Fractal brain connectivity
Functional connectivity using wavelets and graph theory
Part III: Graphs representations and metrics

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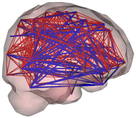


1. Individual image
2. Characterisation of the networks
   - Graph metrics
3. Statistics on groups
   - Comparison between groups
   - Comparison between groups, region level
4. Multivariate approach
   - Machine learning with brain graphs
   - Generative models
   - Resilience to attacks
5. A clinical example on coma patients
6. Conclusion

fMRI data acquisition parameters – first dataset

[Achard et al. 2006, Achard and Bullmore 2007]

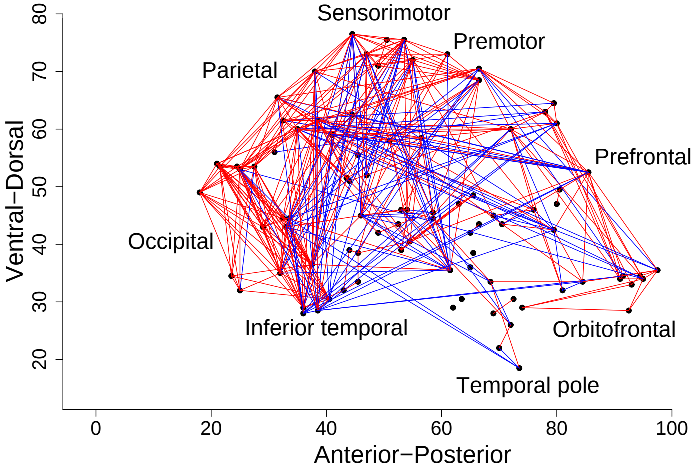
- **90 anatomical regions:** space average of the fMRI time series over all voxels in 90 regions [*Tzourio-Mazoyer et al.* 02]
- **SPM preprocessing:** correction for geometrical displacements
- **Resting state:** lying quietly with eyes closed during 10 minutes
- **Graph analysis:** Mean of the correlation with 5 healthy volunteers
- **Group comparison:**
  15 young healthy volunteers (24.7 years), 11 healthy old volunteers (66.5 years)
  Placebo and drug (sulpiride)

fMRI data acquisition parameters – second dataset

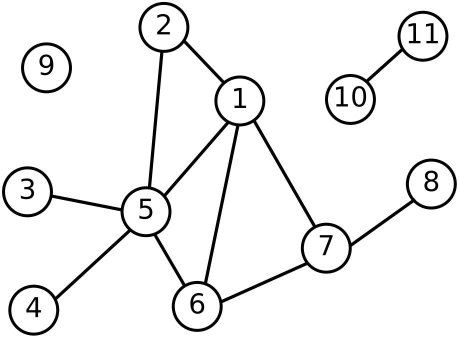
[Achard et al. 2012]

- **90 and 417 anatomical regions:** space average of the fMRI time series over all voxels in 90 and 417 regions [*Tzourio-Mazoyer et al.* 02]
- **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
  Placebo and drug (sulpiride)

Individual graphs: representation of networks for a given threshold



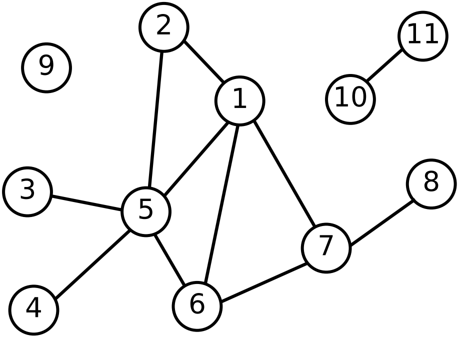
Measures extracted on the network



Node	Degree	Mean minimum path length	Clustering coefficient
1	4	1.41	0.125
5	5	1.42	0.02
9	0	∞	∞

Small-world [*Watts and Strogatz*, 98]

Measures extracted on the network



Node	Degree	Nodal efficiency	Local efficiency
1	4	0.55	0.72
5	5	0.58	0.25
9	0	0	0

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

Degree, Global efficiency and Local efficiency

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

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

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.

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

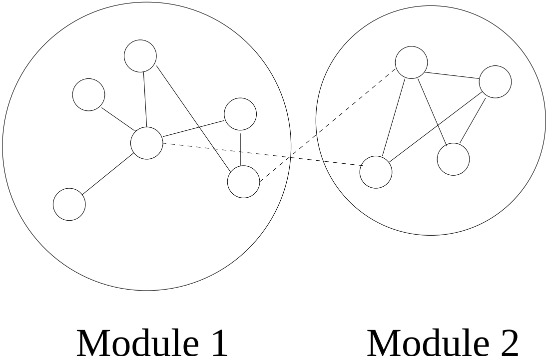
Clustering, also called "local efficiency" = measure of information transfer in the immediate neighbourhood of each node

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

Modular organization of human brain functional networks

[Meunier *et al.* NeuroImage 2009]

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

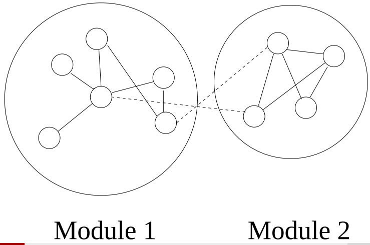


Modularity measure

[Newman *et al.* 2004]

$$M = \sum_{s=1}^{N_M} \left[\frac{l_s}{L} - \frac{d_s}{2L} \right]$$

- N_M = number of modules
- L = total number of edges in the network
- l_s = total number of edges between nodes in module s
- d_s = sum of the degrees of nodes in module s

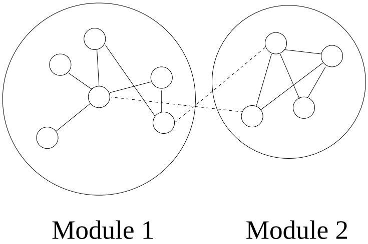


Modularity measure

[Newman *et al.* 2004]

$$M = \sum_{s=1}^{N_M} \left[\frac{l_s}{L} - \frac{d_s}{2L} \right]$$

- $M = 0$ when no edges
- $M = 0$ when all the nodes are connected to each other
- maximisation of M is 'NP-hard' problem



