Limitations on inferring couplings and directionality

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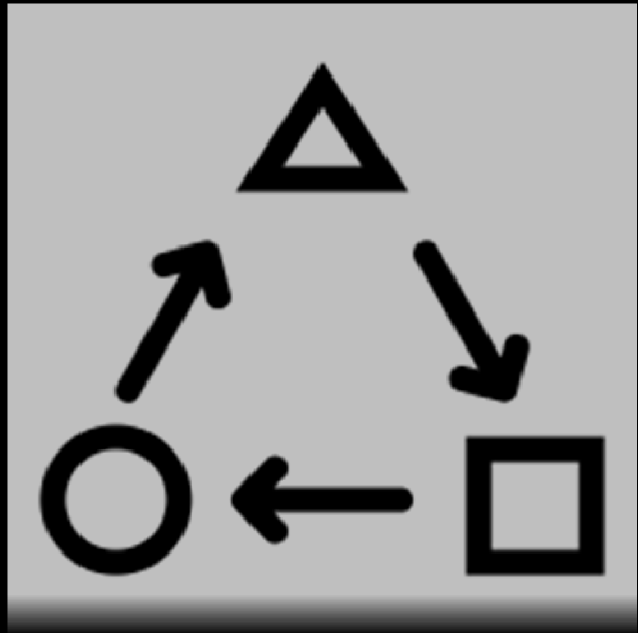
Lessons learned from evolving epileptic brain networks

Klaus Lehnertz



Dept. of Epileptology
Neurophysics Group

IZ KS
Interdisciplinary Center
for Complex Systems

University of Bonn, Germany

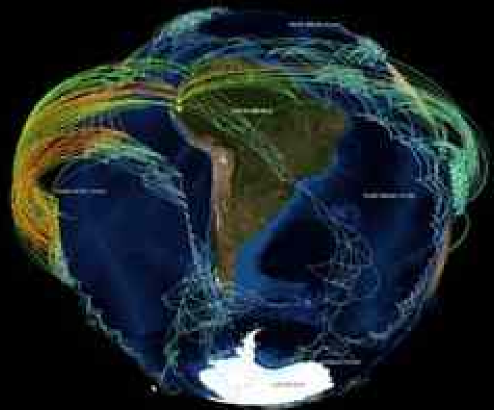
HISKP
Helmholtz-Institute
for Radiation- and
Nuclear Physics

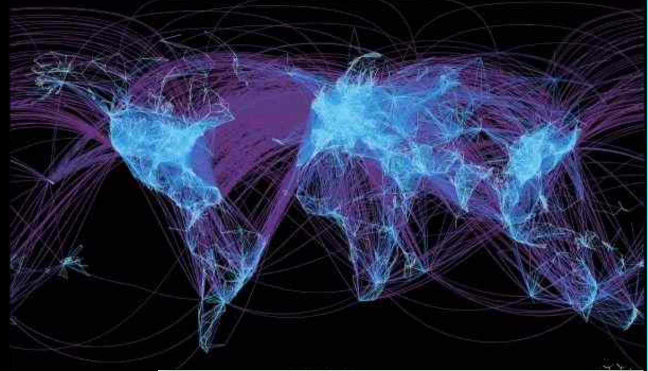
Second International Summer Institute
on Network Physiology (ISINP)
Lake Como School of Advanced Studies - 29 July - 03 August, 2019

Complex Networks

physical

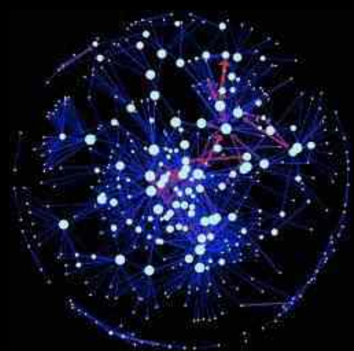
- power grids, roads, airlines, internet, climate

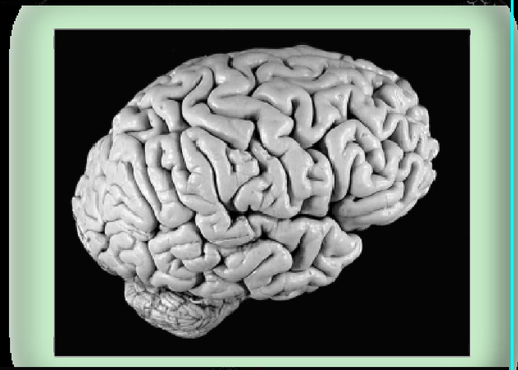


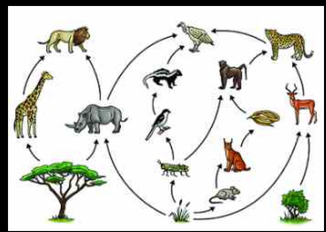


biological

- neurons, metabolism, genes, protein, food, epidemics





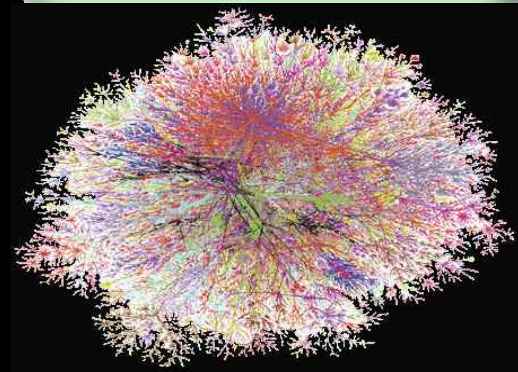


social

- friendships, affiliations, sexual contacts

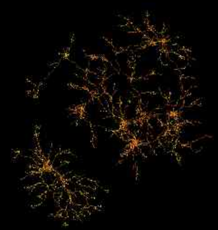
organizational

- firms, markets, governments, finance



knowledge

- citations, words, WWW

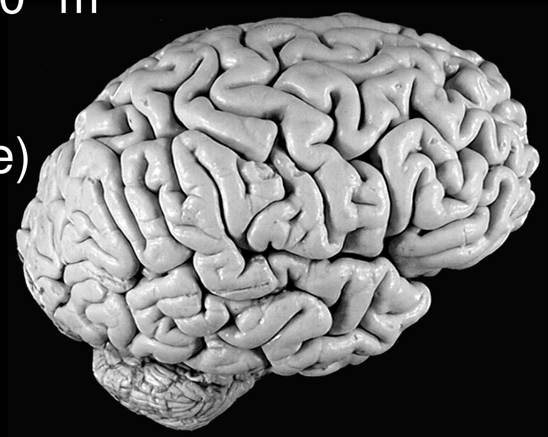


…

pictures: Internet

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

Brain Networks - Relevance

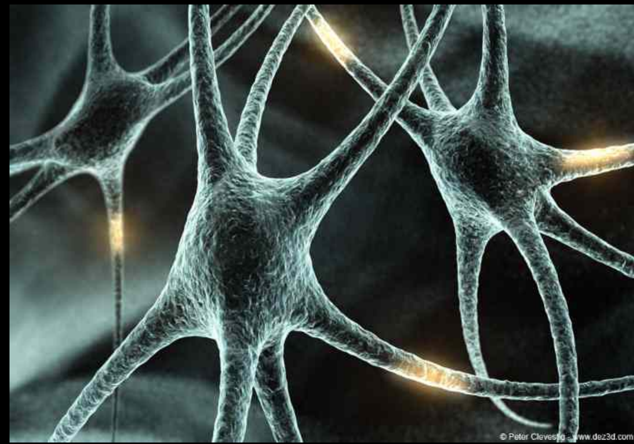
properties of functional/structural brain networks are sensitive to:

behavioral variability	Alzheimer’s disease
cognitive ability	schizophrenia
genetic information	acute depression
shared genetic factors	multiple sclerosis
gender	attention deficit hyperact. dis.
age	spinal cord injury
drugs	epilepsy
…	…

e.g. E. Bullmore & O. Sporns, Nat. Rev. Neurosci. 10, 186, 2009; Stam, Nat. Rev. Neurosci. 15, 683, 2014

Inferring Networks of the Brain - Structure

small-scale:

