Resting-State fMRI (rsfMRI)

Methods & Models for fMRI Analysis 2017

Sandra Iglesias
iglesias@biomed.ee.ethz.ch

Translational Neuromodeling Unit (TNU)
Institute for Biomedical Engineering (IBT)
University and ETH Zürich

Translational Neuromodeling Unit

University of Zurich[UZH]

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Beginning

task-fMRI vs. rsfMRI

- changes in BOLD signal attributed to experimental paradigm
- “brain function mapped onto brain regions” → local
- generally largely ignoring any intrinsic, ongoing (spontaneous) brain activity

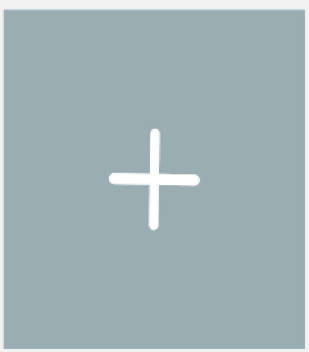
- Investigates spontaneous brain activity in fMRI in the absence of experimental stimulations
- mainly temporally correlated fMRI signal changes across the brain during ‘rest’ is studied, i.e. resting state networks (RSNs)
- the resting brain consumes 20% of the body’s energy
  (Raichle et al. (2001), *PNAS)*

Paradigm shift

Resting state Acquisition

Duration: 5-10 min

Eyes open



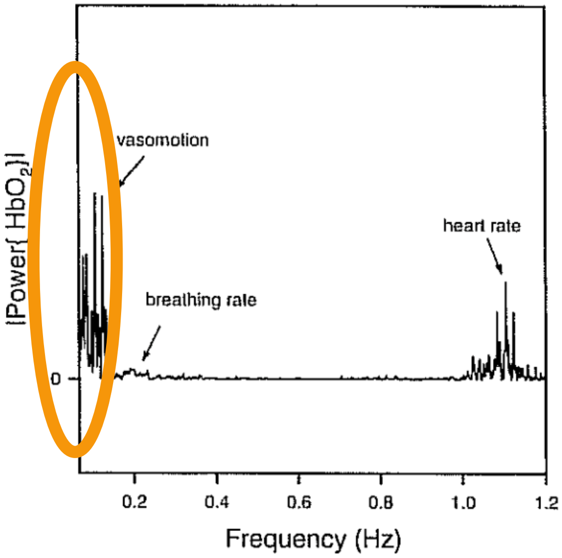
With fixation cross

Without fixation cross

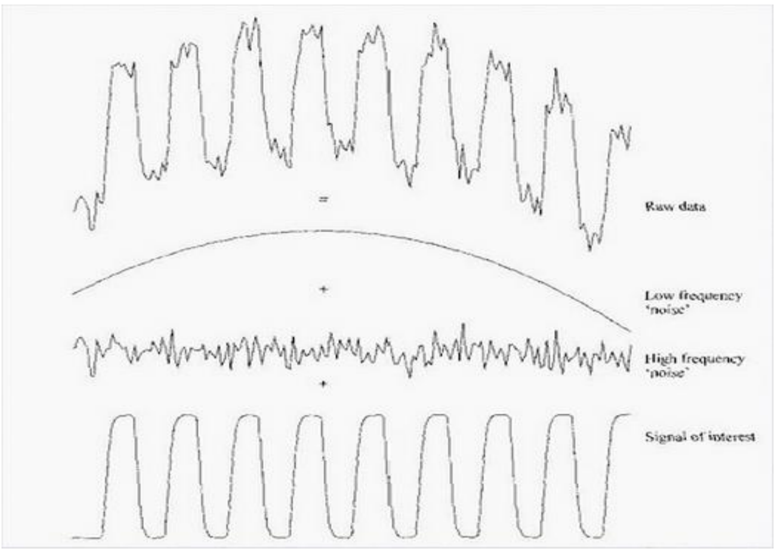
Eyes closed

Spontaneous BOLD activity

- the brain is always active, even in the absence of explicit input or output
  - the resting brain consumes 20% of the body's energy (mostly to support ongoing neuronal signaling), task-related changes in neuronal metabolism are only about 5%
- what is the "noise" in standard activation studies?
  - physiological fluctuations or neuronal activity?
  - peak in frequency oscillations from 0.01 – 0.08 Hz
  - distinct from faster frequencies of respiratory (0.1 – 0.5 Hz) and cardiac responses (0.6 – 1.2 Hz)

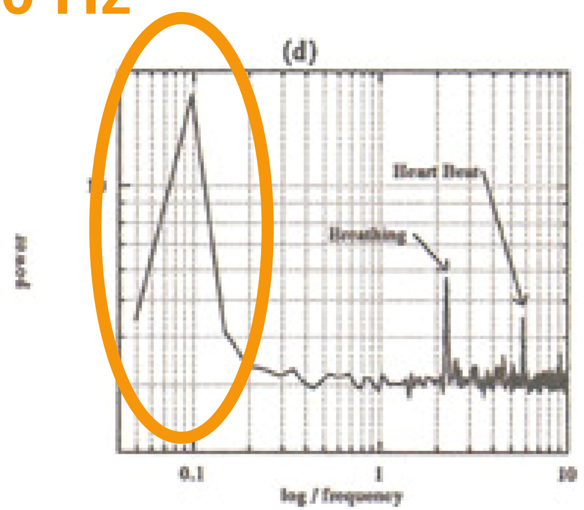


Elwell et al., 1999



Mayhew et al., 1996

< 0.10 Hz



rsfMRI or R-fMRI

Resting state functional MRI […]
is a […] method for evaluating regional interactions that occur when a subject is not performing an explicit task.

http://www.humanconnectome.org/about/project/resting-fmri.html

rsfMRI or R-fMRI

correlated fluctuations

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http://www.humanconnectome.org/about/project/resting-fmri.html

rsfMRI or R-fMRI → resting-state fcMRI

functional connectivity

correlated fluctuations

**Resting state functional MRI […]
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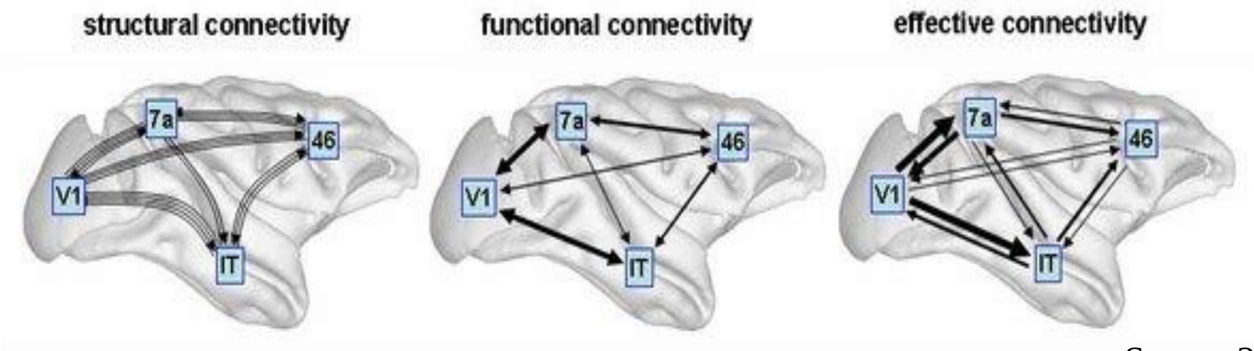
Structural, functional & effective connectivity



