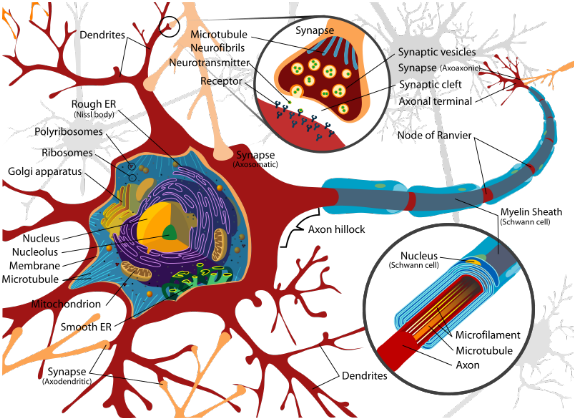
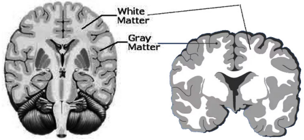
Neuronal cells

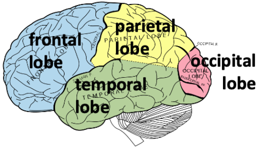
- There are about 100 billion neurons with $10^{14} - 10^{15}$ synapses in the human brain
- Communication takes place via electrical pulses (spikes)
- Synapses are junctions between two neurons that transfer chemical neurotransmitters
- Myelination increases the speed of signal propagation in axon

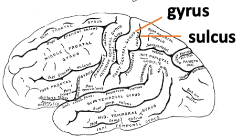


Brain areas

- **Grey matter:** neuronal cell bodies associated with processing and cognition
- **White matter:** glial cells and myelinated axons for coordinating communication between brain regions
- 4 major lobes (named after skull bones):
  - **Occipital lobe:** visual reception, visual-spatial processing, movement, color recognition
  - **Parietal lobe:** somatosensation, hearing, language, attention, spatial cognition
  - **Frontal lobe:** control attention, abstract thinking, behavior, problem solving, physical reactions, personality
  - **Temporal lobe:** auditory/visual memories, language, hearing, speech





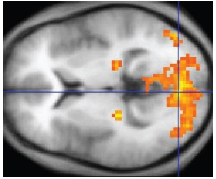


Neuroimaging techniques

- **Neuroimaging:** directly or indirectly make an image of the brain
  - **Structural** vs. **functional** (i.e., while performing "some work")
- Common techniques:
  - **Magnetic resonance imaging (MRI)** measures blood oxygen level associated with brain activity (2–3s per scan, spatial resolution of 2-3mm) $\Rightarrow$ **high spatial, low temporal resolution, requires shielded room**
  - **Magnetoencephalography (MEG)** measures magnetic field produced by electrical activity in the brain (around 100-1000Hz, up to 300 sensors) $\Rightarrow$ **low spatial, high temporal resolution, requires shielded room**
  - **Electroencephalography (EEG)** records electrical activity along the scalp (sampling rate 250-2000Hz, up to 256 electrodes) $\Rightarrow$ **low spatial, high temporal resolution**
- MEG/EEG measure on surface $\Rightarrow$ source localization required for inner areas

Functional MRI

- fMRI is a magnetic resonance (MR) technique that measures **changes in brain function** over time (Seiji Ogawa, 1990)
- When a certain brain area is active, blood flow to that region increases
- Goal: detect signal changes that correspond to neural activity



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OGAWA Seiji conferred the title of Distinguished Honorary Professor

In July 2020, the title of Distinguished Honorary Professor was conferred to OGAWA Seiji, and the Conferral Ceremony for this title was held on September 24, 2020.

The title of Osaka University Distinguished Honorary Professor is conferred to individuals who have made particularly outstanding contributions to academic culture and society and who have exceptional achievements in the development of education and research at Osaka University. OGAWA Seiji is the second individual to receive this title, after Professor Yoichiro Nambu.

Distinguished Honorary Professor Ogawa developed the basic principles of fMRI (functional magnetic resonance imaging), a technique used for measuring brain activity.

fMRI not only serves as a key technology for measuring activity in the healthy human brain in research fields that study higher cognitive function in humans, but also has a wide range of applications in medical fields, such as preoperative diagnosis before surgery, as well as diagnosis and pathogenesis in neurology and psychology.

