Hubs of brain functional networks are radically reorganized in comatose patients

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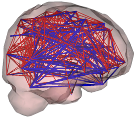
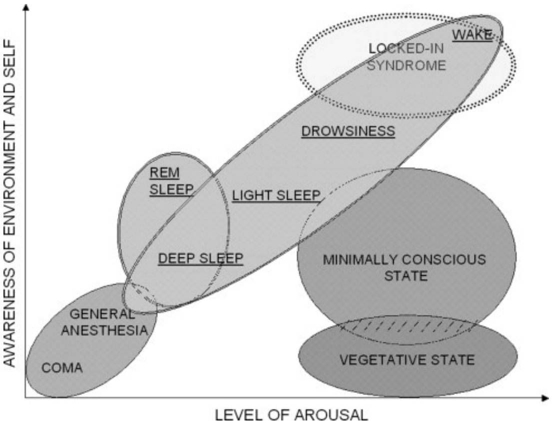


Introduction: Disorders of consciousness

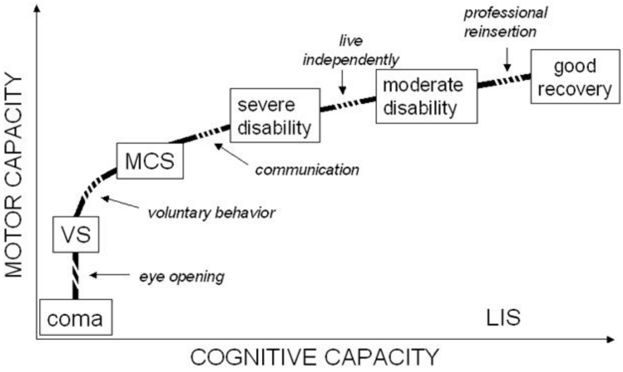
Following Plum and Posner (1983), consciousness has two dimensions: **wakefullness** (also called arousal) and **awareness**.



[Laureys *et al.* Consciousness and Cognition, 2007]

Introduction: Disorders of consciousness

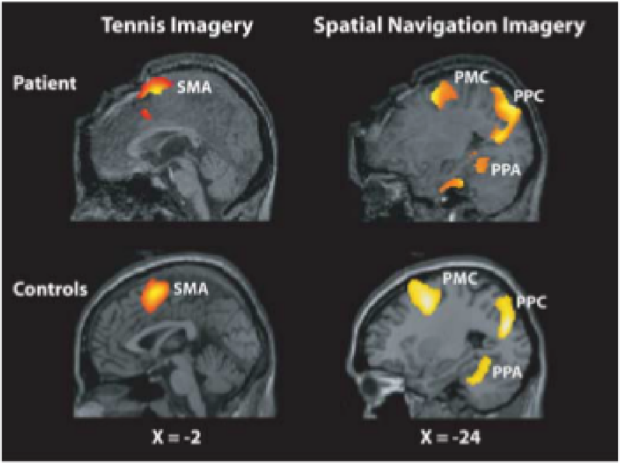
The only way to diagnose a patient in a given state is done by careful and repeated clinical assessments of wakefulness and awareness. High rate of misdiagnosis, especially to distinguish between vegetative state and minimially conscious state (up to 43% evaluated in 1996).



[Laureys *et al.* Current Opinion in Neurology, 2005]

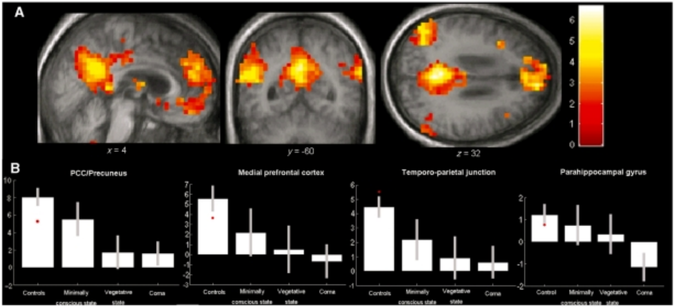
Introduction: Detecting awareness using fMRI

Using Tennis Imagery to detect awareness for patient with traumatic brain injury.



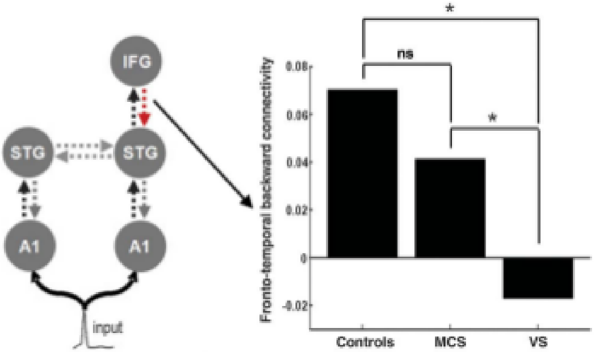
[Owen *et al.* Science, 2006]

Introduction: DMN and consciousness disorders



[Vanhaudenhuyse *et al.* Brain 2010]

Introduction: consciousness disorders measured using EEG



[Boly *et al.* Science 2011]

Subjects description

Patients:

- 25 patients in coma were scanned; age range 21–82 years; 9 male. Exclusion of data on 8 patients (head mouvements)
- The coma severity for each patient was clinically assessed using the 62 items of the Wessex Head Injury Matrix (WHIM) scale: scores range from 0, meaning deep coma, up to 62, meaning full recovery.
- The patients were scanned a few days after major acute brain injury, when sedative drug withdrawal allowed for spontaneous ventilation.
- The causes of coma were different between patients: twelve had a cardiac and respiratory arrest due to various causes; two had a gaseous cerebrovascular embolism; two had hypoglycemia; and one had extracranial artery dissection. Six months after the onset of coma, three patients had totally recovered, 9 had died, and 5 remained in a persistent vegetative state.

Healthy volunteers:
The normal control group comprised twenty healthy volunteers matched for sex (11 male) and approximately for age (range 25–51 years) to the group of patients.

Subjects description

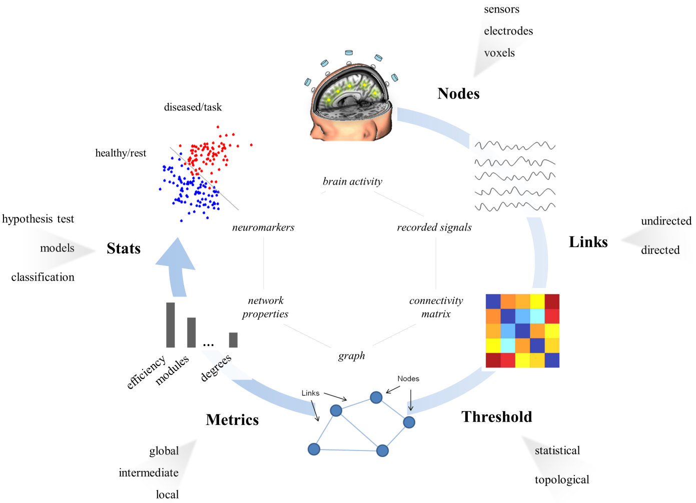
name	age	Etiology	Initial WHIM	Time between accident and scan (days)
Patient 1	36	cardiac and respiratory arrest	10	12
Patient 2	42	extracranial artery dissection	1	18
Patient 3	66	coma after gaseous embolism (coronary by-pass surgery)	1	4
Patient 4	73	cardiac and respiratory arrest	1	3
Patient 5	21	cardiac and respiratory arrest	1	5
Patient 6	32	cardiac and respiratory arrest	1	3
Patient 7	53	cardiac and respiratory arrest	9	3
Patient 8	44	hypoglycemia	2	32
Patient 9	59	cardiac and respiratory arrest	3	15
Patient 10	82	coma after gaseous embolism	14	7
Patient 11	53	cardiac and respiratory arrest	1	5
Patient 12	78	cardiac and respiratory arrest	1	5
Patient 13	71	cardiac and respiratory arrest	1	16
Patient 14	66	cardiac and respiratory arrest	13	8
Patient 15	55	cardiac and respiratory arrest	NA	5
Patient 16	49	hypoglycemia	1	18
Patient 17	25	cardiac and respiratory arrest	37	9

