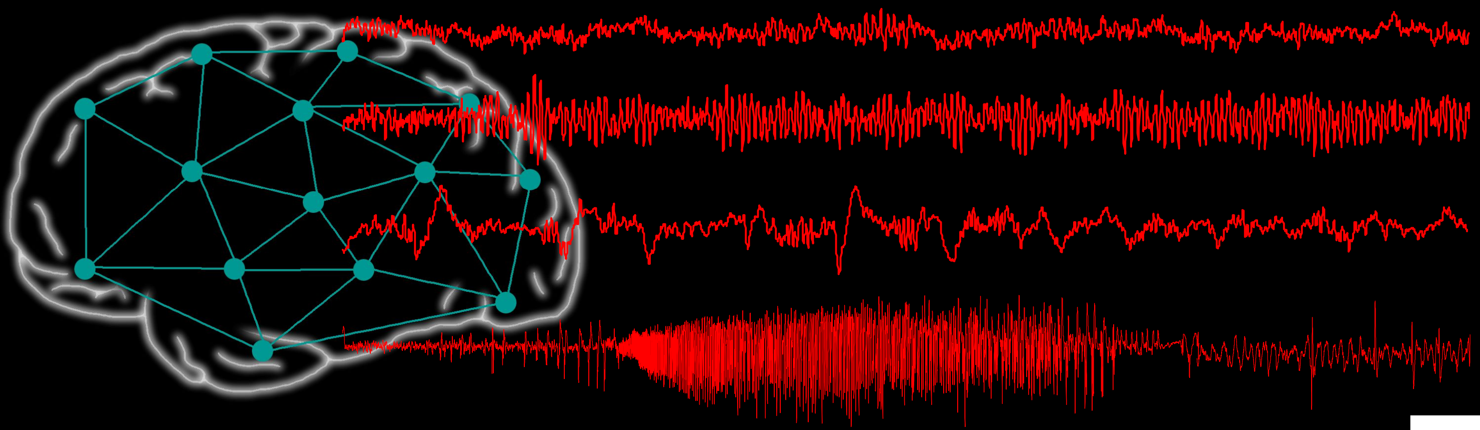
Long-term Dynamics of Large-scale Epileptic Brain Networks

Klaus Lehnertz



IZKS

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Neurophysics Group

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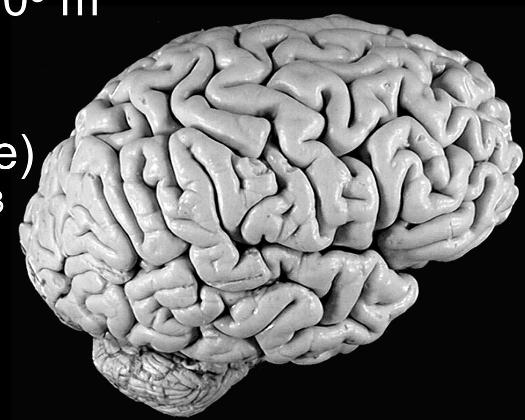
for Radiation- and
Nuclear Physics

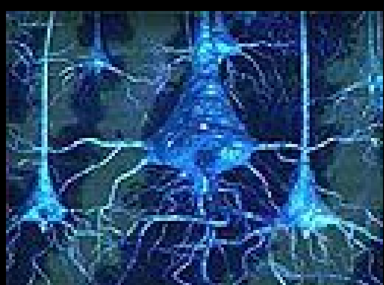
Complex Network Brain

\# neurons: ~ 10^{10}
\# synapses/neuron: ~ 10^3 - 10^4
length of all connections: ~ 10^7- 10^9 m
(~2.5 x distance earth-moon)
connectivity factor: ~ 10^{-6} (adult)
connectivity factor: ~ 10^{-4} (juvenile)
ion channels / neuron: ~ 10^2 - 10^3
neurotransmitter &
other active substances: ~ 50
\# glia cells: ~3-fold # neurons



control; movement;
perception; attention;
learning; memory;
knowledge; emotions;
motivation; language;
thinking; planning;
personality; self-identity;
consciousness; …;
dysfunctions

structure ⟷ function



fluctuations
(endogenous/exogenous)
↓
order ⟷ disorder

Epilepsy

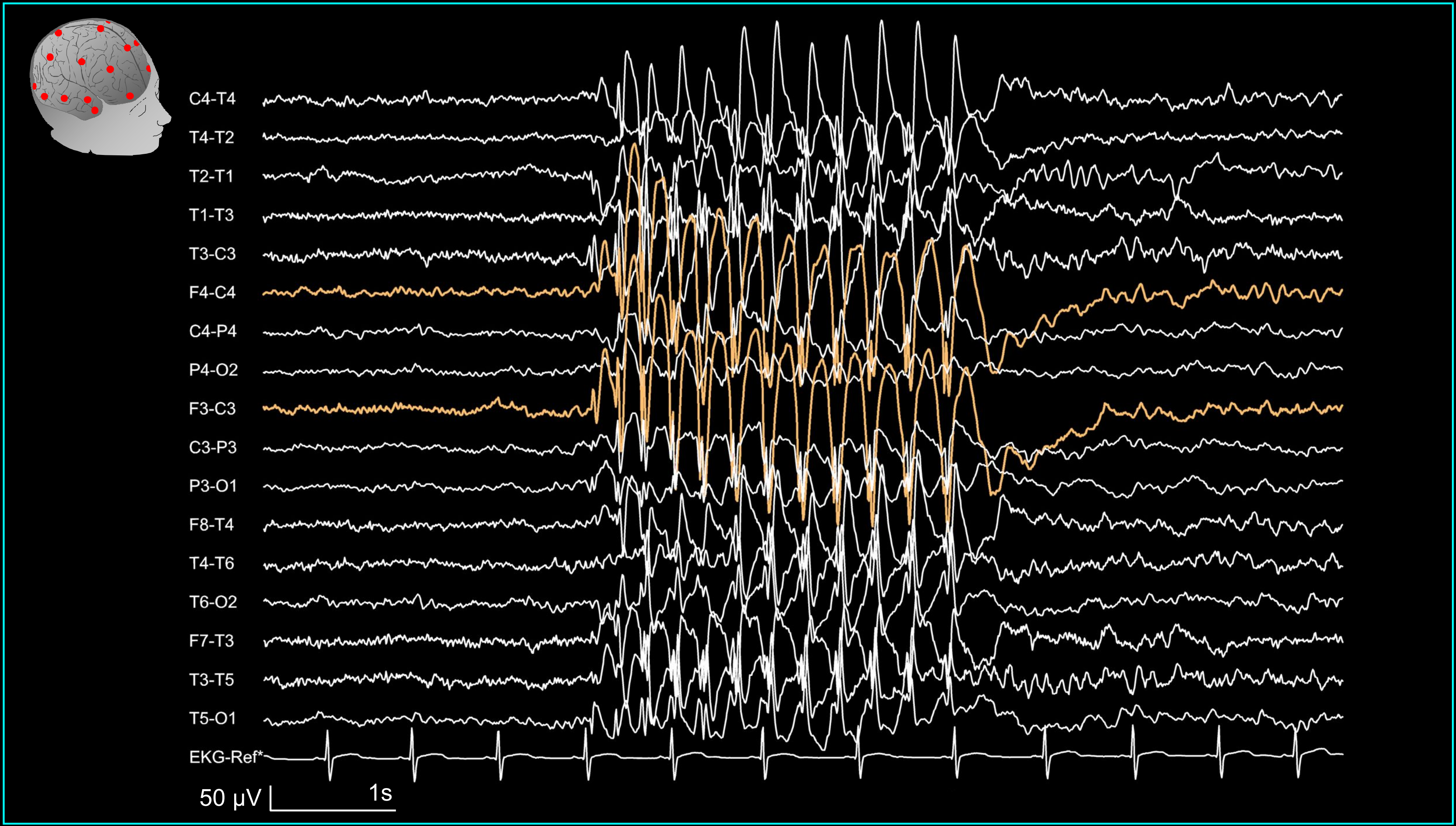
- Greek term for *seizure;* disease first mentioned ~ 1750 BC
- ~ 1 % of world population suffers from epilepsy
- famous people suffering from epilepsy:
  Sokrates, Alexander the Great, Julius Caesar, Lenin, Flaubert, Dostojevski, Carroll, Poe, Berlioz, Paganini, Händel, van Gogh, Newton, Pascal, Helmholtz, Nobel

Extreme Event   Epileptic Seizure

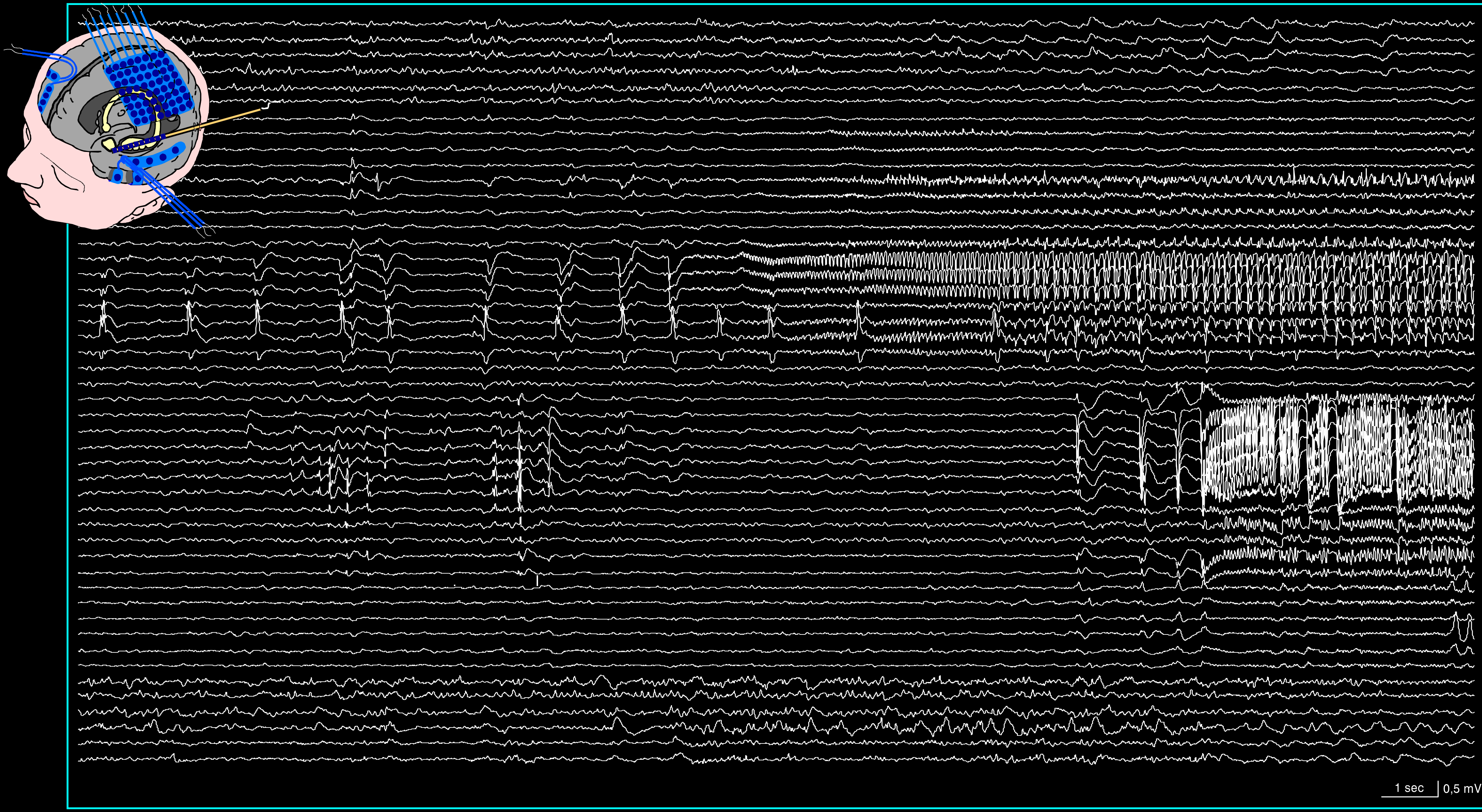
- frequency: ~ 3 szrs/mon (max.: several 100 szrs/day)
- (apparently) non-predictable (exception: reflex epilepsies)
- duration: 1 – 2 min   (exception: status epilepticus > 5 min)
- during the seizure: impaired mental functions, altered consciousness, loss of consciousness, involuntary movements, …
- after the seizure: neurologic dysfunctions, depression, …
- main seizure types:

  focal seizure (with/without generalization)
  generalized seizure (apparently instantaneous)

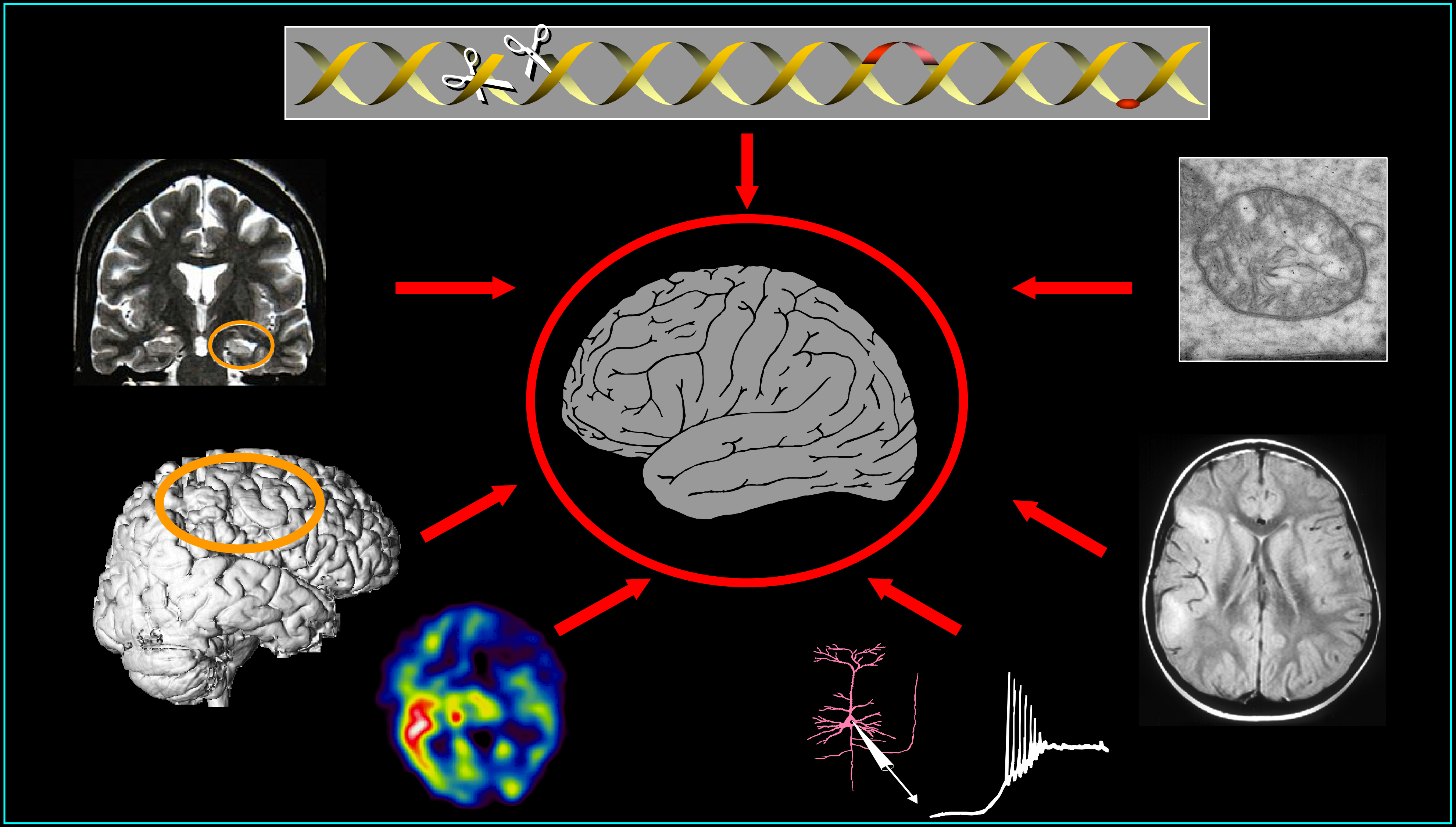
Epilepsy: Primary Generalized Seizure



Epilepsy: Focal Seizure with spreading



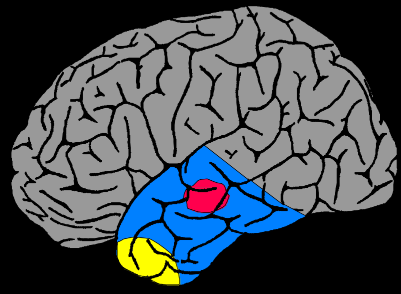
Epilepsy is network disease !



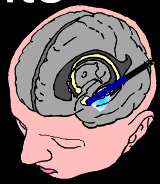
Treatment of Epilepsy

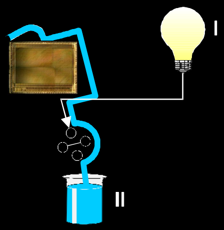
- **antiepileptic drugs**; primary therapy;   success: ~ 70 %
  side effects, long-term treatment

- **epilepsy surgery**; option for ~ 5 – 10 % of patients
  requirement: localize and delineate epileptic focus
  from functionally relevant brain areas
  success: ~ 60 %   (15 % – 85 %)
  long-term outcome, surgery-induced alterations?



