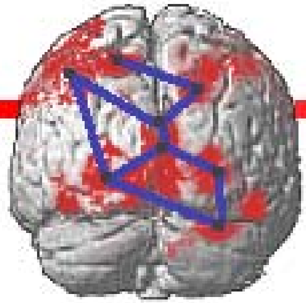
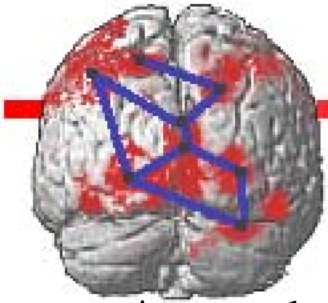


Effect of age and dementia on topology of brain functional networks

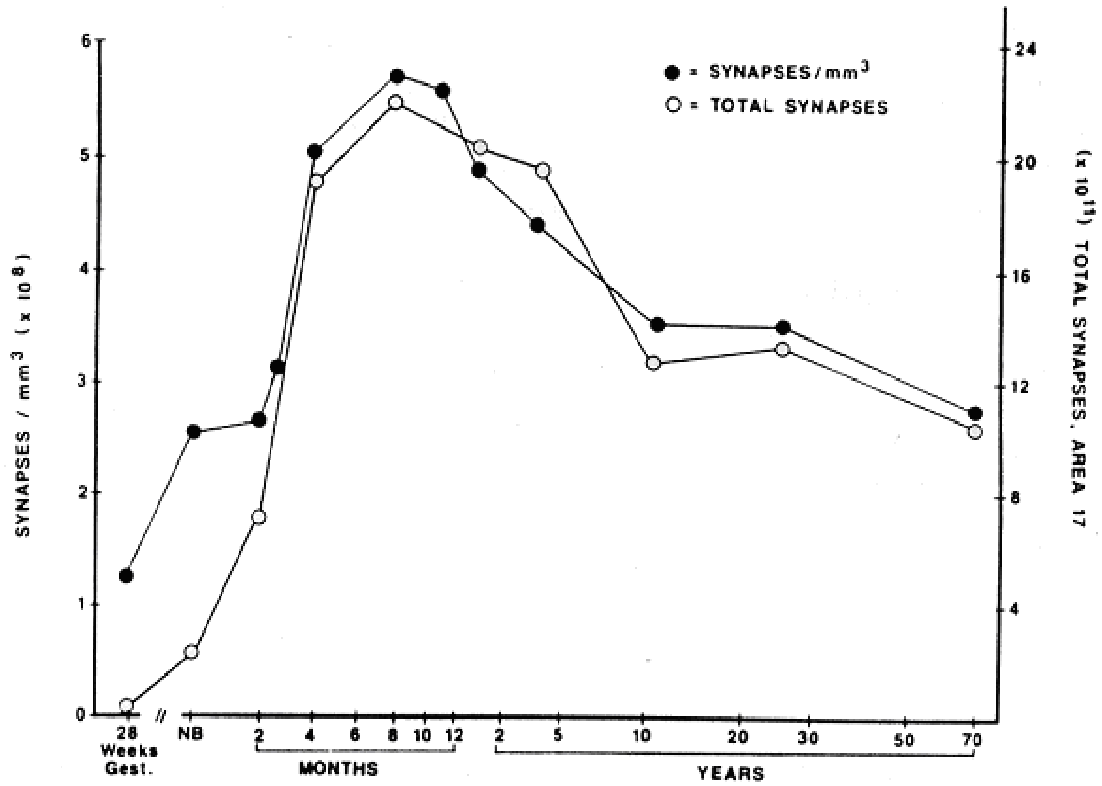
Paul McCarthy, Luba Benuskova, Liz Franz

University of Otago, New Zealand



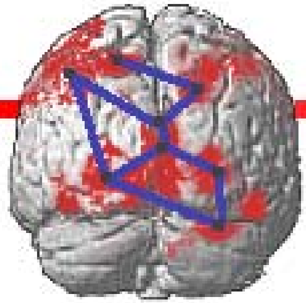
Structural changes in aging brain

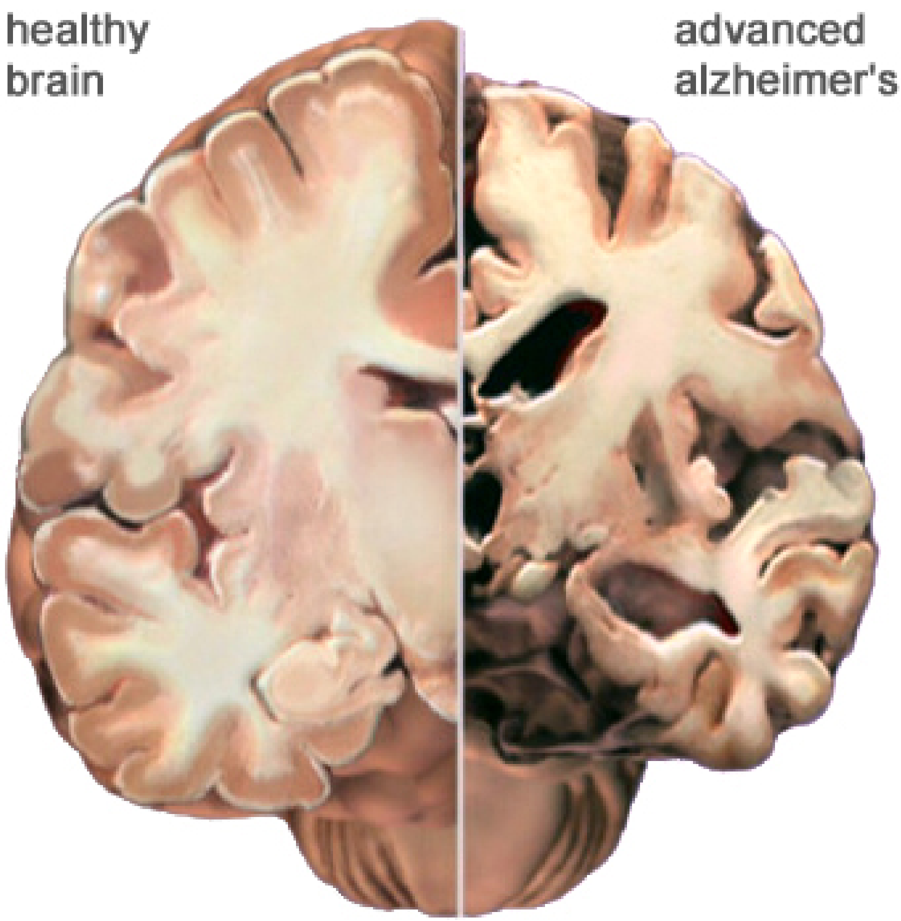
- Age-related changes in the structure and the functionality of the human brain from 25 years on:
  - a decline in total brain volume
  - cortical thinning
  - atrophy of gyri
  - white-matter degradation
  - decrease of # of synapses



- These structural changes might lead to functional changes, which we want to study using graph theory.

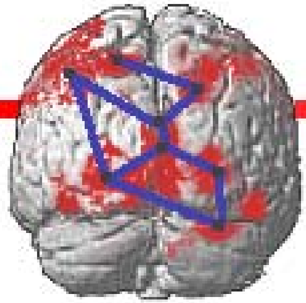
Structural changes in Alzheimer's

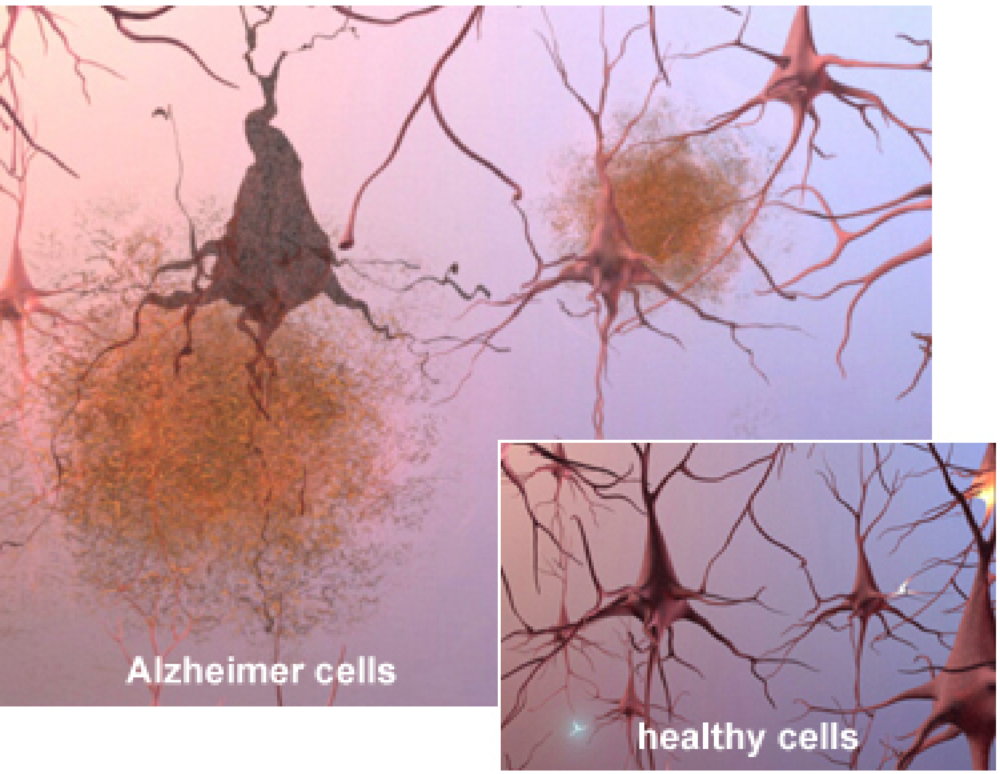




- Alzheimer's disease leads to nerve cell death and tissue loss throughout the brain.
- The brain shrinks dramatically, affecting all its functions.
- Alzheimer tissue has much less nerve cells and synapses than a healthy brain.

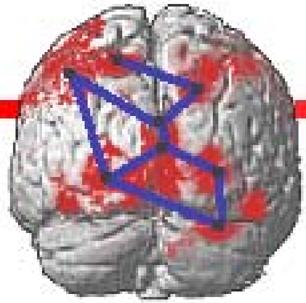
Alzheimer's under the microscope





- Plaques, clusters of protein beta-amyloid fragments, build up between nerve cells. Plaques block communication between neurons and synapses die.