Extracting the connections using fMRI modality

fMRI data acquisition

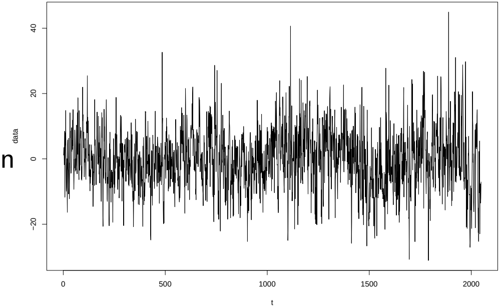
- Functional MRI data were recorded while subjects lay quietly at rest in the scanner for 20 mins. Gradient echo EPI data sensitive to BOLD contrast were acquired using a 1.5 Tesla MR scanner (Avanto, Siemens, Erlangen, Germany) with the following parameters: TR=3 s, TE=50 ms, isotropic voxel size = 4x4x4mm^3, 405 images, and 32 axial slices covering the entire cortex.
- Two templates: 417 or 90 regions with 400 points in time, frequency interval 0.02–0.04Hz (using wavelets).

Extracting the connections using fMRI modality



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

Working data



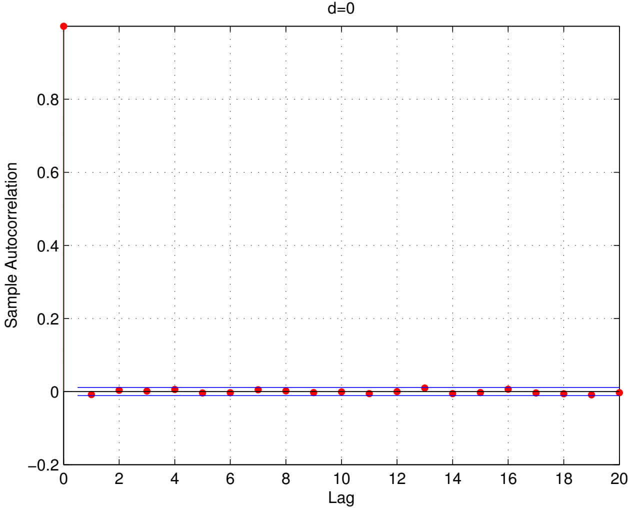
- $\rightarrow$ Brain fMRI : 90 regions
- $\rightarrow$ each region :
  1 time series of length between 512 and 2048
- $\rightarrow$ Brain MEG : 275 channels
- $\rightarrow$ each channel :
  1 time series of length between 6144 and $> 10^6$

fMRI and MEG time series characteristics :

- $\rightarrow$ long memory processes
- $\rightarrow$ difficulties to parametrize them
- $\rightarrow$ short sequence of times series in fMRI
- $\rightarrow$ But large set of time series!

Long memory processes

What is long-memory?



Long memory processes

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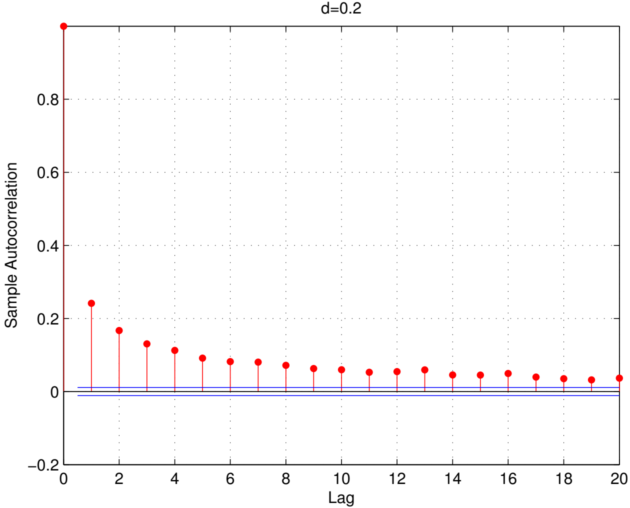

Long memory processes

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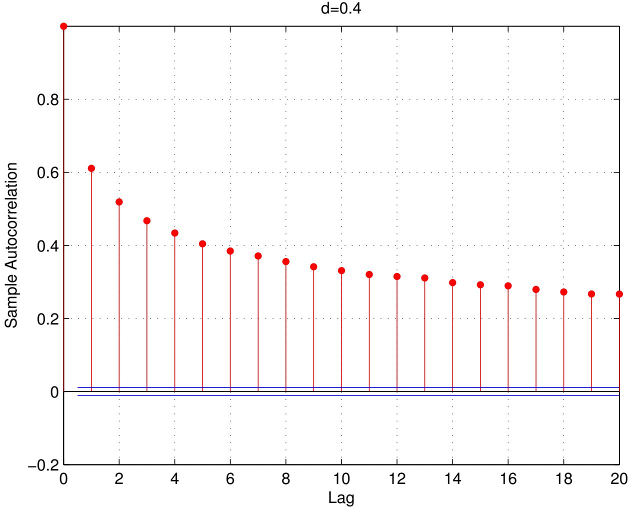
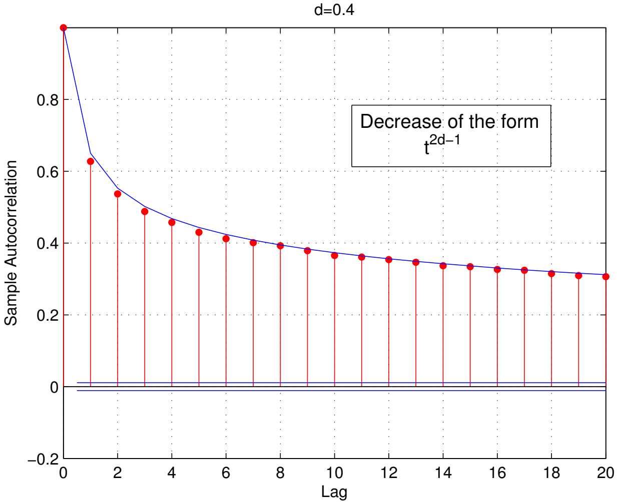


Long memory processes

What is long-memory?



Long memory processes

What is long-memory?
Example: bivariate ARFIMA(0,d,0)

$$\begin{pmatrix} u_1 \\ u_2 \end{pmatrix} \rightsquigarrow \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & 0.4 \\ 0.4 & 1 \end{pmatrix} \right)$$

$$\begin{aligned} (1-\mathbb{L})^{d_1} X_1 &= u_1 \\ (1-\mathbb{L})^{d_2} X_2 &= u_2 \end{aligned}$$

with $\mathbb{L}$ lag-operator.