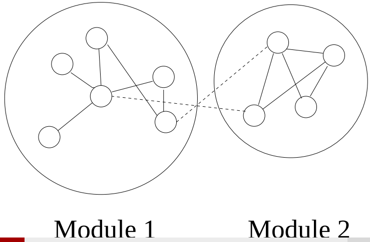
Modularity measure

[Newman *et al.* 2004]

$$M = \sum_{s=1}^{N_M} \left[\frac{l_s}{L} - \frac{d_s}{2L} \right]$$

Objective : Optimization of modularity

- link centrality to incrementally increase network modularity to a maximum [Newman *et al.* 2004]
- direct search with the "greedy" algorithm [Newman *et al.* 2004]
- direct search with the simulated annealing [Guimerà *et al.* 2005]

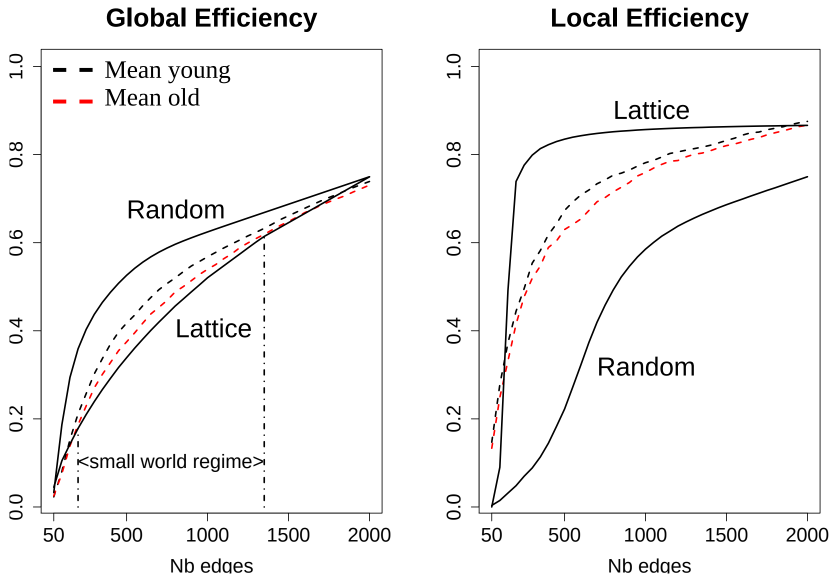


Other graph metrics

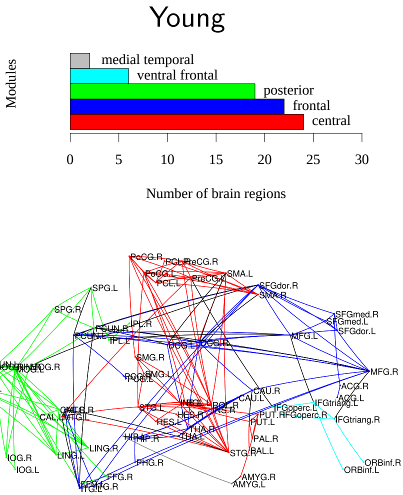
- Betweenness centrality
- Percolation
- Spectral graphs
- Rich club
- ...

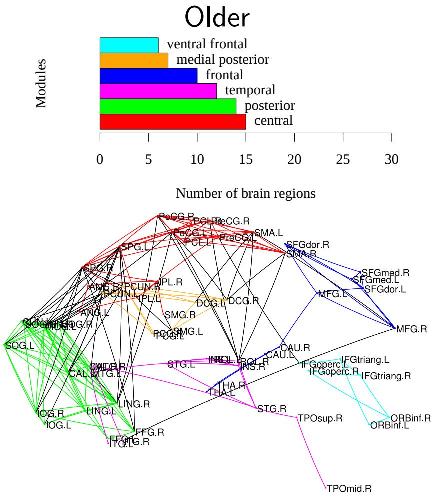
Toolbox on R: igraph Ref: for example [*Rubinov et al.*, 09]