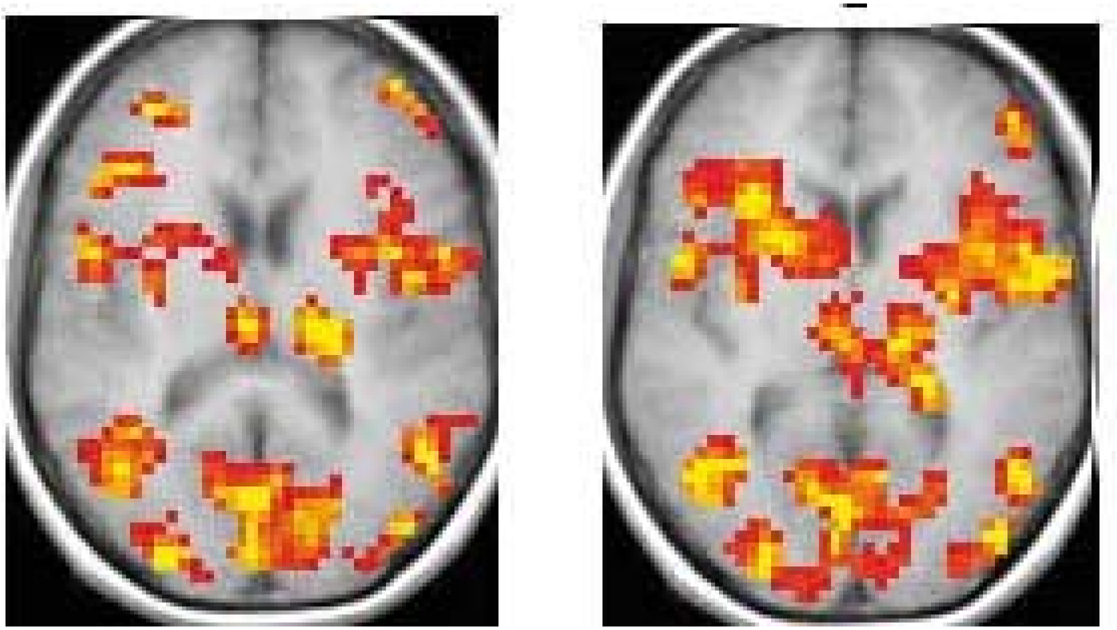
- Dead and dying nerve cells contain tangles, which are made up of twisted strands of another protein (tau). Tangles prevent normal metabolism and neuron dies of starvation.



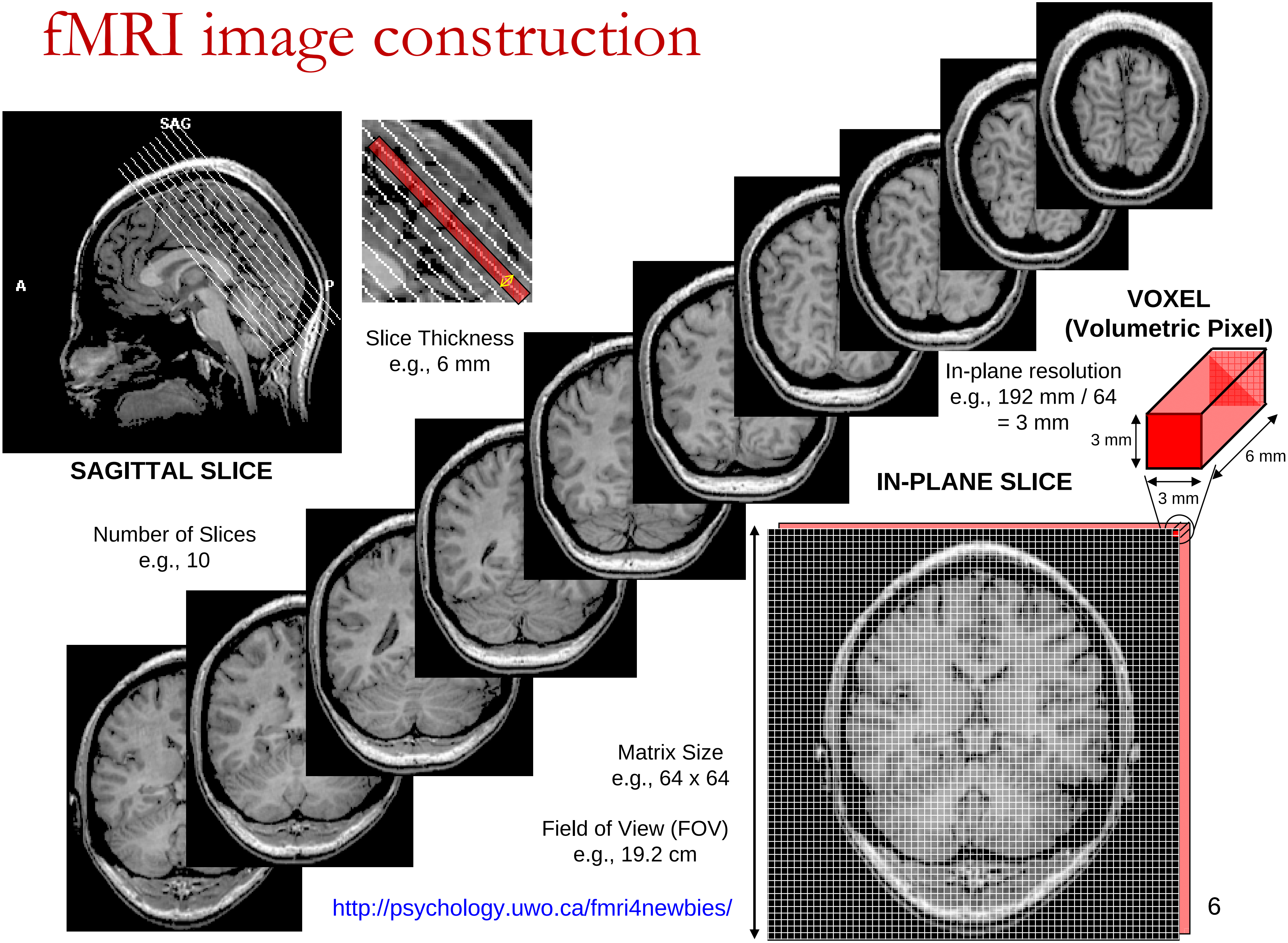
functional Magnetic Resonance Imaging

- Measures neural activity indirectly based on the rate of metabolism - Blood Oxygenation Level Dependent (BOLD) signal

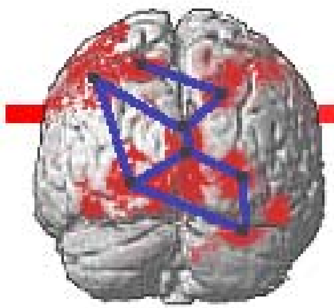
- Spatial resolution is ~3 mm^3 (voxels) and temporal resolution in seconds



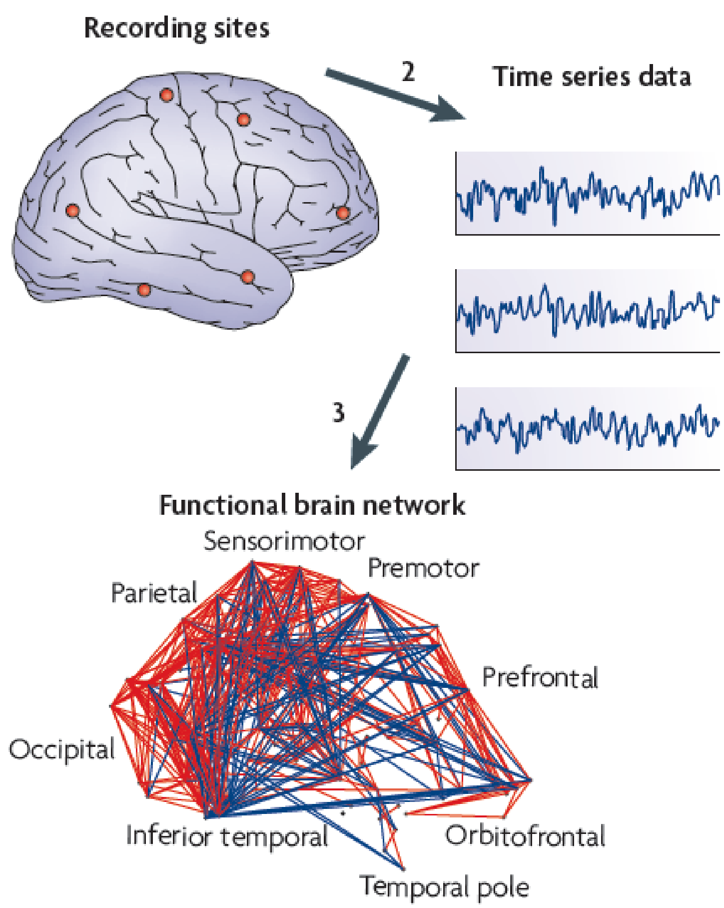
fMRI image construction



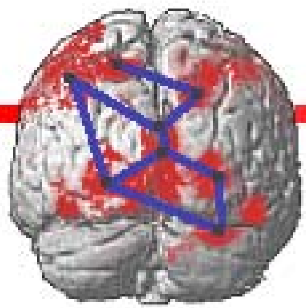
http://psychology.uwo.ca/fmri4newbies/



Four steps of functional network analysis



- Define the network nodes:
  - Voxels in fMRI
  - EEG (MEG) electrodes
  - Anatomically defined regions
- Define links between pairs of nodes
  - Correlation of BOLD
  - Coherence of signals

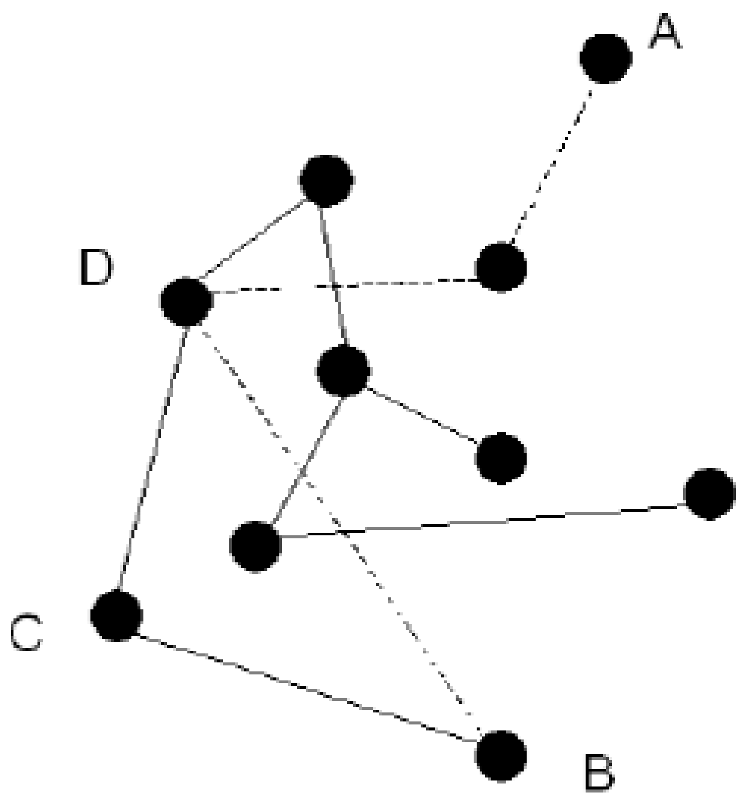


Graph topology: nodes, edges & density

- The **order** of a graph = number of nodes N

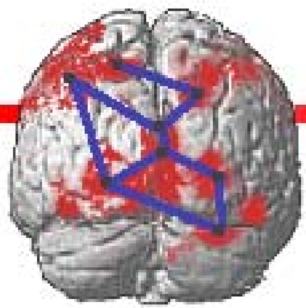
- The **density** of a graph is the ratio of existing edges to all possible edges:

$$D = \frac{2e}{N(N-1)}$$

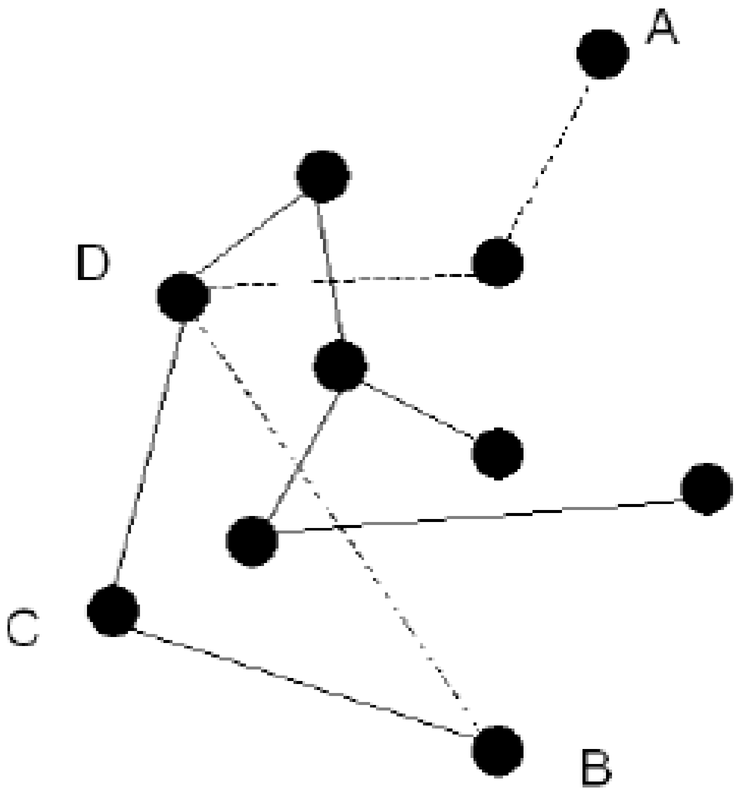


- The numbers of **components** refers to the number of independent (i.e. disconnected) subgraphs.

- The number of **disconnected** nodes refers to the number of nodes with 0 edges.



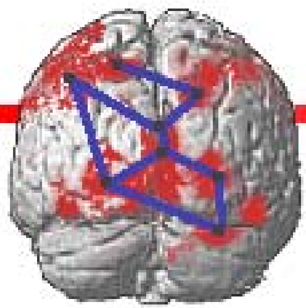
Graph topology: node degree



- Topology is concerned with how the nodes are assembled in space through their links / edges.

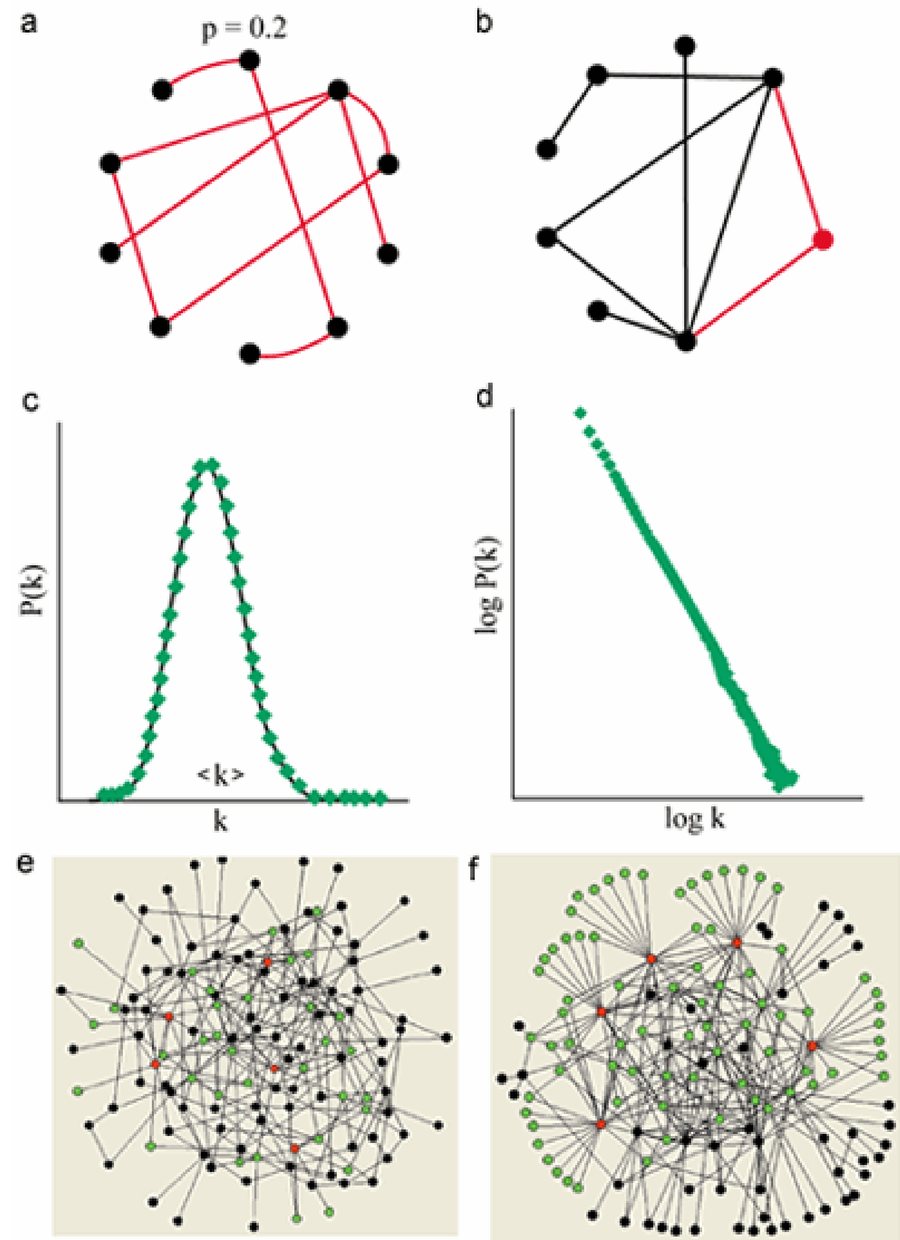
- The degree k_i of a node i is defined as the number of nodes, to which i connects.

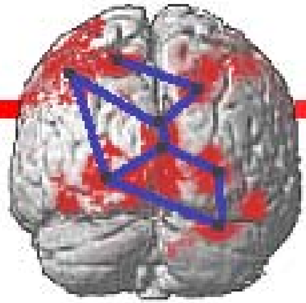
- Degree of A = 1, degree of B and C = 2, degree of D = 4, etc.



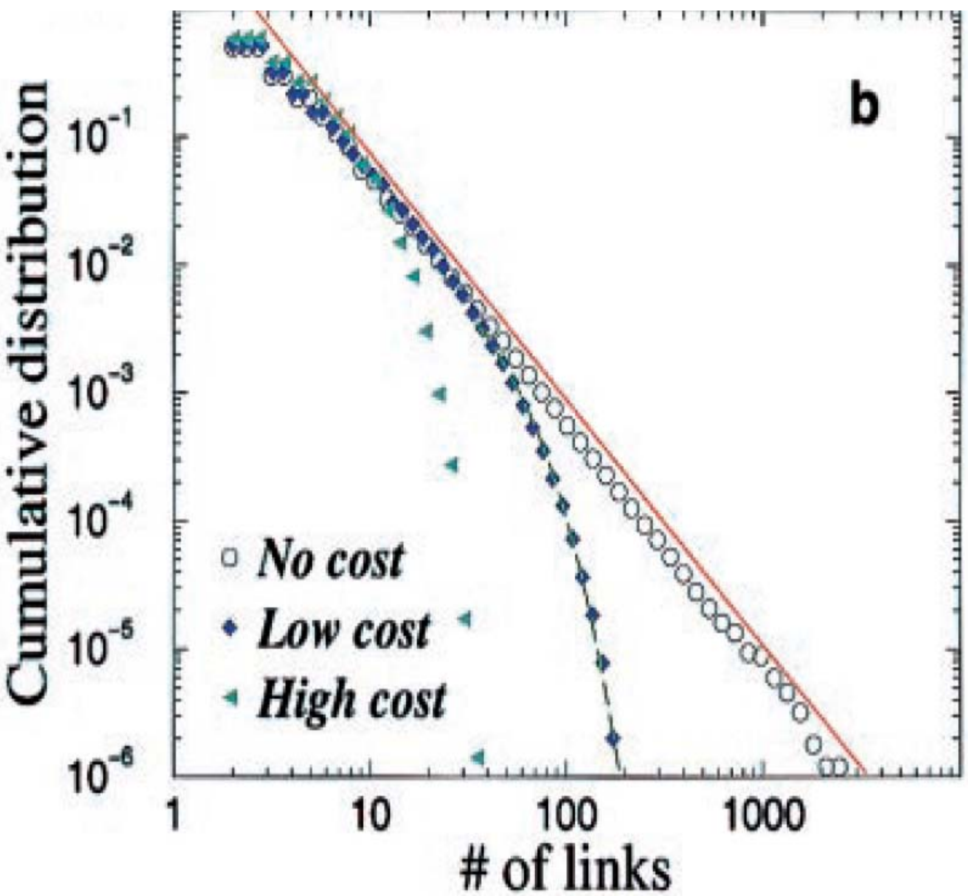
What the degree tells us?

- Random network has a normal (Gaussian) degree distribution.
- The **scale-free** network has a power law degree distribution, i.e. $P(k) \sim k^{-\gamma}$ with $1 < \gamma < 3$.
- Scale-free net has **hubs**, i.e. nodes with many connections.

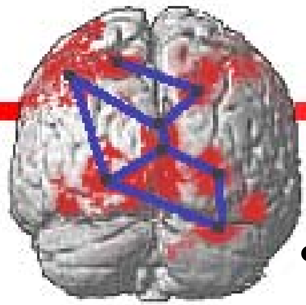




Truncation of scale-free connectivity



- It has been shown by Amaral et al. [PNAS 97(21): 11149, 2000] that a cost of adding new links leads to a cutoff of the power-law distribution of the connectivity.
- The more cost the more truncation (the linear part is shorter)
- for sufficiently large cost, the power law regime disappears altogether.