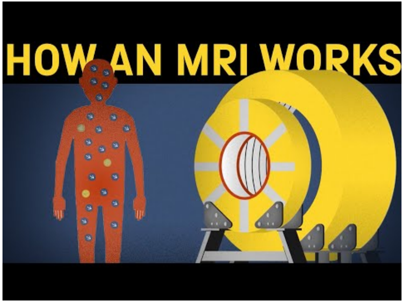
The Center for Information and Neural Networks of Osaka University has world-class fMRI equipment to provide new findings not only in medical fields, but also in other fields, such as immunology, experimental economics, and psychology.

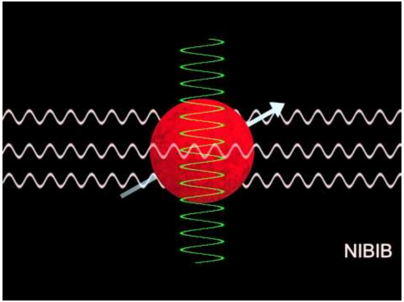
Reference link

https://cinet.jp/japanese/research/

Physical principles of MRI

- Here are two example videos on YouTube that explain the physics behind MRI.





Diffusion MRI (Diffusion Tensor Imaging)

- Measurement of the diffusion of water molecules that gradually reach the surface of an ellipsoid if the medium is anisotropic
- Parameters of each voxel: rate and preferred direction of diffusion (tensor)

$$D = \begin{pmatrix} D_{xx} & D_{xy} & X_{xz} \\ D_{yx} & D_{yy} & X_{yz} \\ D_{zx} & D_{zy} & X_{zz} \end{pmatrix}$$

- Individual fibers are traced to obtain model of anatomical connectivity

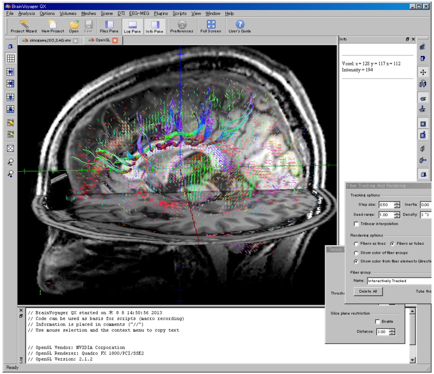
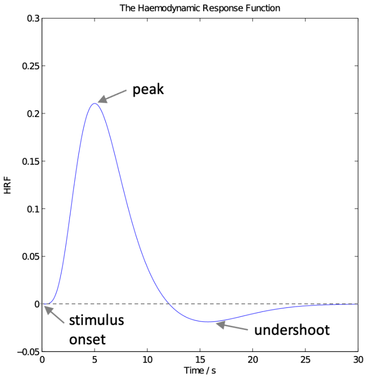


Figure 1: DTI fiber tracing

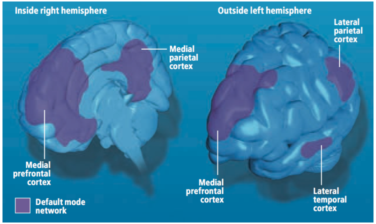
Hemodynamic Response Function (HRF)

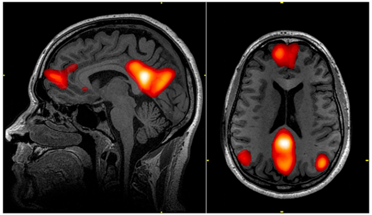
- fMRI uses the change in magnetization between oxygen-rich and oxygen-poor blood: **BOLD (blood oxygen level dependent)** signal
- Neuronal event triggers response after 1-2 seconds and rises to peak about 5 seconds after neuronal firing
- After activity, the HRF first drops under the baseline (undershoot) before slowly returning to the baseline
- HRF is used for **statistical parametric mapping (SPM)** of activation measured in fMRI