Choice of threshold for a given scale

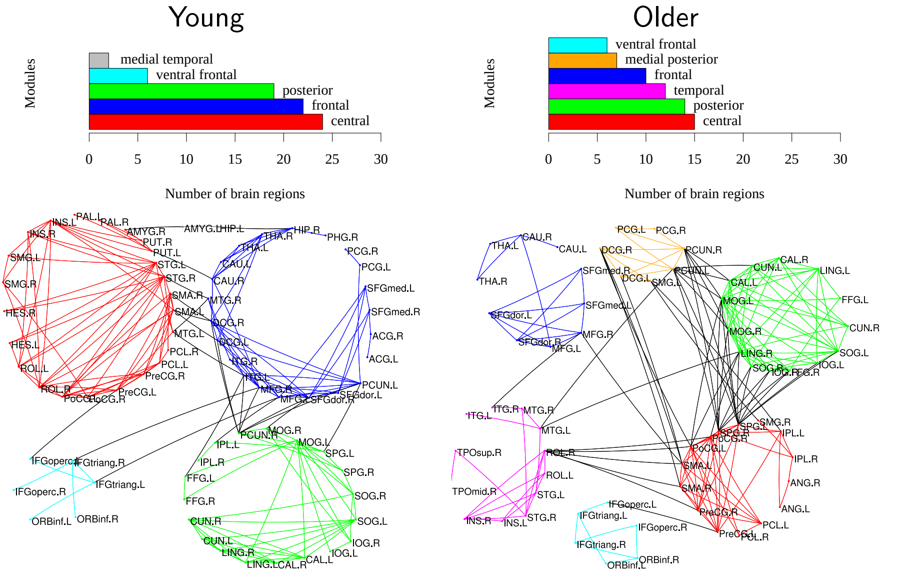


Modular organization of human brain functional networks



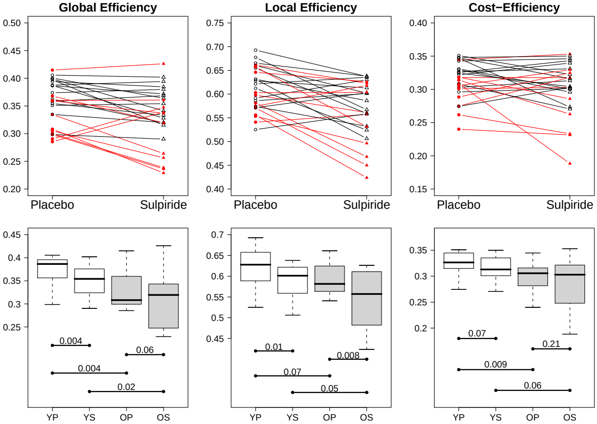


Modular organization of human brain functional networks



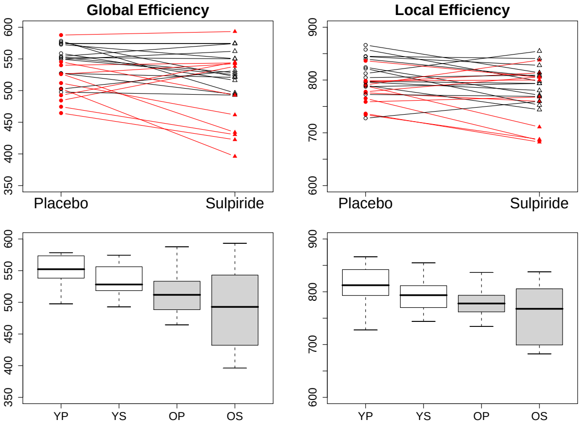
Comparison between groups, for a given number of edges

15 young healthy volunteers (24.7 years), 11 healthy old volunteers (66.5 years). Placebo and drug (sulpiride)

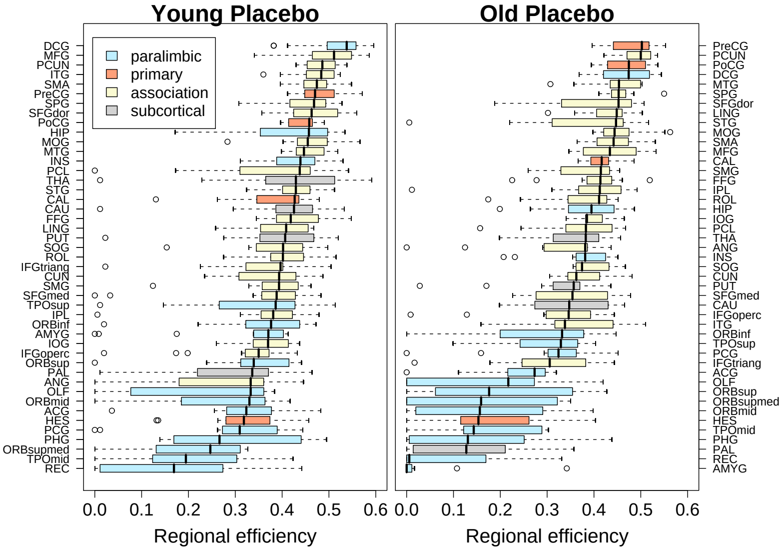


Comparison between groups, without threshold

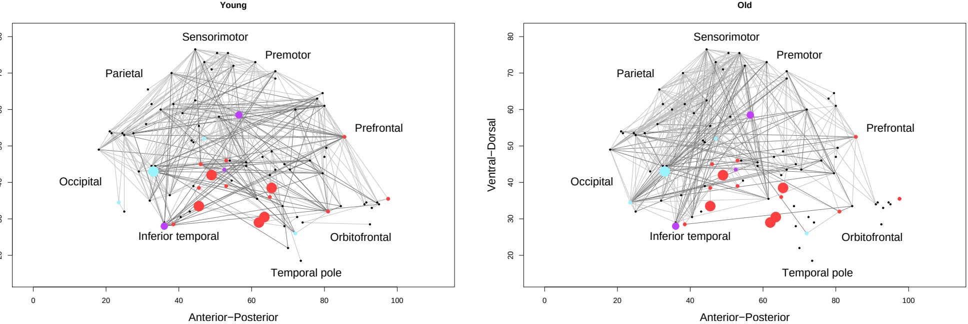
15 young healthy volunteers (24.7 years), 11 healthy old volunteers (66.5 years). Placebo and drug (sulpiride)



Comparison between groups, region level



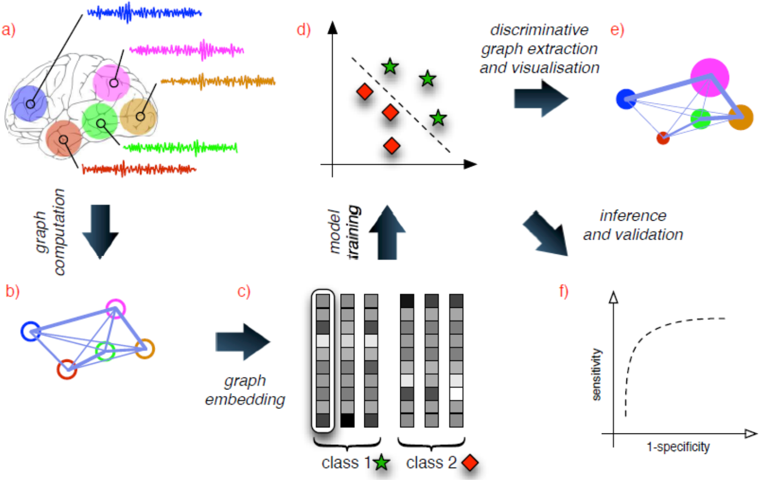
Comparison between groups, region level



effect of age   effect of drug   both effect of age and drug

Machine learning with brain graphs

Why extracting lots of graph metrics?