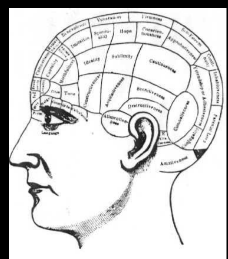


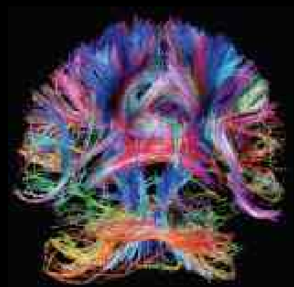
nodes → neurons
links → synapses

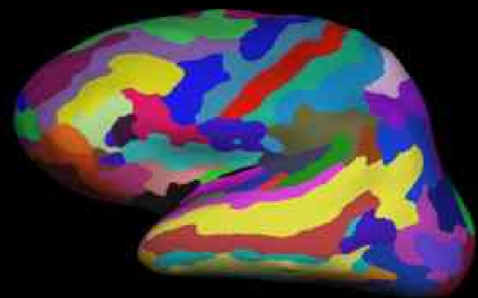
desirable, but hard (impossible?) to access

medium-scale: ???

large-scale:







nodes → brain regions
links → fiber bundles

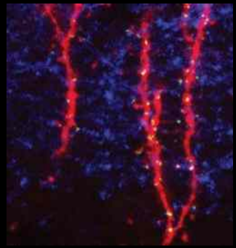
high-res. MRI, DTI, parcellation schemes, …

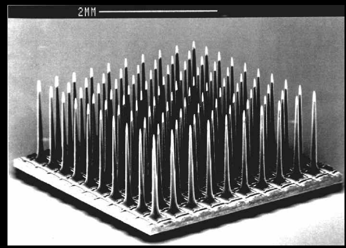
Inferring Networks of the Brain - Function

small-scale:

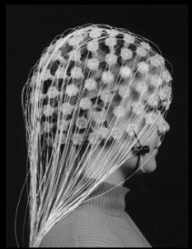
nodes → single neuron (glia) dynamics
links → synaptic (other) interactions

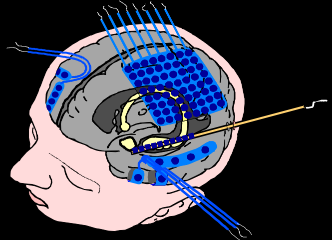
emerging technology





large-scale:





nodes → sensors (dynamics of *networks of neuron networks*)
links → interactions (weighted and/or directed),
time series analysis

EEG, iEEG, MEG, fMRI, …

medium-scale: ???

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Concepts: Brain Connectivity

- structural connectivity:
physical (and chemical) connections between neuronal populations or individual neurons

- functional connectivity:
statistical dependence (or similarity) between neurophysiological signals recorded from distributed and often spatially remote neuronal units, regardless of whether these units are connected by direct structural links

- **effective connectivity:**
influence that one neural system exerts over another. ***Requires a mechanistic model of causal effects (incl. structural parameters) or involves time series analysis***

e.g. Horwitz, NeuroImage 19, 466, 2003; Frackowiak et al., Human Brain Function 2nd ed, 2004; Friston, Brain Connect. 1, 13, 2011

Concepts: Brain Connectivity

- structural connectivity:

fully accessible? limited methodologies

- functional connectivity:

statistical dependence may be due to various reasons

what is a “good measure” ?

- **effective connectivity:**

relates to coupling or directed causal influence

- how to define “***coupling***” (underlying mechanism) ?

- inference of causality is notoriously problematic !

Assessing Couplings from Time Series

(lin./nonlin. uni-/bi-/multivariate) analysis techniques

- statistical approaches
- approaches in time/frequency domain
- information theoretical approaches
- state-space-based approaches
- Fokker-Planck formalism
- …

requirements

- different aspects of dynamics / synchronization phenomena
- robustness against noise/measurement errors
- strength and/or direction of couplings; coupling function
- computing time (field data analyses)
- interpretability (causality? direct vs. indirect; common sources)

Assessing strength and direction of couplings

Phase dynamics

- phase time series (e.g. via Hilbert- or wavelet- transformation)
- strength: phase locking condition
- direction: temporal evolution of the unwrapped phase time series

Information / Entropy

- Granger causality, (conditional) mutual information, transfer entropy
- direction: asymmetry of approaches, strength: other approaches

State space

- state space reconstruction (e.g. time-delay embedding)
- strength and direction: properties of functional relationship, interdependence

Assessing Couplings

probing (*actio est reactio*)

system response due to perturbation (relaxation phen.)
repeated measurements, limited number of data points,
nonstationarity, “true” dynamics?

observing (if probing is not possible)

time series analysis of ongoing activity
large amount of data, nonstationarity

characteristics of couplings

- strength
- direction
- coupling function

} + temporally and spatially resolved

Assessing Directional Couplings

- Time Resolved Analysis -

- ensemble of a sufficiently large number of time series as multiple realizations of a process

- estimate directionality across realizations at each time point

- estimate significance level with surrogates (e.g. permutations of realizations)

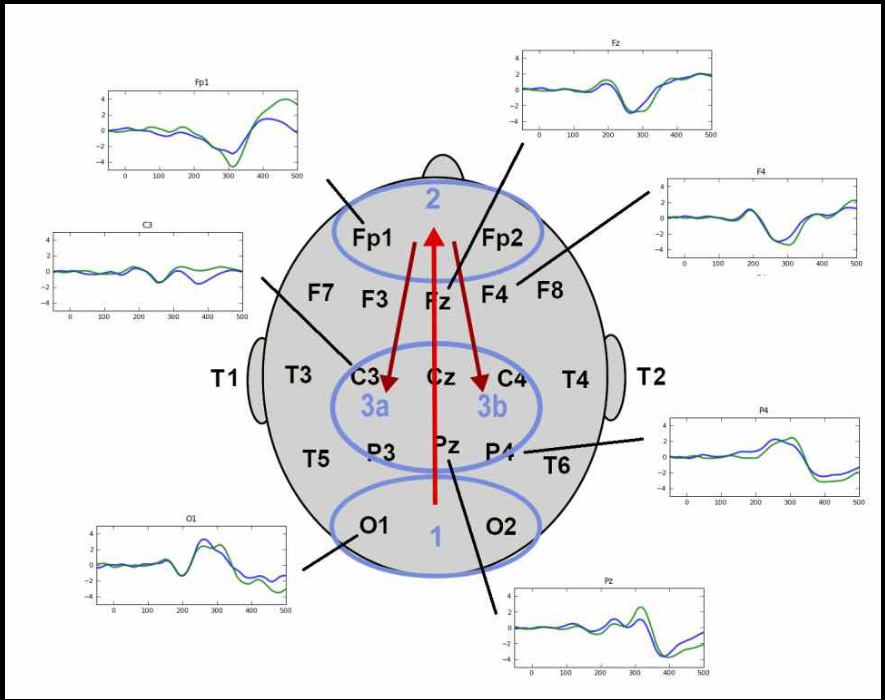
- nonlinear interdependence, cross dependency, symbolic transfer entropy

Andrzejak et al. New J. Physics 8, 6, 2006;
Wagner et al., New J. Physics 12, 053031, 2010;
Martini et al., Phys Rev E 83, 011919, 2011

Directed Couplings from Event-Related Activities
- Time Resolved Analysis of Symbolic Transfer Entropy -

Simon task:
- press right/left button upon presentation of red/blue circles
- 100 repetitions for each possible combination → 400 trials
- 12 healthy volunteers
- scalp EEG recording; ref.: Cz 0.5-300 Hz, Δf: 1000 Hz, 16bit ADC

expected directions of interaction:
- 0 - 100 ms after stimulus onset: occipital → frontal
- 400-500 ms after stimulus onset (mean reaction time): frontal → central and parietal