Task-positive vs task-negative experiments

- Experiments are performed:
  - **task-positive**: while performing a specific task
  - **task-negative**: without any task
- **Resting state fMRI** studies functional organization of brain by looking at spontaneous low-frequency BOLD signal fluctuations
- The **default mode network** (DMN) is activated while brain is at rest (see Raichle, 2006)
- For goal-oriented activity, the DMN is deactivated and a task-positive network is activated





fMRI retinotopy task-based visual experiment

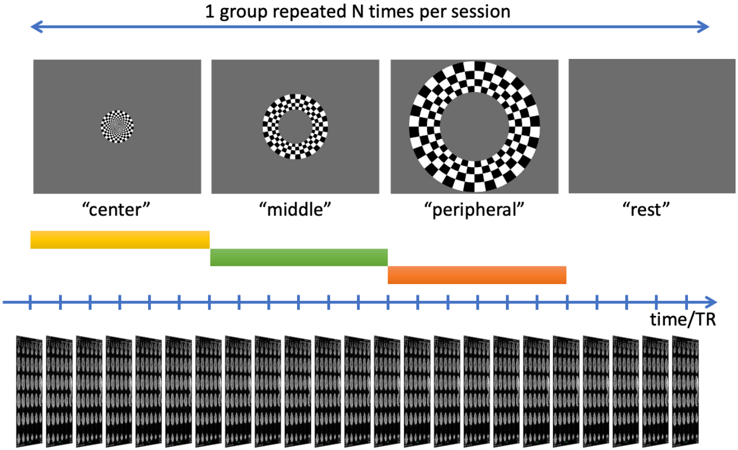


Figure 2: Design matrix of fMRI retinotopy experiment

Preprocessing the fMRI data

- After the scan, the results are 3D **volumes** at a certain **TR** (temporal resolution)
- Each volume consists of several **slices of voxels** (**vo**lume pi**xel**)
- **Sessions** usually consist of several volumes
- Preprocessing steps:
  - Slice timing correction
  - Head motion correction
  - Realignment
  - Normalization
  - Temporal filtering
  - Spatial filtering (smoothing)

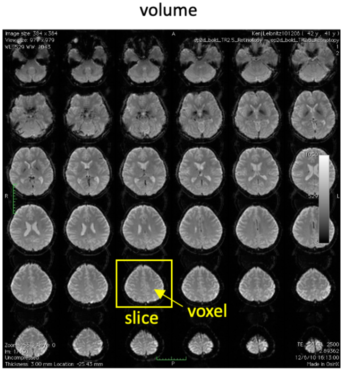
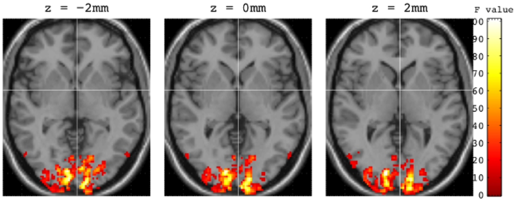
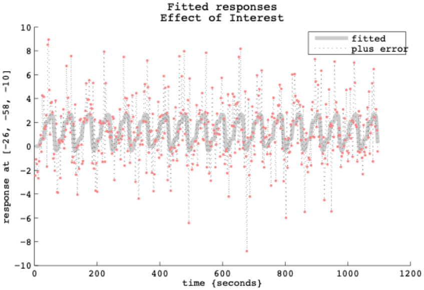


Figure 3: fMRI slice and voxels

Analysis of fMRI data (using SPM Toolbox)

- Convolution of HRF with design matrix gives the expected BOLD responses
- Statistical tests are performed for each voxel to identify activated voxels that are related to the task (F-test, Student's t-test)
- Graphical representation of brain activity as colored patches of F-values on slice images





Example of voxel timeseries during experiment

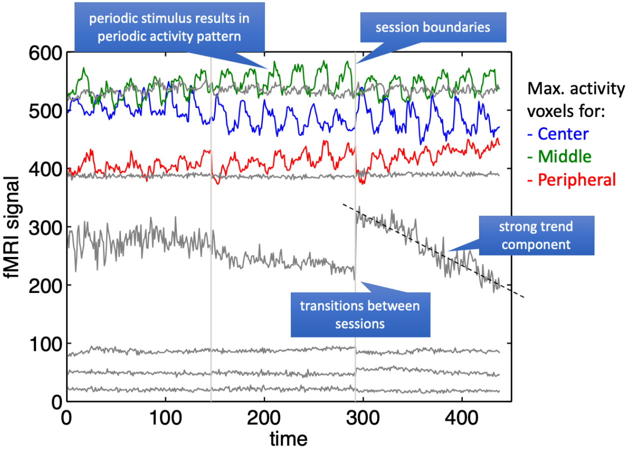


Figure 4: Voxel timeseries concatenated from 3 sessions

Assignments (3.1)–(3.3)

(3.1)

Which two technologies would you combine to measure brain activity at the same time, if you want to record both a high spatial **and** temporal resolution?