Wavelets and correlation

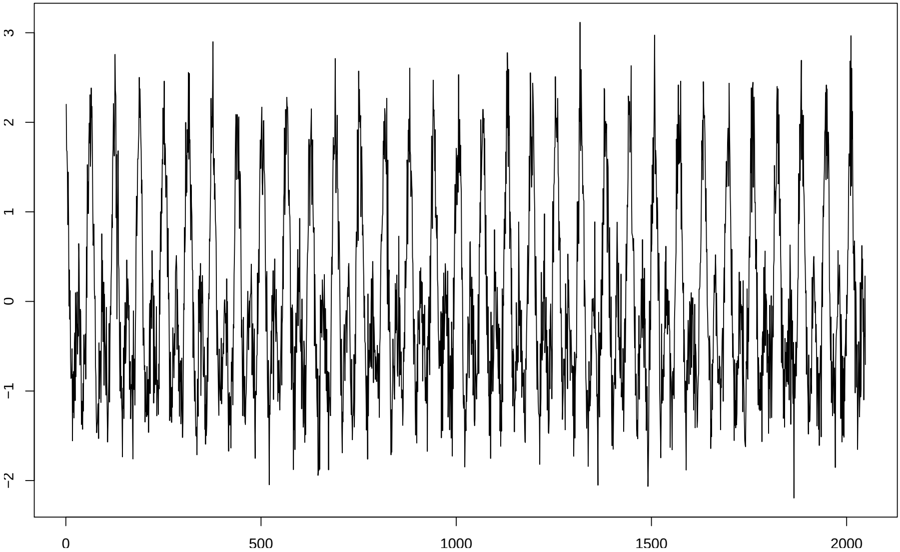
Why using the wavelets ?

- Estimation of correlation non consistent for long memory processes
- Prior observations from EEG : coherence not equal at all frequencies
- Already shown frequency dependent correlation [*Salvador et al.* 04]
  $\rightarrow$ High and low frequency phenomena

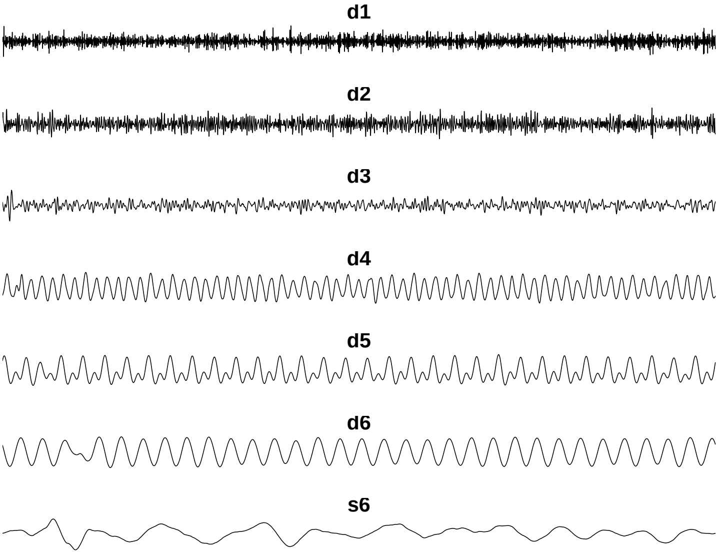
One example of wavelet functions: Daubechies 8

An example of wavelet decomposition

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

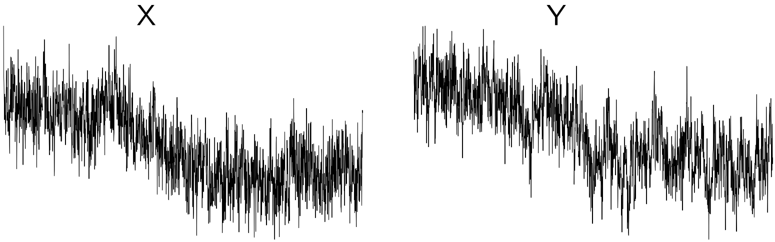


$X(t) = cos(t/5) + cos(t/10) + \mathcal{N}(0, 0.4)$



Wavelets and correlation

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

Discrete Wavelet Transform (DWT)

X a time series of length N

Wavelet coefficients
$$W_{j,t}^{(X)} = \sum_{l=0}^{L_j-1} h_{j,l} X_{t-l \ mod \ N}$$

Scaling coefficients
$$V_{j,t}^{(X)} = \sum_{l=0}^{L_j-1} g_{j,l} X_{t-l \ mod \ N}.$$

where $\{h_{j,l}\ ;\ l = 0, \dots, L_j - 1\}$ and $\{g_{j,l}\ ;\ l = 0, \dots, L_j - 1\}$ be respectively a $j-th$ level wavelet filter and scaling filter. Here $L_j = (2^j - 1)(L - 1) + 1$, with L the width of the initial filter.

- $\rightarrow$ does depend on the starting point for the origin
- $\rightarrow$ orthogonal transform
- $\rightarrow$ energy decomposition:
$$||\mathbf{X}||^2 = \sum_{j=1}^{J_0} ||\mathbf{W}_j||^2 + ||\mathbf{V}_{J_0}||^2$$

Wavelets and correlation

$\rightarrow$ Wavelet variance : [*Percival et al. 2000*]

$\rightarrow$ Wavelet covariance : [*Whitcher et al. 2000*]

$\{X_t\}$ and $\{Y_t\}$ stochastic processes whose backward differences of order d_X and d_Y are stationary processes:

$$Cov\{X_t, Y_{t+\tau}\} = Cov\{V_{J,t}^{(X)}, V_{J,t+\tau}^{(Y)}\} + \sum_{j=1}^{J} \gamma_{\tau,XY}(\lambda_j)$$

where V are the scale coefficients, and W are the wavelet coefficients, and for $\lambda_j = 2^{j-1}$,

$$\gamma_{\tau,XY}(\lambda_j) = Cov\{W_{j,t}^{(X)}, W_{j,t+\tau}^{(Y)}\}$$

Wavelets and correlation

lag:$\tau = 0$

$\rightarrow$ $Cov\{V_{J,t}^{(X)}, V_{J,t}^{(Y)}\} \rightarrow 0$ when $J \rightarrow \infty$

$\rightarrow$ At each scale λ_j, $\widehat{\gamma}_{XY}(\lambda_j)$ is unbiased, Gaussian distributed

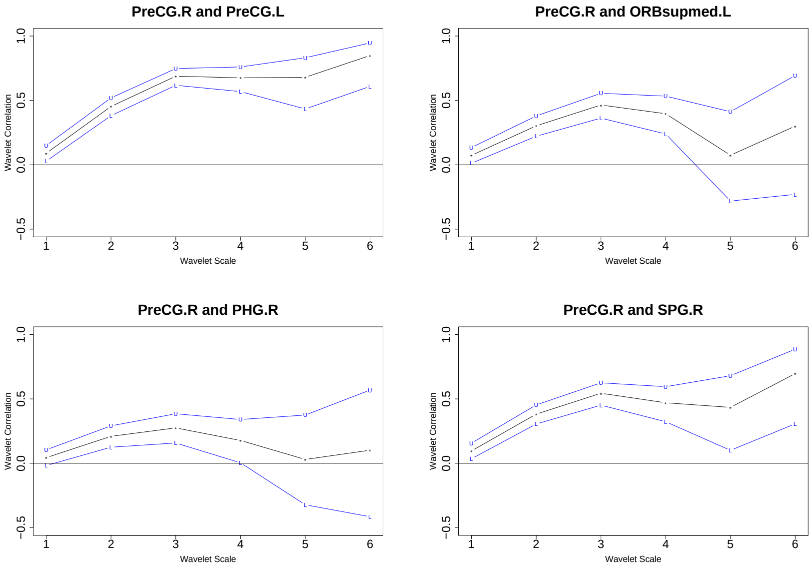
$$\widehat{\rho}_{XY}(\lambda_j) = \frac{\widehat{\gamma}_{XY}(\lambda_j)}{\widehat{\nu}_X(\lambda_j)\widehat{\nu}_Y(\lambda_j)} \rightarrow \mathcal{N}(\rho_{XY}(\lambda_j), \Sigma)$$

where $\widehat{\nu}_X^2(\lambda_j) = var(\mathbf{W}_j)/2\lambda_j$ is the wavelet variance for the time serie $\mathbf{X}$.