Martini et al., Phys Rev E 83, 011919, 2011

Directed Couplings from Event-Related Activities
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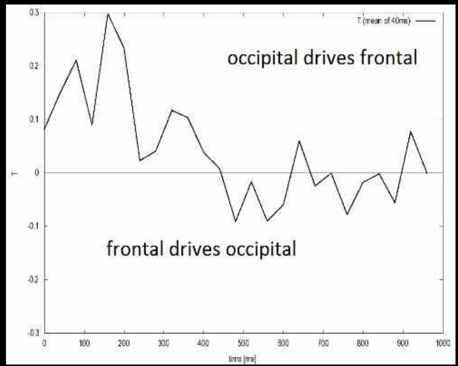
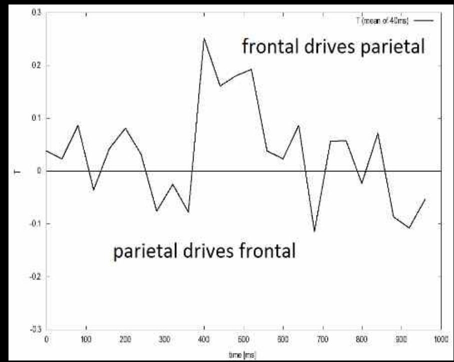


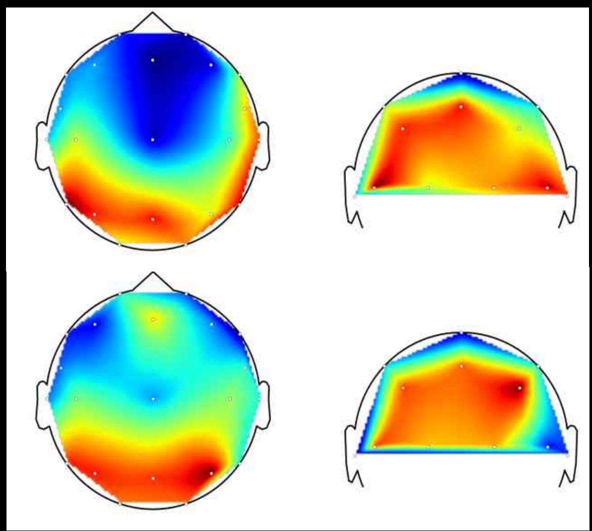


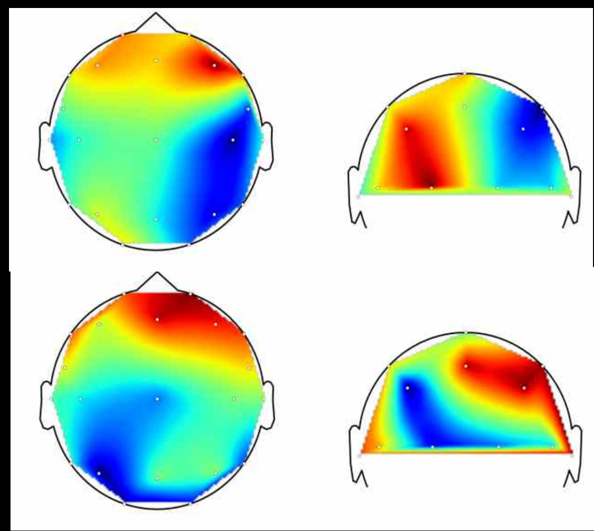
0 - 100 ms post-stimulus

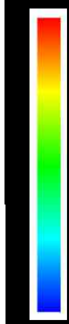
400 - 500 ms post-stimulus

red circle
left button

red circle
right button





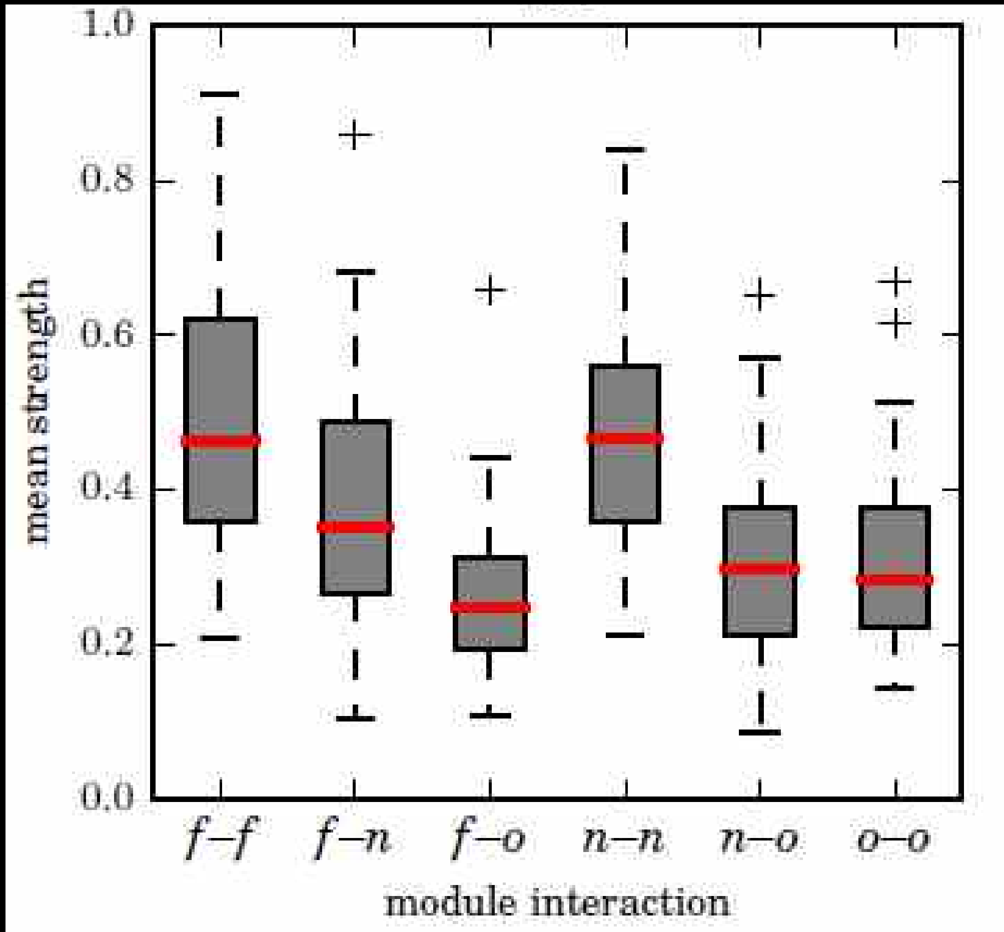


N=12

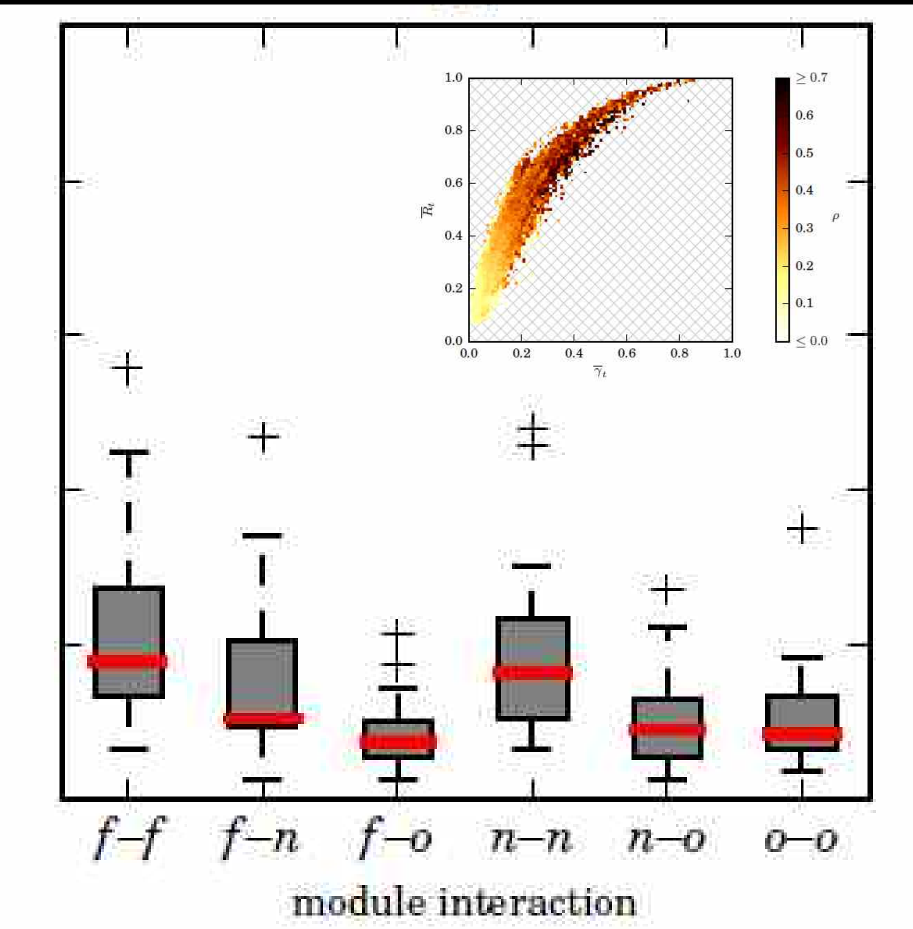
Martini et al., Phys Rev E 83, 011919, 2011

