Graph theory to explore resting state brain functional connectivity

Sophie Achard

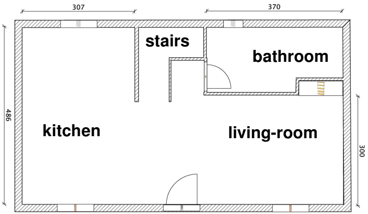
GIPSA-lab, CNRS, Univ. Grenoble Alpes

Journées Graphes et Neuroscience
Marseille
18 november 2016

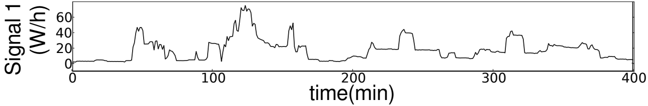
Multivariate time series structured in a network

A simple example: recording electric consumption

A simple sensor recording the overall electrivity consumption



Observed univariate time series

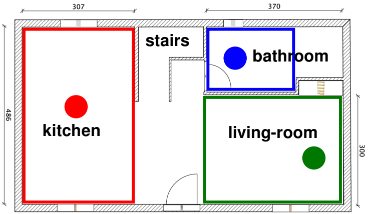


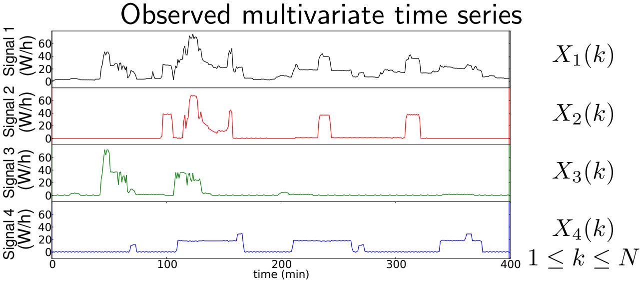
$$X(k)$$
$$1 \leq k \leq N$$

[**Harlé** *et al.* IEEE Trans. Sig. Proc. 2016]

Multivariate time series structured in a network

Multiple sensors in different places of the house

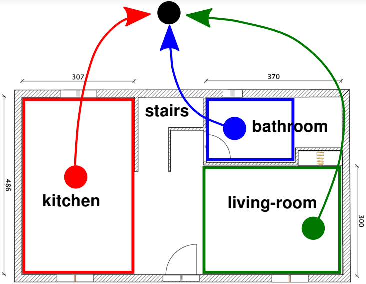




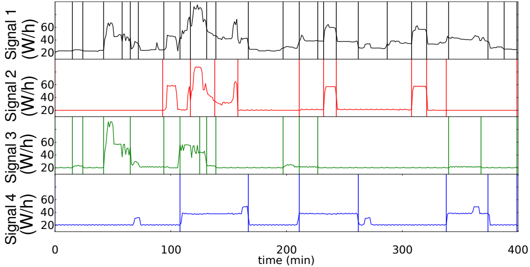
[**Harlé** *et al.* IEEE Trans. Sig. Proc. 2016]

Multivariate time series structured in a network

Multiple sensors in different places of the house with possible links



Observed multivariate time series with multiple change point detection

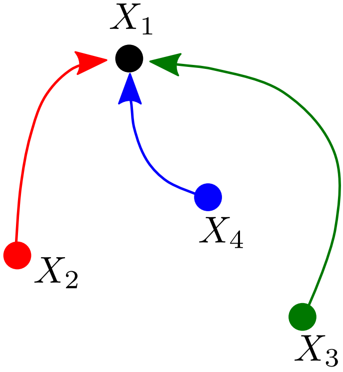


$$\begin{pmatrix} X_1(k) \\ X_2(k) \\ X_3(k) \\ X_4(k) \end{pmatrix} = \mathbf{X}(k)$$

$$1 \leq k \leq N$$

[**Harlé** *et al.* IEEE Trans. Sig. Proc. 2016]

Multivariate time series structured in a network



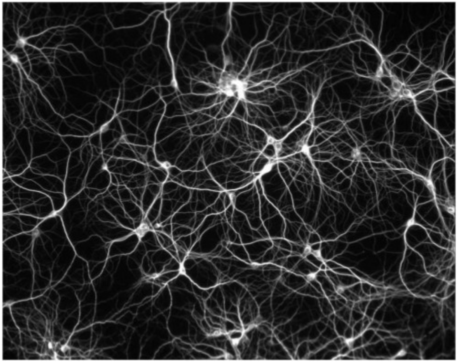
Definition of the network (or graph):

- nodes: X_1, X_2, X_3 and X_4
- edges: X_2-> X_1, X_3-> X_1, X_4-> X_1
- adjacency matrix:

$$\begin{bmatrix} 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{bmatrix}$$

[**Harlé** *et al.* IEEE Trans. Sig. Proc. 2016]

The brain as a network



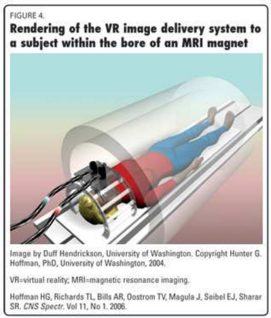
- 10^{11} neurons
- Connected via axons and dendrites (10^{14} connections)
- Transmission of nerve signals (segregated and distributed information)

Functional Magnetic Resonance Imaging – fMRI:

[Ogawa 1990, Kwong 1991]

Measure of the haemodynamic response related to neural activity in the brain.

