fMRI quantification analysis and multiple regression

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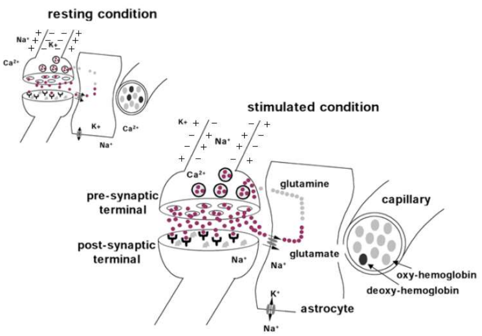
Outline

- Functional MRI review
- fMRI data analysis
  - 1st-level individual analysis
  - 2nd-level group analysis
  - multiple regression
- Resting-state fMRI quantification
- Graph theoretical analysis
- Demo

Physiology during neural activation

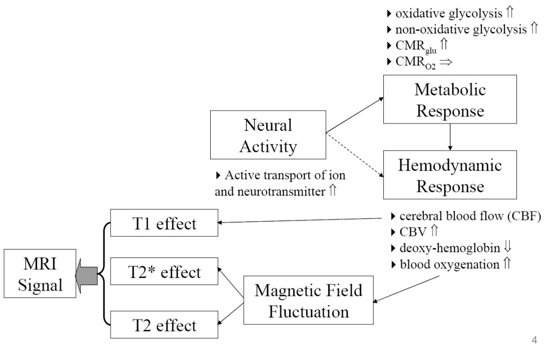


Kida and Hyder, Magnetic Resonance Imaging Methods and Biologic Applications 2006; chapter 7.

Energy during neural activation

- **Neuronal firing: electrical activity**
  - Excitatory and inhibitory
    - Neurotransmitter release and uptake
  - Action & graded potential
    - Ion flow
  - Hormone
- **Biochemical reaction: metabolic activity**
  - Active transport of ion pumps
  - Oxidative / non-oxidative glycolysis
- **Vascular response: hemodynamic activity**
  - Energy demand, clean up waste
  - Blood flow, blood volume, blood oxygenation

BOLD fMRI physiology



Interpretation of fMRI signal

- fMRI signal is an index of ensemble of neural activity
  - presumably monotonic relation
- Neural source of BOLD signal is not clear
  - spiking activities vs. synaptic activity
  - excitatory vs. inhibitory
- Difficult to compare fMRI signals across cortical regions and subjects
  - BOLD signal depend on vascular structure and volume

Other issues

- **Normal physiology condition**
  - Age
    - inferior vascular response for aged people (CBF decrease)
    - neonate: deoxyHb increase
  - Disease
    - transient global ischemia: vascular response abolished
    - carotid stenosis: vascular response diminish
  - Drug
    - alter vascular response, cardiopulmonary function,…
- **Meaning of negative response**
  - Negative response -> decreased activity?
  - Inhibitory activity also increase glucose uptake

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Challenge of quantification

- **Electrical activity**
  - Tiny perturbation in magnetic field: MRI phase
  - Ca^{2+} : manganese (Mn^{2+}) enhanced MRI
  - Glutamate, GABA : H^1-MRS
- **Metabolic activity**
  - Lactate : H^1-MRS
  - $CMRO_2$: combine CBF and BOLD
- **Hemodynamic activity**
  - Oxygenation: BOLD fMRI
  - CBF: Arterial Spin Labeling (ASL) MRI
  - CBV: contrast-injection / VASO

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fMRI analysis tools

- SPM (Statistical Parametric Mapping)
  - Wellcome Trust Centre for Neuroimaging, UCL, UK
  - http://www.fil.ion.ucl.ac.uk/spm/software/
- FSL (FMRIB Software Library)
  - Oxford, UK
  - http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/
- AFNI (Analysis of Functional NeuroImages)
  - NIH, USA
  - http://afni.nimh.nih.gov/afni/download
- REST (Resting-State fMRI Data Analysis Toolkit)
  - Lab of Cognitive Neuroscience and Learning, Beijing Normal University, China
  - http://restfmri.net/forum/index.php

