Fractal brain connectivity
Functional connectivity using wavelets and graph theory
Part II: Extration of connectivity graphs

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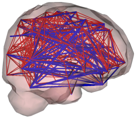
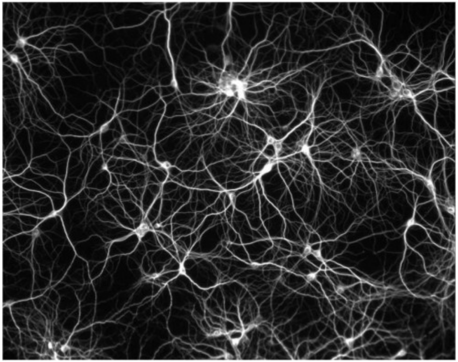


1. Why the brain can be modelled as a complex network?
   - Microscale
   - Macroscale
   - The challenges

2. Extraction of brain functional networks
   - Measuring the activity of the brain
   - Construction of functional networks
   - Wavelets
   - Correlations
   - Parcellation based approaches
   - Choice of threshold

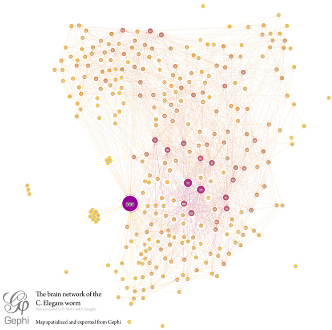
The human brain as a complex network : anatomical description

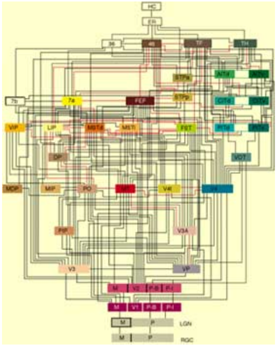


- 10^{11} neurons
- Connected via axons and dendrites (10^{14} connections)
- Transmission of nerve signals (segregated and distributed information)

Examples of microscopic anatomical description of brains

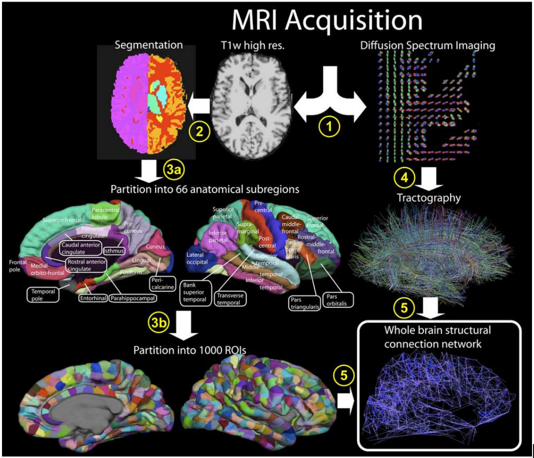
macaque visual cortex	305 conn.	32 areas	Felleman, Van Essen 1991 Young 1992/93
C. elegans	2462 conn.	282 neurons	Brenner 1974 Watts et al. 1998
cat	1139 conn.	65 areas	Young 1992/93



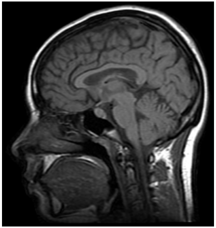


Human brain complex network : Anatomical connectivity

- diffusion tensor imaging
- diffusion spectrum imaging
- cortico thickness

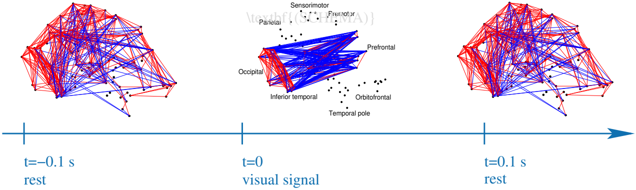


[Hagman 2008]



The challenges

- How can we describe the processing of information in the brain ?
- How can we predict the resilience of the brain functions in case of illness or stroke ?
- How can we characterize the brain dynamics during a task ?