(3.2)

Search the Internet for the **differences between MRI and fMRI**. Give examples for situations in which you would use either of them.

(3.3)

In an experiment, it is common to **also record a structural MRI** scan after the functional MRI scan. Why is this useful?

Connectivity in the brain

Connectivity in the brain can be observed in 3 major ways, see Sporns et al., 2004:

- **Anatomical connectivity:** structural connectivity among neurons, remains rather static over short time scales (directional links)
- **Functional connectivity:** statistical dependence, e.g., correlation, among spatially distributed neurons based on similarity (undirected links)
- **Effective connectivity:** relationship between neural systems inferred by causal interaction models, e.g., Granger causality (directional links)
- Nodes in brain networks are often based on **regions-of-interest (ROI)**: all voxels from the same ROI in a brain atlas are combined (averaged) to one representative node with its time series.

Basic principle of functional networks

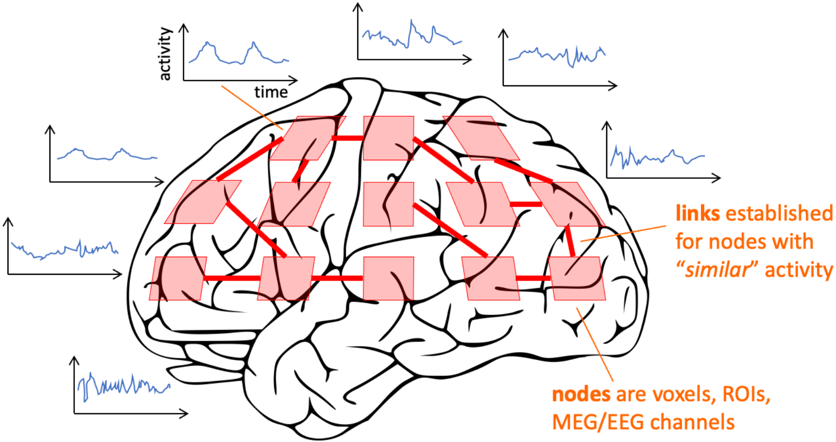


Figure 5: "Similarity" of time series leads of two ROIs leads to a link between them

Similarity measures between time series

- Most common method is to establish a relationship between time series $x_i(t)$ and $x_j(t)$ of nodes i and j with **Pearson's correlation coefficient**:

$$\rho_{x_i,x_j} = \frac{\langle x_i(t)\, x_j(t)\rangle - \langle x_i(t)\rangle\langle x_j(t)\rangle}{\sigma(x_i)\,\sigma(x_j)} \qquad \text{with} \qquad \sigma(x) = \sqrt{\langle x(t)^2\rangle - \langle x(t)\rangle^2}$$

- Other possible metrics that have been applied are:
  - mutual information
  - coherence
  - synchronization likelihood
  - joint recurrence rate
  - wavelet correlation
  - ...

Examples of correlation between time series

Assume we have these four time series $f_1 = \sin(x)$, $f_2 = \cos(x)$, $f_3 = \cos(x) + \eta$, and $f_4 = \eta$ with η being an independent Gaussian noise term $\sim N(0, 0.5)$.