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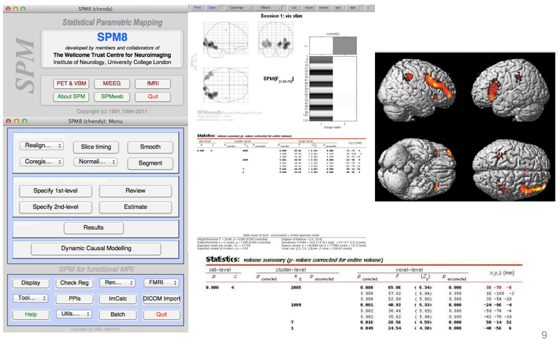
SPM (Statistical Parametric Mapping)



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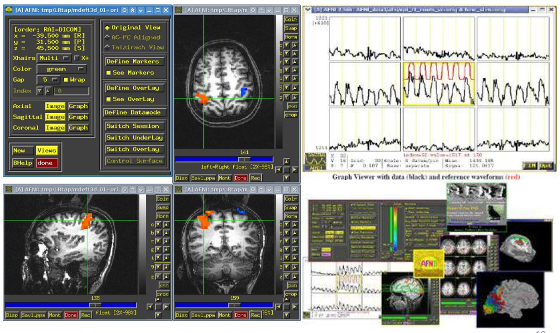
AFNI (Analysis of Functional NeuroImages)



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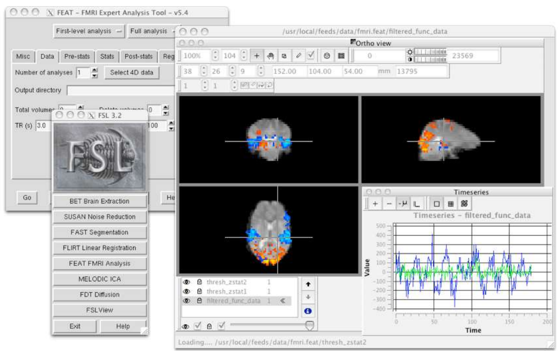
FSL (FMRIB Software Library)



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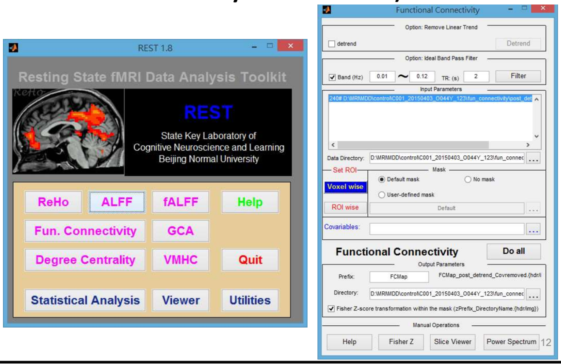
REST (Resting-State fMRI Data Analysis Toolkit)



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Analysis tools comparison

	SPM	AFNI	FSL	REST
Features	最多人使用，資料分析流程易標準化且便於操作，但細節不易作修改	資料分析流程適合略懂Unix指令人員，每一步驟均可做調整，有較大之自由度	資料分析流程亦適合初學者，為一免費之工具，並可由介面或是指令兩方面著手	適合resting-state fMRI初學者，為一免費之工具
Operating system	Any OS with Matlab	Mac, Linux, some Matlab-compatible scripts	Mac, Linux, Windows	Any OS with Matlab
User interface	MATLAB scripts and button-press	Unix functions and GUI	Unix functions and GUI	MATLAB scripts and button-press

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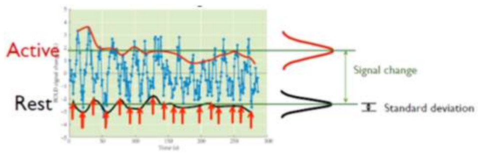
Pre-processing and processing

DICOM Import → Realignment (Motion Correction) → Slice-Timing →

Normalization → Smoothing → 1st-level individual analysis →

Estimate → Result → 2nd-level group analysis

Activity evaluation



- Use concept of **normal distribution** to model **each condition** in BOLD signal.
- Find which voxels have time courses that match the predicted response.
- An unrelated brain region should have no response!