How to explore the functional brain network ?

Non-invasive techniques:

- Electroencephalograpy – EEG
- Magnetoencephalography – MEG
- Functional Magnetic Resonance Imaging – fMRI

How to explore the functional brain network ?

Non-invasive techniques:
Electroencephalograpy – EEG:

[Caton 1875, Beck 1890, Pravidich-Neminsky 1912, Cybulsky et al. 1914, Berger 1920]

Recording of the brain's spontaneous electrical activity from multiple electrodes placed on the scalp.

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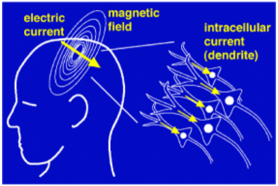
Wikipedia

How to explore the functional brain network ?

Non-invasive techniques:

Magnetoencephalograpy – MEG:[Cohen 1968]

Measure of the magnetic fields produced by electrical activity in the brain via extremely sensitive devices such as superconducting quantum interference devices (SQUIDs).



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How to explore the functional brain network ?

Non-invasive techniques:
Functional Magnetic Resonance Imaging – fMRI:

[Ogawa 1990, Kwong 1991]

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

$\rightarrow$ changes in blood flow and blood oxygenation in the brain (hemodynamics) are closely linked to neural activity. [Roy and Sherrington, 1890]

$\rightarrow$ increase in blood flow to regions of increased neural activity, occurring after a delay of approximately 1-5 seconds.

hemodynamic response :

- blood releases oxygen to active neurons at a greater rate than to inactive neurons
- magnetic signal variation = difference in magnetic susceptibility between oxyhemoglobin and deoxyhemoglobin (thus oxygenated or deoxygenated blood)

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

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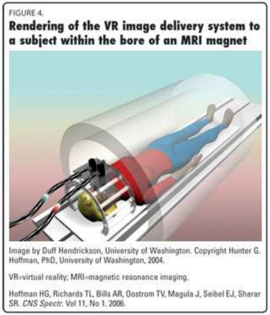

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Wikipedia

Contruction of functional networks : choosing the nodes

- With EEG : the nodes will be the sensors (64-128)
- With MEG : the nodes will be the sensors (300)
- With fMRI : the nodes can be the voxels (10^5) or some pre-defined anatomical of functional areas (100-2000)

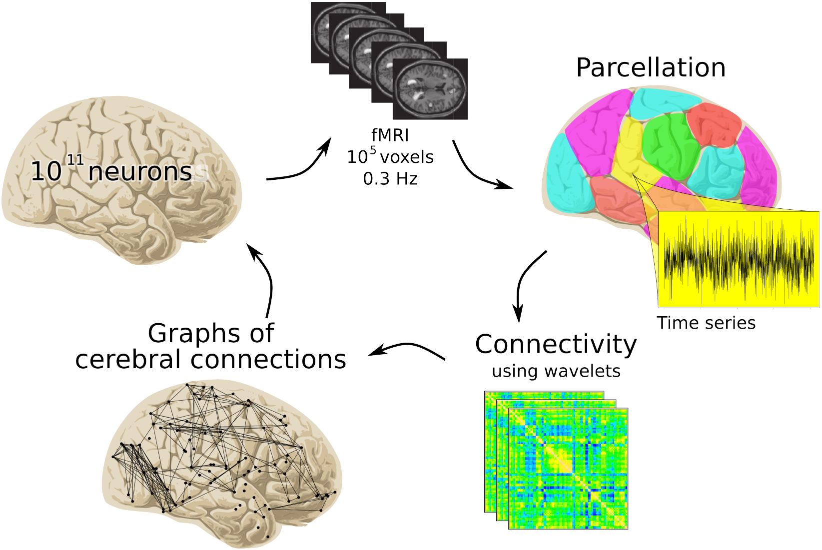
Choosing the nodes in fMRI

- Computational cost is too high when considering the voxels
- The voxels are noisy
- Anatomical definitions of brain areas is independent of the explored brain function

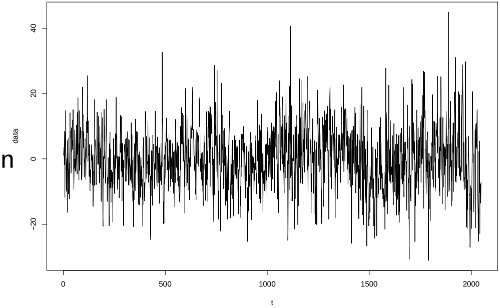
There is no perfect solutions! It is still under investigations!

