How does network analysis help curing patients with neurological disease?

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Some of the main questions in neuroscience:

- How does the communication between brain regions take place in order to come to a higher level of functioning?
- What are the neural bases of neurological and mental diseases?
The brain, that's my second most favourite organ - Woody Allen

The human brain – some facts

- contains roughly $10^9$ neurons
- each neuron has, on average, 10 000 synapses connecting it to other neurons
- It’s way of functionning is not understood completely
How and what we register
How to come to a neuronal network?
MEG resting state

8-13 Hz

PC

PLI
How to come to a neuronal network?
Synchronization
1. EEG recording and epoch selection

2. Computation of Synchronization Likelihood for each sensor pair

3. Thresholding to produce binary connectivity matrix

4. Using connectivity matrix to form unweighted graph

5. Extracting variables from network

6. Creating surrogate networks by keeping network size constant and randomly reshuffling weights

7. Obtaining normalized variables

\[ Y = \frac{C_p}{C_p-s} \]
\[ \lambda = \frac{L_p}{L_p-s} \]

What is the relation between cognitive status and network characteristics?
The hippocampus as a cognitive graph

Muller RU, Stead M, Pach J.

J Gen Physiol. 1996.
Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network?

Stam CJ.

Neurosci Lett. 2004

5 subjects
MEG, n=126
SL
threshold of SL value resulted in k=15 (unweighted)
Normalized, c and l
Neurophysiological architecture of functional magnetic resonance images of human brain.

Salvador R, Suckling J, Coleman MR, Pickard JD, Menon D, Bullmore E

Cereb Cortex 2005

Figure 4. Multidimensional scaling (MDS) solution for healthy group mean partial correlation matrix. The axes of the two-dimensional MDS solution have been labelled ‘anteriorposterior’ (x-axis) and ‘inferomedial-superolateral’ (y-axis) to acknowledge the anatomical constraints on functional configuration of the regions. Regions are color-coded according to their membership of the six main systems identified by hierarchical cluster analysis and lines between them are drawn to indicate statistically significant inter-regional partial correlation coefficients.

12 subjects
fMRI, n= 90 anatomical regions
coherence
unweighted
Not normalized, c and I
Scale-free brain functional networks.

Eguiluz VM, Chialvo DR, Cecchi GA, Baliki M, Apkarian AV.

Phys Rev Lett. 2005
Small-world and scale-free organization of voxel-based resting-state functional connectivity in the human brain.

van den Heuvel MP, Stam CJ, Boersma M, Hulshoff Pol HE.

fMRI, 28 subjects
n= voxel based (+/- 10 000)
correlation coefficient
unweighted
Normalized, c, l, degree
Network analysis of resting state EEG in the developing young brain: structure comes with maturation.

Boersma M, Smit DJ, de Bie HM, Van Baal GC, Boomsma DI, de Geus EJ, Delemarre-van de Waal HA, Stam CJ.

Hum Brain Mapp. 2011

227 subjects
EEG, n=21
SL, weighted graphs
Normalized, c and l

* p<.05
** p<.01
Heritability of “Small-World” Networks in the Brain: A Graph Theoretical Analysis of Resting-State EEG Functional Connectivity

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EEG’s of 574 mono- and dizygotic twins and some siblings
SL, threshold, binary graph
C, L in various frequency bands

- 46-89% of individual differences in clustering coefficient C and 37-62% of individual differences in path length L are heritable

- C, L and a ‘small-world’ organization are valid markers of genetic differences in brain network organization
Efficiency of functional brain networks and intellectual performance
M.P. van den Heuvel, C.J. Stam, R.S. Kahn, H.E. Hulshoff Pol

19 subjects
Resting state fMRI (Normalized) C and L
Loss of 'small-world' networks in Alzheimer's disease: graph analysis of FMRI resting-state functional connectivity
Sanz-Arigita EJ, Schoonheim MM, Damoiseaux JS, Rombouts SA, Maris E, Barkhof F, Scheltens P, Stam CJ.

