CONNECTIVITY ANALYSIS BASED ON HIGH DENSITY EEG RECORDINGS: APPLICATION TO MOTOR AND COGNITIVE TASKS IN HUMANS

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Introduction

The aim of this presentation is show and critically discuss some typical situations in EEG based connectivity studies, with caveat related to possible pitfalls and some practical suggestions for the application of Granger-based estimators.

I will show some examples of applications providing insights into the neural mechanisms at the basis of cognitive functions, their modifications resulting from different pathological conditions and their reorganization due to a specific treatment or to spontaneous recovery (cortical plasticity)

Outline of the presentation

1. How to treat EEG data in connectivity studies: source space or sensors space
2. Importance of preprocessing
3. Data interpretation: contrasting networks
4. Data interpretation: graph theoretical approach
5. Stationary and non stationary data
6. Bivariate Vs multivariate approach
7. Implications of the statistical assessment
8. Applications, future perspectives

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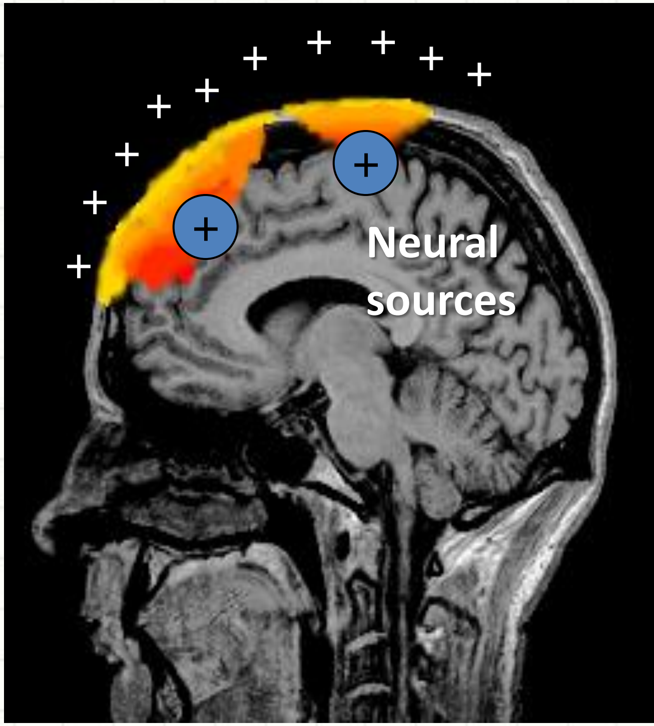
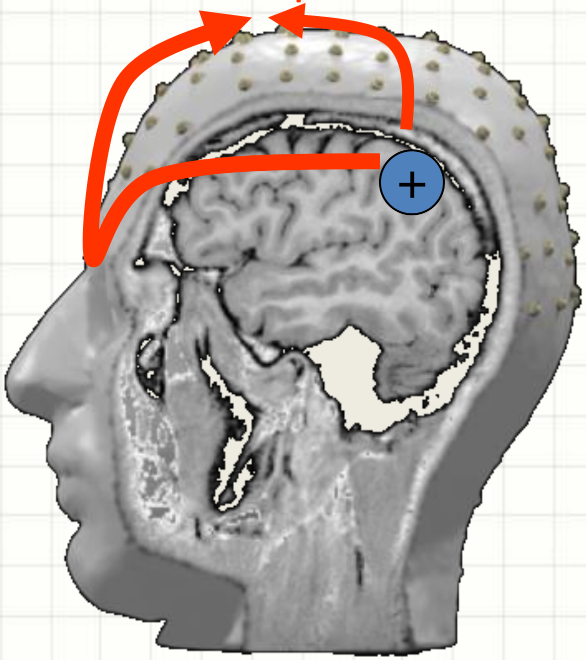
Spatial blur of the EEG

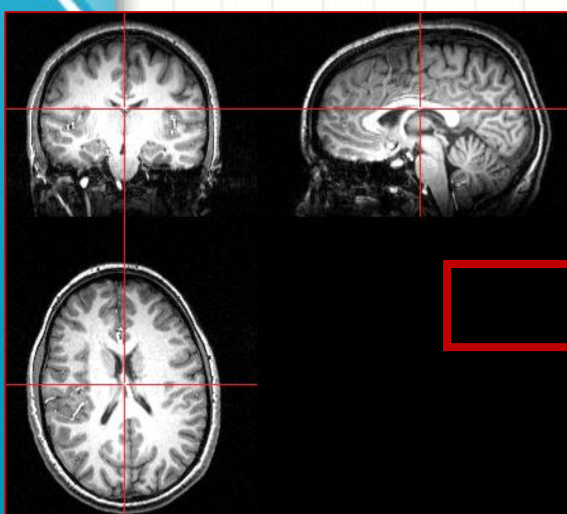
- An accurate modelling of the structures allows to treat efficiently the problems of standard EEG
- Poorly conductive skull spatially blurs scalp potentials

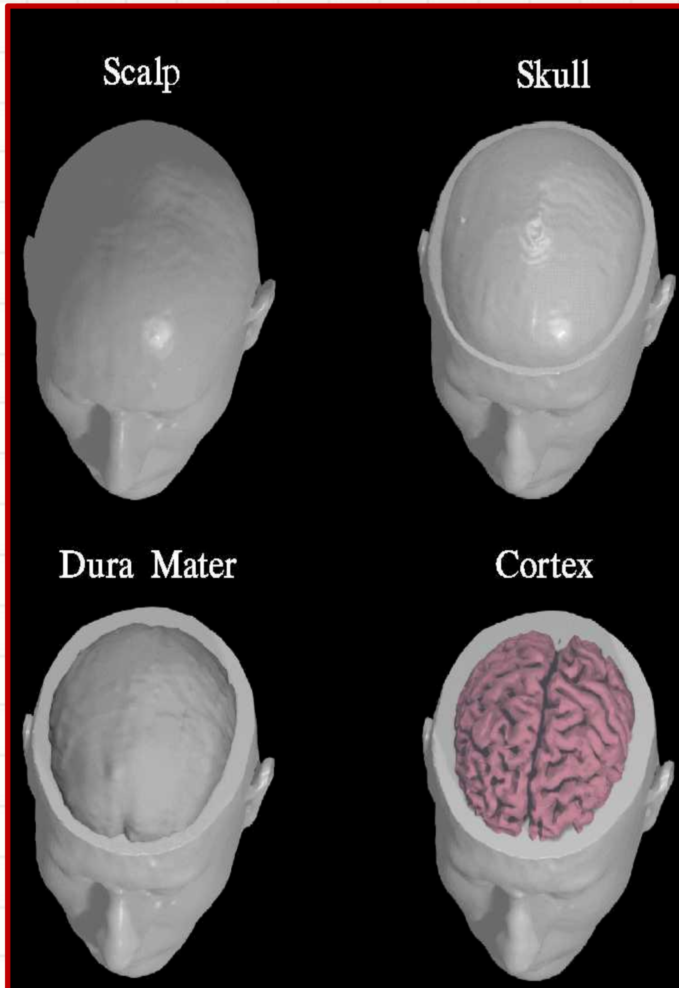


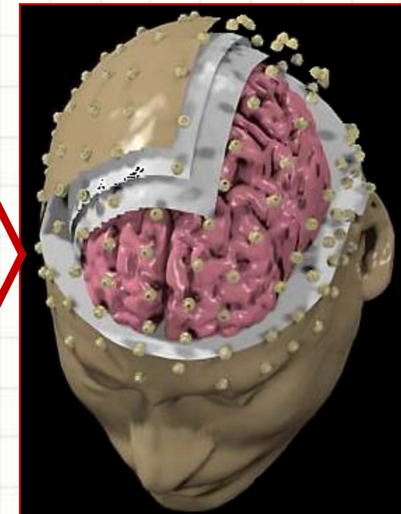
- Electrical reference depresses near sources



Steps to improve the spatial resolution of the linear inverse estimation

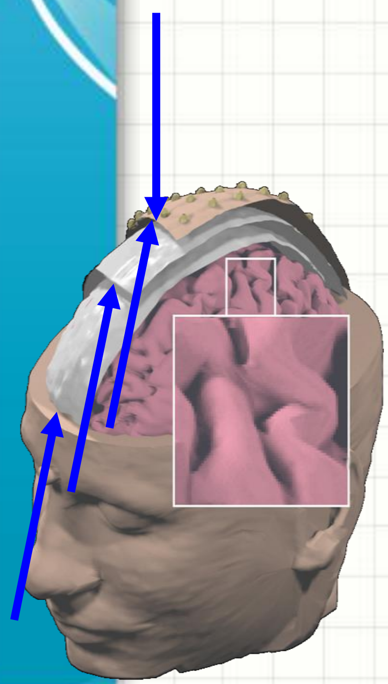


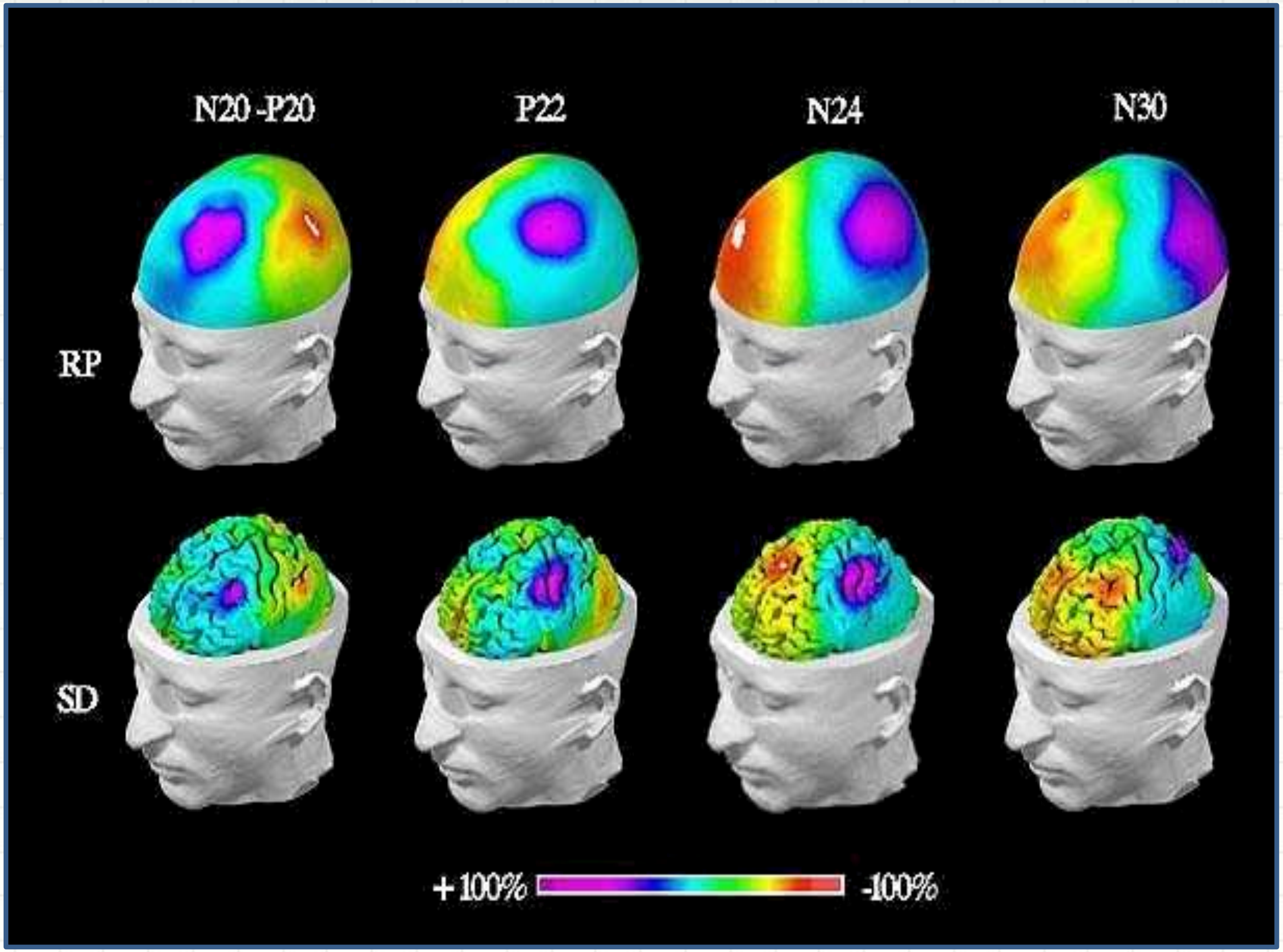




Insertion of the geometry of scalp, skull and dura mater in the linear inverse problem