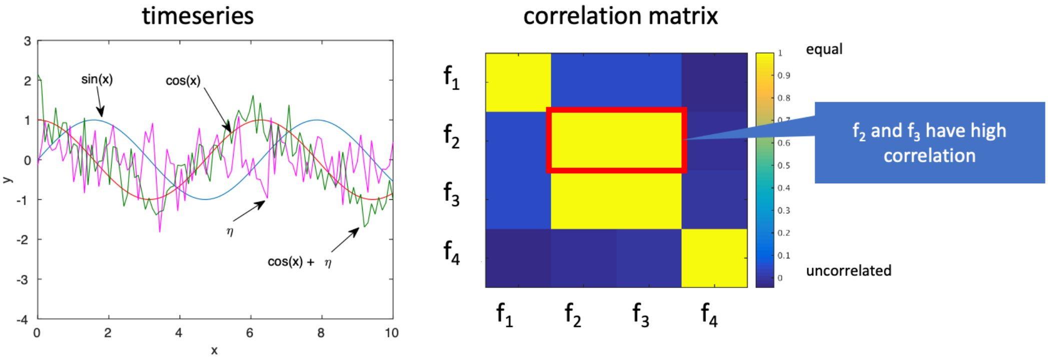


Figure 6: Correlation among time series $f_1, \ldots f_4$

Generating an adjacency matrix from correlations

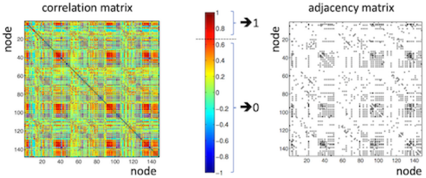


Figure 7: Thresholding correlation matrix C to adjacency matrix A

- **Correlation matrix** $C = (c_{ij})$ shows pairwise correlations among all ROIs
  - symmetric matrix, since $c_{ij} = c_{ji}$
  - diagonal elements are 1, since $c_{ii} = 1$
- Setting a threshold on the correlation matrix yields a binary matrix with only highly correlated connections $\Rightarrow$ **adjacency matrix** of network
- But what happens with **large negative correlations**?

Retinotopy checkerboard experiment

- Visual experiment with stimulation of 3 different areas of retina: center, middle, peripheral
- MRI scan timings known when each of the different stimulus onsets are presented ⇒ correlation matrix for each stimulus (and for "rest")

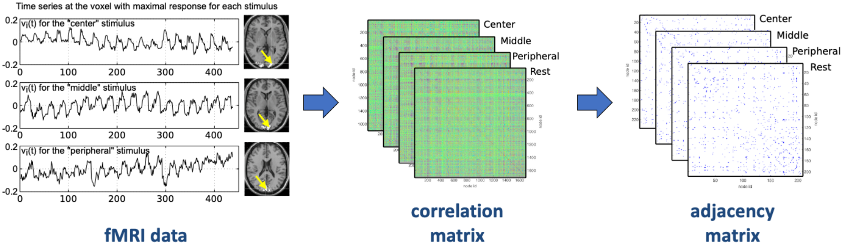


Figure 8: Adjacency matrices of fMRI retinotopy experiment

Activation areas vs functional network

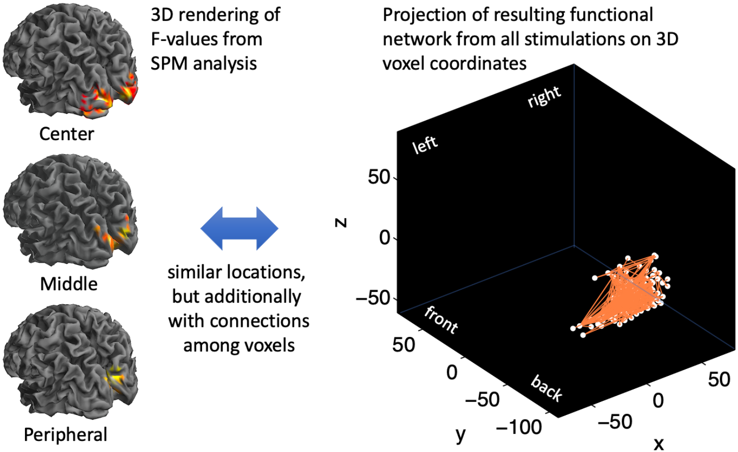


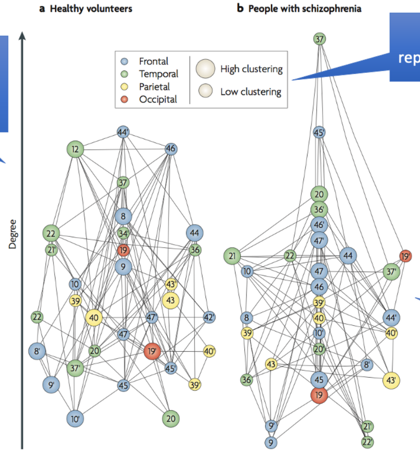
Figure 9: Activation areas of retinotopy experiment

Brain Functional Networks: Properties & Clinical Findings

- Network Properties
  - **Small-World Properties** in ROI-based and voxel-based studies (related to high modularity)
  - **High Clustering Coefficient**: Dense interconnections between functionally related regions
  - **Scale-Free Degree-Distribution** found in voxel-based networks
- Clinical Implications
  - **Aging**: Negative influence on cost efficiency of small-world structure
  - **Alzheimer's Disease**: Abnormalities in high-degree hub nodes and high-centrality nodes
  - **Schizophrenia** (EEG studies): Clustering and path length resembling random networks

