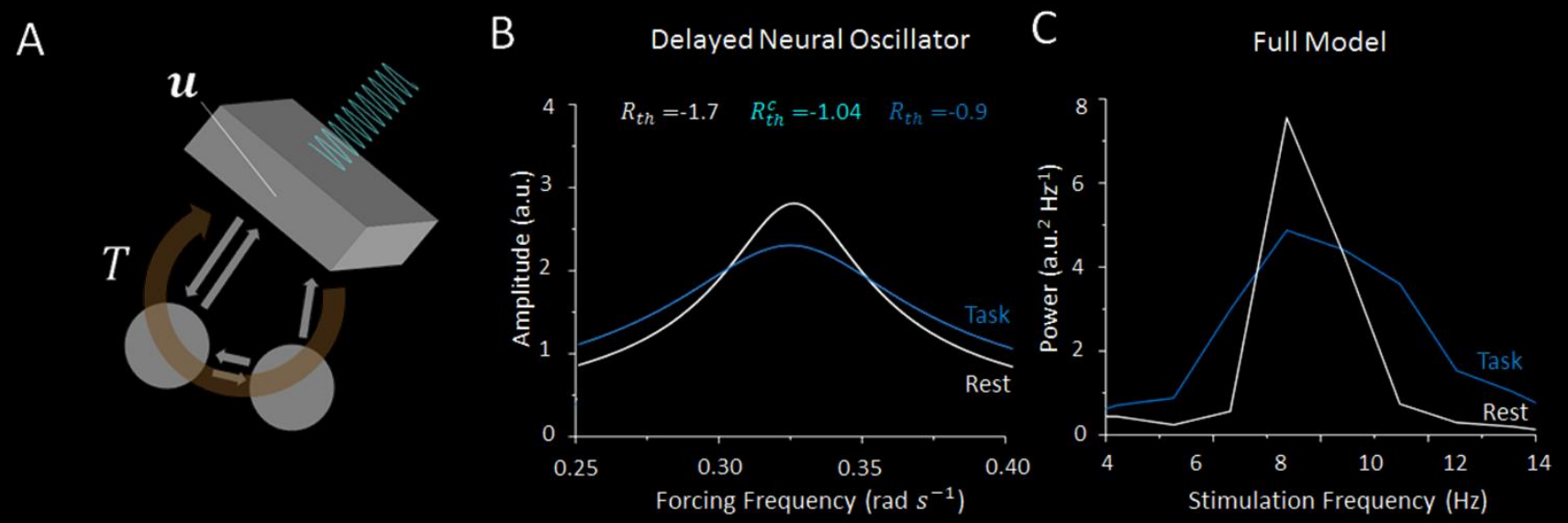
Frohllich, Lefebvre (In Preparation)

Theoretical questions

In this model, susceptibility to entrainment (and stimulation in general) is gated by the proximity to an instability. Consider the non-linear delayed oscillator corrected for additive noise effects

$$\frac{d}{dt}\bar{u}(t) = -\bar{u}(t) + g\,F[u(t-\tau)] + I_o + S(t)$$

With $F = \left(1 + \mathrm{erf}\left[\frac{\bar{u}(t-\tau)}{\sqrt{2D}}\right]\right)$ (*), bias I_o and stimulation signal $S(t)$. If we linearize this system about its fixed point we can calculate its (linear) power spectrum. For $S(t) = S_{stim}\cos(\omega_{stim}t)$, we can also compute the resonance curves and investigate the effect of « state » (proximity to an instability) on the power/amplitude found at the stimulation frequency.



(*) :Lefebvre et al. 2016, Hutt et al. 2016

Summary

- Neural variability plays an important role in gauging controllability of cortical circuits and remains a real challenge for brain stimulation;
- How can we compensate for this variability to guide oscillatory brain activity for therapeutic interventions?
- Our results reveal that in presence of rhythmic stimulation, non-linear noise-induced effects combine to resonance and entrainment to shape synchronous activity in cortical networks;
- When such networks are embedded within a thalamo-cortical loop, “state-dependence” of stimulation corresponds to fluctuations in cortical susceptibility to entrainment, mediated by sub-cortical populations
- These results open new perspectives on the optimal control of brain oscillations for basic and clinical research.