fMRI data : (2048 points in the time series)

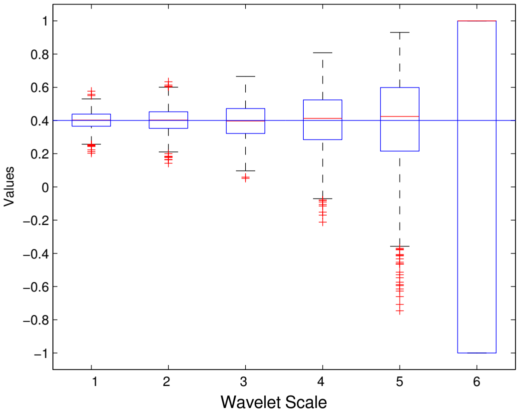
Scale	1	2	3	4	5	6
Hz	0.23-0.45	0.11-0.23	0.06-0.11	0.03-0.06	0.01-0.03	0.007-0.01
Mean cor.	0.12	0.21	0.39	0.45	0.44	0.41

Wavelets and correlation : fMRI examples



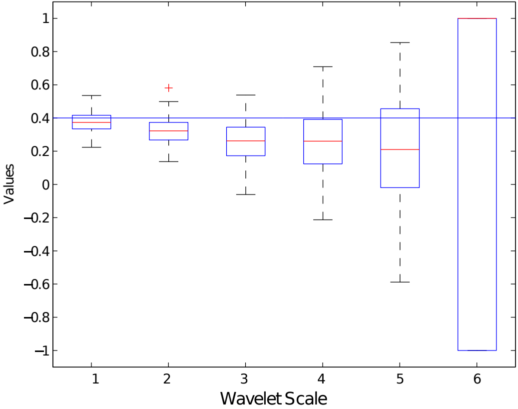
Long-memory effects on sample correlation

Boxplots of $Corr\{W_{j,t}^{(X)}, W_{j,t}^{(Y)}\}$ for $d_X = 0.2$ and $d_Y = 0.2$.



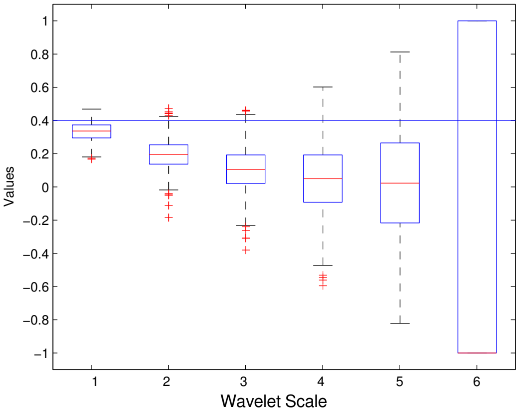
Long-memory effects on sample correlation

Boxplots of $Corr\{W_{j,t}^{(X)}, W_{j,t}^{(Y)}\}$ for $d_X = -0.2$ and $d_Y = 0.4$.



Long-memory effects on sample correlation

Boxplots of $Corr\{W_{j,t}^{(X)}, W_{j,t}^{(Y)}\}$ for $d_Y = 0.2$ and $d_X = 1.2$.



Mathematical formulation

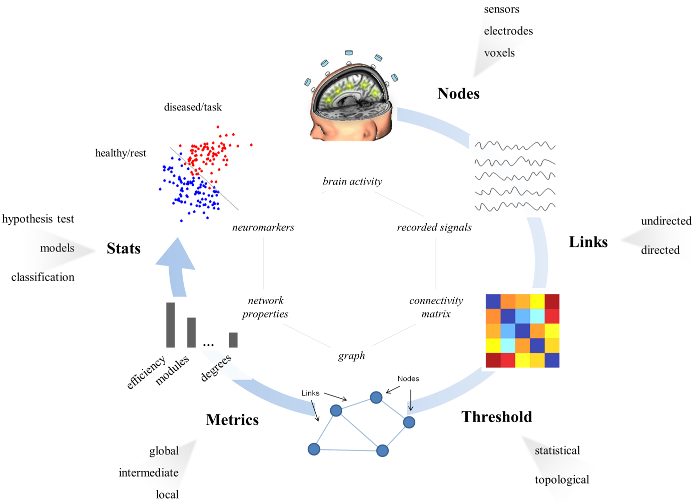
We consider a multivariate process $\mathbf{X}$, with spectral density:

$$\mathbf{f}(\lambda) = \boldsymbol{\Omega} \circ (((1 - e^{-i\lambda})^{-\mathbf{d}})\mathbf{f}^S(\lambda)((1 - e^{+i\lambda})^{-\mathbf{d}}))$$

- $\boldsymbol{\Omega}$ long-run covariance matrix, corresponding to the fractal connectivity
- $\mathbf{d}$ vector of long-range dependences of each series
- $\mathbf{f}^S(\cdot)$ short-range behaviour
  $\forall \lambda \in (-\pi, \pi)$, $\|\mathbf{f}^S(\lambda) - 1\|_\infty \leq L|\lambda|^\beta$
  with $L > 0$ and $0 < \beta \leq 2$.

$\rightarrow$ Multivariate wavelet Whittle estimation in long-range dependence [*Achard and Gannaz 2015*]

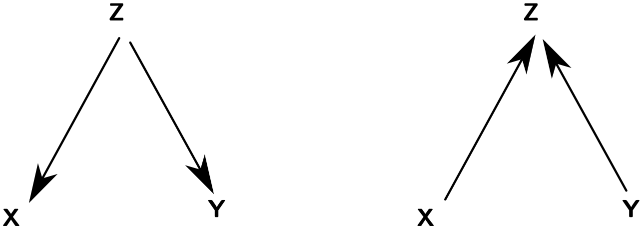
Extracting the connections using fMRI modality



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

Correlation or Partial correlation

These are complementary measures that bring different informations!