Disease-related disorganization of brain networks

healthy subjects have hierarchical organization by low clustering of high-degree nodes



clustering coefficient represented by size of node

numbers indicate Brodmann region (prime symbol for left-sided region)

patients with schizophrenia: high-degree nodes are often more highly clustered

Figure 10: Schizophrenia study by Bullmore and Sporns, 2009

Comparison of real and modeled networks in the 8–10Hz band

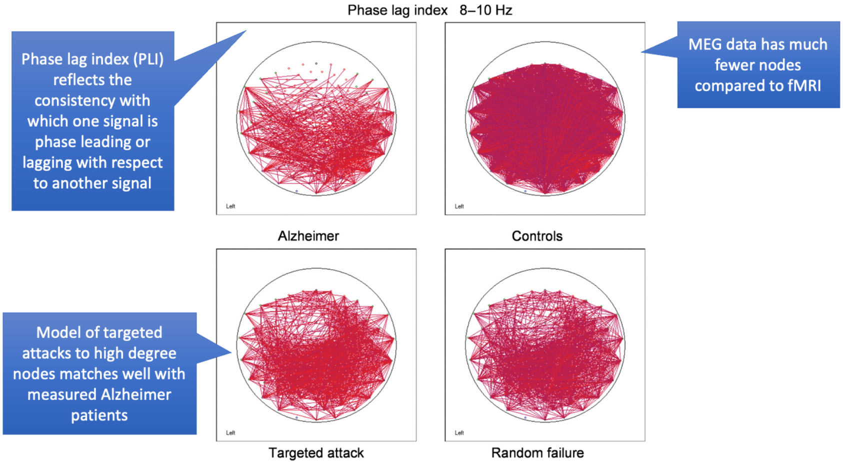


Figure 11: Phase lag index for Alzheimer and control subjects by Stam et al., 2008

Intrinsic complexity of brain networks

- By randomly rewiring all links with probability α, the internal properties of retinotopy brain networks (all stimuli C, M, P) are more affected than engineered networks
- Modularity and clustering decrease more rapidly than for engineered networks

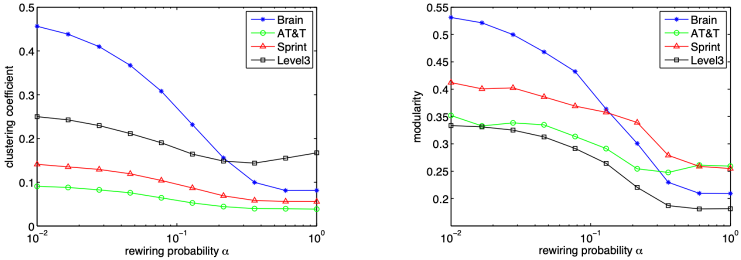


Figure 12: Random rewiring of networks by α

Simulating routing on structural brain network

- Simulation of randomized routing on structural Macaque connectome
- Data sizes: send entire messages or broken down into packets
- Randomized routing schemes:
  - Random walk (RW)
  - Shortest path (SP)
  - Informed RW (avoid busy nodes and/or direct transmission)
  - Biased RW (tuneable between RW and SP with parameter c)

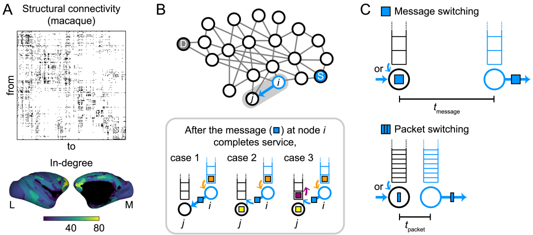


Figure 13: Simulating signal propagation on Macaque connectome by Fukushima et al., 2024

Hub disruption index

- To quantify the reorganization of the brain network due to coma or chronic back pain, hub disruption index has been considered in Achard et al., 2012
  - x-axis: mean degree of each node in healthy group
  - y-axis: difference between groups in mean degree of each node
- Hubs may change from healthy to patients
- Slope of this line is **hub disruption index**
- Mano et al., 2018 extended hub disruption index to other graph metrics: clustering coefficient, betweenness centrality

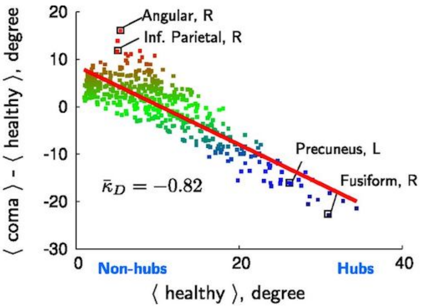


Figure 14: Hub disruption index

Assignments (3.4)–(3.6)

(3.4)

Which of the graph theoretic metrics we learned in the previous lecture do you think are most suitable for comparing brain networks of healthy subjects and patients suffering from a neurological disease? Explain your decision.