[Richiardi *et al.* 13]

Comparison between metrics and correlations

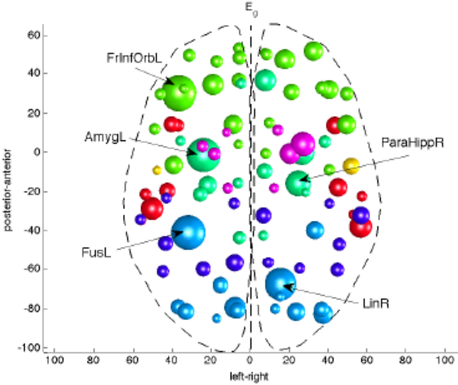
Two groups comparisons using a set of metrics (y=young, o=elderly, b=balance)

- When using correlation coefficients (SVM):

  Py = 87%, Po = 64%, Pb = 76%.

- Embedding the thresholded 400-edges weighted graphs in the same way (C4.5 tree):

  Py =93%, Po = 73%, Pb = 83%

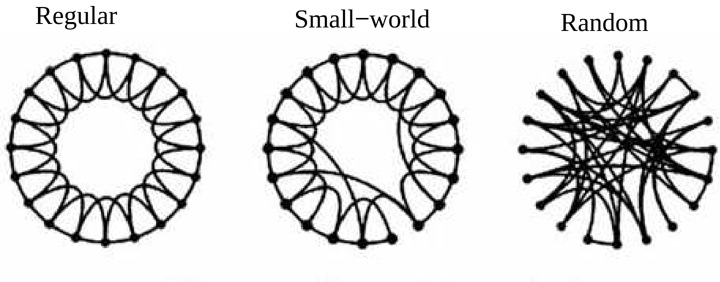


[Richiardi *et al.* 11, Achard *et al.* 07]

Generative models

A simple one: the Watts and Strogatz model.

How to move from a regular graph to a random one by rewiring the edges?



[Watts and Strogatz 1998]

Generative models

Objective: Based on observations of real networks, how to generate networks with a simple mathematical expression.

- Barábisi model: scale-free graphs. Based on preferential attachement
- Economical model: [Kaiser and Hilgetag 2004]

$$P_{ij} \sim exp(-\eta d_{ij})$$

- Economical preferential attachement: [Yook *et al.* 2002]

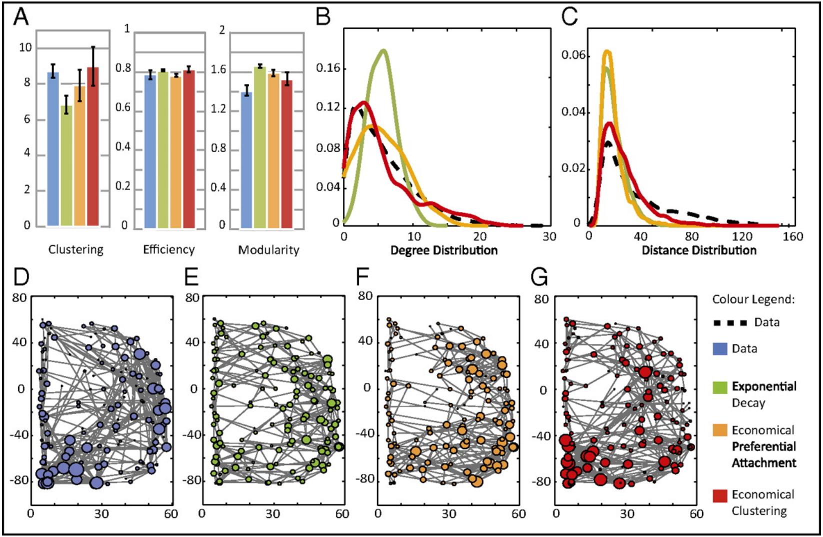
$$P_{ij} \sim (k_i k_j)^{\gamma} d_{i,j}^{-\eta}$$

- Economical clustering model: [Vértes *et al.* 2012]

$$P_{ij} \sim (k_{i,j})^{\gamma} d_{i,j}^{-\eta}$$

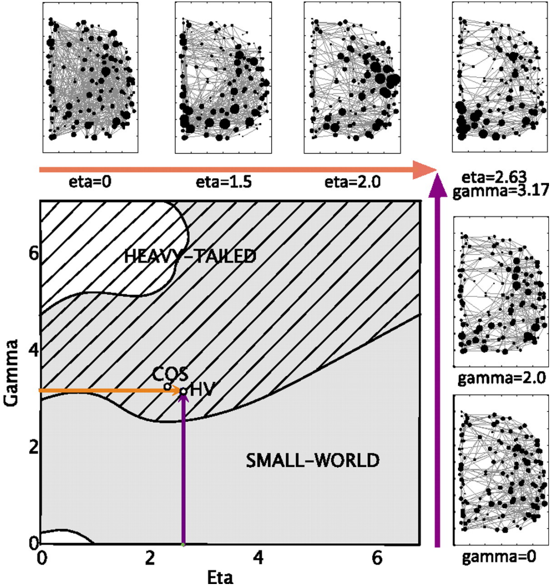
where k_i is the degree of node i and $k_{i,j}$ is the number of nearest neighbours in common between nodes i and j.

