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Introduction to fMRI and connectivity

Centre de recherche iugm
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UNF Unité de neuroimagerie fonctionnelle

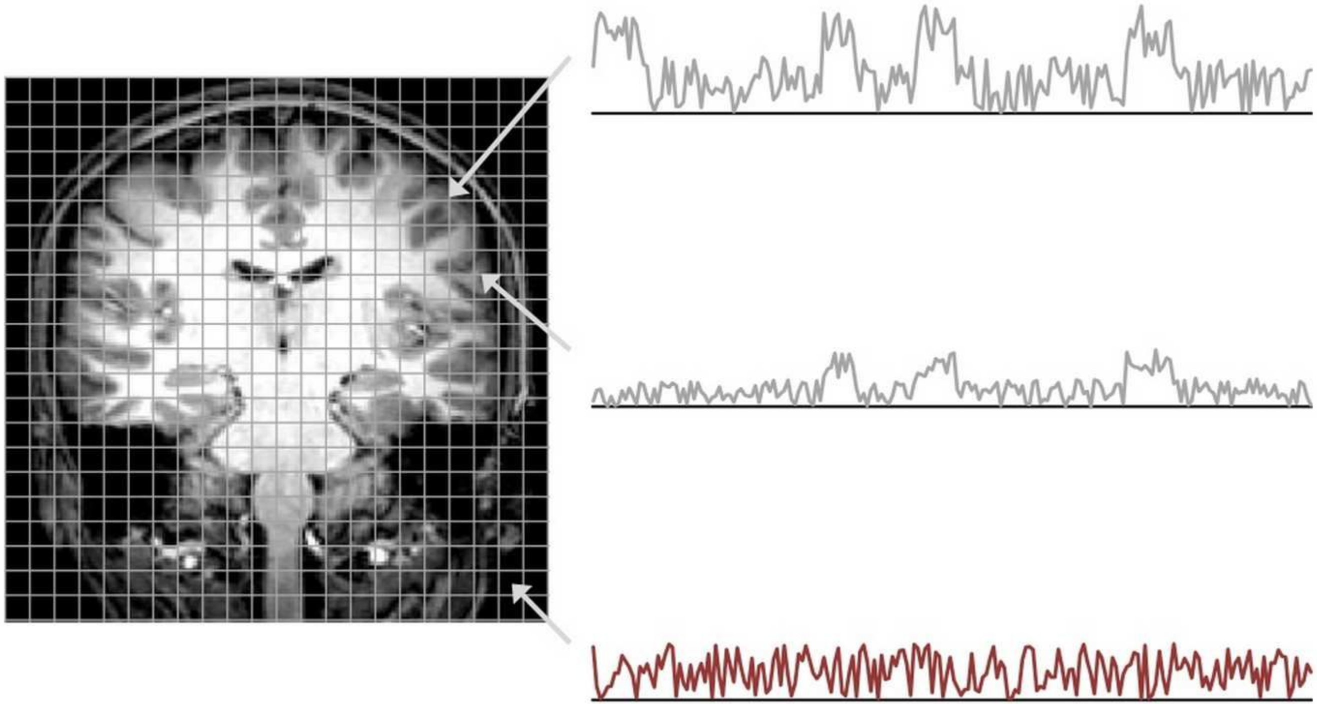
Objectives

1. Understand the basis of the signal used in functional magnetic resonance imaging
2. Know the main steps of preprocessing fMRI data
3. Know how functional connectivity is calculated, and how it is most commonly used
4. Know the main brain parcellations and associated technical challenges

The BOLD signal

1. Neurovascular coupling
2. Magnetic properties of hemoglobin
3. The hemodynamic response function model

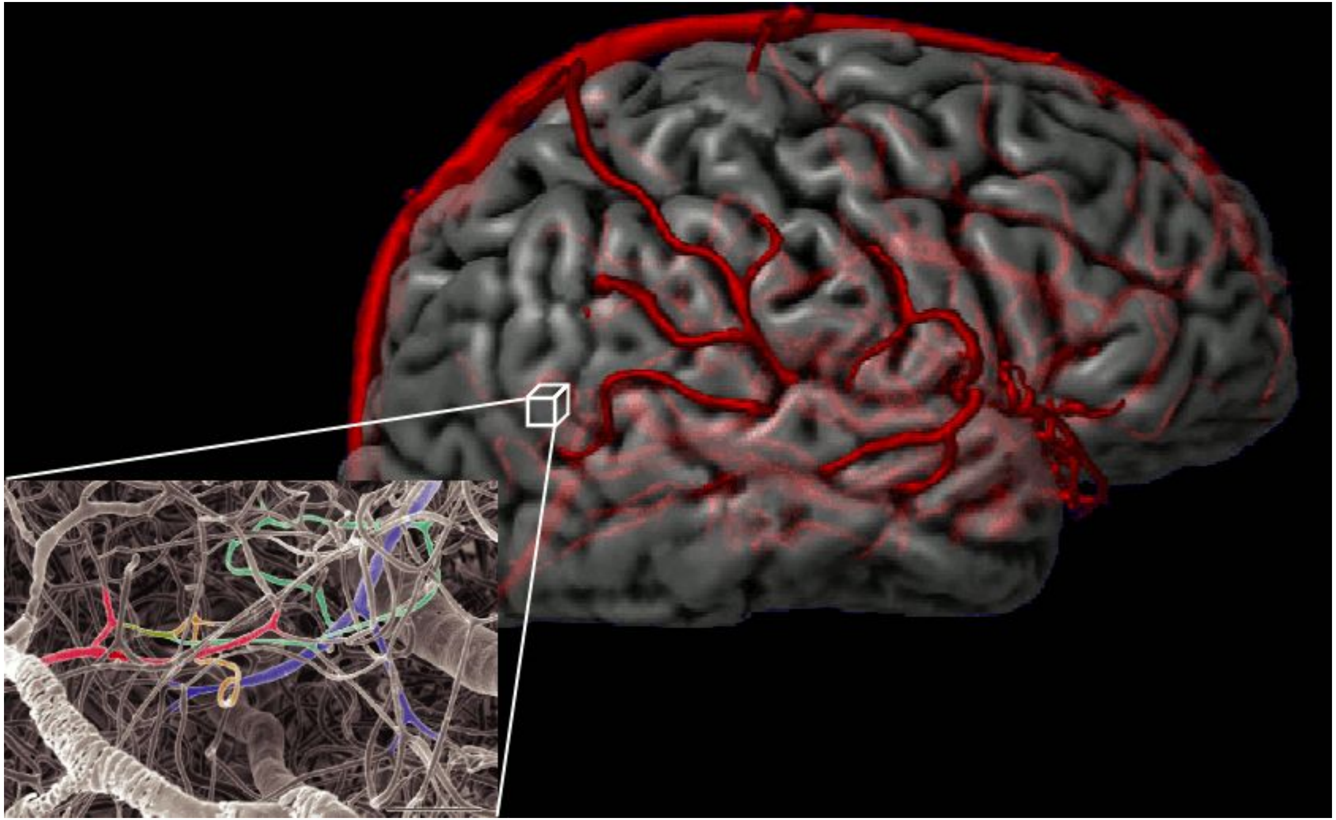
Functional MRI



fMRI is a 4D imaging modality: volume (3D) + time.

At each voxel, a series of time samples ar recorded (typically a few hundreds), with a repetition time of 100s of ms to a few seconds.

Neurovascular coupling

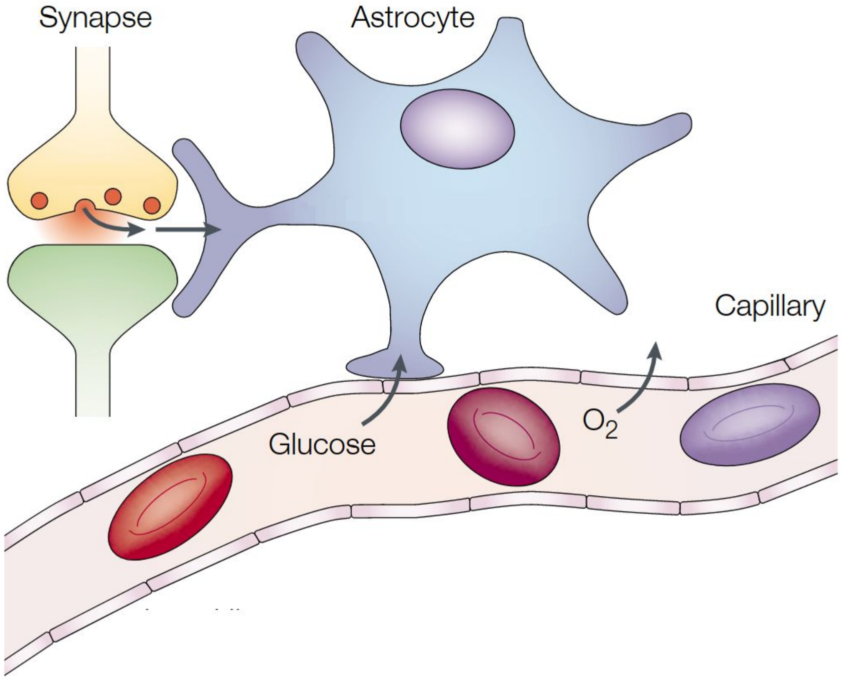


Vasculature meshes with neuronal population at a very fine spatial scale, (~10 microns), with micro-capilaries regulating blood oxygenation in a highly local and precise way.

This result has its roots in early physiological works, e.g. Roy C.S. Sherrington C.S. On the regulation of the blood supply of the brain. J. Physiol. 1890; 11: 85-108.

Figure adaptée de Harrison, 2002 et Dr Bruce Pike.

Neurovascular coupling

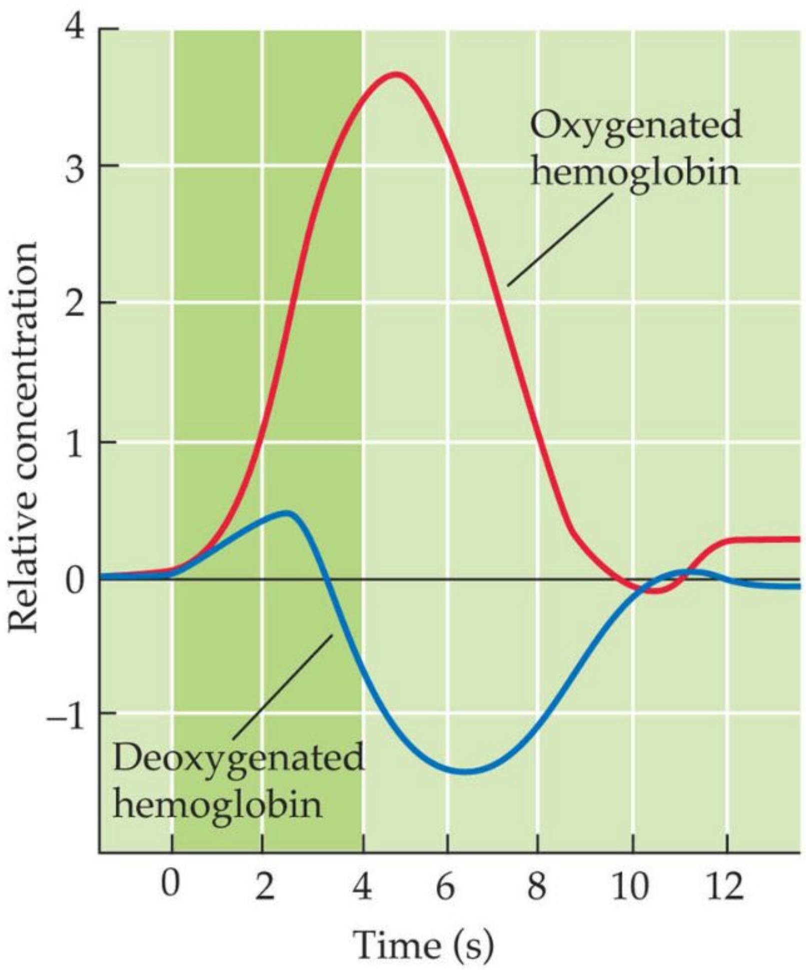


The metabolic activity associated with neuronal activity, in particular the release of neurotransmitters in the synaptic cleft, results in an increase of oxygen extraction in the blood. The vascular response to this increased extraction is an increase in blood volume and blood flow, and a paradoxical increase in local concentration of oxygenated hemoglobin.

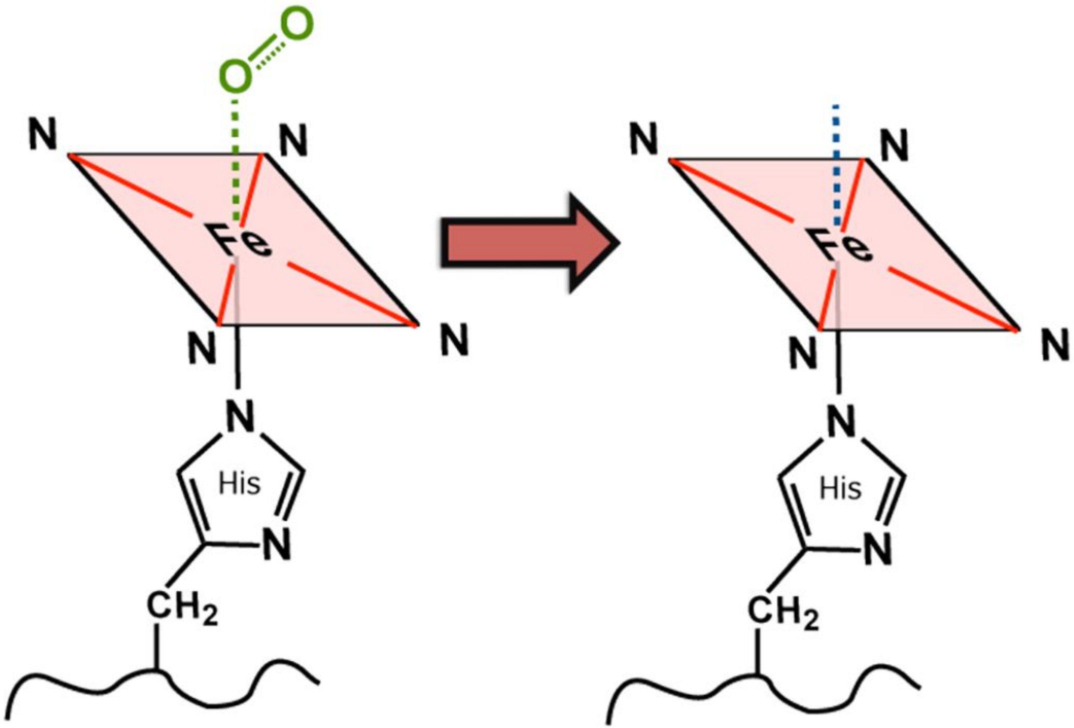
Adapted from Heeger and Ress, 2002, Nature reviews neuroscience, 3: 142-151.

Hemodynamic response

The hemodynamic response function (HRF) is the increase in the relative concentration of oxyhemoglobin which follows an increase in neuronal activity.



Oxy- vs Déoxy- hemoglobin

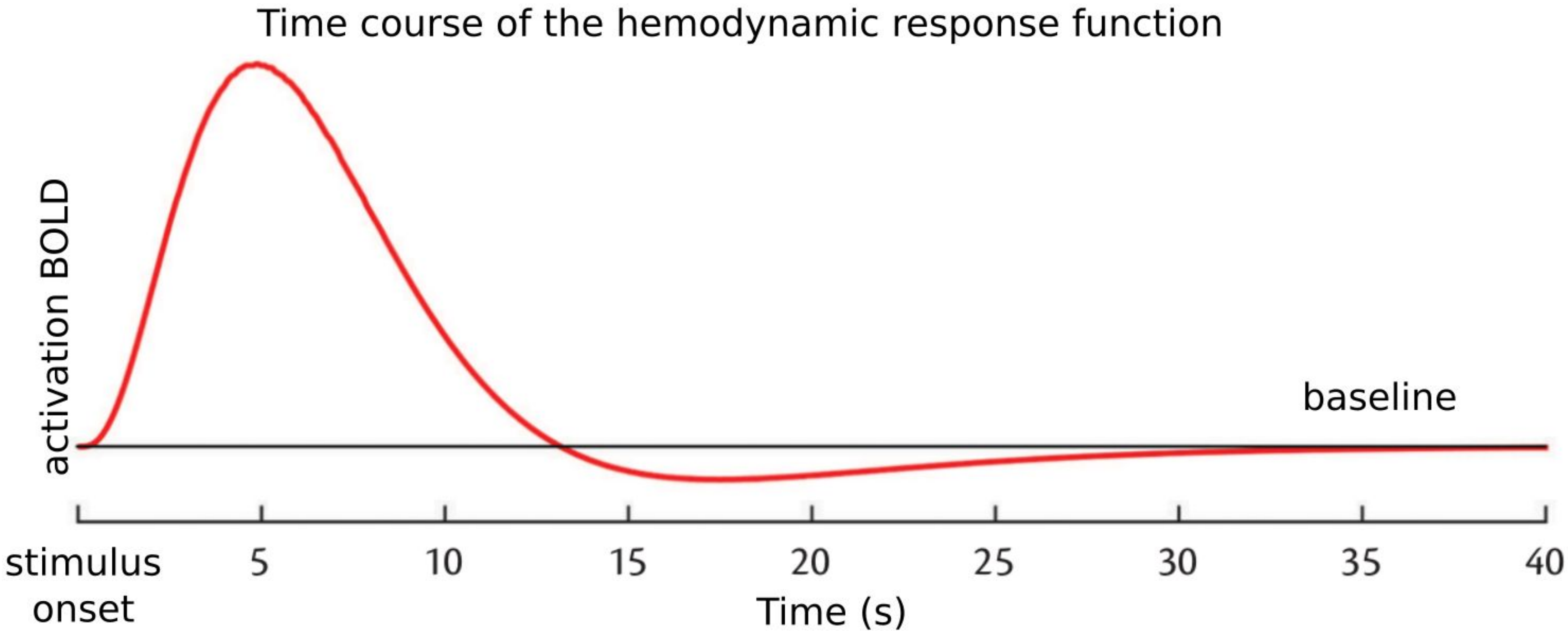


oxyhemoglobin(diamagnetic) Deoxyhemoglobin (paramagnetic)

Dioxygen changes the magnetic properties of hemoglobin.