[Lemoine *et al.*, GRETSI, 2009]

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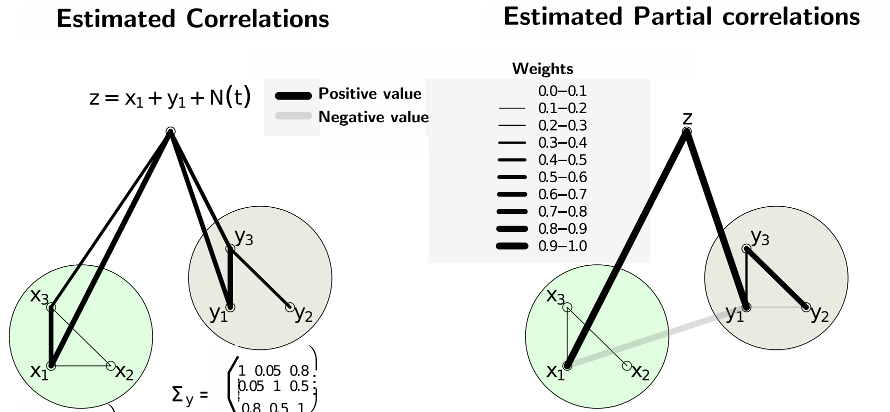


$$\Sigma_y = \begin{pmatrix} 1 & 0.05 & 0.8 \\ 0.05 & 1 & 0.5 \\ 0.8 & 0.5 & 1 \end{pmatrix}$$

$$\Sigma_x = \begin{pmatrix} 1 & 0.1 & 0.6 \\ 0.1 & 1 & 0.2 \\ 0.6 & 0.2 & 1 \end{pmatrix}$$

[Lemoine *et al.*, GRETSI, 2009]

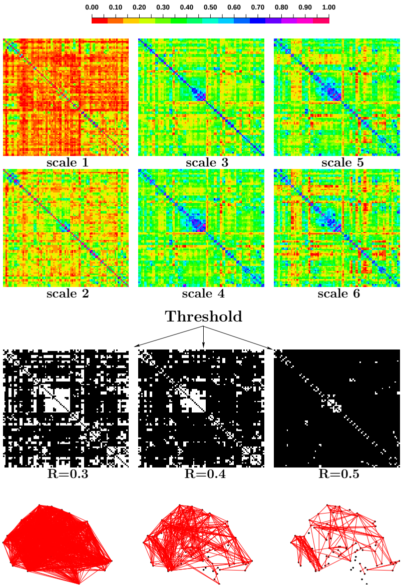
Construction of the adjacency matrices

→ pair-wise inter-regional correlations

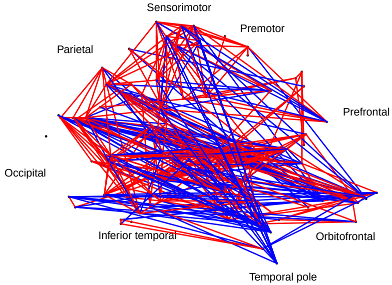
- Wavelets MODWT
- Connectivity = Correlation

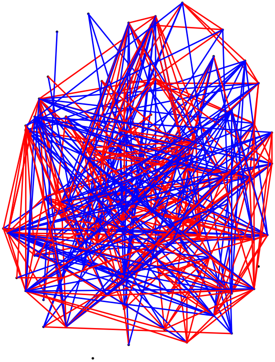
→ adjacency matrix
multiple testing
Threshold ?

→ Undirected graphs :
small-world properties



Parcellation based approaches





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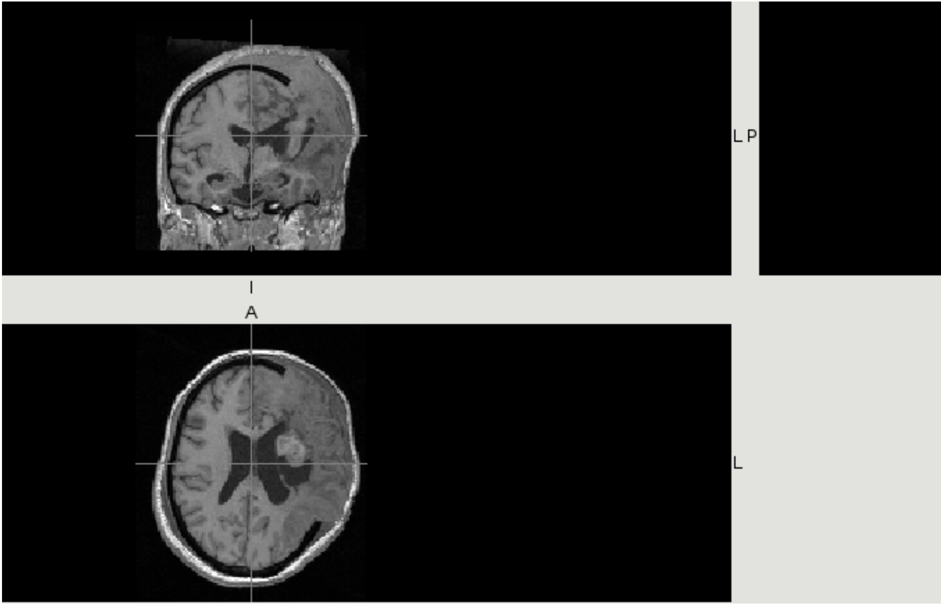
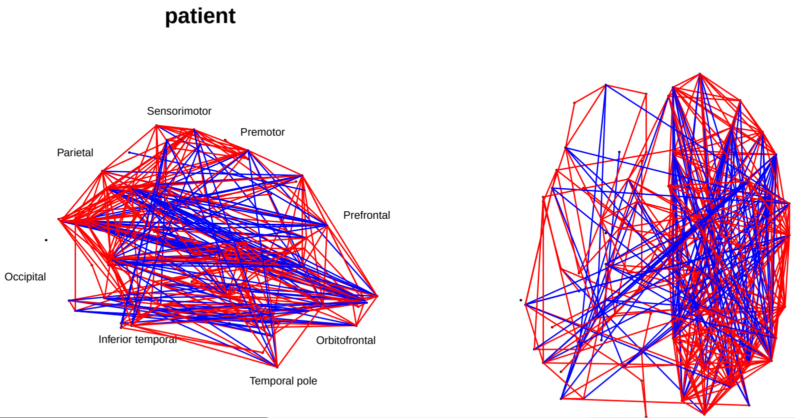


Parcellation based approaches

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

- 90 regions
- 400 mostly connected pairs (without multiple corrections)

Using 405 points in time



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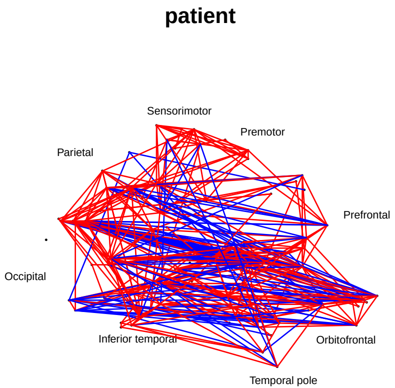
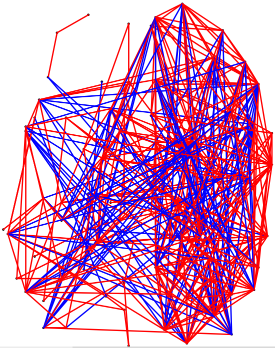
Using 200 points in time





Parcellation based approaches

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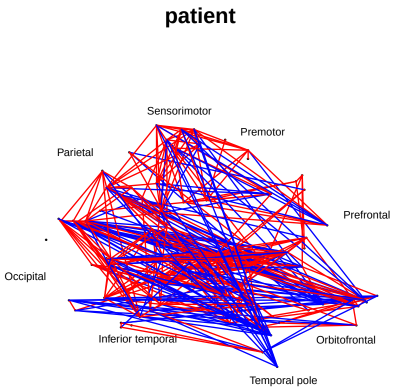
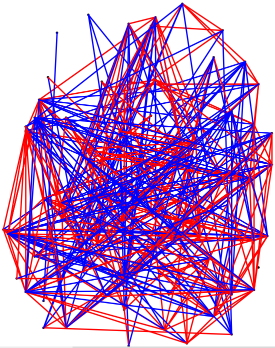
Using 70 points in time