Generative models



[Vértes *et al.* 2012]

Generative models

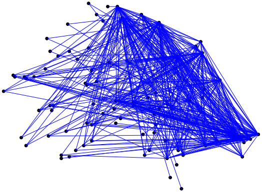


Resilience to attacks

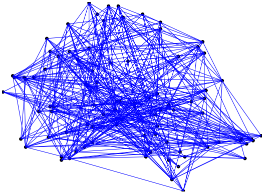
Comparison of the human brain functional network with other networks:

- Erdos-Renyi random graphs : randomly chosen connections
- Scale-free graphs : distribution of the degree = power law (e.g. WWW)

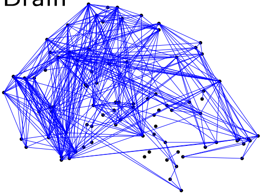
Scale-free



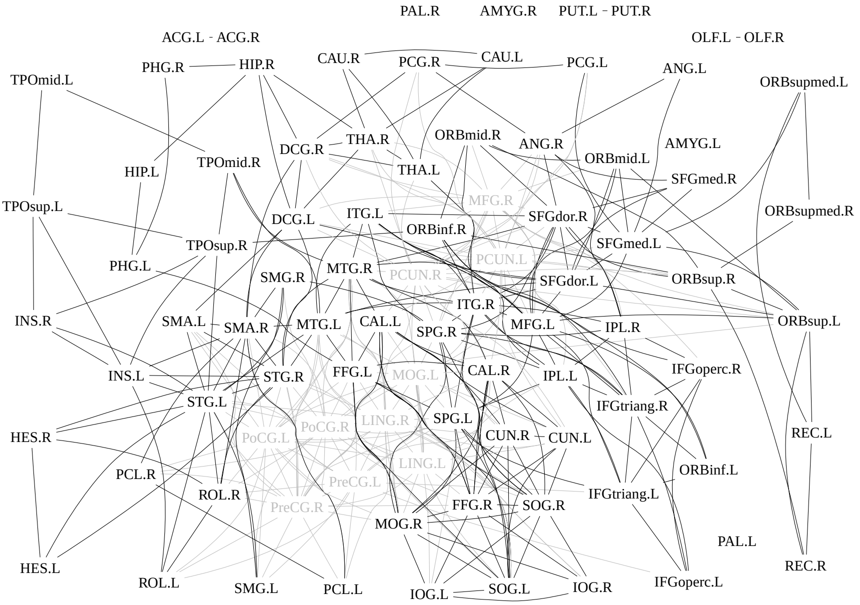
Random



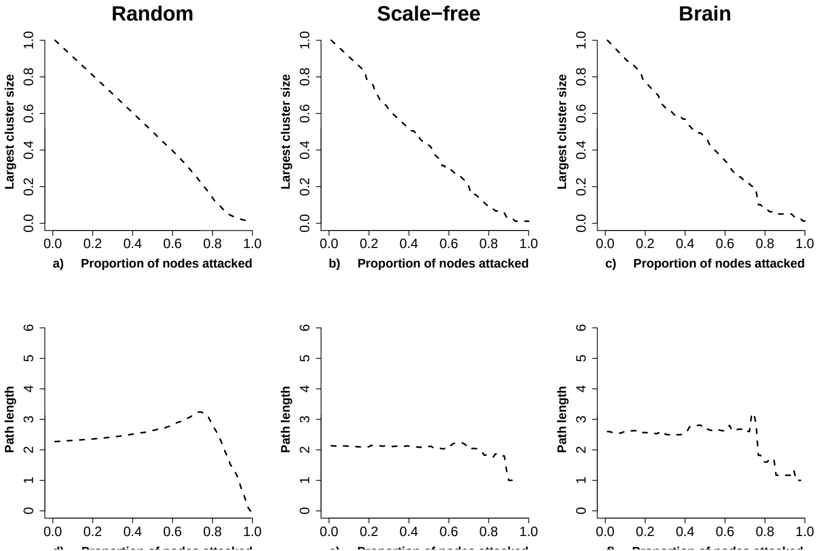
Brain



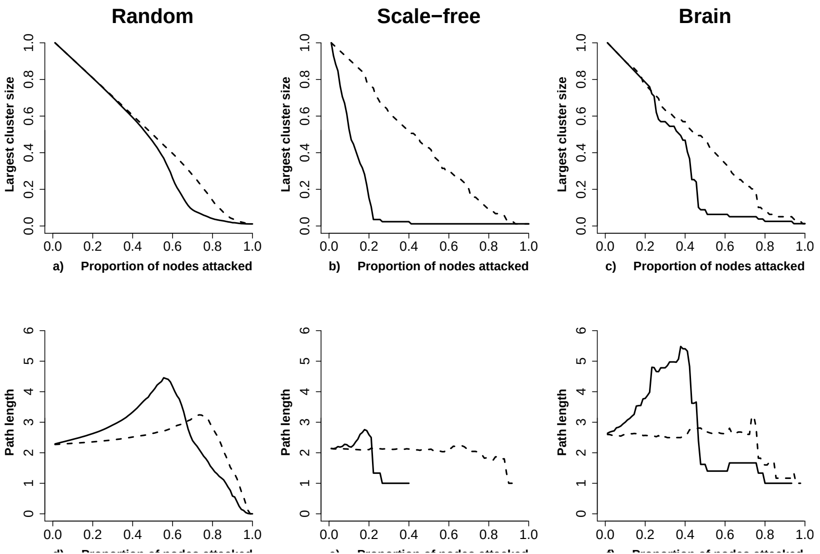
Resilience of human brain functional network



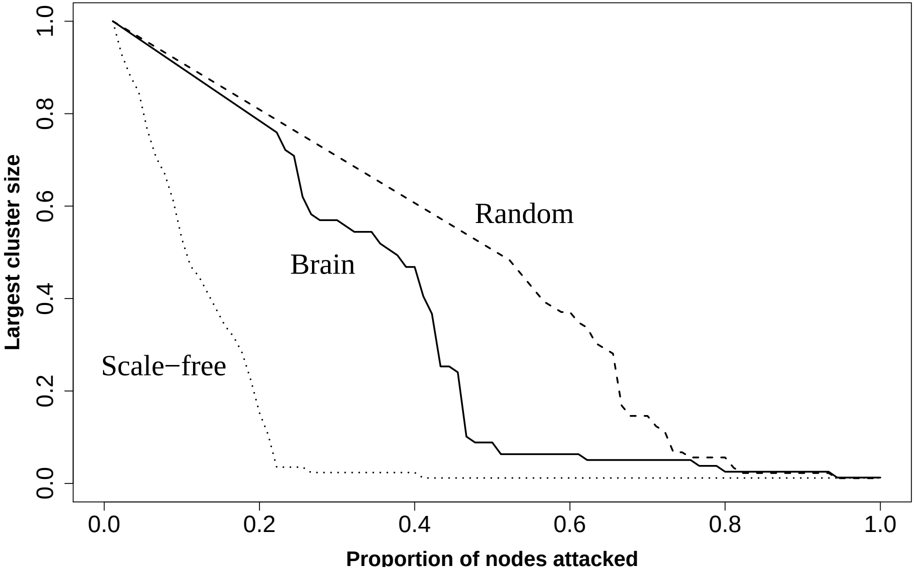
Resilience of human brain functional network