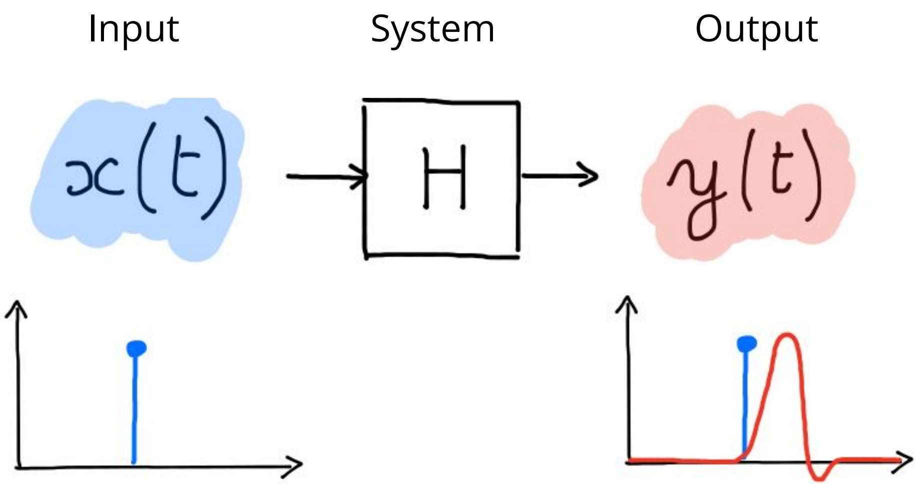
From http://mriquestions.com/bold-contrast.html

“blood-oxygenation level-dependent” (BOLD) signal



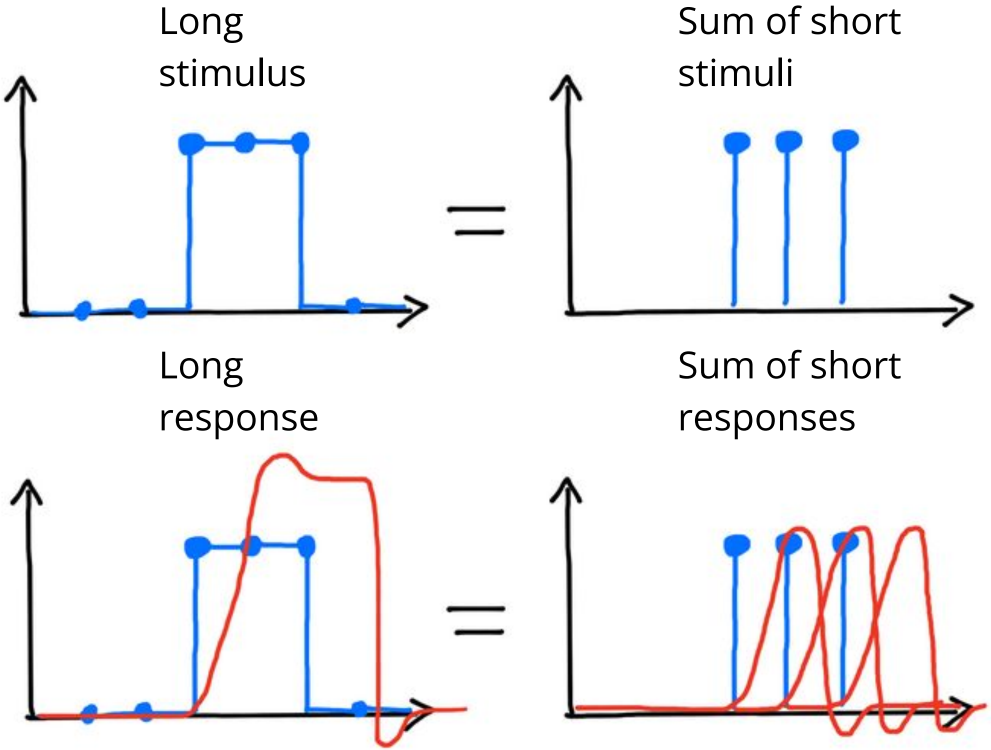
The BOLD signal is complex, and mixes several physiological and physical process

The neurovascular coupling as a linear time-invariant system



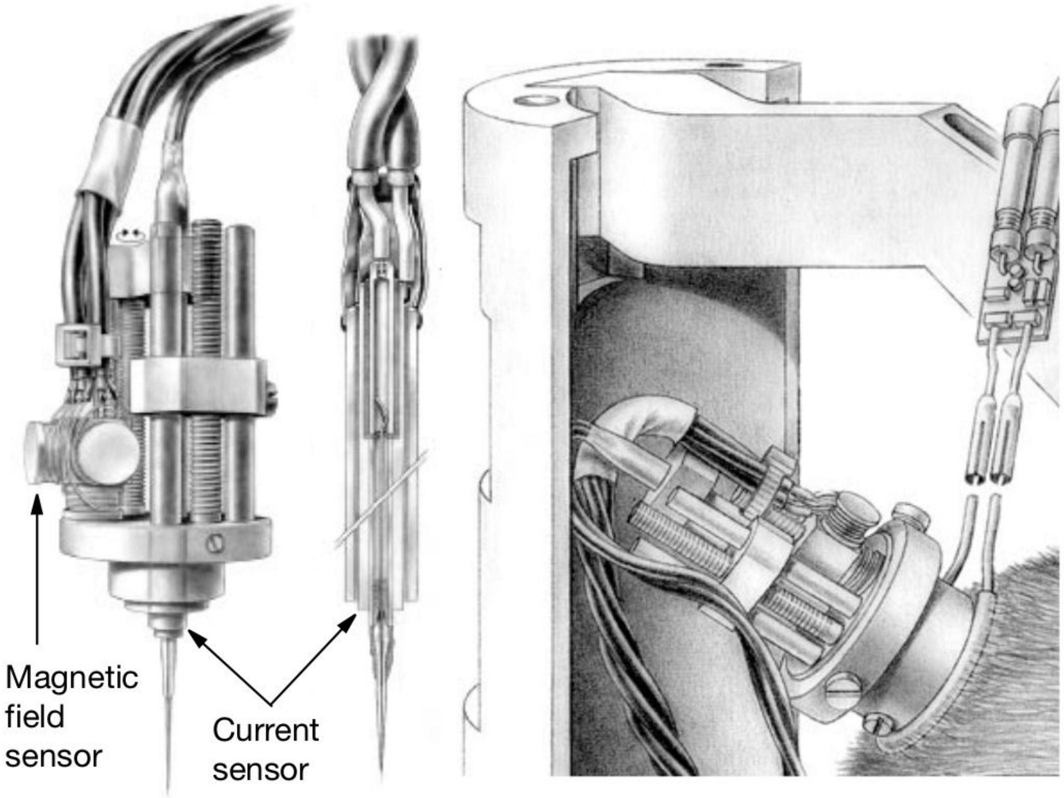
The hemodynamic response function is a simplified model linking the neuronal activity and the BOLD signal, approximating that system as linear and time invariant. The first biophysical model of neurovascular coupling (the balloon model) was proposed by Buxton et al., MRM 1998).

The additivity hypothesis



A common, key hypothesis on the hemodynamic response function is additivity: the response to a series of short impulsions is the sum of the responses to these impulsions, taken separately.

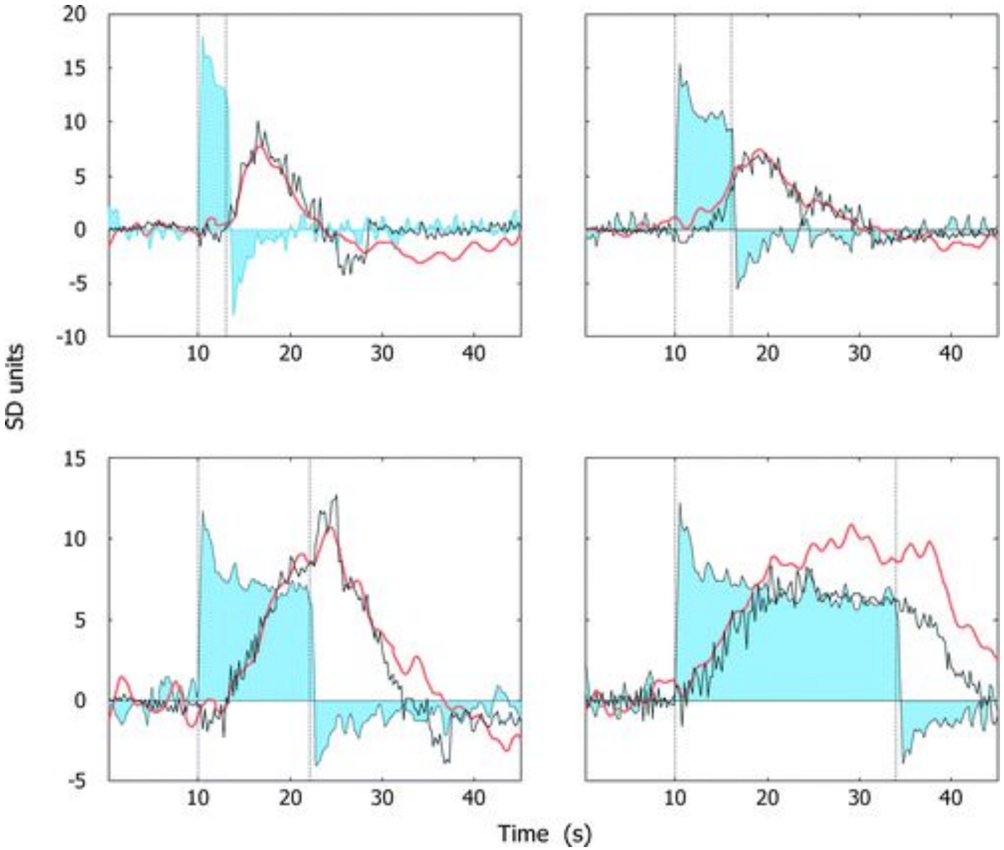
Experimental validation of neurovascular coupling



Simultaneous measure of intra-cortical local field potential activity and BOLD signal (visual cortex) in monkeys.

Figure and protocol from Logothetis et al. Nature Neuroscience (2001).

Hemodynamic response additivity



Simultaneous recordings of local field potentials and BOLD in the visual cortex of a monkey. Response to stimulations of 3, 6, 12 and 24 seconds respectively (from left to right, and top to bottom). Blue curve: LFP, red curve: BOLD signal, grey curve: predicted BOLD signal using LFPs as an input and a linear time-invariant system.

Figure tirée de Logothetis et al. (2004).

A brief BOLD history

modulation of vasculature
by neuronal activity

Roy et
Sherrington
J. Physiol.

1890

1936

Paulling and Coryell
PNAS

magnetic properties of oxy-
and deoxy-hemoglobin

fMRI activation maps

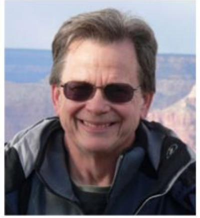
Ogawa et al.
PNAS

Kwong et al.
PNAS

Bandettini et al.
MRM

1991-2

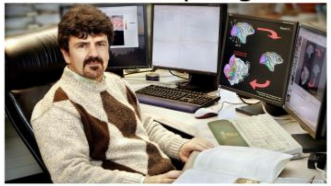
1998



Buxton et al.
MRM

mathematical model of
neurovascular coupling

experimental validation of
neurovascular coupling in animals



Logothetis et al.
Nature Neuro.

2001

Main steps of fMRI preprocessing

- Image registration
- Confound regression
- Spatial smoothing

Image registration: linear

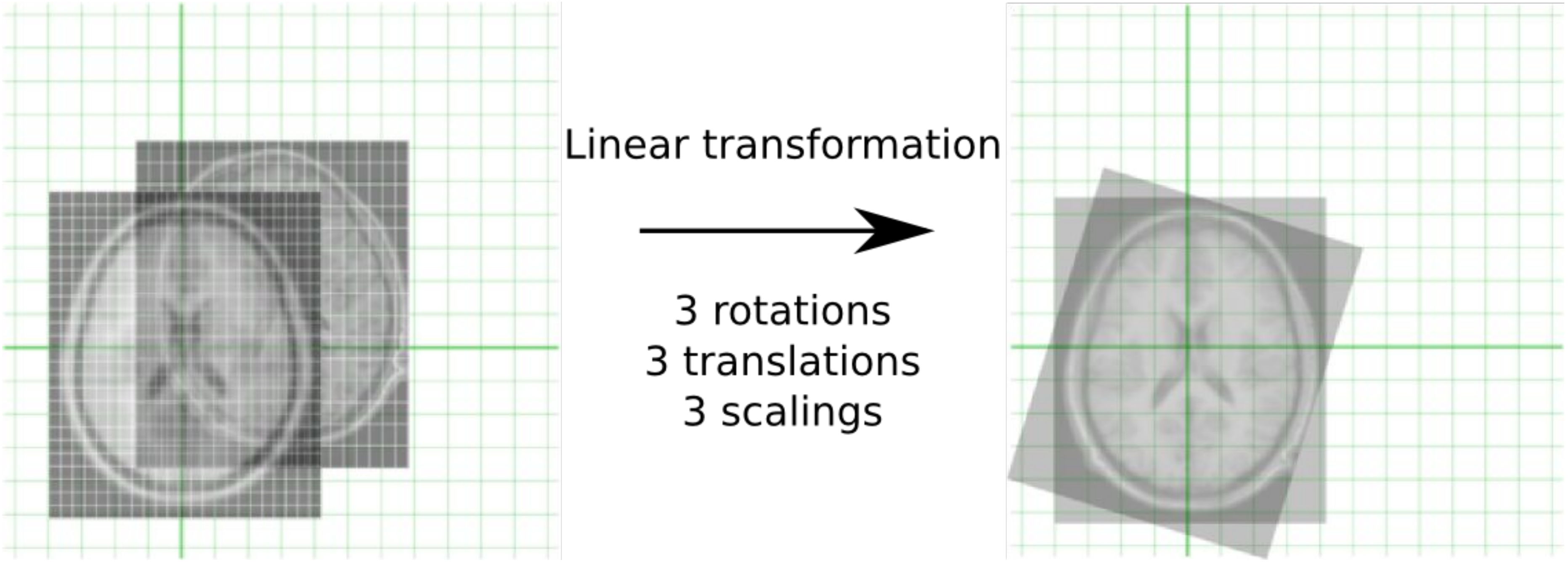
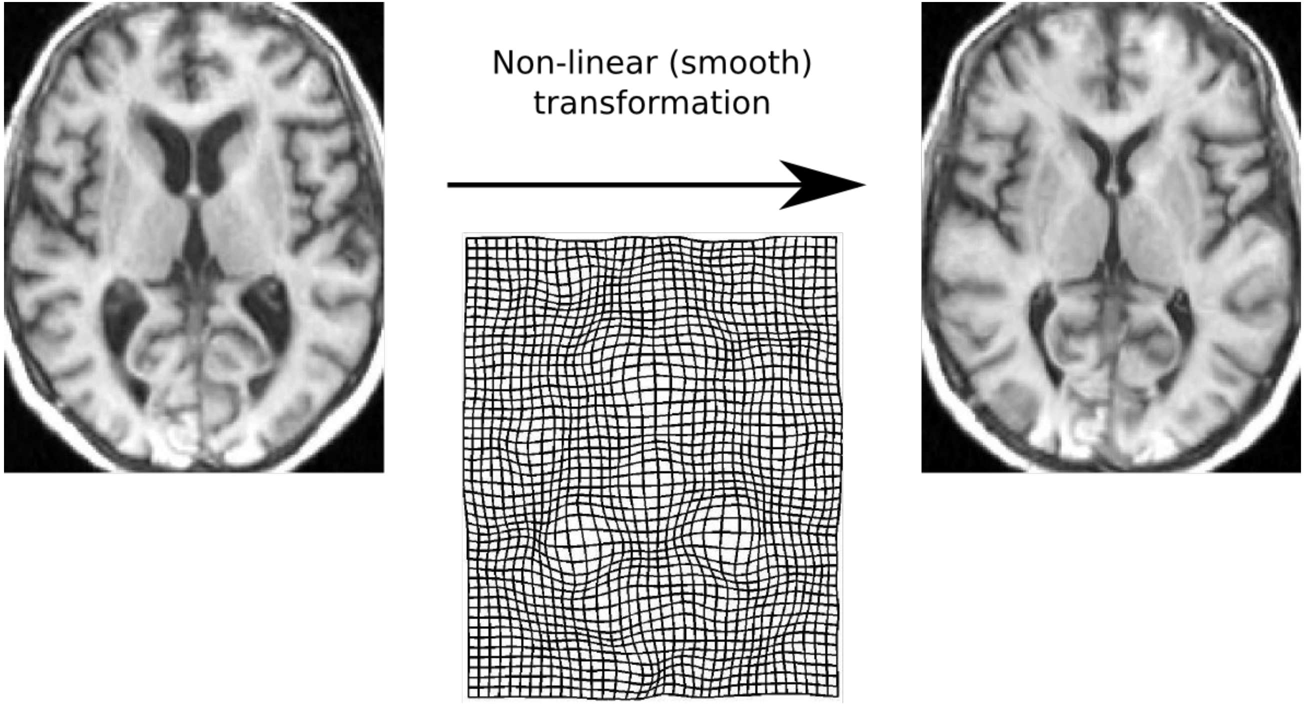
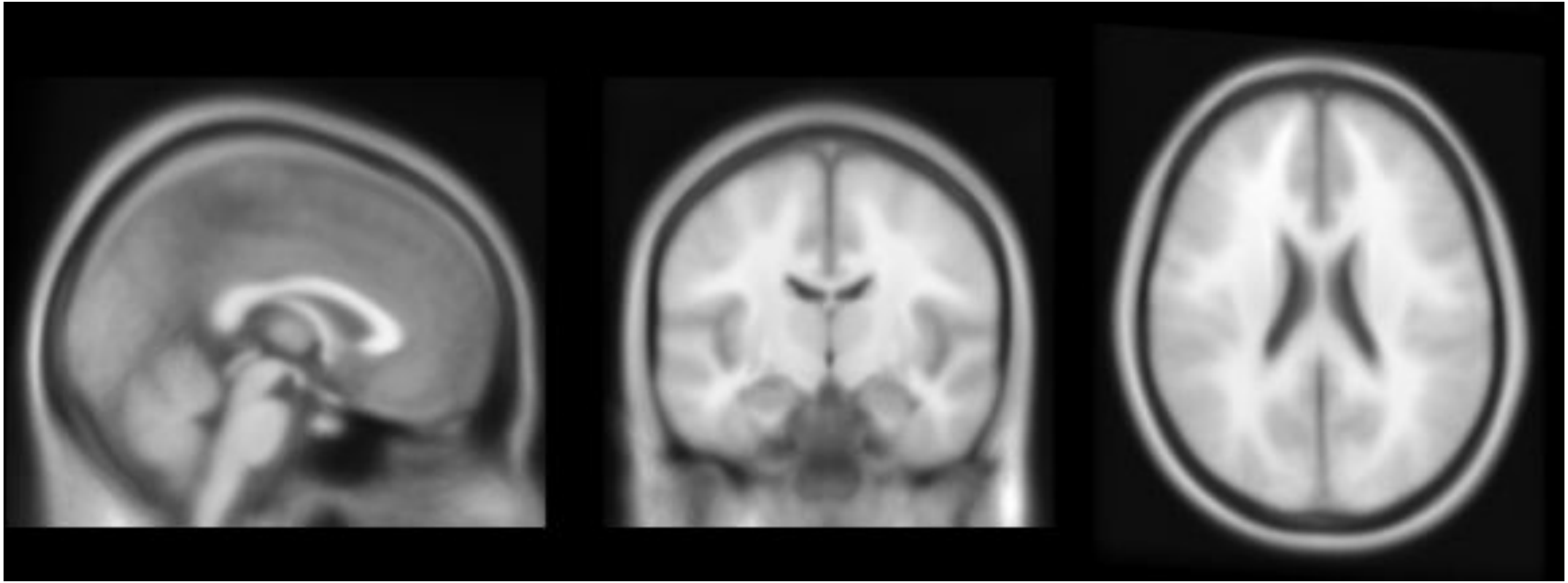