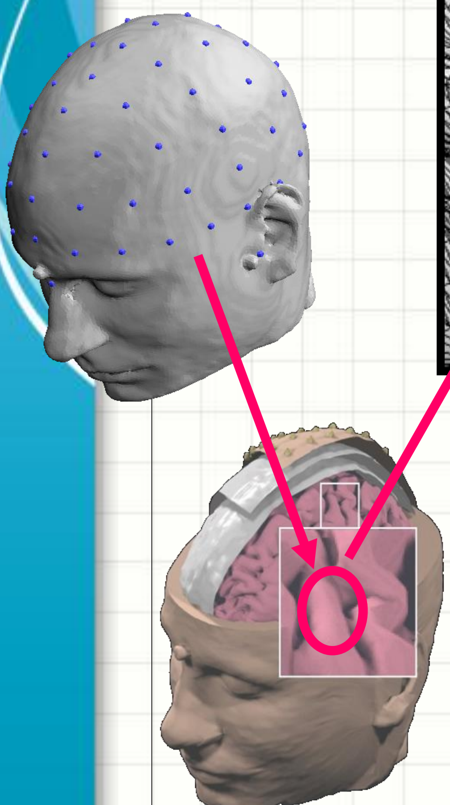
Steps to improve the spatial details of recorded EEG Data



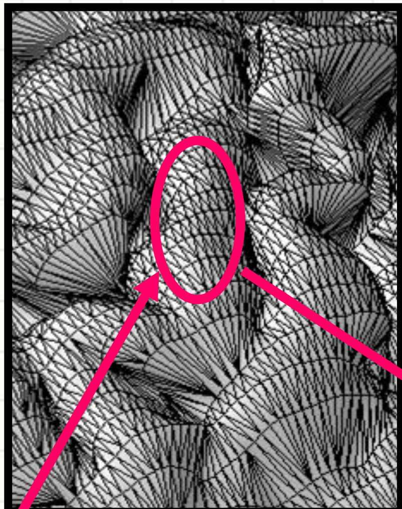


From scalp to cortical signals in ROIs

Scalp EEG

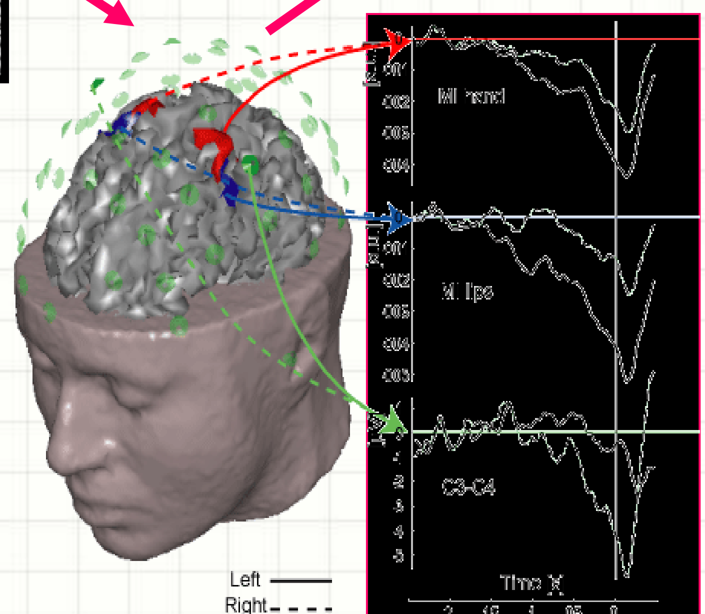


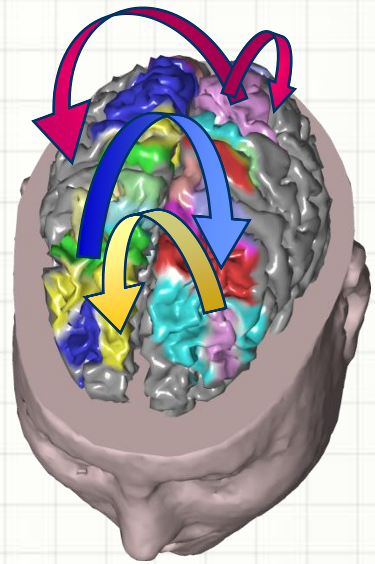
"Virtual" electrode



M1 Hand area ROI

Linear inverse estimates within a ROI are collapsed (mean)





Cortical connectivity patterns between ROIs

Caveat

- All procedures that alter the correlation between data can result in false positives or false negatives
- Instantaneous correlation should NOT affect Granger-based methods (Kaminski and Blinowska, 2014) but this is debated (Haufe et al, 2013)
- Scalp analysis is more difficult to relate to brain circuits
- In case of lesions (of the brain or of the structures of the head, e.g. for TBI) average models cannot be used
- When moving to the source space, the need for large dimensional model increases (need to include all the possible sources)

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Preprocessing for connectivity analysis needs attention

- All procedures that alter the correlation between data can result in false positives or false negatives
- Artifact correction by means of subtraction or ICA analysis can affect the data correlation
- Averaging data across dipoles/voxels can alter the signals phase
- Normalization to avoid scale difference problems (or using the right index, e.g. gPDC or iPDC)

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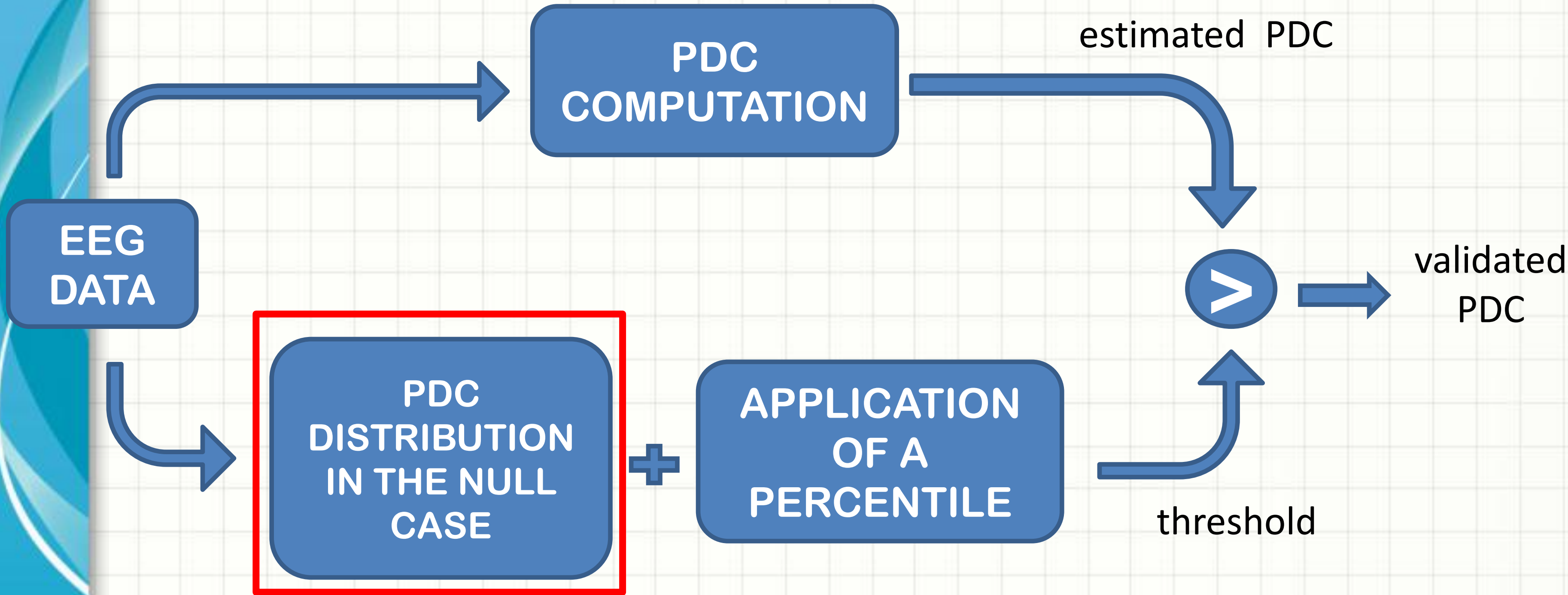
Statistical comparison between networks

- Important for data interpretation
- Comparison between tasks (task-rest, task-task)
- Comparison between groups (patients- controls, different interventions, …)
- Evaluations of significant changes in time for a single subject (patients clinical conditions, recovery…)

Validation against the null case



Surrogate Distribution (shuffling procedure)

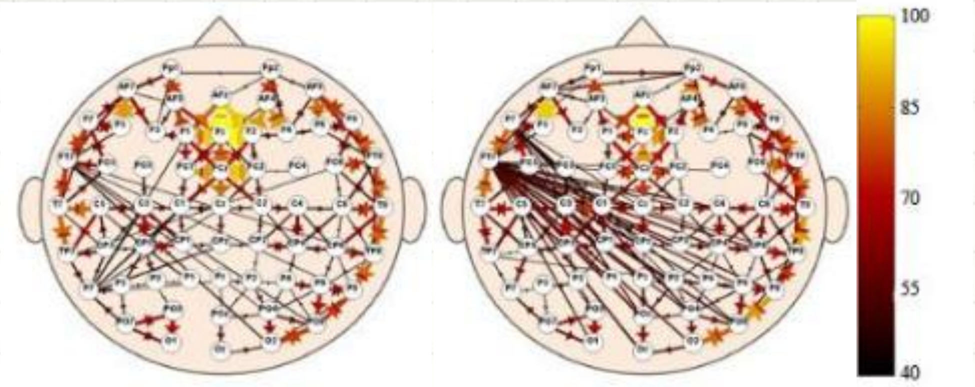
- PDC-null case distribution built by iterating PDC estimation on surrogate data-sets obtained randomly shuffling the phases of considered data. (Theiler 1992, Faes et al, 2008, 2010)

Asymptotic Statistic

- PDC in the null case tends to a χ^2 distribution (Takahashi et al. 2007);