- **alternative therapies;** for ~ 22 % of patients
  seizure prediction, seizure control
  success: ?



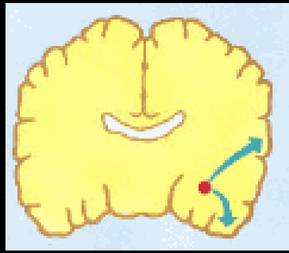


Epilepsy --- Unsolved Issues

- basic mechanisms in humans
- where in the brain and when and why do seizures start ?
- seizure precursors ?
- where and why do seizures spread ? consistency ?
- when and why do seizure end ? consistency ?
- seizure-free interval: normal? pathologic?
- interactions epilepsy ↔ normal brain functioning (cognition)
- long-term (yrs) dynamics
- epileptic focus vs. epileptic network

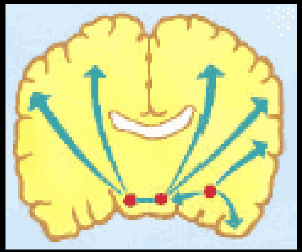
Epileptic Focus vs. Epileptic Network

traditional concept: ***epileptic focus***



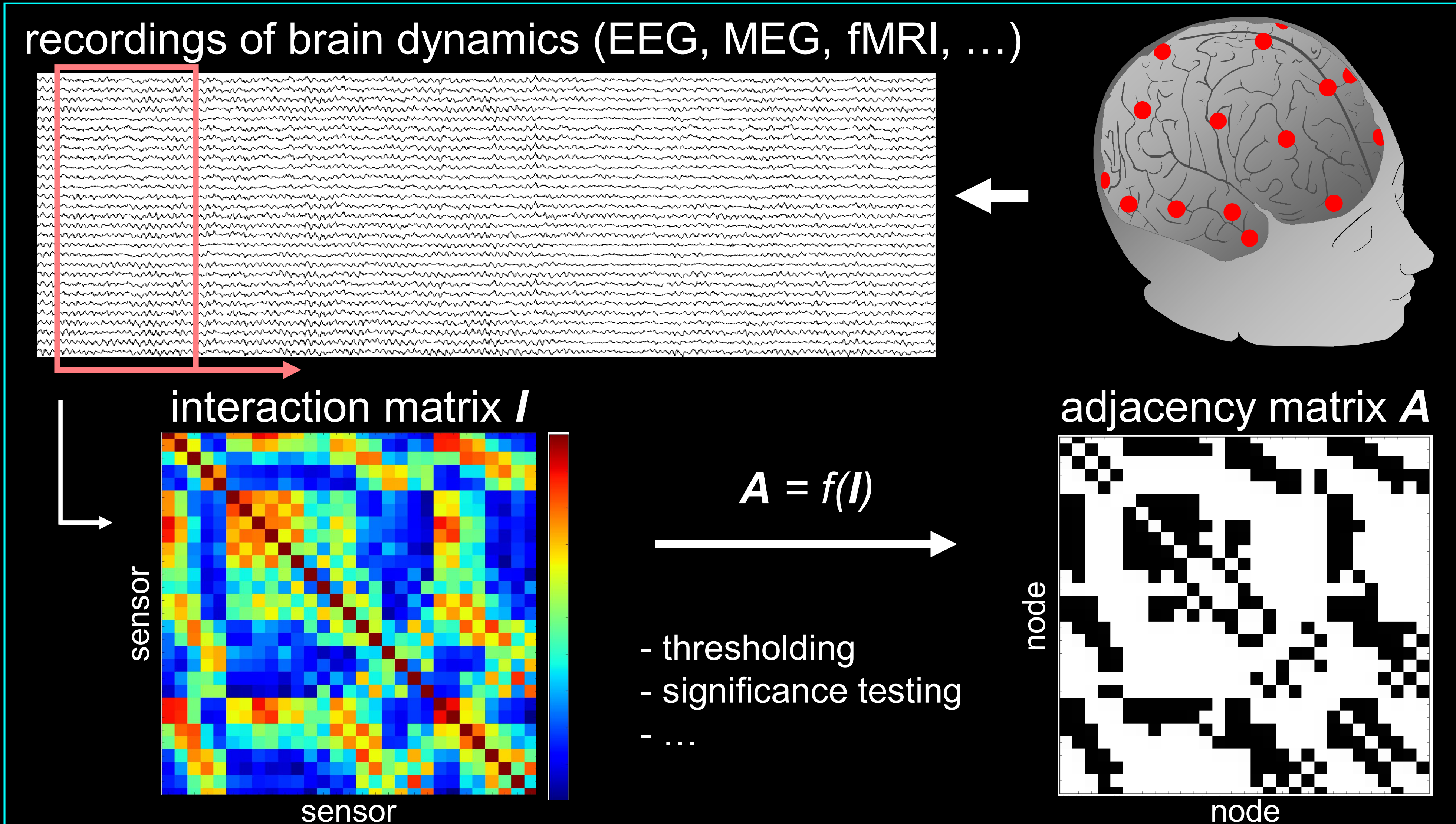
- circumscribed area of the brain
- critical amount of neurons → epileptic seizures

recent evidence: ***epileptic network***
- functionally and anatomically connected brain structures
- activity in any one part affects activity in all the others
- vulnerability to seizures in any one part of the network influenced by activity everywhere else in the network
- seizures may entrain large neural networks from any given part
- growing evidence from imaging, electrophysiological, and modeling studies



*e.g. S. S. Spencer, **Epilepsia**, 43, 219, 2002*
*T. Berg & I. E. Scheffer, **Epilepsia**, 52, 1058, 2011*
*KL et al., **Physica D** 267, 7, 2014*

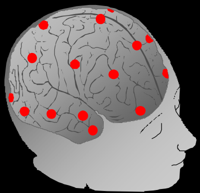
Inferring Functional (Interaction) Brain Networks

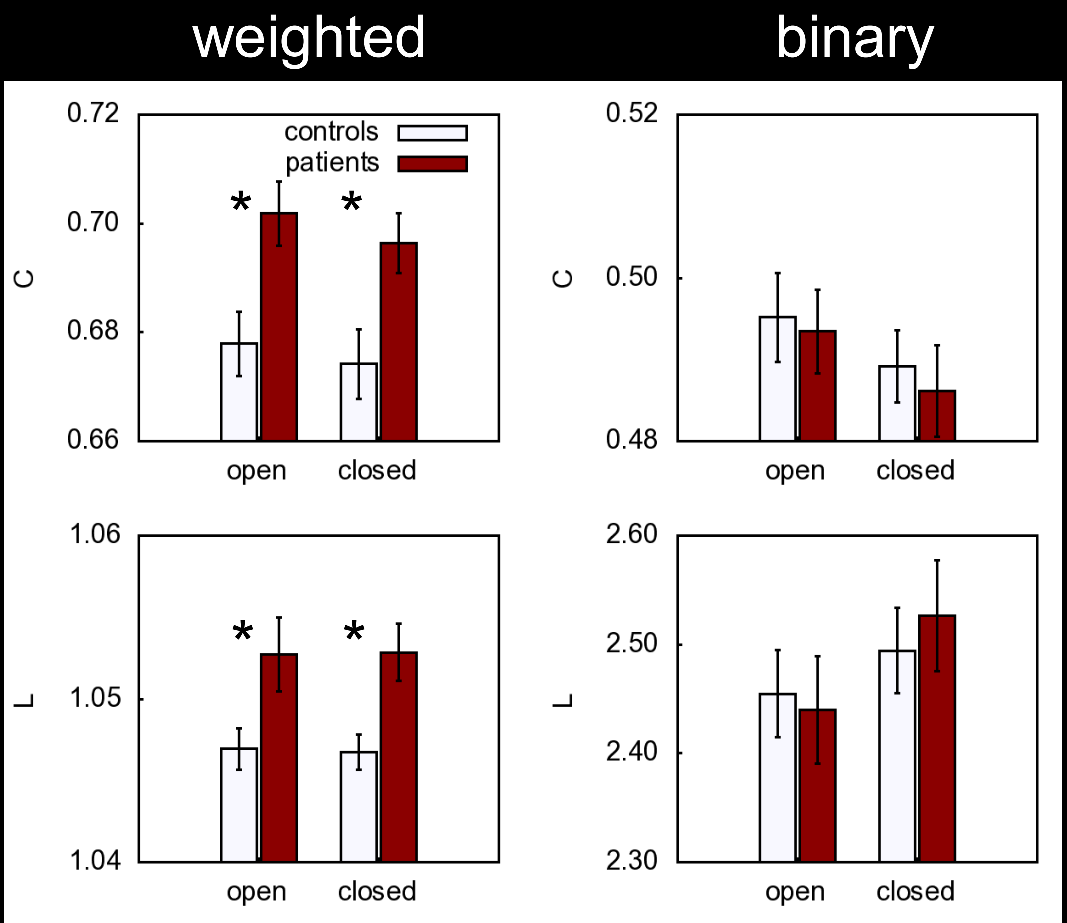


Functional Brain Networks: Epilepsy vs. Controls

epileptic networks are more regular than healthy ones

- 21 patients, 23 controls
- scalp EEG recordings (29 sites)
- eyes-open (15 min)
- eyes-closed (15 min)
- mean phase coherence
  (frequency-adaptive; -selective)
- binary networks
  (fixed mean degree, thresholding)
- weighted networks
  (different normalizations)
- clustering coefficient *C*
- average shortest path length *L*



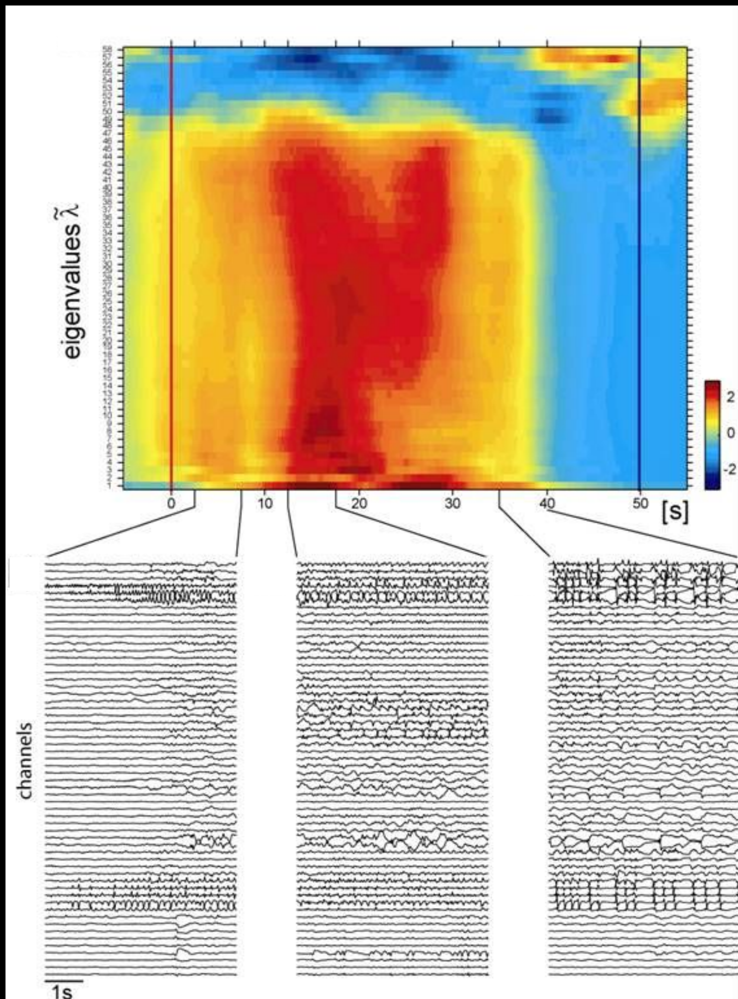


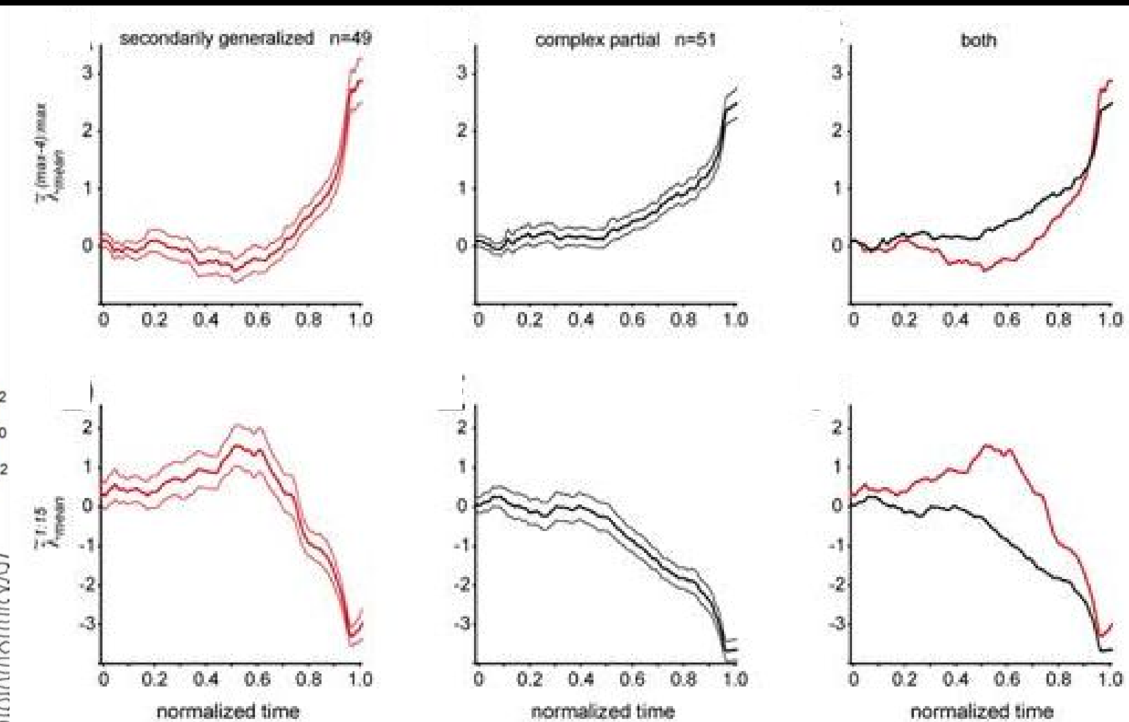
0.5 – 5 Hz (δ-band)   * $p < 0.05$

M.T. Horstmann et al.,
***Clin. Neurophysiol.** 121, 172, 2010*

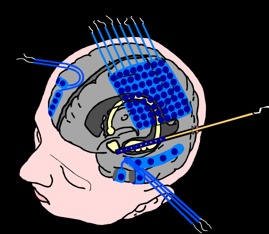
Epileptic Networks during Seizures

network sync: a mechanism for seizure termination?





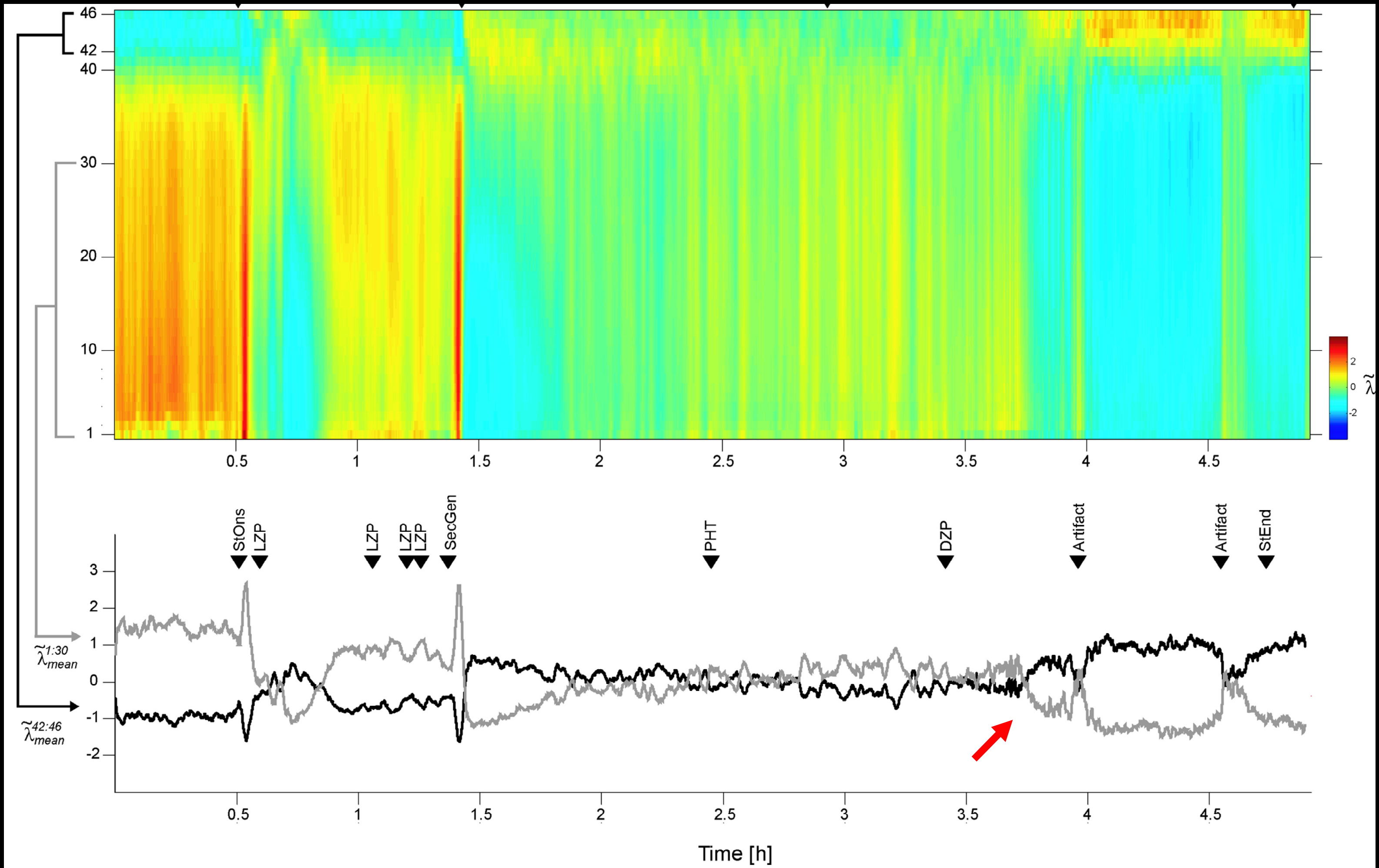
- 60 patients, 100 seizures
- intracranial EEG recordings (53 ± 21 sites)
- cross-correlation
- spectrum of eigenvalues



K. Schindler et al., **Brain** 130, 65, 2007

Epileptic Networks during Status Epilepticus

network sync: a mechanism for seizure termination?