Graph topology: clustering coefficient

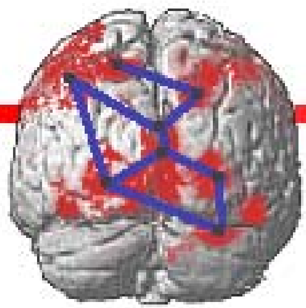
- Clustering coefficient C_i of the node *i* with the degree k_i is the ratio of the number of existing edges between neighbours of *i*, and the maximum possible number of edges between neighbours if *i*.

$$C_i = \frac{2e_i}{k_i(k_i - 1)}$$

- Mean C of the graph:

$$C = \tfrac{1}{N}\sum_{i=1}^{N} C_i$$

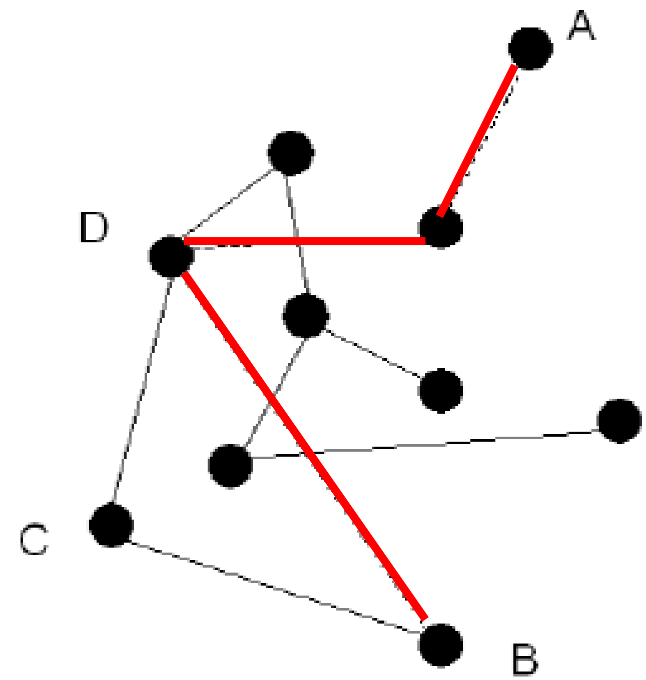
- The clustering coefficient has been interpreted as a measure of resilience to random error (if the node *i* is lost, its neighbours still remain connected).



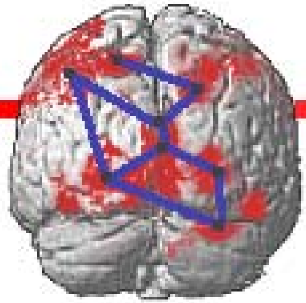
Graph topology: path length

- Characteristic path length L is the mean of the shortest path lengths between all possible pairs of nodes.

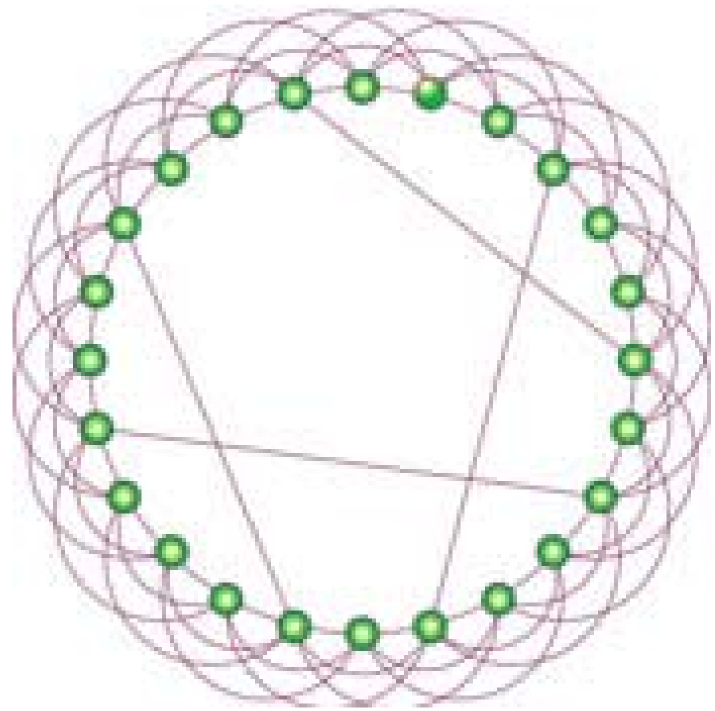
- The shortest path length d_{ij} between node i and node j is the minimal number of edges that have to be travelled from i to j. (e.g., $d_{AB} = 3$)



$$L = \frac{1}{N(N-1)} \sum_{\substack{i,j \in N \\ i \neq j}} d_{ij}$$



Graph topology: small-world index

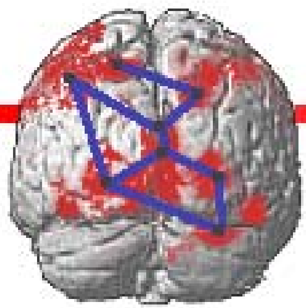


- A small-world network is characterized by high level of local clustering, i.e. $C >> C_{random}$ and by the small characteristic path, i.e. $L \approx L_{random}$.

- A small-world index is a ratio:

$$S = \frac{C / C_{random}}{L / L_{random}}$$

- A small-world index: many local clusters with occasional global interactions.



Graph topology: efficiency & assortativity

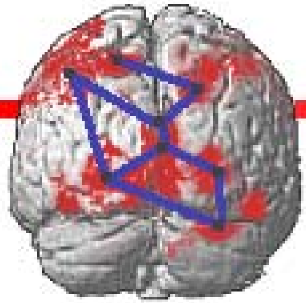
- **Global efficiency** is a measure of information flow through the graph, based on average path lengths:

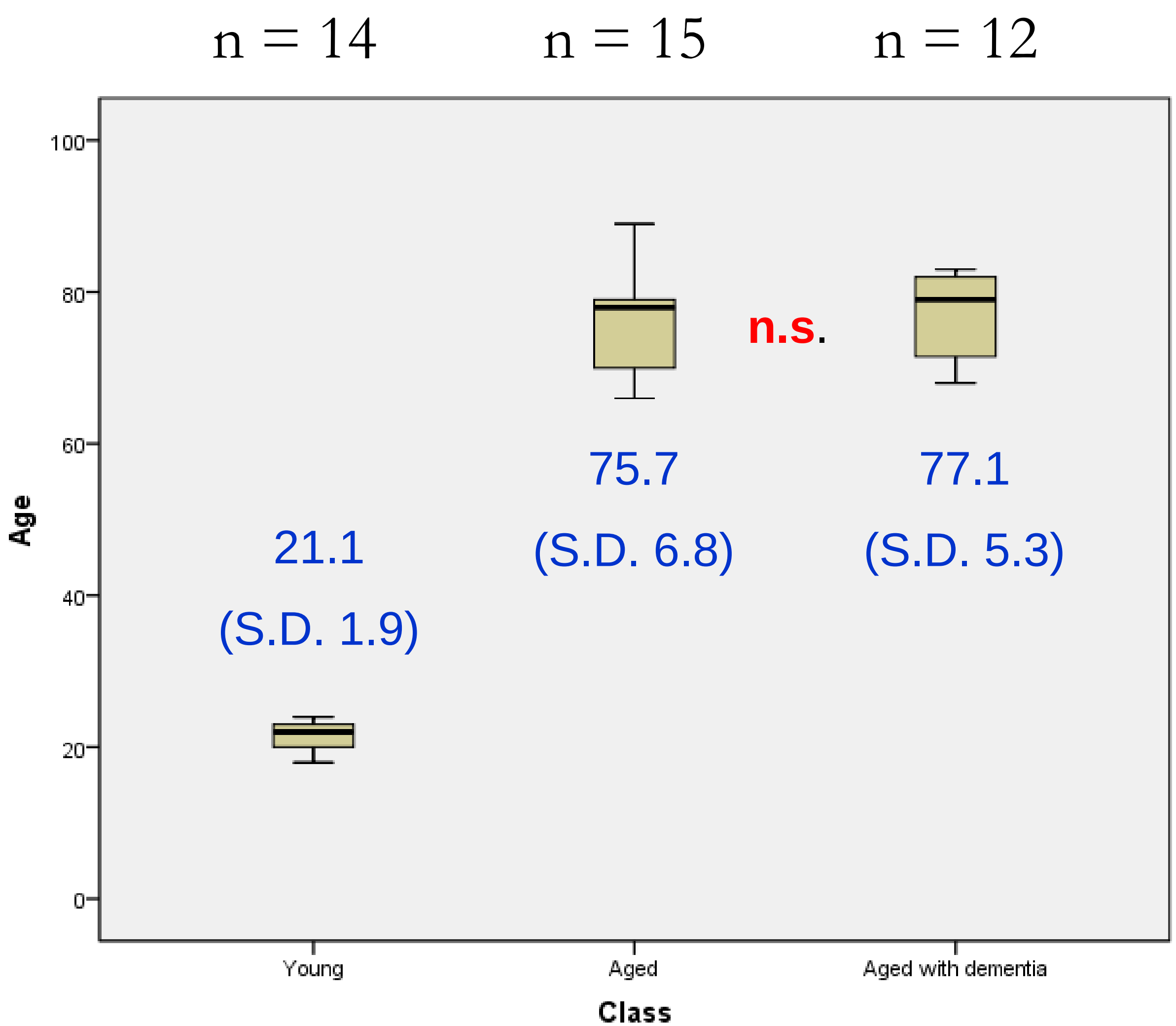
$$E_{Global} = \frac{1}{N(N-1)} \sum_{\substack{i,j \in N \\ i \neq j}} \frac{1}{d_{ij}}$$

- **Local efficiency** is calculated by the same formula applied to the subgraph formed by the neighbours of each node.

- **Assortativity** (-1, +1) measures the tendency that nodes in the graph are connected to other nodes of a similar degree.