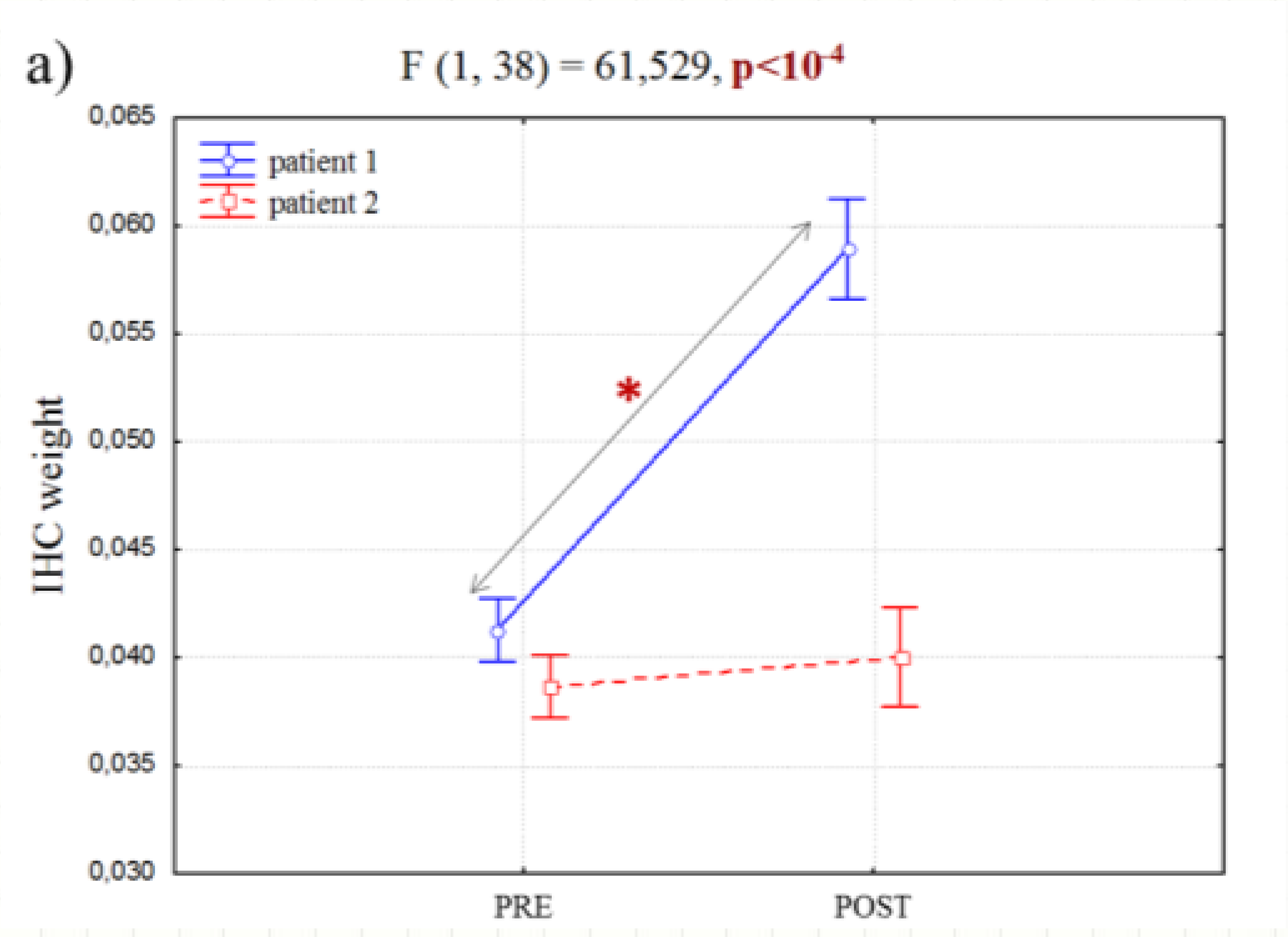
Comparison between different conditions

- Two possible approaches:
  - Distribution of the baseline condition, Z-score task-baseline
  - Distribution in each condition through a resampling approach
- Comparison between different times, tasks, ….
- No need to build a homogeneous group (patients)



Single subject assessment

- Group analysis on the basis of individual indices



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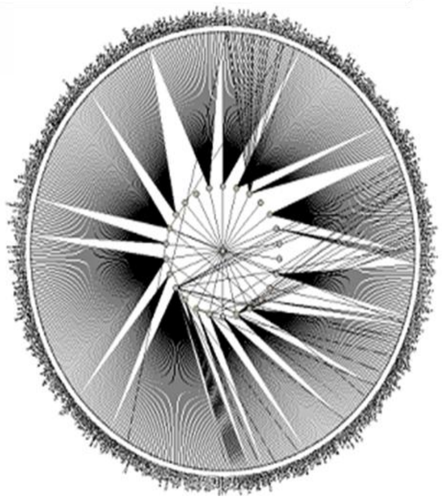
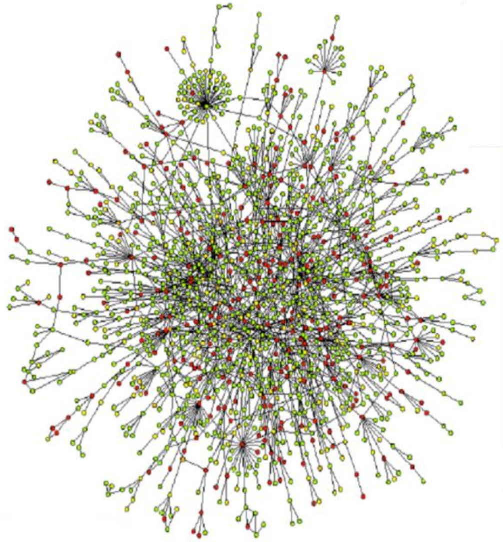
Graph Theory

- A graph is a mathematical model that represents the interactions within a network.
- It is composed of nodes and connections



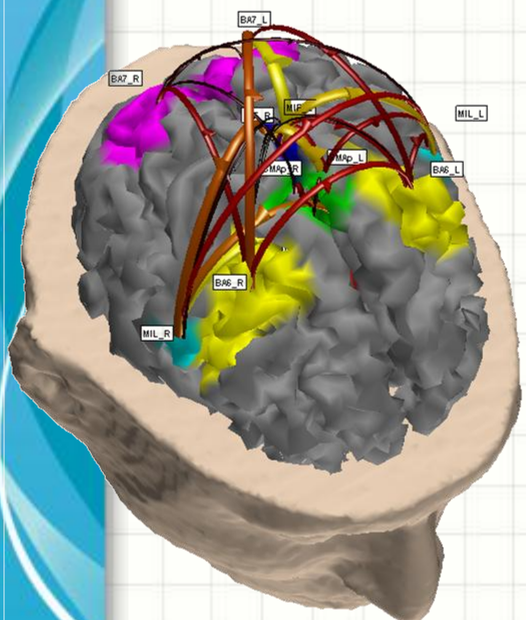
Social (Newman, 2000)

World Wide Web

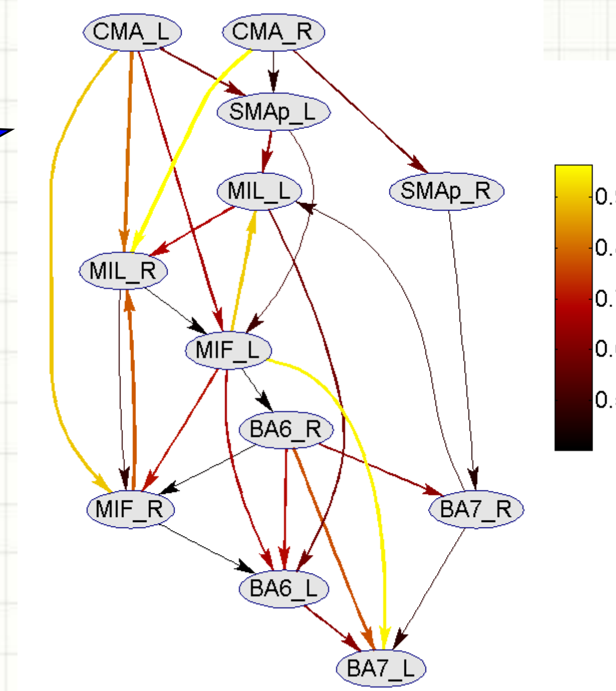


Proteomics (Jeong, 2001)

It is possibile to associate a network to a connectivity pattern by means of the connection matrix *A:*

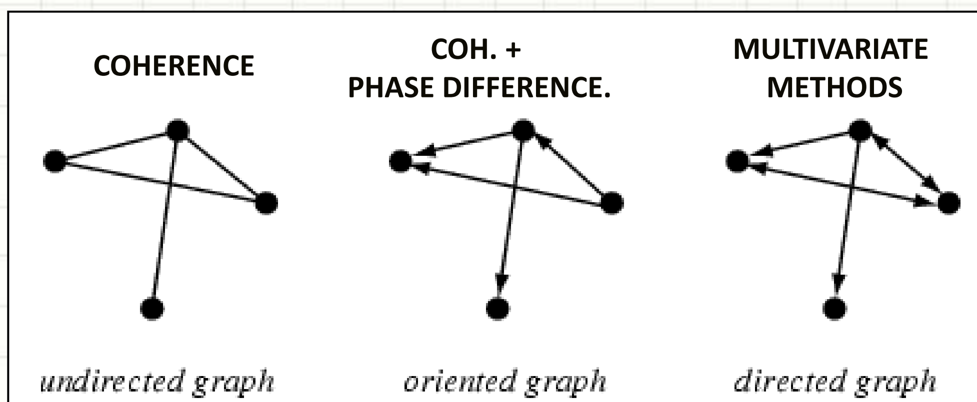


$$A = \begin{pmatrix} 0 & 0 & 0 & 0 & 0{,}6 & \dots \\ 0 & 0 & 0 & 0 & 0{,}5 & \dots \\ 0 & 0 & 0 & 0 & 0 & \dots \\ 0 & 0 & 0{,}7 & 0 & 0 & \dots \\ 0 & 0 & 0 & 0 & 0 & \dots \\ \dots & \dots & \dots & \dots & \dots & \dots \end{pmatrix}$$



A graph is a mathematical model that represents the interactions within the network

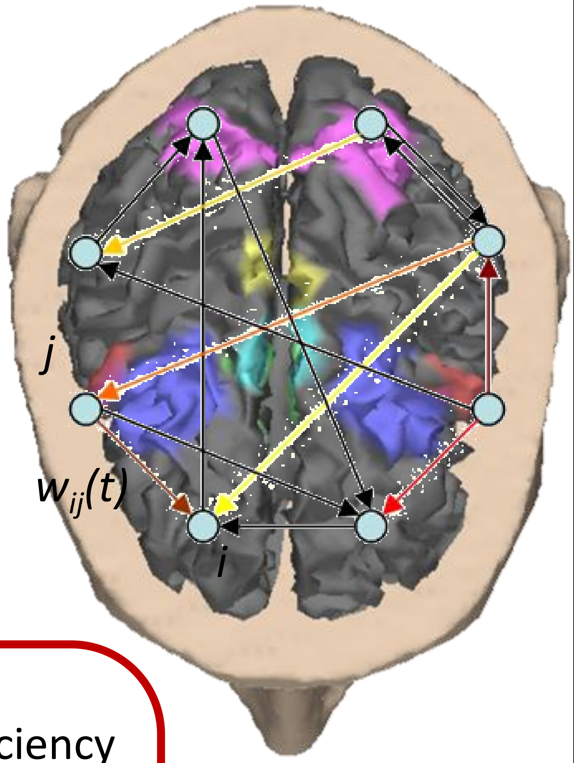
It is composed by
-Nodes (ROIs,Electrodes)
-Edges (Information flows)