Strength of Couplings in Epileptic Networks

phase-based approach



information-theoretic approach



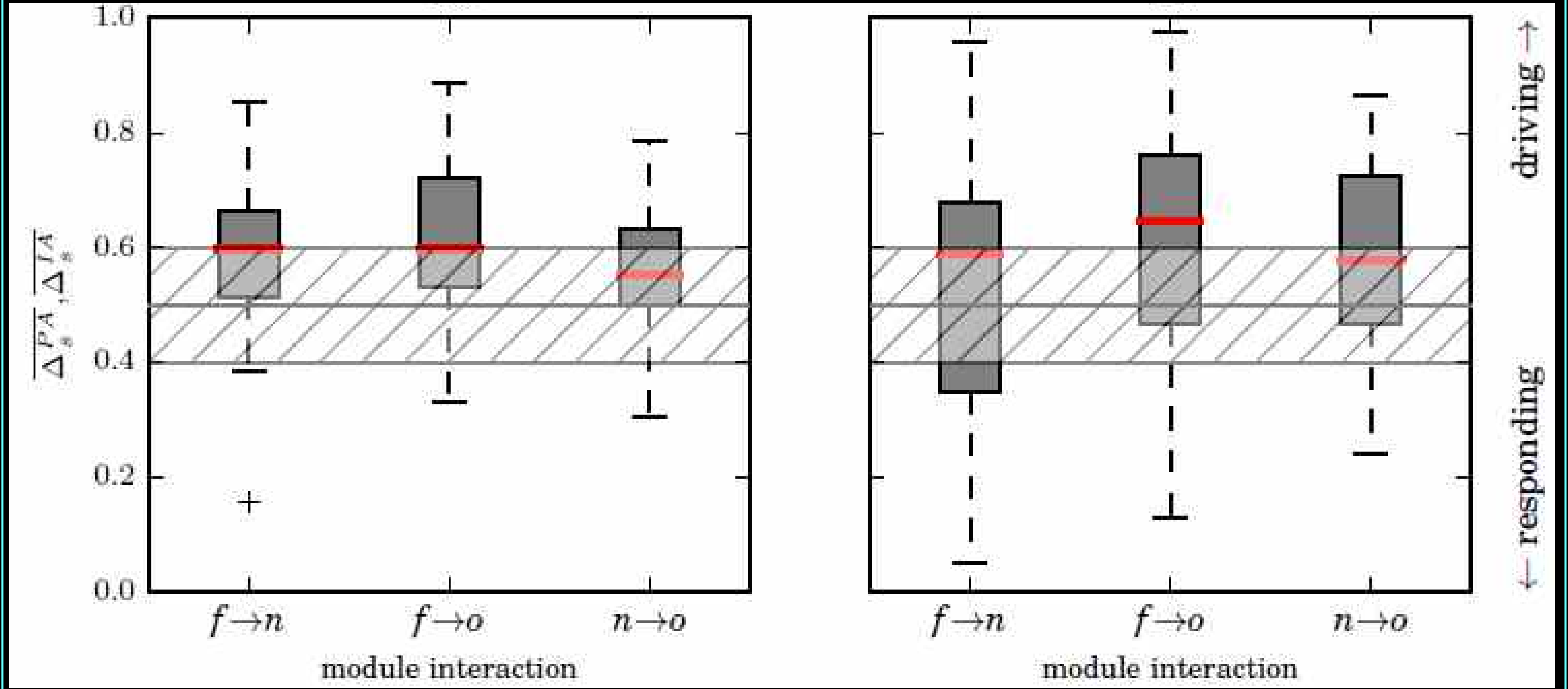
35 patients; Ø 51 sites; Ø 114 hrs iEEG recording; szr-free interval only

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

f = focus, n = neighborhood, o = other

Direction of Couplings in Epileptic Networks

phase-based approach | information-theoretic approach



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 Couplings

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

Confounding Variables: Common Sources

mean phase coherence

$$R = \left| \frac{1}{N} \sum_{j=1}^{N} \exp\left(i(\Phi_a(j) - \Phi_b(j))\right) \right|.$$

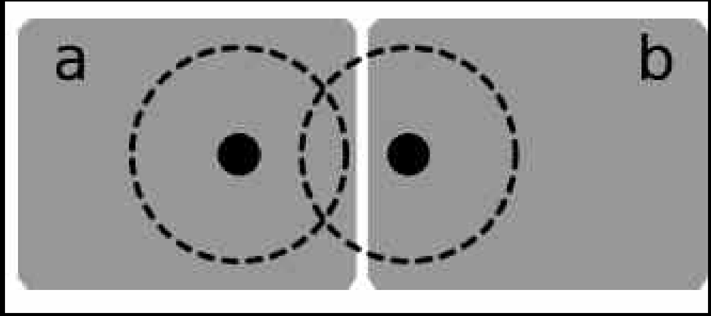
phase lag index

$$P = \left| \frac{1}{N} \sum_{j=1}^{N} \mathrm{sgn}\left[\sin(\Phi_a(j) - \Phi_b(j))\right] \right|.$$

weighted phase lag index

$$P_{\mathrm{w}} = \frac{\left| \sum_{j=1}^{N} \sin\left(\Phi_a(j) - \Phi_b(j)\right) \right|}{\sum_{j=1}^{N} \left| \sin(\Phi_a(j) - \Phi_b(j)) \right|}.$$

Modeling impact of common sources (CS)