Resilience of human brain functional network

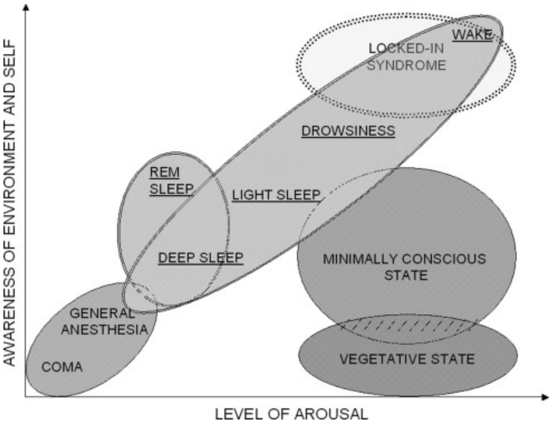


Resilience of human brain functional network



Introduction: Disorders of consciousness

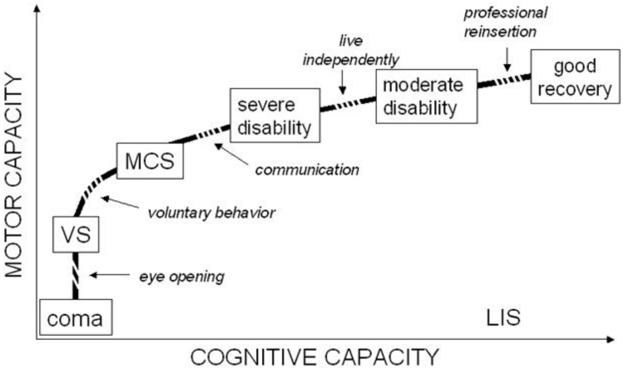
Following Plum and Posner (1983), consciousness has two dimensions: **wakefullness** (also called arousal) and **awareness**.



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

Introduction: Disorders of consciousness

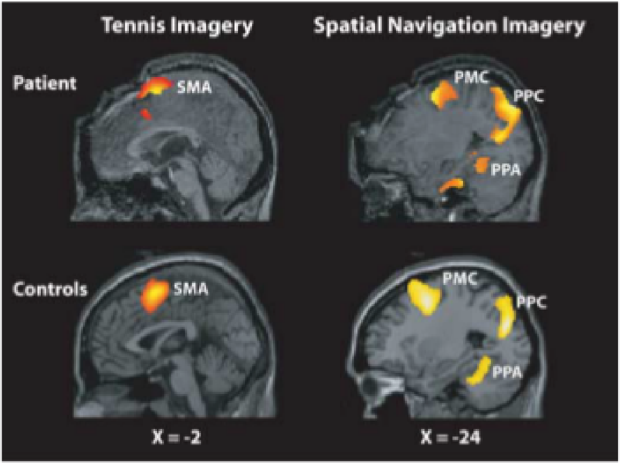
The only way to diagnose a patient in a given state is done by careful and repeated clinical assessments of wakefulness and awareness. High rate of misdiagnosis, especially to distinguish between vegetative state and minimially conscious state (up to 43% evaluated in 1996).



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

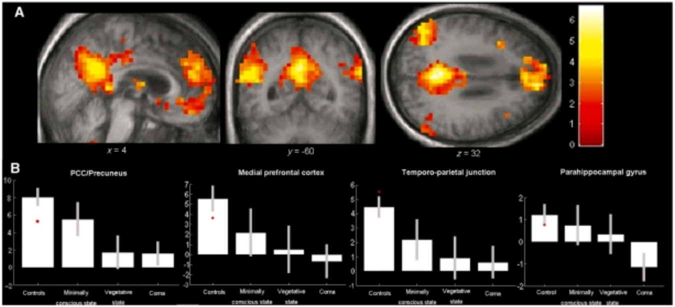
Introduction: Detecting awareness using fMRI

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



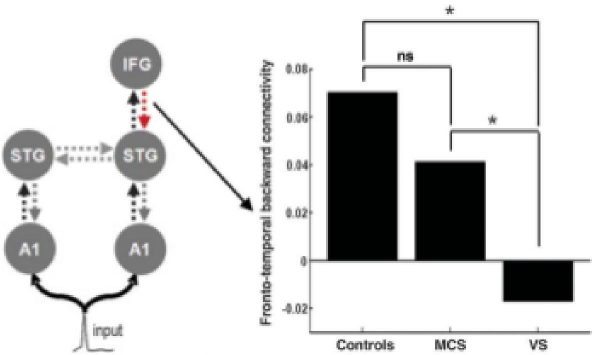
[Owen *et al.* Science, 2006]

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.