Dataset from Buckner et al. 2000: fMRI of 3 groups of subjects

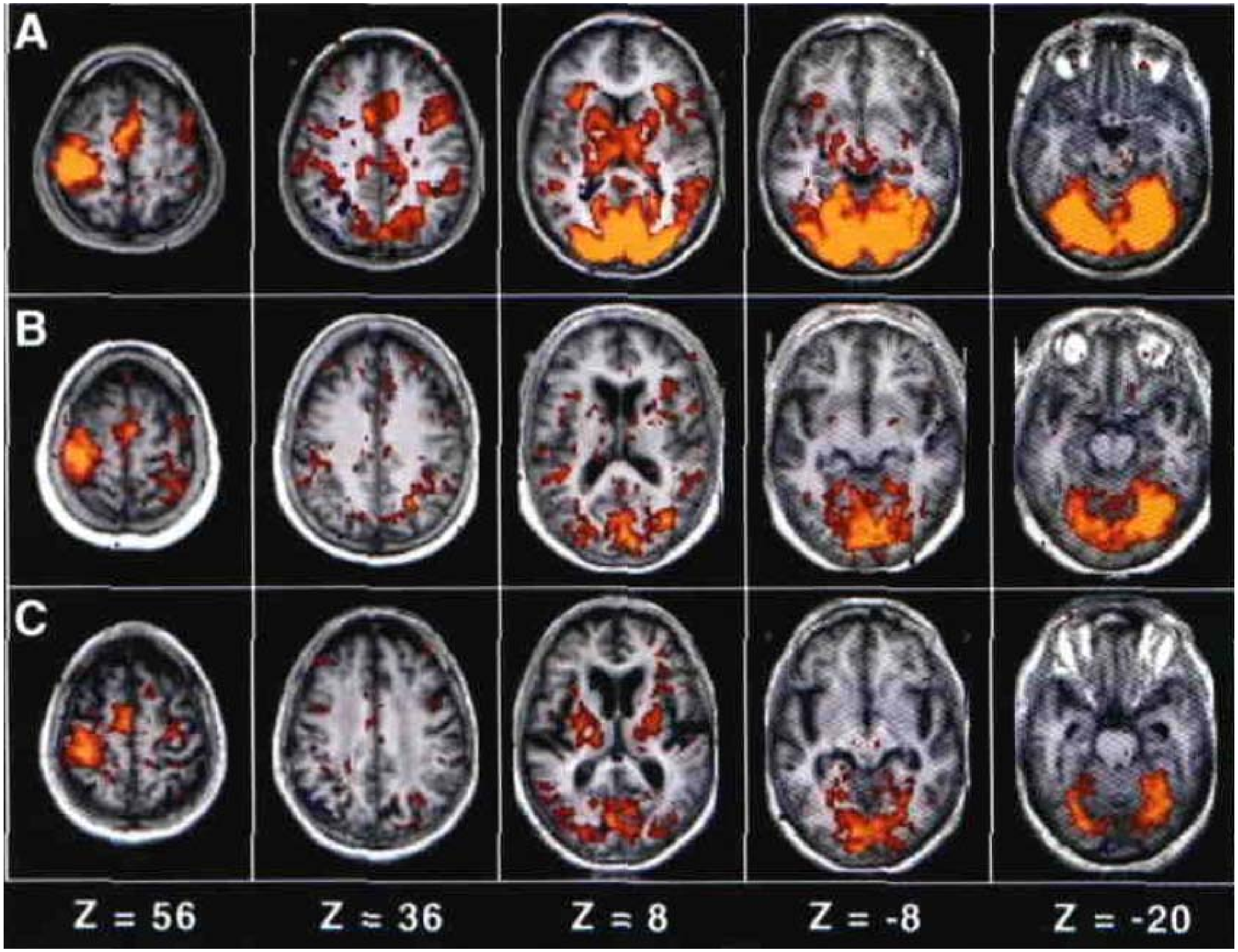




- A box plot contains:
  - The smallest observation (sample minimum),
  - lower quartile (Q1),
  - median (Q2),
  - upper quartile (Q3), and
  - largest observation (sample maximum).

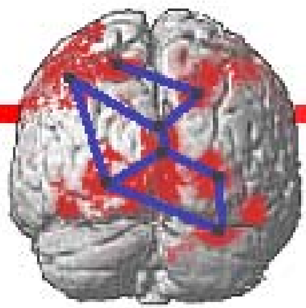
- A box plot may also indicate which observations, if any, might be considered outliers.

fMRI: a simple visual-motor task

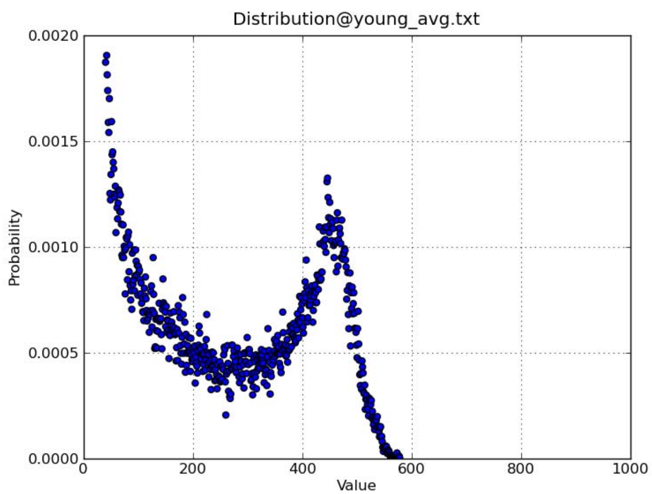


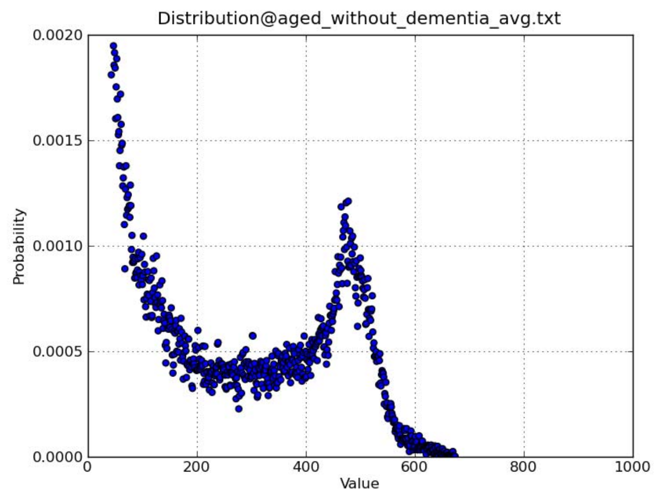
- fMRI of 3 groups of subjects: A) young, B) aged and C) aged with dementia.

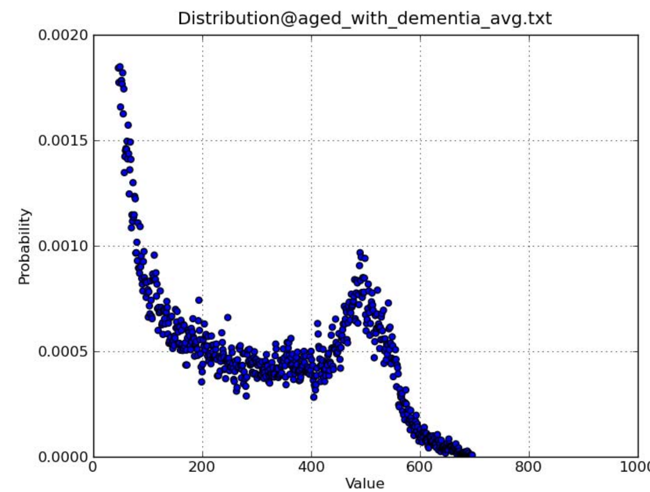
Distribution of BOLD



- Averaged voxels were calculated by averaging the BOLD value in that particular voxel over all subjects in the group over all trials of both tasks (~ 100,000 voxels).



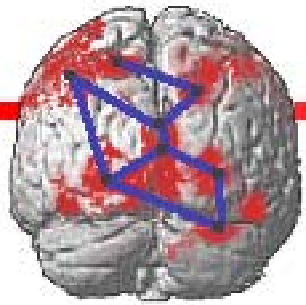




384.69 *	404.72 $^{*,\$}$	405.9 $^{*,\$}$
(S.D. 91.51)	*(S.D. 104.5)*	*(S.D. 114.9)*

* *values with this superscript on the same row are significantly different (p<0.01)*

$^{*,\$}$ *values with these superscripts are significantly different (p = 0.016)*



Functional net for voxels with BOLD ≥ 200

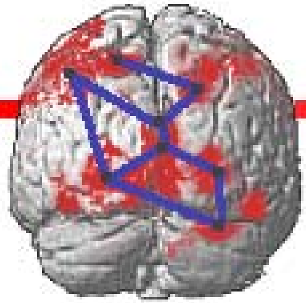
- According to Eguíluz et al. 2005, the functional link between voxels *i* and *j* is established when the Pearson's linear correlation coefficient exceeds some threshold, e.g., $|r(i, j)| \geq 0.9$, where

$$r(i, j) = \frac{\langle V(i,t)V(j,t)\rangle - \langle V(i,t)\rangle\langle V(j,t)\rangle}{\sigma(V(i,t))\sigma(V(j,t))}$$

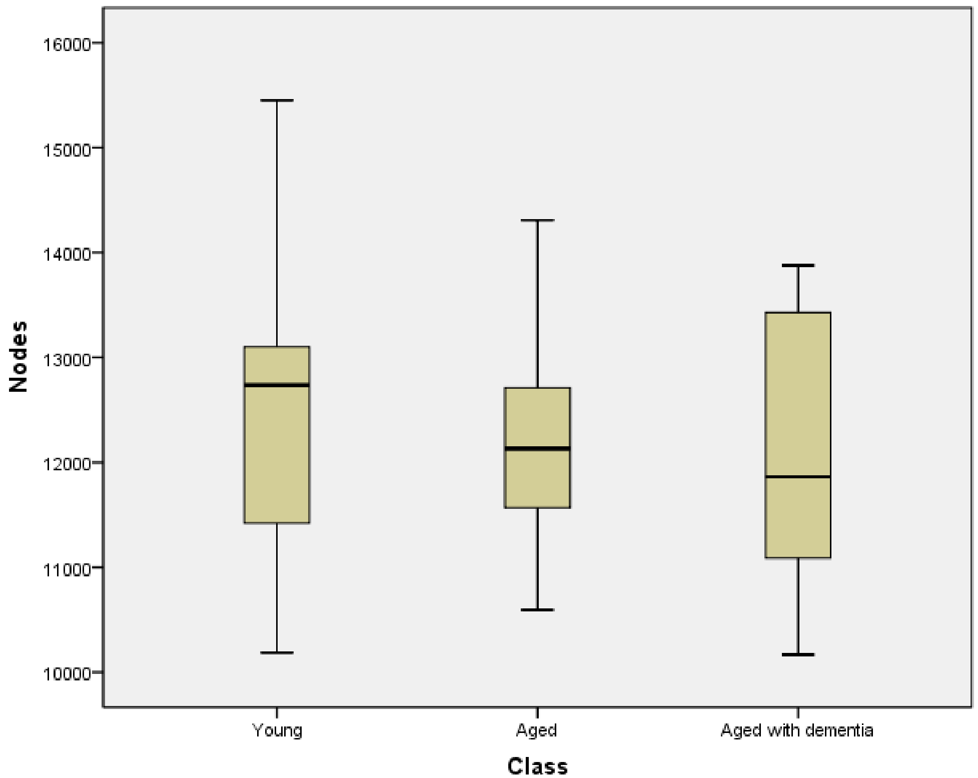
- $V(i, t)$ is the activity of voxel *i* at time *t*, $\langle \ldots \rangle$ represents the time average, and

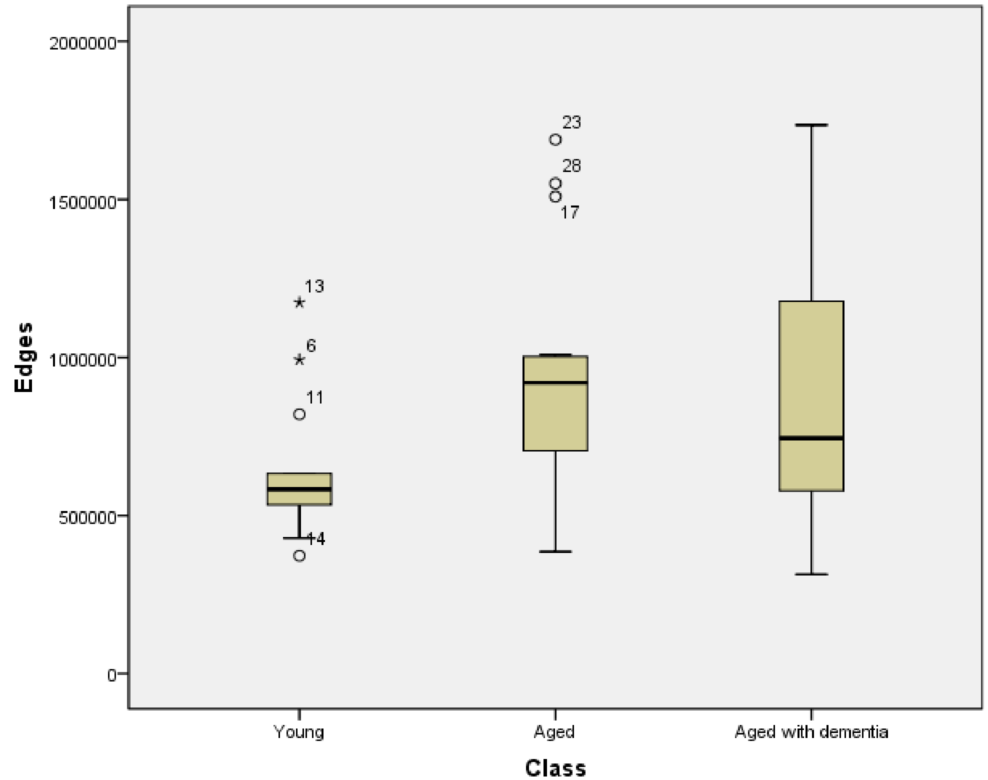
$$\sigma^2 = \langle V(i,t)^2 \rangle - \langle V(i,t)\rangle^2$$