superposition with $\alpha \in [0,1)$

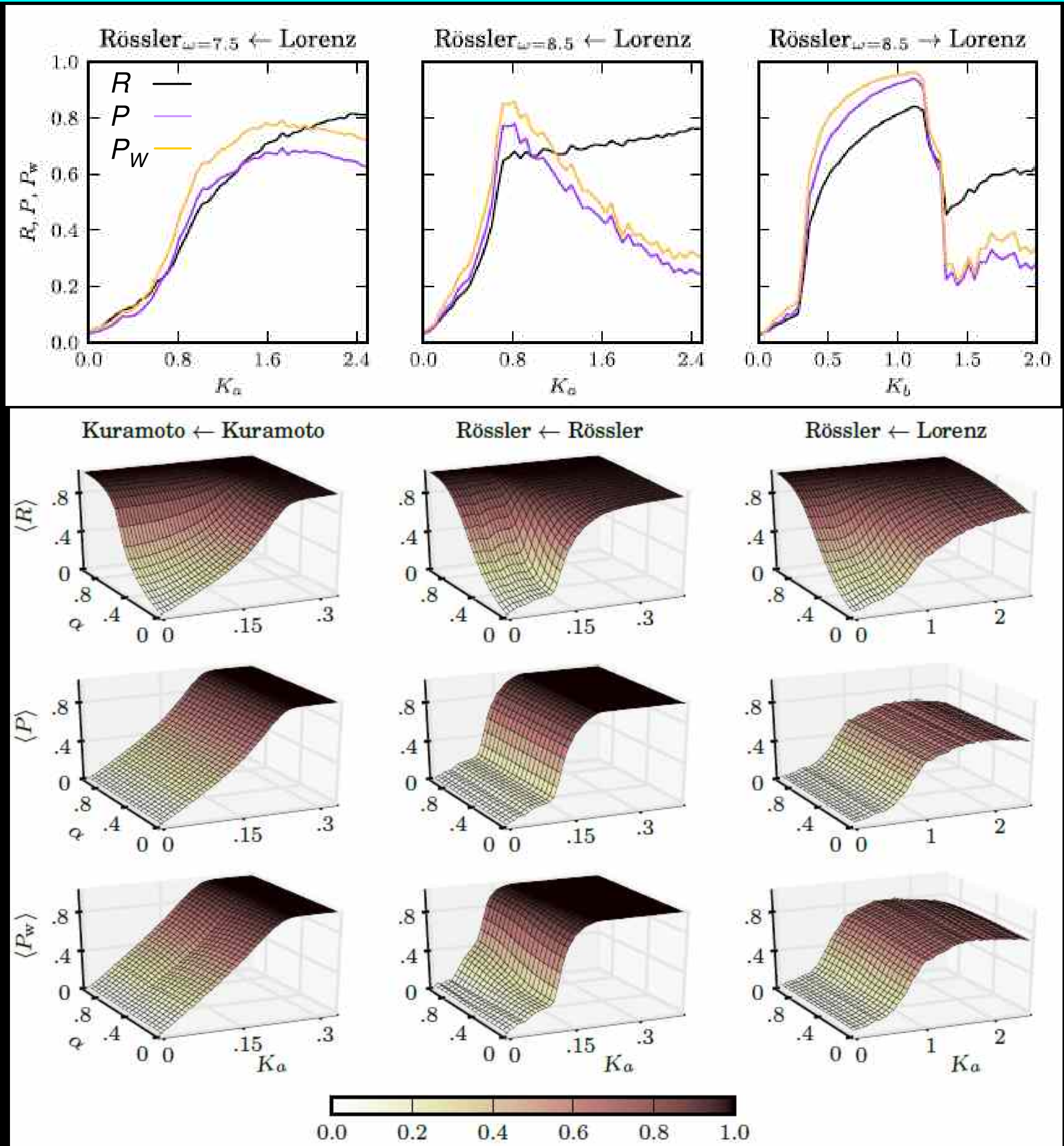
$$\tilde{s}_a(j) = (1-\alpha)s_a(j) + \alpha s_b(j),\ \tilde{s}_b(j) = s_b(j),\ \text{or}$$
$$\tilde{s}_b(j) = (1-\alpha)s_b(j) + \alpha s_a(j),\ \tilde{s}_a(j) = s_a(j),$$

mixing with $\alpha \in [0,0.5)$

$$\tilde{s}_a(j) = (1-\alpha)s_a(j) + \alpha s_b(j),$$
$$\tilde{s}_b(j) = (1-\alpha)s_b(j) + \alpha s_a(j),$$

Mormann et al., Physica D 144, 358, 2000; Porz et al., Chaos 24, 033112, 2014

Confounding Variables: Common Sources



coupled oscillator models

R

- strongly affected by CS
- more robust to noise (meas. + dyn.)

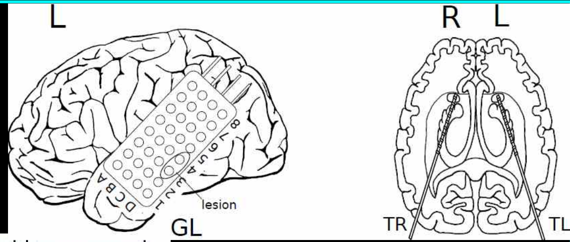
P and P_W

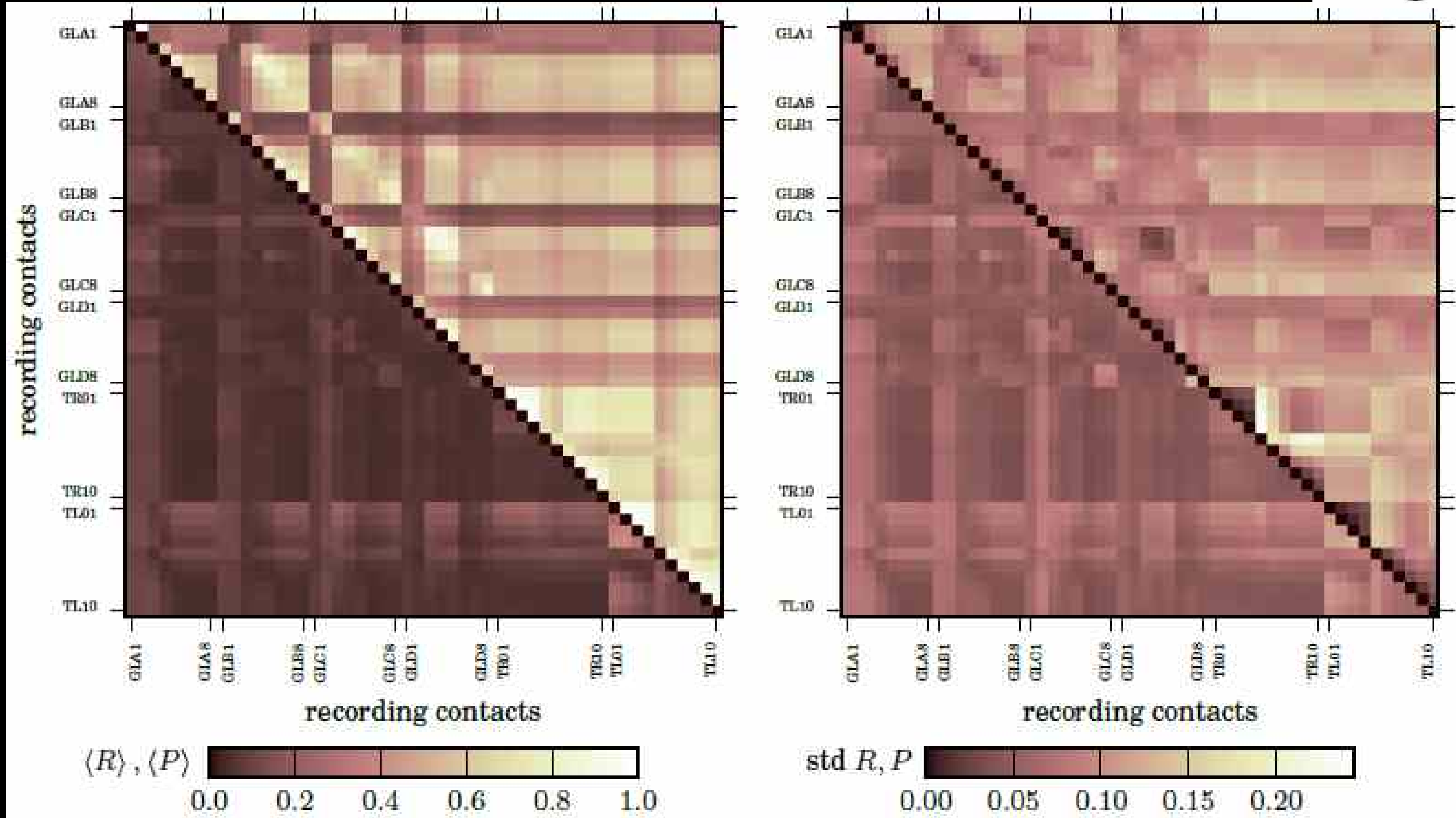
- less influenced by CS
- less robust to noise (compared to *R*)
- dependent on oscillator type and direction of coupling !
- no advantage of P_W over *P*

Porz et al., Chaos 24, 033112, 2014

Confounding Variables: Common Sources

- 20 h iEEG recording, seizure-free interval
- moving-window analysis (20.48 s; 4096 data points)