Some references [Eguiluz 2005, Salvador 2008, Wang 2009, Fornito 2009]

Extracting the connections using fMRI modality



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!

Wavelets and correlation

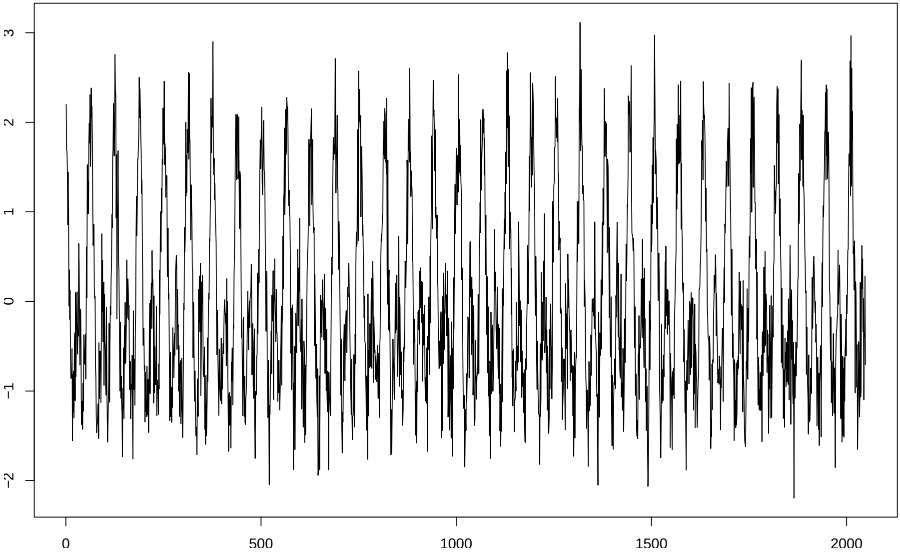
Why using the wavelets ?

- 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

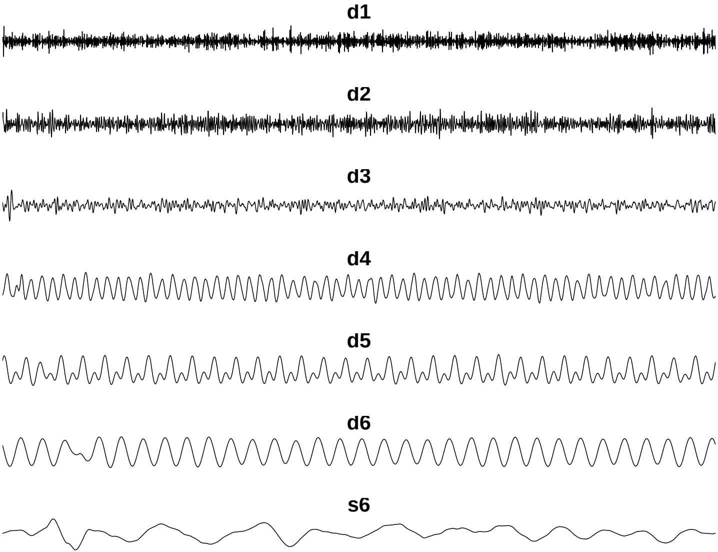
One example of wavelet functions: Daubechies 8