LOCAL INDICES

$$s_{in}(i,t) = \sum_{j \in V} w_{ij}(t)$$ In-strength

$$s_{out}(i,t) = \sum_{j \in V} w_{ji}(t)$$ Out-strength



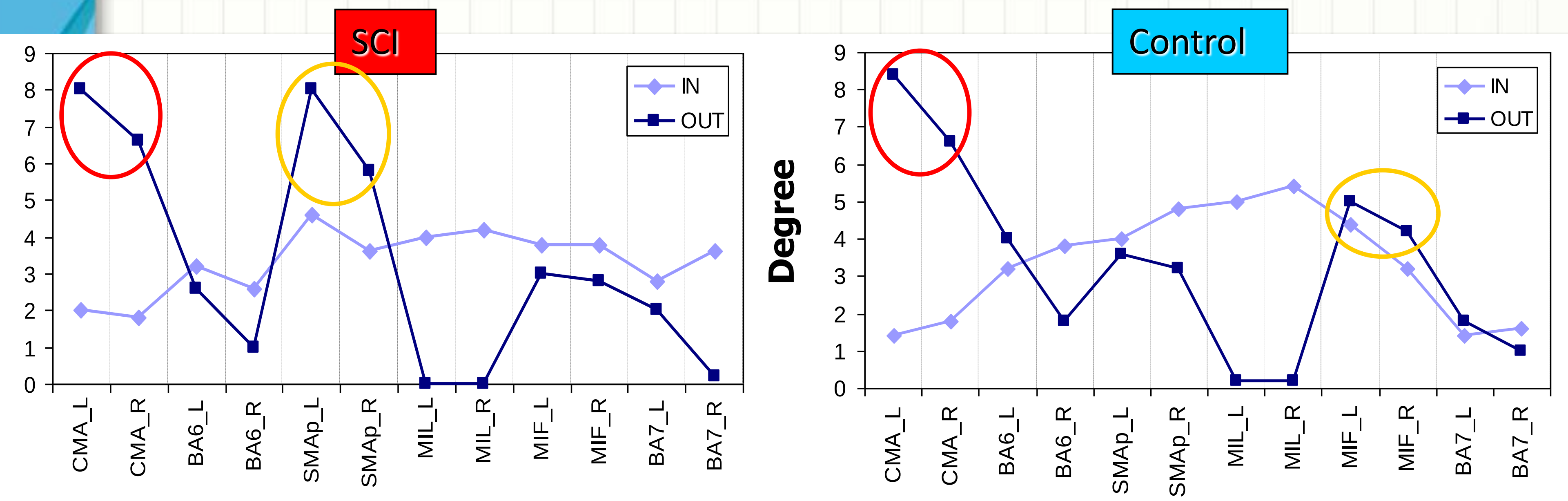
$$E_{glob}(A,t) = \frac{1}{N(N-1)} \sum_{i \neq j \in V} \frac{1}{d_{i,j}(t)}$$ Global efficiency

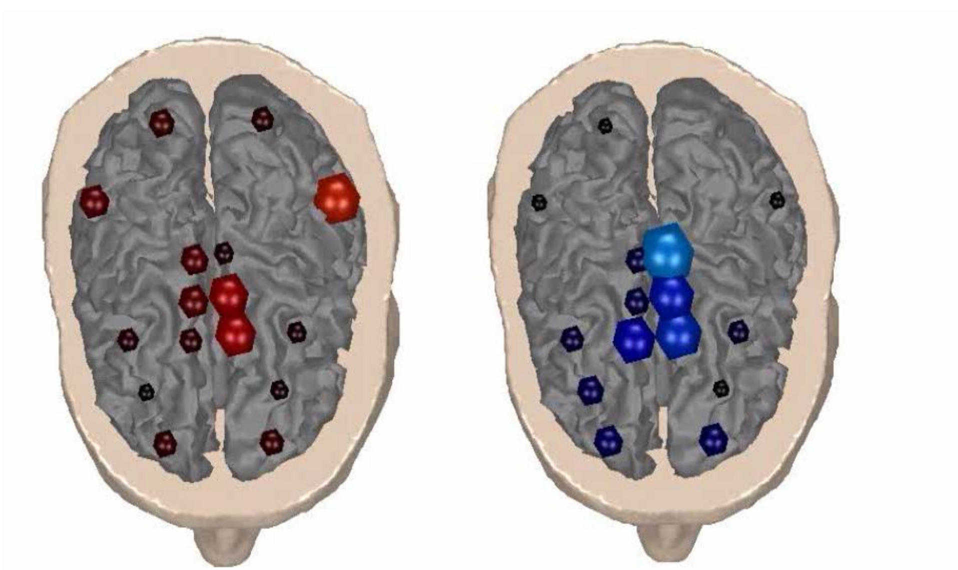
$d_{ij}(t) = 1 / w_{i,j}(t)$

$$E_{loc}(A,t) = \frac{1}{N} \sum_{i \in V} E_{glob}[A_i(t)]$$ Local Efficiency

GLOBAL INDICES

Average Graph Indexes





DEGREES:
total number of connections incoming (indegree) to a vertex or outgoing (outdegree) from the same vertex, respectively.

De Vico Fallani et al., HBM 2007

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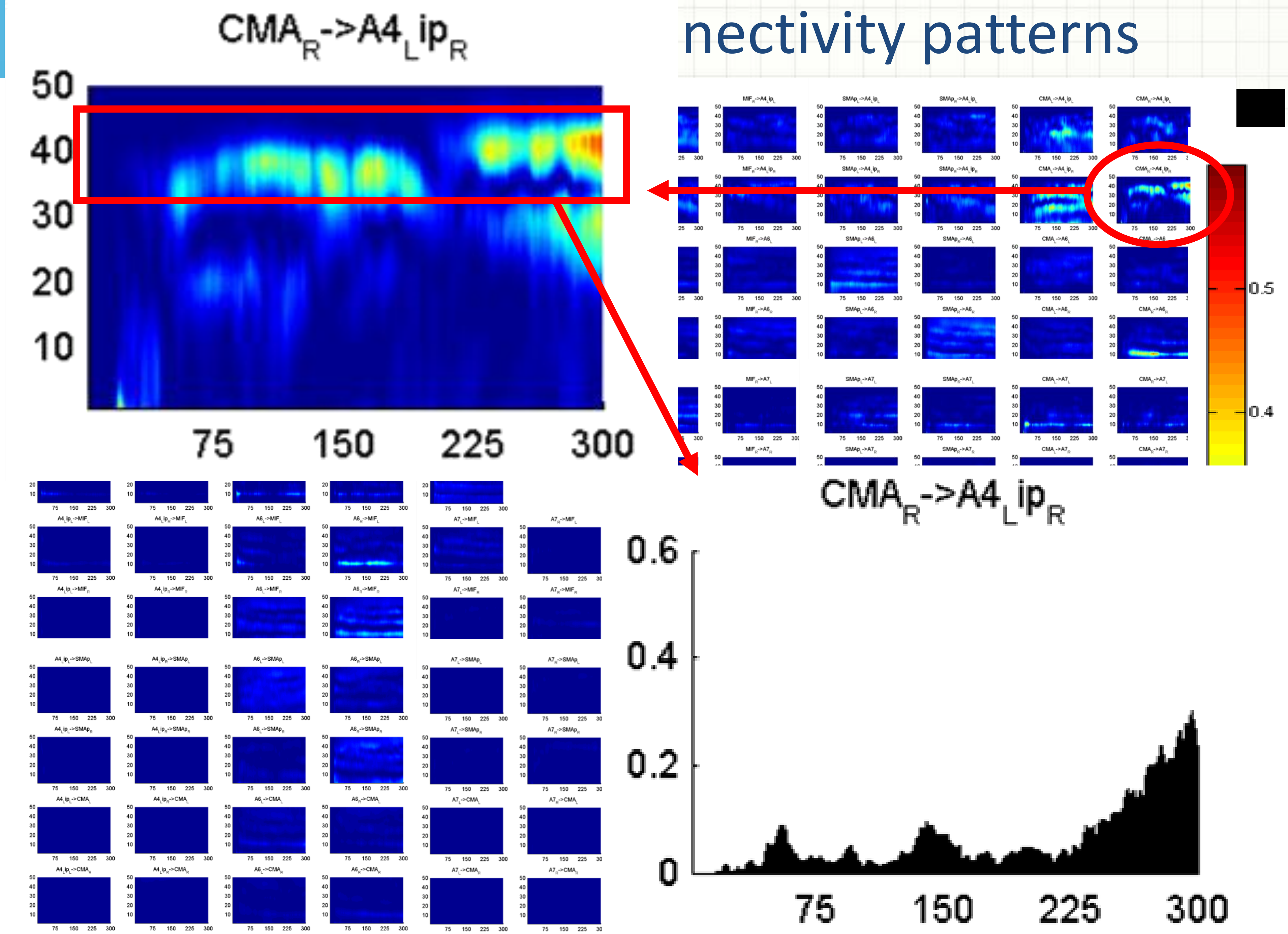
Stationarity of the data

- Not always possible
- Transients are lost
- Two possible approaches:
  - Sliding window approach (Ding et al, 2000)
  - Time-varying estimators based on an MVAR model with time-dependent parameters (adaptive fit, Recursive Least Squares with Forgetting Factor, Hesse et al, 2003; General Linear Kalman Filter, Milde et al, 2010)

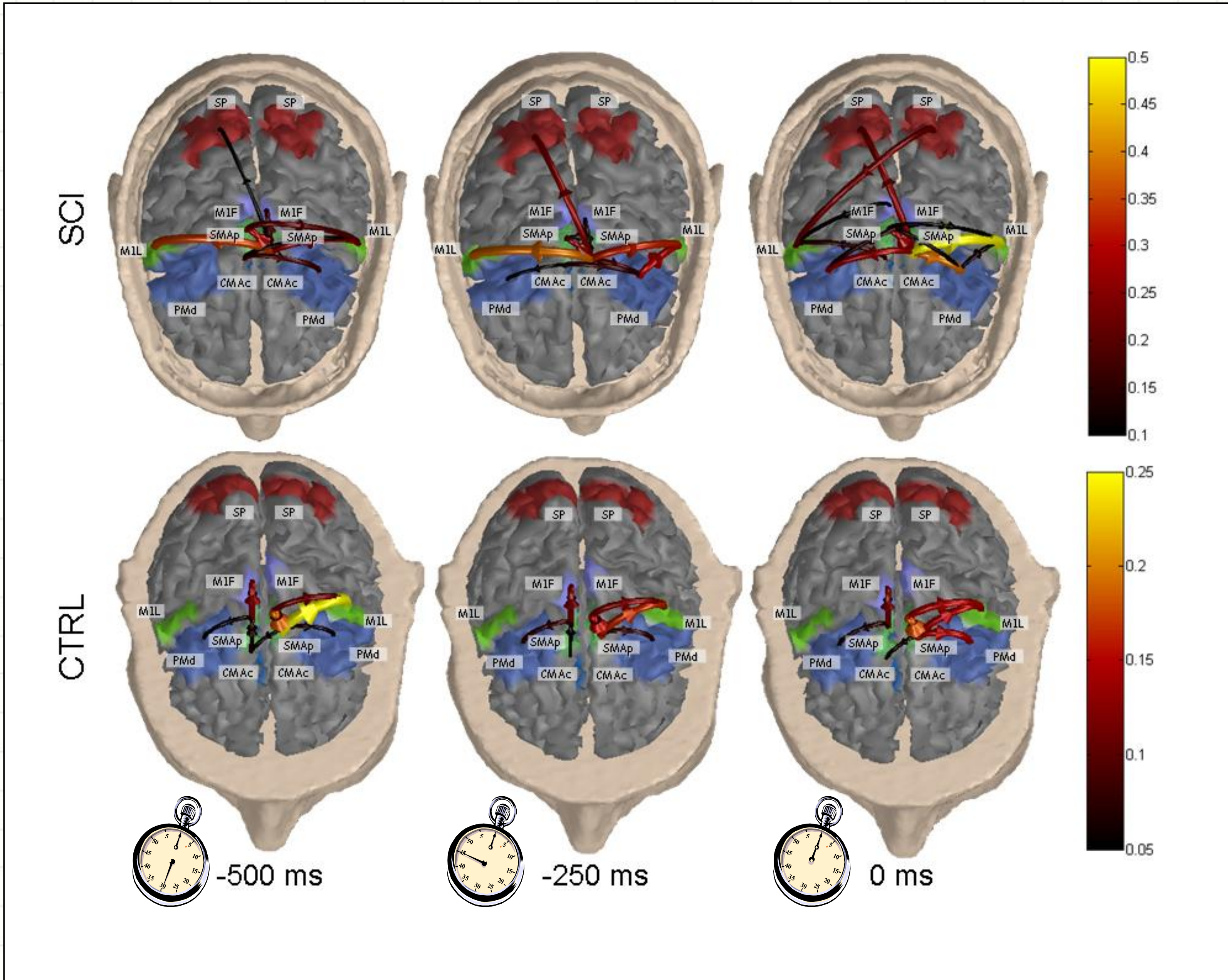
RESULT: Time-frequency distributions of Granger causality