Sporns 2007, *Scholarpedia*

- **anatomical/structural connectivity**
  = presence of axonal connections
- **functional connectivity**
  = statistical dependencies between regional time series
- **effective connectivity**
  = causal (directed) influences between neurons or neuronal populations

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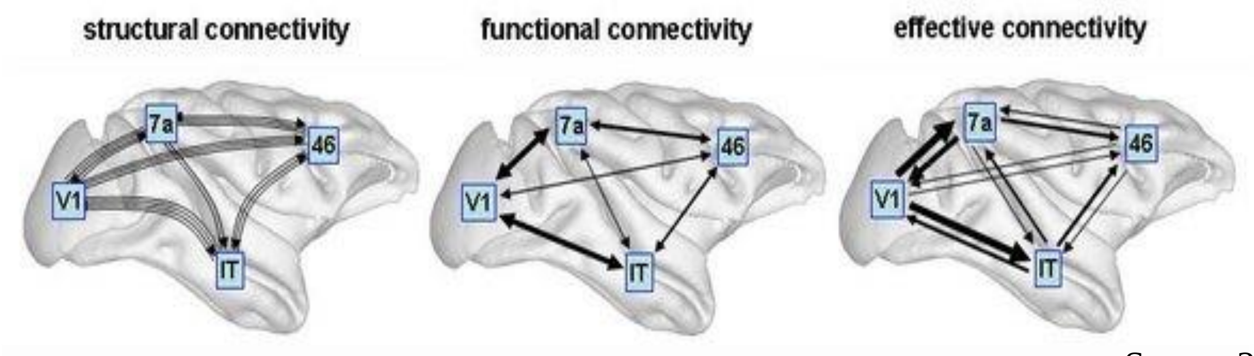
Structural, functional & effective connectivity



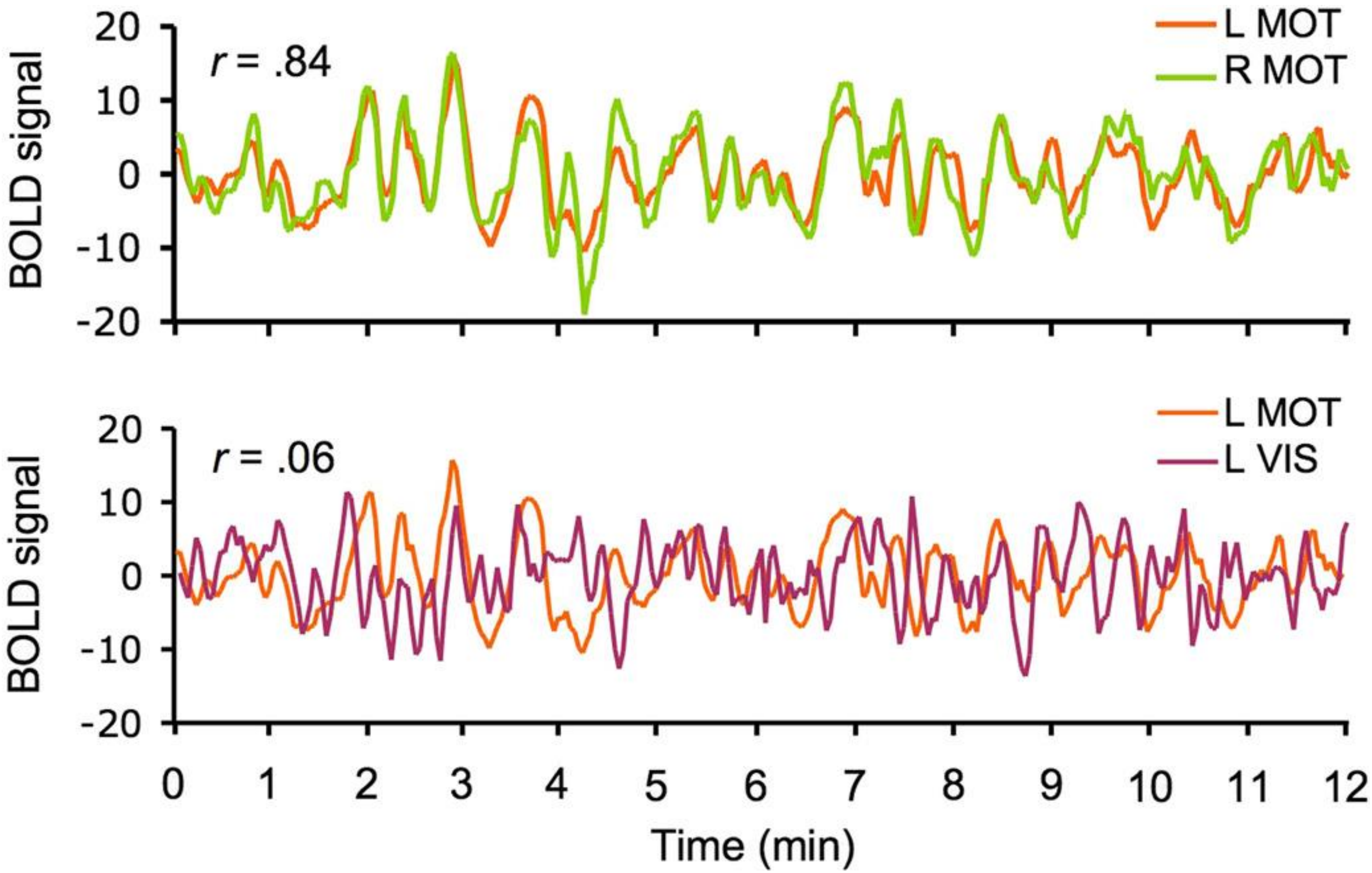
Sporns 2007, *Scholarpedia*

- **anatomical/structural connectivity**
  = presence of axonal connections

- **functional connectivity**
  → resting-state fcMRI might provide indirect information about the structural connectivity of the brain

- **effective connectivity**
  = causal (directed) influences between neurons or neuronal populations