An example of wavelet decomposition

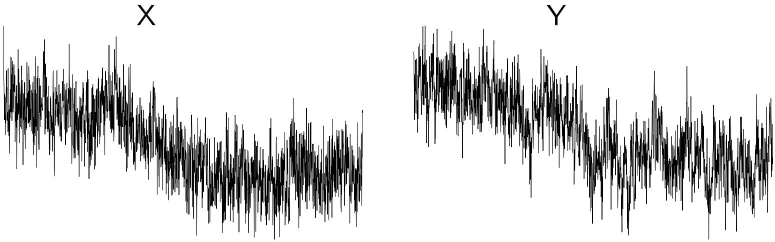
Example with a signal $X(t) = cos(t/5) + cos(t/10) + \mathcal{N}(0, 0.4)$**:**



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



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)

$\mathbf{X}$ 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

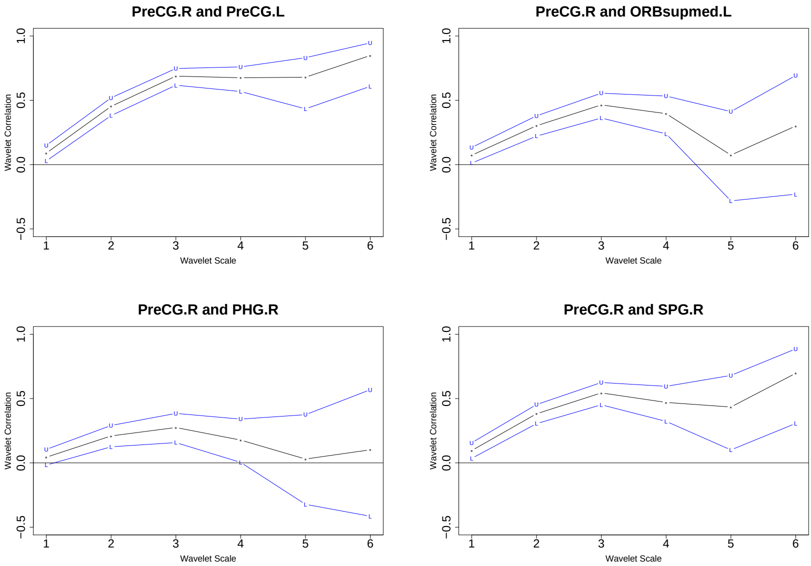
$$\widehat{\rho}_{XY}(\lambda_j) = \frac{\widehat{\gamma}_{XY}(\lambda_j)}{\widehat{\nu}_X(\lambda_j)\widehat{\nu}_Y(\lambda_j)} \rightarrow \mathcal{N}(\rho_{XY}(\lambda_j), \Sigma)$$

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



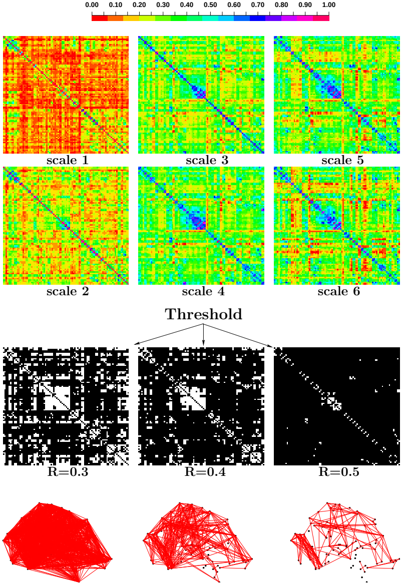
Construction of the adjacency matrices

→ pair-wise inter-regional correlations

- Wavelets MODWT
- Connectivity = Correlation

→ adjacency matrix
Threshold ?