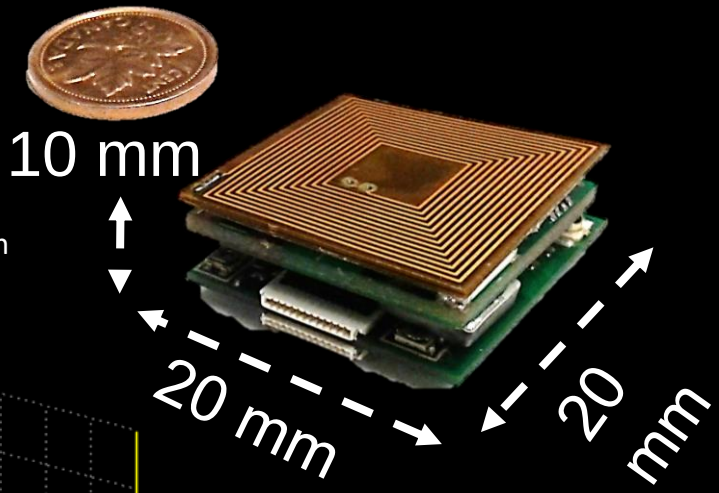
Application: Closed-loop control of seizures

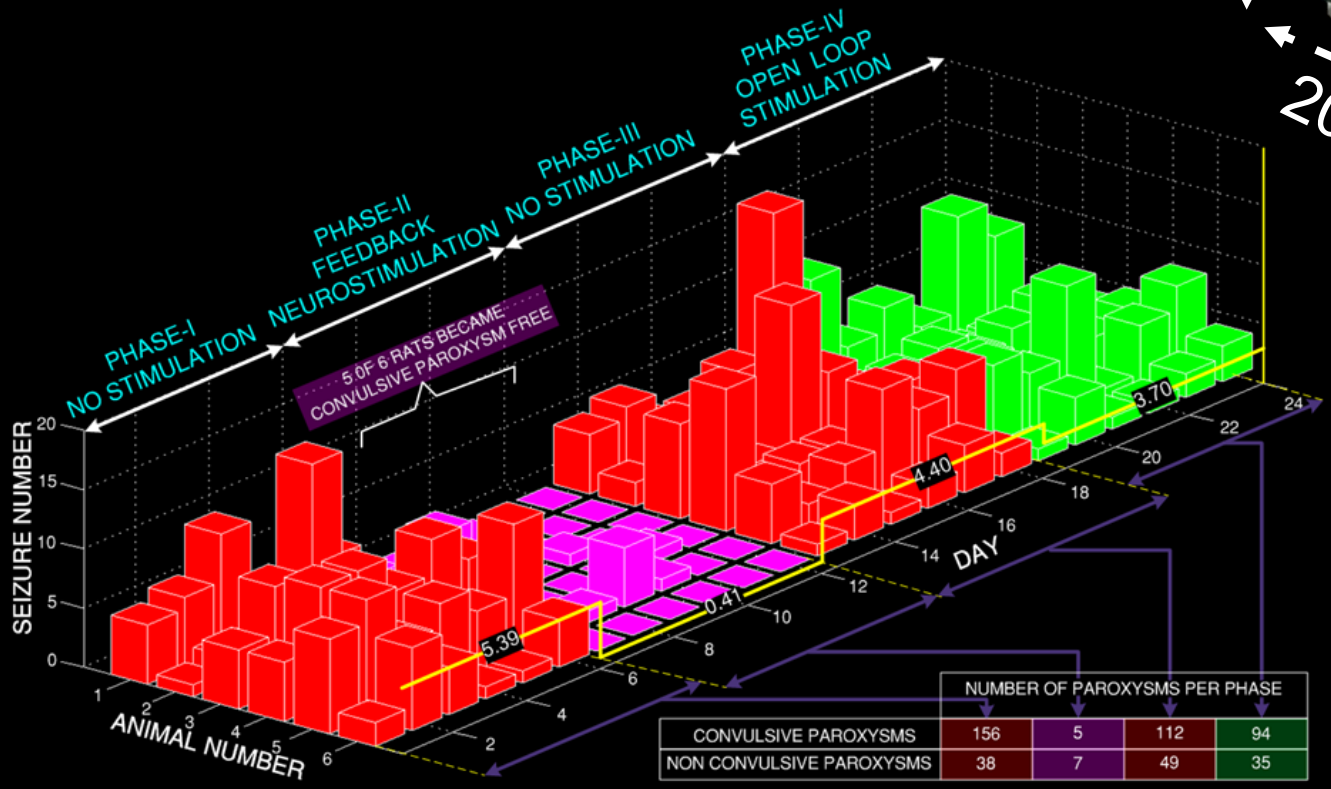
Diagnostics

Wireless monitoring e.g., preoperative epileptic seizure localization

Treatment

Automated (closed-loop) control e.g., intractable epilepsy, seizure abortion





Taufik Valiante

Roman Genov

(Non-local) Collaborators

Lausanne, Switzerland (EEG, TMS, fMRI)
Micah Murray(UNIL, CHUV)
Silvio Ionta (UNIL-Ambizione)
Jean-Francois Knebel (CHUV)

Sherbrooke, Canada (EEG, fMRI)
Kevin Whittingstall (CHUS, USherbrooke)