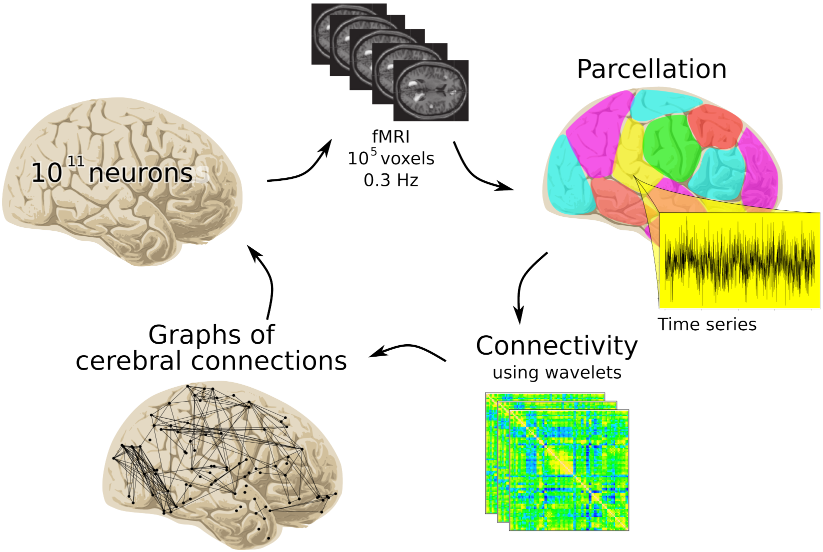
Subjects description

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

fMRI data acquisition

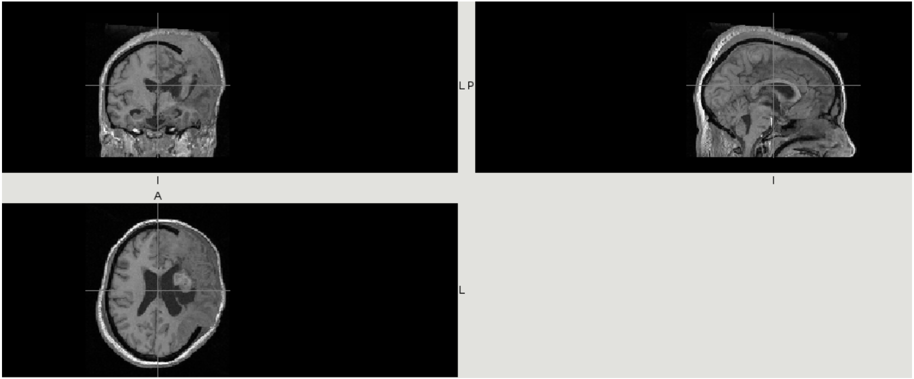
- Functional MRI data were recorded while subjects lay quietly at rest in the scanner for 20 mins. Gradient echo EPI data sensitive to BOLD contrast were acquired using a 1.5 Tesla MR scanner (Avanto, Siemens, Erlangen, Germany) with the following parameters: TR=3 s, TE=50 ms, isotropic voxel size = $4x4x4mm^3$, 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