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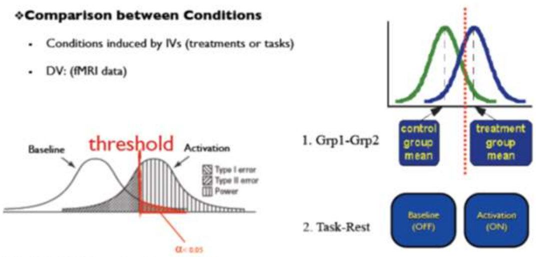
Statistical comparison

❖**Comparison between Conditions**
- Conditions induced by IVs (treatments or tasks)
- DV: (fMRI data)



H_0: Null Hypothesis: no difference
H_1: Alternative Hypothesis: difference exists

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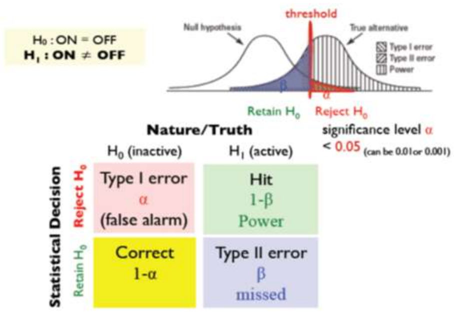
Hypothesis testing in statistics



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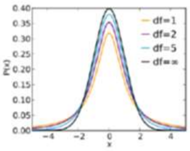
Statistics: t-test

- Identify differences in the "means"
  - Single condition (compared to 0)

$$t = \frac{\bar{x} - \mu_0}{s/\sqrt{n}},$$

μ_0: population mean
s: sample standard deviation
n: sample size
Degree of freedom: (n-1)

t ⇑ ⇔ p ⇓
⇒ more likely has significant difference

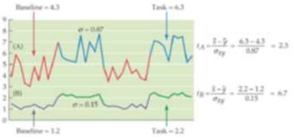


  - Two conditions (unequal sample size, unequal variance)

$$t = \frac{\bar{X}_1 - \bar{X}_2}{S_{X_1X_2} \cdot \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

$$S_{X_1X_2} = \sqrt{\frac{(n_1 - 1)S_{X_1}^2 + (n_2 - 1)S_{X_2}^2}{n_1 + n_2 - 2}}.$$

X_1 & X_2: population mean
n_1 & n_2: sample size
$S_{X_1X_2}$: standard deviation of 2 samples
Degree of freedom: (n_1 + n_2 -2)



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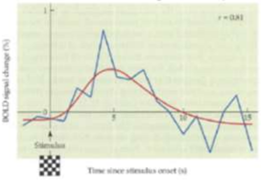
Statistics: correlation

- Quantify how well the data match HRF response.
- Strategy:
  1. Paradigm + fMRI data
  2. Covariance
  3. Normalization (divide by std)

$$\rho_{X,Y} = \frac{\text{cov}(X,Y)}{\sigma_X \sigma_Y} = \frac{E((X-\mu_X)(Y-\mu_Y))}{\sigma_X \sigma_Y},$$

μ_X & μ_Y: population mean
σ_X & σ_Y: standard deviation
Degree of freedom: (n_X + n_Y -2)

- Correlation coefficients
  - range: (-1, +1)
  - irrelevant to amplitude



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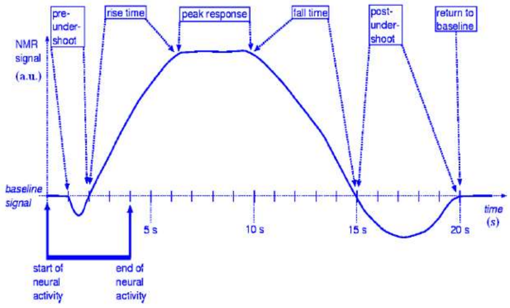
Hemodynamic response function (HRF)