Spontaneous BOLD activity



Van Dijk et al., 2009

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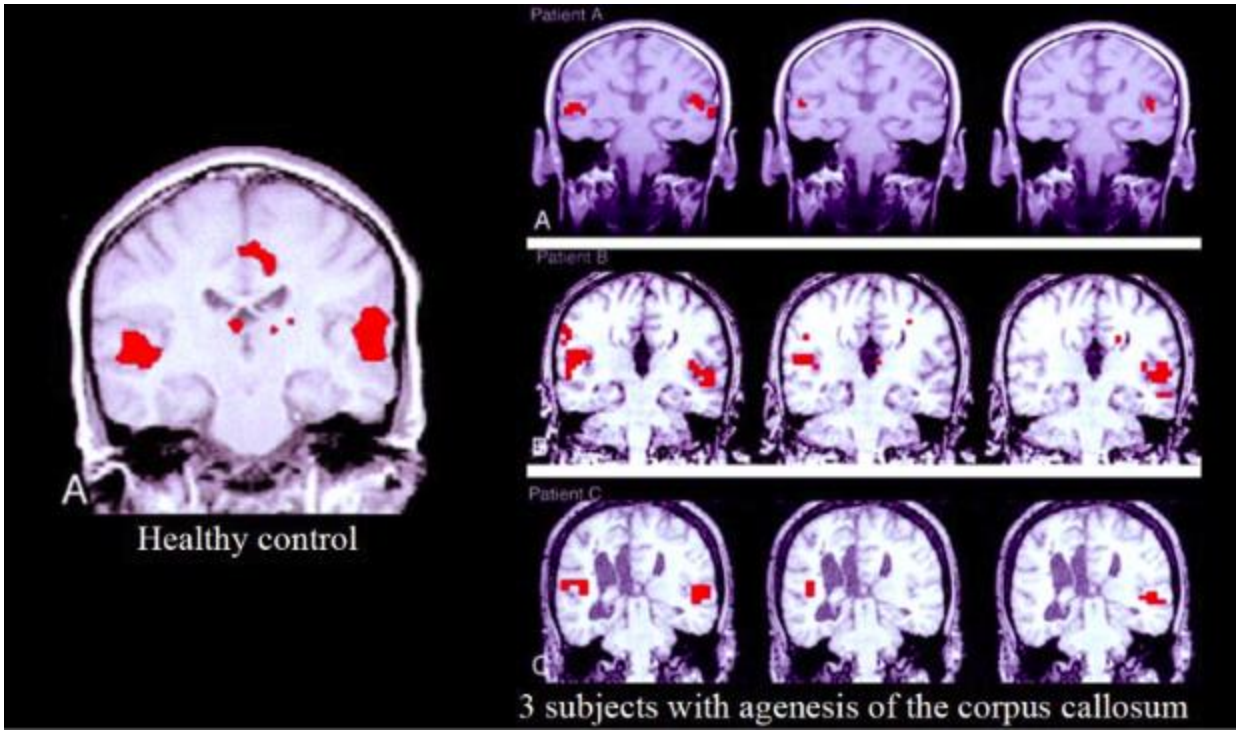
Functional connectivity = anatomical connectivity ?

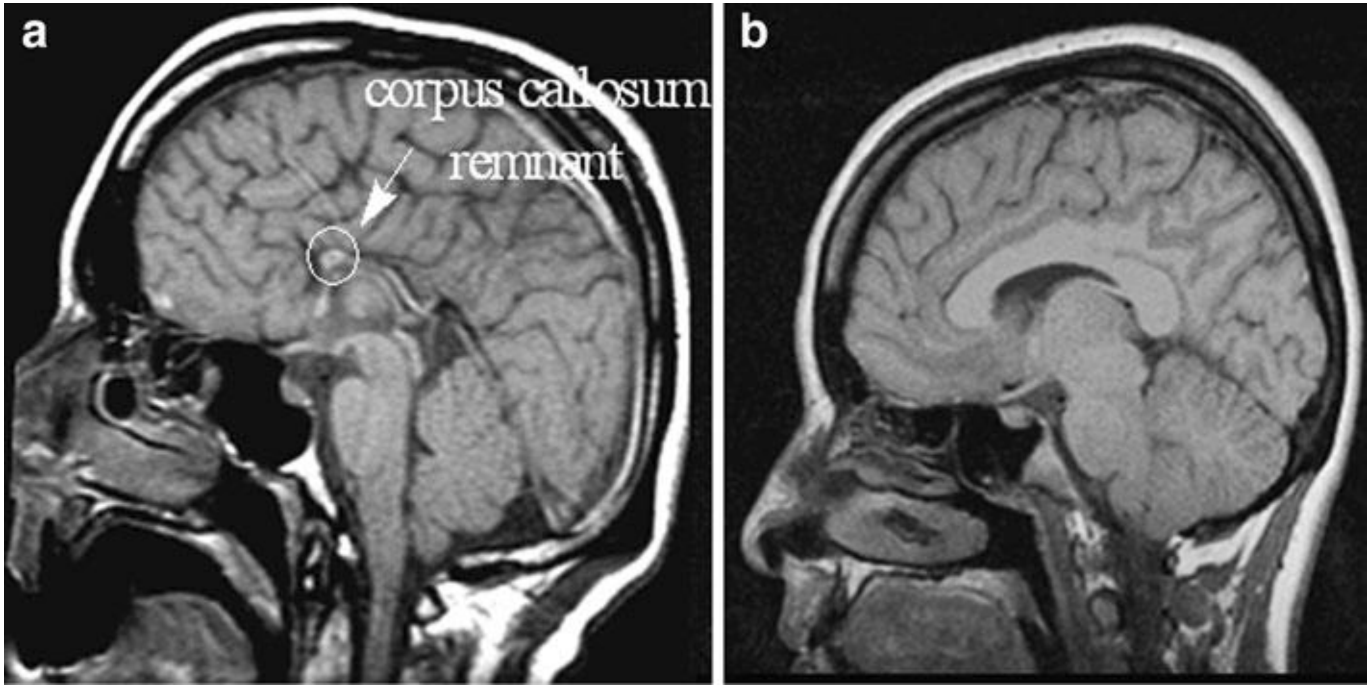
Healthy control: seed voxel from the right auditory cortex



Patients:
Left: activation data from the auditory cortex during a text-listening task.
Middle: functional connectivity with seed voxel selected in the right auditory cortex.
Right: functional connectivity with seed voxel selected in the left auditory cortex

Quigley et al. (2003), *AJNR*

Corpus callosum



Lowe (2010), *Magn Reson Mater Phy*

Functional connectivity = anatomical connectivity ?

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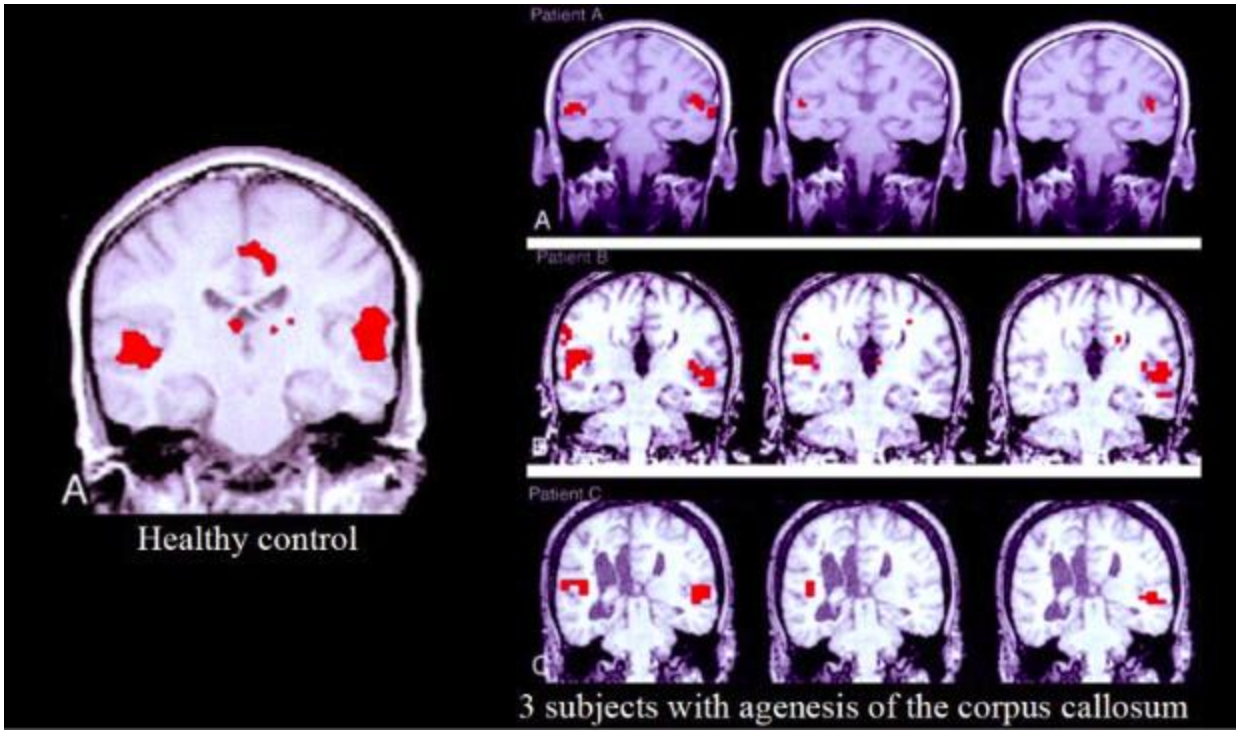