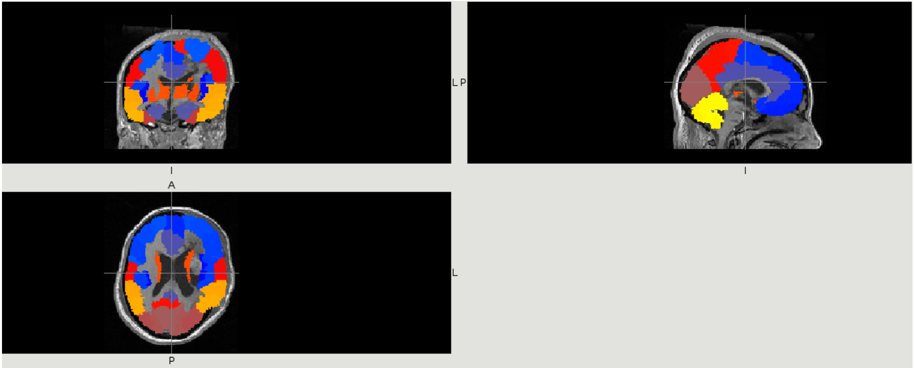
Patient view

Illustration of DARTEL normalisation



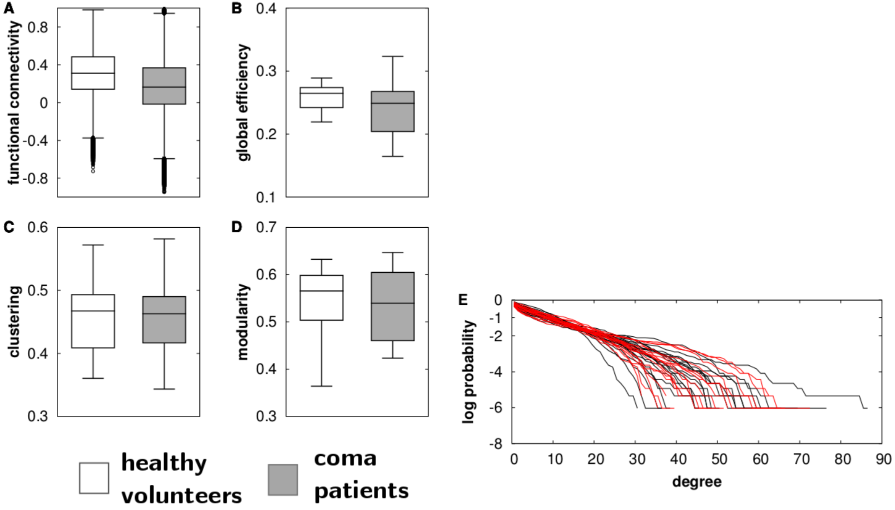
Patient view

Illustration of DARTEL normalisation

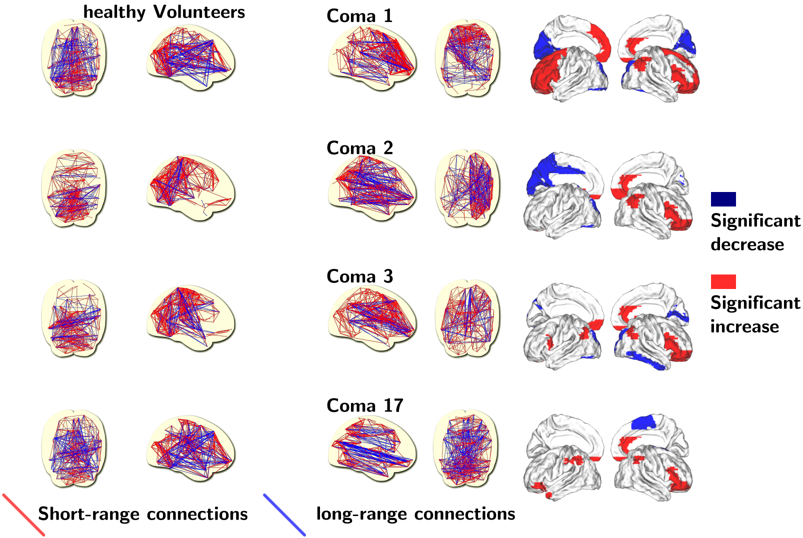


Results: global connectivity and network topology

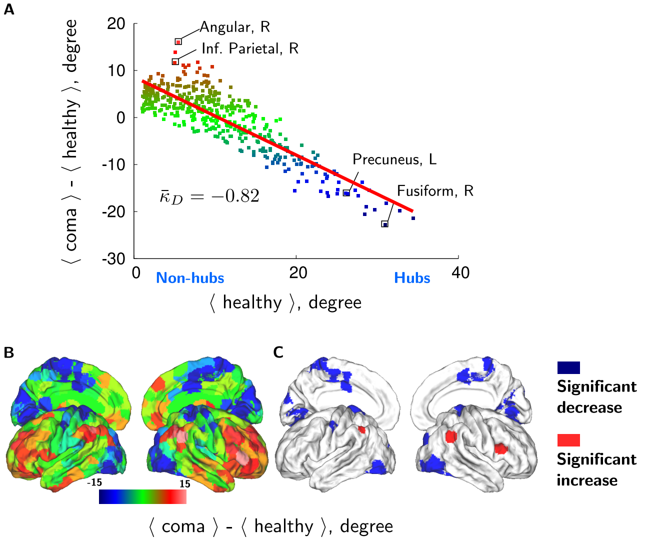
No significant difference on global measure of functional connectivity



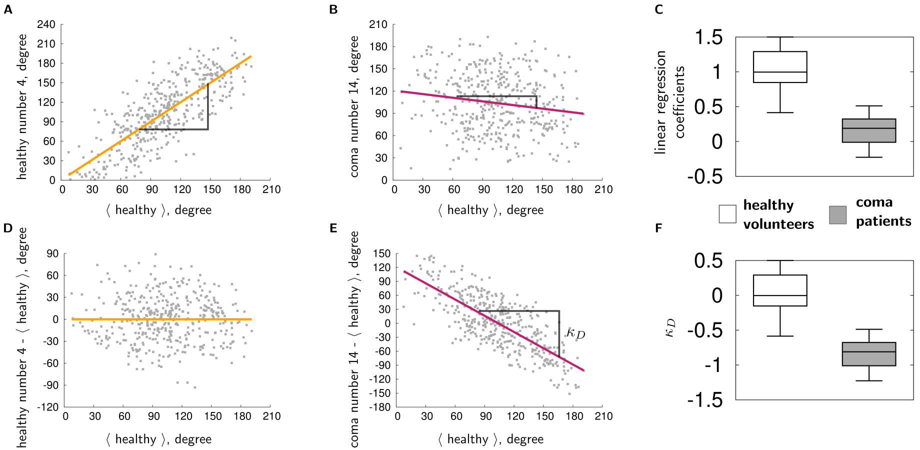
Examples of connectivity graphs



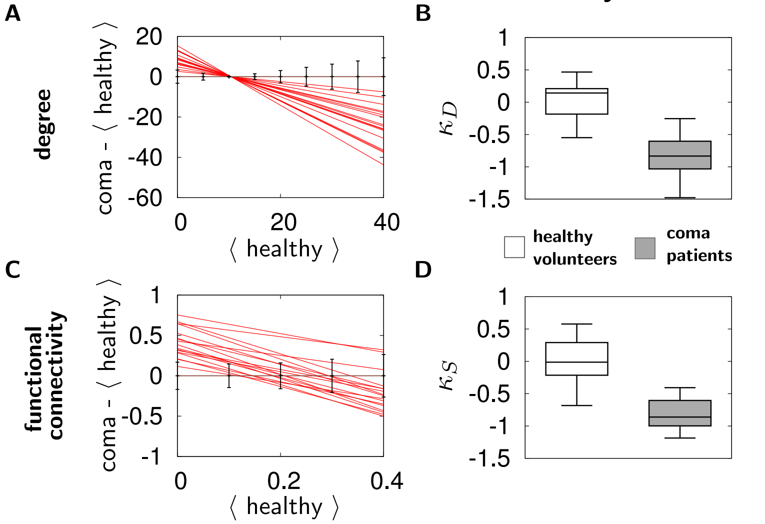
Results: nodal connectivity



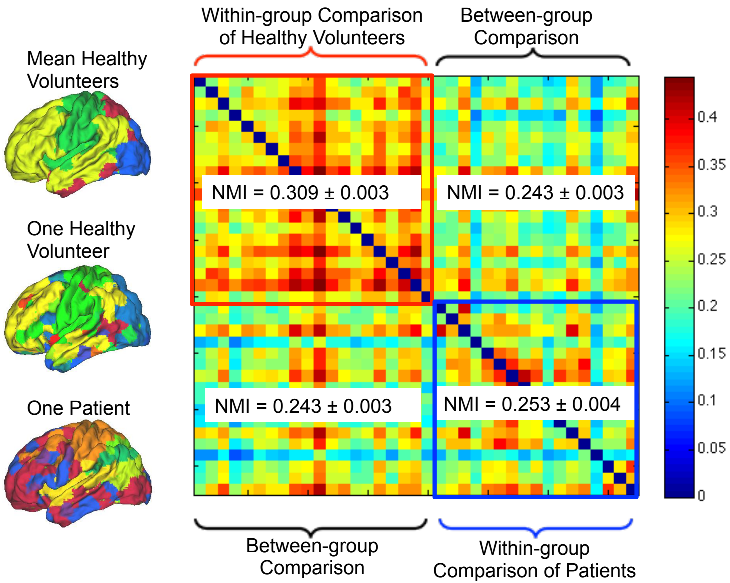
Results: hub disruption index



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

- The brain function is a complex network
- The networks characteristics can discriminate between groups
- The visualisation of the global brain is possible