K. Schindler et al., ***Clin Neurophysiol.*** *118, 1955, 2007*

Epileptic Networks during Seizures

functional topology

from

more random

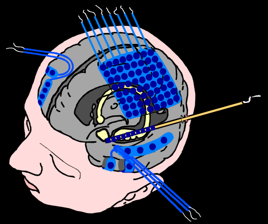
to

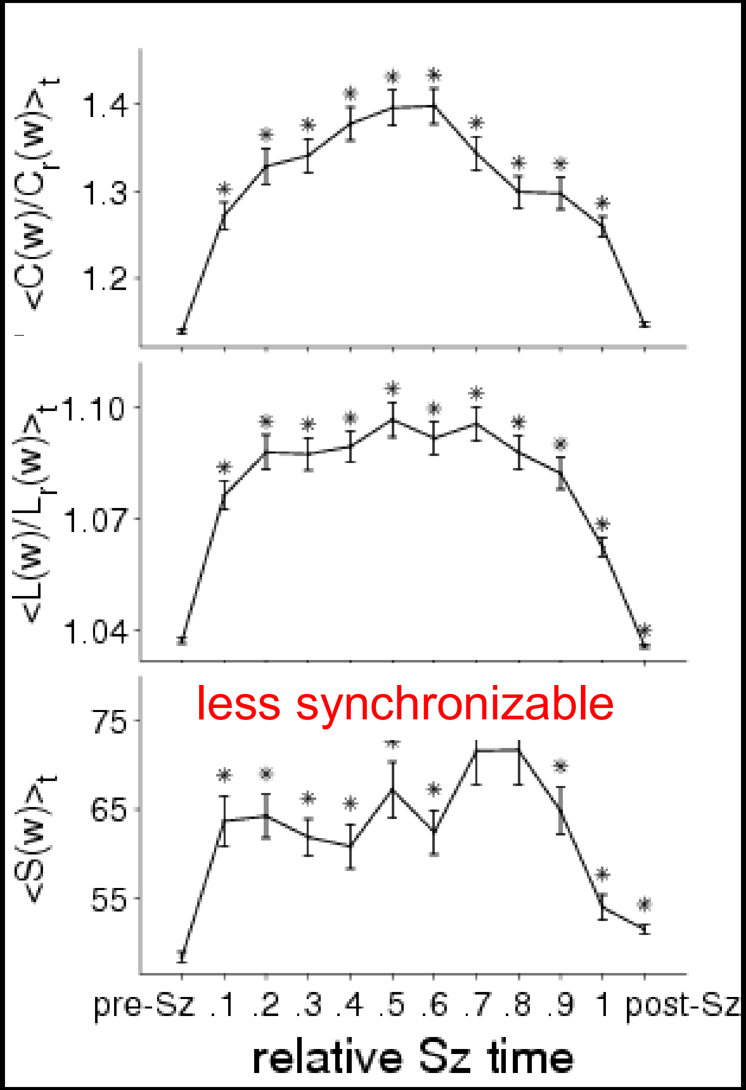
more regular

back to

more random

- 60 patients, 100 seizures
- intracranial EEG recordings (53 ± 21 sites)
- max. cross-correlation fct.
- thresholding (***A*** fully connected)
- clustering coefficient *C*
- average shortest path length *L*
- *synchronizability* $S=\lambda_{max}/\lambda_{min}$ from Laplace matrix
- comparison with random networks (prescribed degree sequence)

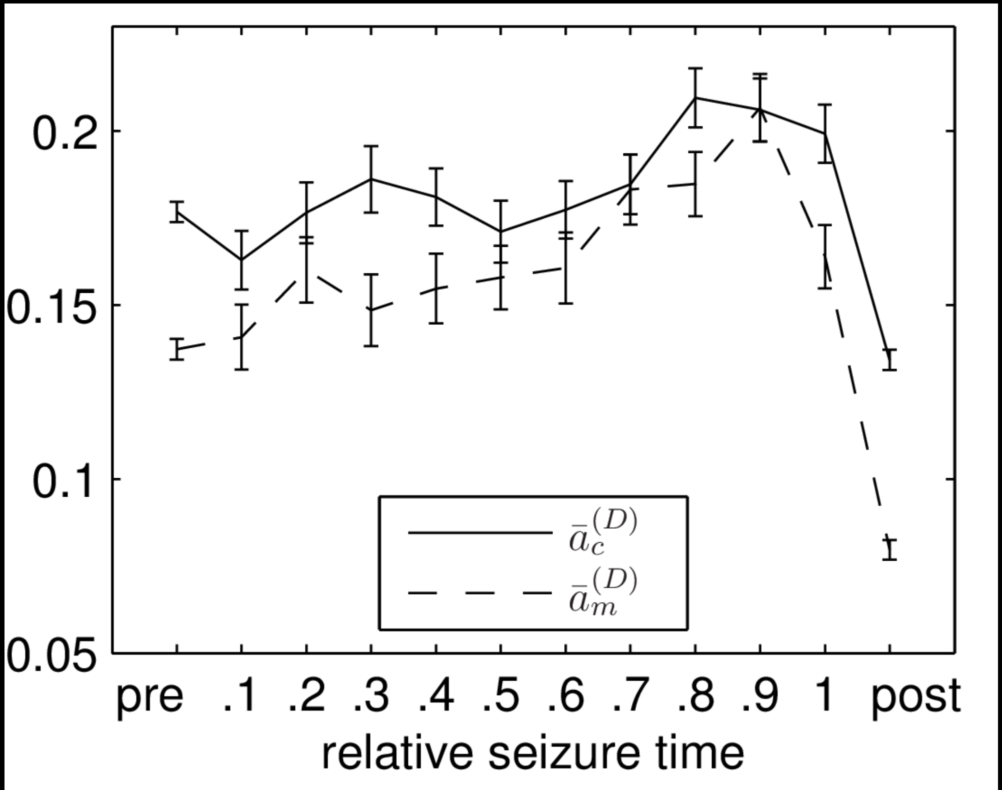




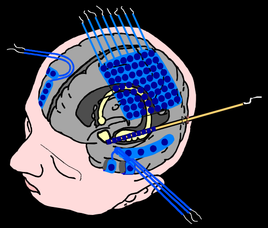
Epileptic Networks during Seizures

networks are assortative

- ***harder to synchronize***
- ***network disintegration***
- ***less vulnerable to attacks***



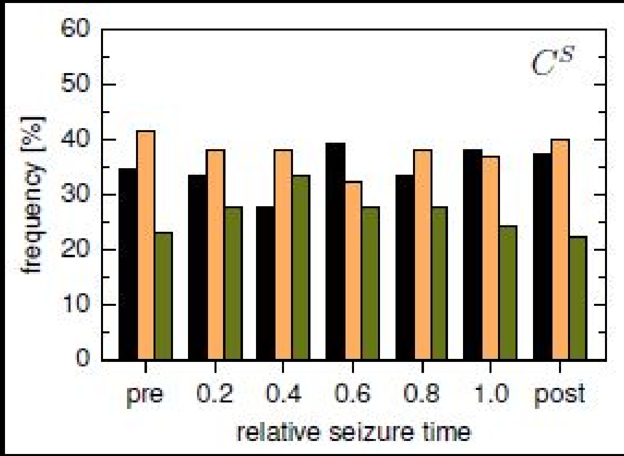
- 60 patients, 100 seizures
- intracranial EEG recordings (53 ± 21 sites)
- correlation coefficient
- max. of cross-correlation fct
- thresholding (***A*** fully connected)
- assortativity coefficient *a*
- comparison with surrogate networks (based on IAAFT time series surrogates)



Epileptic Networks during Seizures

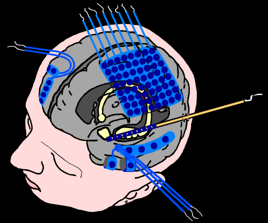
how important is the epileptic focus?

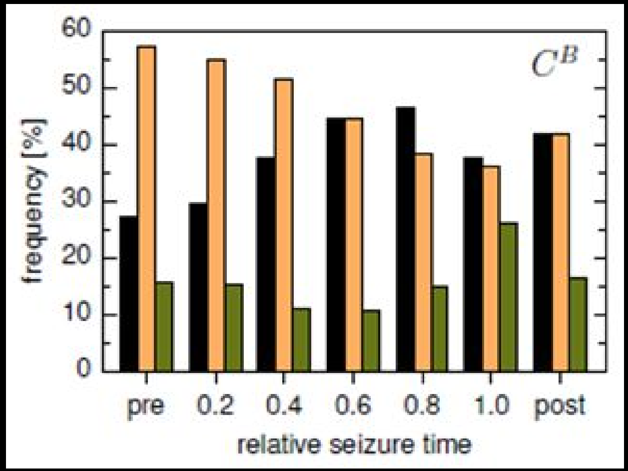
- ***important in only 35 % of cases***
- ***neighborhood more important (>50%)***
- ***neighborhood → bridge***
- ***improved prevention techniques?***



similar findings with eigenvector centrality

- 52 patients, 86 seizures
- intracranial EEG recordings (53 ± 21 sites)
- correlation coefficient
- max. of cross-correlation fct
- weighted networks (***A*** normalized)
- various centrality indices: strength (C^S), eigenvector, closeness, betweenness (C^B)
- comparison with surrogate networks (based on IAAFT time series surrogates)

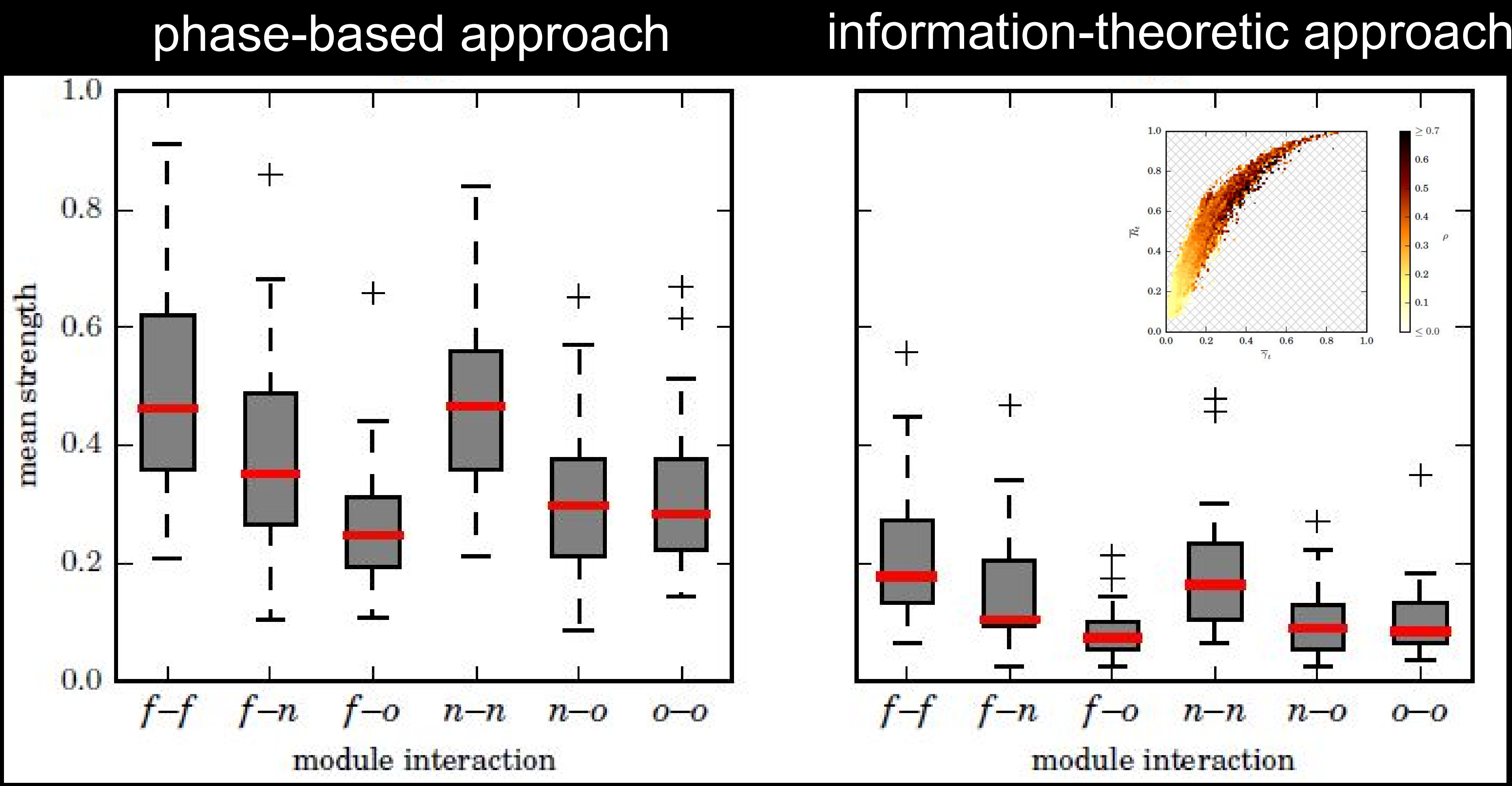




similar findings with closeness centrality

focus (black), *neighborhood* (orange), *other* (green)

Strength of Interactions in Epileptic Networks

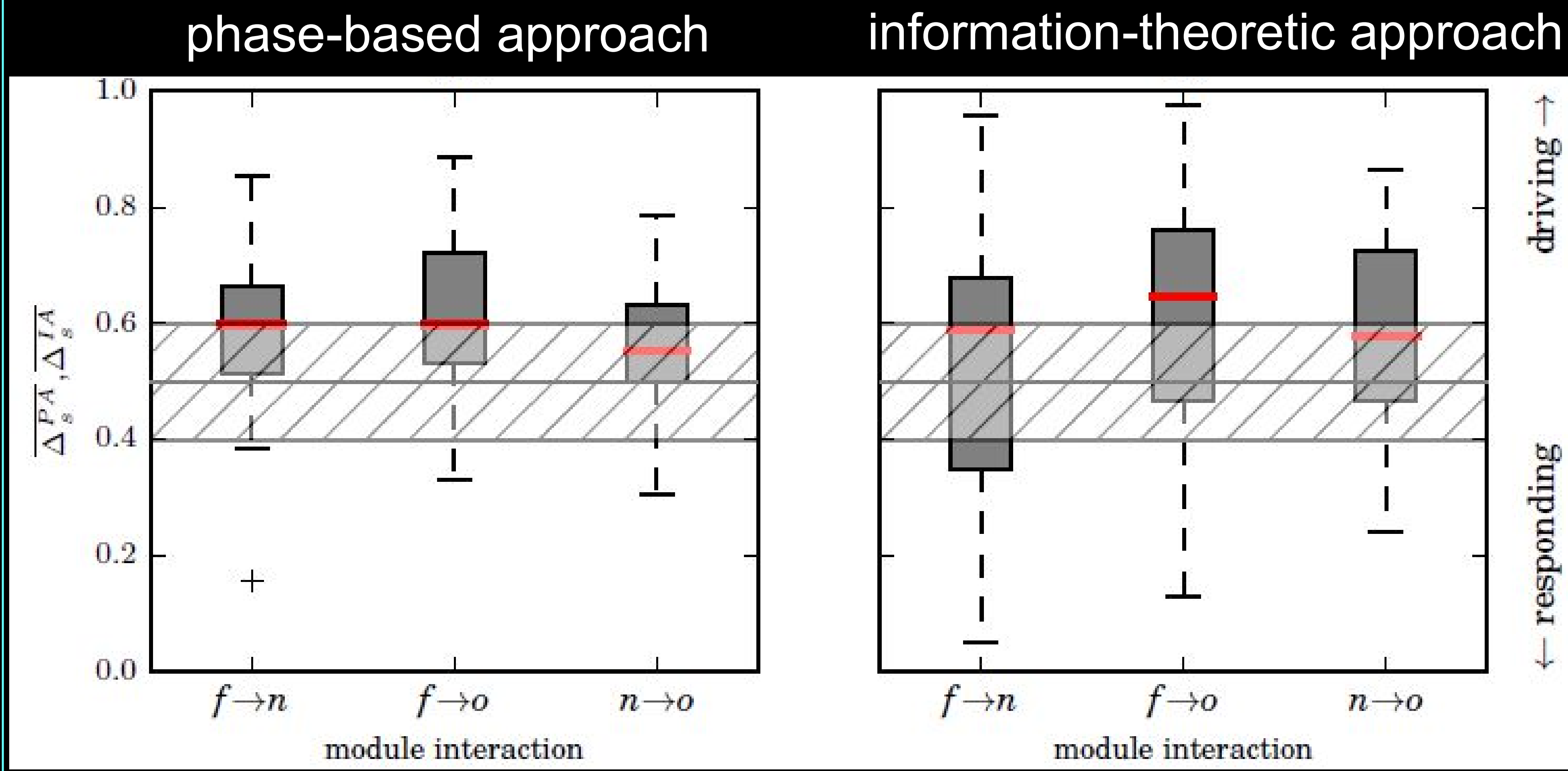


35 patients; Ø 51 sites; Ø 114 hrs iEEG recording; szr-free interval only

H. Dickten et al, **Sci. Rep.** 6, 34824, 2016

f= focus, n = neighborhood, o = other

Direction of Interactions in Epileptic Networks



35 patients; Ø 51 sites; Ø 114 hrs iEEG recording; szr-free interval only

H. Dickten et al, ***Sci. Rep.*** *6, 34824, 2016*

f= focus, *n = neighborhood*, *o = other*

Strength and Direction of Interactions

patient group:
- highest strength of interactions within the epileptic focus (gradually declines with increasing distance)
- epileptic focus “drives” all other brain areas
- largely unaffected by physiological activities (e.g. circadian rhythms)