Image registration: non-linear

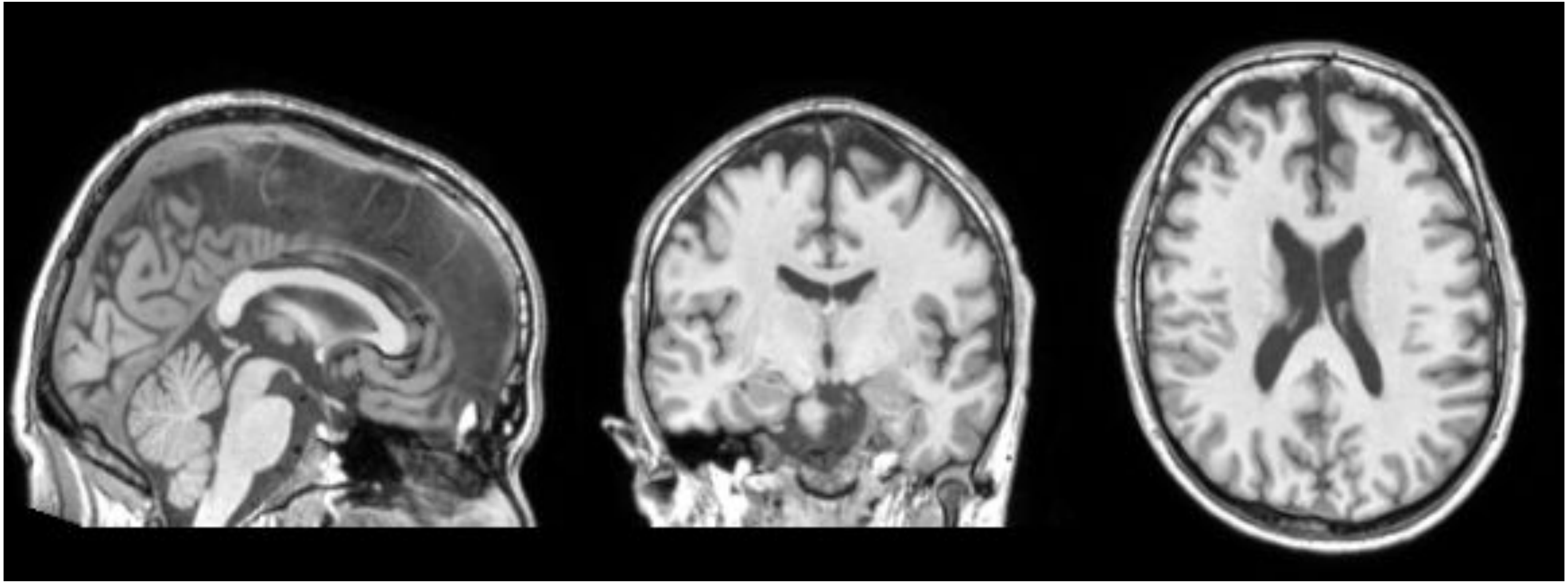


Linear stereotaxic space

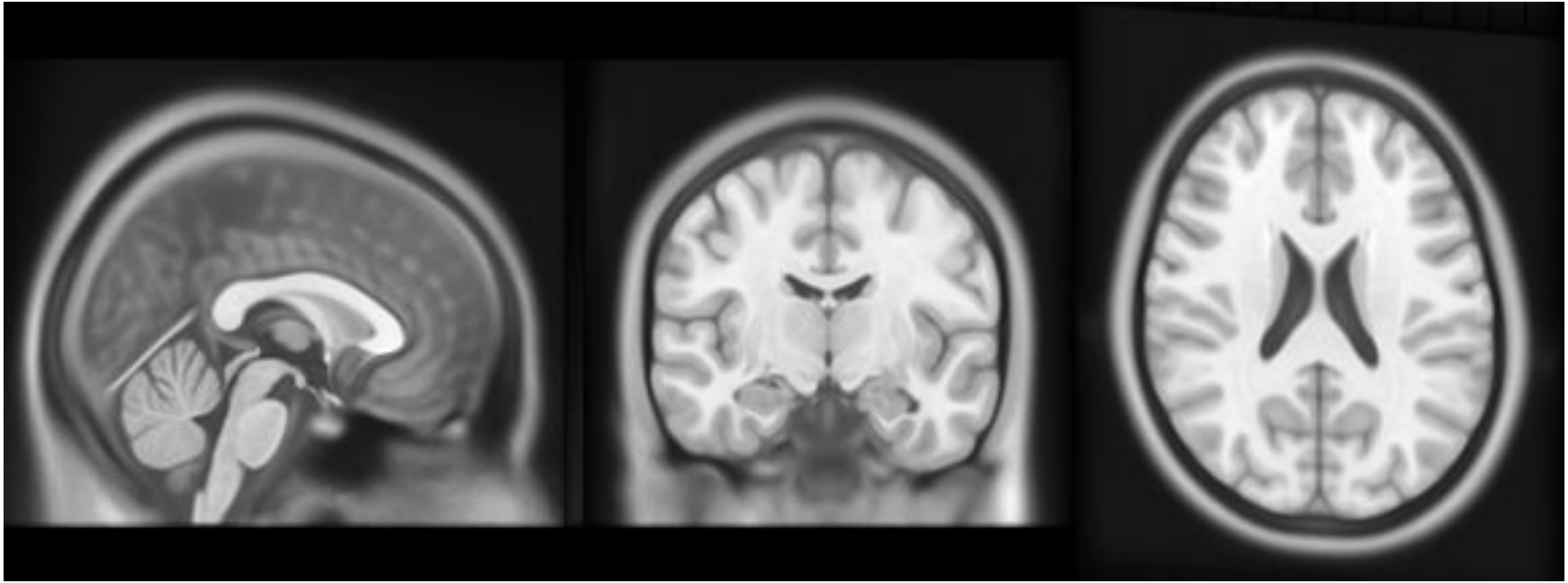


Linear ICBM stereotaxic space (average of N=152 T1 MRIs from young adults). Holmes et al. J. Comput Assist Tomogr. 1998.

Individual MRI after linear registration

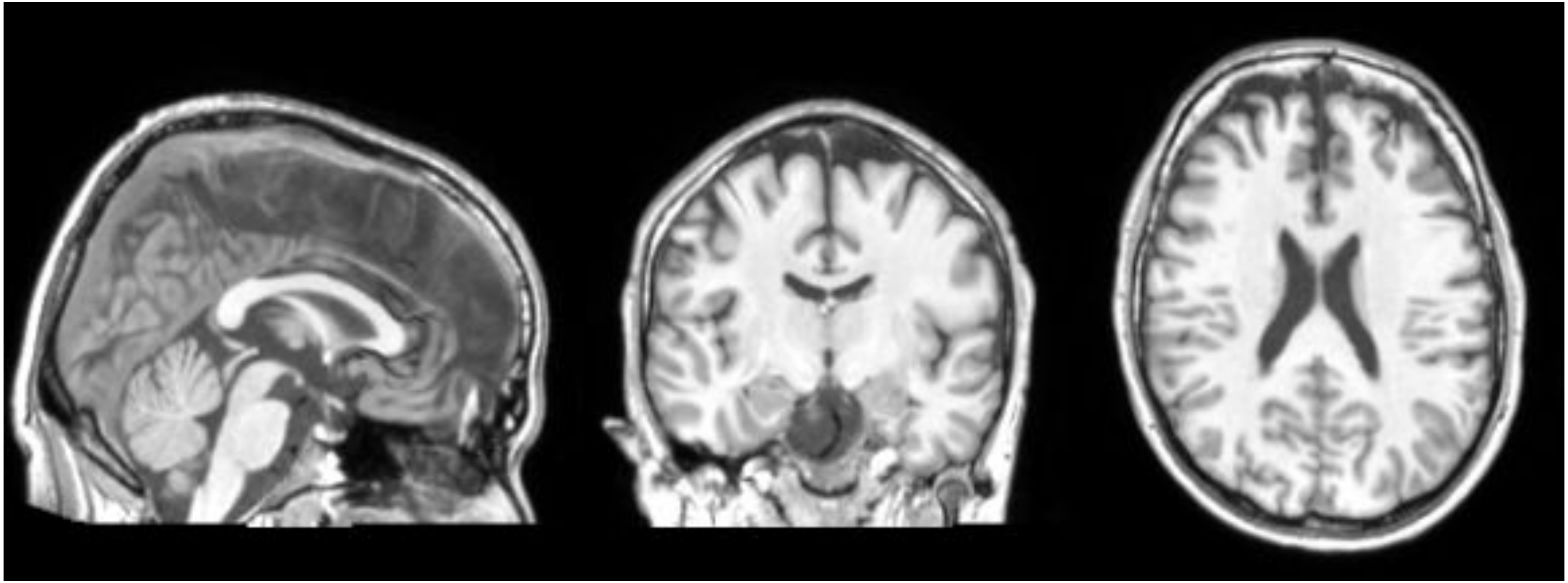


Non-linear template

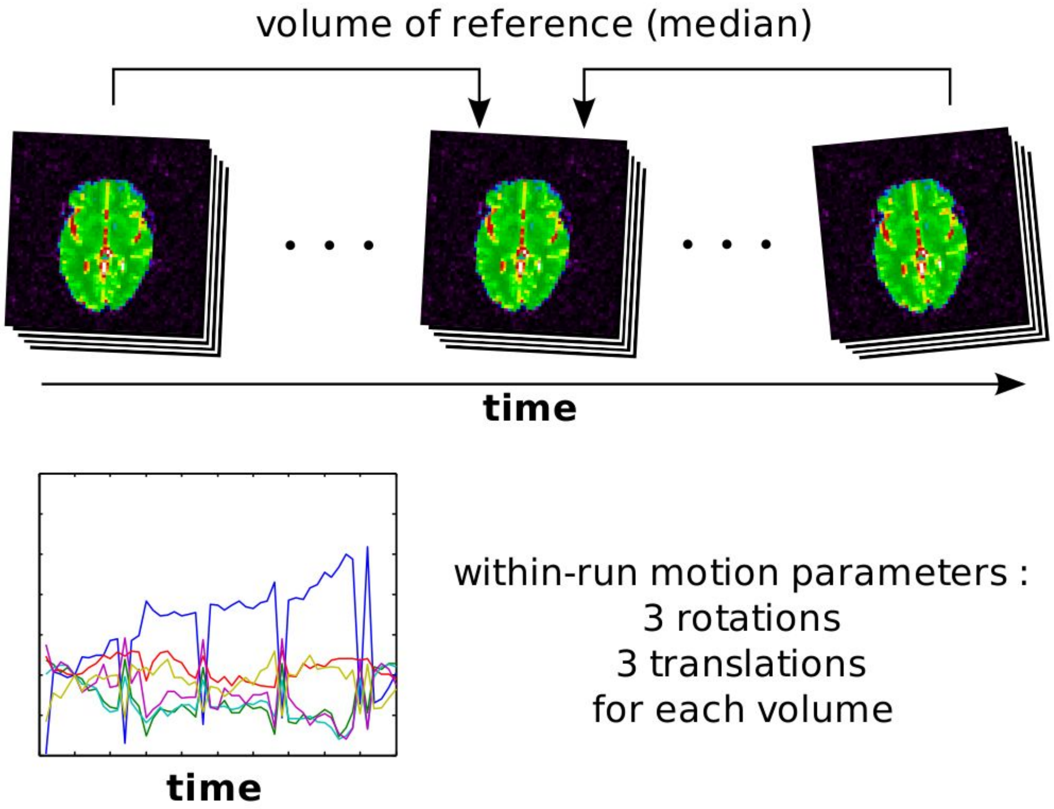


Non-linear ICBM stereotaxic space (average of N=152 T1 MRIs from young adults). Holmes et al. J. Comput Assist Tomogr. 1998.

Individual MRI after non-linear registration

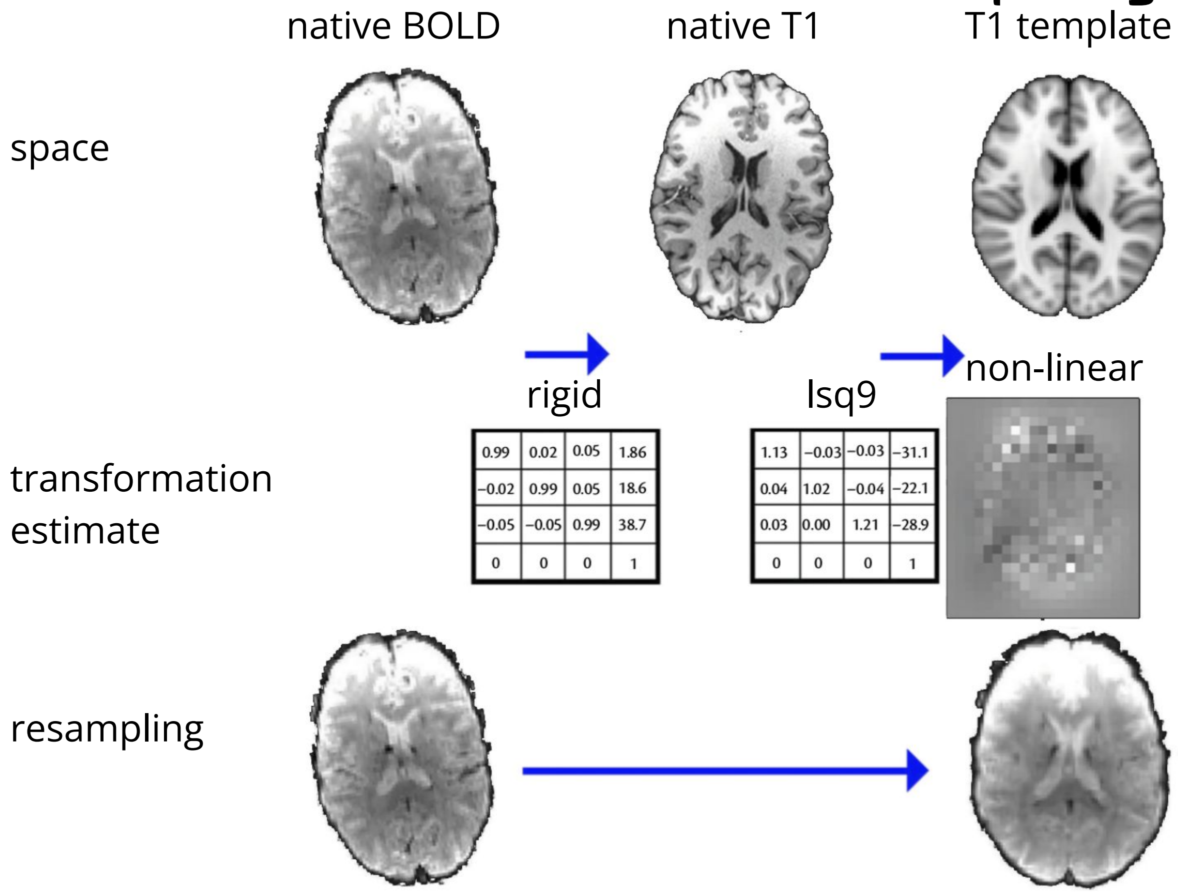


Motion estimation



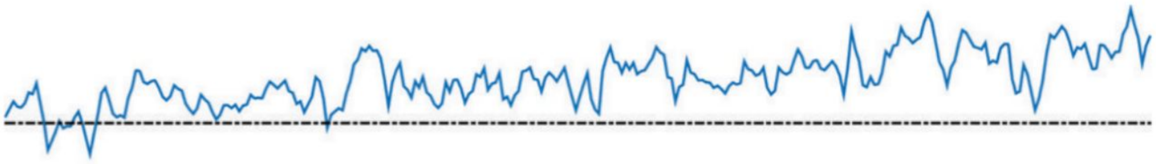
Different registration parameters are estimated at each time point.

Coregistration BOLD vs T1 and resampling



Temporal filtering

original time series

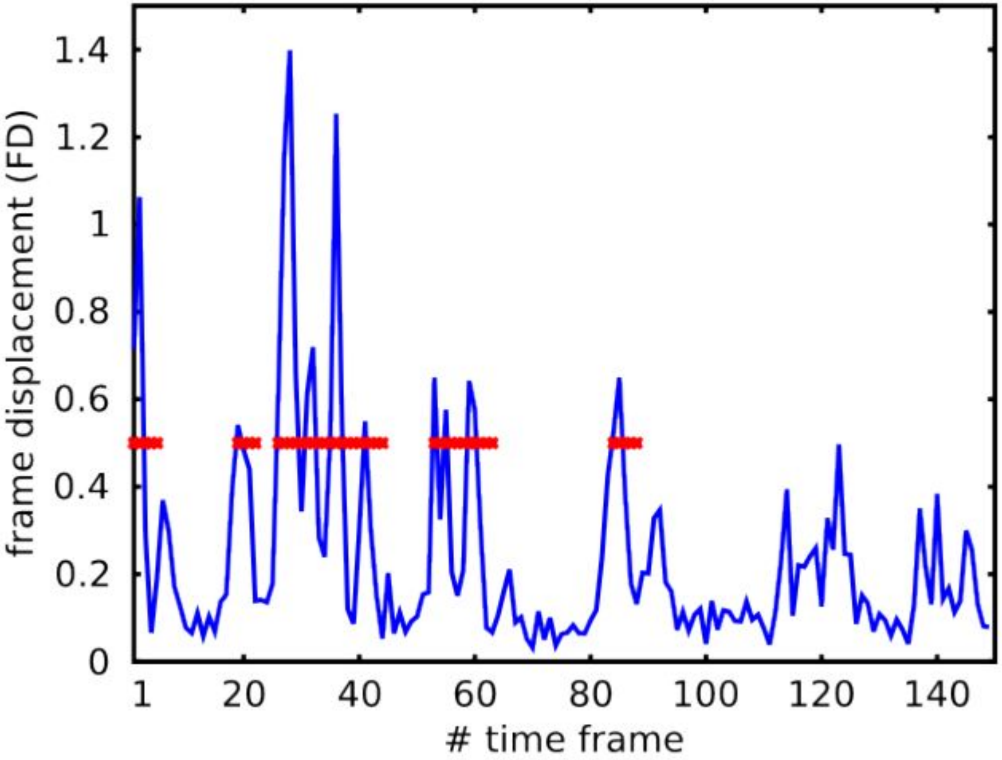


filtered time series (high-pass filter, 0.01 Hz cut-off)

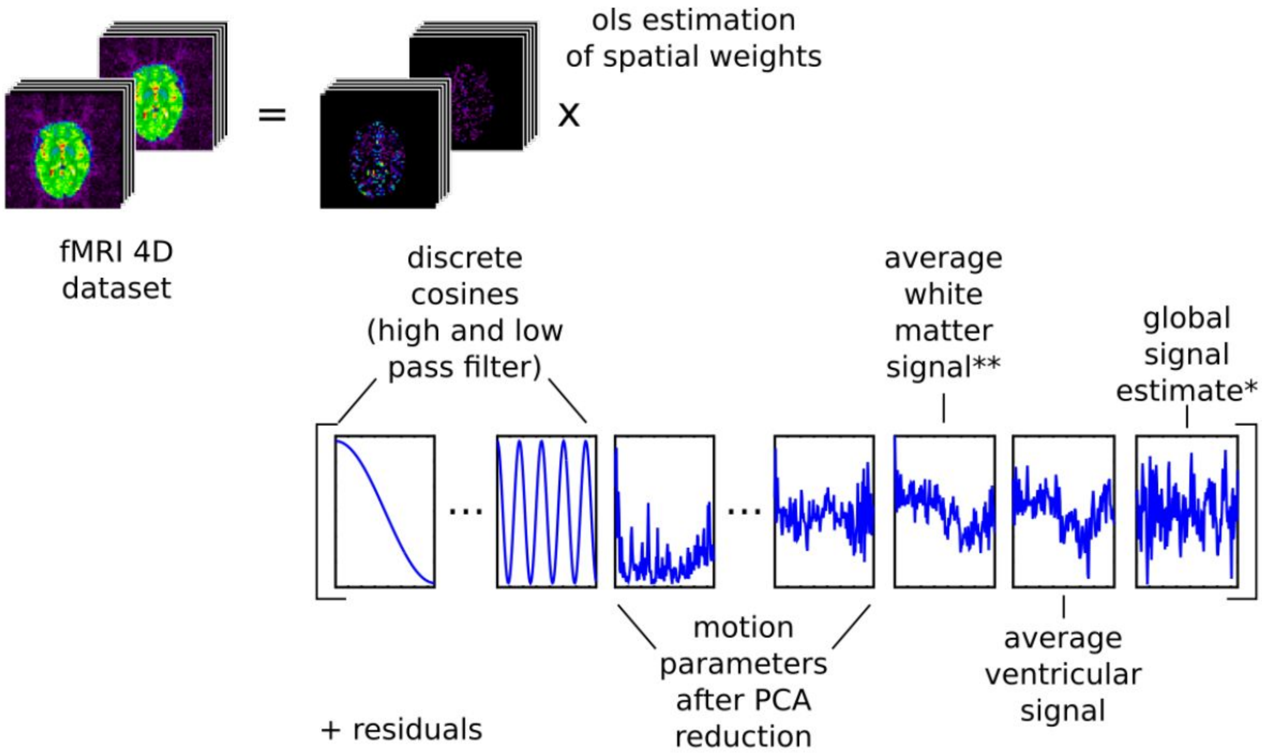
A temporal filter is applied to remove certain confounding factors from the BOLD time series. For example, here slow time drifts (<0.01Hz) are suppressed.