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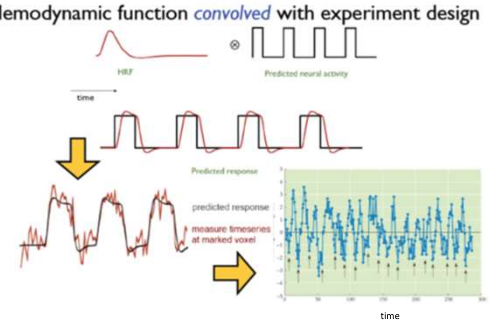
BOLD fMRI signal and linear model

- Hemodynamic function *convolved* with experiment design



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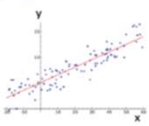
Basics of linear model: regression

- Regression: relationship between a response/outcome (dependent) variable and one or more explanatory (independent) variables (regressors)
  - ➢ Simple regression: fit data with a straight line
    $y = \alpha + \beta x + \varepsilon$
    - α is the intercept (constant), β is the slope (like amplitude)
  - ➢ Some statisticians just call it linear model



- Mathematical crystallization
  - ➢ $y_i = \alpha + \beta x_i + \varepsilon_i$, or $y_i = \alpha + \beta_1 x_{1i} + \ldots + \beta_k x_{ki} + \varepsilon_i$
  - ➢ $y = X\beta + \varepsilon$, $X = [1, x_1, x_2, \ldots, x_k]$
  - ➢ Assumption
    - o linearity
    - o white noise (independence) and Gaussianity $\varepsilon \sim N(0, \sigma^2 I)$

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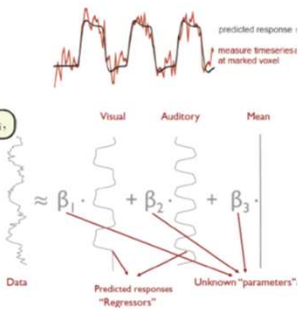
Statistics: regression

- Observed data (y_i)
  - regressors (x_i)
  - variable weighting (β_i)
  - residual noise (ε)

$$y_i = \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip} + \varepsilon_i,$$

- Regressors for fMRI Curve fitting
- If β is non-zero, then voxel is "active"
  - β has *amplitude* info.



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fMRI data

- Data partition: Data = Signal + Noise
  - Data = acquisition from scanner (voxel-wise time series)
    - What we have
  - Signal = BOLD response to stimulus; effects of interest + no interest
    - We don't really know the real signal!!!
    - Look for idealized components, or search for signal via repeated trials
    - Of interest: effect size (response amplitude) for each condition: *beta*
    - Of no interest: baseline, *slow drift, head motion effects*, …
  - Noise = components in data that interfere with signal
    - Practically the part we have don't know and/or we don't care about; that is, noise is the part we can't explain in the model
    - Will have to make some assumptions about its distribution
- Data = baseline + slow drift + other effects of no interest + response_1 + … + response_k + noise

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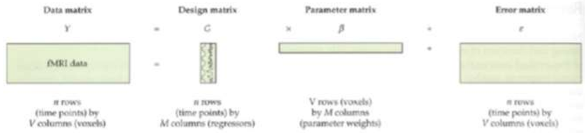
General linear model (GLM) model in fMRI

Data = baseline + slow drift + other effects of no interest + response_1 + … + response_k + noise

$$y = X\beta + \varepsilon$$



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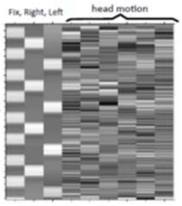
Design matrix