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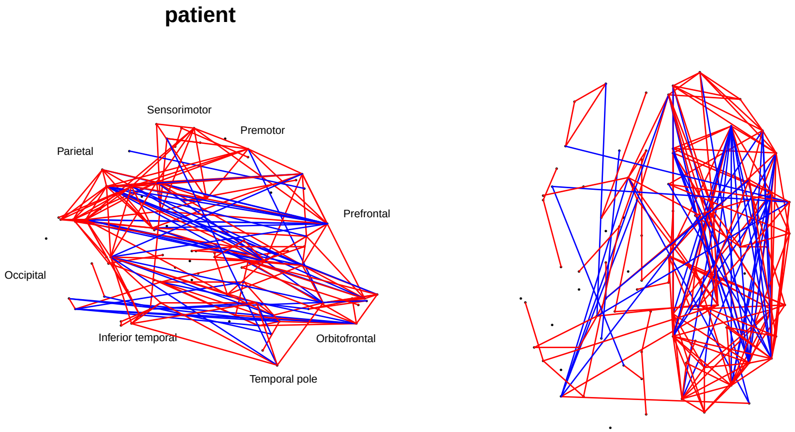
Using 405 points in time



- 90 regions
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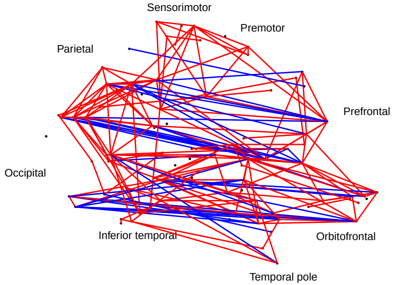
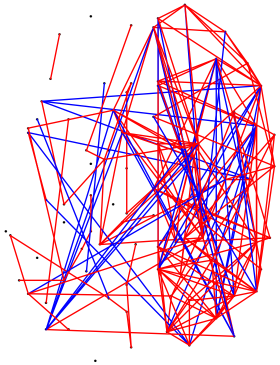
Using 200 points in time

patient

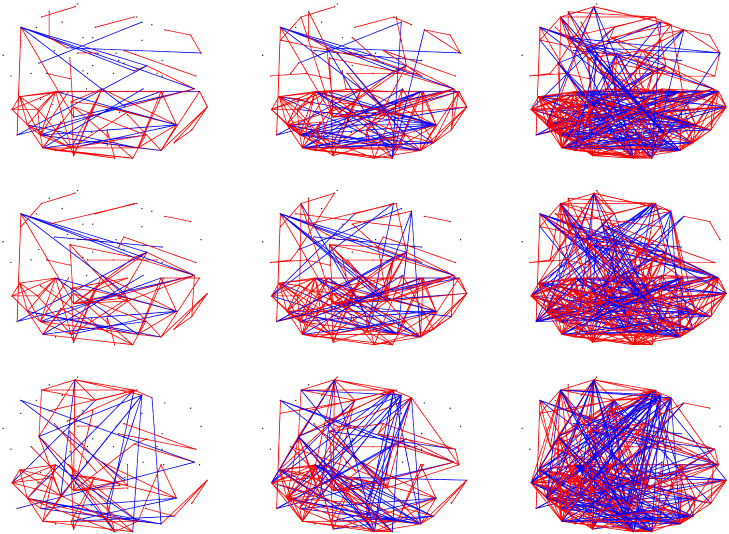




400 ↑

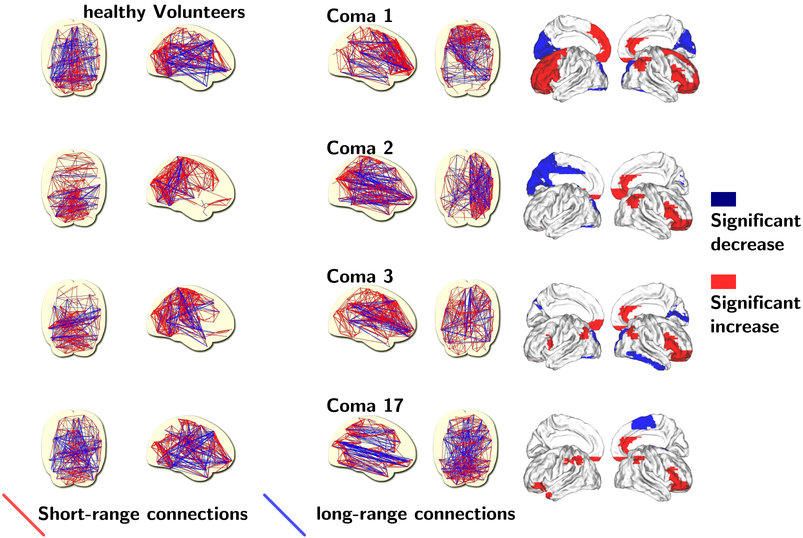
200

100

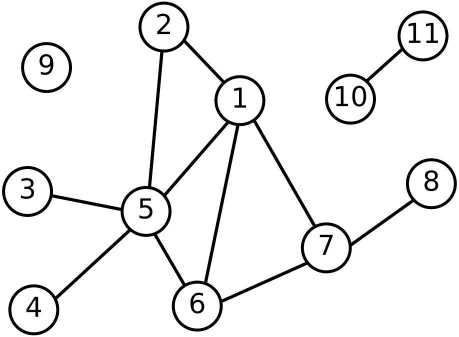


time points 100 200 400 edges →

Examples of connectivity graphs



The graph metrics

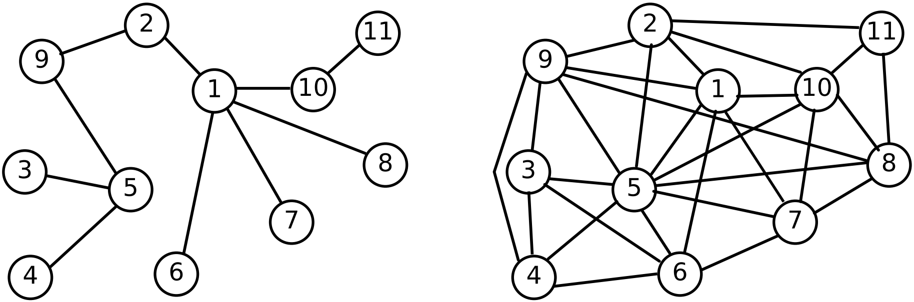


$$\text{Vertices} = V \quad = \quad \{1,2,3,4,5,6,7,8,9,10,11\}$$

$$\text{Edges} = E \quad = \quad \{\{1,2\}, \{1,5\},\{1,6\}, \{1,7\}, \{2,5\}, \{3,5\}, \{4,5\}, \{5,6\}, \{6,7\}, \{7,8\}, \{10,11\}\}$$

In practice: graph metrics

A graph is still a multivariate representation of the data. One should summarize them in some sense.