- Thus, we extract an undirected and unweighted graph



t-test results: nodes and edges





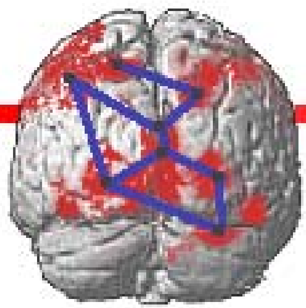
n.s. **n.s.**

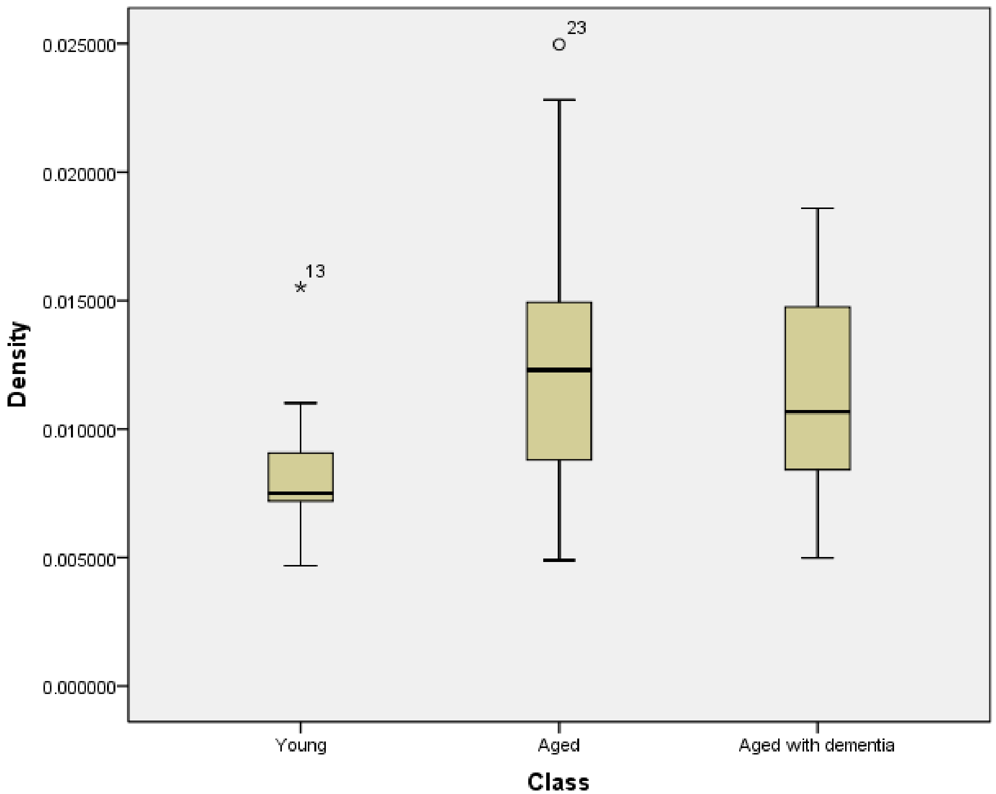
n.s.

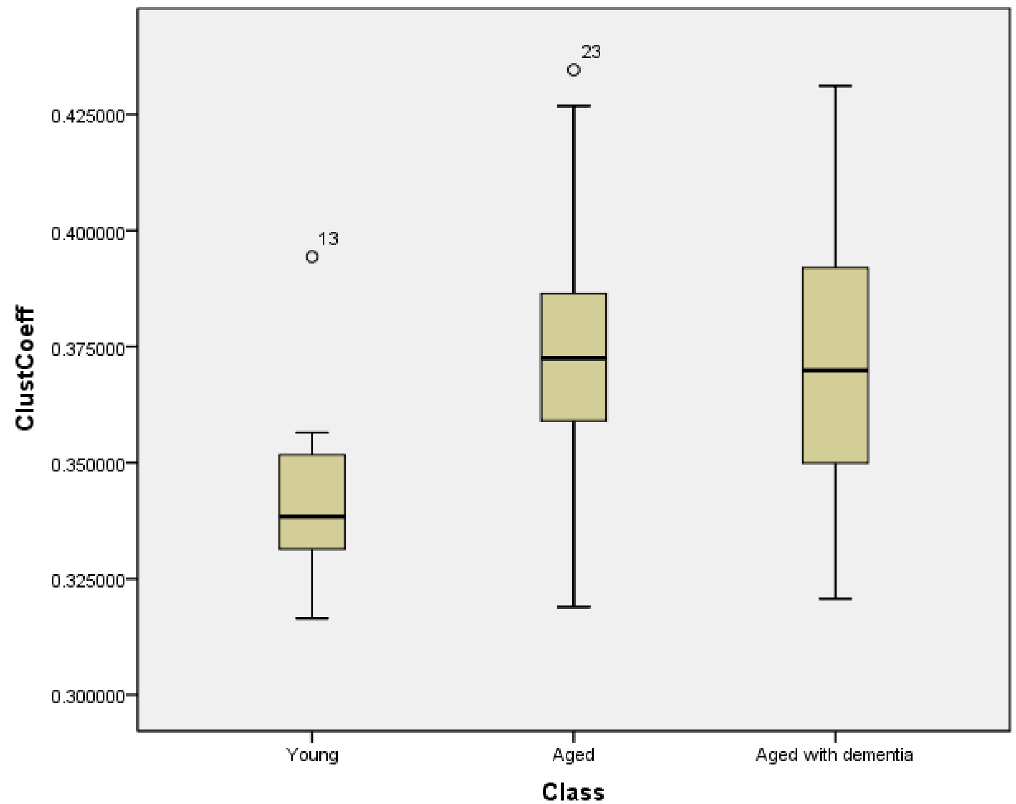
p=0.015 **n.s.**

n.s.

t-test: density & clustering coeff.