PLoS One. 2010 Nov

18 AD patients, 21 controls
fMRI
SL, threshold datadriven
Fixed number of edges
C and L, gamma and lambda
Small-world structure of functional brain networks is lost in Alzheimer’s disease.
Functional neural network analysis in frontotemporal dementia and Alzheimer's disease using EEG and graph theory

de Haan W, Pijnenburg YA, Strijers RL, van der Made Y, van der Flier WM, Scheltens P, Stam CJ

BMC Neurosci. 2009

20 AD, 15 FTLD, 23 controls
SL C, L, R
Normalized for network size (fixed average degree)
Degree correlations are decreased in AD, but pathologically increased in FTLD.

disassortative

assortative
Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease

Stam Cj, de Haan W, Daffertshofer A, Jones BF, Manshanden I, van Cappellen van Walsum AM, Montez T, Verbunt JP, de Munck JC, van Dijk BW, Berendse HW, Scheltens P

Brain 2009

- Study population
  - Alzheimer patients
    - N = 18
    - 72.1 year, S.D. 5.6
  - Healthy controls
    - N = 18
    - 69.1 year, S.D. 6.8

- Recordings
  - 151 channel MEG
  - Rest / eyes closed

- Analysis
  - Correlations between MEG signals (phase lag index)
  - Network analysis
Weighted graph analysis of MEG

Computation of Phase lag Index

randomisation

Cw/Cw-r
Lw/Lw-r
Cw-r
Lw-r
Weighted MEG graphs

Alzheimer patients (N=18)

Control subjects (N=18)

0.5-4 Hz 4-8 Hz 8-10 Hz 10-13 Hz 13-30 Hz 30-45 Hz
Weighted graphs 8-10 Hz

Alzheimer

Controls

[Graphs showing network connections with nodes and edges, indicating differences between Alzheimer and control groups]

[Bar graph comparing the ratios Cw/Cw-s and Lw/Lw-s for AD and control groups]

[Diagram showing network types: Regular, Small-world, Random, with increasing randomness from p = 0 to p = 1]
Twee scenarios for network damage:

1. ‘random failure’
   - Random loss of vertices / edges

2. ‘targeted attack’
   - Loss of critical edges or Vertices (‘hubs’)
Phase lag index  8-10 Hz

Alzheimer
Controls

Targeted attack
Random failure
Simulation of network changes

**Cw/Cw-s**
- AD: 1,040 ± 20
- Target: 1,060 ± 20
- Random: 1,080 ± 20
- Control: 1,100 ± 20

**Lw/Lw-s**
- AD: 1,150 ± 10
- Target: 1,160 ± 10
- Random: 1,170 ± 10
- Control: 1,180 ± 10


fMRI: 127 healthy controls
PET: 29 healthy controls, 10 AD patients
Correlation, unweighted graphs,
Degree, standardized to z-scores
(for comparison between subjects)


Ann Neurol. 2006

Disturbed functional connectivity in brain tumour patients: evaluation by graph analysis of synchronization matrices.


Clin Neurophysiol. 2006

Bosma I, Douw L, Bartolomei F, Heimans JJ, van Dijk BW, Postma TJ, Stam CJ, Reijneveld JC, Klein M.

MEG, 23 patients
PLI, C/(C-s) and L/(L-s), small world-ness (S), and degree correlation (R).
Small-world networks and epilepsy

**Epilepsy in small-world networks.**
Netoff TI, Clewley R, Arno S, Keck T, White JA.
J Neurosci. 2004

- Hippocampal model
- Seizure activity corresponds with a small-world regimen of neurons

**Transition from local to global phase synchrony in small world neural network and its possible implications for epilepsy.**
Percha B, Dzakpasu R, Zochowski M, Parent J.

- 2 dimensional lattice model of coupled neurons
- Abrupt state transitions in SWN may be a mechanism of seizure development
7 patients with epilepsy
Intracerebral electrodes
SL C and L
### SWN and epilepsy ~ Results

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SWN and epilepsy ~ Conclusions

- During seizure activity the neuronal network changes in the direction of a small-world network.
- Interictal neuronal network has a more random configuration.
New hypothesis:

- Brain pathology is associated with network randomisation
- Random networks have higher synchronizability / lower seizure threshold
Network changes during absence seizures

pre ictal

ictal

Synchronization likelihood

coherence

Ponten et al. Exp Neurol 2009