BOLD(Blood-oxygen-level dependent)= MRI contrast of blood deoxyhemoglobin



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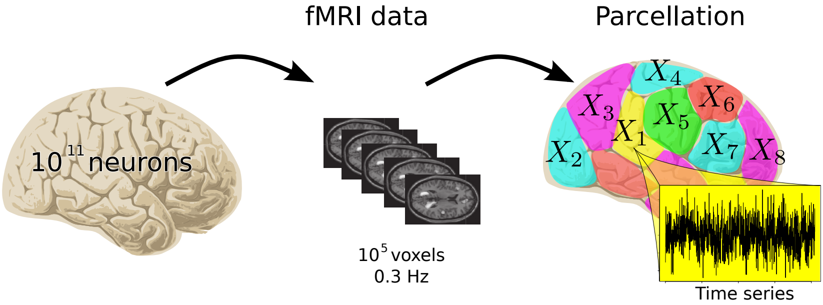
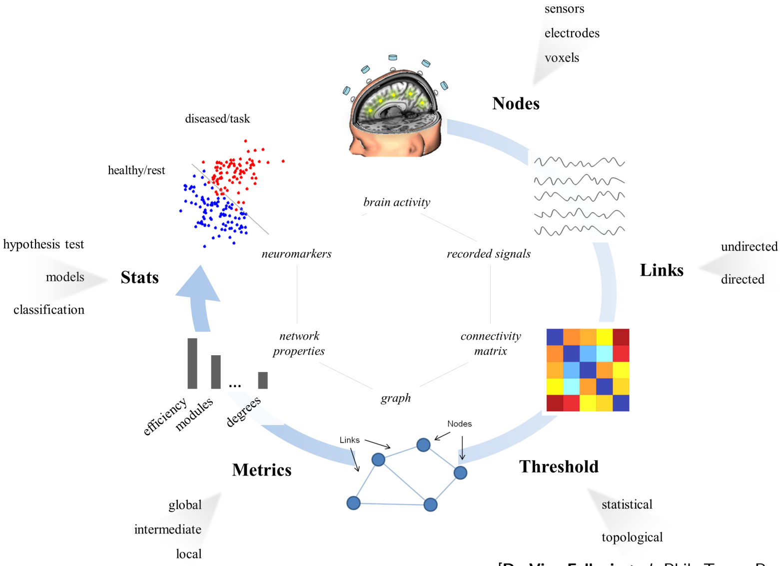
IRMaGe, GIN, UGA

Hundreds of time series corresponding to brain regions

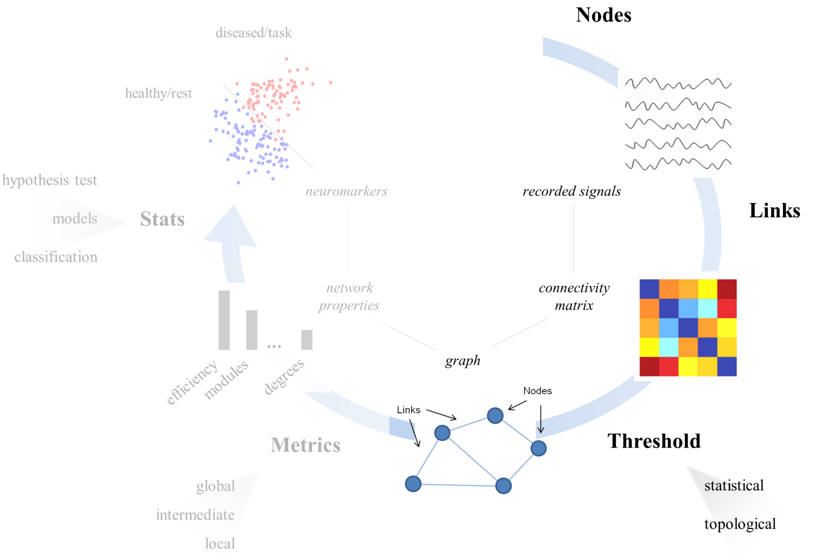


Exploring the brain using networks analysis

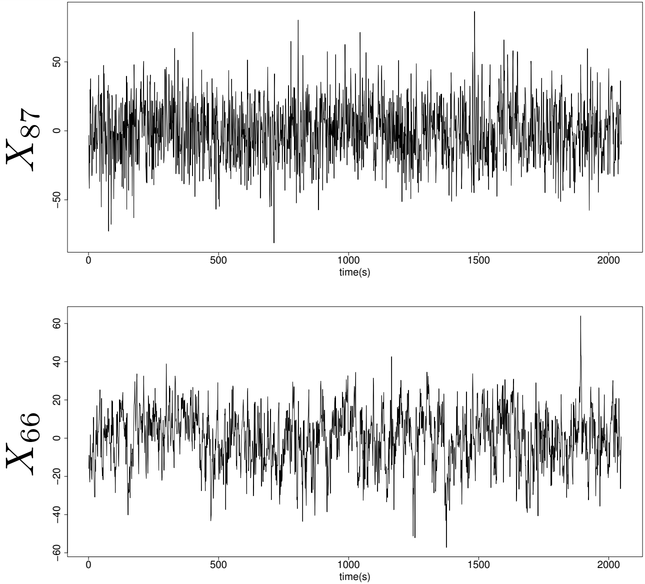


[**De Vico Fallani** *et al.* Phil. Trans. Roy. B 2014]

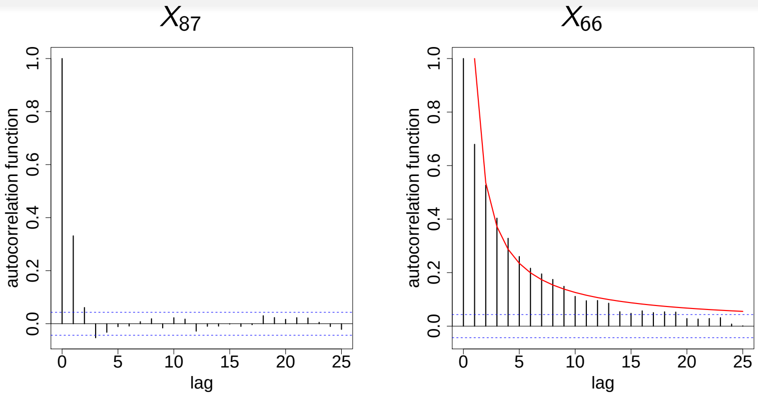
Part I: Inference of networks



Long memory property of the brain time series



Long memory property of the brain time series



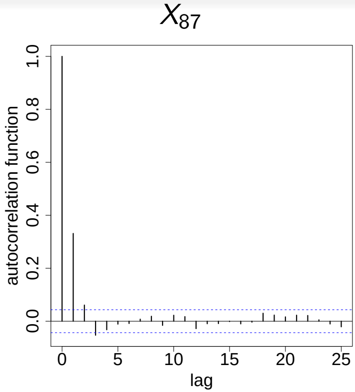
autocorrelations not summable

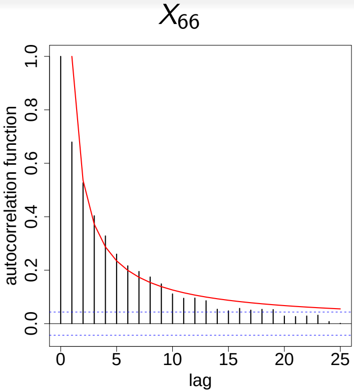
$$\rho(\lambda) = Corr(X(t+\lambda), X(t)) \sim \lambda^{2d-1}$$