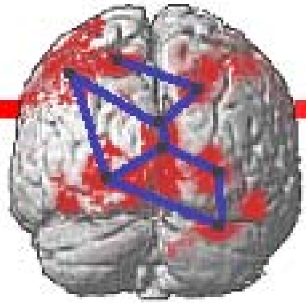
$p=0.015$ **n.s.**

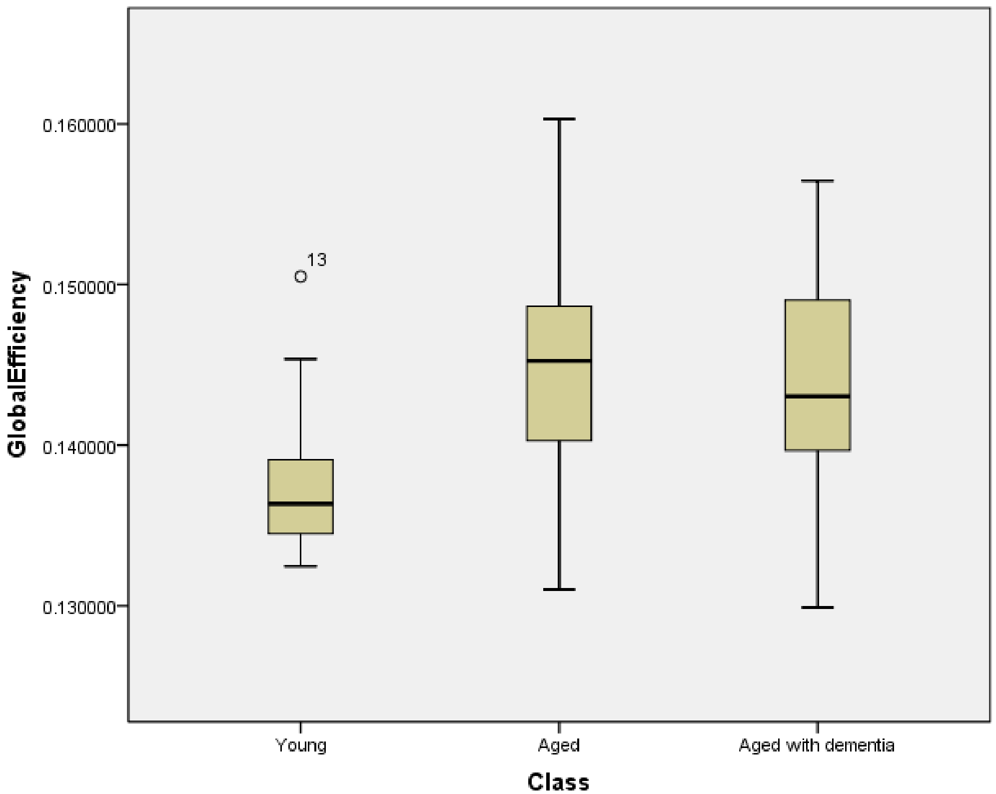
$p<0.05$

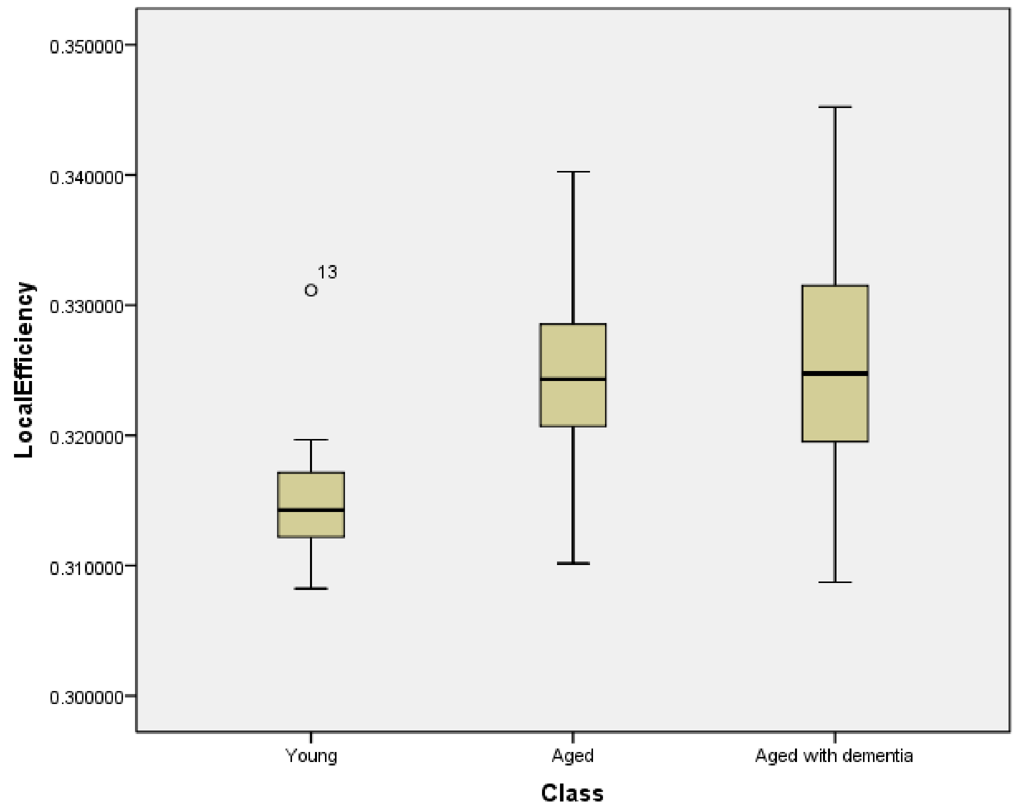
$p<0.005$ **n.s.**

$p<0.05$

t-test: global & local efficiency







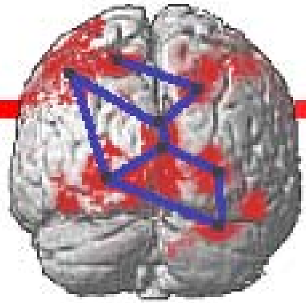
$p < 0.01$ **n.s.**

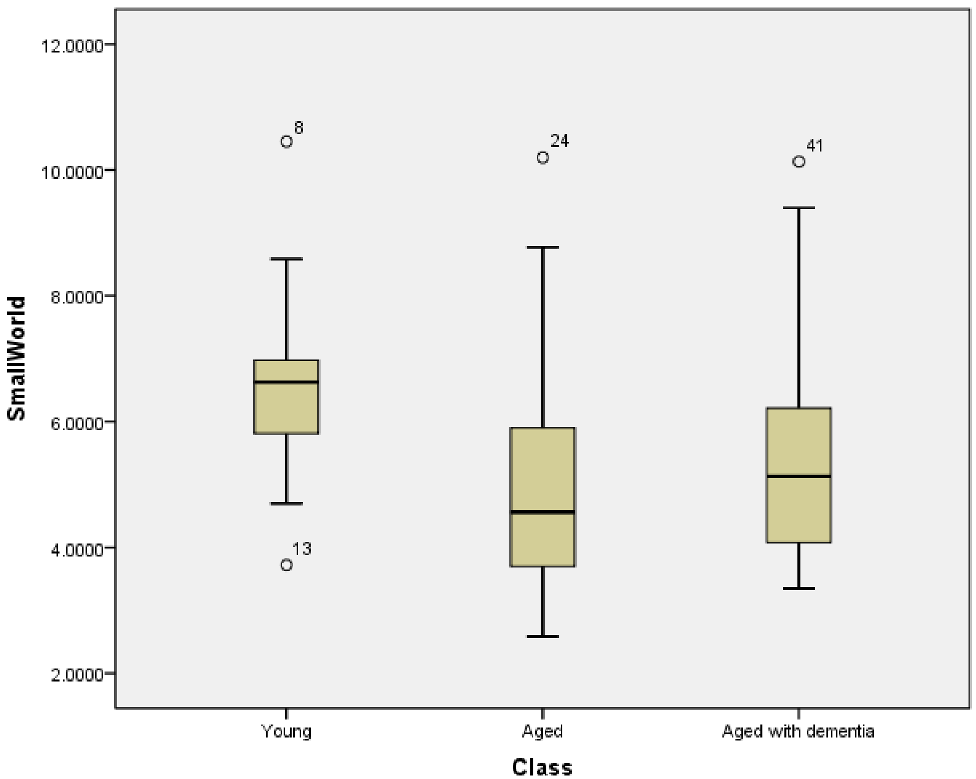
$p<0.05$

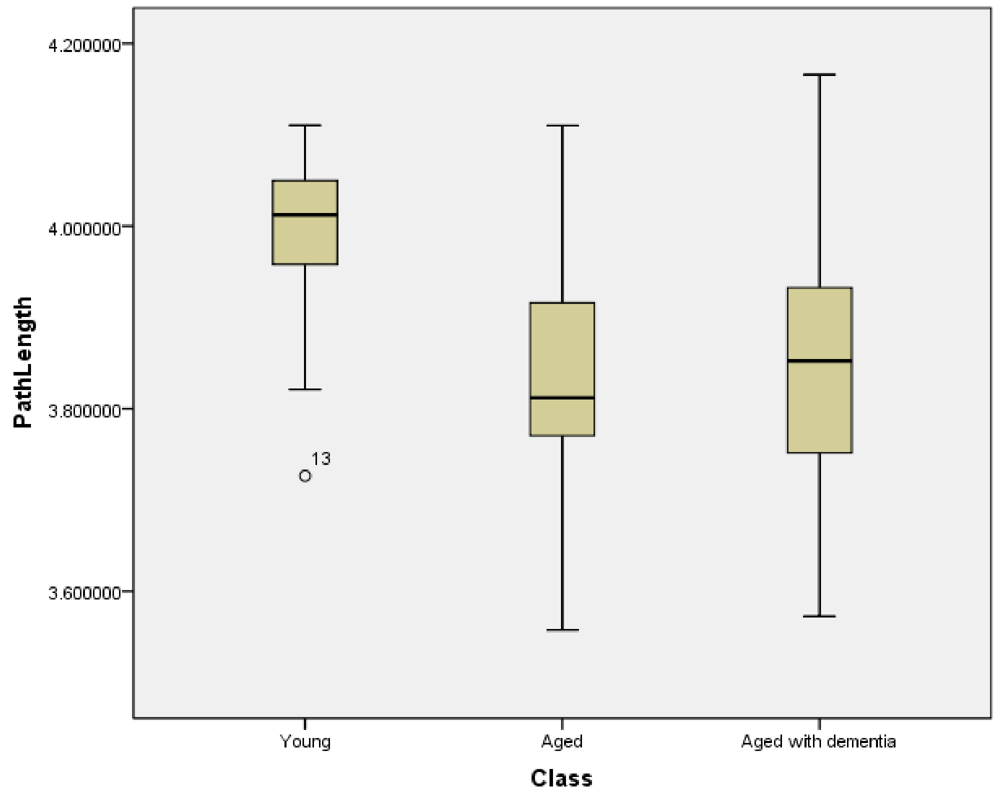
$p=0.001$ **n.s.**

$p<0.01$

t-test: small-world & path length







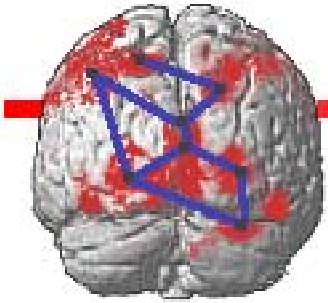
p=0.055 **n.s.**

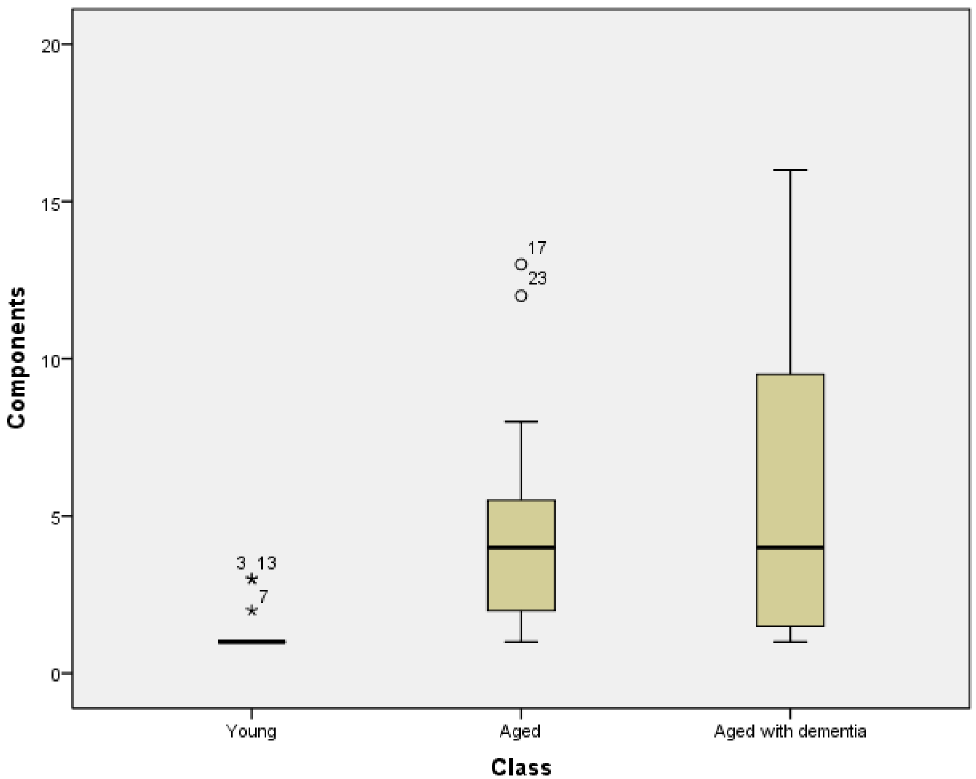
n.s.

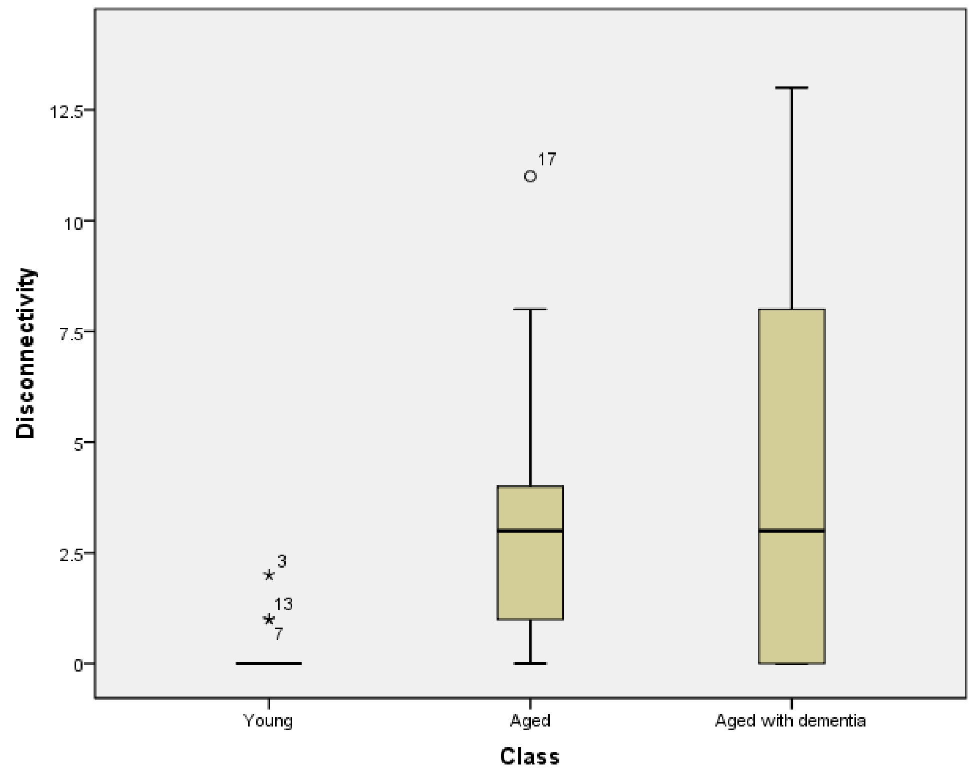
p<0.01 **n.s.**

p<0.05

t-test: components & 0 degree nodes







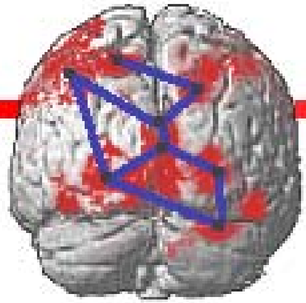
$p<0.005$ n.s.