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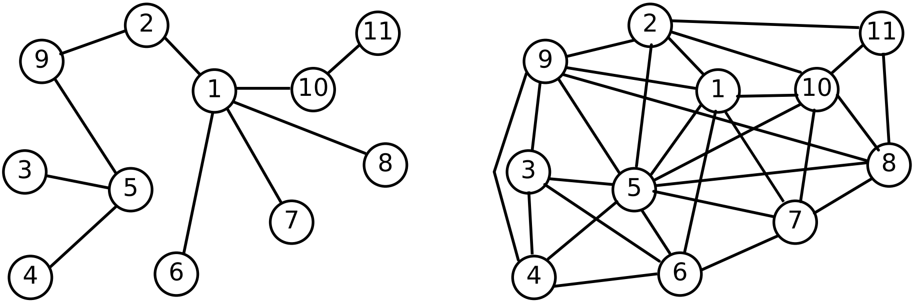

Degree: the number of connections that node makes to other nodes in the graph

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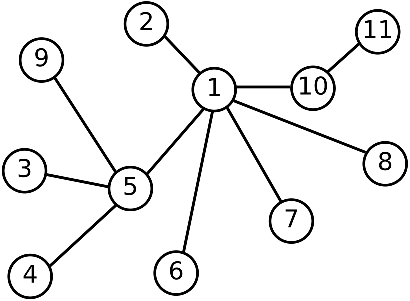

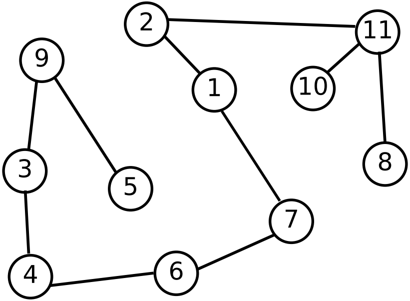

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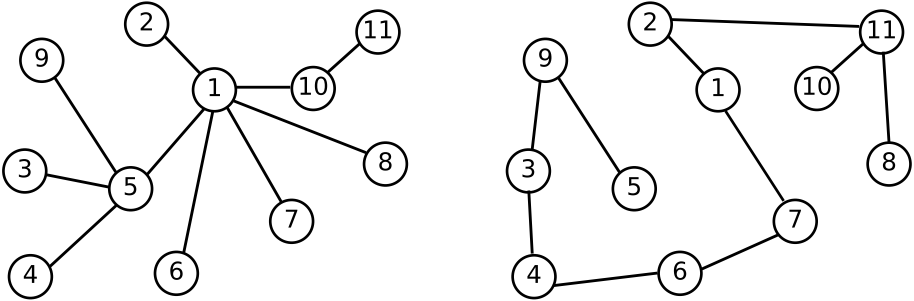

The **global efficiency** measures how the information is propagating in the whole network.

In practice: graph metrics

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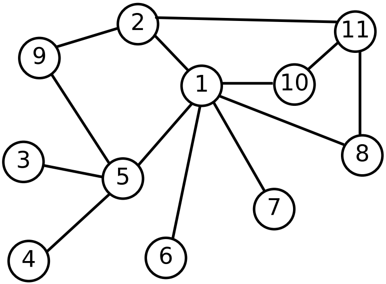
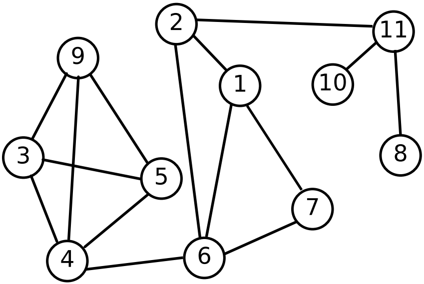
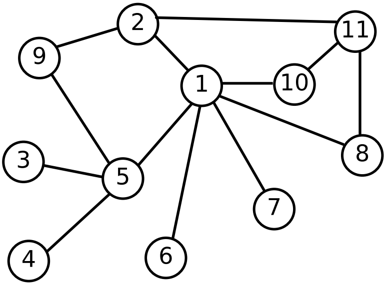
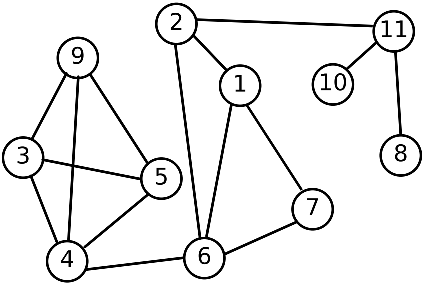




In practice: graph metrics

A graph is still a multivariate representation of the data. One should summarize them in some sense.





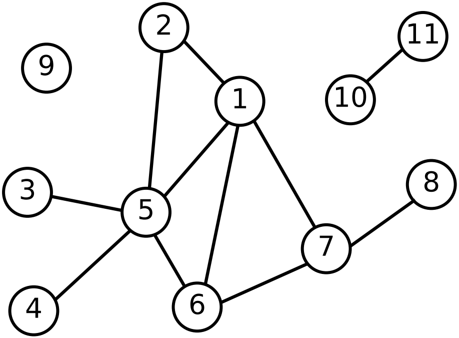
Clustering, also called "local efficiency", can be regarded as a measure of information transfer in the immediate neighbourhood of each node.

Other graph metrics

- Modularity
- Betweenness centrality
- Percolation
- Spectral graphs
- Rich club
- ...

Toolbox on R: igraph
Toolbox on Matlab: Brain Connectivity Toolbox
Ref: for example [*Rubinov et al.*, 09]

Nodal graph metrics



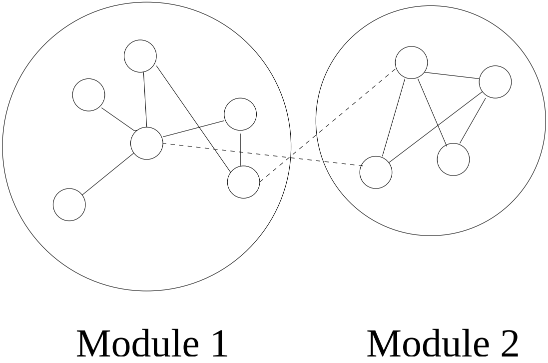
Node	Degree	Eglob	Clustering
1	4	0.55	0.72
5	5	0.58	0.25
9	0	0	0

Economical efficiency [*Latora et al.*, 01]

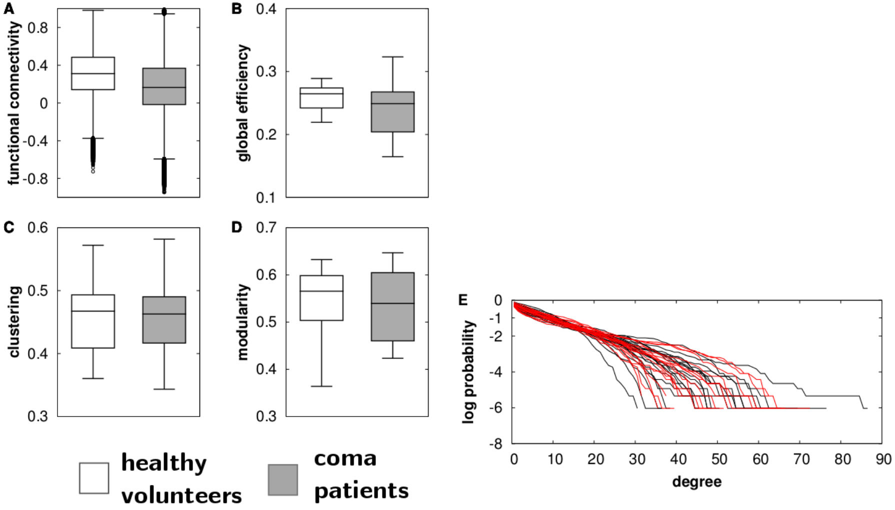
Modular organization of human brain functional networks

[Girvan and Newman PNAS 2002]