Note: For an *ARMA process*,

$$|\rho(\lambda)| \leqslant b|a|^{\lambda}, \qquad 0 < b < \infty, \qquad 0 < a < 1$$

Long memory property of the brain time series





autocorrelations not summable

A simple example, $X(1), \ldots, X(N)$, random variables,

$$\widehat{X} := N^{-1} \sum_{i=1}^{N} X(i), \qquad \mathbb{V}(\widehat{X}) = \frac{\sigma^2}{N^2} \sum_{i,j=1}^{N} Corr(X(i), X(j))$$

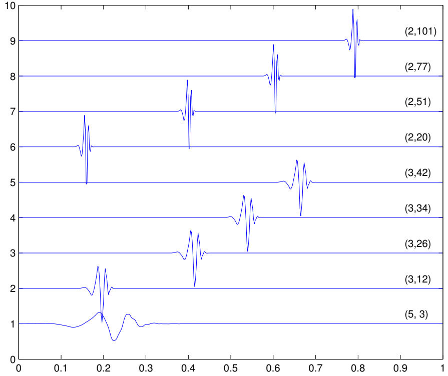
Wavelets and long memory time series

Let (ϕ, ψ) define a father and a mother wavelets

For any scale $j \geqslant 0$ and location $k \in \mathbb{Z}$ we consider the wavelet coefficient of the signals $X_\ell(\cdot)$, for $\ell = 1, \ldots, p$,

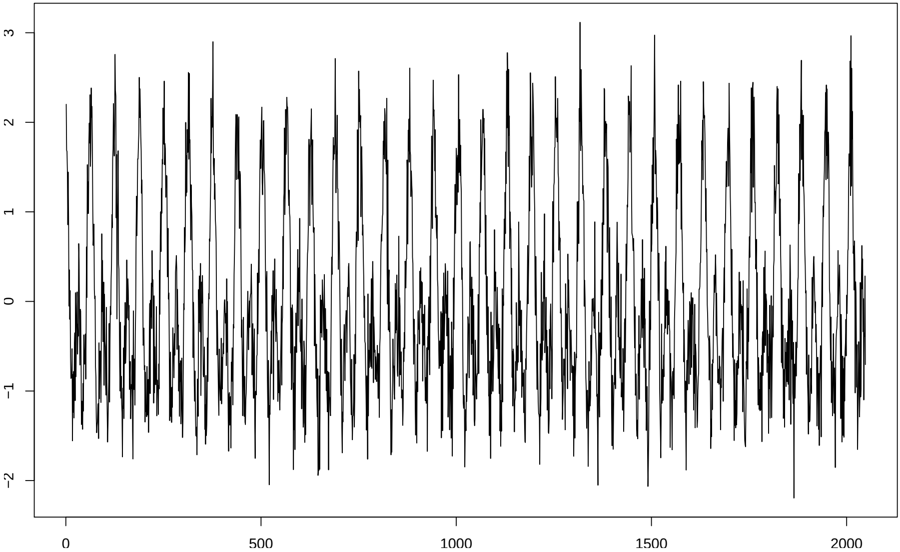
$$W_{j,k}(\ell) \approx \int X_\ell(t)\psi_{j,k}(t)dt$$

An example of ψ, Daubechies 8

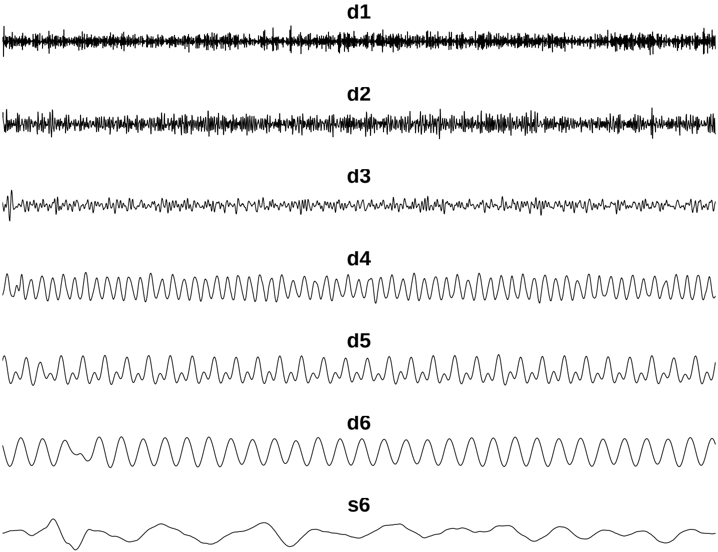


An example of wavelet decomposition

Example with a signal $X(t) = cos(t/5) + cos(t/10) + \mathcal{N}(0, 0.4)$**:**



$$X(t) = cos(t/5) + cos(t/10) + \mathcal{N}(0, 0.4)$$



Wavelets and correlation

$\mathbf{X} = \{\mathbf{X}(k), k \in \mathbb{Z}\}$ long memory process, $1 \leqslant \ell, m \leqslant p$,

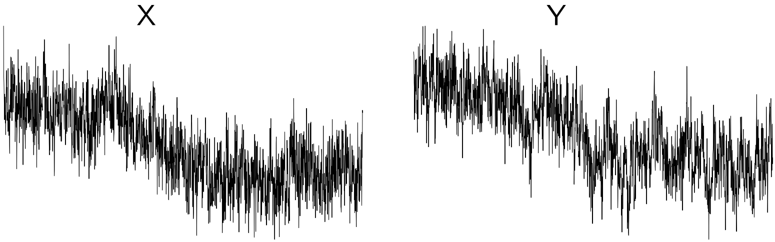
Wavelet variance	Wavelet covariance
$\sigma_\ell^2(j) = \mathbb{V}(W_{j,k}(\ell))$	$\theta_{\ell,m}(j) = \mathrm{Cov}(W_{j,k}(\ell), W_{j,k}(m))$
$\widehat{\sigma}^2(j) := \frac{1}{n_j}\sum_{k=0}^{n_j} W_{j,k}^2$	$\widehat{\theta}_{\ell,m}(j) := \frac{1}{n_j}\sum_{k=0}^{n_j}(W_{j,k}(\ell)W_{j,k}(m))$

[**Percival** *et al.* 2000]
[**Whitcher** *et al.* 2000]

Wavelet correlation

$$\rho_{\ell,m}(j) = \frac{\theta_{\ell,m}(j)}{\sigma_\ell(j)\sigma_m(j)}$$

Example of the non consistency of the classical estimator of correlation:



Correlation(X,Y) = 0.597

Wavelet correlation :

Scale 1	Scale 2	Scale 3	Scale 4	Scale 5	Scale 6	Remainder
0.059	0.053	0.029	0.08	0.115	0.041	1

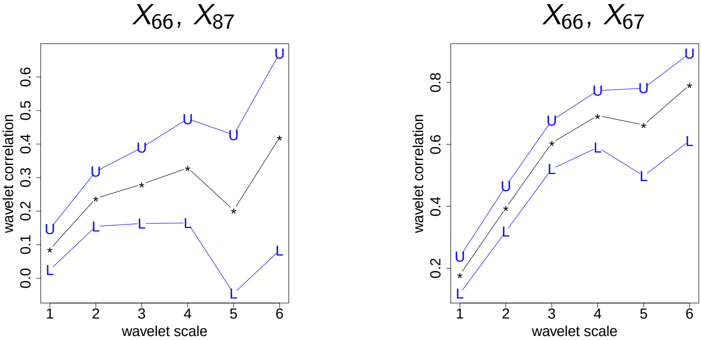
Wavelets and correlation

Proposition

$\mathbf{X} = \{\mathbf{X}(k), k \in \mathbb{Z}\}$ *long memory process,* $\widehat{\rho}_{\ell,m}(j) := \widehat{\theta}_{\ell,m}/(\widehat{\sigma}_\ell(j)\widehat{\sigma}_m(j))$

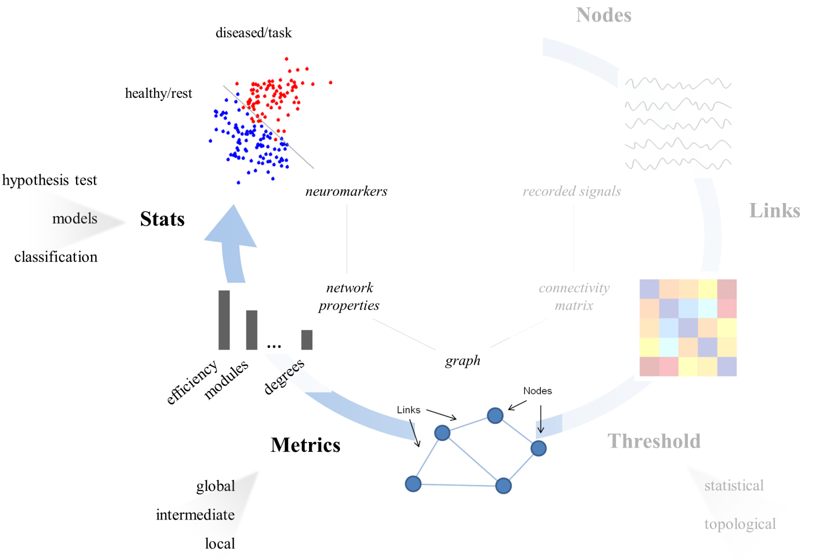
$$\sqrt{(n_j - 3)}(z(\widehat{\rho_{\ell,m}}(j)) - z(\rho_{\ell,m}(j))) \xrightarrow{\mathcal{L}} \mathcal{N}(0,1)$$

where z in the Fisher transform.



[**Achard and Gannaz** J. Time Series Analysis 2015] [**Achard** *et al.* J. Neurosci. 2006] [**Whitcher** *et al.* 2000]

Part II: Comparison of networks, assessing reliability



Construction of the adjacency matrices

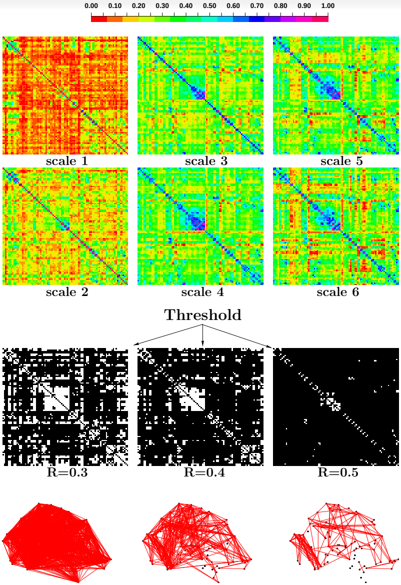
→ pair-wise inter-regional correlations

- Wavelets MODWT
- Connectivity = Correlation

→ adjacency matrix
Threshold ?

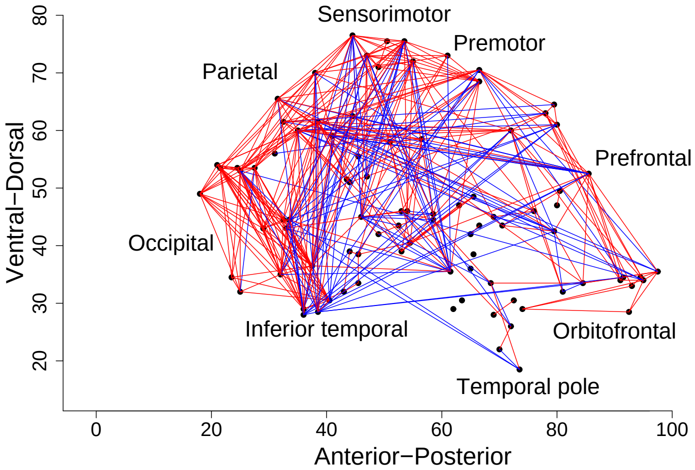
→ Undirected graphs :
small-world properties

[**Achard** *et al.* J. Neurosci. 2006]



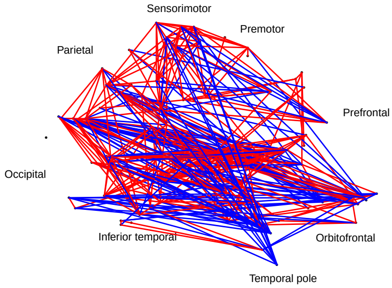
Individual graphs: representation of networks for a given threshold

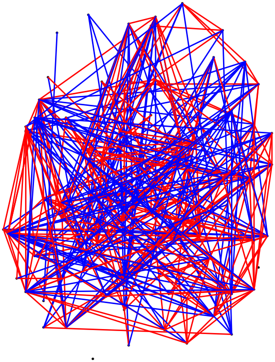
90 regions in the brain – 40 minutes scanning – 400 mostly connected pairs