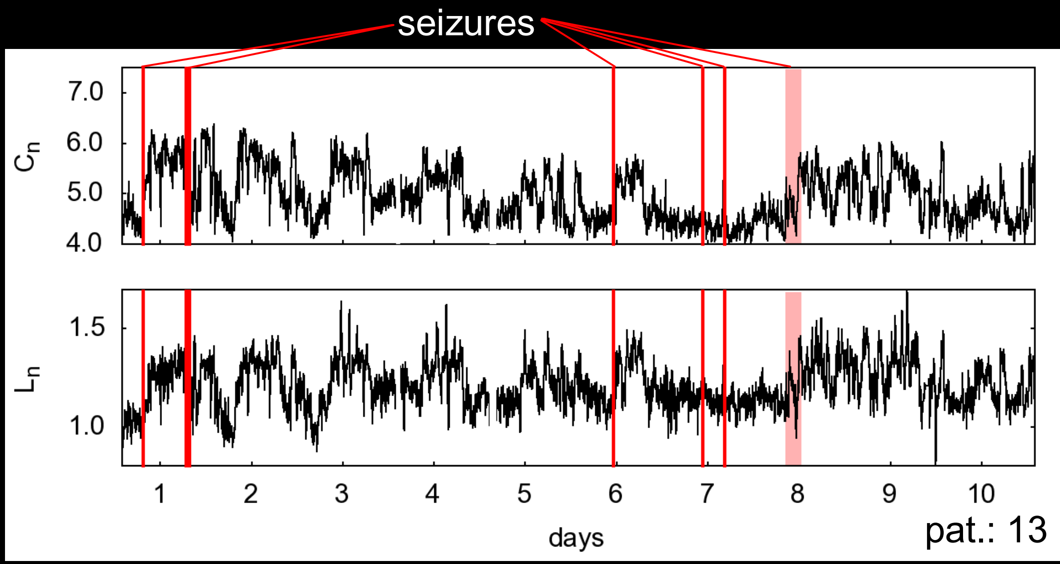
single patient
- very high variability (… reasons?)

similar findings (phase-based vs information-theoretic approaches)
- what kind of synchronization phenomena ? (phase, generalized, …) ?
- confounding variables ?

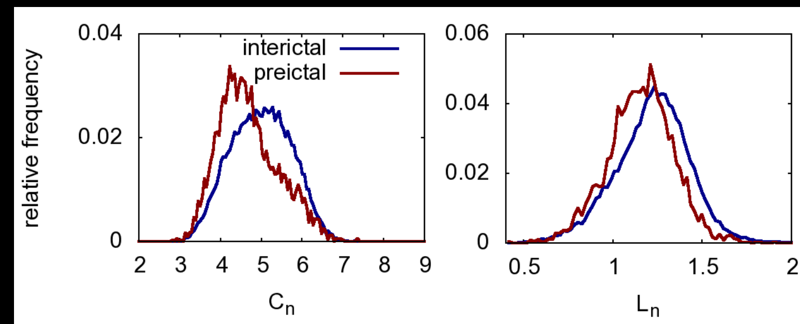
*H. Dickten et al, **Sci. Rep.** 6, 34824, 2016*

Long-Term Dynamics of Epileptic Networks (*C*, *L*)

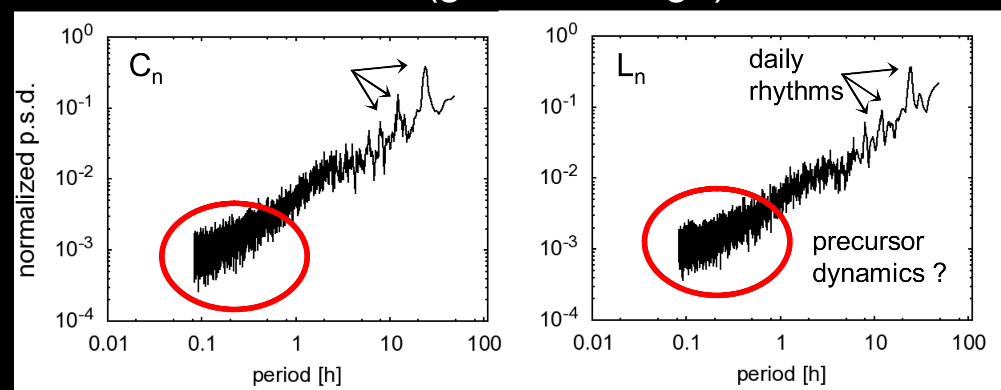
mainly reflects daily rhythms, epileptic process only marginally



exemplary frequency distributions



power spectral density estimates
(grand average)

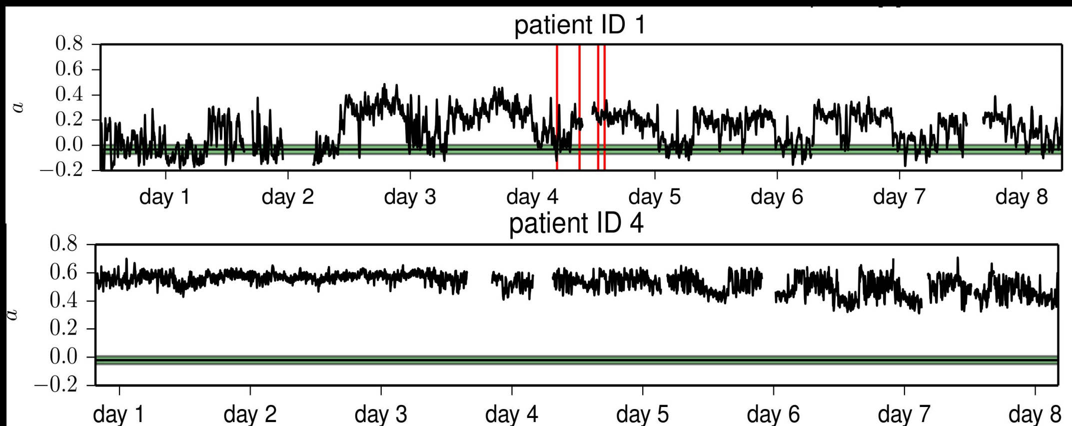


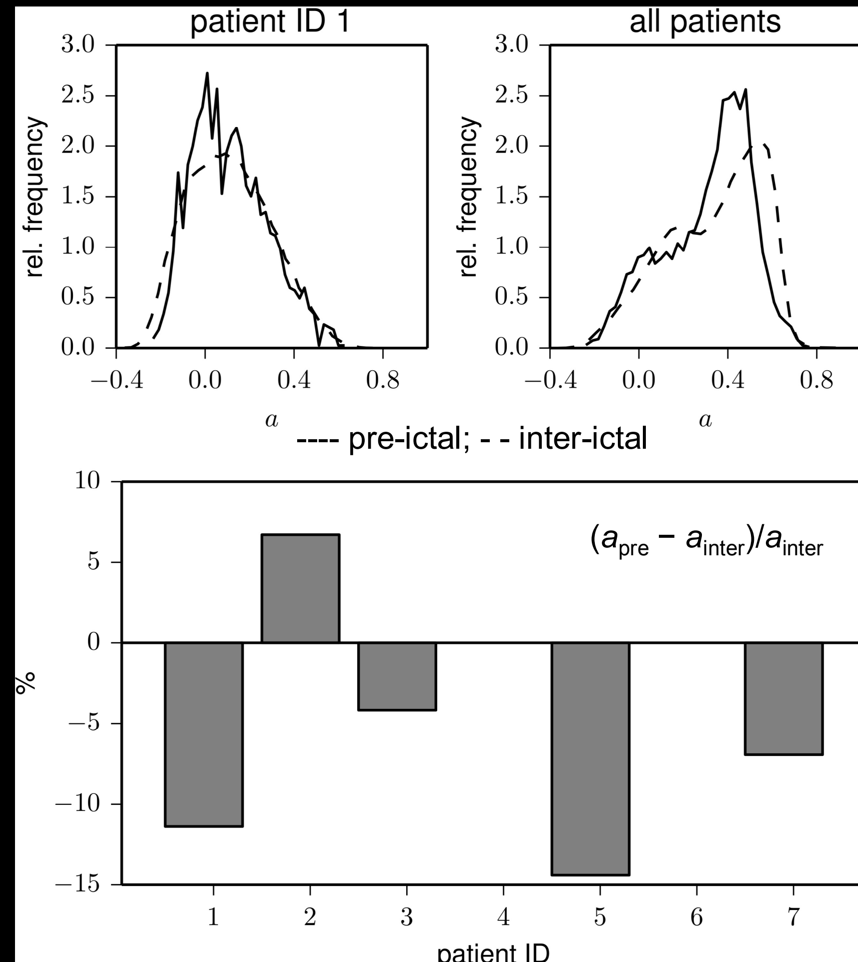
- 13 patients, 75 seizures
- intracranial EEG recordings (> 2100 h)
  (56 sites, range: 24-72)
- mean phase coherence (frequency-adaptive)
- thresholding (fixed mean degree)
- clustering coefficient *C*
- average shortest path length *L*

M.T. Kuhnert et al., ***Chaos*** *20, 043126, 2010*

Long-Term Dynamics of Epileptic Networks (*a*)

mainly reflects daily rhythms, easier to synchronize pre-ictally?



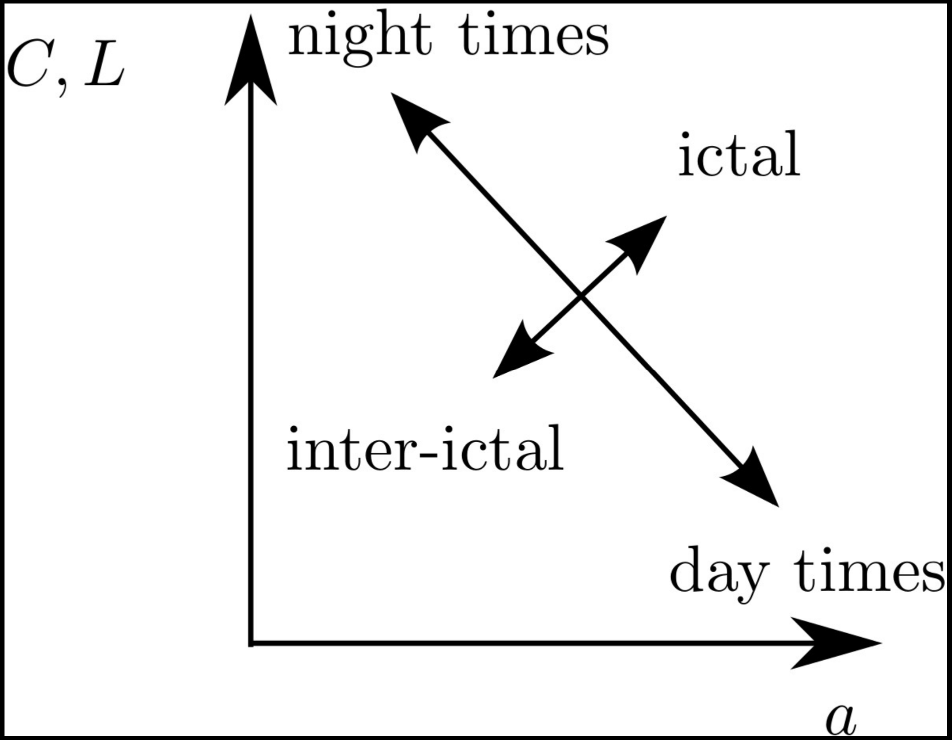


- 7 patients, 16 seizures
- intracranial EEG recordings (> 1000 h)
  (90 sites, range: 44-90)
- mean phase coherence (frequency-adaptive)
- thresholding (pre-def. link density)
- assortativity *a*
- comparison with surrogate networks

C Geier et al., ***Front. Hum. Neurosci.*** *9, 462, 2015*

Long-Term Dynamics of Epileptic Networks

how epileptic brain networks explore the space (a,C,L) of accessible network topologies

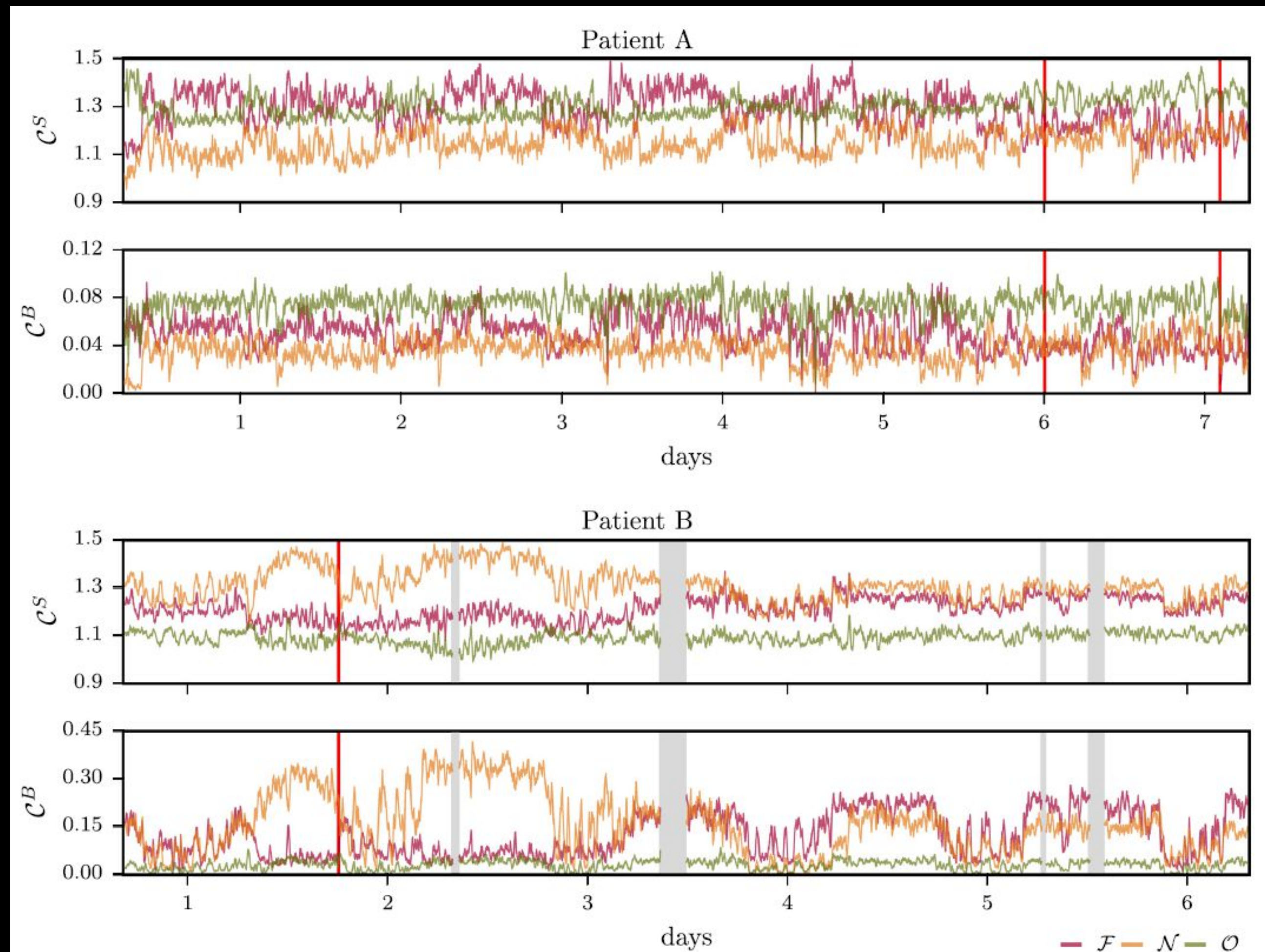


C Geier et al., ***Front. Hum. Neurosci.*** *9, 462, 2015*

Long-Term Node Importance in Epileptic Networks

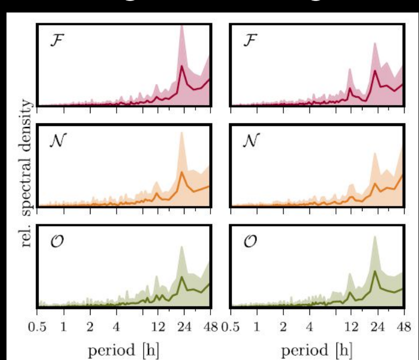
importance of brain regions is highly variable