(3.5)

When extracting a functional network, we only look at the strongest positive correlations. How would you interpret strong negative correlations in this case?

(3.6)

Instead of using graph theory, can you think of any other tools (maybe from your field) that may seem suitable for analyzing and comparing brain networks?

Brain decoding

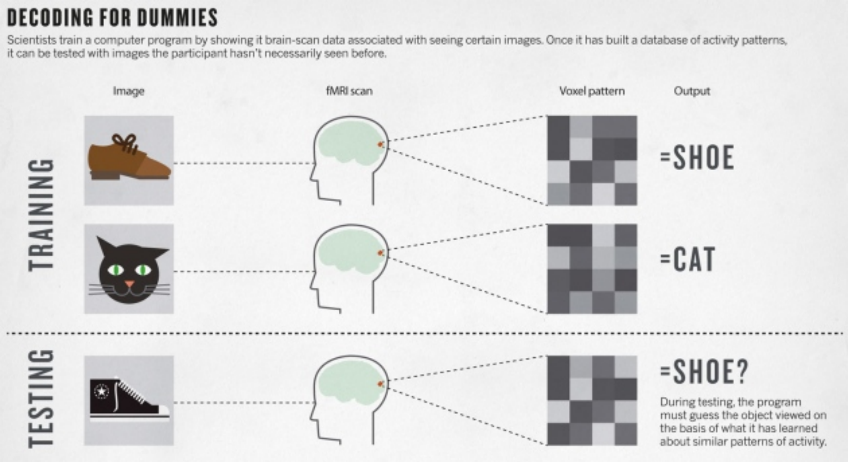


Figure 15: Decoding the brain by Smith, 2013

Decoding of visual stimuli

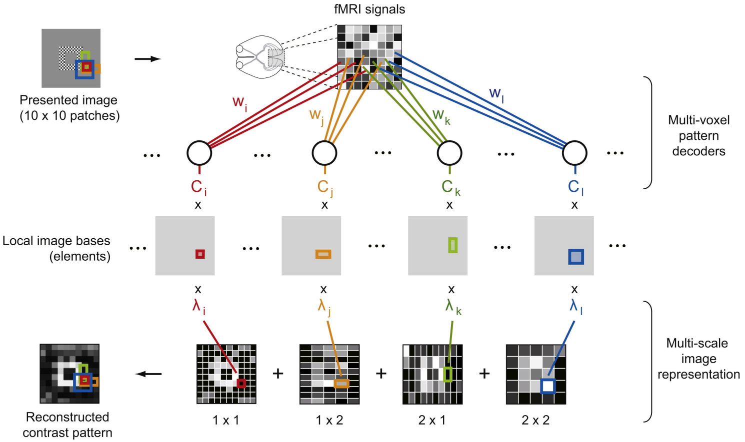


Figure 16: Visual image reconstruction from fMRI by Miyawaki et al., 2008

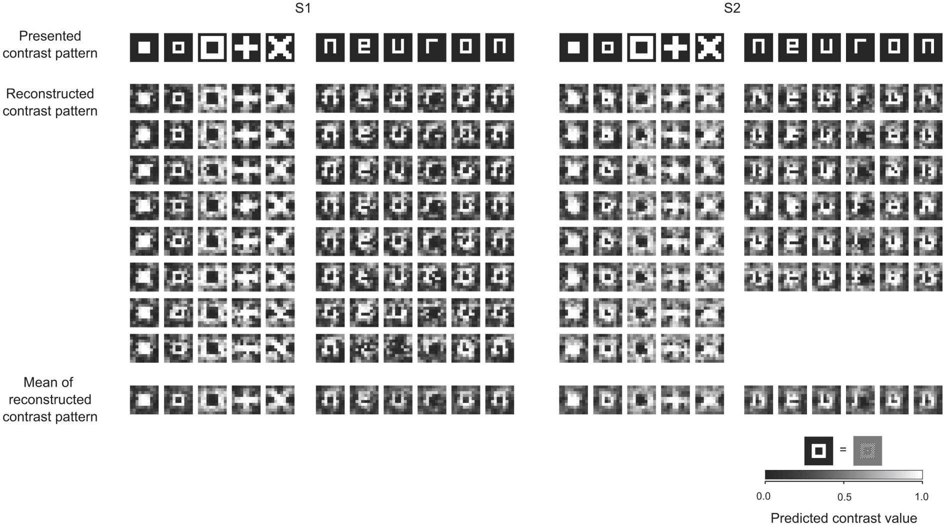
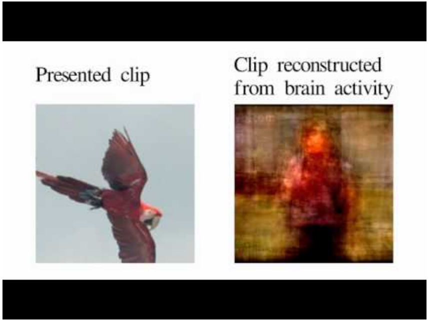