An example with fMRI data

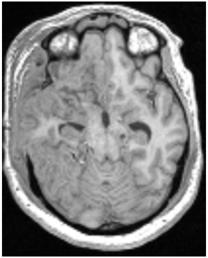
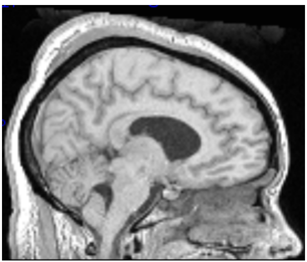
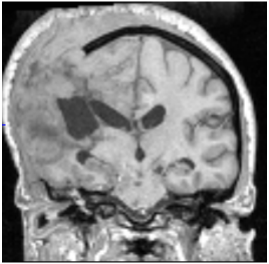
90 regions in the brain – 5 minutes scanning – 400 mostly connected pairs

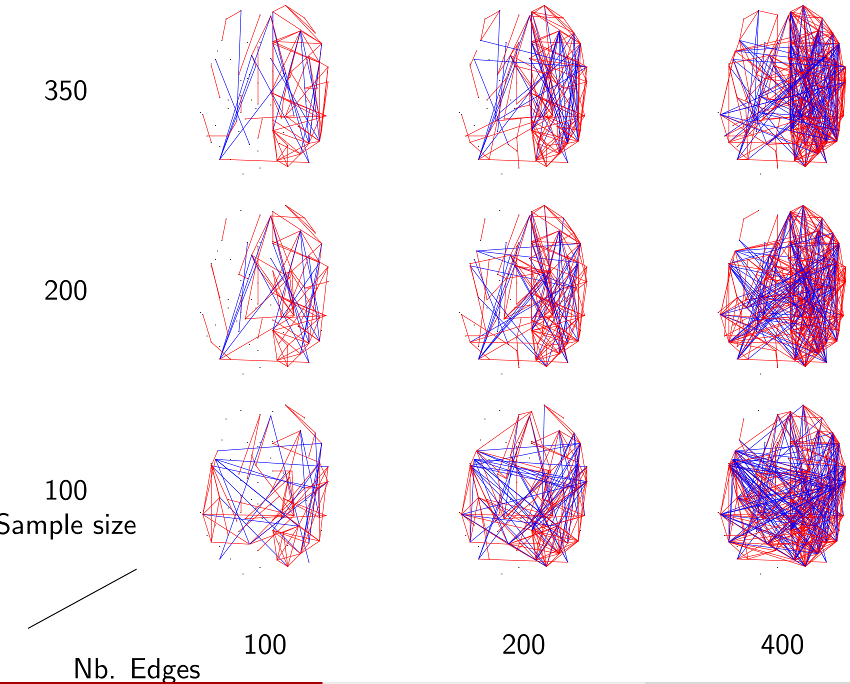




An example with fMRI data

An example using a patient with craniectomy on the left part of the brain.


350
200
100
Sample size
100
200
400
Nb. Edges

Construction of the adjacency matrices

Hypothesis tests: for all i, j, $1 \leqslant i, j \leqslant p, \quad i \neq j$

$$\mathcal{H}_0 : \rho_{i,j} = 0 \qquad \mathcal{H}_1 : \rho_{i,j} \neq 0$$

Problems :

- Multiple hypotheses tests : 4005 tests
  $\rightarrow$ Need to compare graphs with same number of edges
  $\rightarrow$ Maximise interesting properties
- The tests are dependent, classical approaches are not working

[**Achard** *et al.* J. Neurosci. 2006]
[**Hero** *et al.* 2013]
[**Drton** *et al.* 2004]

Multiple hypotheses tests

Number of errors committed when testing 4005 null hypothesis
n_0 = number of true null hypotheses

	Not rejected	Rejected	Total
True null hypotheses	**U**	**V**	n_0
Non-true null hypotheses	**T**	**S**	$4005 - n_0$
	$4005 - \mathbf{W}$	**W**	4005

- $PCER = E(\mathbf{V}/4005) < \alpha$ if each tests control at level α.
  $\rightarrow$ do not take into account the multiple test.
- $FWER = P(\mathbf{V} \geqslant 1) < \alpha$ if each tests control at level $\alpha/4005$.
  $\rightarrow$ Problem when the number of hypotheses is large, too conservative.
- $FDR = P(\mathbf{W} > 0)E(\mathbf{V}/\mathbf{W}|\mathbf{W} > 0)$, i.e. control of the proportion of rejected null hypotheses which are erronously rejected.
  $\rightarrow$ less stringent, and a gain in power.

Marine Roux PhD

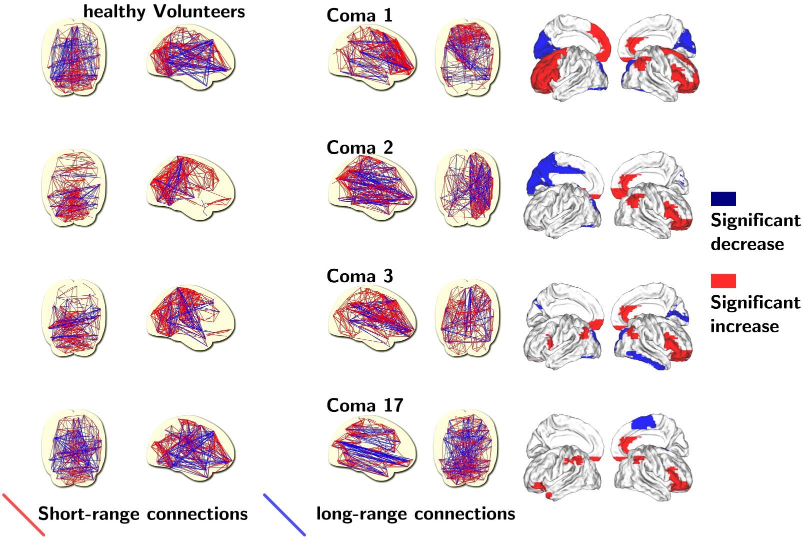
A clinical example: brain connectivity for coma patients

fMRI data acquisition parameters

- **90 and 417 anatomical regions:** space average of the fMRI time series over all voxels in 90 (AAL) and 417 regions
- **SPM preprocessing:** correction for geometrical displacements
- **Resting state:** lying quietly with eyes closed during 20 minutes
- **Group comparison:**
  20 young healthy volunteers, 17 patients in coma