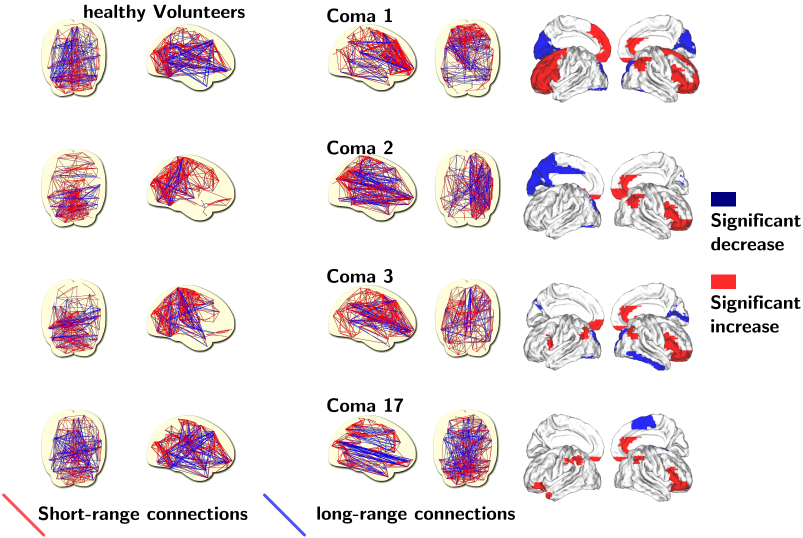
- Partitioning the networks into a set of modules
- dense inter-modular connectivity
- sparse inter-modular conmnectivity



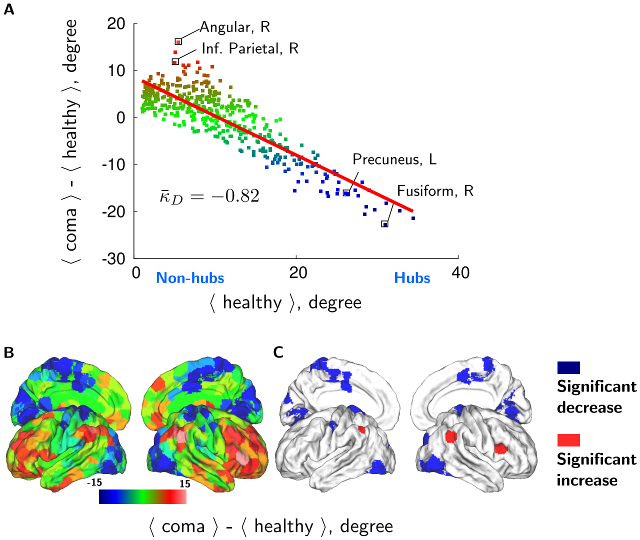
No significant difference on global measure of functional connectivity



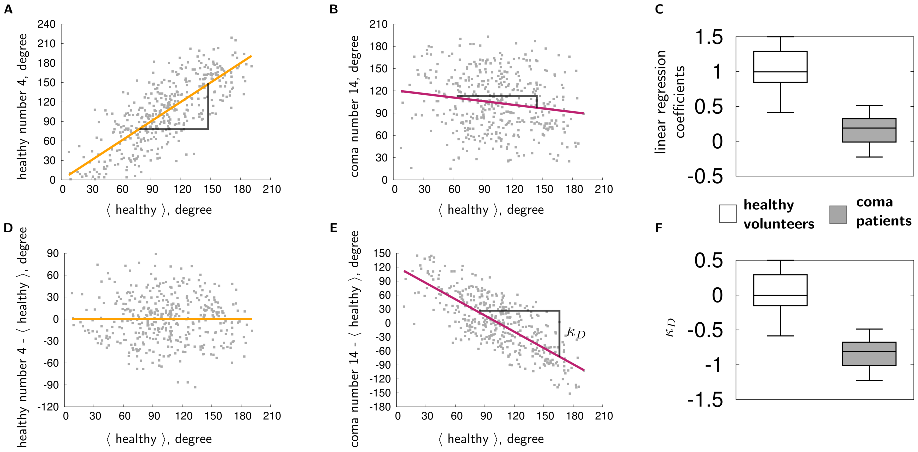
Examples of connectivity graphs



Results: nodal connectivity

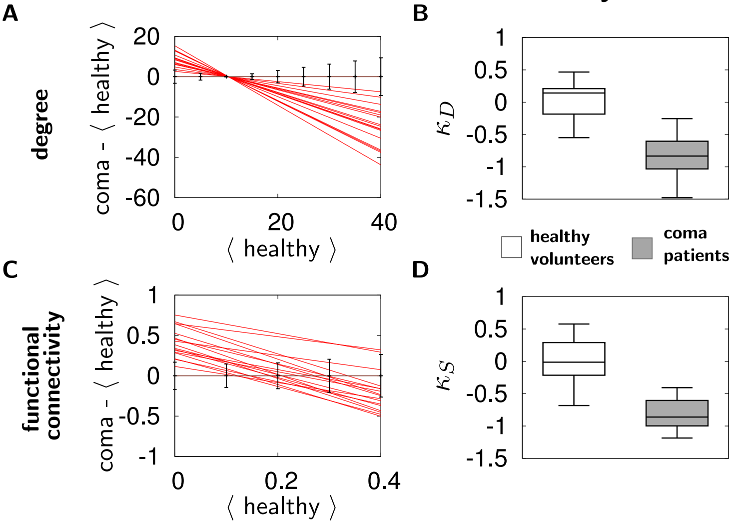


Results: hub disruption index

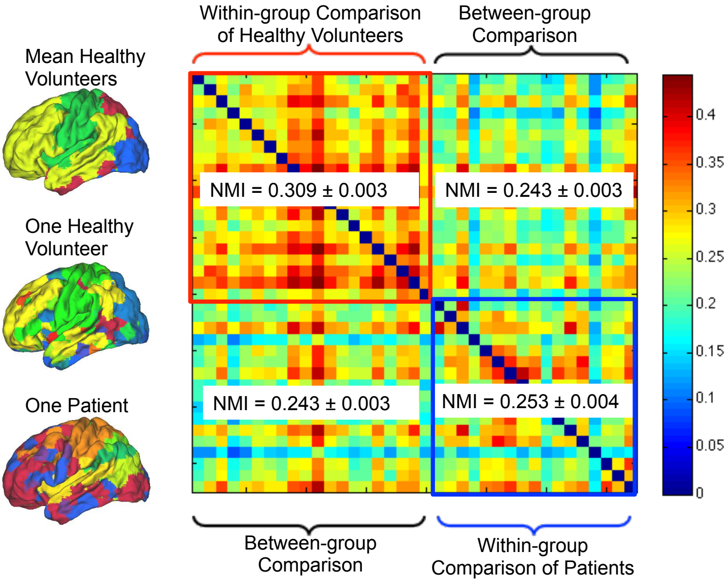


Results: hub disruption index

One index to discriminate the coma and healthy volunteers



Results: modularity



Discussion

- GABAergic disinhibition of secondary pathways between undamaged brain regions that were not used during normal functioning of the brain. [Chen *et al.* Neuroscience 2002, Hagmann *et al.* PNAS 2010]
- All the patients experienced an acute crisis of extreme cerebral hypoxia or hypoglycemia and it is known from prior studies that functional network hubs tend to be metabolically more expensive, e.g., having greater rates of glucose metabolism, than non-hubs. [Bullmore and Sporns, Nat Rev Neurosci 2012]
- The emergence of new hubs in anatomical regions that were not so topologically important before the injury represents an immediate, perhaps interneuronally-mediated, response to brain injury. [Honey *et al.* 2007]

Conclusion

- global topological properties, such as small-worldness and modularity, are not suffcient to describe the brain network organization required for consciousness
- Disruption of hubs rank order
- Characterisation of each patient individually

Questions ?

- How can we explain this global conservation ?
- Can metabolic data such as PET help ?
- Why some patients recover ?