Scrubbing

Frame displacement is the sum of absolute displacements in translation and rotation of motion parameters. For each frame with excessive FD (here FD> 0.5), four frames are suppressed (the target one + one before + two after, marked with red stars on the figure). The original method was proposed by Power et al. Neuroimage 2012.



Confound regression

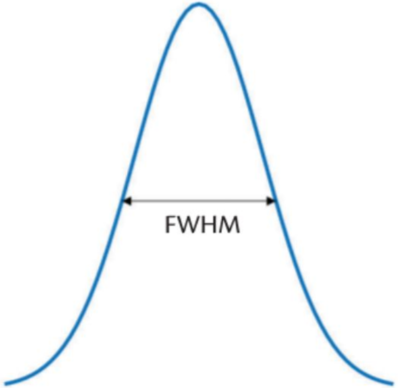


* the global signal estimate is based on a PCA decomposition (Carbonell et al., Brain connectivity 2012).

** can be replaced by a PCA reduction, aka anat COMPCOR (Chai et al., NeuroImage 2012).

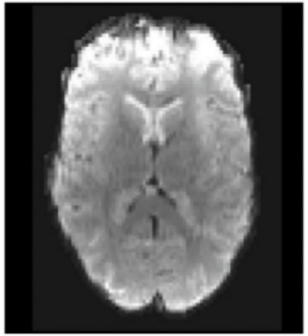
Spatial smoothing

A spatial smoothing operation is applied to (1) improve signal-to-noise ratio; (2) reduce the impact of inter-subject misrealignment.

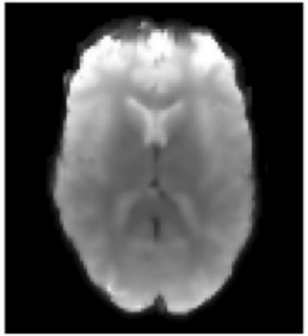


0.1	0.3	0.4	0.3	0.1
0.3	0.6	0.8	0.6	0.3
0.4	0.8	1.0	0.8	0.4
0.3	0.6	0.6	0.6	0.3
0.1	0.3	0.4	0.3	0.1

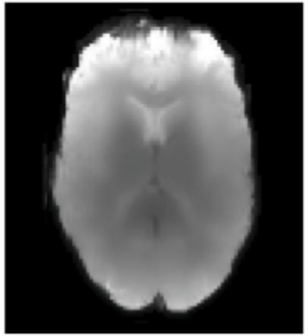
FWHM



No smoothing



Smoothing FWHM=5 mm

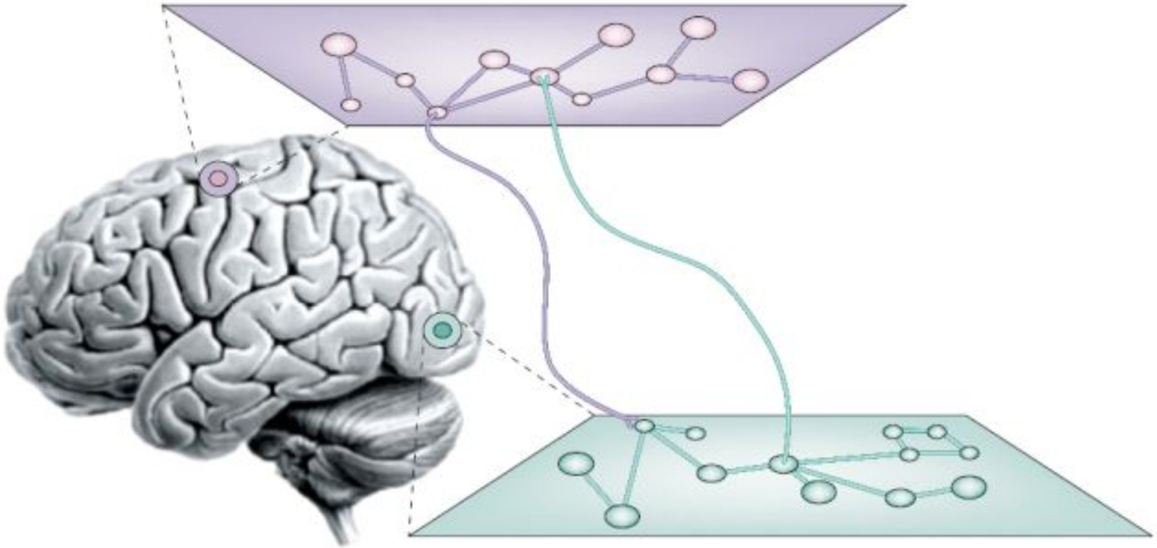


Smoothing FWHM=10 mm

Functional connectivity

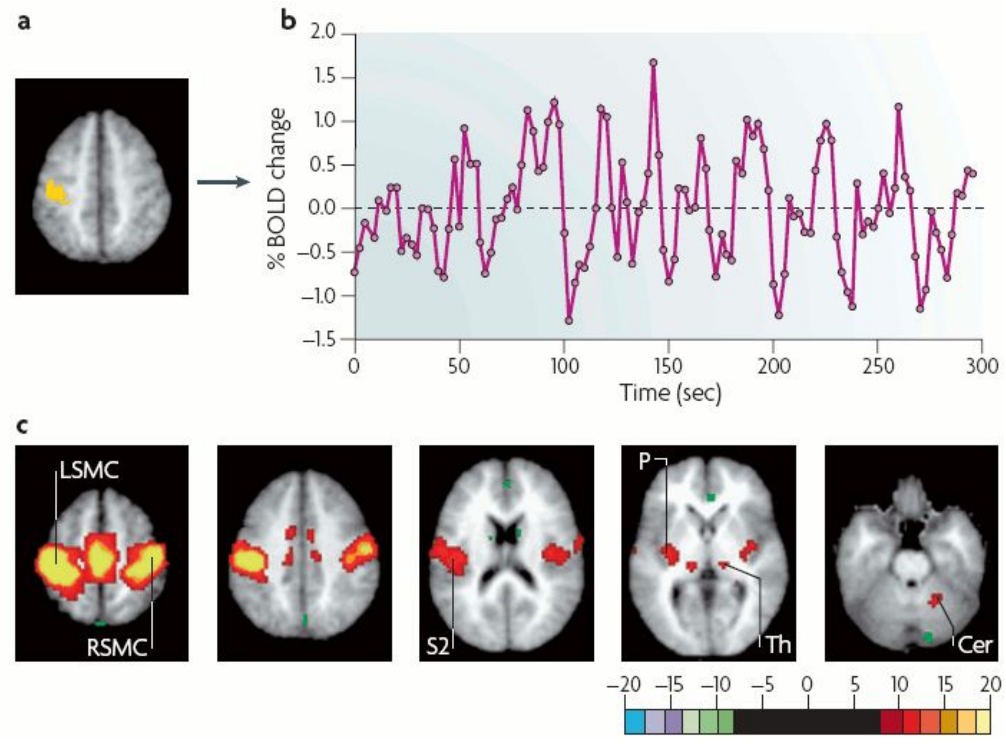
- Understand the definition of functional connectivity
- Difference between intrinsic and extrinsic activity.
- A basic regression analysis in fMRI connectivity.

The brain as a network



Local and distributed connectivity lead to the emergence of both local and distributed neuronal assemblies. From Varela et al., 2001.

Resting-state functional connectivity map



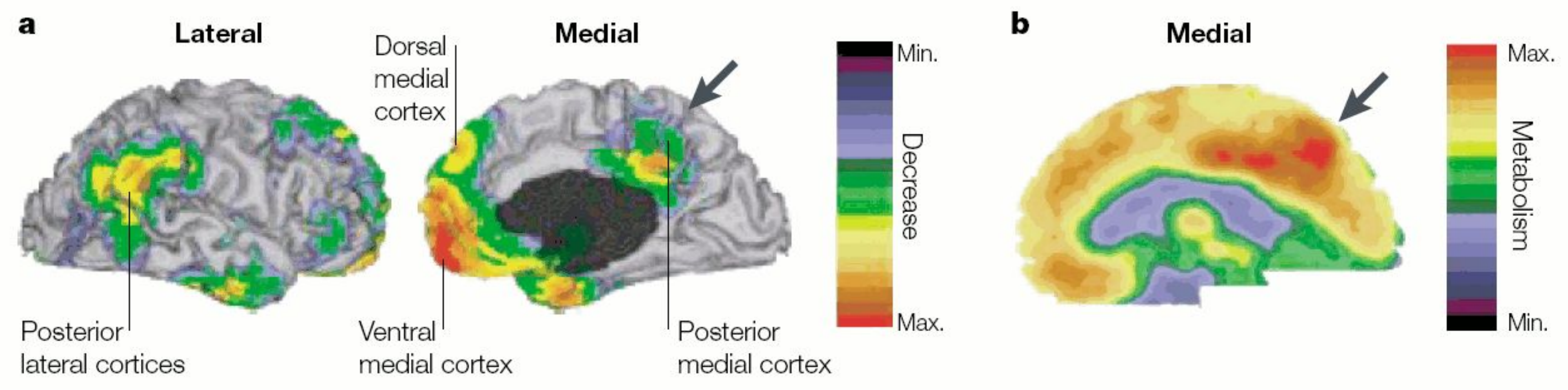
(a) Activation map, motor task (individual);

(b) Spontaneous activity in the activated region;

(c) The activated region is used as a seed for a functional connectivity map, i.e. the Pearson's correlation between the time series of the seed and time series of every voxel.

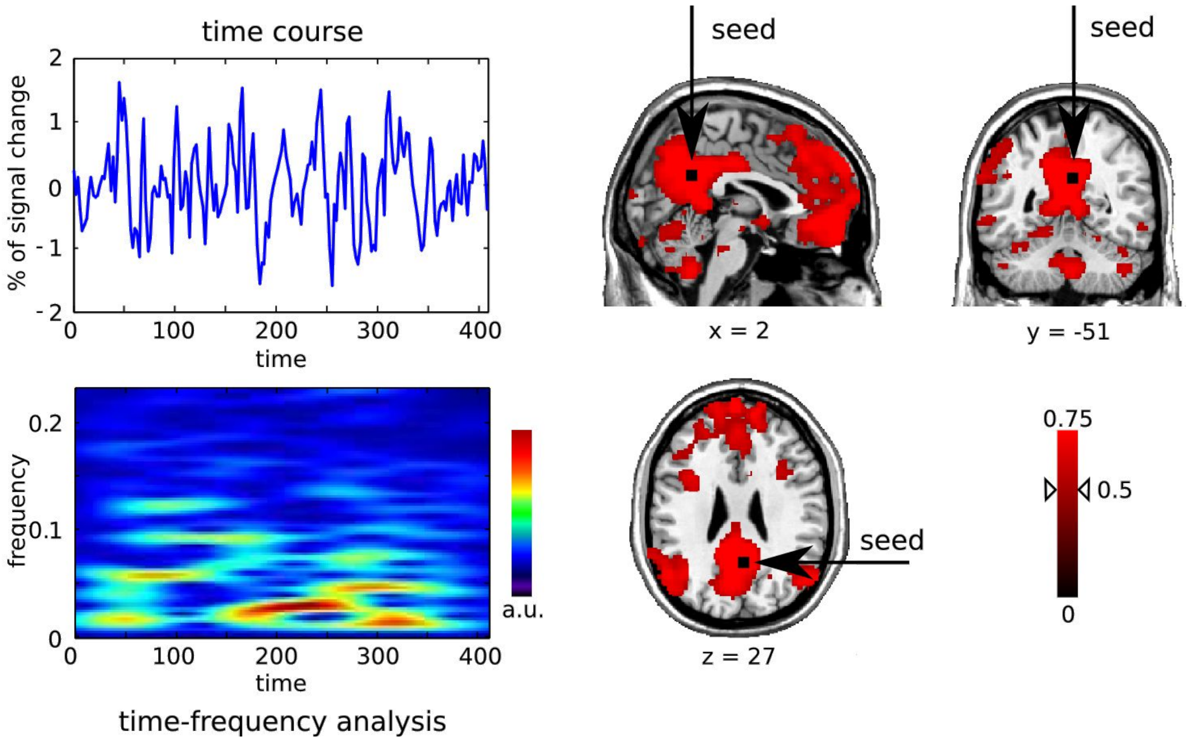
Original experiment by Biswal et al., MRM 1995. Figure from Fox et al, 2007, Nature Reviews Neuroscience, 8: 700-711.

Deactivations and the default-mode network



Left: a meta-analysis of 9 FDG PET (Shulman et al. J. Cogn. Neurosc. 1997) show that there is a consistent network of regions that are less active during the execution of a task than at rest. Right: the posterior cingulate cortex is the area of the brain with highest glucose consumption at rest (mean of 22 subjects).

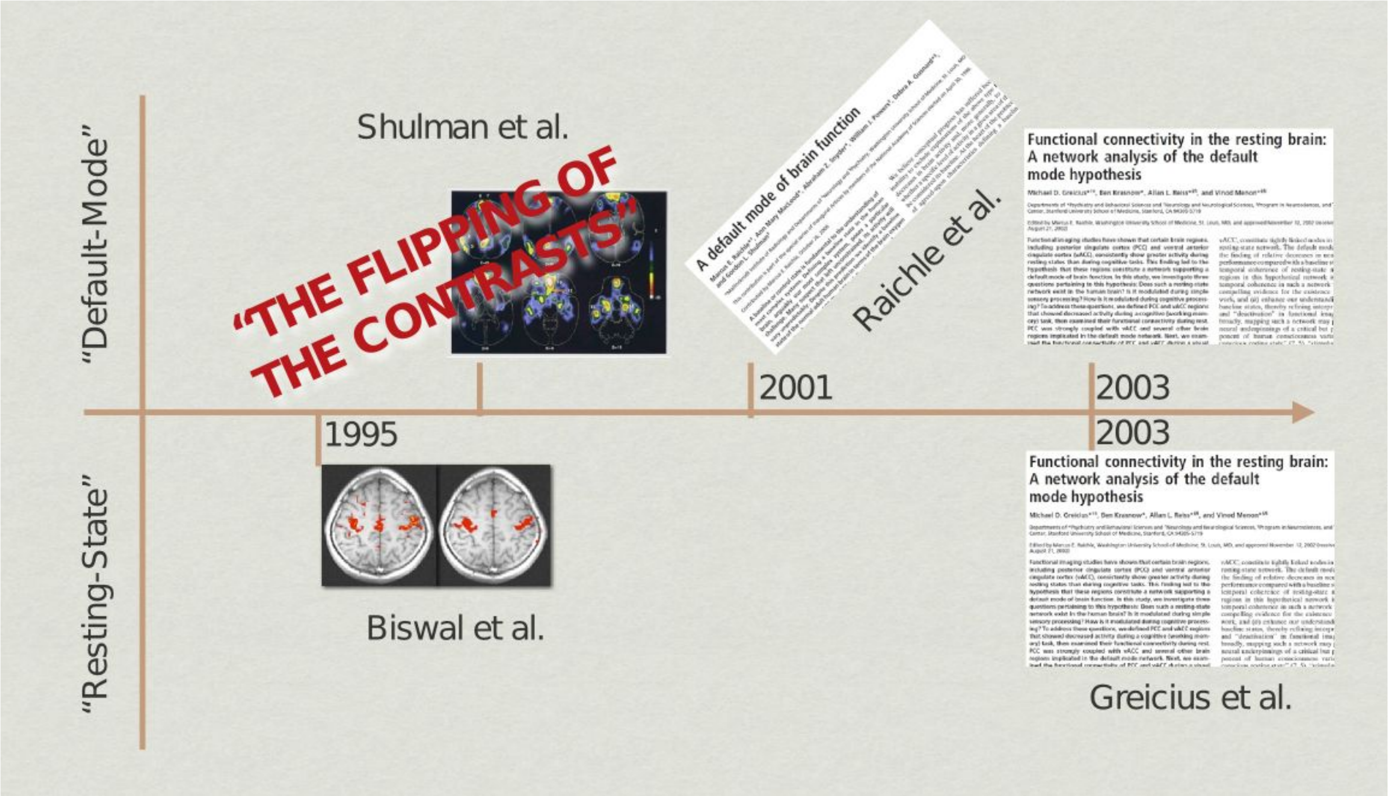
Resting-state connectivity and the default-mode



Greicius et al. (PNAS 2003) used the same methodology as Biswal et al (1995), with resting-state fMRI and a seed region located in the posterior cingulate cortex. This analysis revealed a network of spatially distributed regions, largely overlapping the regions identified based on deactivations in TEP. Temporally, the fluctuations were dominated by slow waves, as previously observed by Biswal and colleagues.