→ Undirected graphs :
small-world properties



Construction of the adjacency matrices

Hypothesis tests: for all i, j, $1 \leq i, j \leq 90, \quad i \neq j$

$$\mathcal{H}_0 : P(\rho_{i,j} \leq R) \qquad \mathcal{H}_1 : P(\rho_{i,j} > R)$$

Problems :

- Multiple hypotheses tests : 4005 tests
  $\rightarrow$ Application of the False Discovery Rate [*Benjamini et al.* 01]
- Choice of threshold R:
  $\rightarrow$ Free parameter
  $\rightarrow$ No rationale for its choice
  $\rightarrow$ Need to compare graphs with same number of edges
  $\rightarrow$ Maximise interesting properties

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	$\mathbf{U}$	$\mathbf{V}$	n_0
Non-true null hypotheses	$\mathbf{T}$	$\mathbf{S}$	$4005 - n_0$
	$4005 - \mathbf{W}$	$\mathbf{W}$	4005

Multiple hypotheses tests

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Non-true null hypotheses	$\mathbf{T}$	$\mathbf{S}$	$4005 - n_0$
	$4005 - \mathbf{W}$	$\mathbf{W}$	4005

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

Multiple hypotheses tests : FDR procedure

[*Benjamini et al.* 01]

Hypotheses : $\mathcal{H}_1, \mathcal{H}_2, \ldots, \mathcal{H}_{4005}$

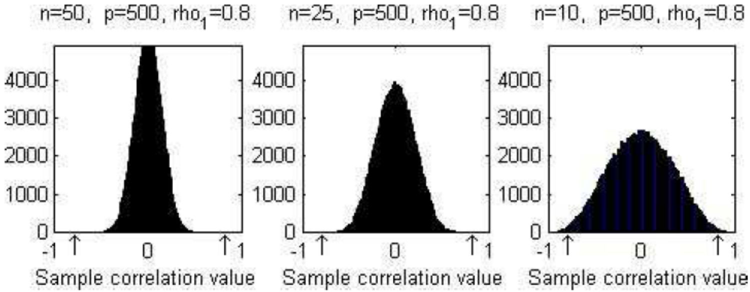
Corresponding p-values : $p_1, p_2, \ldots, p_{4005}$
and $p_{(1)}, p_{(2)}, \ldots, p_{(4005)}$ the ordered p-values. ($\mathcal{H}_{(i)}$ the null hypothesis corresponding to $p_{(i)}$)

$$\text{Let } k \text{ be the largest } i \text{ for which } p_{(i)} \leq i\alpha/4005$$
$$\text{then reject all } \mathcal{H}_{(i)},\ i = 1, 2, \ldots, k$$

For independent test statistics and for any configuration of false hypotheses, the *FDR* is controled at α.

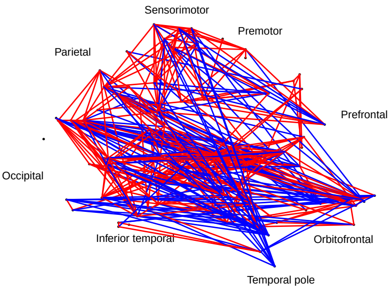
Parcellation based approaches

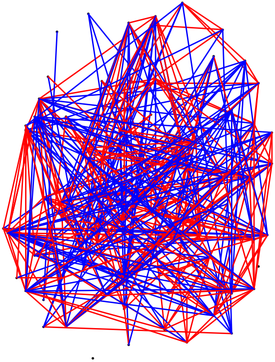
Trade-off between the number of point in time series and the number of connections to explore.



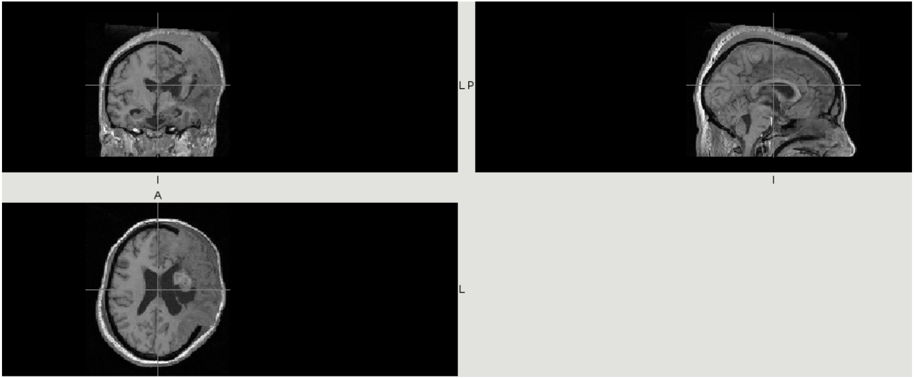
Multivariate normal sample where all but two of the p = 500 variables are mutually uncorrelated as n decreases over the range 50, 25, 10. These two variables have a correlation coefficient equal to 0.8.
[*Hero et al.* 11]