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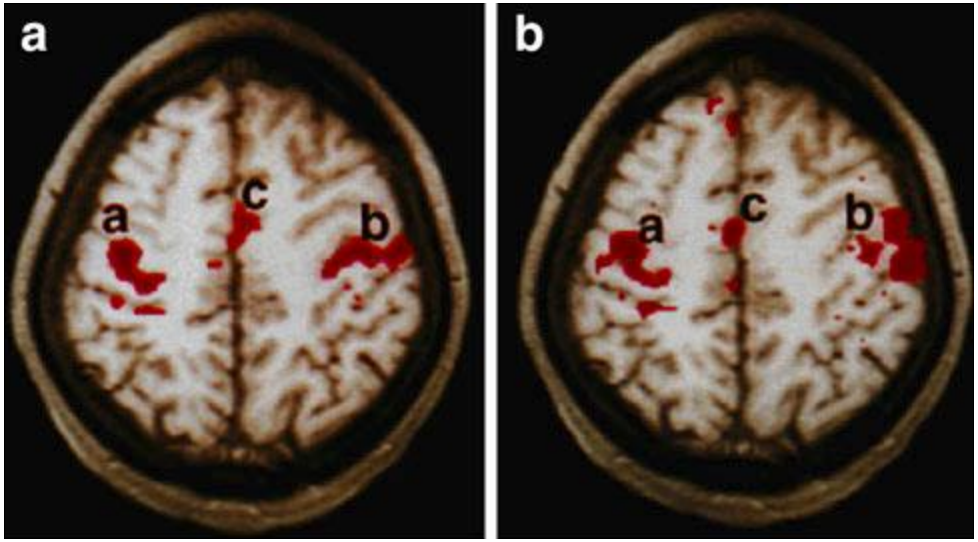
Early studies - fMRI



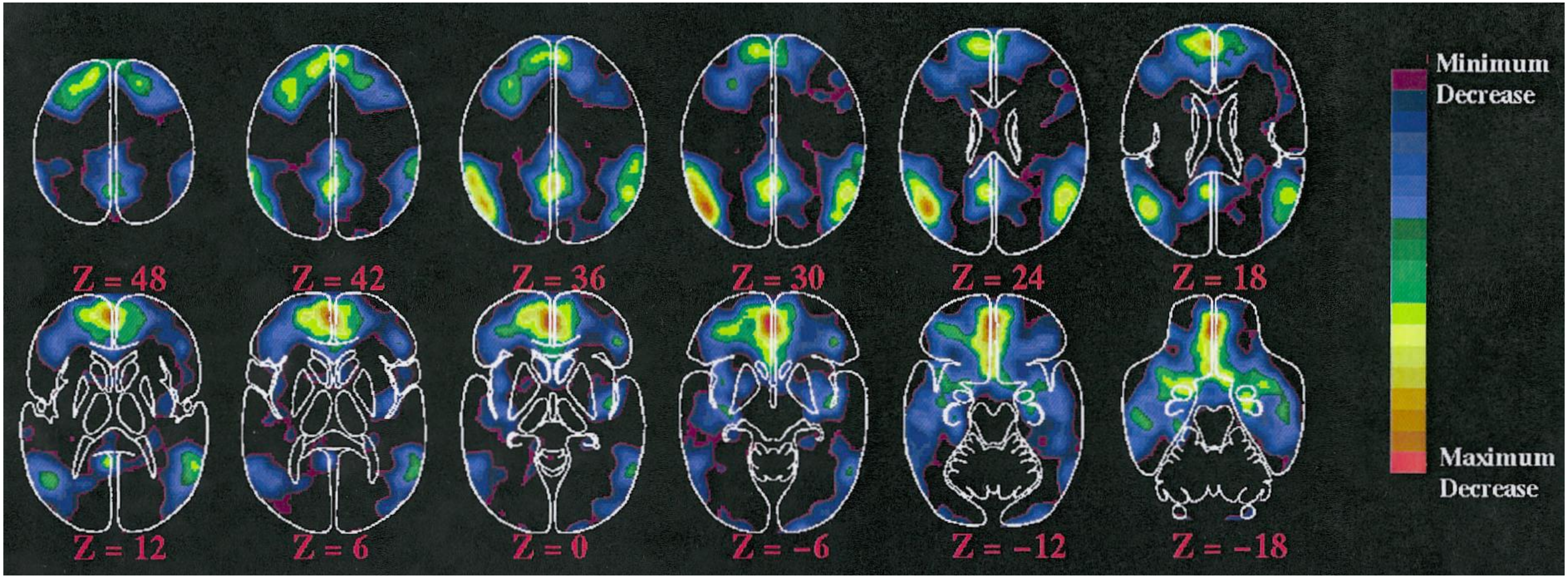
a) fMRI task-activation response to bilateral finger movement

b) functional connectivity map using as seed region the left motor cortex

Biswal et al. (1995), *Magn Reson Med*

Early studies - PET

Brain regions showing a decrease in metabolic activity during attention demanding cognitive tasks



default mode of brain function

Raichle et al. (2001), *PNAS*

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Early studies - fMRI

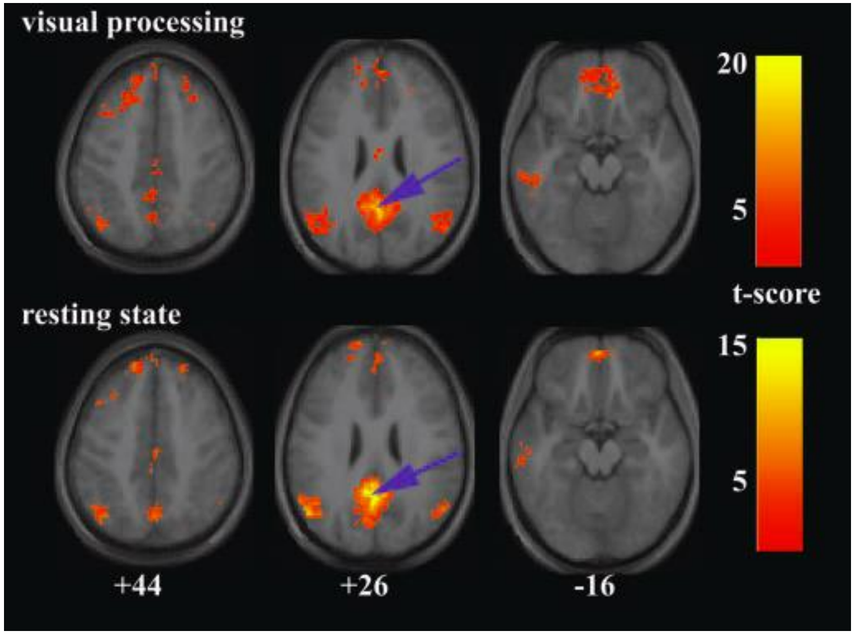
Tasks

- Resting state:
  - Eyes closed
  - do not think of anything in particular
- Visual processing
  - black-and-white radial checkerboard pattern
- Working memory
  - N-back spatial paradigm