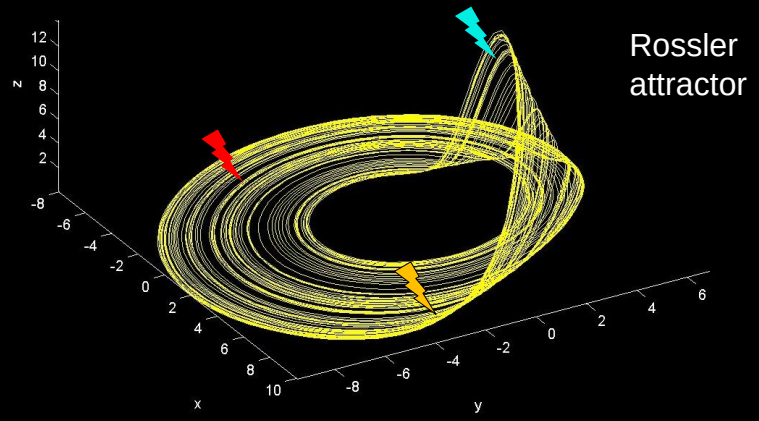
Oldenburg, Germany (EEG, TACS)
Christoph Herrmann (Oldenburg University)

Frankfurt, Germany (Theory)
Axel Hutt

Chapel Hill, USA (Ecog, EEG)
Flavio Frohlich (UNC)

Köln, Germany(EEG)
Andreas Mierau (DSK)

Manipulating oscillatory dynamics in chaotic systems



Why control brain oscillations?

Anomalies in brain oscillations are closely linked to many neurological dysfunctions ("oscillopathies")

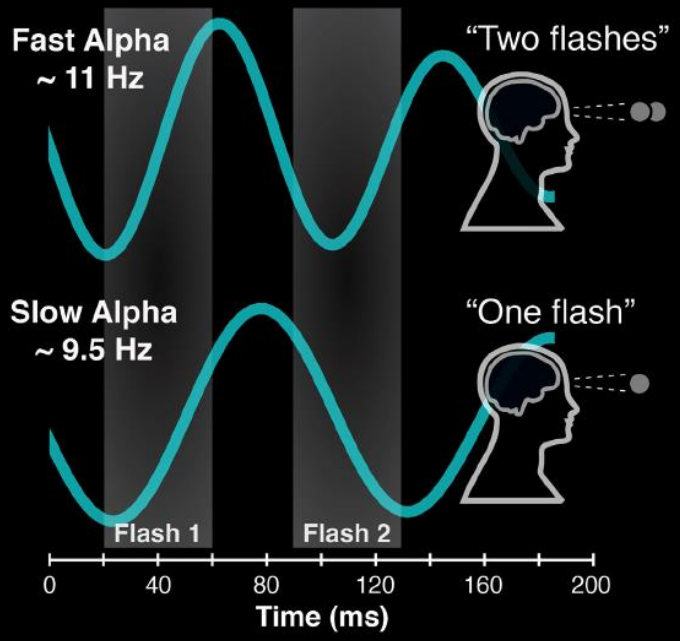
Table 1. Selected Neurobiological Elements of Cognitive Dysfunction