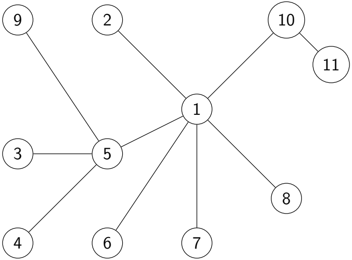
[**Achard** *et al.* PNAS 2012]

Brain connectivity of coma patients

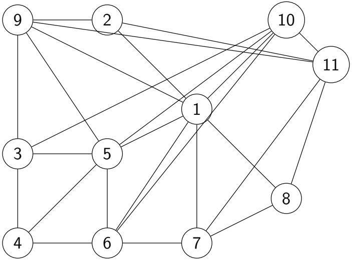


[**Achard** *et al.* PNAS 2012]

Graph features: degree



low degree

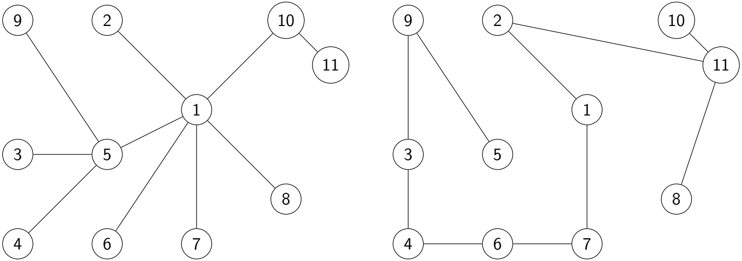


high degree

Degree = number of connections that node makes to other nodes.
$G = [G_{ij}]_{1 \leqslant i,j \leqslant N}$ is the adjacency matrix $1 \leqslant i, j \leqslant N$, $\quad G_{ij} = 0$ or 1.

$$D_i = \sum_{j \in G} G_{ij}.$$

Graph features: global efficiency



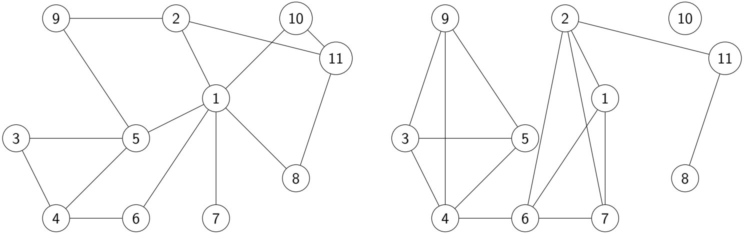
Eglob close to 1 Eglob close to 0

Efficiency = inverse of the harmonic mean of the minimum path length L_{ij} between a node i and all the other nodes j in the graphs.

$$Eglob_i = \frac{1}{N-1} \sum_{j \in G} \frac{1}{L_{ij}}$$

[**Latora** *et al.* 2002]

Graph features: clustering



Clust close to 0 Clust close to 1

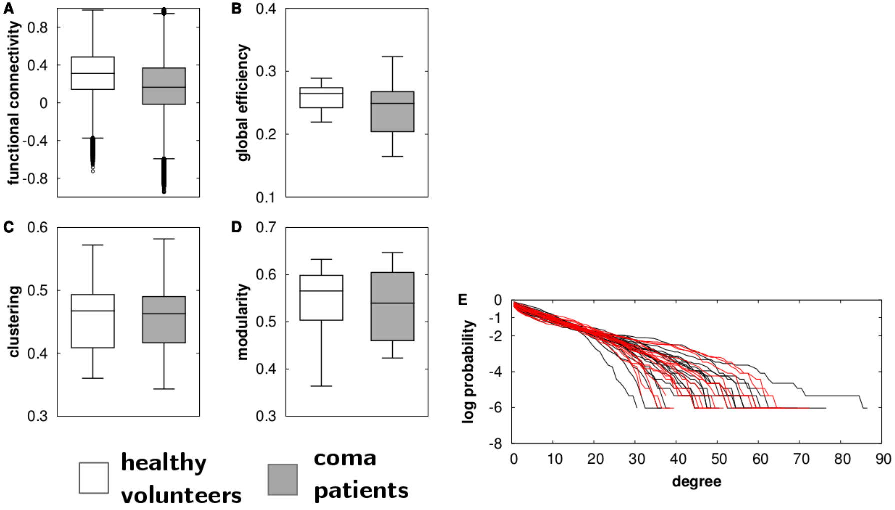
Clustering, also called "local efficiency" = measure of information transfer in the immediate neighbourhood of each node.

$$Clust_i = \frac{1}{N_{G_i}(N_{G_i}-1)} \sum_{j,k \in G_i} \frac{1}{L_{jk}},$$

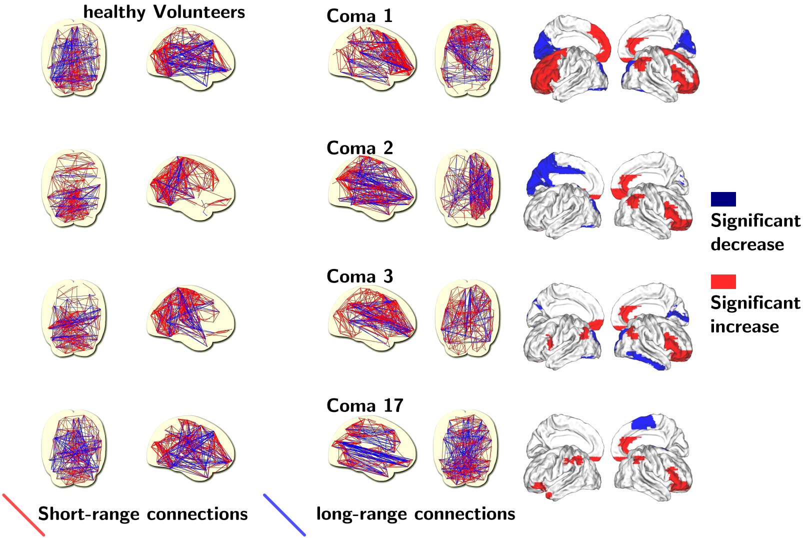
[**Latora** *et al.* 2002]