Figure 17: Reconstructed patterns from Miyawaki et al., 2008

Movie decoding



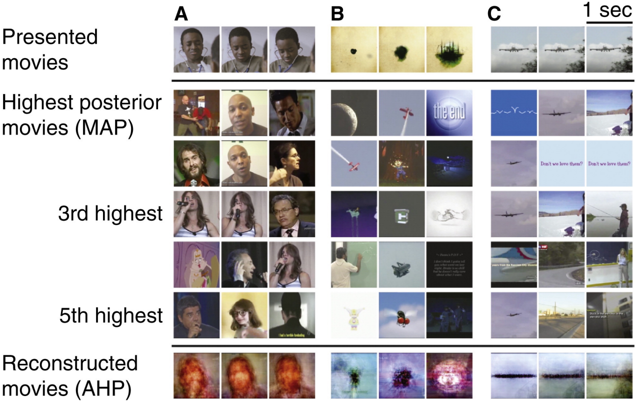


Figure 18: Decoding of natural movies by Nishimoto et al., 2011

Assignments (3.7)–(3.8)

(3.7)

In the papers by Miyawaki and Nishimoto, fMRI measurement data are used as “grayscale images” that map to a target label of what the subject sees. Do you think that recording and mapping the brain’s activations is like “mind reading” and is an invasion of privacy? Explain your viewpoint on this matter in several sentences.

(3.8)

In BrainNet (see also this YouTube video), the authors explain how to interconnect 3 brains over the Internet. Please read the abstract of that paper and explain in several sentences what kind of possible applications could be realized by such technology.

Conclusion

- Network science has been increasingly applied to systematically analyzing networks of the brain
- Brains usually display small-world and scale-free properties, and they are extremely modular in topology
- Analysis of brain networks can be used for clinical assessment of brain disorders
- Different imaging and analysis methods may lead to different complex network measures being most relevant

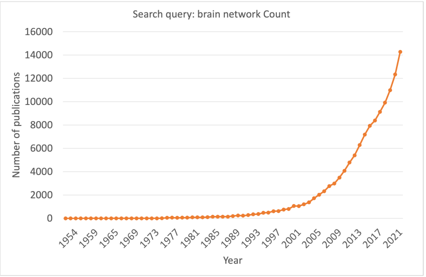


Figure 19: Publications per year on "brain networks" in PubMed

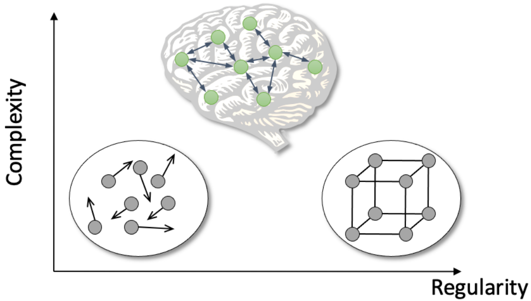


Figure 20: Regularity vs complexity of the brain by Tononi et al., 1998

- Brain networks show higher complexity when compared to completely regular or random network topologies
- The characteristics of the brain (cognition, learning, memory) can be perhaps applied towards designing better information networks or machine learning methods

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- O. Sporns (2011), "Networks of the Brain", MIT Press.
- O. Sporns (2012), "Discovering the human connectome", MIT Press.
- Brain Connectivity Toolbox (Matlab version, Python version)