Astolfi et al, IEEE Tr Biomed Eng, 2008

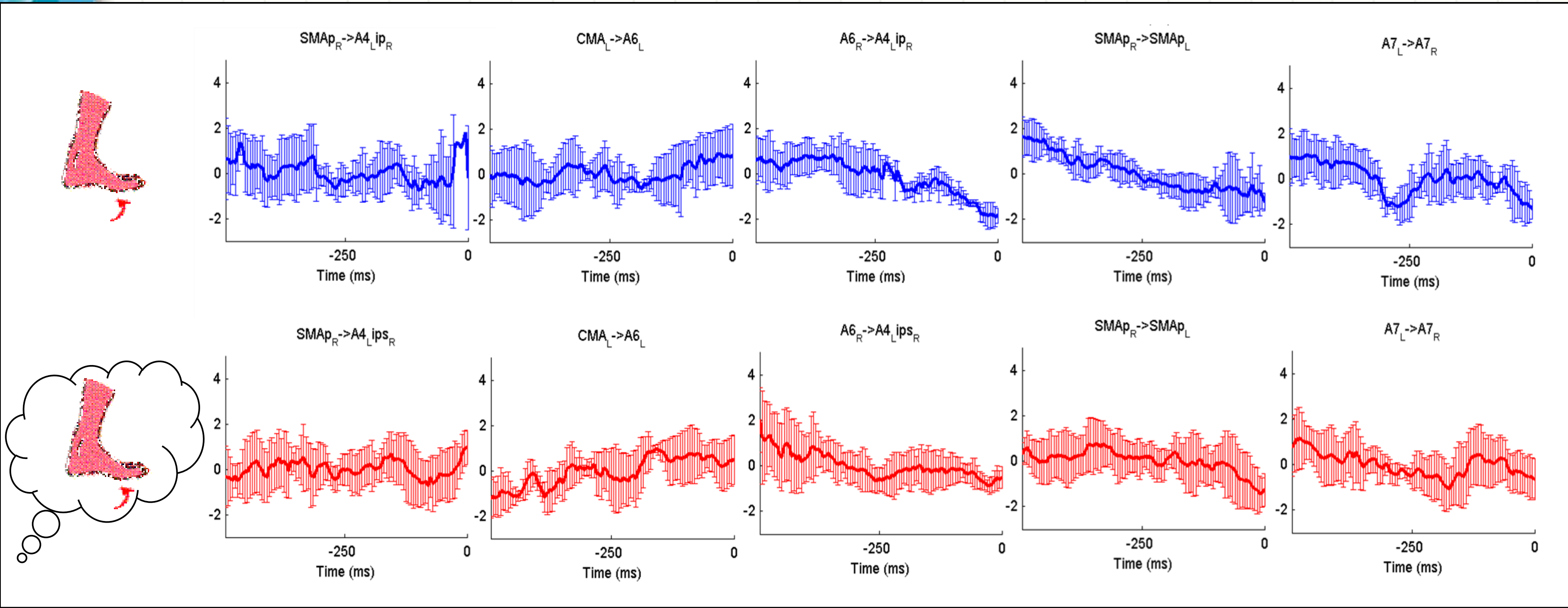
nectivity patterns



Connectivity patterns at different latencies



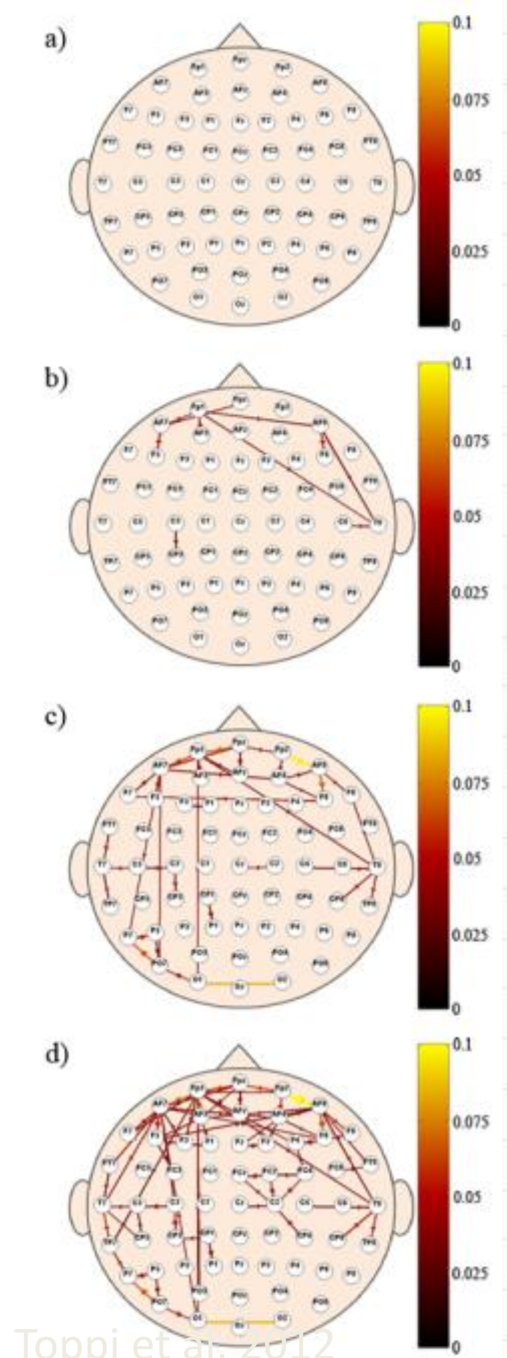
Grand average connectivity time-course



Average and standard deviation of significant connectivity links common to at least 3 of 5 subjects

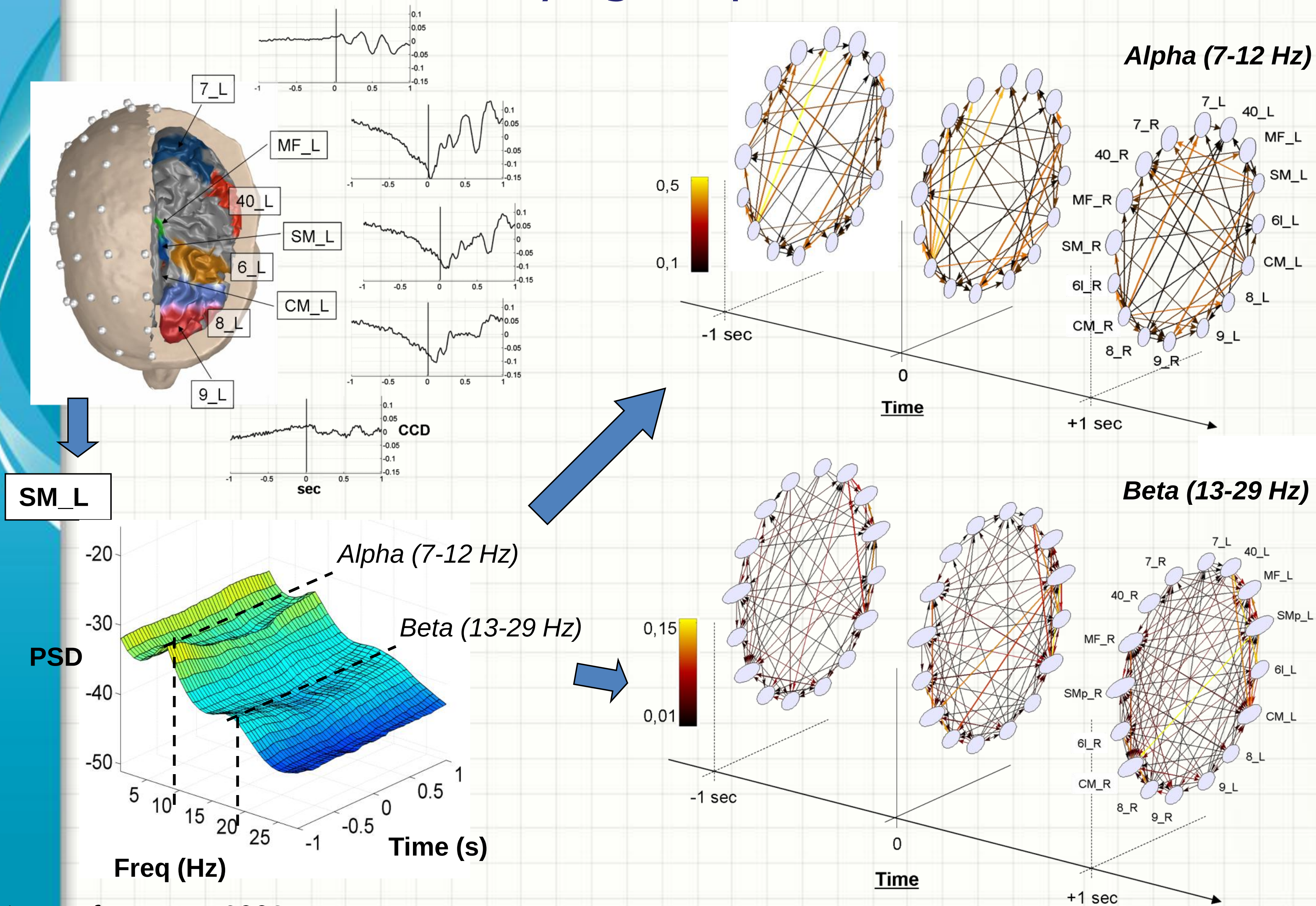
General Linerar Kalman Filter (GLKF) approach

- The GLKF approach to the estimation of adaptive MVAR was recently introduced to deal with a high number of time series in a full multivariate analysis (Milde et al, 2010)
- Simulations showed an accurate estimation of functional connectivity patterns in high dimensional models (up to 100 nodes) (Toppi et al, 2012)