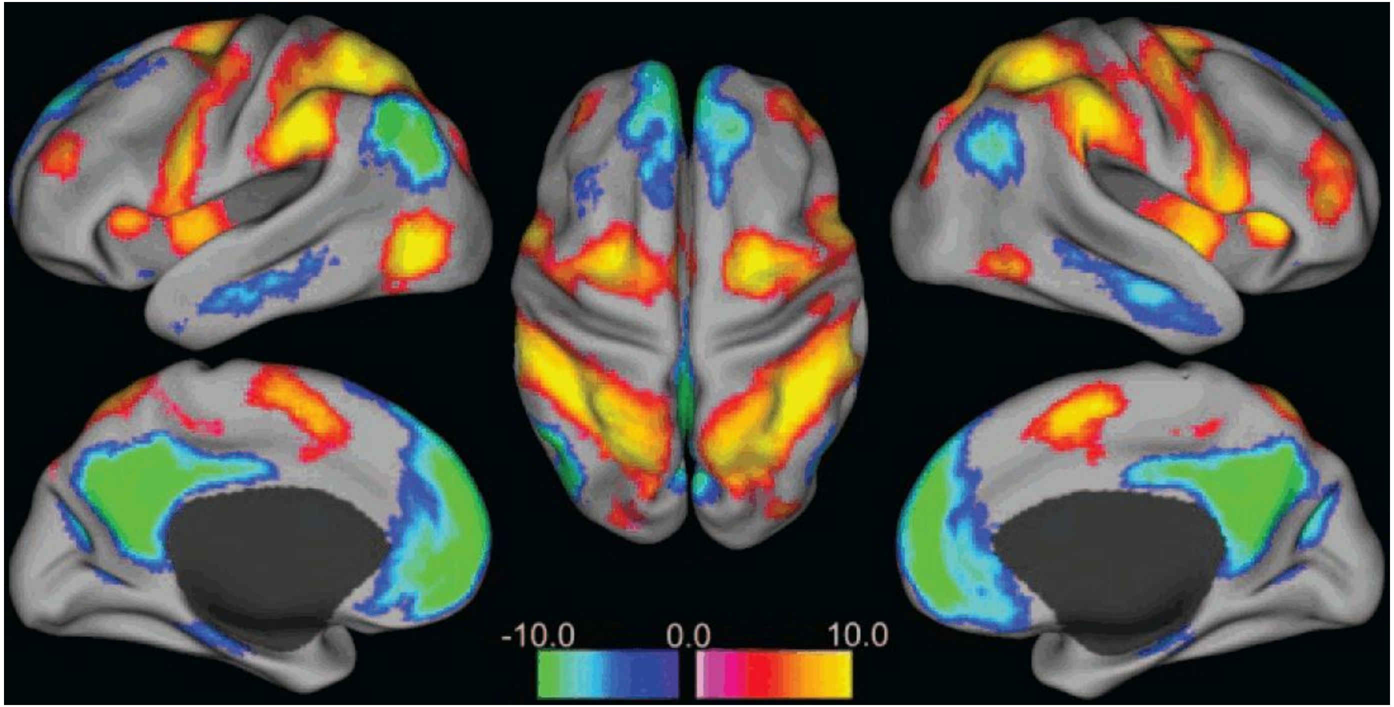
Figure from Bellec et al. (2011).

Functional connectivity vs default-mode



Courtesy: Daniel Margulies.

Negative correlations



Fox and coll. (2005) show a negative correlation between the regions of the default-mode network and a task-positive fronto-parietal network.

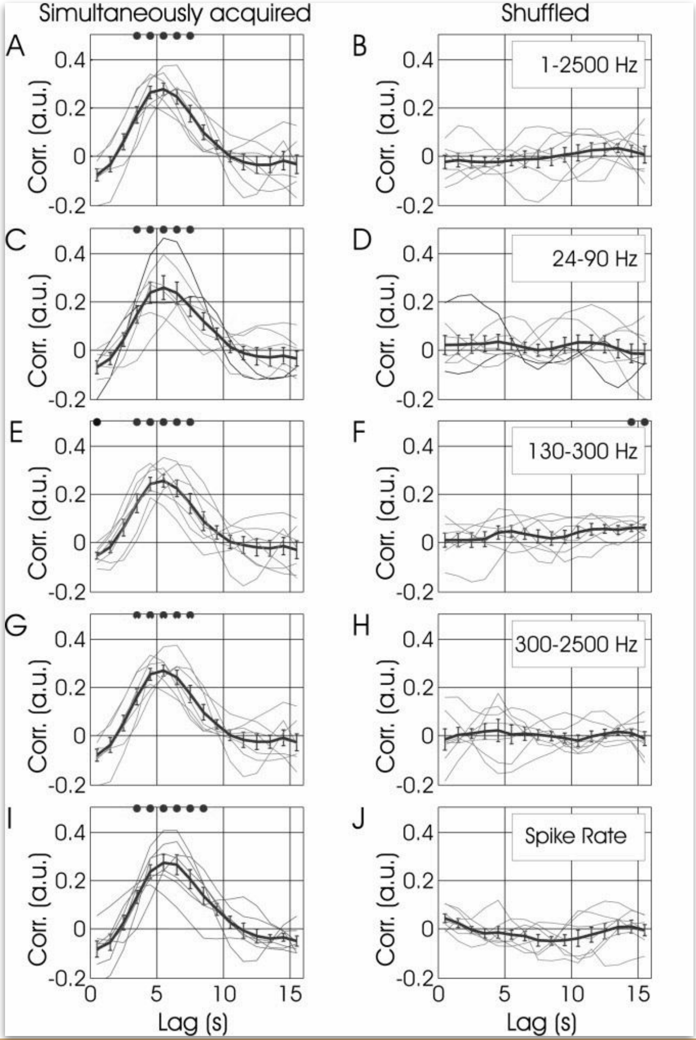
Physiological basis of spontaneous brain activity

Correlation between electrophysiological neuronal activity and the BOLD signal, at rest, in the visual cortex and at different time lags. The thick curves represent data averaged on 7 experiments and 5 monkeys.

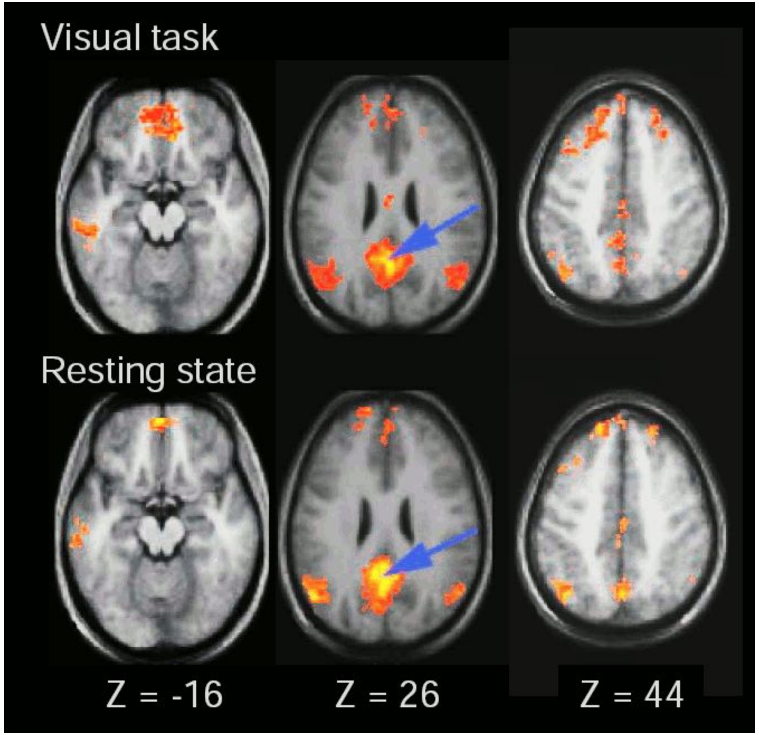
Electrophysiological signals have been decomposed over different frequency bands.

Left column are the original experimental results, and the right column is a control experiment where the two time series have been shuffled over time, as to be independent of each other.

From Shmuel et al. HBM 2008



Intrinsic vs extrinsic brain activity



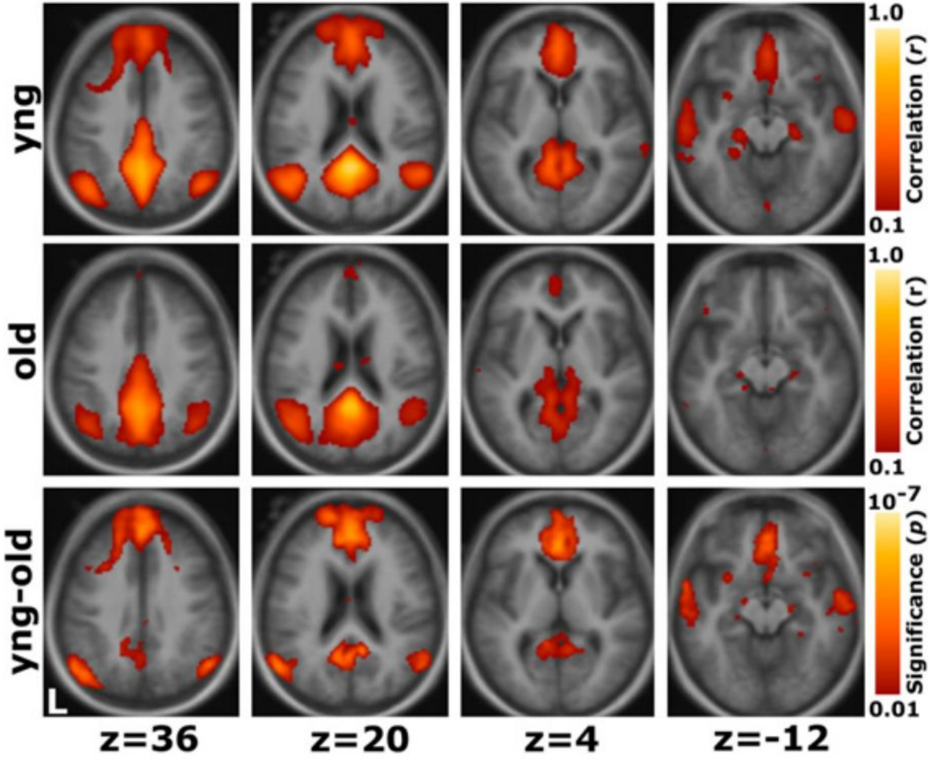
Greicius et al. (2003) already noted that connectivity in the default-mode network was present while performing a task, just like it was at rest. Extrinsic and intrinsic brain activity always co-exist and interact.

Example of application: age effects on connectivity

Average of the
“young” group

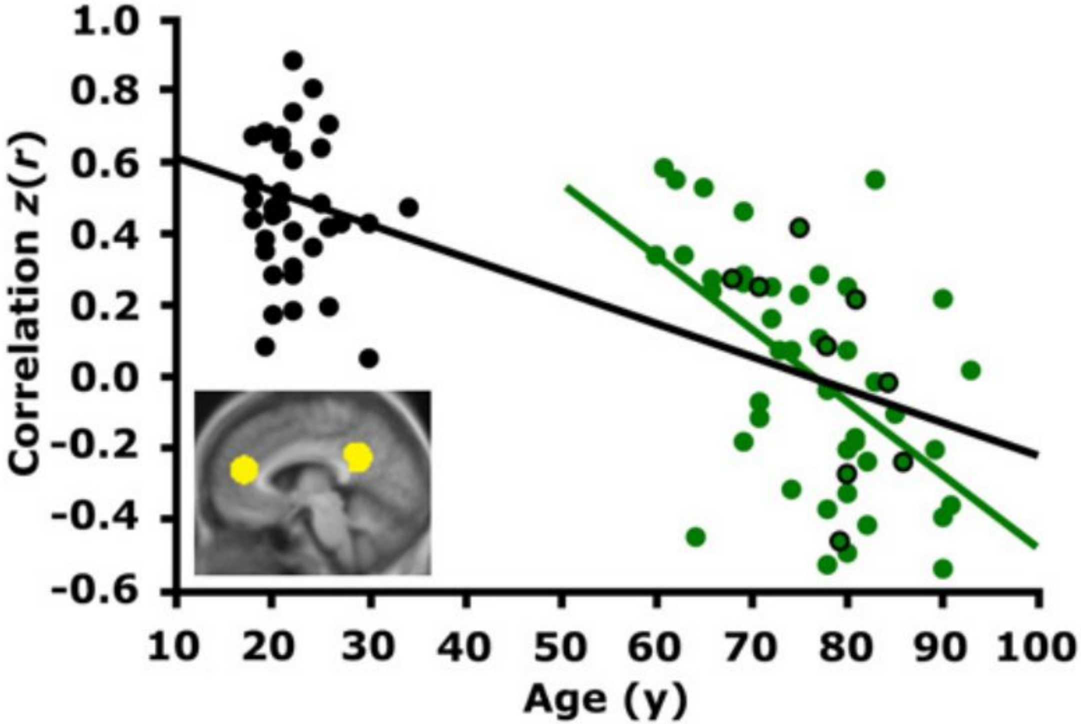
Average of the
“old” group

Difference in average
between the two
groups



Group comparison between young subjects (N=38) and old subjcets (N=55). Seed-based connectivity map using the posterior cingulate cortex as a seed. From Andrews-Hana et al., Neuron, 2007.

Example of application: age effects on connectivity

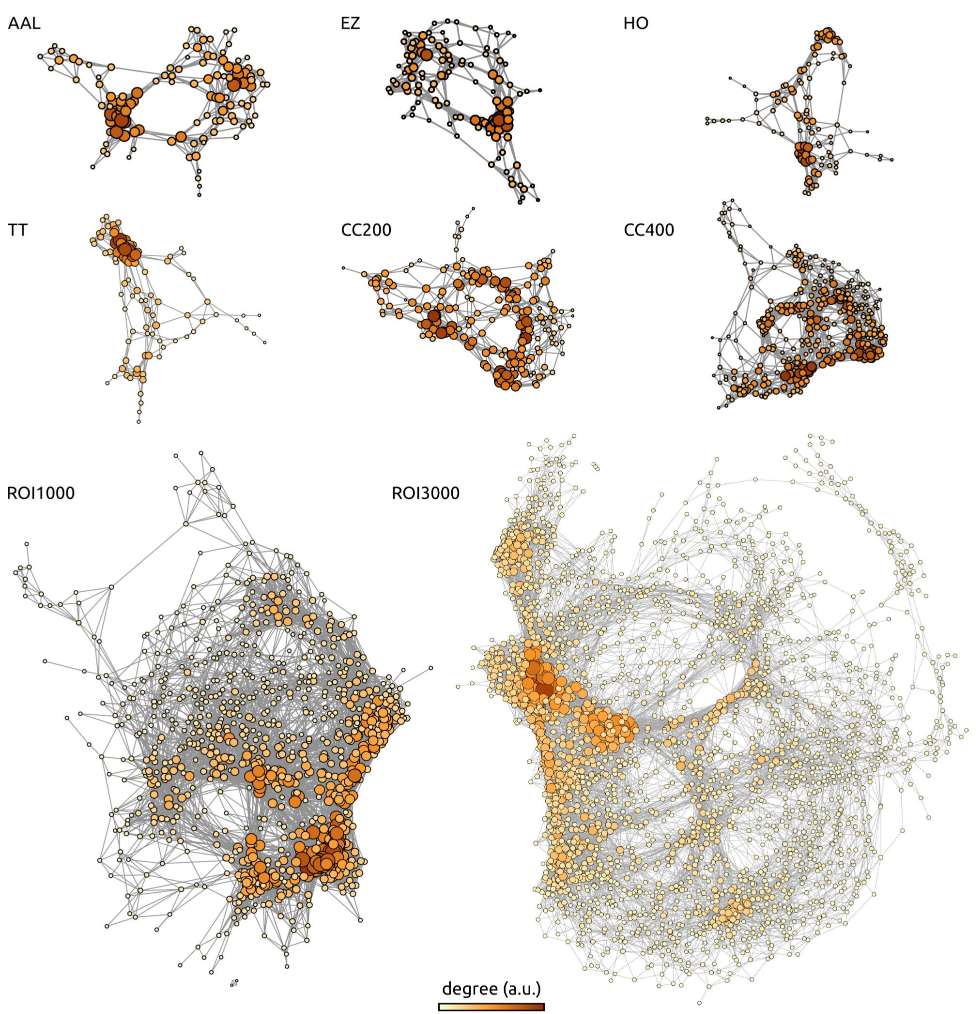


By focussing on a pair of brain regions (anterior and posterior cingulate cortices), we observe a group difference, as well as a continuous effect of age, both within the young group and the old group. From Andrews-Hana et al., Neuron, 2007.

Brain parcellation

- Understand the definition of functional connectivity
- Difference between intrinsic and extrinsic activity.
- A basic regression analysis in fMRI connectivity.

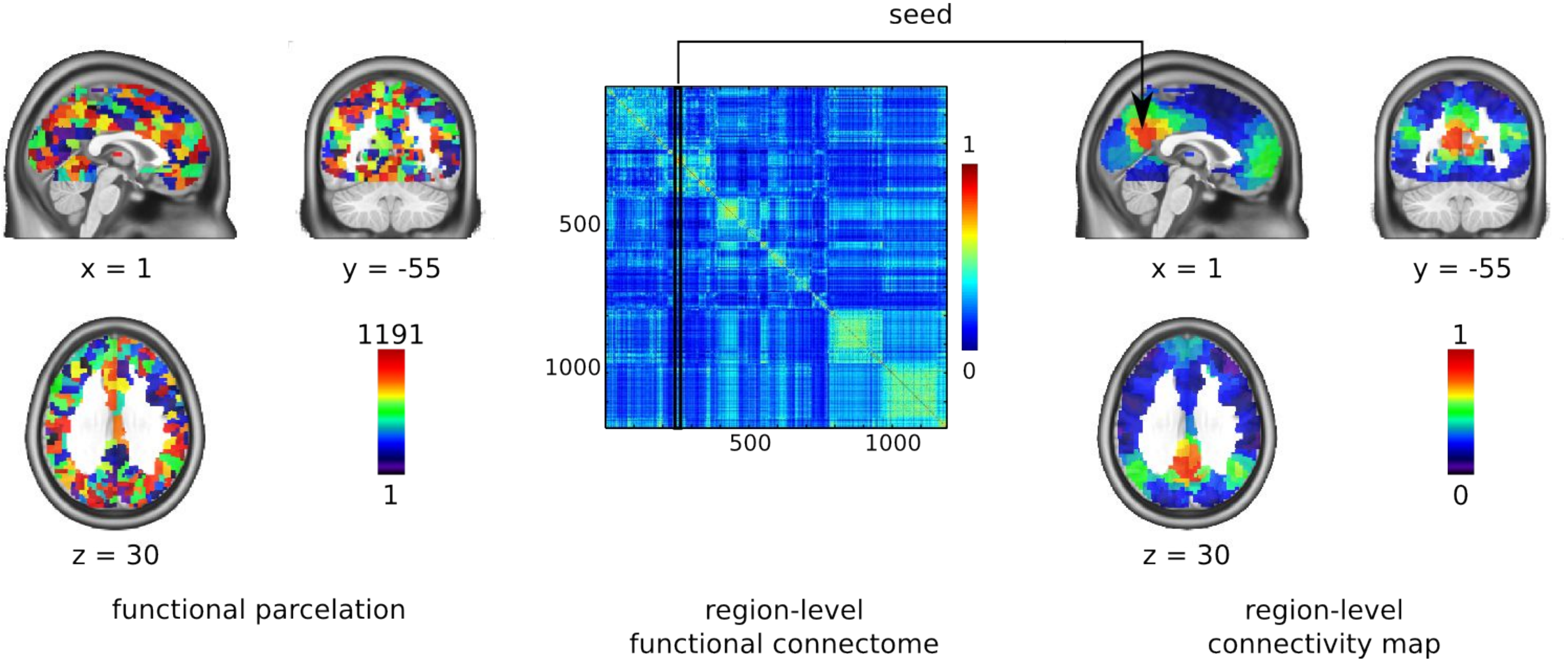
Why parcellations? Reduce dimension



Parcels can be used as nodes to approximate brain networks as graphs. Here, the average connectome of the ADHD-200 sample is represented with several different parcellations, of varying resolutions.