Parcellation based approaches





Parcellation based approaches

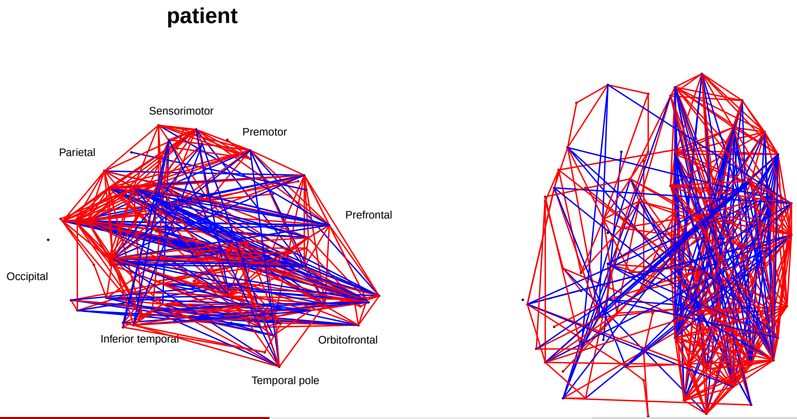


Parcellation based approaches

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



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

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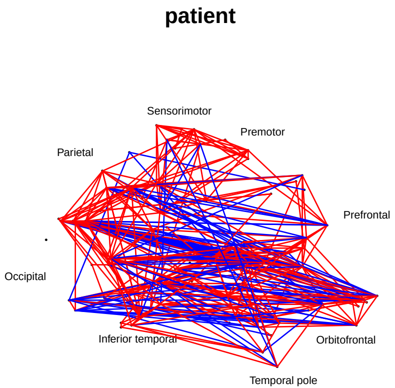
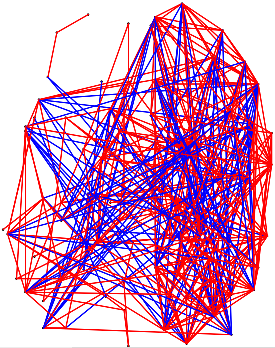
Using 200 points in time





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

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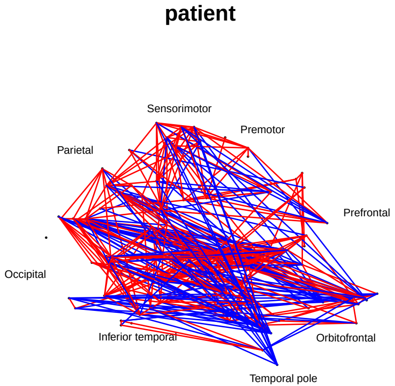
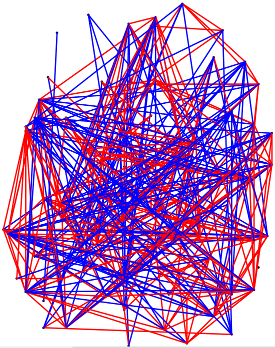
Using 70 points in time





- 90 regions
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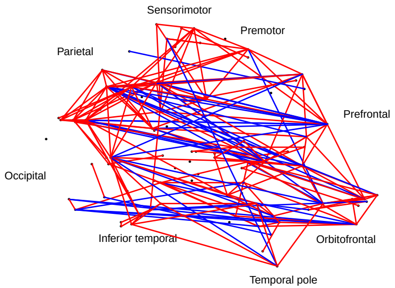
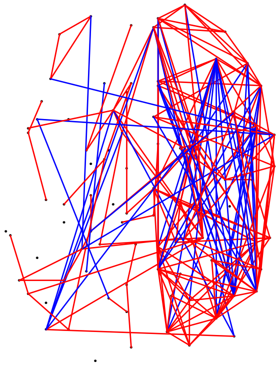
Using 405 points in time