- Voxel-wise (massively univariate) linear model: $y = X\beta+\varepsilon$
  - X: explanatory variables (regressors) – same across voxels
  - y: data (time series) at a voxel – different across voxels
  - β: regression coefficients (effects) – different across voxels
  - ε: anything we can't account for – different across voxels
- Visualizing design matrix $X = [\, x_1, x_2, \ldots, x_k, \ldots]$ in grayscale



stimuli	Onset (for scan)
fixation	0 20 40 60 80 100 120 140 160
right	10 50 90 130
left	30 70 110 150

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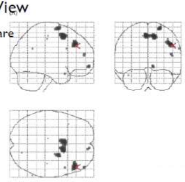
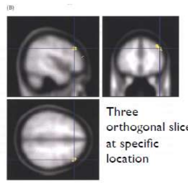
Displaying statistical results: statistical parametric mapping

Glass Brain View

All activations are visible in each orientation





Three orthogonal slices at specific location

Rendered Brain View

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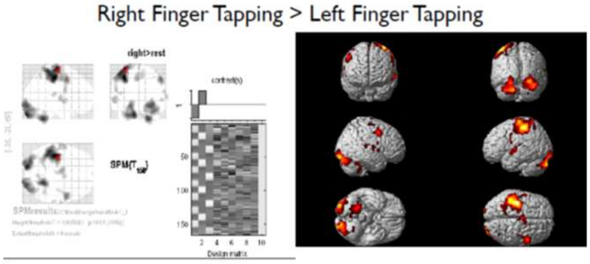
Example result of single subject in SPM (1^{st} level analysis)

Right Finger Tapping > Left Finger Tapping



Significant difference can be found in the left hemisphere.

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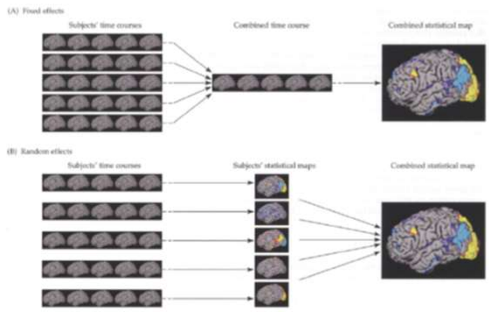
Group analysis: fixed effect vs. random effect



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Examples of groups analysis

- **One-Sample Case**
  - One group of subjects ($n \geq 10$)
    - One condition (house or face) effect
    - Linear combination of multiple effects (house - face)
  - Null hypothesis H_0: average effect = 0
    - Rejecting H_0 is of interest!
  - Results
    - Average effect at group level
    - Significance: t-statistic
- **Two-Sample Case**
  - Two groups of subjects ($n \geq 10$): ex:males and females
    - One condition (house or face) effect
    - Linear combination of multiple effects (house - face)
    - Example: Gender difference in emotion effect?
  - Null hypothesis H_0: Group1 = Group2
    - Results
      - Group difference in average effect
      - Significance: t-statistic

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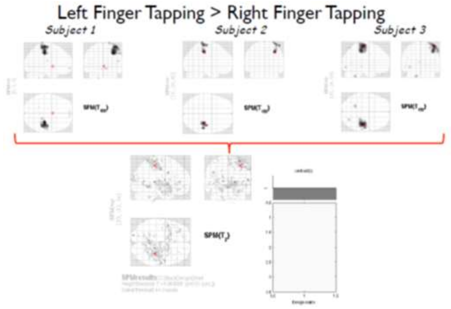
Example result of 3 subject in SPM (2nd level analysis)



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Resting-state functional MRI data analysis

- rs-fMRI
- Resting-State Data Analysis toolkit v1.8
- (REST v1.8, Center for Cognition and Brain Disorders, Hangzhou Normal University, Zhejiang, China) (Chao-Gan and Yu-Feng 2010)
- rs-fMRI indices
  - mean fractional amplitude of low-frequency fluctuations (mfALFF)
  - mean regional homogeneity (mReHo)

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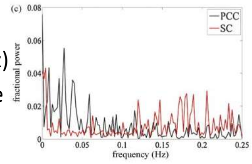
mean fractional amplitude of low-frequency fluctuations (mfALFF)