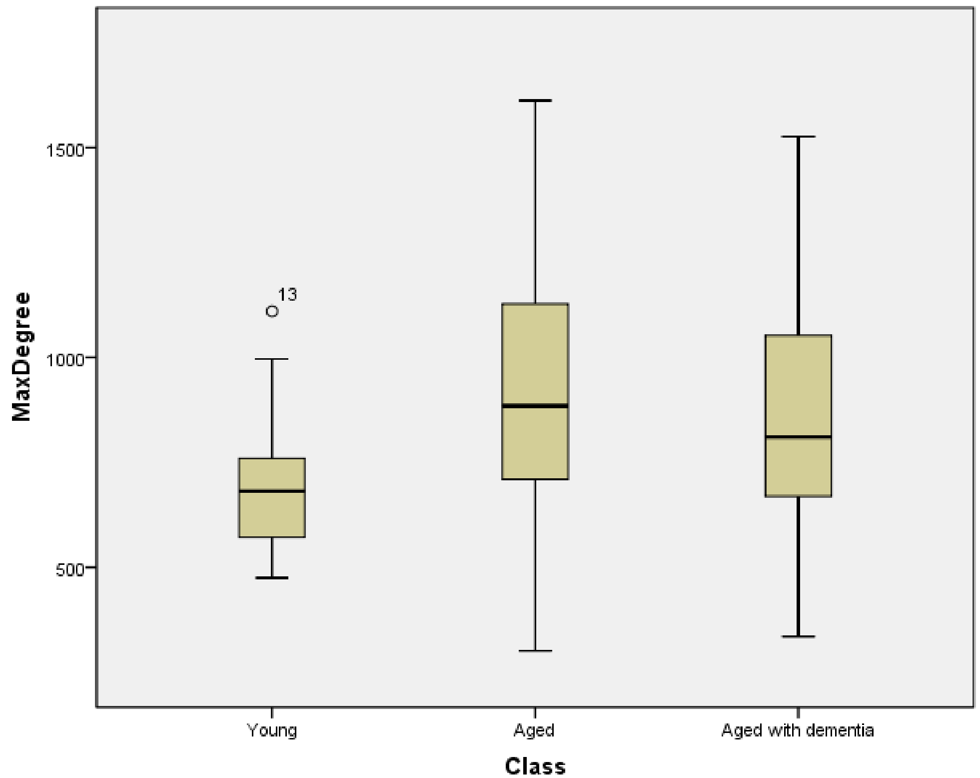
$p<0.05$

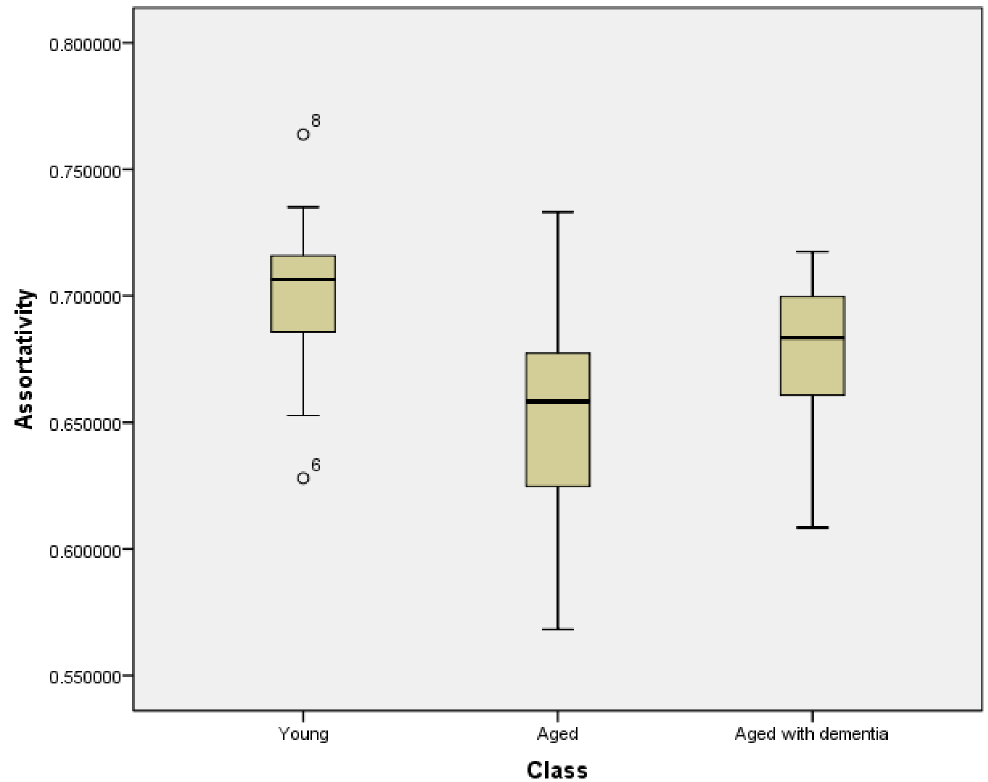
$p<0.005$ n.s.

$p<0.05$

t-test: max degree & assortativity







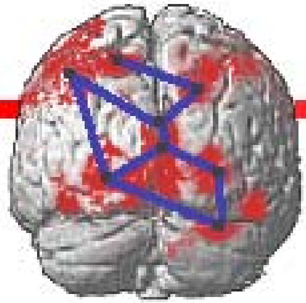
n.s. n.s.

n.s.

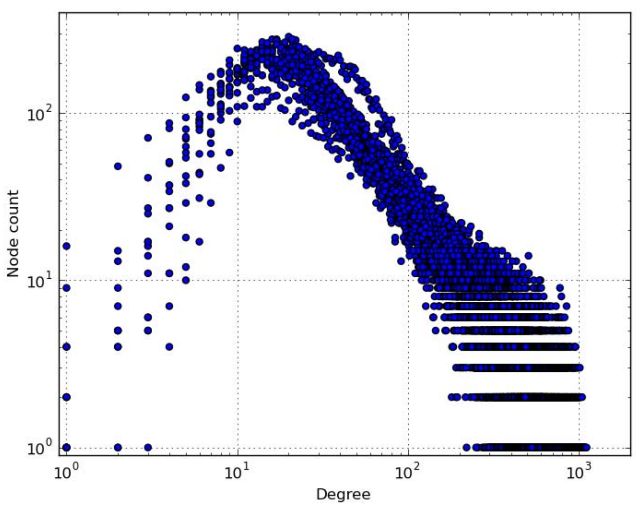
p<0.01 n.s.

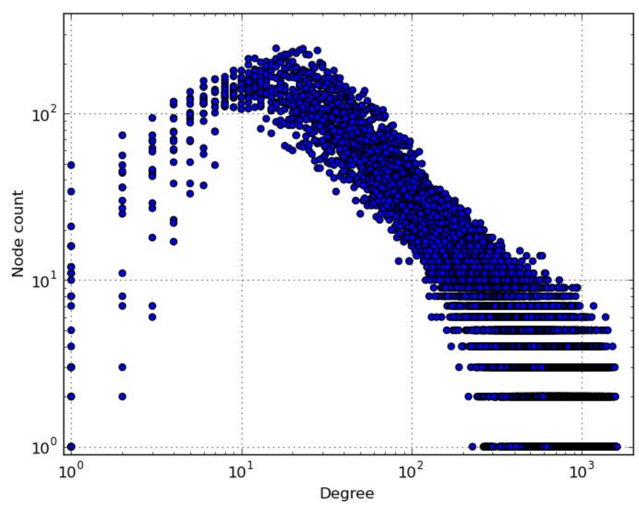
n.s.

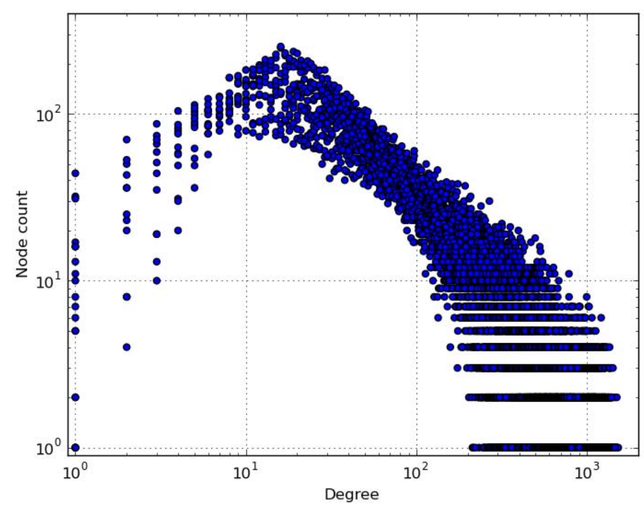
Degree distributions



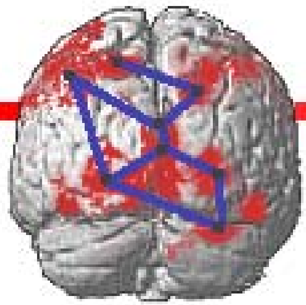
- Degree distributions of all subjects in the three groups.







- Degree distributions have the truncated power-law character. This means there is a cost associated with adding the nodes to the network.

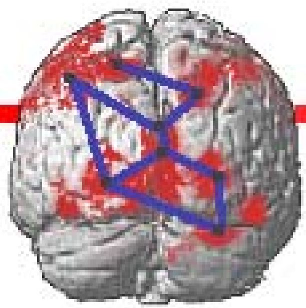


Conclusions

- There seems to be a prominent effect of age on the structure / topology of functional networks. There is a significant increase in
  - the density of functional networks (i.e. edges per node);
  - clustering coefficient;
  - global and local efficiency;
  - number of isolated components/subgraphs of functional networks (fragmentation)
  - increased disconnectivity (i.e number of nodes with 0 degree) with age.

- The assortativity (hubs connected with hubs) of functional nets decreases with age significantly. The average path length significantly decreases with age, too.

- There were no statistically significant differences in functional networks of aged subjects versus aged subjects with dementia.



Future plans

- Analysis of pre-processed data (motion correction, slice alignment,…). So far, we analyzed raw data only.

- Analysis of anatomically labelled voxels – where are the hubs?

- Analysis of subnetworks, maybe the differences lie in particular areas like temporal lobe (memory)

- Analysis of accompanying structural scans – what is the topology of underlying anatomical networks, how it relates to function?