- 17 patients, 83 seizures
- intracranial EEG recordings (> 2100 h; sites range: 16-64)
- mean phase coherence (frequency-adaptive)
- normalized weighted networks
- strength and betweenness centrality (C^S, C^B) and relationship to
  - focus (F), neighborhood (N), other brain areas (O)



all patients

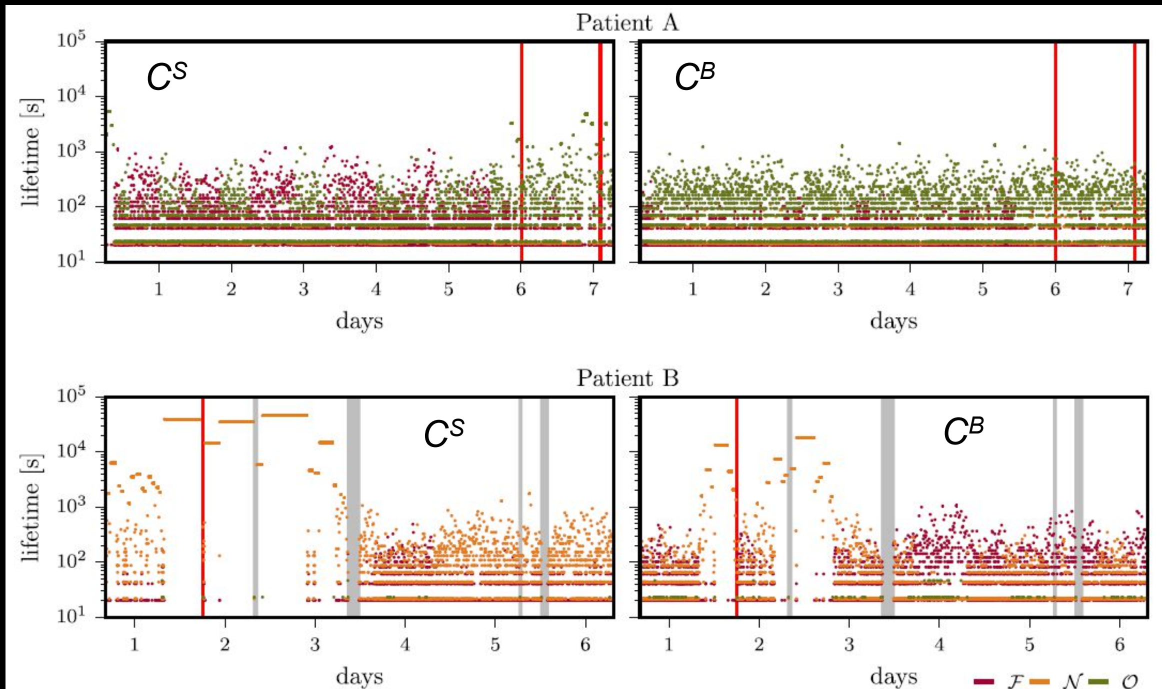
C^S C^B



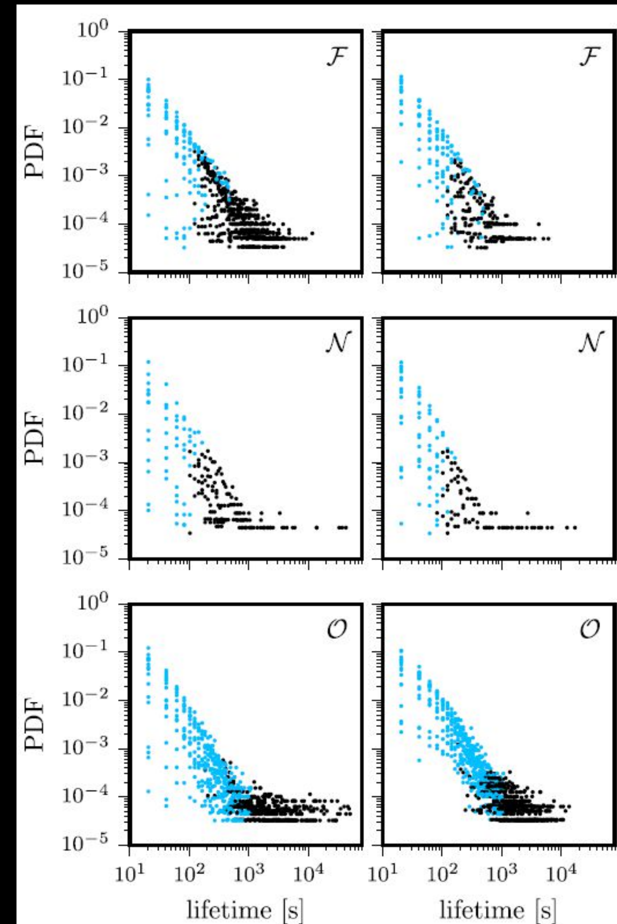
*C Geier & KL, **Chaos** 27, 043112, 2017*

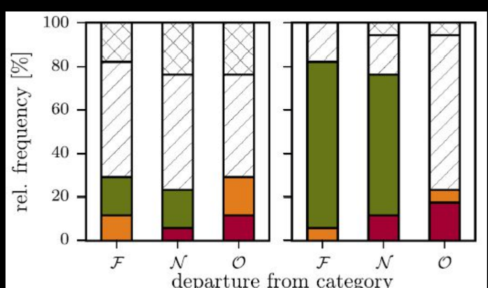
Long-Term Node Importance in Epileptic Networks

importance of brain regions is highly variable



C^S C^B





left: C^S
right: C^B
hatched bars: patients with no significant alterations
cross-hatched bars: patients with no alterations

blue dots: epochs with lifetimes shorter than expected under null hypothesis: occurrence probabilities determined by population densities of *F,N,O*

*C Geier & KL, **Chaos** 27, 043112, 2017*

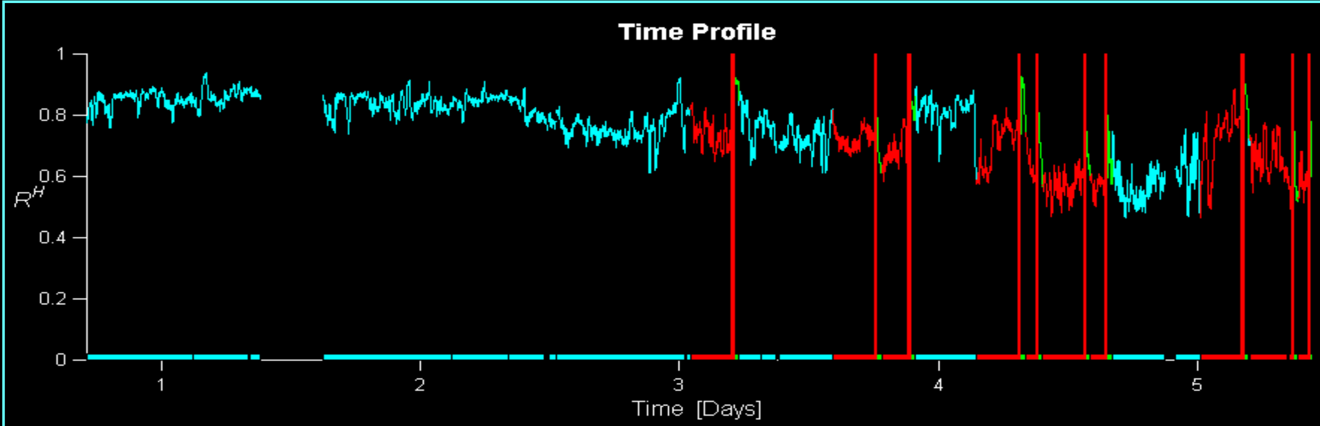
Seizure Prediction and Prevention

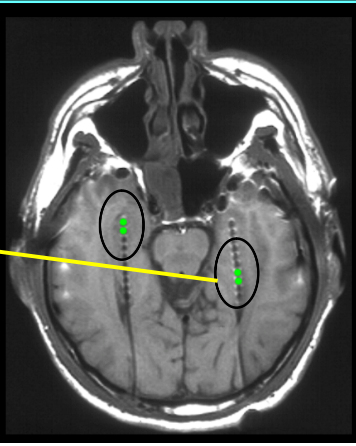
prediction feasible, but …
… not in all patients
… not in all seizures

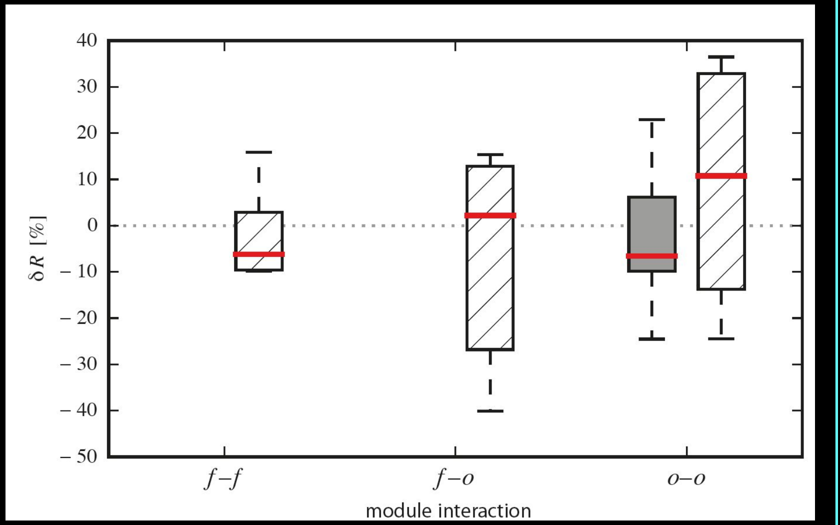
unsolved issues:
- when to prevent
- where to prevent
- how to disturb
an adaptive system?

from: Cook et al., Lancet Neurol 2013; 12: 563

Searching for Seizure Precursors







f= focus, n = neighborhood, o = other

seizure precursors

- **best identifiable from interaction measurements**
- synchronization vs. de-synchronization
- when: up to hours before onset
- where: mostly far off epileptic focus
- dependent on epilepsy type
- targeted interventions

unifocal epilepsies (N=20) multifocal epilepsies (N=16)

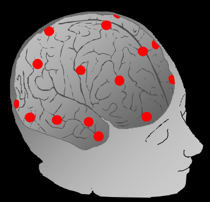
*F. Mormann et al., **Physica D** 144, 358, 2000;*
***Clin Neurophysiol,** 116, 569, 2005;*
***Brain** 130, 314, 2007; KL et al, **Sci Rep** 6, 24584, 2016*

Cognition modifies Functional Brain Networks

incidental					intentional				
rest	T_1^l	FF	rest	T_1^r	rest	T_2^l	FF	rest	T_2^r
5 min	3 min	1 min	3 min	3 min	5 min	3 min	1 min	3 min	3 min

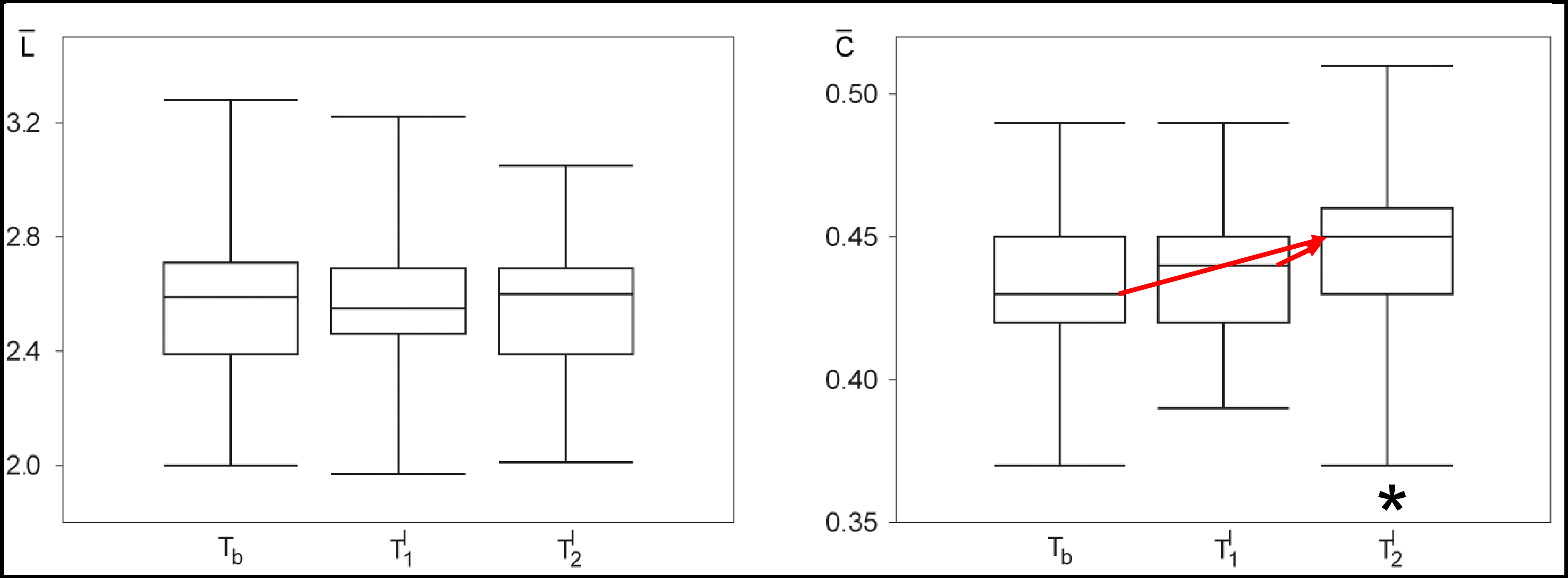
Learning- and memory-related processes

- incidental vs. intentional learning; free recall of learned material
- number of recalled words N_1, N_2
- 13 patients, 20 healthy controls; non-invasive EEG, 29 sites
- mean phase coherence
- binary networks (thresholding)
- clustering coefficient C
- average shortest path length L



*MT Kuhnert et al., **PLoS One** 8, e80273, 2013*

Cognition modifies Functional Brain Networks

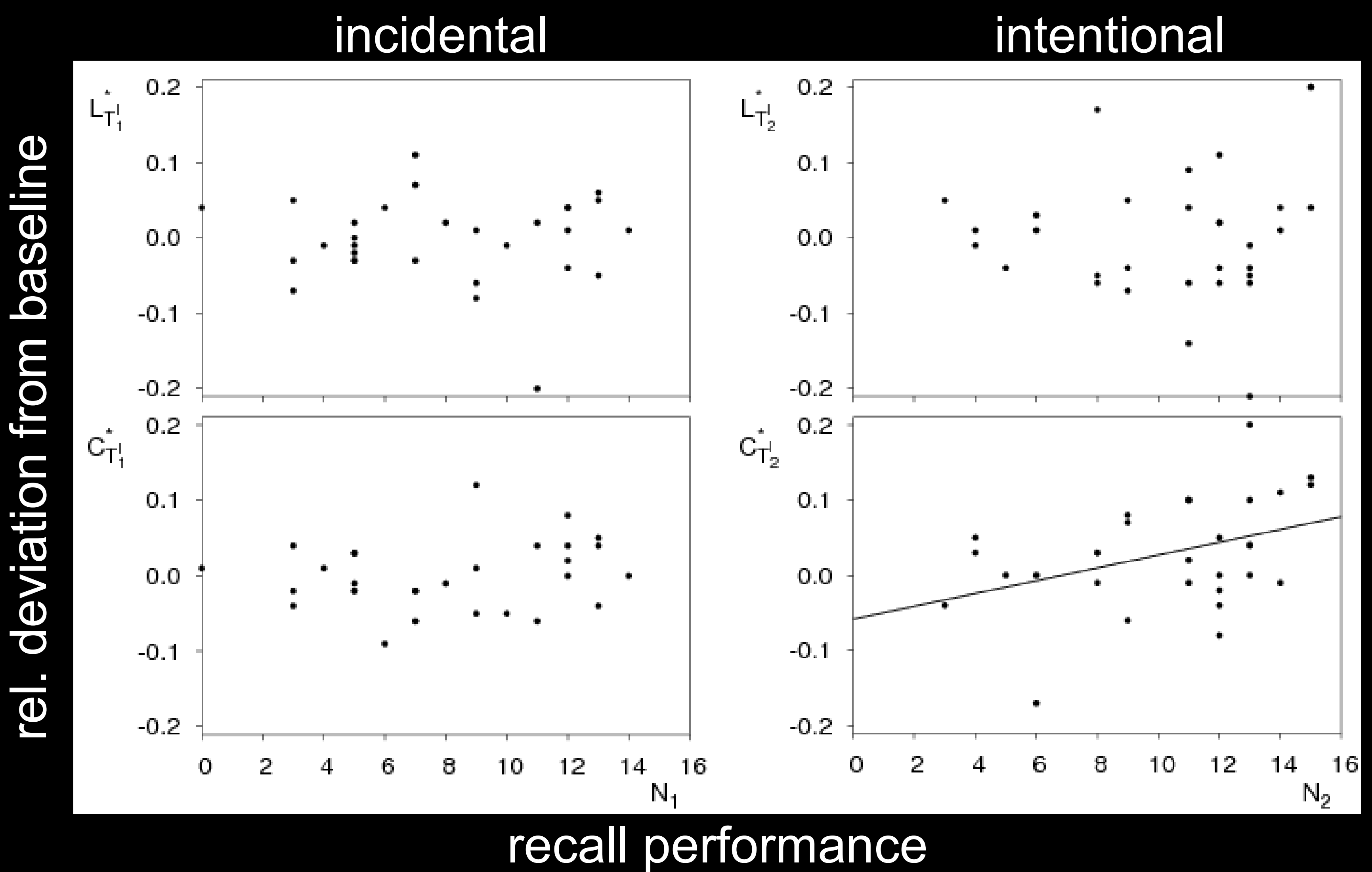


group statistics:

- clustering coefficient: slightly larger ($p<0.05$) during intentional learning T_2 than during incidental learning T_1 or during baseline T_b
- average shortest path length: no significant change

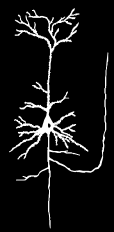
*MT Kuhnert et al., **PLoS One** 8, e80273, 2013*

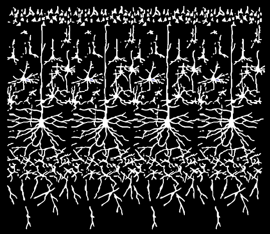
Cognition modifies Functional Brain Networks

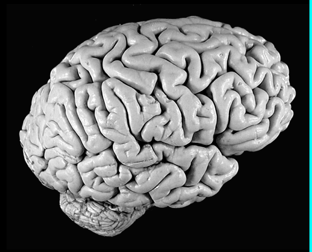


MT Kuhnert et al., ***PLoS One*** *8, e80273, 2013*

Modeling the Epileptic Process: On which Scales ?







integrate-and-fire
FitzHugh-Nagumo
Morris-Lecar
Hodgkin-Huxley

ion channels
neurotransmitter
synapses

branching structure

single cell models
distributed neuronal networks

network size ($\sim 10^5$)
connectivity

inhibition/excitation
feed back/ feed forward coupling

interneurons / glia cells

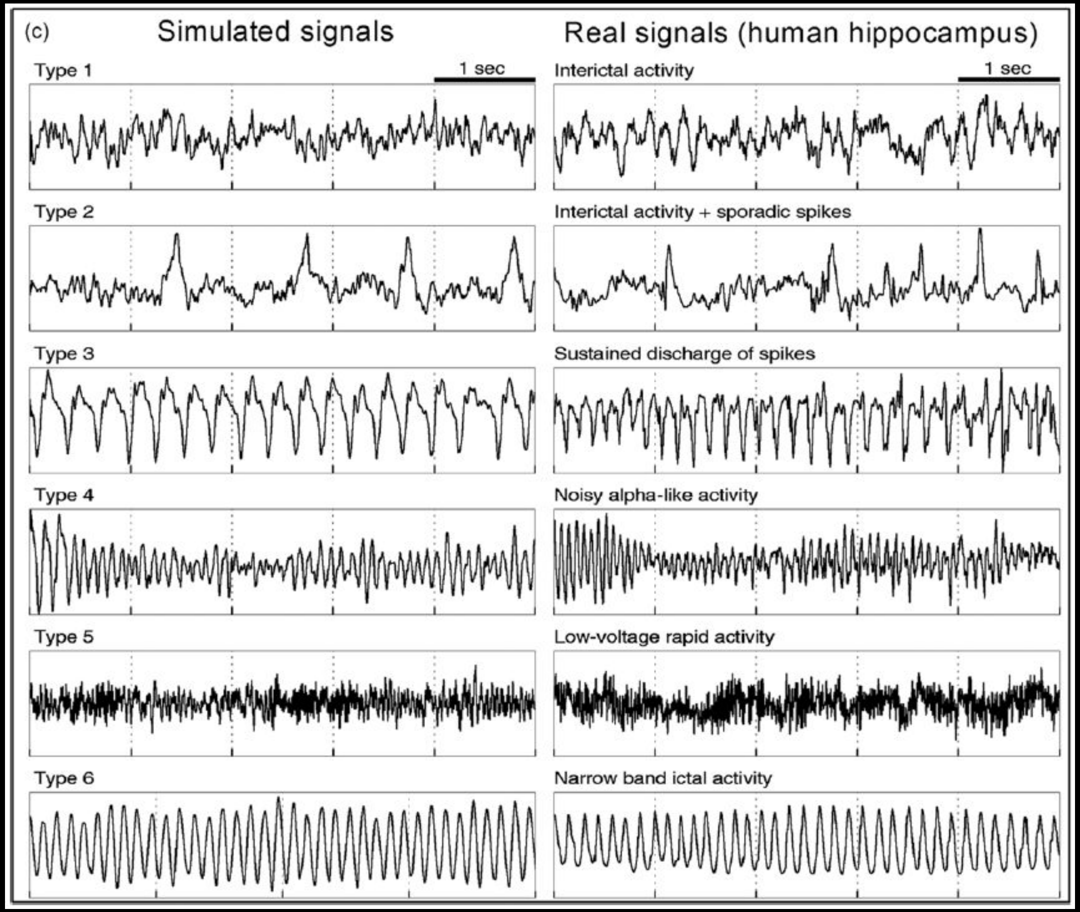
neuronal population models

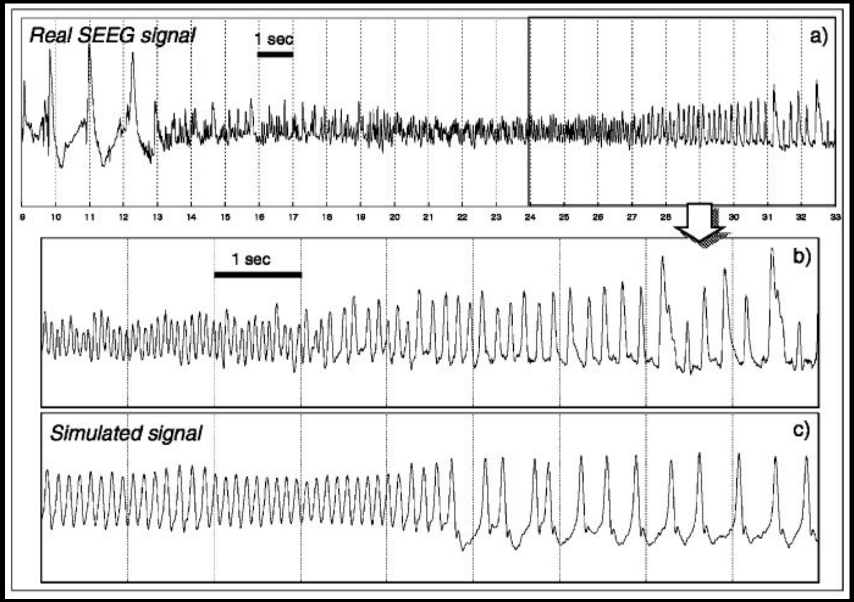
NDE, SDE, coupled ODEs, (s)PDE, NODE, lumped parameter, mean field approaches

EEG phenomena

transitions
- bistability
- parameter changes, noise

Modeling the Epileptic Process: Neural Mass Models





+ models able to "seize"
+ transition to seizure-like activity
+ spread of seizure-like activity

- no self-termination of activity
- mostly noise driven
- time dependent control parameter

Lopes da Silva et al. (1974), Freeman (1987),
Wendling et al. (2000), Suffczynski et al. (2006)

Modeling Epileptic Network Dynamics

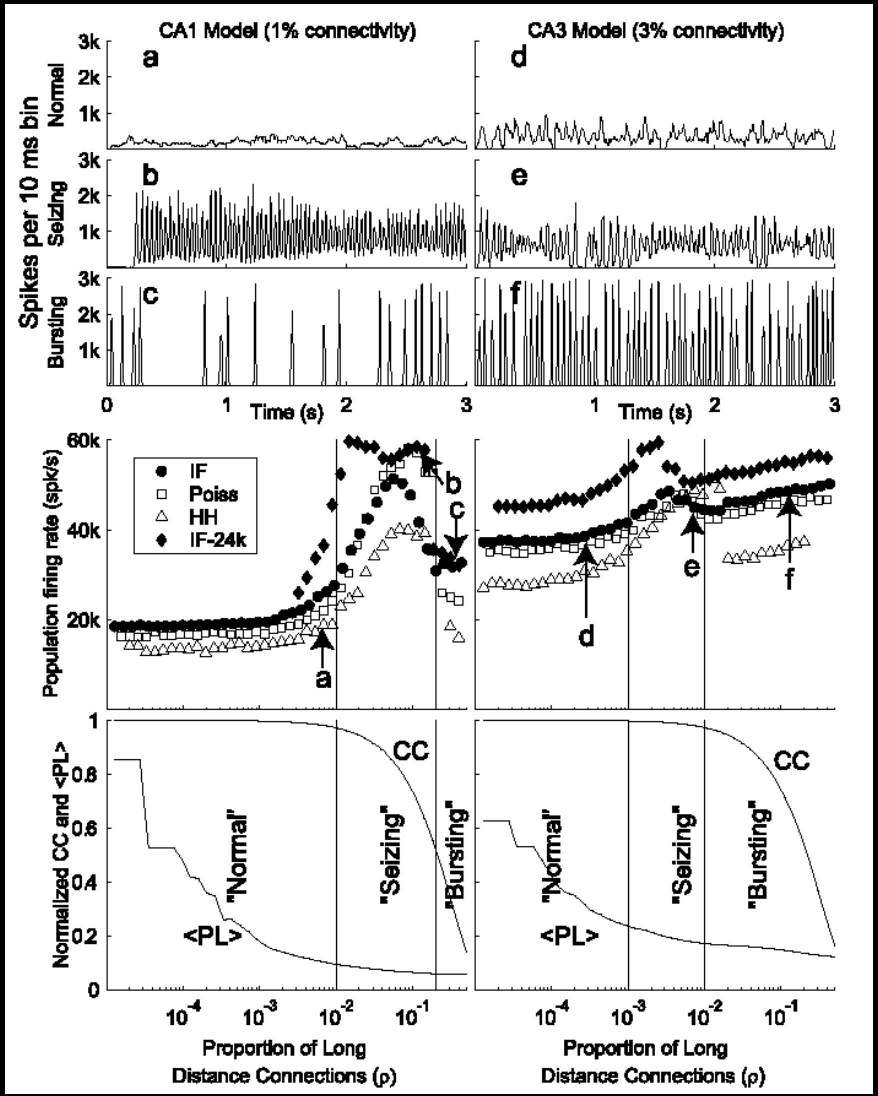
The Journal of Neuroscience, September 15, 2004 • 24(37):8075–8083 • 8075

Neurobiology of Disease

Epilepsy in Small-World Networks

Theoden I. Netoff,[1,3] Robert Clewley,[2,3] Scott Arno,[1,3] Tara Keck,[1,3] and John A. White[1,3]
[1]Department of Biomedical Engineering, [2]Department of Mathematics and [3]Center for BioDynamics and Center for Memory and Brain, Boston University, Boston, Massachusetts 02215

"By ***changing parameters*** such as the synaptic strengths, number of synapses per neuron, proportion of local versus long-distance connections, we induced normal, seizing, and bursting behaviors. […] explains *how specific changes in the topology or synaptic strength* in the model *cause transitions from normal to seizing and then to bursting*. These behaviors appear to be general properties of excitatory networks."



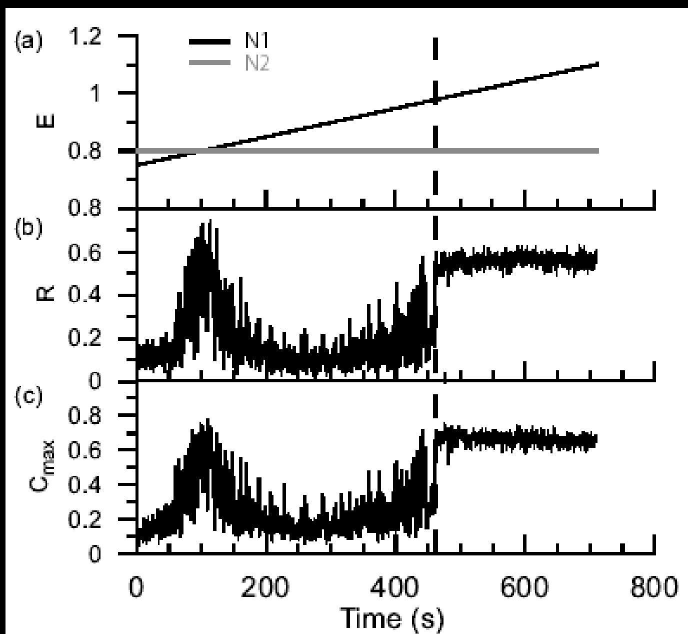
Modeling Epileptic Network Dynamics

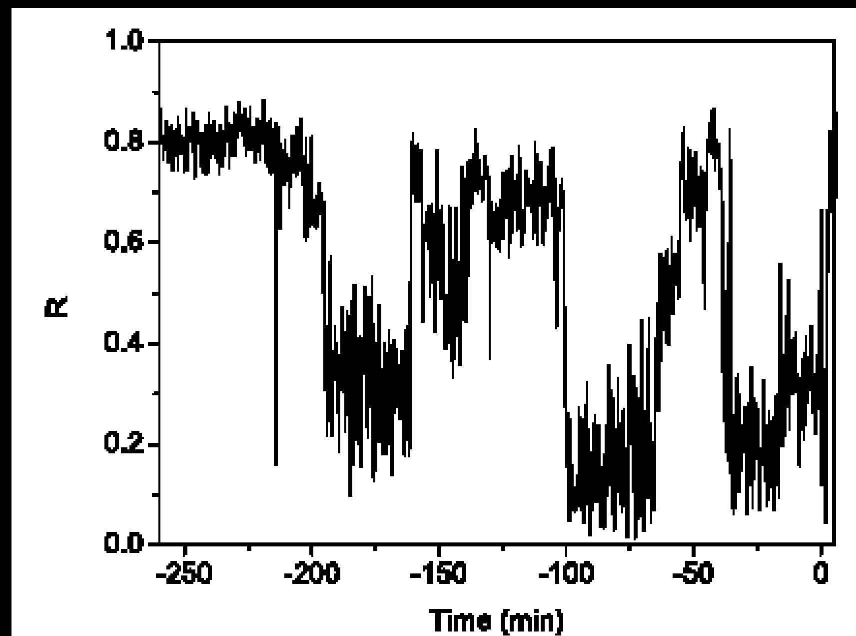
PHYSICAL REVIEW E **76**, 021920 (2007)

Internetwork and intranetwork communications during bursting dynamics: Applications to seizure prediction

S. Feldt,[1,*] H. Osterhage,[2,3] F. Mormann,[2,4] K. Lehnertz,[2,3,5] and M. Żochowski[1,6]
[1]*Department of Physics, University of Michigan, Ann Arbor, Michigan 48109, USA*
[2]*Department of Epileptology, University of Bonn, Bonn, Germany*
[3]*Helmholtz-Institute for Radiation and Nuclear Physics, University of Bonn, Bonn, Germany*
[4]*California Institute of Technology, Division of Biology, 216-76, Pasadena, CA 91125, USA*
[5]*Interdisciplinary Center for Complex Systems, University of Bonn, Bonn, Germany*
[6]*Biophysics Research Division, University of Michigan, Ann Arbor, Michigan 48109, USA*
(Received 9 March 2007; revised manuscript received 23 May 2007; published 20 August 2007)