- ALFF: Total power of slow fluctuations within a low frequency range (0.01~0.08 Hz)
- fALFF: Dividing the ALFF by the total power in the entire detectable frequency range
- mfALFF: fALFF after normalization



The example of the slow fluctuations of brain activity (Zou, Zhu et al. 2008)

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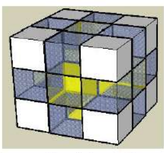
mean regional homogeneity (mReHo)

- Evaluate the similarity between the time series of a voxel and other nearest voxels
- Kendall's coefficient of concordance (KCC)
- from 0 (no agreement) to 1 (complete agreement)



$$R_i = \sum_{j=1}^{m} r_{i,j} \quad \bar{R} = \frac{1}{n}\sum_{i=1}^{n} R_i \quad S = \sum_{i=1}^{n}(R_i - \bar{R})^2 \quad W = \frac{12S}{m^2(n^3 - n)}$$

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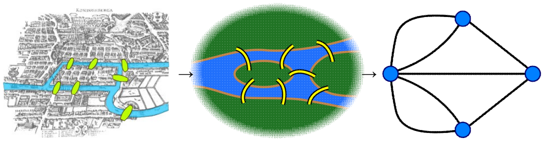
Origins of graph theory

- In 1736, Euler showed that it was impossible to traverse the city of Königsberg's seven bridges across the river Pregel exactly once and return to the starting point

Origins of graph theory

- To prove this conjecture, Euler represented the problem as a graph, and his original publication is generally taken to be the origin of a new branch of mathematics called graph theory



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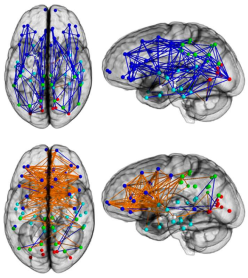
Complex brain networks

- Graph theoretical analysis of structural and functional systems
- Brain networks show increased connectivity in males (Upper) and females (Lower)



- Madhura Ingalhalikar et al., PNAS 2014, 111(2): 823-828.

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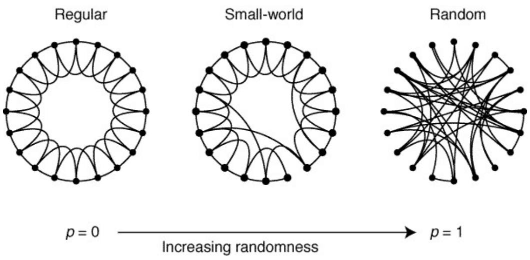
Complex brain networks



- Watts DJ, Strogatz SH, Nature 1998; 393: 440-442.

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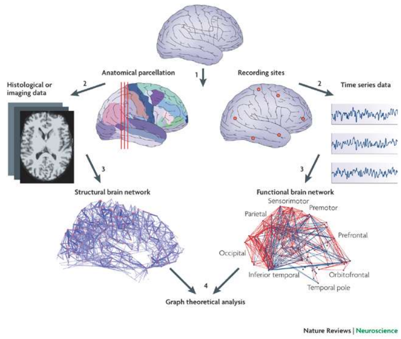
Graph theoretical analysis of structural and functional systems



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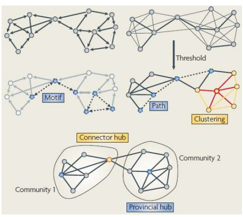
Network topological measures

- Nodes (N)
- Edges (E)
- Node degree
- Degree distribution
- Connection density
- Hubs
- Centrality
- Assortativity
- Modularity
- Transitivity



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Whole brain network organization

- Local segregation:
  - Clustering coefficient (C)
  - Normalized clustering coefficient (ϒ)
  - Local efficiency (E_{local})
- Global integration:
  - Characteristic path length (L)
  - Normalized shortest path length (λ)
  - Global efficiency (E_{global})
- Small-worldness index (σ) $\frac{\gamma}{\lambda}$

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Demo

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