Disorder	Neural synchrony	Cognitive dysfunctions	Anatomical connectivity	Neurotransmitters
Schizophrenia	consistent evidence for a reduction of local- and long-range synchronization	perception, executive processes, memory, attention, social cognition	evidence for reduced anatomical connectivity	glutamate, GABA, dopamine
Epilepsy	increase in local synchrony; evidence for a reduction in long-range synchronization	specific cognitive deficits in relationship to seizure focus	reduced connectivity between seizure focus and surrounding cortical areas	GABA, glutamate
Autism	reduced functional connectivity; preliminary evidence for impaired neural synchrony	perception, executive functions, social cognition, attention, memory	increased connectivity during early development, but possibly hypoconnectivity in mature cortex	GABA, glutamate, serotonin
Alzheimer's disease	reduced neural synchrony during resting state; evidence for reduced functional connectivity	working memory, perception, attention, executive processes	reduction in anatomical connectivity	acetylcholine, glutamate
Parkinson's disease	increase in neural synchrony in the basal ganglia, but also between subcortical-cortial structures	especially motor functioning, but also perception, working memory, attention, executive functions	unknown	dopamine

Uhlaas & Singer, 2006

Why control brain oscillations?

Double-flash illusion: when two flashes are presented within 100 ms together with one flash, a second illusory flash is often perceived. The hypothesis is that alpha activity sets the frames and timing of sensory perception.



Cecere et al. 2015, Samaha et al. 2015

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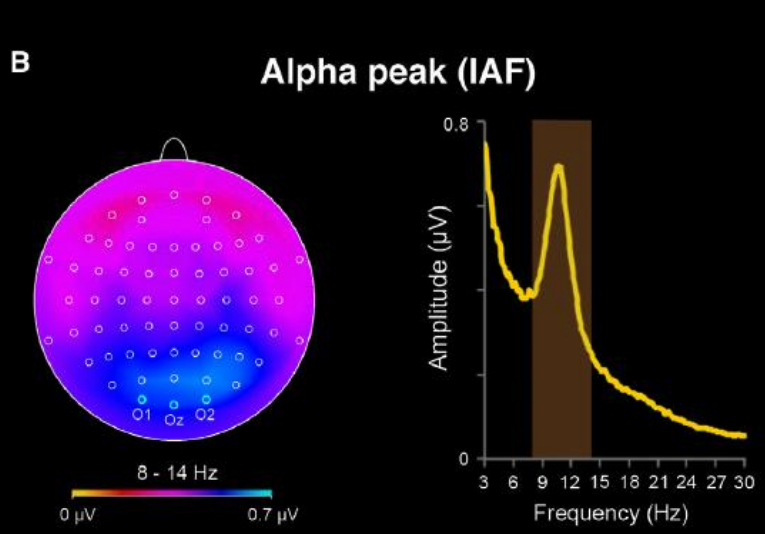

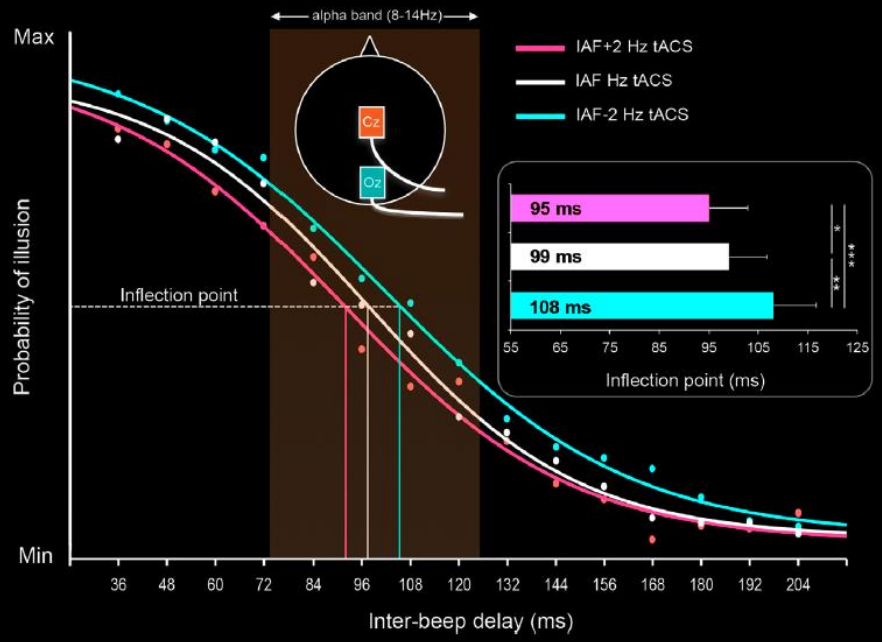

Cecere et al. 2015, Samaha et al. 2015