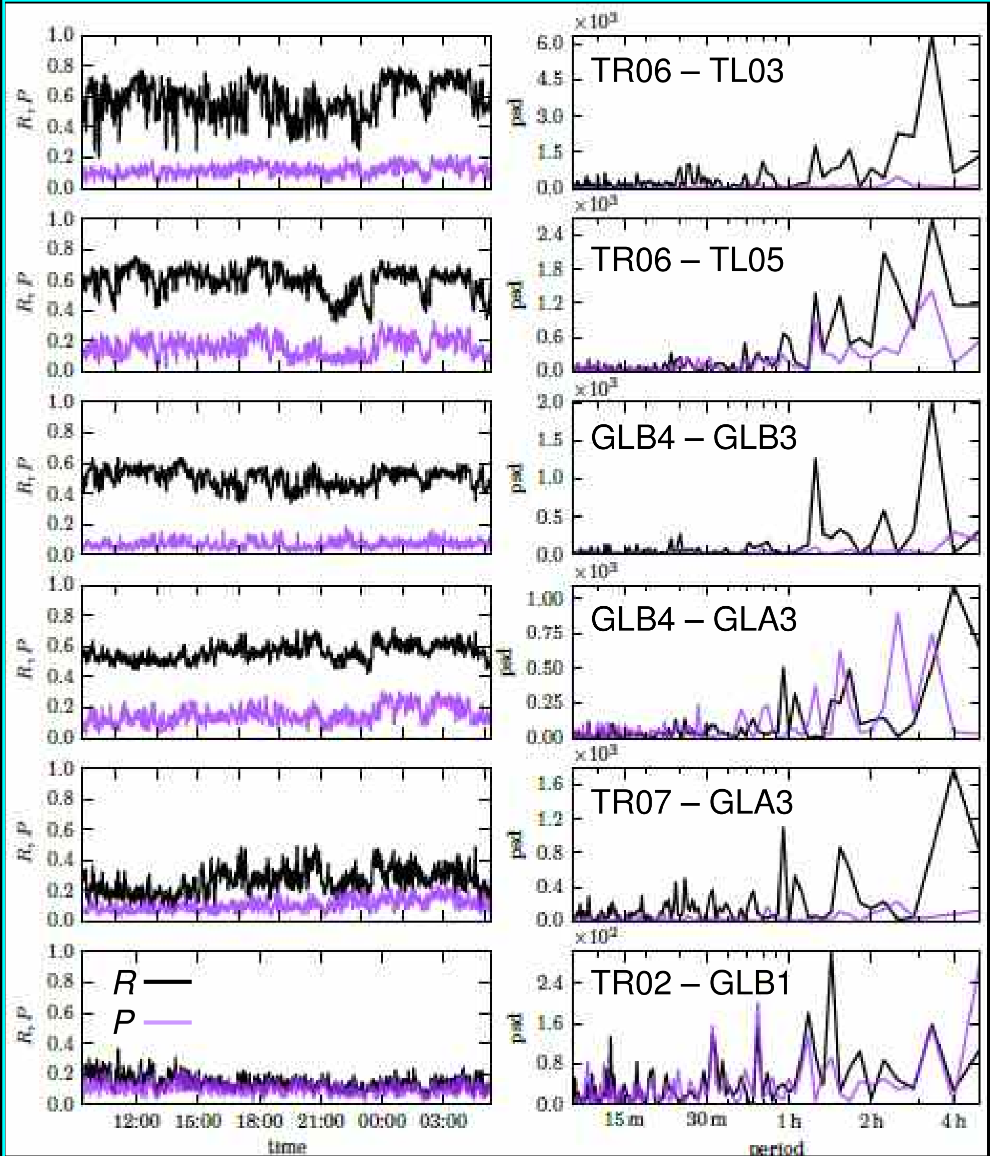
Ref-Electr.:
GLA1+GLA2

SOZ:
GLA6

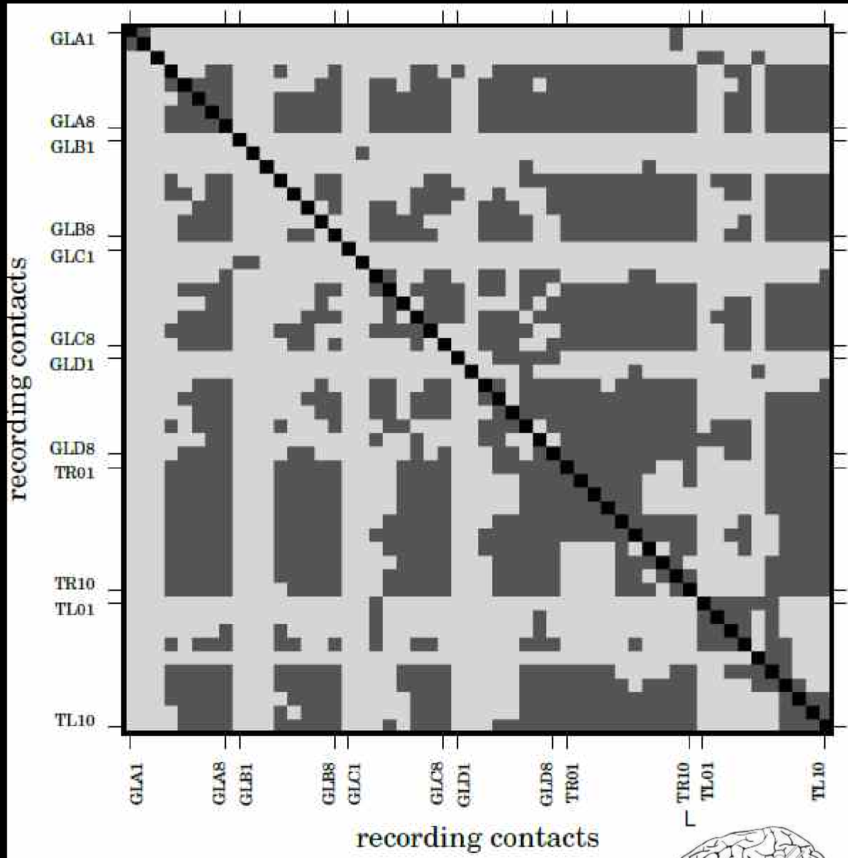
Lesion:
GLD3+GLD4

Porz et al., Chaos 24, 033112, 2014

Confounding Variables: Common Sources

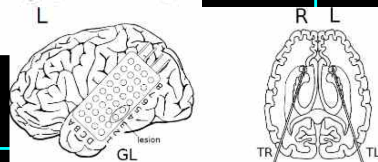


equivalence (light gray)
non-equivalence (dark gray)
of power spectra



$R - P$

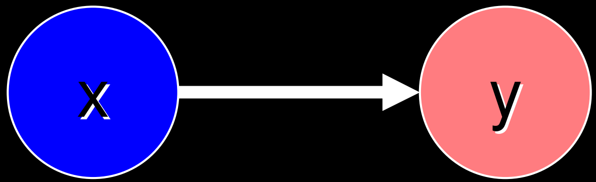
$R - P_W$



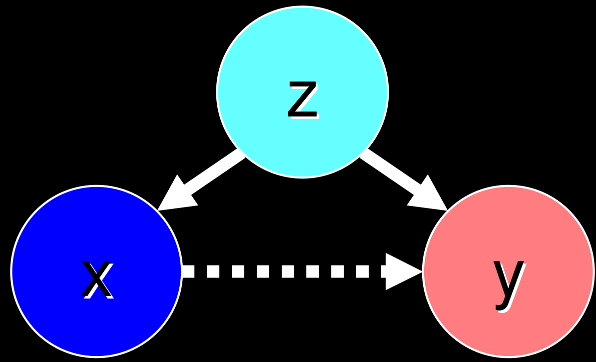
Porz et al., Chaos 24, 033112, 2014

Confounding Variables: Indirect Interactions

direct interaction



indirect interaction



(Pearson) correlation coefficient

$$r_{ij} = \frac{\mathrm{cov}(i,j)}{\sqrt{\mathrm{var}(i)\mathrm{var}(j)}}$$

partial correlation coefficient

$$r_{ij|k} = \frac{r_{ij} - r_{jk} r_{ik}}{\sqrt{(1-r_{ik}^2)(1-r_{jk}^2)}}$$

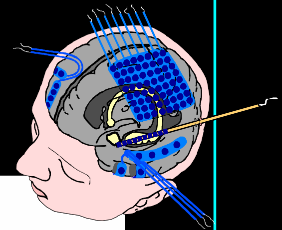
similar approaches for other measures:

(renormalized) partial directed coherence, partial (symbolic) transfer entropy, partial phase dynamics, ….