Results: global connectivity and network topology

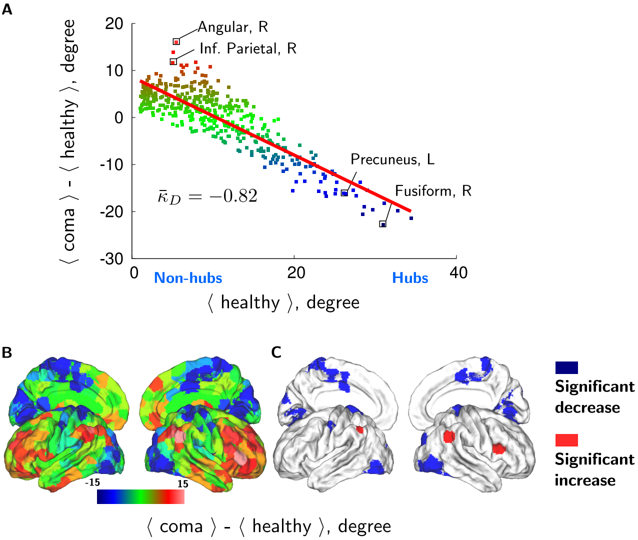
No significant difference on global measure of functional connectivity



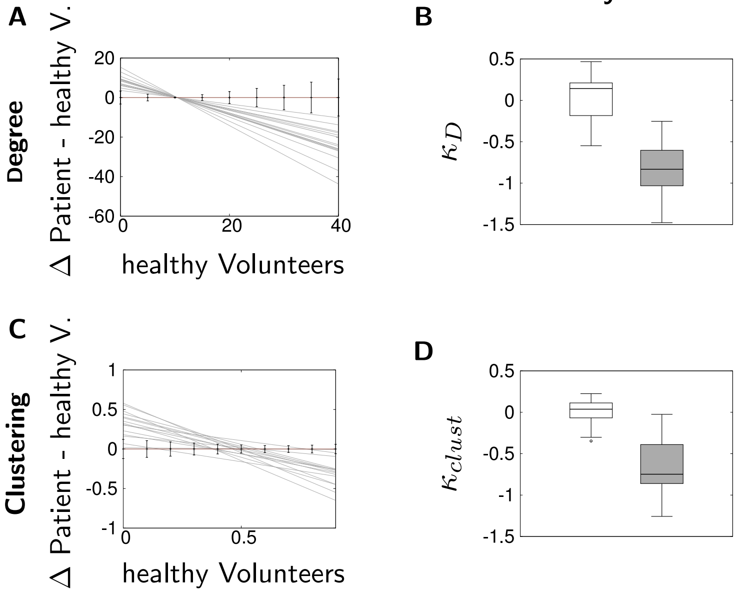
Examples of connectivity graphs



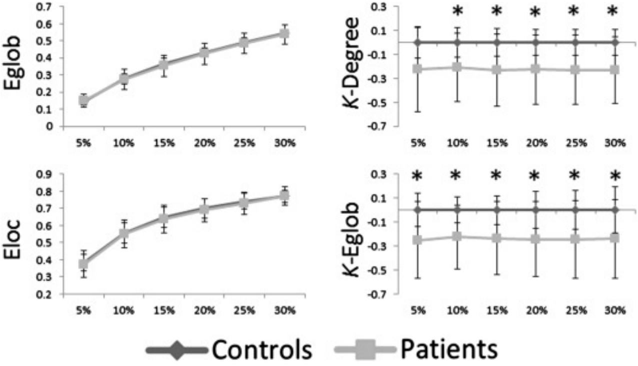
Results: nodal connectivity



One index to discriminate the coma and healthy volunteers



Same results on epilepsy patients



[**Ridley** *et al.* Neuroimage 2015]

Test-retest datasets

- Freely available data from **Human Connectome Project**
- **90 and 417 anatomical regions:** space average of the fMRI time series over all voxels in 90 (AAL) and 417 regions
- **SPM preprocessing:** correction for geometrical displacements
- **Resting state:** lying quietly with eyes closed during 20 minutes
- **Group comparison:**
  100 healthy controls scanned twice

[**Termenon** *et al.* Neuroimage 2012]

Assessing reliability of graph analysis

Taking global efficiency as the metric studied and computed with the whole 1200 time points

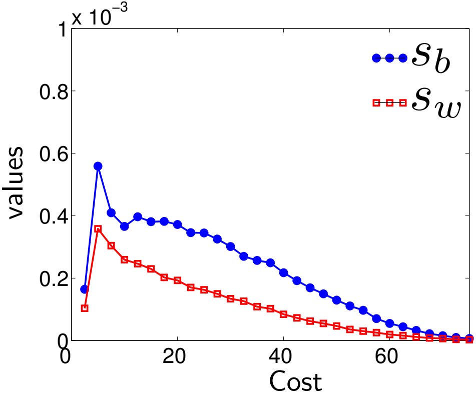
$$ICC = \frac{s_b - s_w}{s_b + (k-1)s_w} \qquad (1)$$

where s_b is the variance between subjects, s_w is the variance within subjects and k is the number of sessions per subject.

[**Fisher** *et al.* 1925] [**Donner** *et al.* 1986]

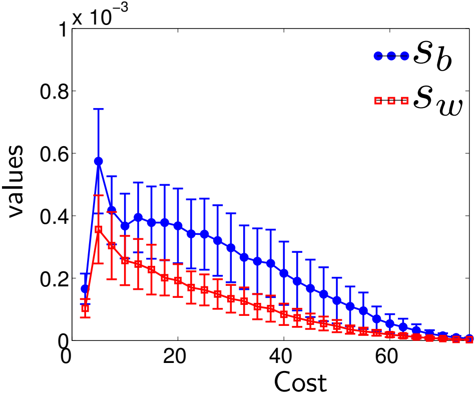
Assessing reliability of graph analysis

Taking global efficiency as the metric studied and computed with the whole 1200 time points
For the 100 healthy volunteers scanned twice



Assessing reliability of graph analysis

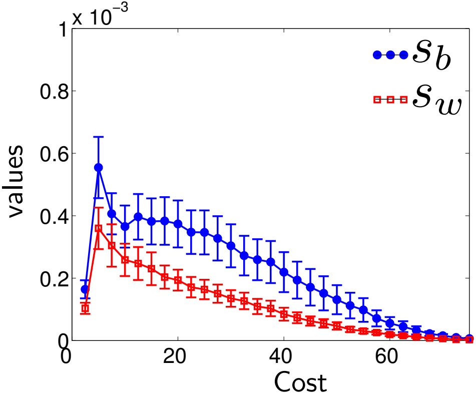
Taking global efficiency as the metric studied and computed with the whole 1200 time points
For 20 healthy volunteers taken at random using subsampling