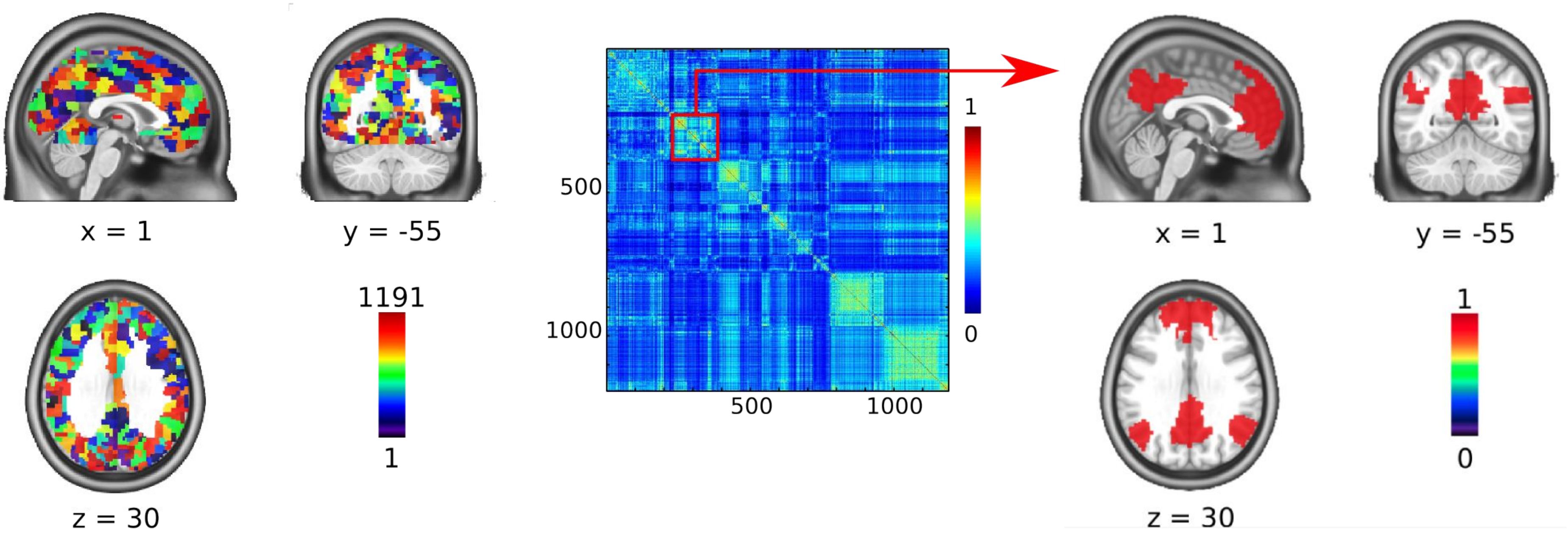
From Bellec et al., Neuroimage 2017.

Functional connectome



A functional connectome essentially is a collection of seed-based connectivity maps, approximated on parcels, and using all possible seeds.

Functional networks



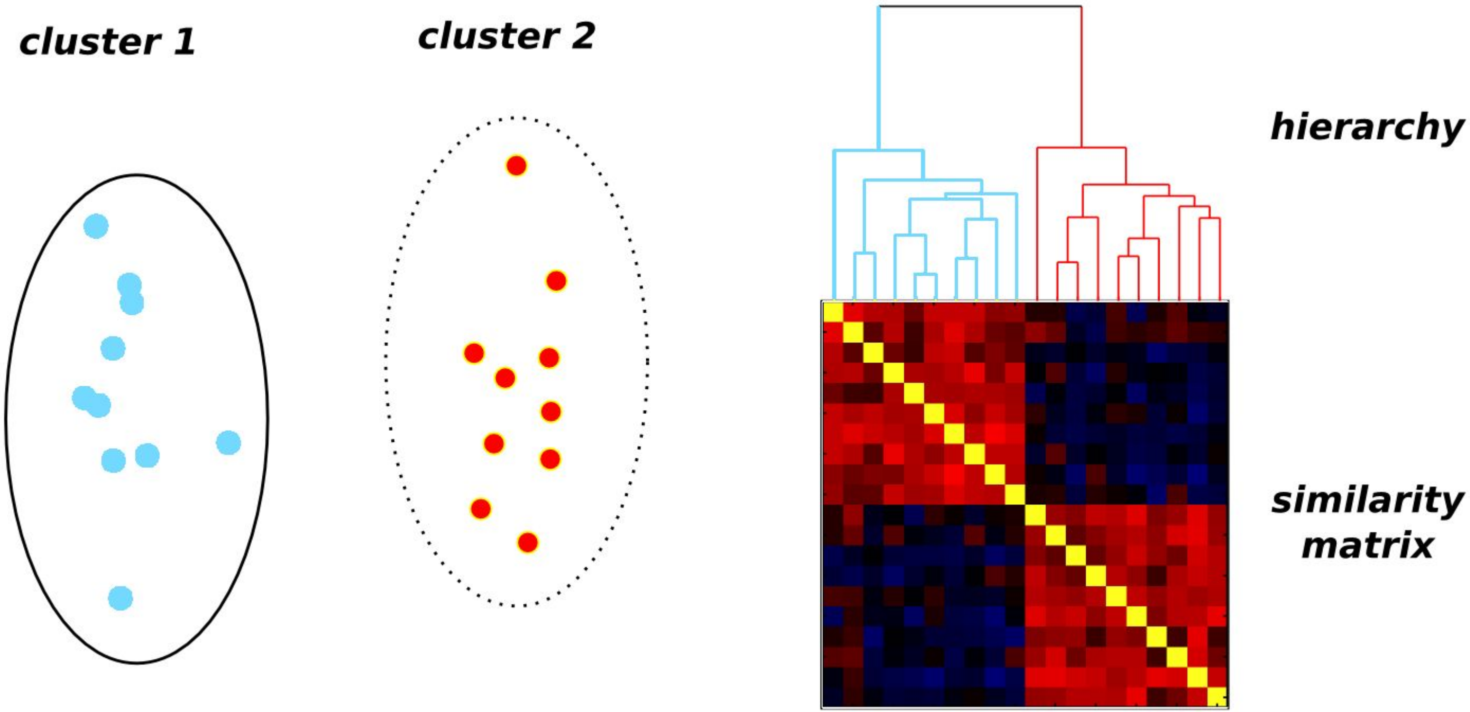
functional parcelation

region-level
functional connectome

resting-state
network

If we order the parcels correctly, we can see functional networks as diagonal squares with high connectivity on the diagonal.

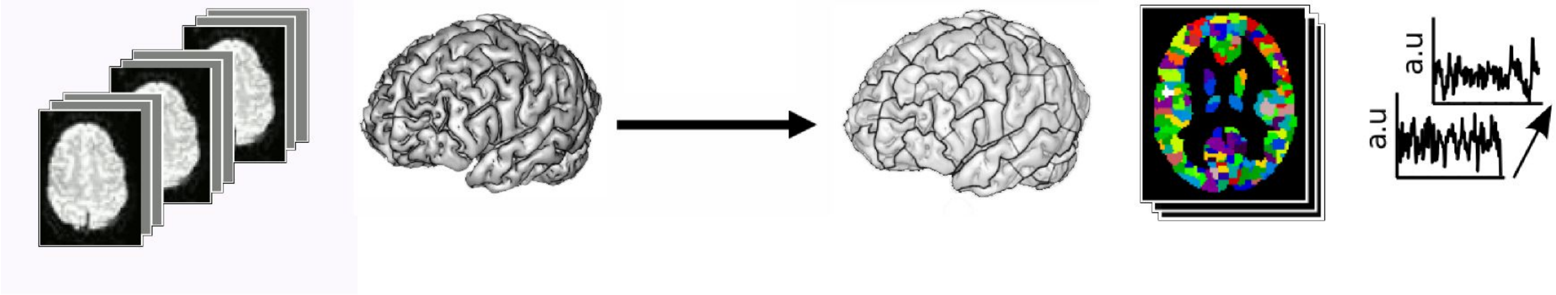
General purpose cluster analysis



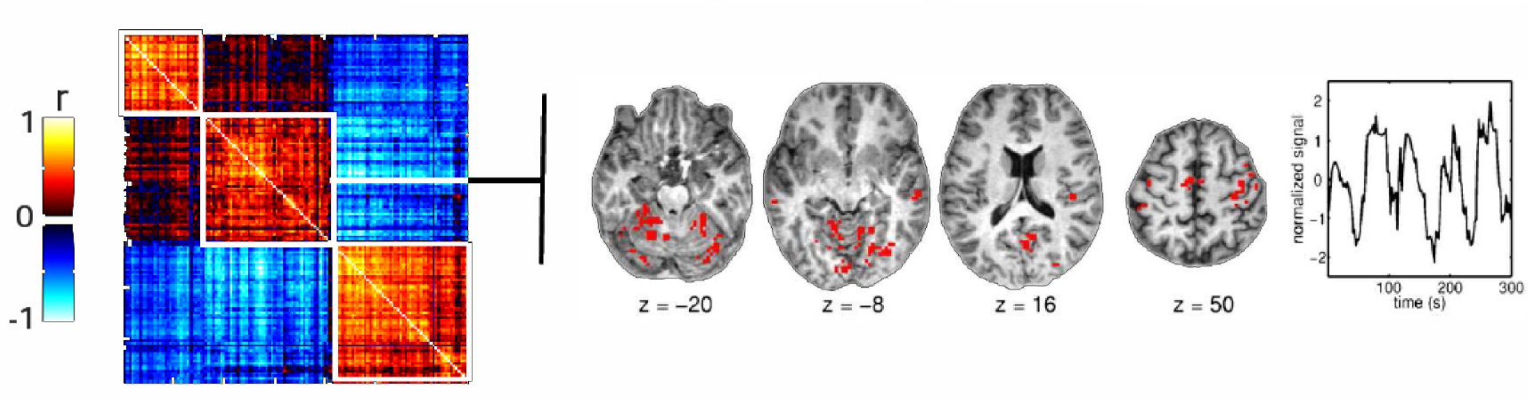
On the left, coordinates of individuals define their similarities; on the right, agglomerative hierarchical clustering proceeds by iterative mergings. Many clustering algorithms exist, e.g. k-means, fuzzy k-means, spectral clustering, SOM, neural gas. See Jain, Pattern Recognition Letters, 2009, for a review of classic approaches.

Brain cluster analysis

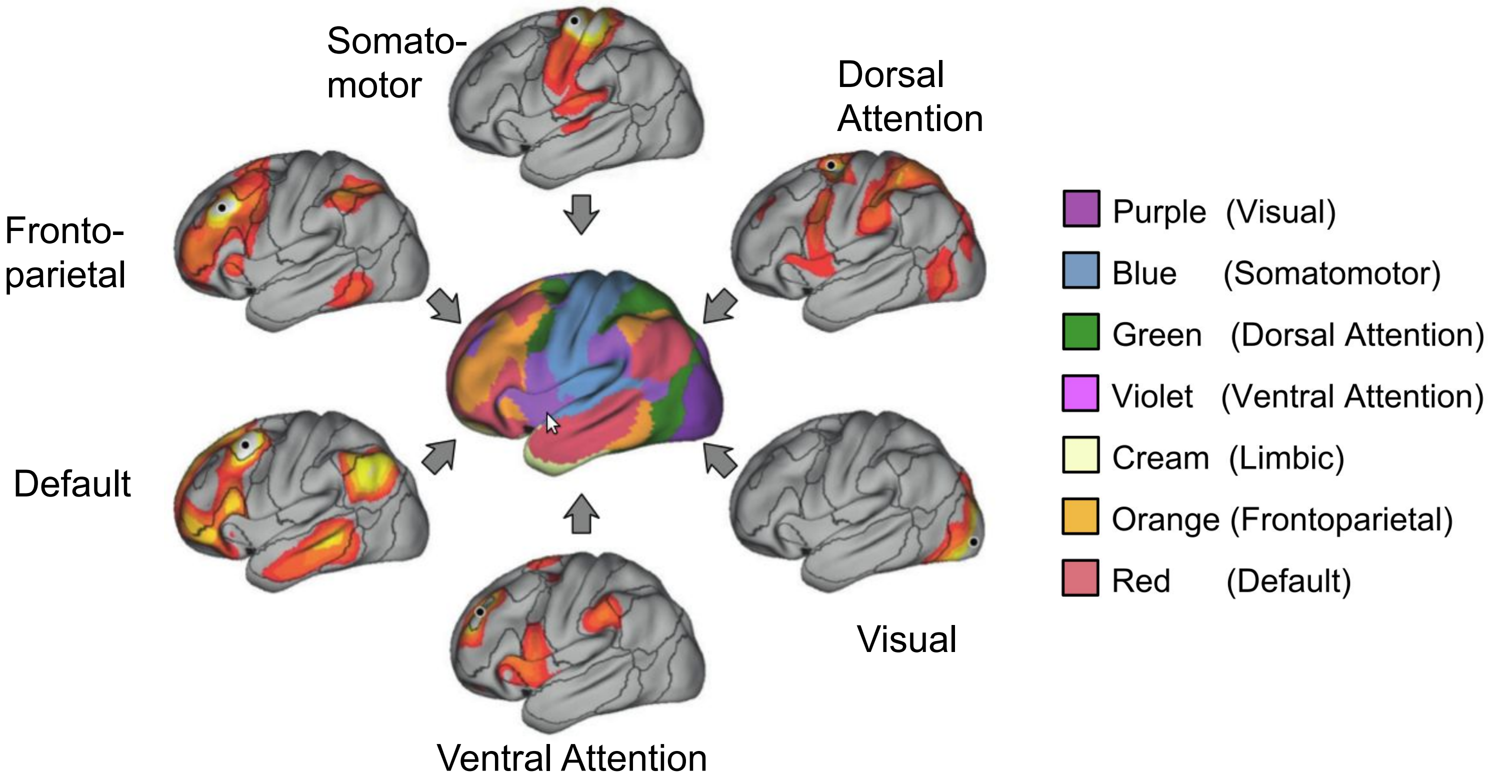
region growing at the voxel level



clustering at the region level

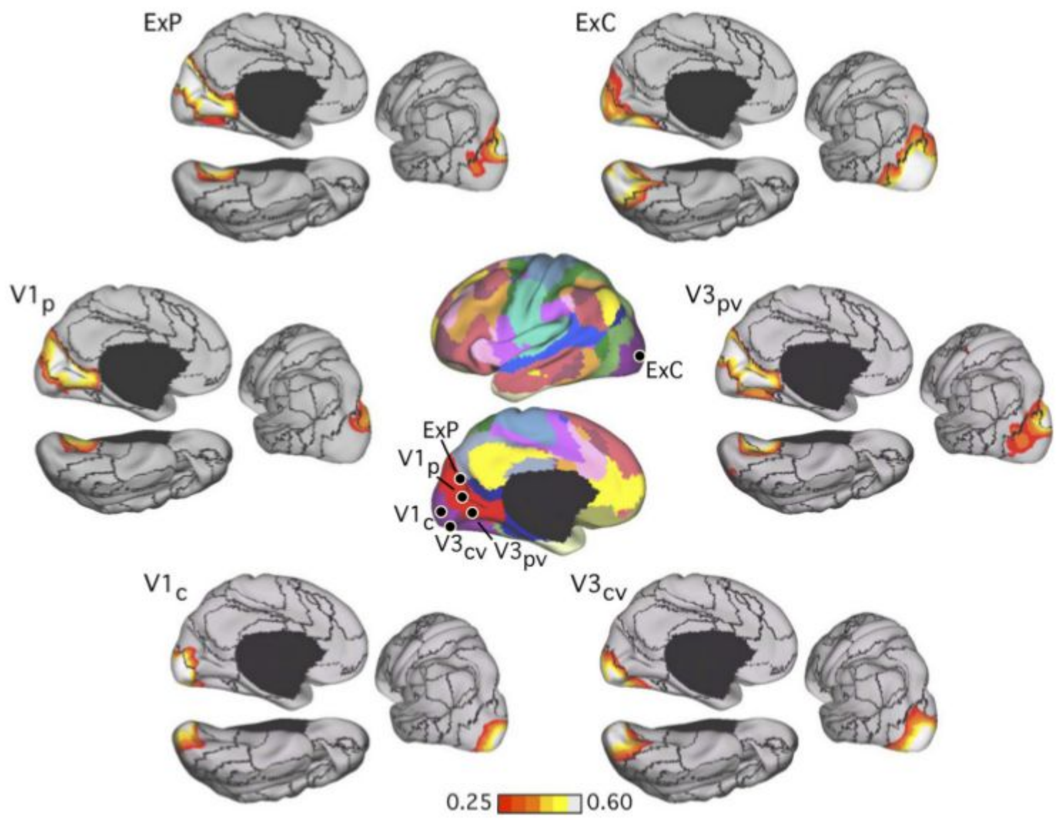


Yeo-Krienen-7-clusters



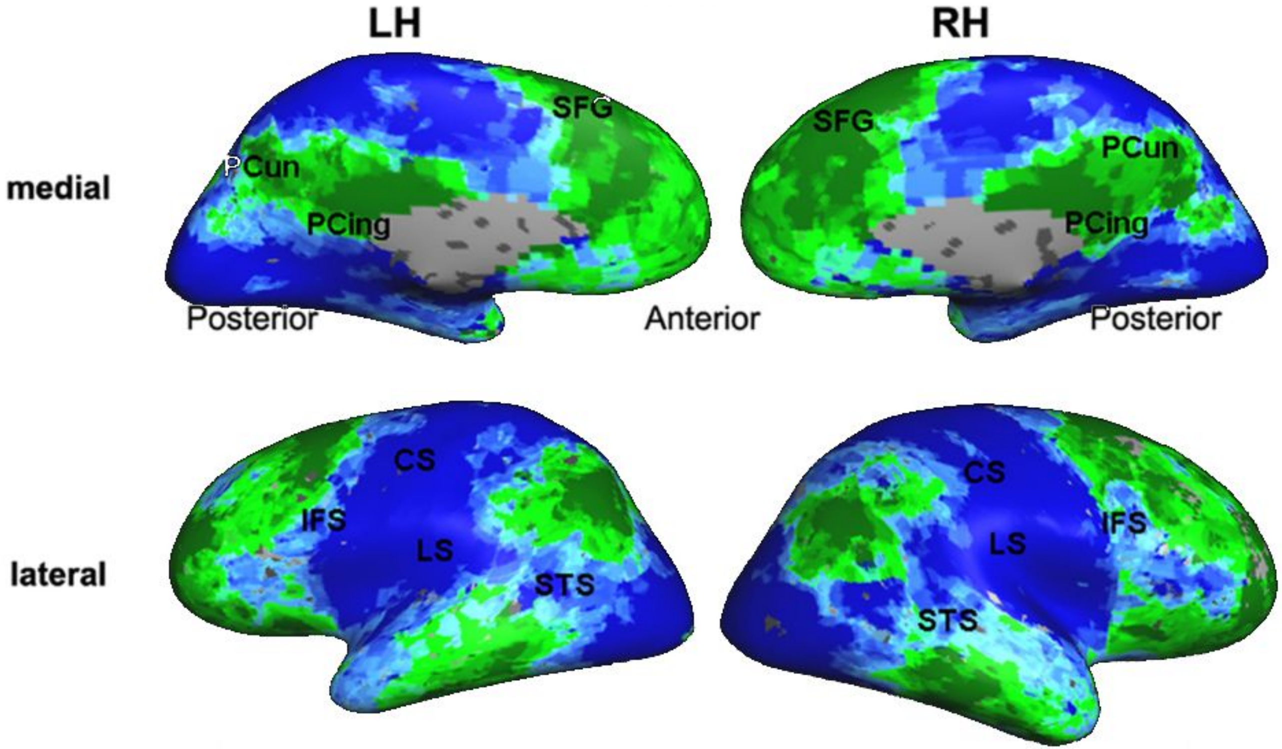
Decomposition of the brain into 7 group networks by Yeo, Krienen et al (2011).