- two interacting networks
- IF neurons (N=225)
- small-world topology

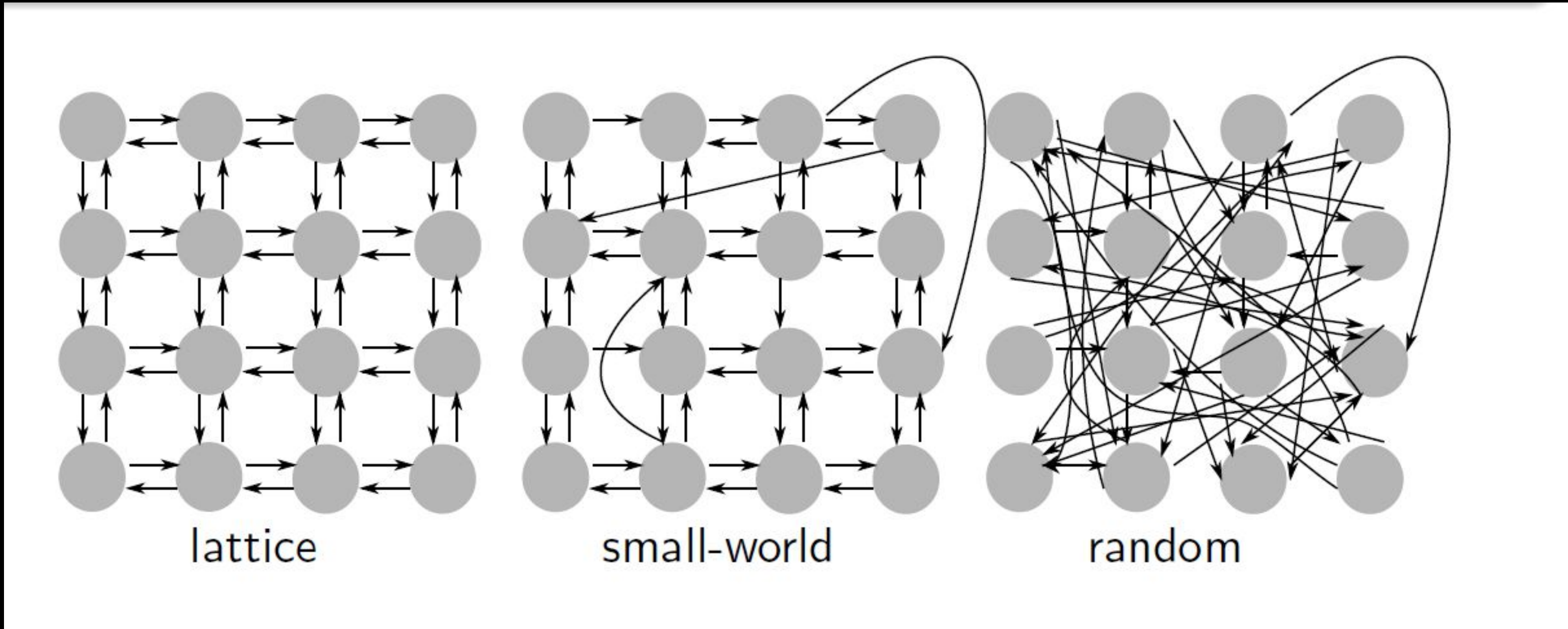




- EEG data
- MTLE patient

Self-Initiation and -Termination of Sz-like Events

- $N \times N$ oscillators
- connect each oscillator to its m nearest neighbors
- cyclic boundary conditions (torus)
- replace fraction p of connections by connections between randomly chosen oscillators

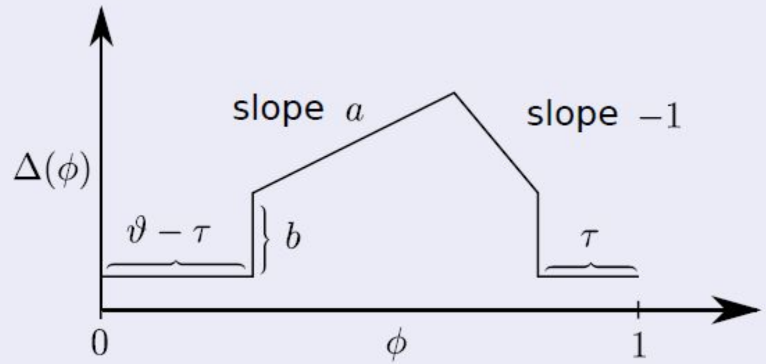


*A Rothkegel & KL, **EPL**, 95, 38001, 2011;*
***EPL**, 105, 30003, 2014;*
***New J. Phys.** 16, 055006, 2014*

Self-Initiation and -Termination of Sz-like Events

pulse-coupled phase oscillators (IF neurons)

- intrinsic dynamics: $\dot{\phi}_n = 1, \phi_n \in (0,1]$
- oscillator n fires $(\phi_n(t_f) = 1)$
  - excite all oscillators n' connected to n
    $\phi_j(t_f^+) = R(\phi_{n'}(t_f)) = \Delta(\phi_{n'}(t_f)) + \phi_{n'}(t_f)$
  - reset oscillator n: $\phi_n(t_f^+) = 0$



integrate-and-fire oscillators

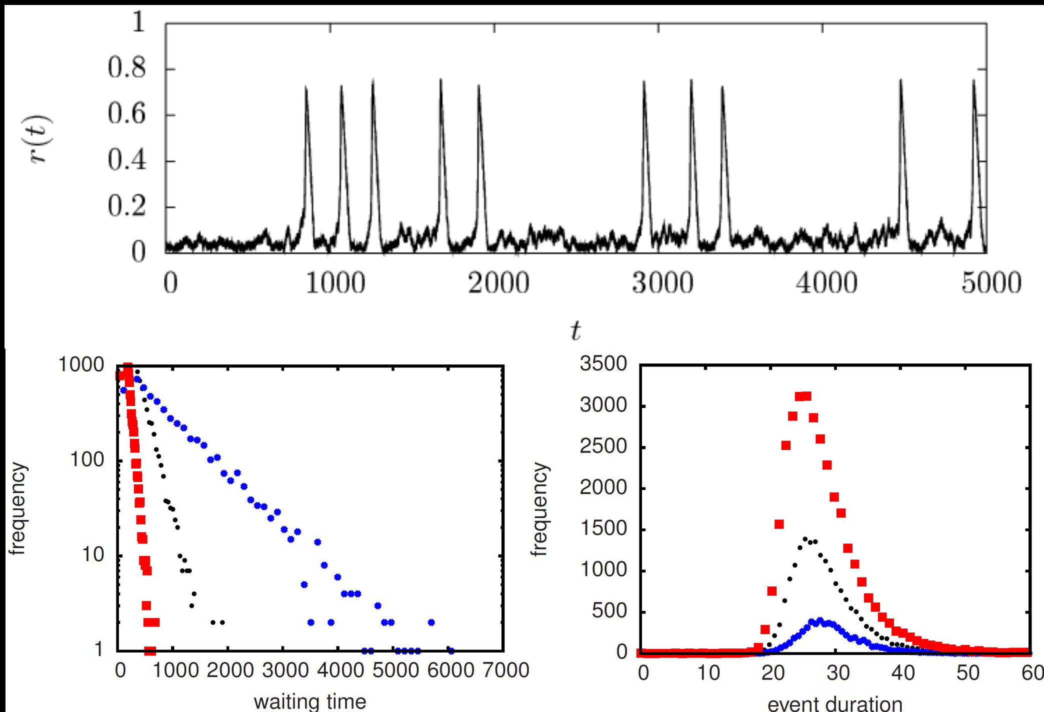
- τ time delay
- ϑ refractory period
- b coupling strength

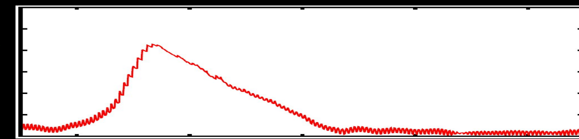
Measuring synchrony with Kuramoto's order parameter: $r(t) = 1/|N| \left| \sum_{n \in N} e^{2\pi i \phi_n(t)} \right|$

*A Rothkegel & KL, **EPL**, 95, 38001, 2011;*
***EPL**, 105, 30003, 2014;*
***New J. Phys.** 16, 055006, 2014*

Self-Initiation and -Termination of Sz-like Events

N = 500 x 500, *m* = 50, τ = 0.01, *b* = 0.01, various ν





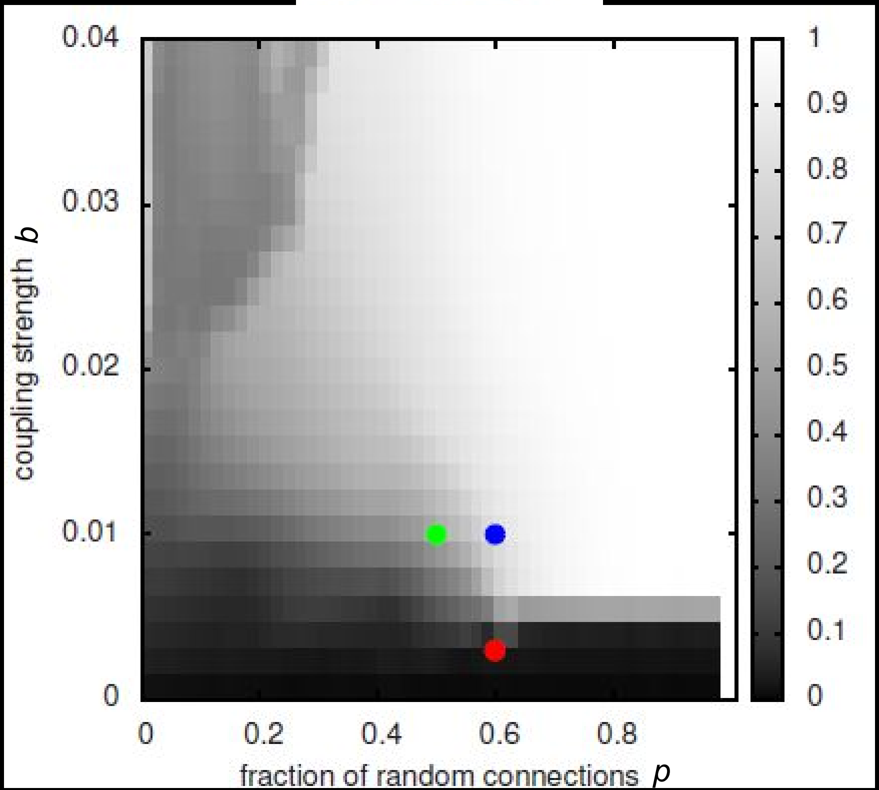
N = 500 x 500, *m* = 50, τ = 0.01, *b* = 0.01, ν = 0.05

*A Rothkegel & KL, **EPL**, 95, 38001, 2011;*
***EPL**, 105, 30003, 2014;*
***New J. Phys.** 16, 055006, 2014*

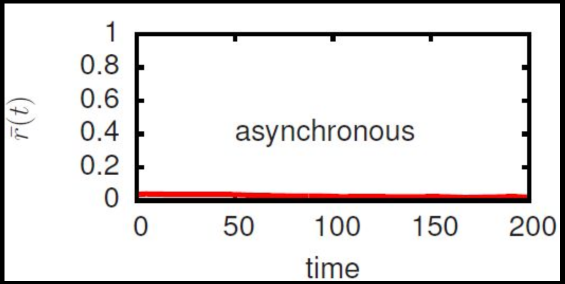
Self-Initiation and -Termination of Sz-like Events

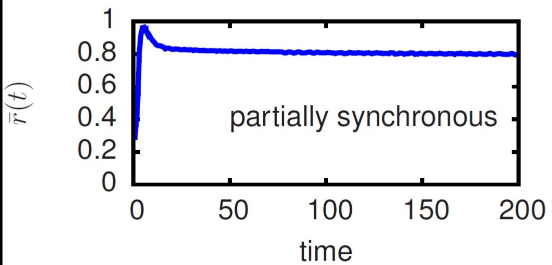
$$r(t) = 1/N \left| \sum_n e^{2\pi i \phi_n(t)} \right|, \qquad \bar{r}(t) \text{ local maxima of } r(t)$$

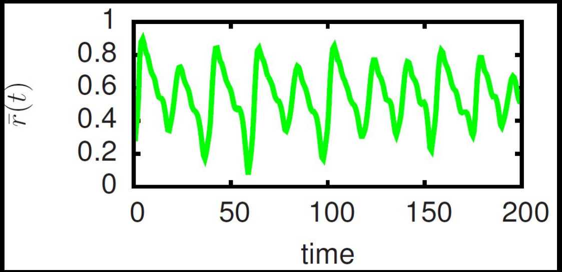
mean of $\bar{r}$



$N = 500 \times 500,\ m = 50,\ \tau = 0.01,\ \vartheta = 0.05;$







*A Rothkegel & KL, **EPL**, 95, 38001, 2011;*
***EPL**, 105, 30003, 2014;*
***New J. Phys.** 16, 055006, 2014*

Self-Initiation and -Termination of Sz-like Events

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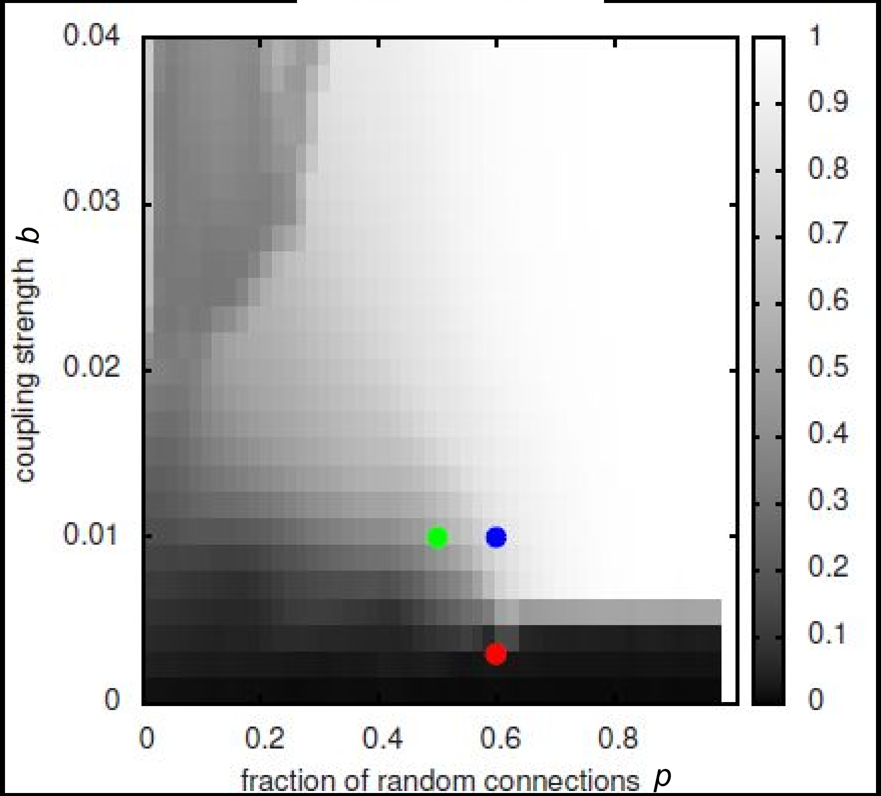
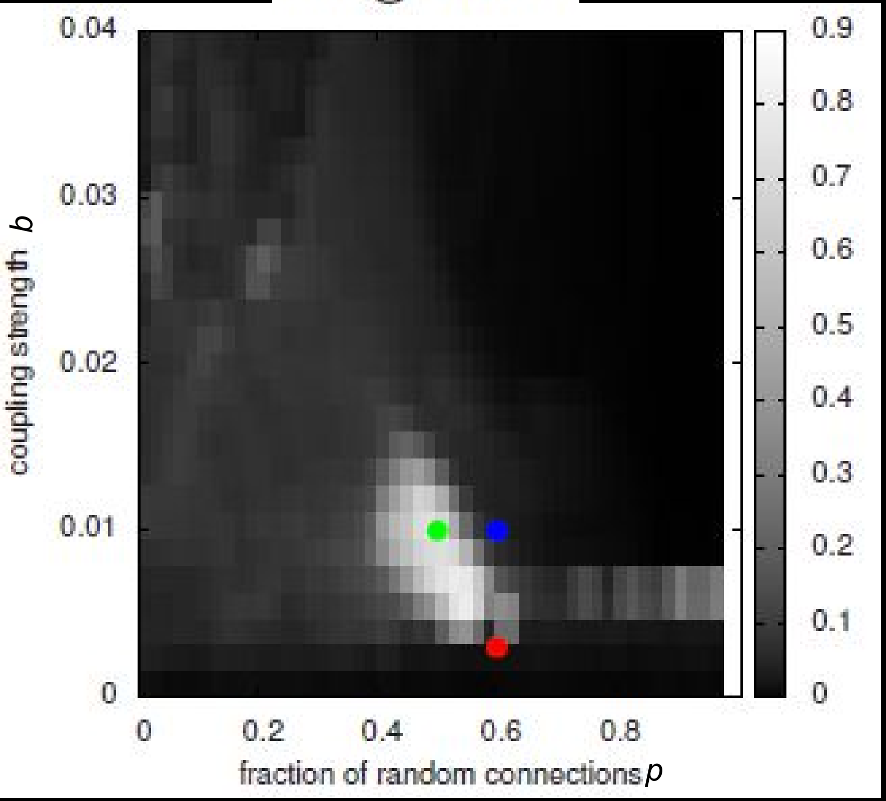
mean of $\bar{r}$