  - task-related decreases in the PCC, vACC, medial prefrontal cortex (MPFC), and left inferior parietal cortex (IPC)
  - task-related increase in lateral prefrontal areas

Visual processing and resting-state neural connectivity for the PCC

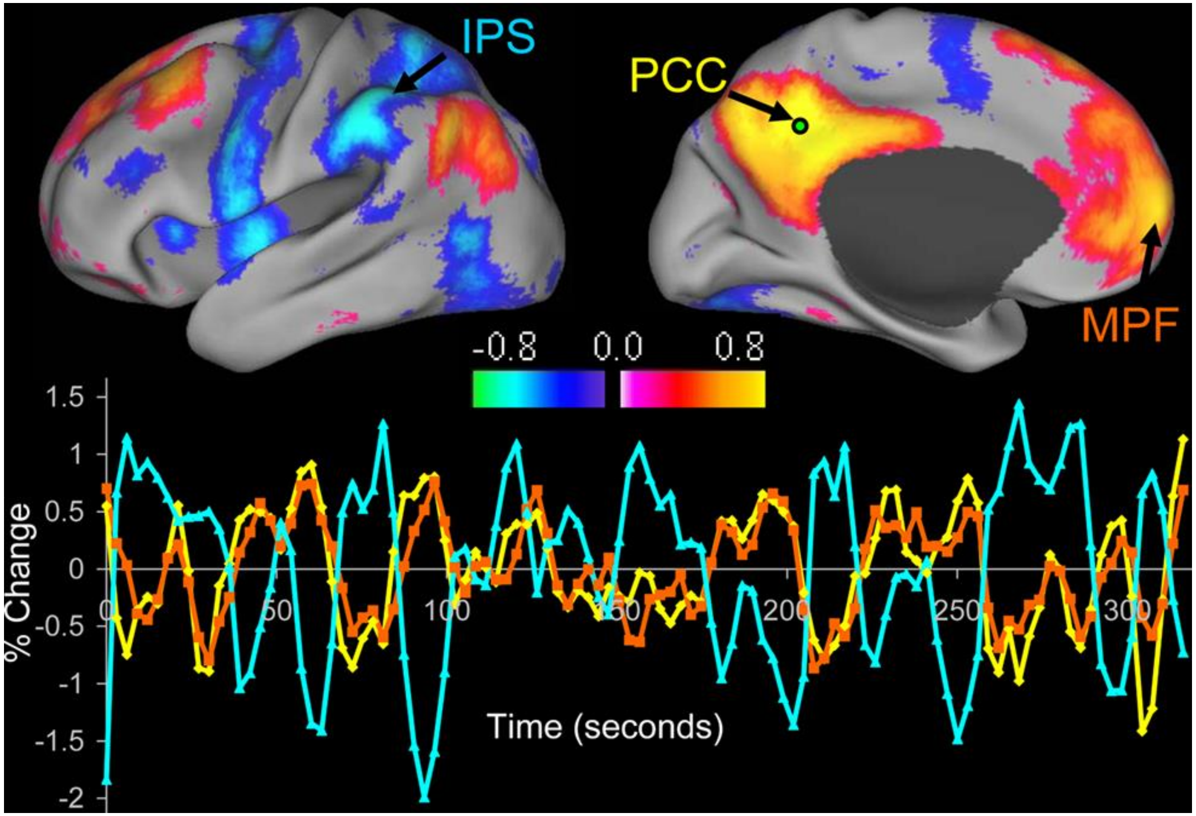
[-2 -51 27]



Greicius et al. (2003), *PNAS*

Default mode network (DMN)

- A set of brain regions whose activation tends to
  - decrease during the performance of active, engaging tasks
  - increase during conditions of resting and reflection



Fox & Greicius (2010), *Front Syst Neurosci*

Resting-state Networks (RSNs)

“RSNs are “activation-like”,
spatially structured maps of grey matter brain areas exhibiting correlated BOLD signal changes”

Niazy et al., 2015

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Resting-state Networks (RSNs) characteristics

- Spatial
  - localize the grey matter regions of the brain (Beckmann et al. 2005; De Luca et al. 2006), including;
    - sensory and motor cortices,
    - language, memory, and higher cognitive systems
  - appear to be either upregulated or downregulated during specific cognitive tasks.
    - ‘task positive’ vs ‘task negative’ (e.g. DMN)

- Temporal
  - Low frequency/ slow fluctuations
  - Frequencies < 0.1 Hz account for 90% of the cross-correlation between connected areas (Cordes et al., 2000,2001)
  - But higher frequencies contribute equally consistent (Niazy et al. 2008)