Yeo-Krienen-17-clusters (visual)



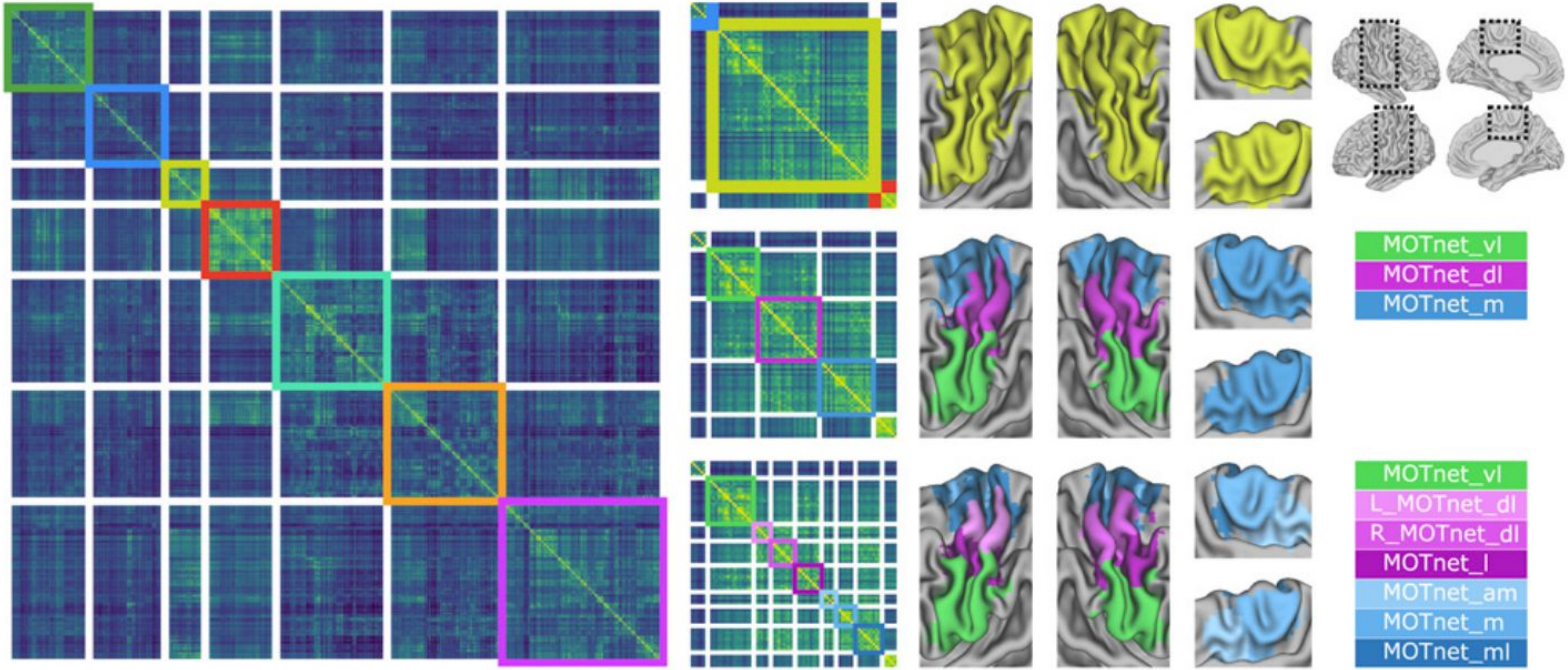
Networks can be further divided into subnetworks, here in the visual cortex. From Yeo, Krienen et al. (2011).

Golland-2-clusters



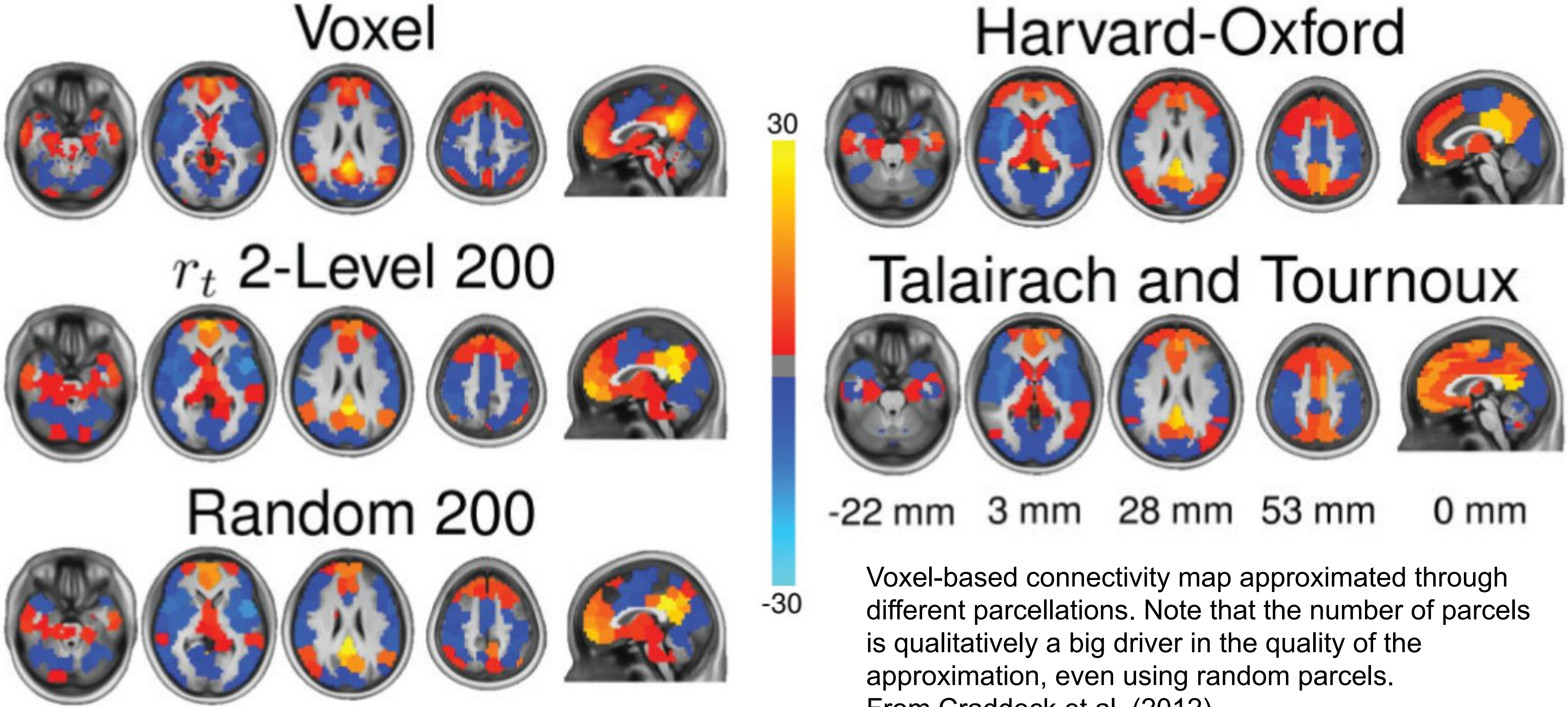
Note that Networks can also be merged into reliable “exogeneous” vs “endogeneous” systems. From Golland et al. (2008).

What is the number of clusters?



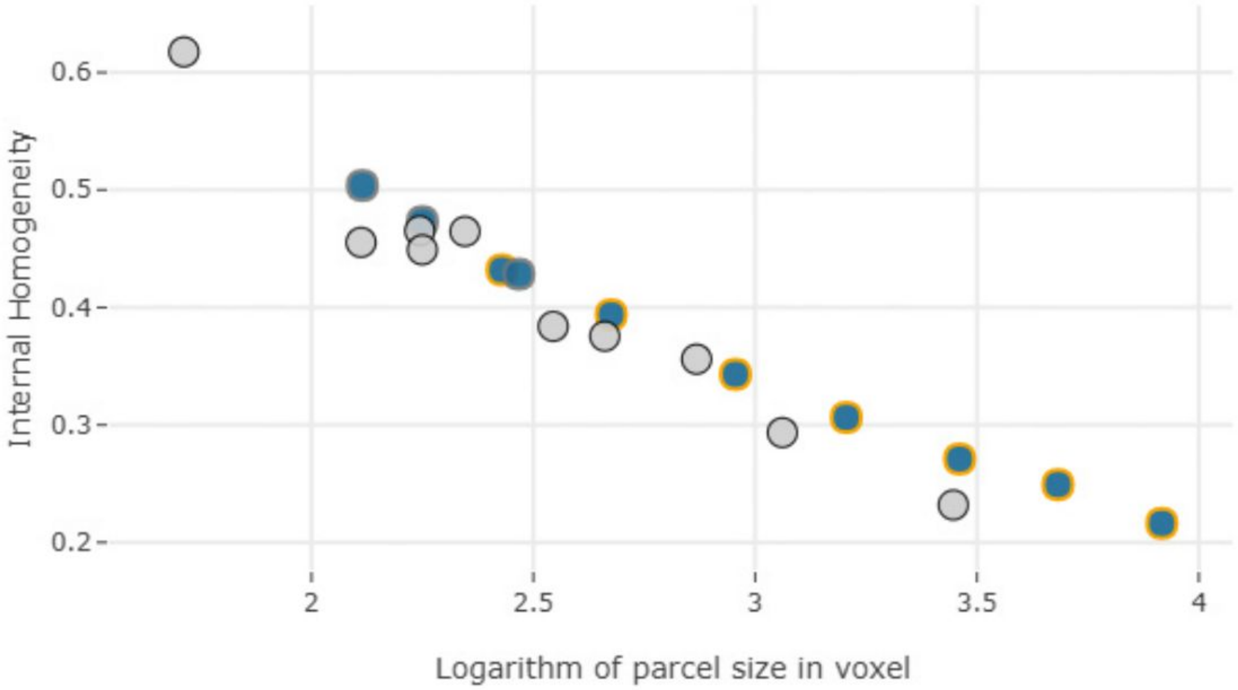
Functional brain parcels break down into a pseudo-hierarchy, here illustrated in the sensorimotor network. There thus exists multiple numbers of acceptable decomposition in brain parcels. From Urchs et al, MNI open research (2017).

How homogeneous are parcels?



Voxel-based connectivity map approximated through different parcellations. Note that the number of parcels is qualitatively a big driver in the quality of the approximation, even using random parcels.
From Craddock et al. (2012).

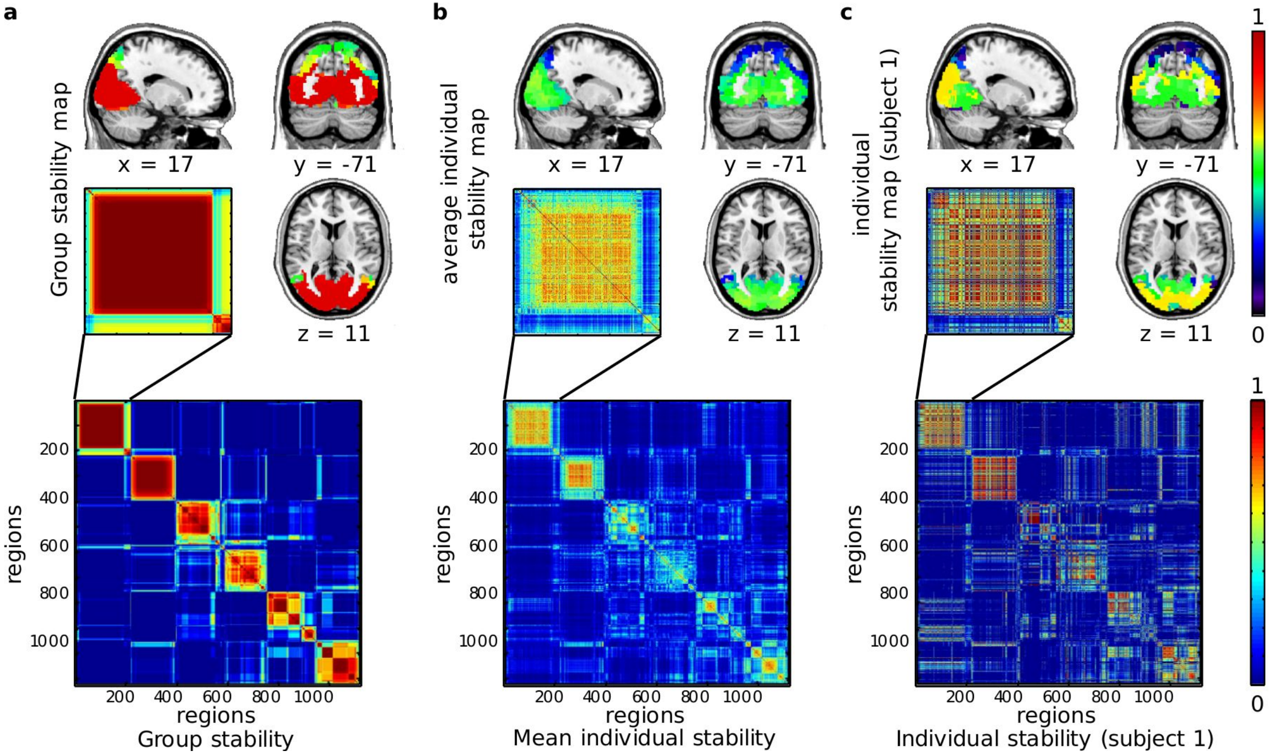
How homogeneous are parcels?



Homogeneity of group brain parcels as a function of the average parcel size for a series of multiresolution functional parcels (MIST) as well other published parcellations (Yeo-Krienen-7, Yeo-Krienen-17, OasisTRT, AAL, Aicha, Brainnetome, Hammersmith, Shen, Gordon, Glasser). Note that homogeneity can closely be predicted from size alone. From Urchs et al. MNI open research (2017).

How stable are parcels?

Stability matrices represent the probability of any given pair of super-voxel to be in the same cluster, either at the group (a), average individual (b), and individual (c), through replications of the clustering process. Group parcels are already quite stable with a moderate number of individuals (N=43), while individual parcels are quite contrasted, with a few stable networks and several areas of low stability (15 mns of resting-state fMRI). These areas are not consistent across subject, leading to moderate average individual stability. From Bellec et al. (2010).



What is a good parcellation?

A number of metrics are emerging as standard benchmarks for parcellation:

- Homogeneity
- Stability
- Agreement with task activation (shown here on the left).
- Overlap with cytoarchitecture and myelination gradient.

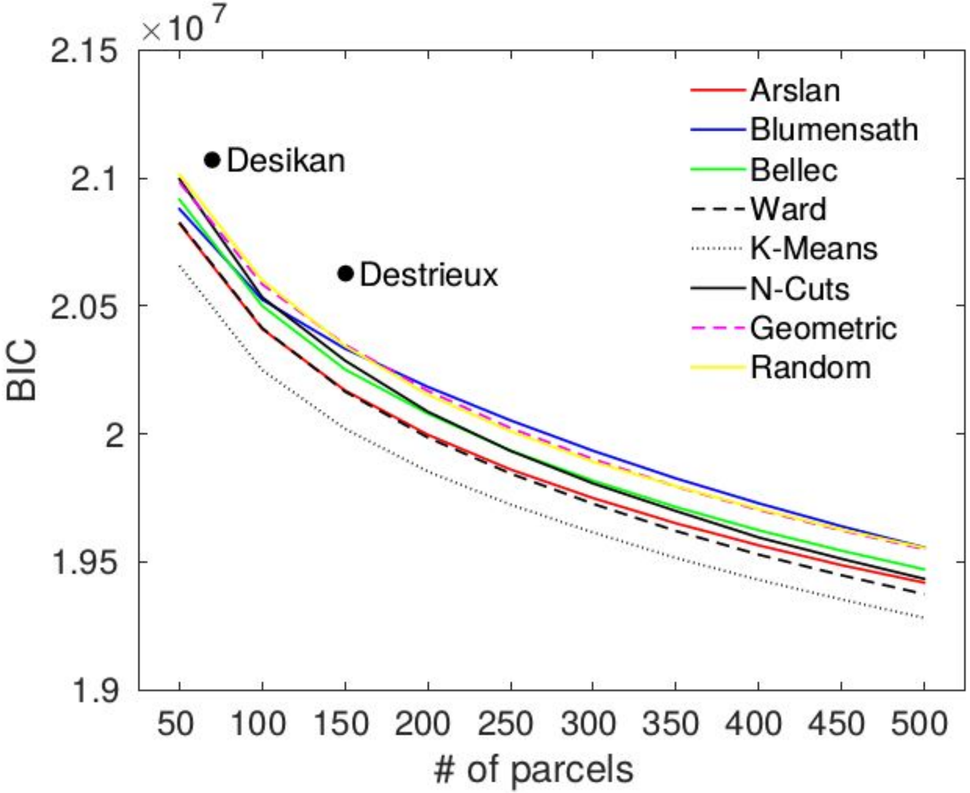
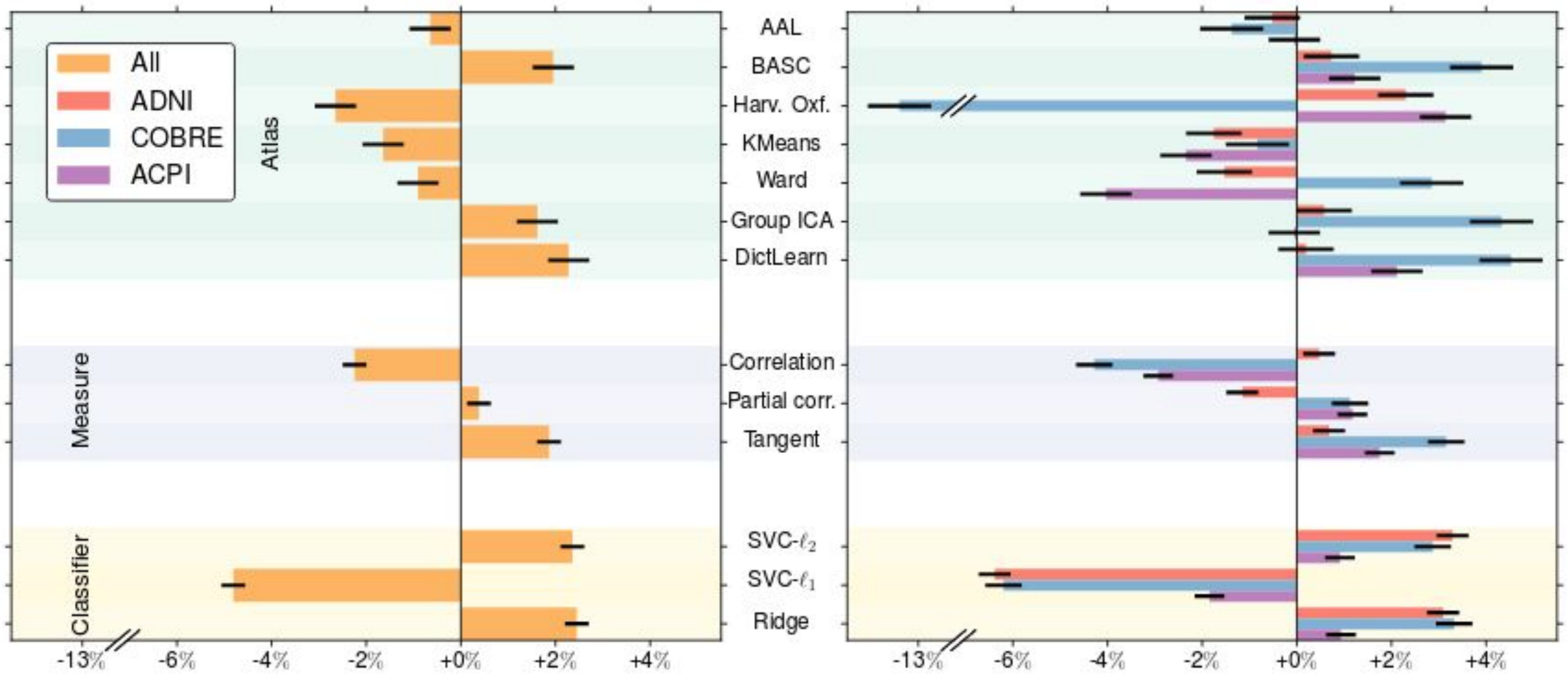


Figure and benchmarks from Arslan et al. Neuroimage 2017 (HCP data).