Assessing reliability of graph analysis

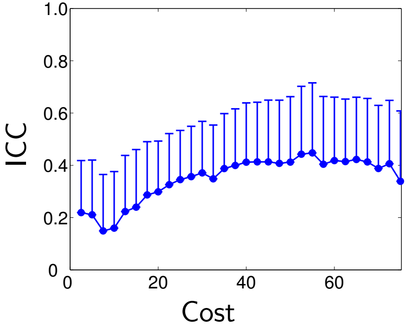
Taking global efficiency as the metric studied and computed with the whole 1200 time points

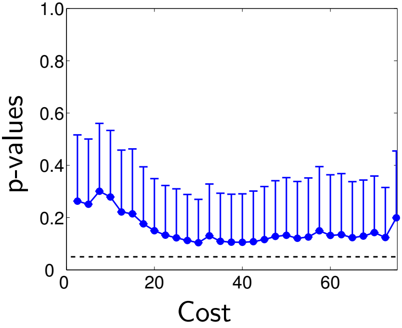
For 40 healthy volunteers taken at random using subsampling



Assessing reliability: p-values of ICC

Permutation tests to compute p-values
For 20 subjects, 1200 time points, global efficiency

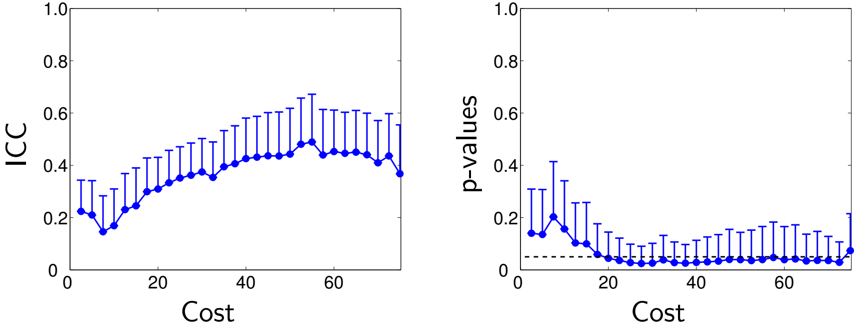




Simctest [**Gandy** *et al.* 2009]

Assessing reliability: p-values of ICC

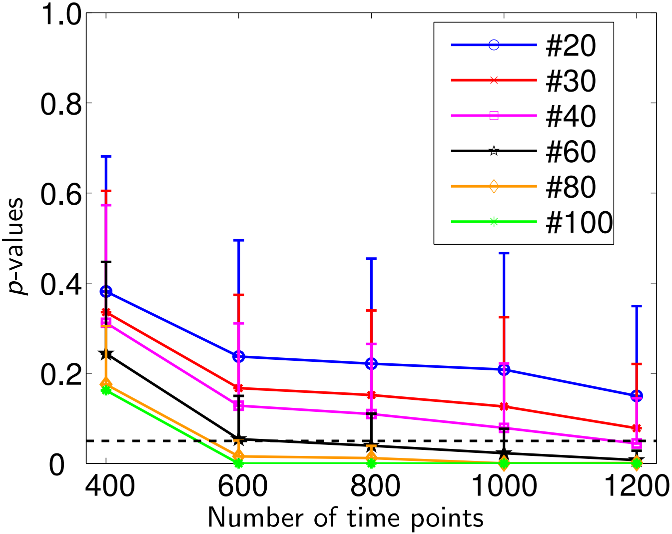
Permutation tests to compute p-values
For 40 subjects, 1200 time points, global efficiency



Simctest [**Gandy** *et al.* 2009]

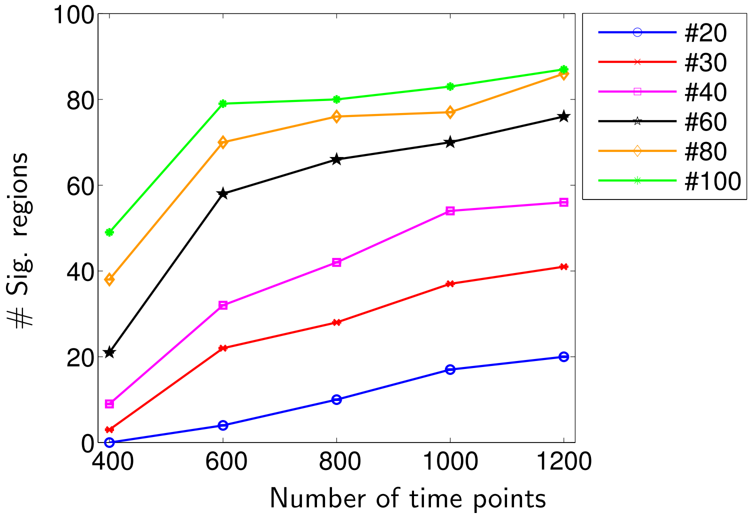
Choice of number of subjects and scan duration

Comparisons for global efficiency for a cost equal to 20%

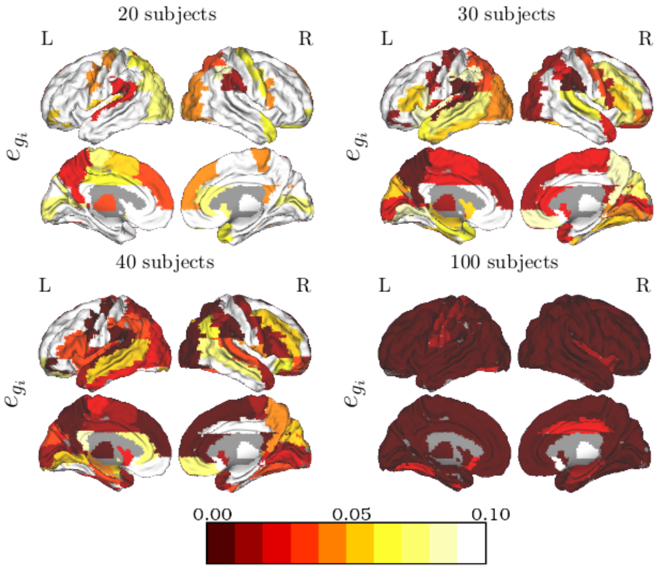


Significant regions versus number of subjects

At the regional level, global efficiency of each region separately



Localisation of significant regions



Conclusions and future works

- Graphs are providing a complete representation of brain connectivity
- New graph metrics are needed
- Assessing reliability is worthwhile for any new approaches

Feel free to use the test-retest datasets
(email: `sophie.achard@gipsa-lab.fr`)

Thanks to my collaborators