RSNs

a) & b) Visual

c) Sensory

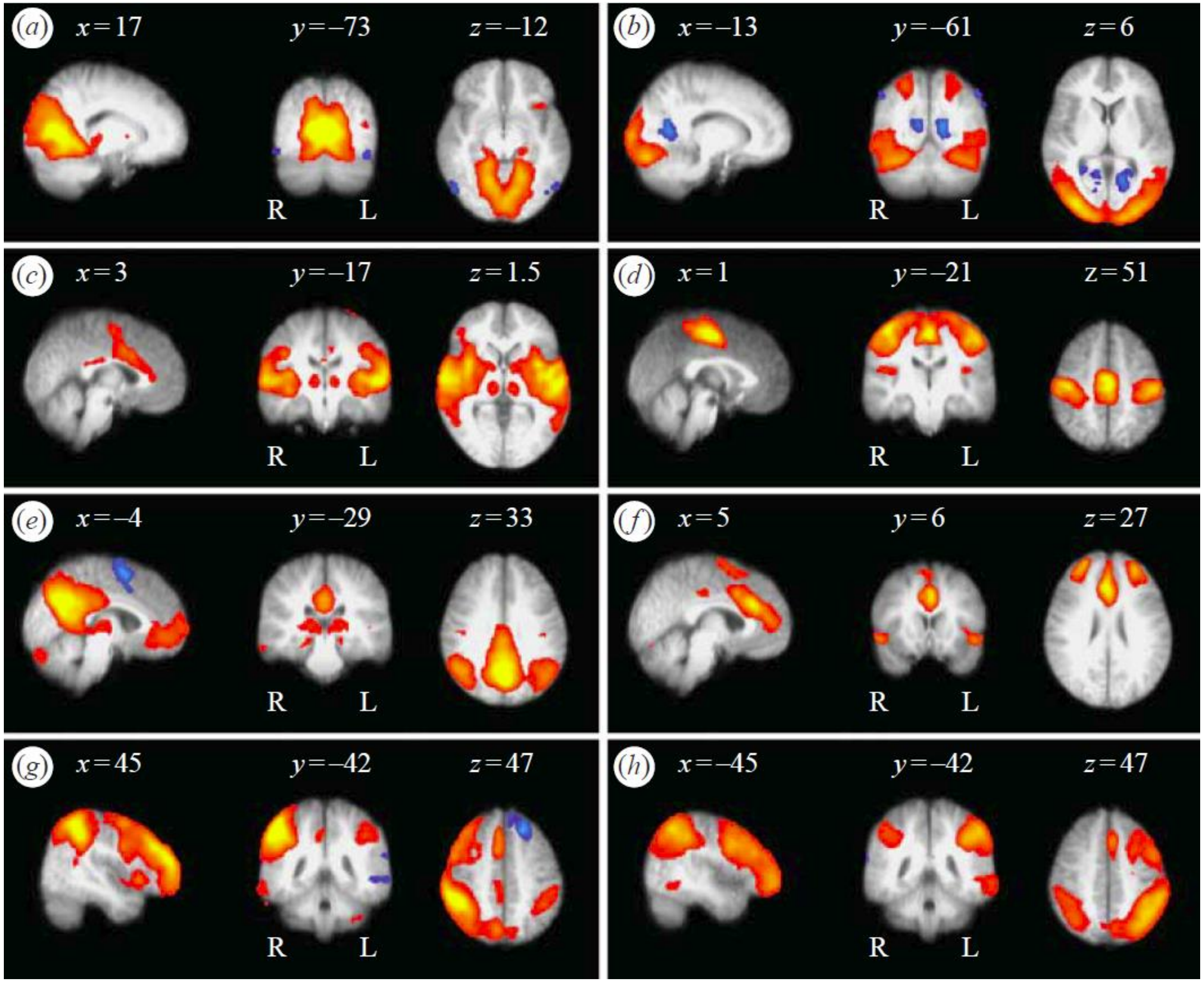
d) Motor

e) DMN
(default mode network)

f) executive control & salience

g) right fronto-parietal
(~attention RSN)

h) Left fronto-parietal
(~attention RSN)



Beckmann et al. (2005), *Phil Trans R Soc B*

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What is so interesting about ‘rest’?

- Usefulness?
  - Not a measure of structural connectivity
  - Not a measure of effective connectivity
- Interpretability?
  - Confounds
    - RSNs reflect artifacts, i.e. cardiac and respiratory effects (Krüger and Glover, 2001, Birn et al., 2006)
    - vascular processes (unrelated to neuronal function) (Wise et al., 2004)
    - participants might fall asleep, be planning what to do next, or might be thinking about the previous task ...

→ However, RSNs have been found to be distinct from cardiac and respiratory artefacts (spatially and temporally) (De Luca et al., 2006)
→ rsfMRI has revealed a number of networks consistently found in healthy subjects, different stages of consciousness and across species
→ may present a valuable data resource for delineating the human neural functional architecture (Cole et al., 2010)

Methods

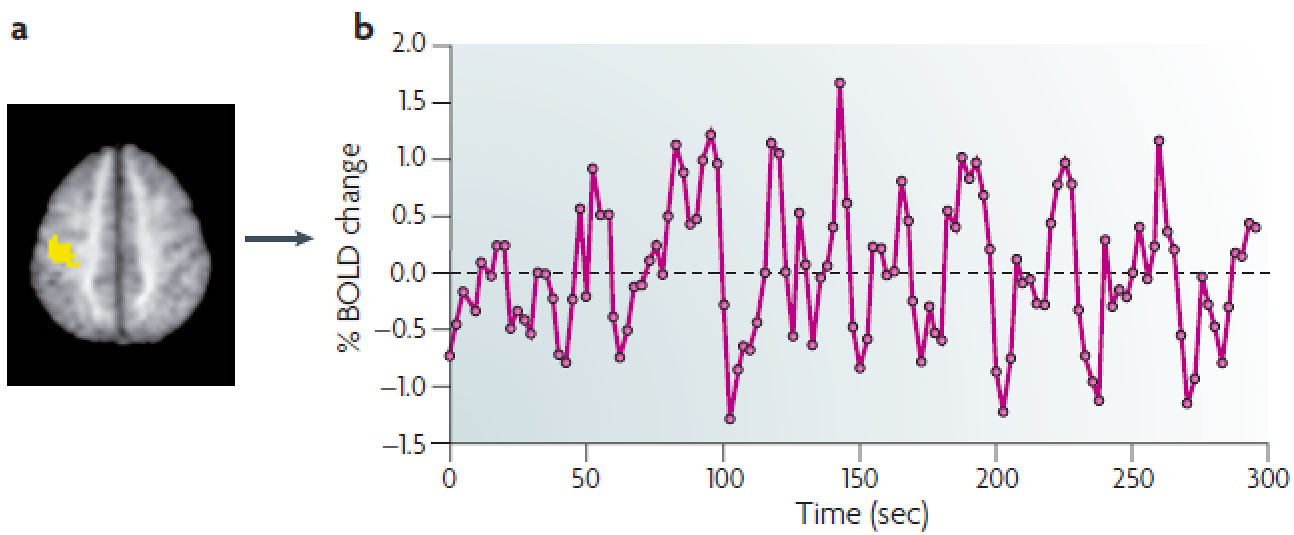
- Model-based
  - Seed based correlation analysis
- Model-free
  - Decomposition
    - Independent component analysis (ICA), principal component analysis (PCA)
  - Clustering
    - Fuzzy clustering analysis (FCA), hierarchical clustering analysis (HCA)

Methods: model-based

- Seed based correlation analysis (SCA; seed = region of interest)

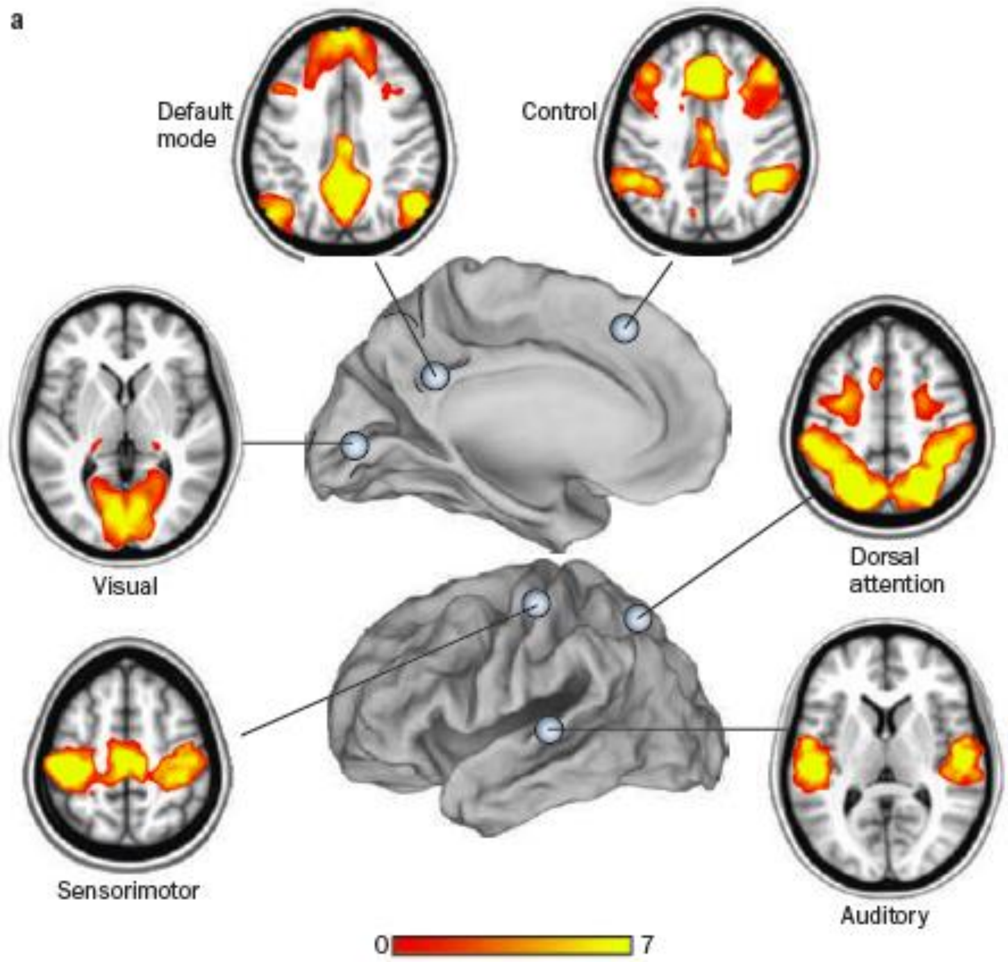
→ Temporal correlation between the time course of every voxel in the brain and the time course from a seed voxel