range of $\bar{r}$

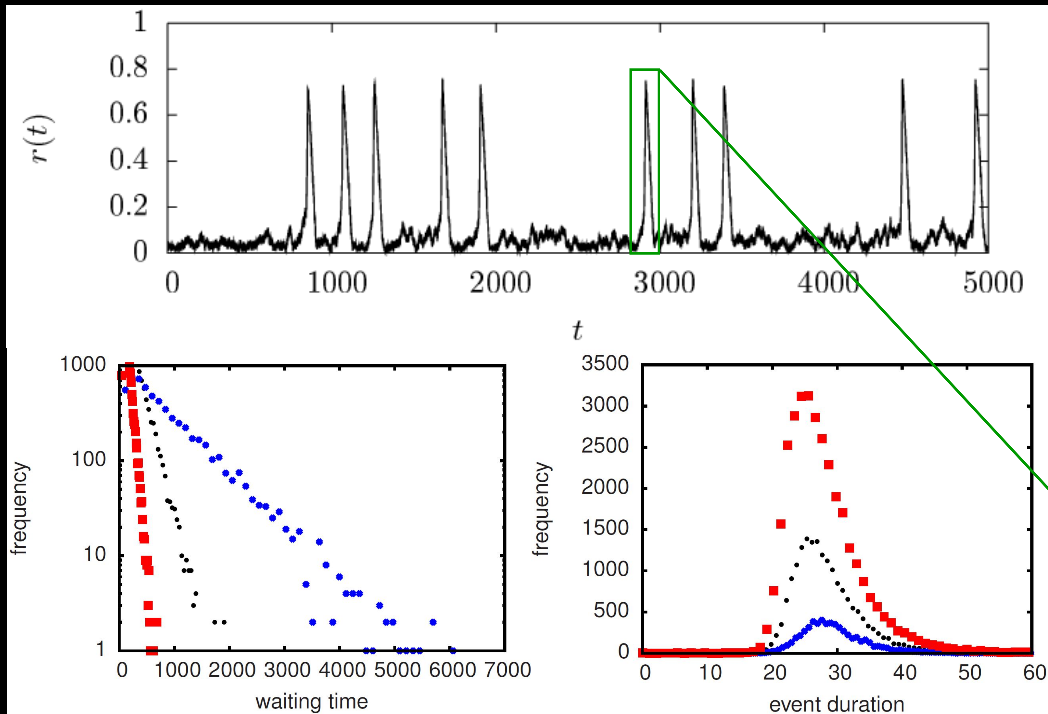


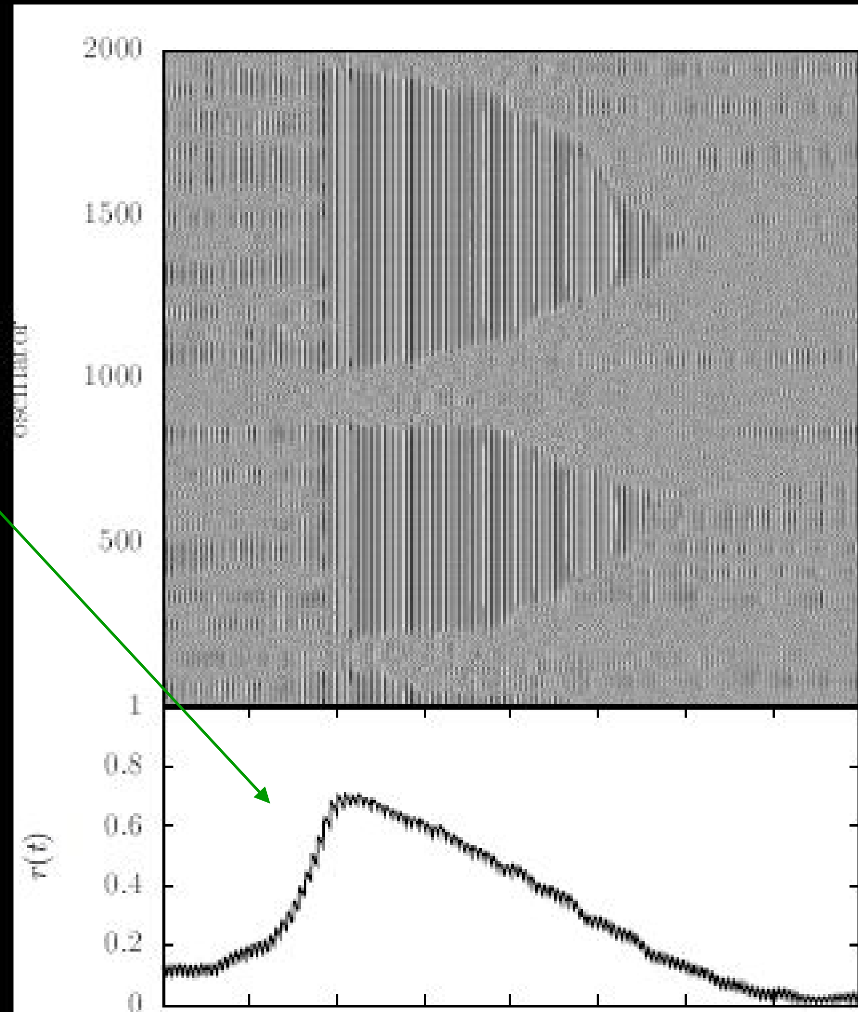
$N = 500 \times 500, m = 50, \tau = 0.01, \vartheta = 0.05;$

*A Rothkegel & KL, **EPL**, 95, 38001, 2011;*
***EPL**, 105, 30003, 2014;*
***New J. Phys.** 16, 055006, 2014*

Self-Initiation and -Termination of Sz-like Events

N = 500 x 500, p = 0.5, m = 50, τ = 0.01, b = 0.01, various ν



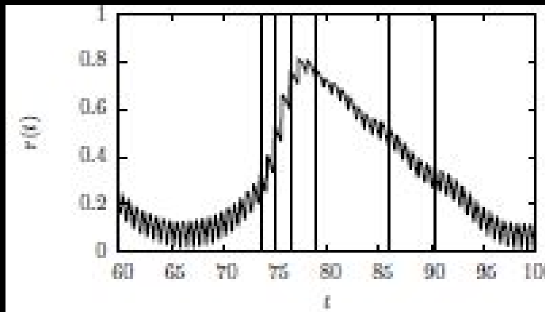


- small-amplitude oscillations with average phase velocity of oscillators

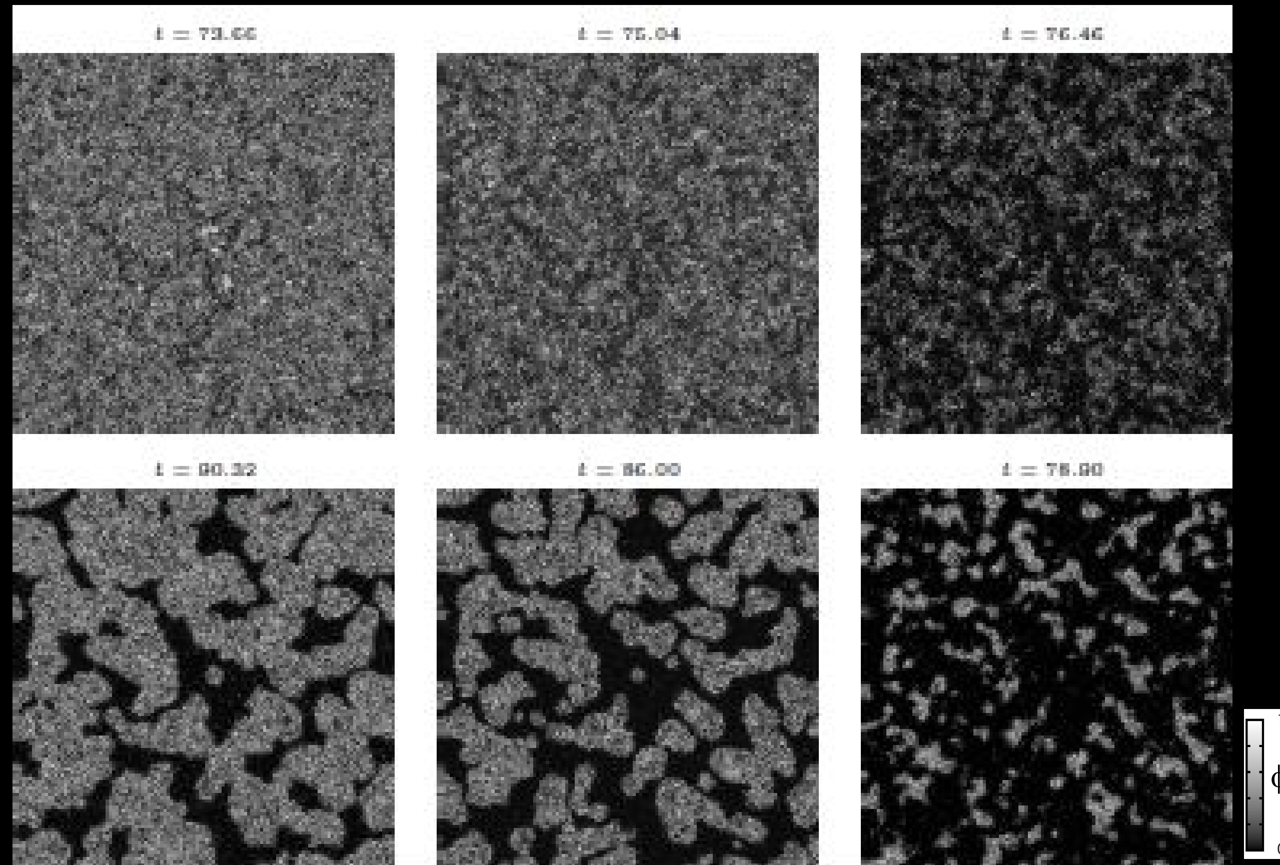
- non-converging macroscopic behavior, network-generated rhythms

A Rothkegel & KL, ***EPL***, *95, 38001, 2011;*
EPL, *105, 30003, 2014;*
New J. Phys. *16, 055006, 2014*

Self-Initiation and -Termination of Sz-like Events



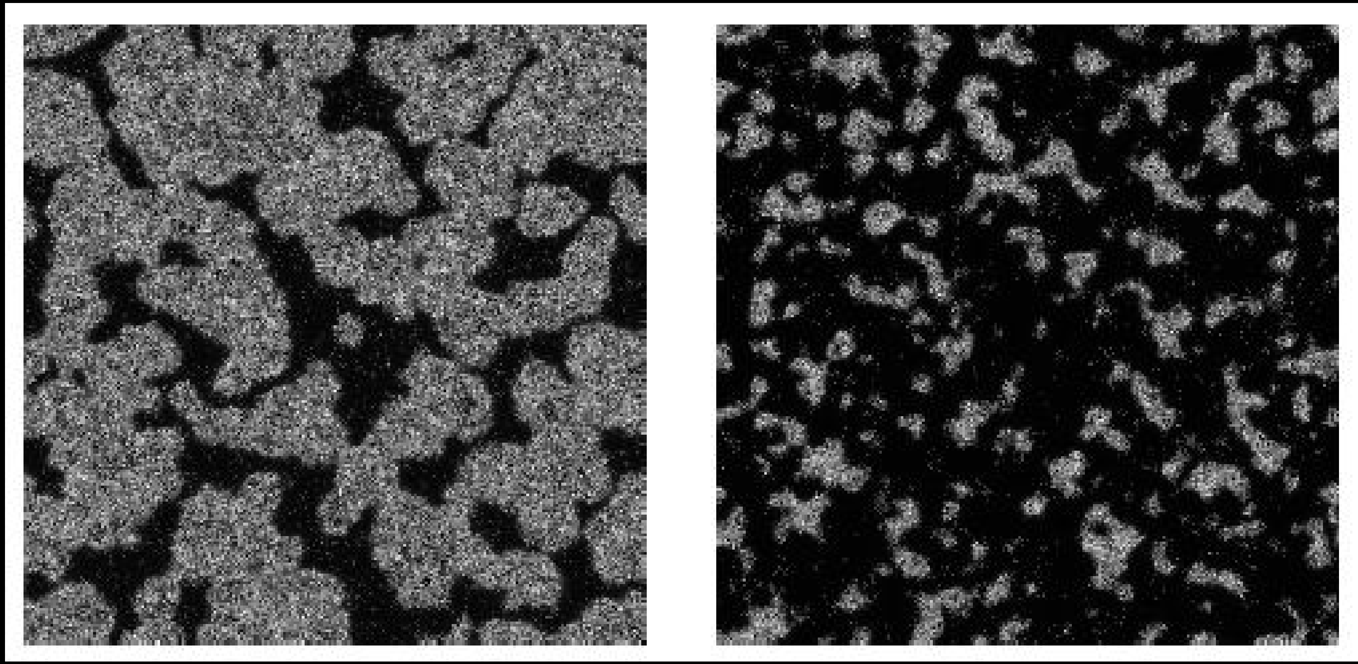
N = 500 x 500, m = 50, τ = 0.01, b = 0.01, ν = 0.05



- comparable values of *r(t)* during ascending and descending part of event
- distributed asynchronous regions during ascending part
- connected asynchronous regions during descending part

A Rothkegel & KL, ***EPL***, *95, 38001, 2011;*
EPL, *105, 30003, 2014;*
New J. Phys. *16, 055006, 2014*

Self-Initiation and -Termination of Sz-like Events

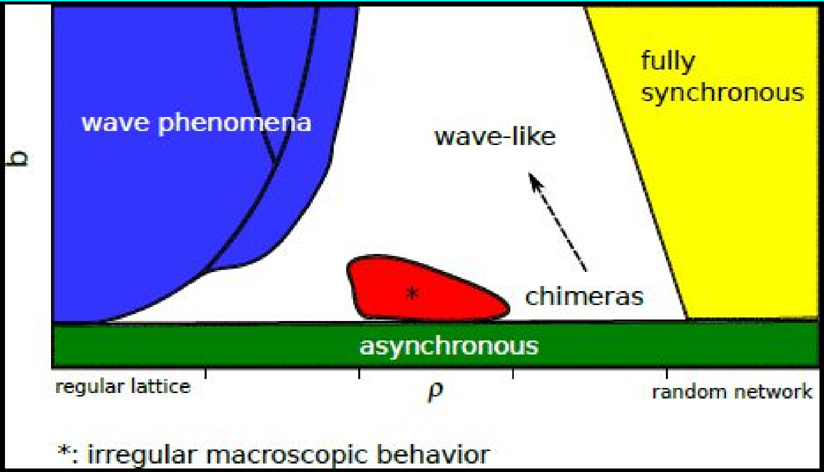


mechanisms:

- stability of asynchronous regions — long-range connections
- stability of synchronous regions
- growing of asynchronous regions — short-range connections
- shrinking of asynchronous regions

*A Rothkegel & KL, **EPL**, 95, 38001, 2011;*
***EPL**, 105, 30003, 2014;*
***New J. Phys.** 16, 055006, 2014*

Self-Initiation and -Termination of Sz-like Events



- ***no inhibition***
- ***no pacemaker***
- ***rhythm is network phenomenon***

- irregular macroscopic dynamics and sz-like events due to self-organized generation of chimera states
- cumulative size of asynchronous regions determined by control parameters
- event initiation via long-range connections
- even termination via short-range connections

- importance of complex coupling topology

*A Rothkegel & KL, **EPL**, 95, 38001, 2011;*
***EPL**, 105, 30003, 2014;*
***New J. Phys.** 16, 055006, 2014*

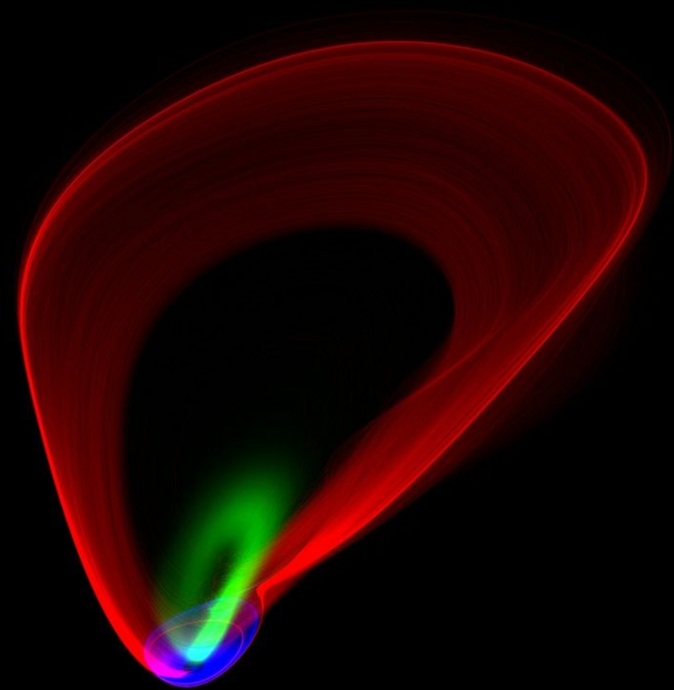
Self-Initiation and -Termination of Sz-like Events

FitzHugh-Nagumo oscillators

$$\dot{x}_i = x_i(a - x_i)(x_i - 1) - y_i + k\sum_{j=1}^{n} A_{ij}(x_j - x_i),$$

$$\dot{y}_i = b_i x_i - c y_i. \qquad (1)$$

- small-world network based
  on n = 100 x 100 lattice
- weak coupling (k ~10^{-3})
- cyclic boundary conditions
- 60 nearest neighbors
- rewiring probability of p = 0.2
- a, b_i, c fixed
- observable: spatial mean of x



- “critical mass”
- channel-like structures
- mixed-mode oscillations

G Ansmann et al. ***Phys. Rev. E*** *88, 052911, 2013*
R Karnatak et al. ***Phys. Rev. E*** *90, 022917, 2014*
G Ansmann et al. ***Phys. Rev. X*** *6, 011030, 2016*

Conclusions

- epilepsy: disorder of large-scale neuronal networks (structure & function)

- paradigm shift: epileptic focus → epileptic network

- seizure self-termination through synchronization
→ new therapeutic options?

- characterization of individual epileptic network
→ individualized treatment?