patient





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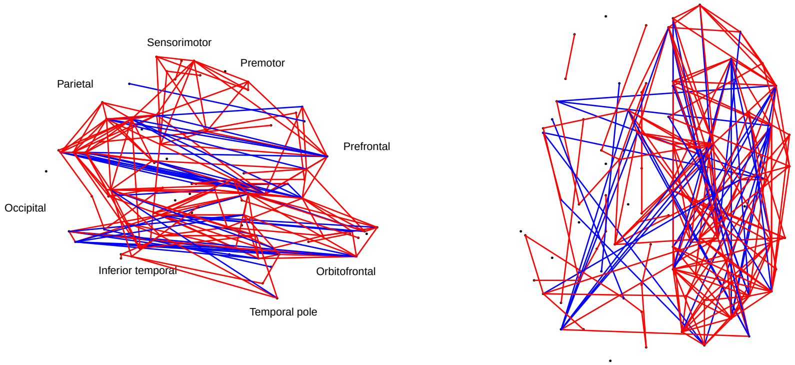
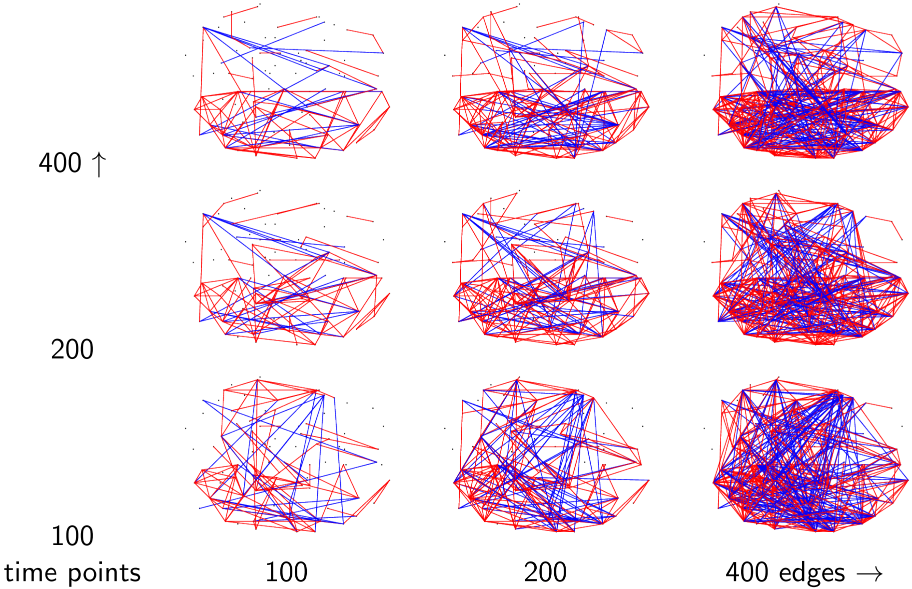
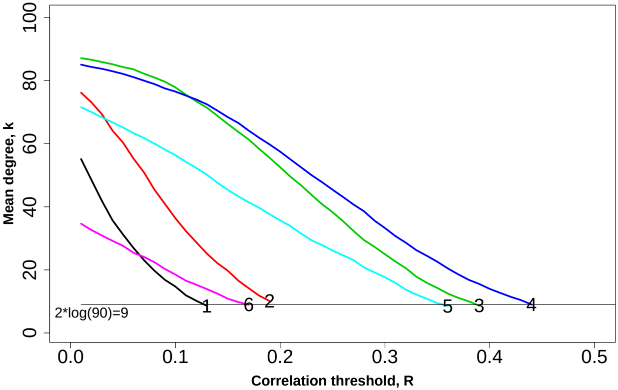



400 ↑
200
100
time points
100
200
400 edges →

Choice of threshold in terms of scales

Here 2048 points in time. [*Achard et al.* 06,*Achard et al.* 08]



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