  - hypothesis-driven: a priori selection of a voxel, cluster, or atlas
  - the extracted time series is used as regressors in a GLM analysis
  - univariate approach



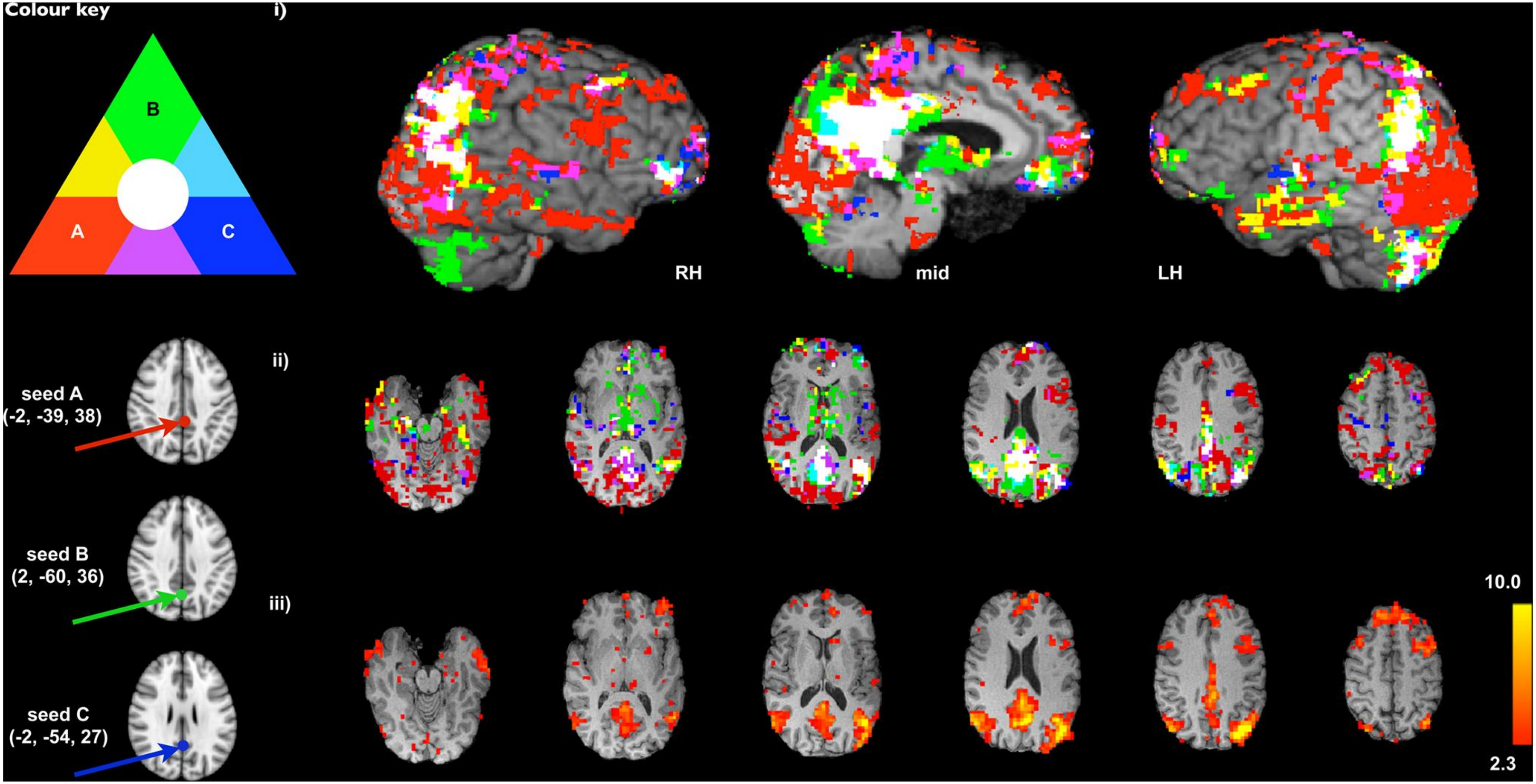
Fox & Raichle, 2007, *Nature Reviews, Neuroscience*

SCA



Zhang & Raichle, 2010, *Nature Reviews, Neurology*

DMN versions using 3 different seed voxels



Cole et al. (2010), *Front Syst Neurosci*

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Methods: model-based

- Seed based correlation analysis (SCA; seed = region of interest)

- Advantage:
  - Direct answer to a direct question (straightforward interpretation)
  - Has moderate-to-high reliability
- Weakness:
  - Residual confounds in the SCA time series (e.g. head motion)
  - Bias attached to seed selection (see previous slide)
  - Anatomical restrictions on the measurement of network connectivity (multiple regions must be manually defined before analysis in order to generate multiple network maps)