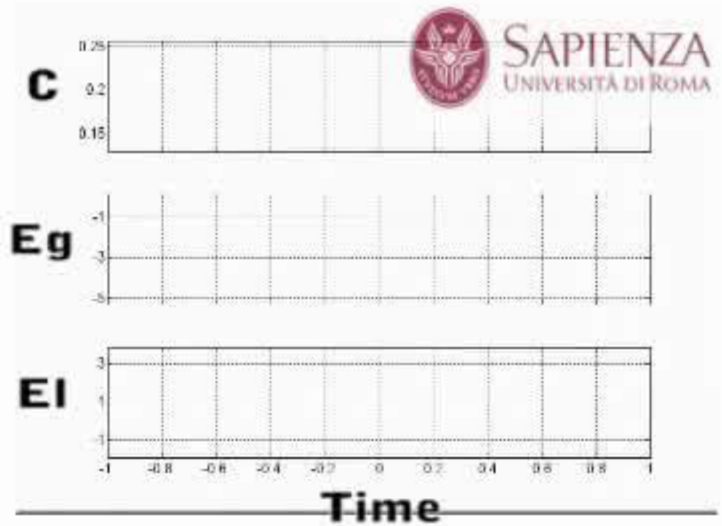
Toppi et al, 2012

Time-Varying Graph Indices

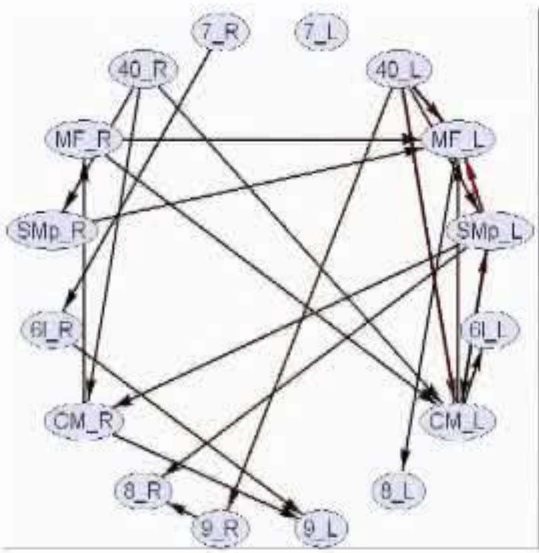


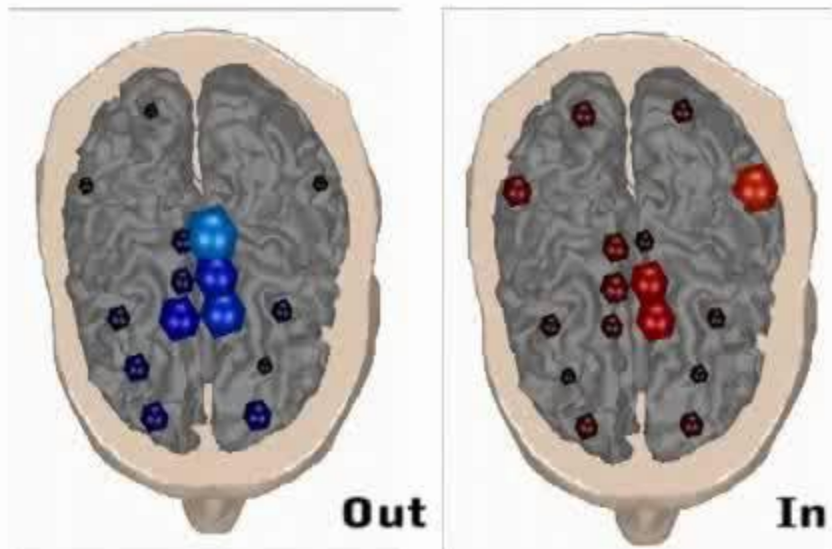
Neuroinformatics, 2008

Time-Varying Network Architecture



Cortical network





Degree

Neuroinformatics, 2008

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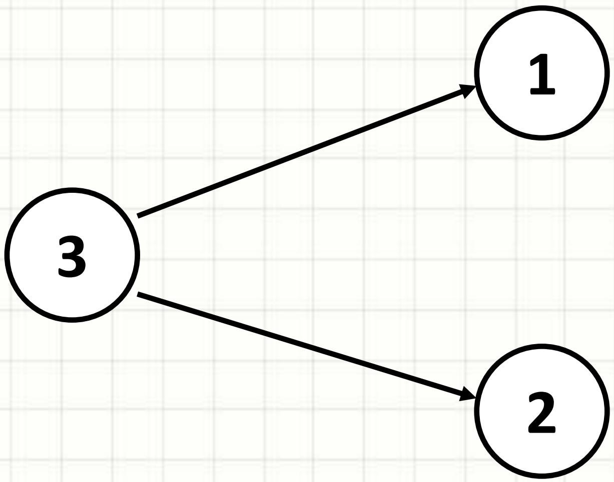
Limitations of the bivariate methods

If the sources of activities for the problem are more than 2:



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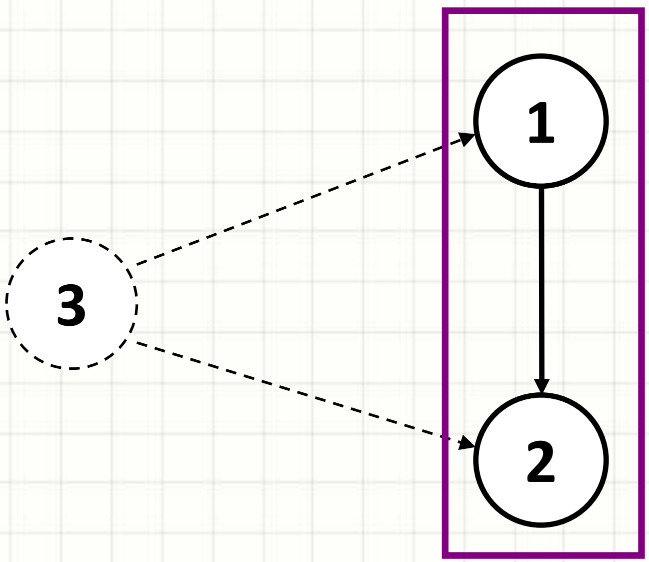
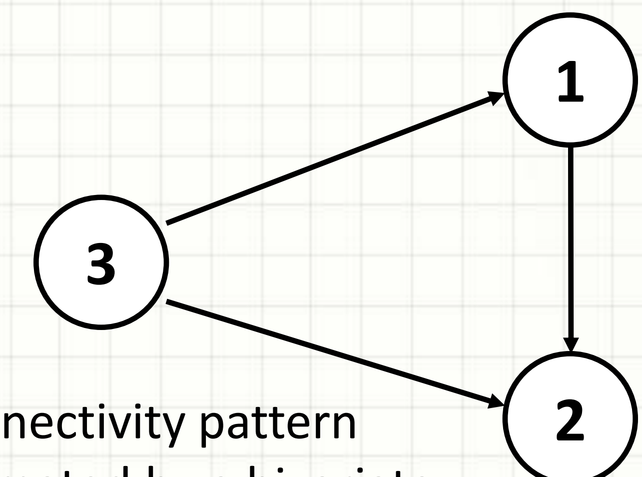
Bivariate modelization of signals 1 and 2 does not recognize that the correlation between the two signals is due to a common effect of 3 (which is not included in the model)

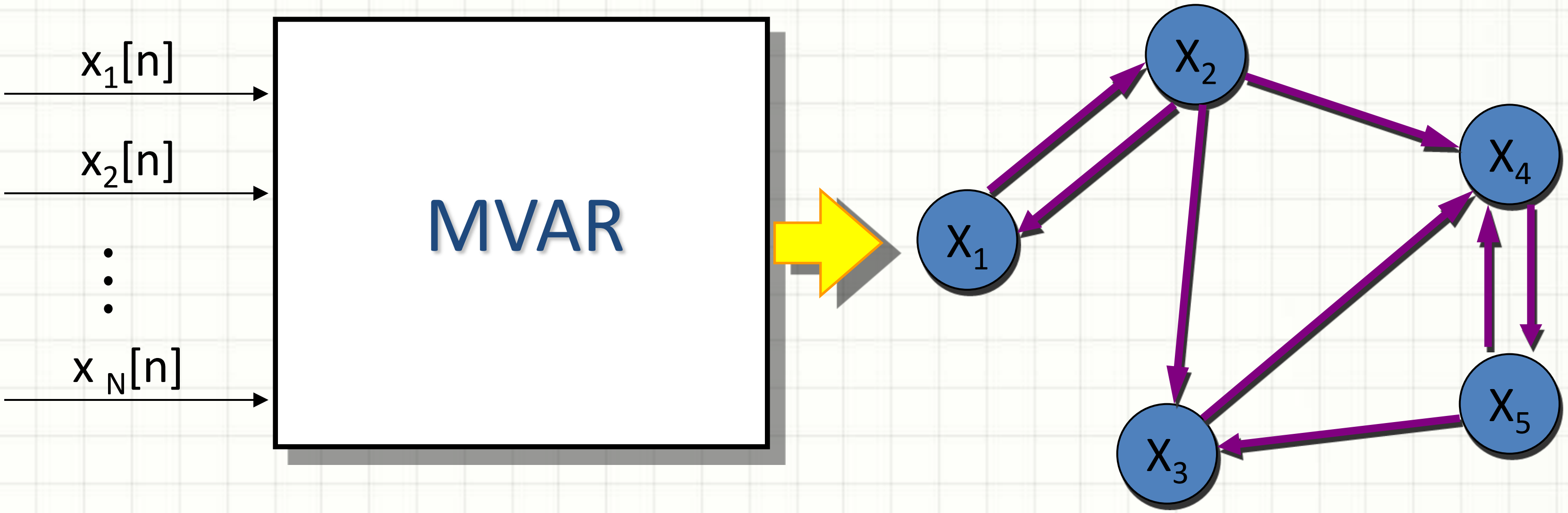




Connectivity pattern estimated by a bivariate method

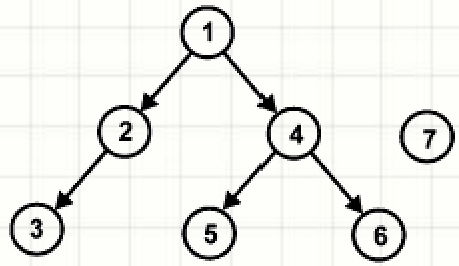
Multivariate methods

MLTIVARIATE METHODS: The connectivity pattern is obtained by a unique model estimated on the entire set of data and takes into account all their interactons



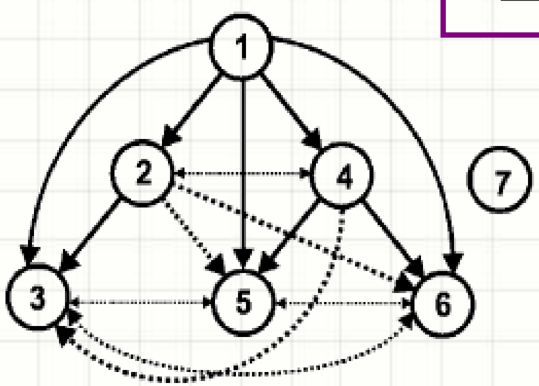
A comparison of bivariate vs multivariate methods

Imposed model (correct)

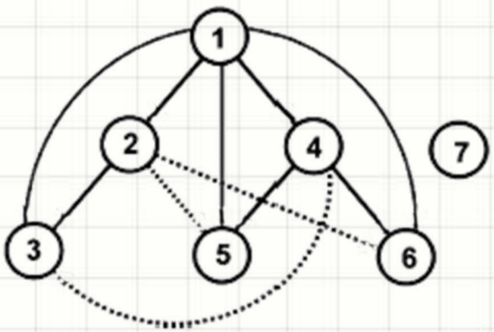


From: Kus R, Kaminski M, Blinowska KJ, Determination of EEG activity propagation: pair-wise versus multichannel estimate. *IEEE Trans Biomed Eng*, 2004.