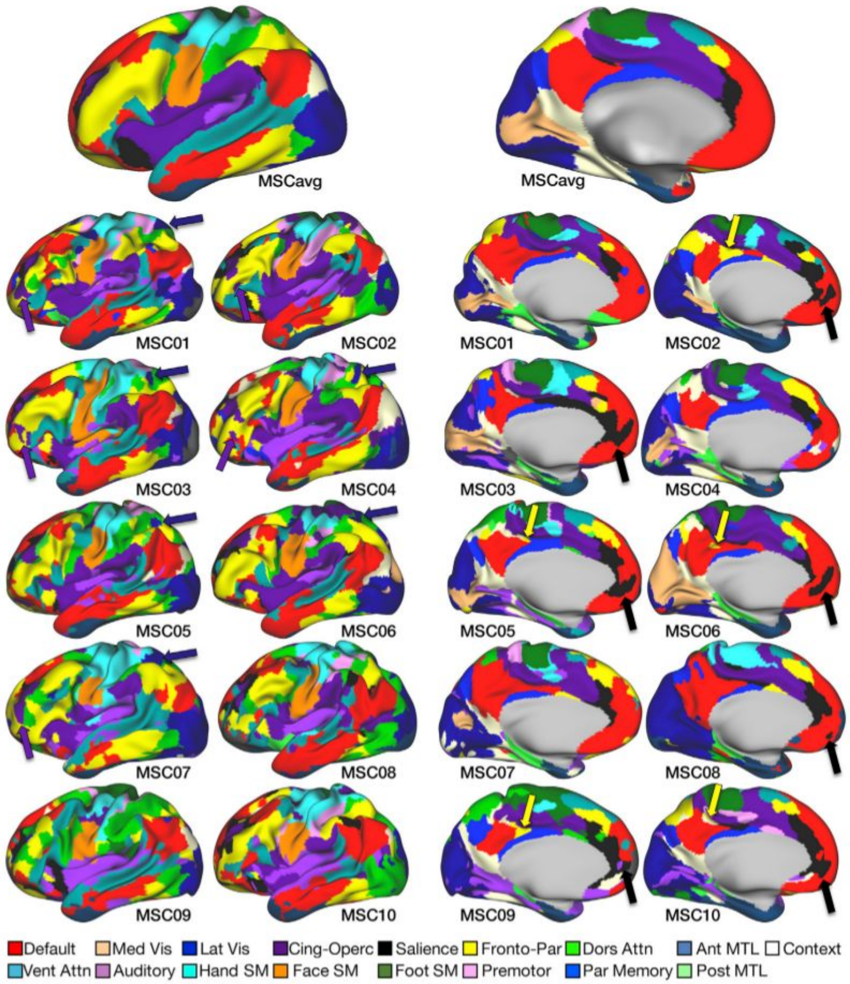
What is a good parcellation?



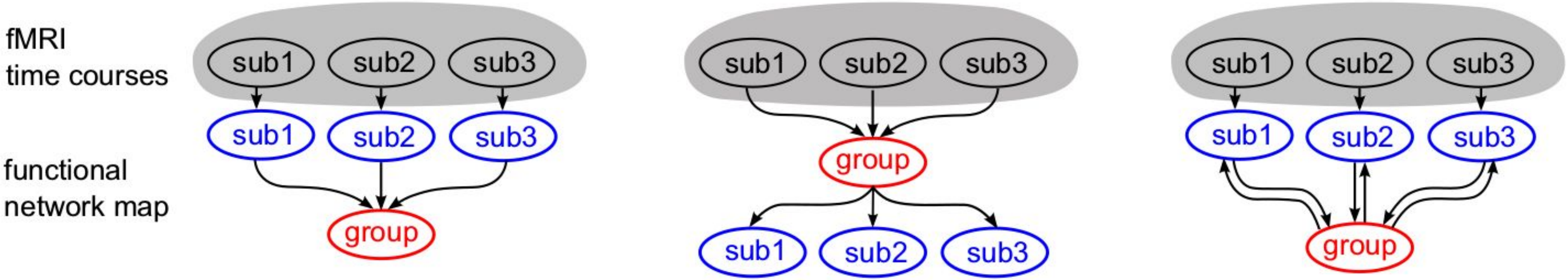
Comparison of the impact of different methodological choices on the accuracy of different classification tasks (ADNI, COBRE, ACPI). AAL and “legacy” (Kmeans, Ward) techniques perform poorly, while functional parcels (BASC, Group ICA, DictLearn) have good performance, and Harv Oxf has uneven performances. From Dadi et al., PRNI 2016.

How to go from group to individual parcels?

For ten densely sampled individuals (10 runs of 30 mns resting-state over ten days) identify details in individual parcellations that cannot be observed at the level of group parcellations (indicated by arrows, group parcellation at the top).



How to go from group to individual parcels?



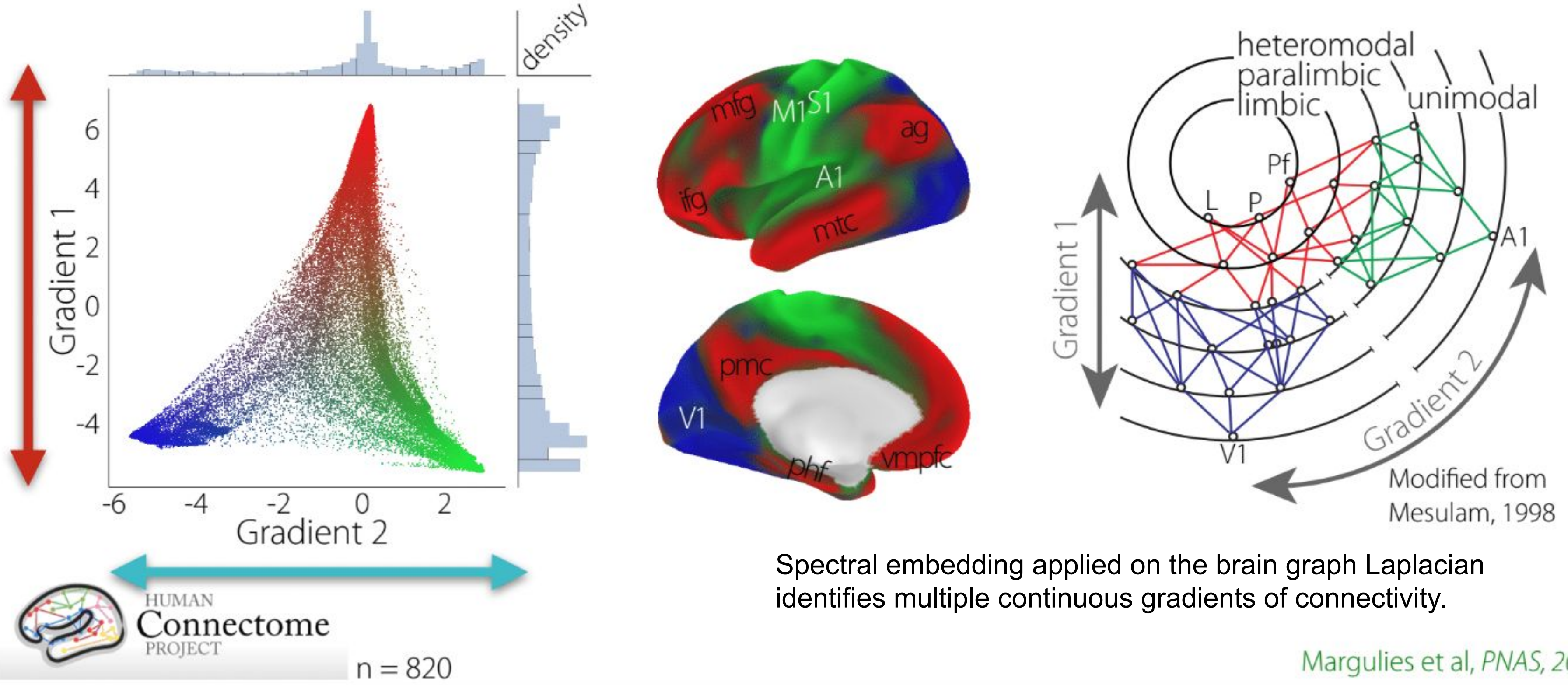
[Bellec, 2010]
[Van Den Heuvel, 2008]
[Esposito, 2005]

[Calhoun, 2001b]
[Beckmann, 2009]
[Filippini, 2009]

[Varoquaux, 2010, 2011]
[Ng, 2010]
[Liu, 2014]
[Salehi et al., 2018]
[Kong et al., 2018]

Adapted from Liu et al., Neuroimage 2014.

Parcels or gradients?

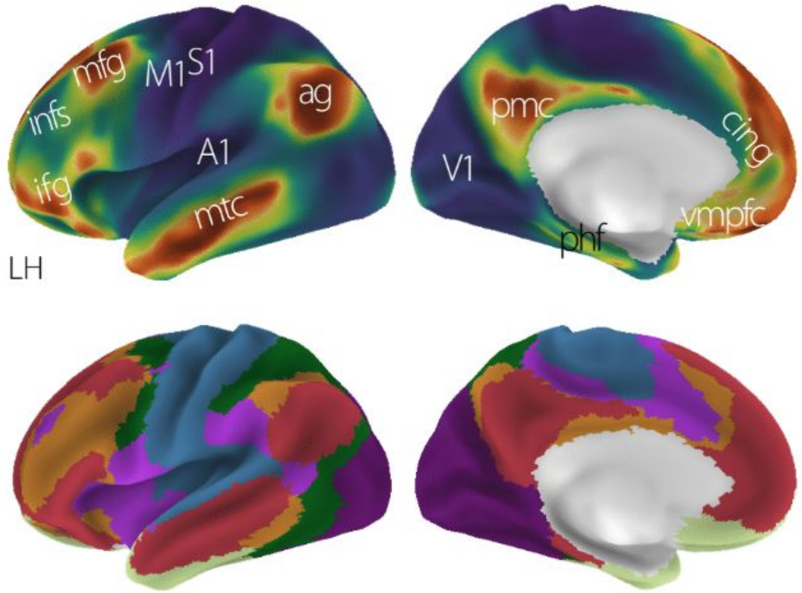


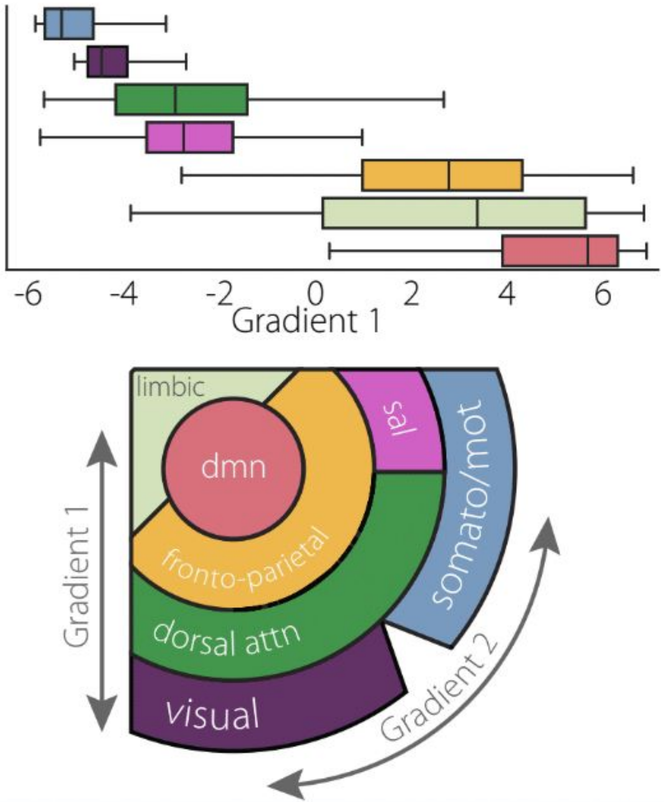
HUMAN Connectome PROJECT

Spectral embedding applied on the brain graph Laplacian identifies multiple continuous gradients of connectivity.

Margulies et al, *PNAS, 2016*

Parcels or gradients?





The first gradient orders sequentially the main networks from the Yeo-Krienen-7-clusters parcellation.
From Margulies et al., PNAS 2016.

Resources

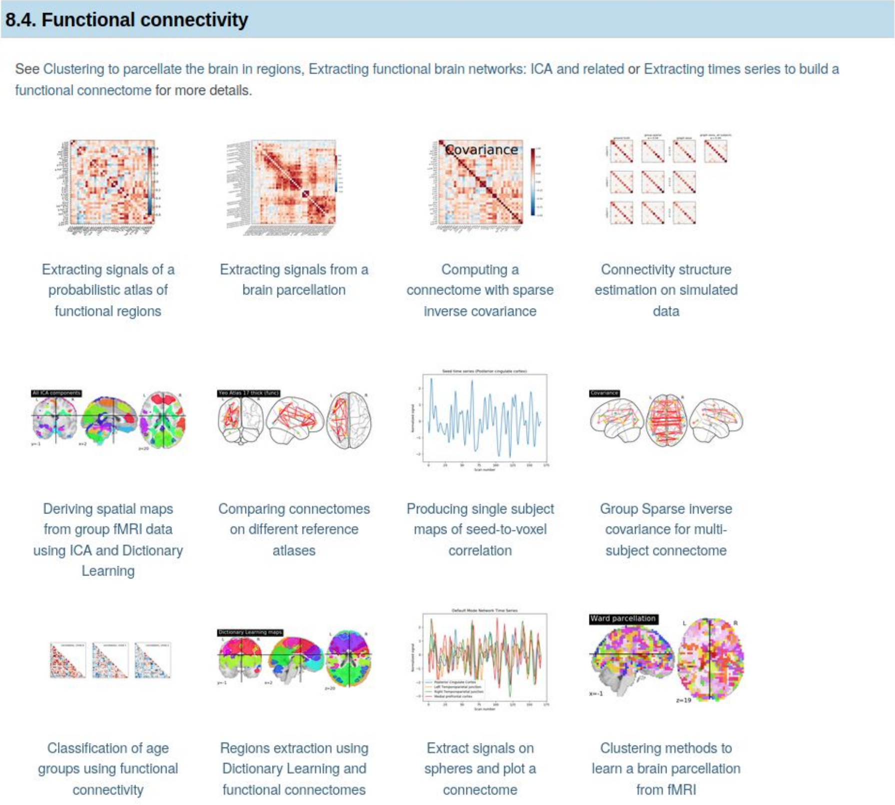
- Preprocessing
- Statistical analyses and machine learning
- Conceptual knowledge

Preprocessing: fMRIprep

- The fMRIprep pipeline, with detailed documentation https://fmriprep.readthedocs.io/en/stable/
- The intro to fMRIprep by Basile Pinsard https://youtu.be/WTcucXAAVBU
- Basile is available on slack and to help with your project.

Statistical analyses and machine learning

https://nilearn.github.io


8.4. Functional connectivity

See Clustering to parcellate the brain in regions, Extracting functional brain networks: ICA and related or Extracting times series to build a functional connectome for more details.

Extracting signals of a probabilistic atlas of functional regions

Extracting signals from a brain parcellation

Computing a connectome with sparse inverse covariance

Connectivity structure estimation on simulated data

Deriving spatial maps from group fMRI data using ICA and Dictionary Learning

Comparing connectomes on different reference atlases

Producing single subject maps of seed-to-voxel correlation

Group Sparse inverse covariance for multi-subject connectome

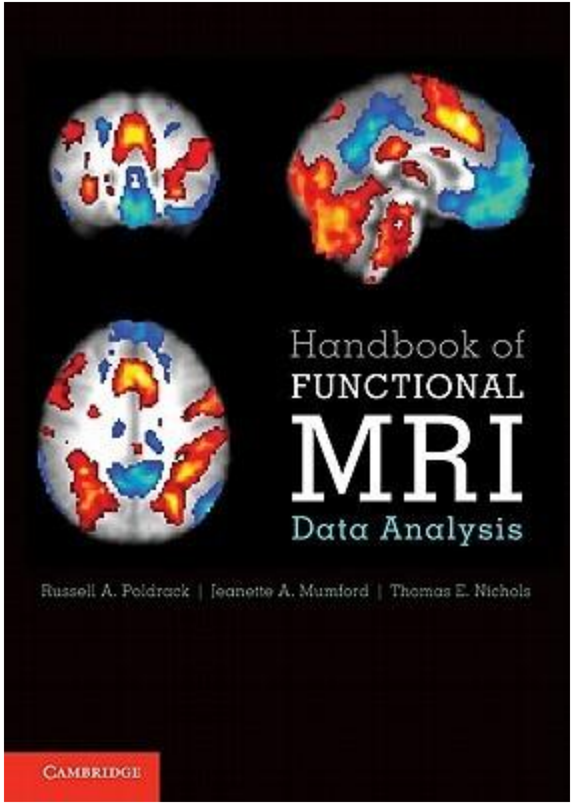
Classification of age groups using functional connectivity

Regions extraction using Dictionary Learning and functional connectomes

Extract signals on spheres and plot a connectome

Clustering methods to learn a brain parcellation from fMRI

Handbook of functional MRI data analysis



The resting-state network