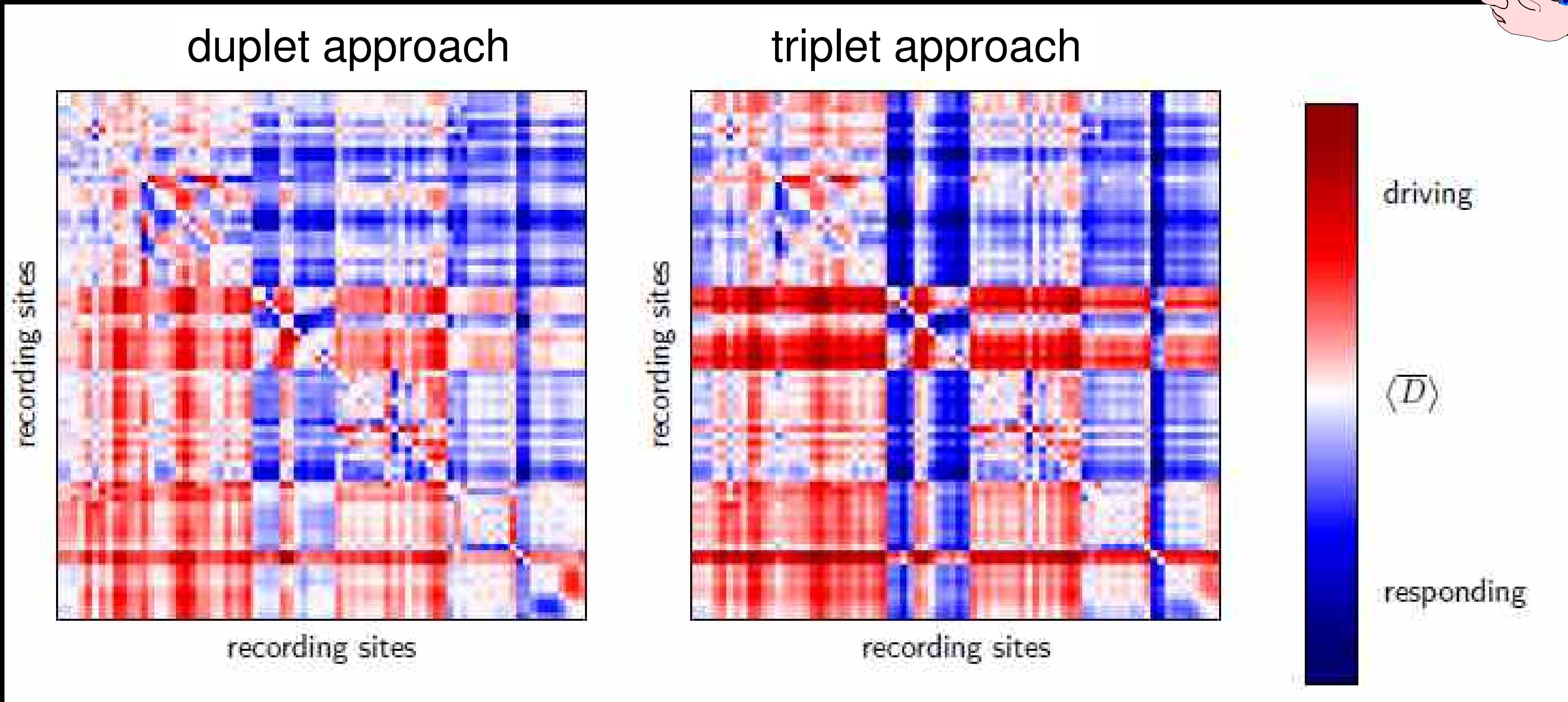
larger networks (n >10), higher order (>1) … effectiveness ?

E. Langford, N. Schwertman, M. Owens, "Is the property of being positively correlated transitive?" Am Stat 55, 322, 2001
LA Baccalá, K Sameshima, Biol Cybern 84, 463, 2001; R Dahlhaus, Metrika 51, 157,2000; L Sommerlade et al., Phys Rev E 80, 051128,2009;
D Kugiumtzis, Phys Rev E 87, 06291, 2013; Kralemann et al., New J Physics 16, 085013, 2014

Confounding Variables: Indirect Interactions



intracranial EEG recording (76 hrs) from an epilepsy patient
76 recording sites, moving-window phase-based directionality estimation

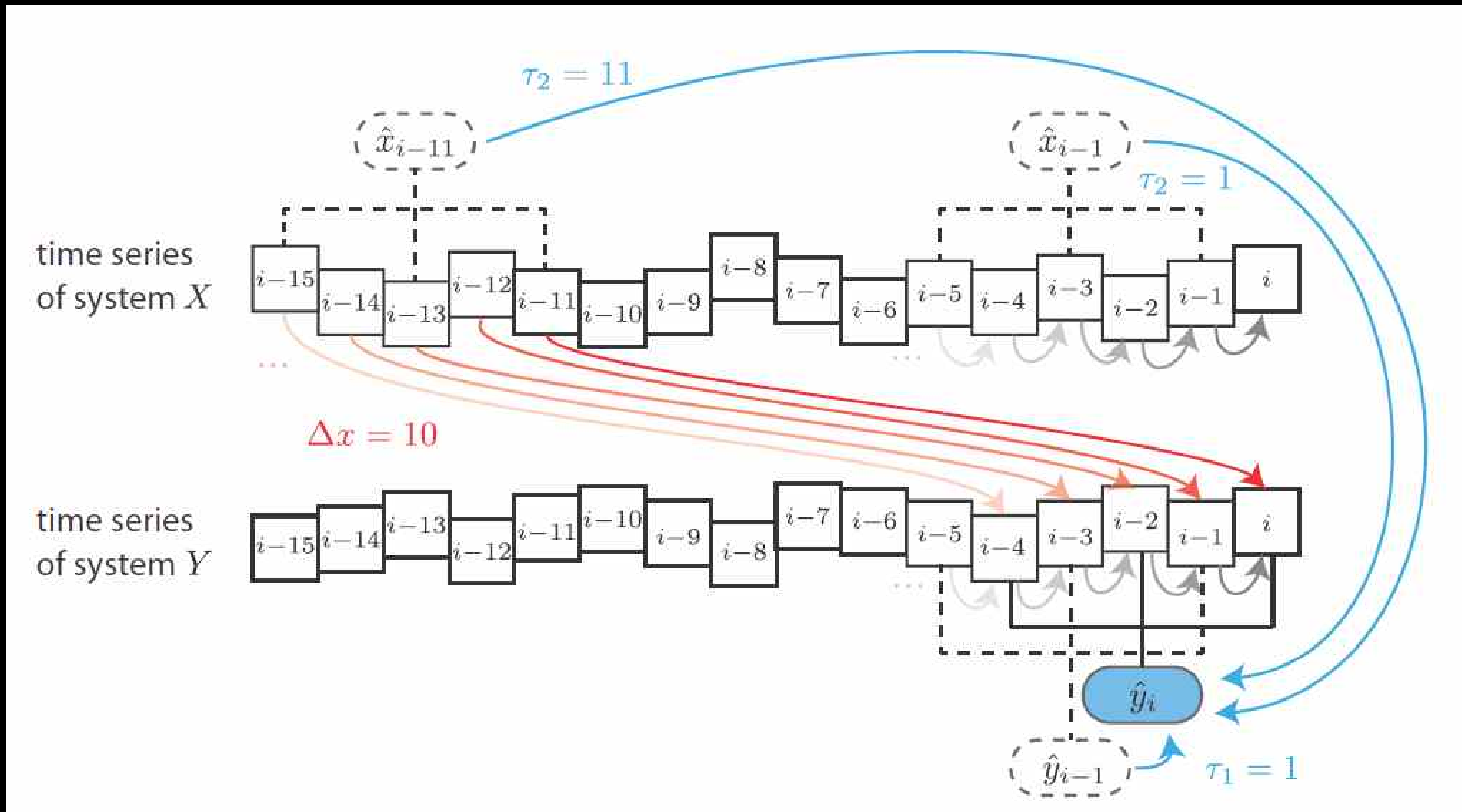


consistent estimation of directionality: 95 % match

$$\overline{\mathcal{D}}_{k,l} = \frac{\mathcal{D}_{k\to l} - \mathcal{D}_{l\to k}}{\mathcal{D}_{k\to l} + \mathcal{D}_{l\to k}}$$

*T. Rings & KL, **Chaos**, 26, 093106, 2016*

Delayed Directed Couplings



delayed symbolic transfer entropy with directionality index:

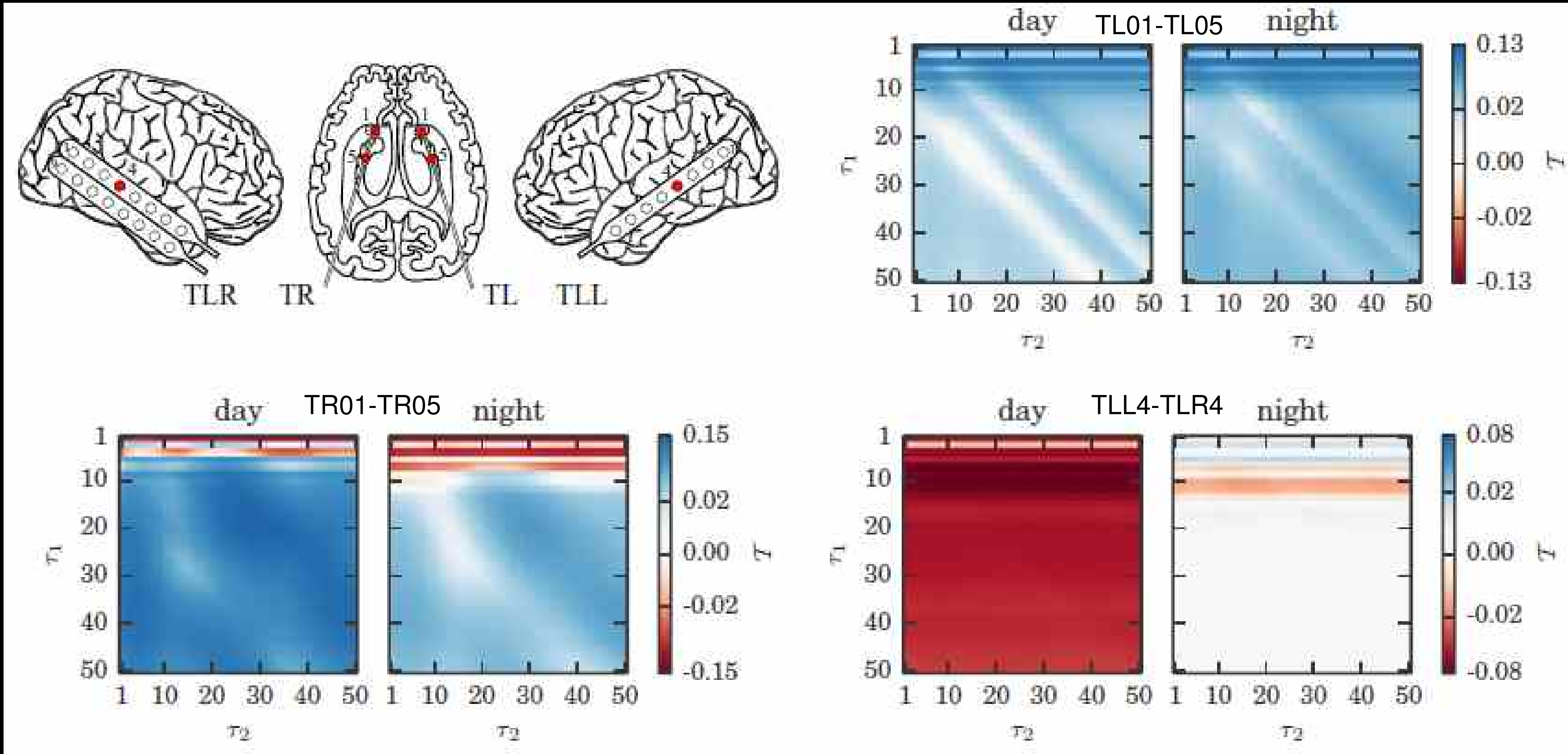
$$\mathcal{T}(\tau_1,\tau_2) := \underset{X\to Y}{\mathcal{T}}(\tau_1,\tau_2) - \underset{Y\to X}{\mathcal{T}}(\tau_1,\tau_2)$$

$$\underset{X\to Y}{\mathcal{T}}(\tau_1,\tau_2) := \sum p\left(\hat{y}_i, \hat{y}_{i-\tau_1}, \hat{x}_{i-\tau_2}\right) \log \frac{p\left(\hat{y}_i \mid \hat{y}_{i-\tau_1}, \hat{x}_{i-\tau_2}\right)}{p\left(\hat{y}_i \mid \hat{y}_{i-\tau_1}\right)}$$

$$\underset{Y\to X}{\mathcal{T}}(\tau_1,\tau_2) := \sum p\left(\hat{x}_i, \hat{x}_{i-\tau_1}, \hat{y}_{i-\tau_2}\right) \log \frac{p\left(\hat{x}_i \mid \hat{x}_{i-\tau_1}, \hat{y}_{i-\tau_2}\right)}{p\left(\hat{x}_i \mid \hat{x}_{i-\tau_1}\right)}$$

H Dickten & KL, Phys Rev E 90, 062796,2014

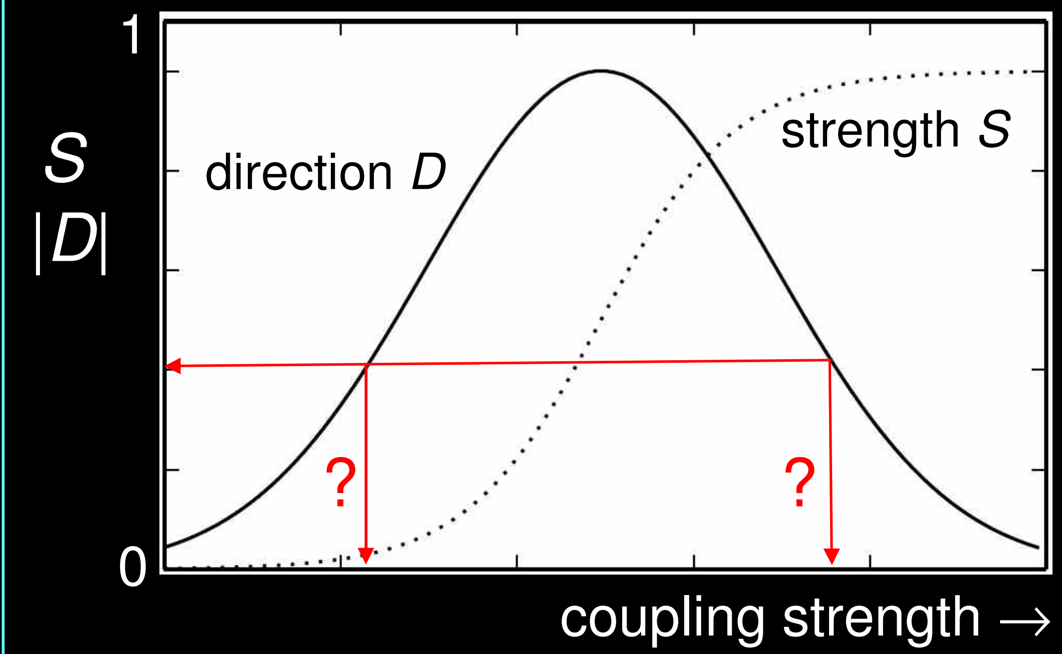
Delayed Directed Couplings



- 36 h iEEG recording, patient with right MTLE
- averaged delayed symbolic transfer entropy
- driving post. MTL -> ant. MTL
- delay times: ~ 50 - 60 ms

H Dickten & KL, Phys Rev E 90, 062796,2014

Assessing Directional Couplings



influencing factors:

- system properties
  intrinsic frequencies,
  noise distributions,
  dimensionalities,..

- time scales / number of data points

- uncoupled vs. fully coupled

- bias due to time series analysis techniques

evaluate both
strength ***and*** direction

Osterhage et al., Phys Rev E 77, 011914, 2008; KL & H. Dickten, Phil Trans Roy Soc A 373, 20140094, 2015

Conclusions

- inferring couplings and directionality remains notoriously difficult
- impact of influencing factors often poorly understood
- other potential confounders?

- networks
  application to all pairwise interactions justified ?
  true multivariate approaches rare….. reliable ?
  …..other? …. wide applicability not yet shown

- network physiology
  different systems with different properties
  interactions poorly understood
  requires matching of (vastly different) time scales