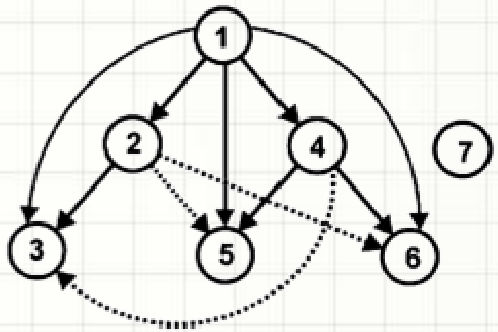
Estimated patterns



Granger causality test



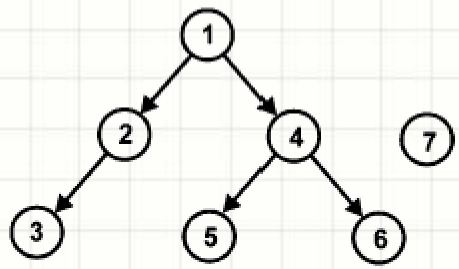
Ordinary Coherence



Directed Coherence

A comparison of bivariate vs multivariate methods

Imposed model (correct)



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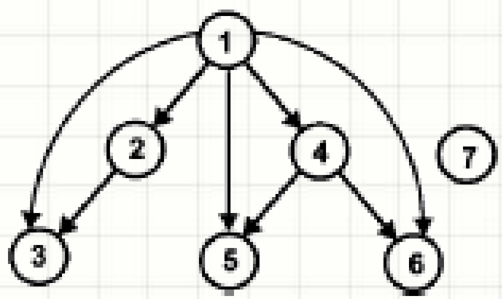
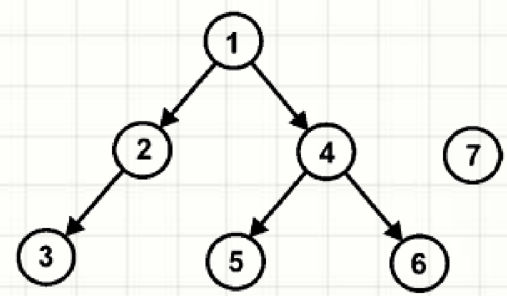
Estimated patterns



Directed Transfer Function



Partial Directed Coherence

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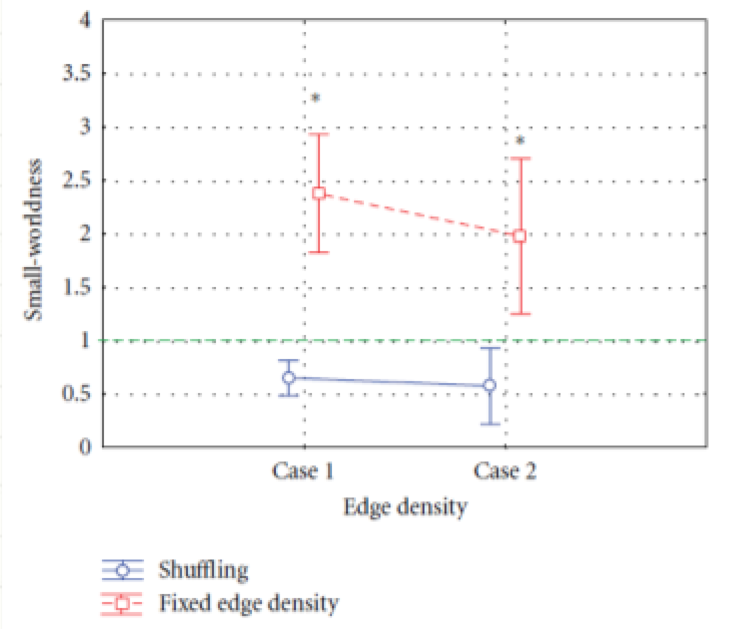
Implications of statistical assessment



- The lack of a validation procedure can lead to erroneously derive properties of the networks even in random, uncorrelated data (Toppi et al, 2012)

Caveat with graph analysis interpretation

- The lack of an appropriate validation procedure can lead to erroneously derive properties of the networks even in random, uncorrelated data
- A bivariate approach can induce false positives and affect the networks general and local properties (Efficiencies, degrees,….)

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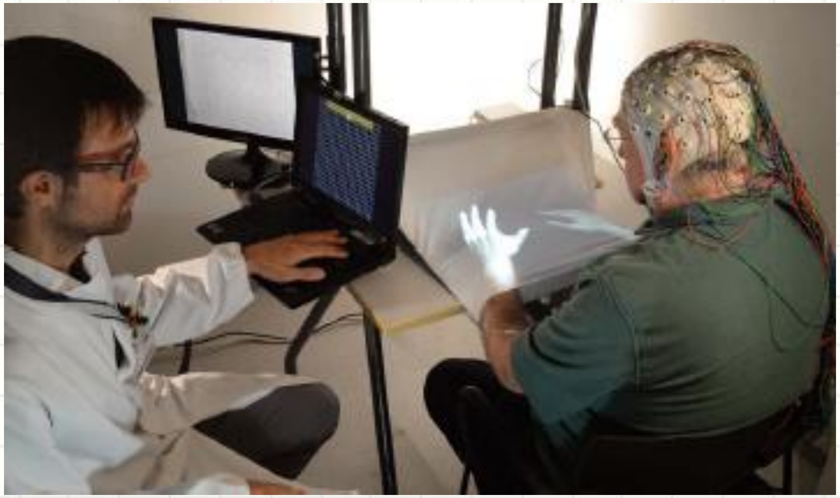
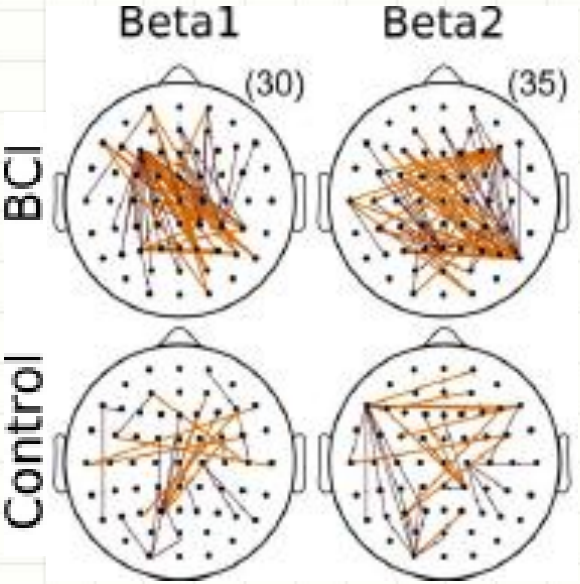
1. Evaluation of a BCI-based motor rehabilitation after stroke

Pichiorri et al, Annals of Neurology, 2015



BCI-supported motor imagery training of the upper limb (28 post-stroke patients)

Better functional outcome in the BCI group (relevant increase in the FMA score)



Post-Pre training connectivity contrast

Inter-hemispheric connectivity significantly increases after the training (only for BCI group)

2. Assessment of cognitive functions and their recovery in post-stroke patients

CONTRAST EU project - The objective is to define stable, reliable EEG-based descriptors of the brain networks underlying memory tasks able to:

1. characterize the cortical reorganization subtending improvements in the task execution

2. support the neuropsychological assessment in evaluating the efficacy of a memory training directly in the brain

3. be sensitive to different outcomes of the rehabilitative intervention

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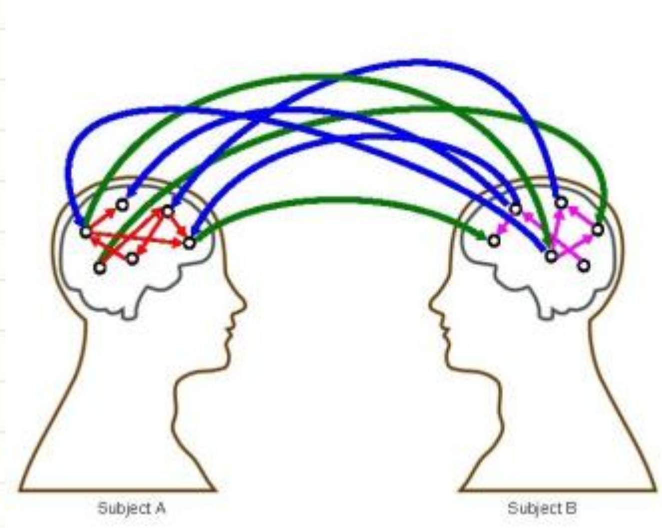
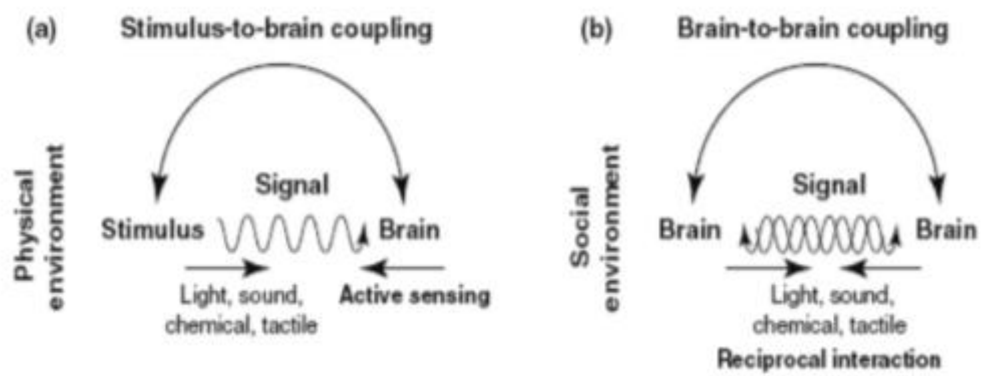
3- Multi-subjects recordings during social interaction

- A complex system behavior (group) cannot be fully understood by analyzing its single elements (single subjects): we need to study their interaction



- People act differently according to the person(s) they are interacting with, and this must be reflected by their brain activity

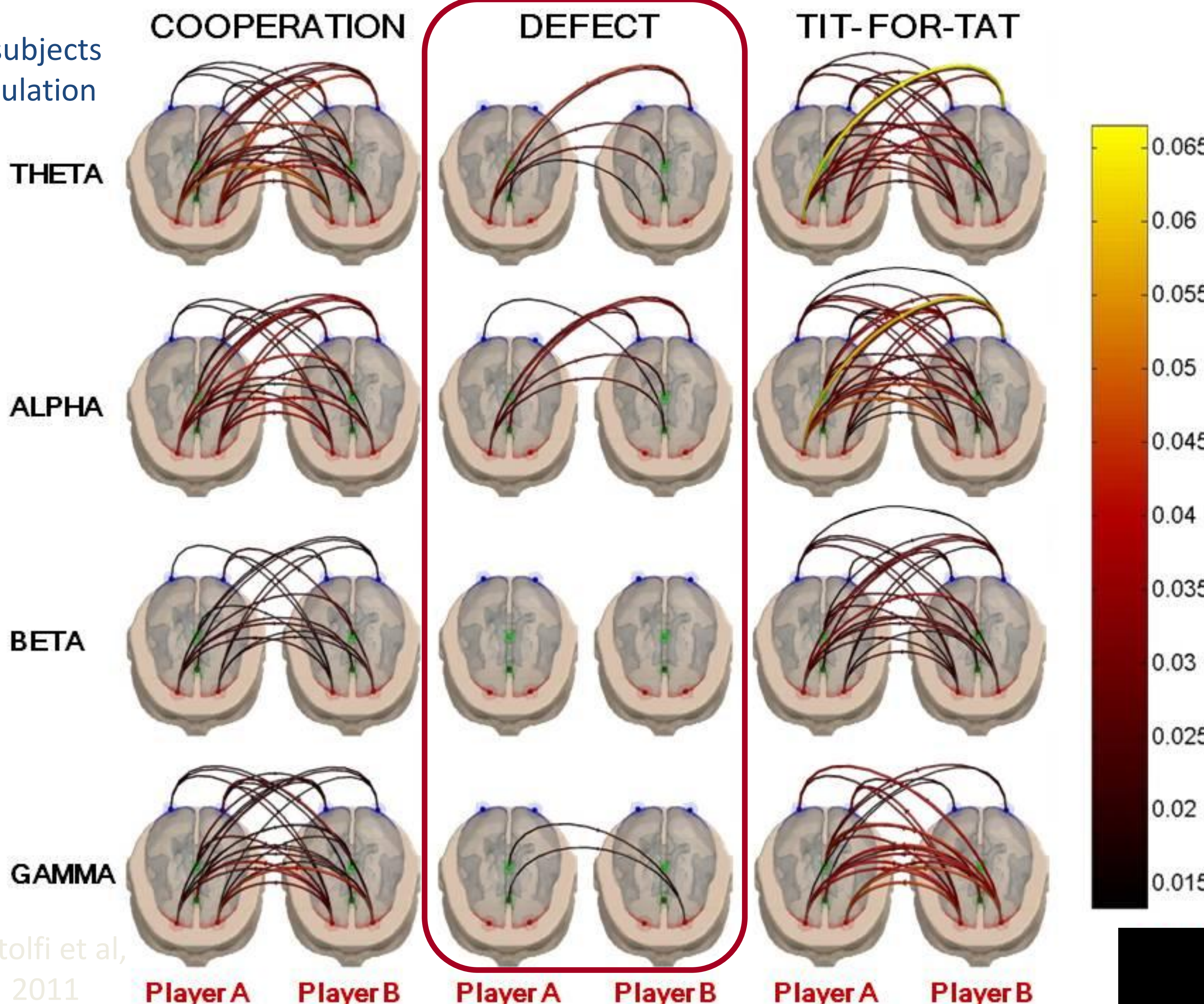
- The task-related activity in the brain of one subject needs
  to be related to the one of the other subject(s) he/she is interacting with



Brain-to-brain coupling constrains and shapes the actions of each individual in a social network, leading to complex joint behaviors that could not have emerged in isolation.

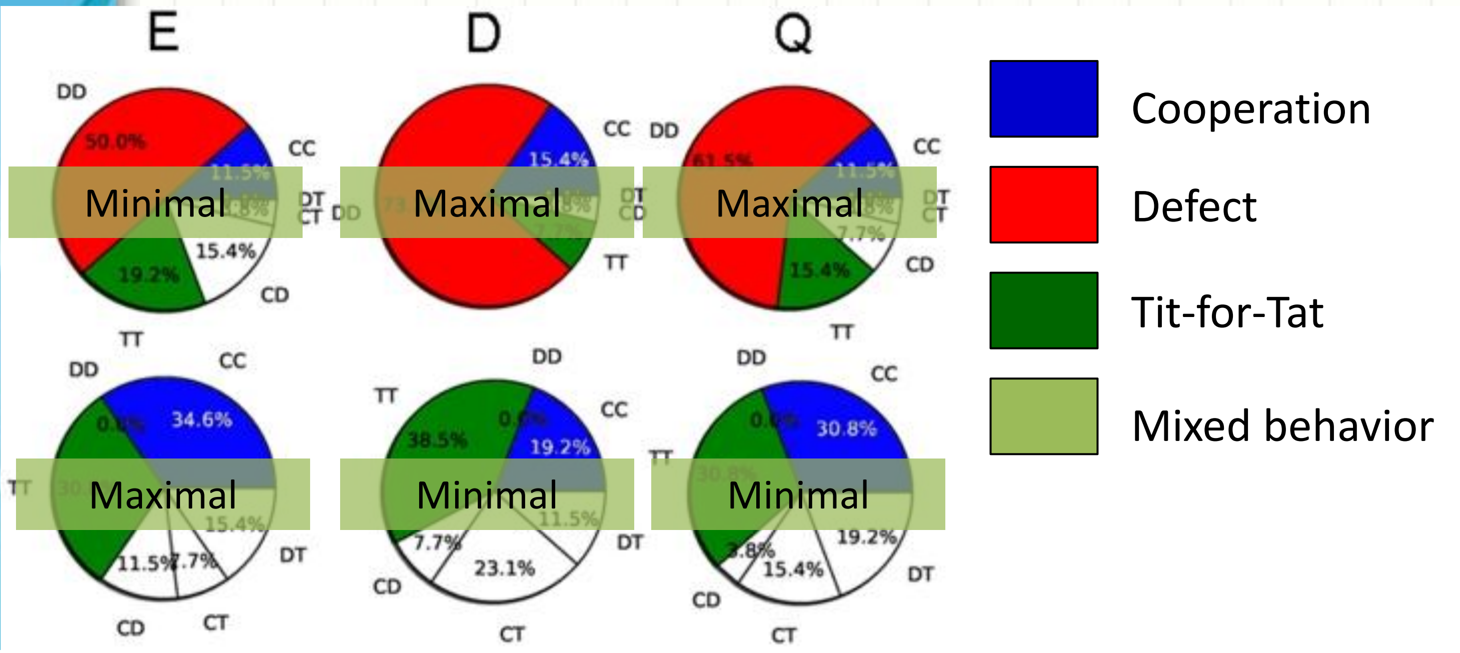
Hasson et al., Trends Cogn Sci, 2011

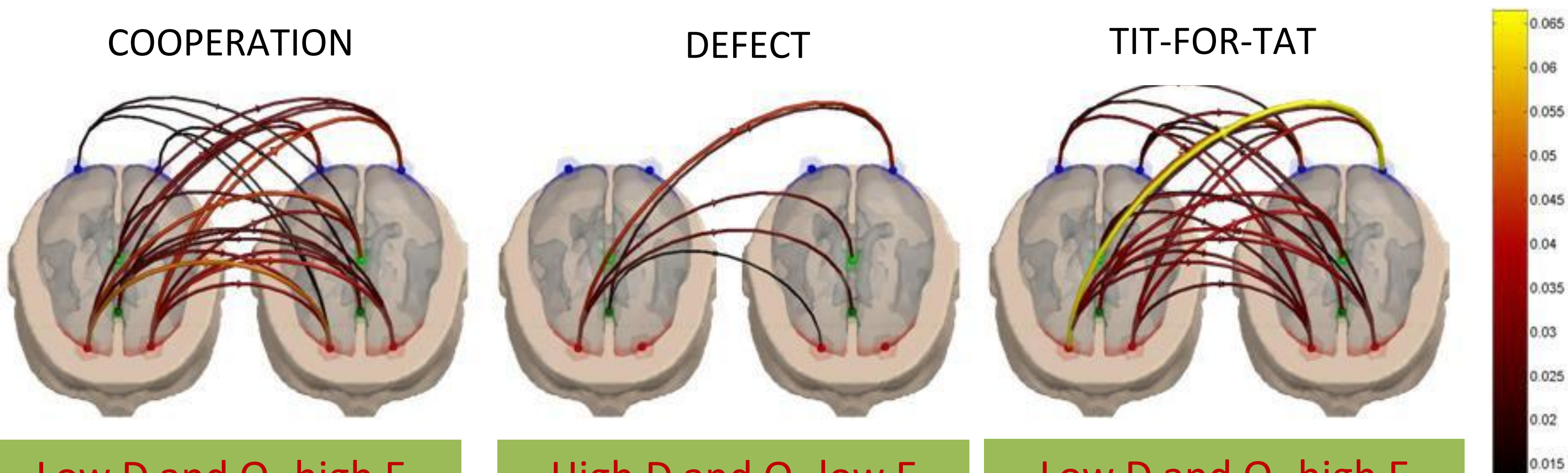
52 subjects population



Astolfi et al, 2011

Features of multi-subject connectivity patterns





Low D and Q, high E

High D and Q, low E

Low D and Q, high E

Features extraction

$$E = \frac{1}{N(N-1)} \sum_{i \neq j = 1}^{N} \frac{1}{d_{ij}}$$

Efficiency

$$D = \frac{W}{\sum w_{ij} [1 - \delta(C_i, C_j)] + k}$$

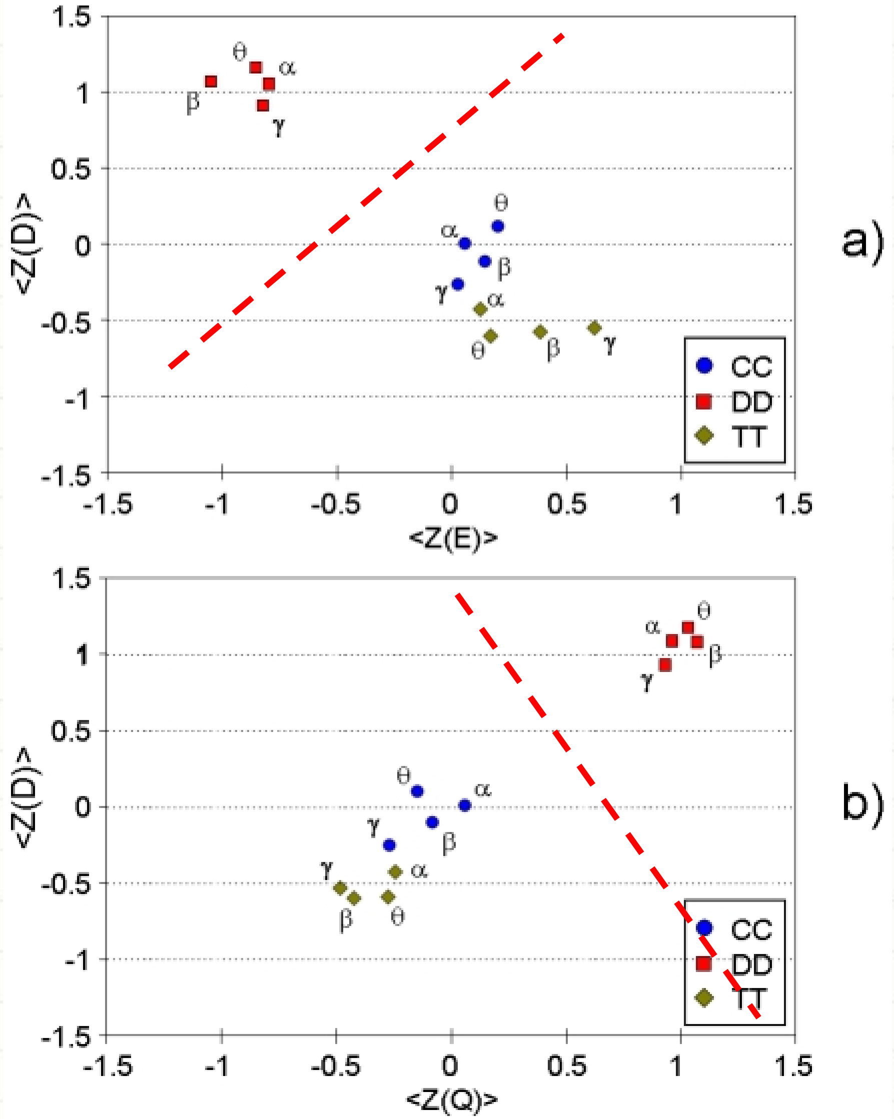
Divisibility

$$Q = \frac{1}{W} \sum_{ij} \left(w_{ij} - \frac{S_{iout} S_{jin}}{W} \right) d(C_i, C_j)$$

Modularity

Classification of connectivity patterns

- Neural network classification
- Features E, D and Q (z-score)
- Cross-validation procedure: 80% of the data for the training set and 20% for the validation set
- The accuracies obtained by the classifiers, i.e. the fraction of validation patterns correctly classified as both defectors are 91%, 73%, 88% and 80% for the Theta, Alpha, Beta and Gamma frequency bands



De Vico Fallani, Nicosia, Sinatra, Astolfi et al

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Coming soon

Minisymposium:

Advances in brain connectivity analysis: perspectives and pitfalls

Friday, 11:00-13:30, Sorcerers Apprentice 2

Invited Session:

Healthy and Altered Functional Brain Connectivity Revealed in Multimodal Data

Wednesday, 8:00-9:30, Fantasia C

Thank you for your kind attention

Questions?

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