Methods: model-free

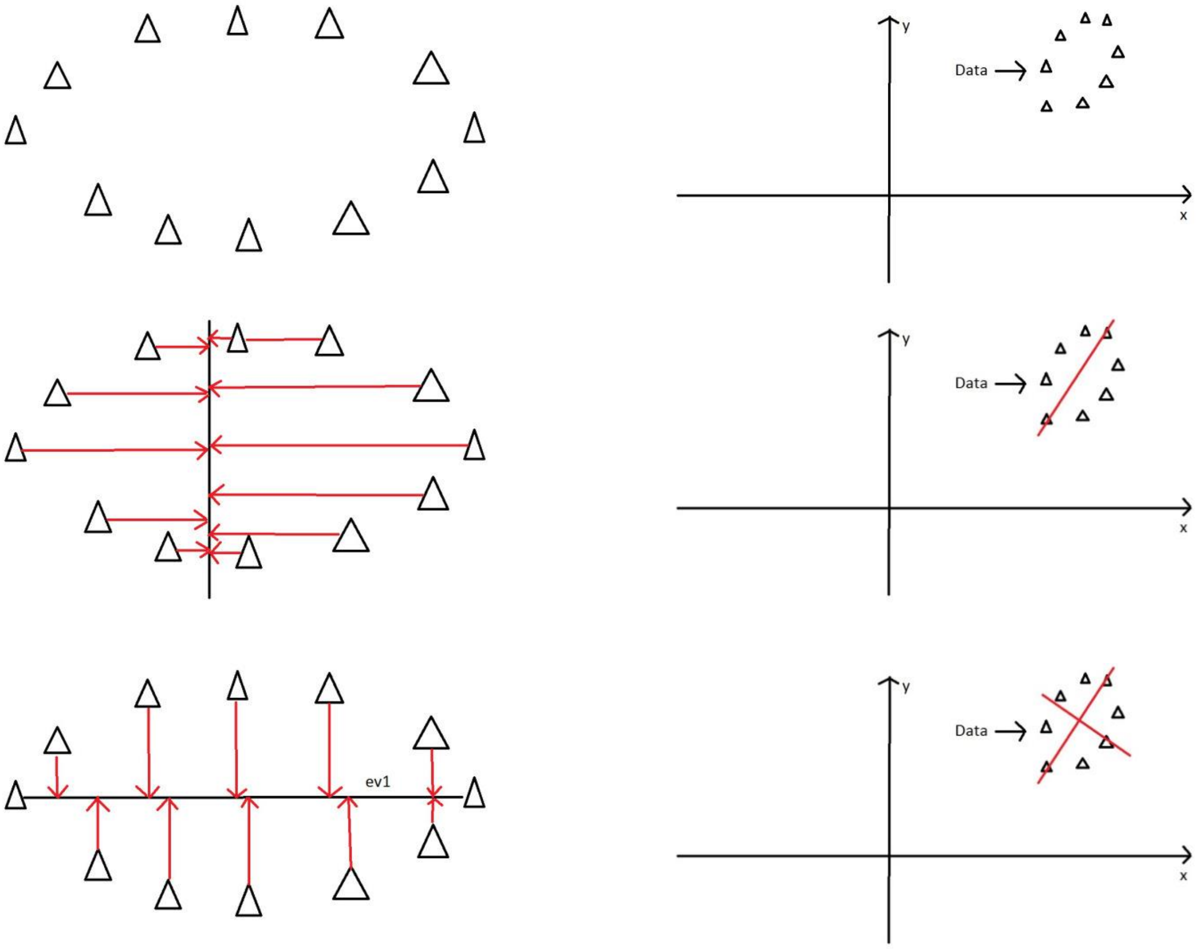
- Decomposition
  - Independent component analysis (ICA), principal component analysis (PCA)
    - multivariate-approach
- The signal in fMRI data is composed out of different sources of variability:
  - machine artefacts
  - physiological pulsation
  - head motion and
  - Spontaneous fluctuations in the blood oxygen level-dependent (BOLD) – signal
- Goal: to express the original fMRI dataset as a linear combination of basis vectors (PCA) or statistically independent components (ICA)

Principal component analysis (PCA)

- Can treat fMRI dataset (1 time & 3 spatial dimensions) as a 2D matrix (time x voxels)
  - Decomposes the data into spatial maps (~ functional networks) with associated time series
  - Goal: finding components which explain max/most the variance in the dataset
  - iterative in defining each component in relation to the previous components
  - the components are orthogonal (uncorrelated) to each other

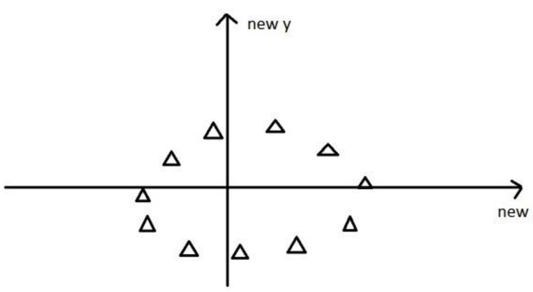
PCA example

Finding directions of maximum variance for 2 sources



number of variables =
number of eigenvectors/
eigenvalues =
number of dimensions

e.g.:
x = age
y = hours spent in the
internet



Principal Component Analysis

The core of **PCA** is to represent the observed fMRI time courses X with a combination of orthogonal contributors. Each contributor is made of a temporal pattern (a principal component) multiplied with a spatial pattern.

Singular Value Decomposition (SVD): method for eigen-decomposition of matrices:

$$[U, S, V] = SVD(M)$$

$$M = USV^T$$

M: observed data

S: singular value

U: eigenvariate (extent to which an eigenimage is expressed over time)

V: eigenimage

Friston and Büchel, 2007, *Chapter 37, in Statistical Parametric Mapping*

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SVD: an example using simulated data

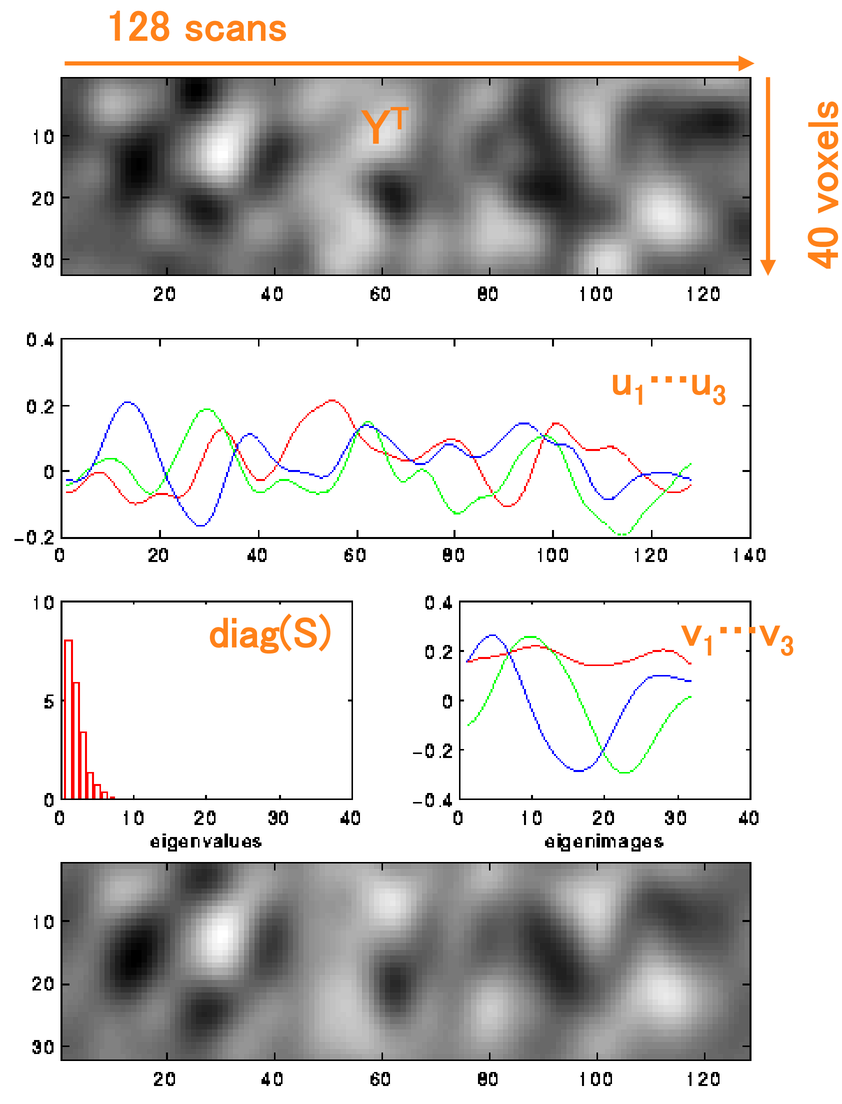
A time-series of 1D images:
128 scans of 40 “voxels”

(note: for display reasons, the transpose of the data matrix is shown)

Eigenvariates U:
Temporal expression of the first three eigenimages over time

Singular values S and eigenimages V ("spatial modes")

The time-series reconstructed from the first three eigenimages



$Y^* = s_1 u_1 v_1^T + s_2 u_2 v_2^T + s_3 u_3 v_3^T$

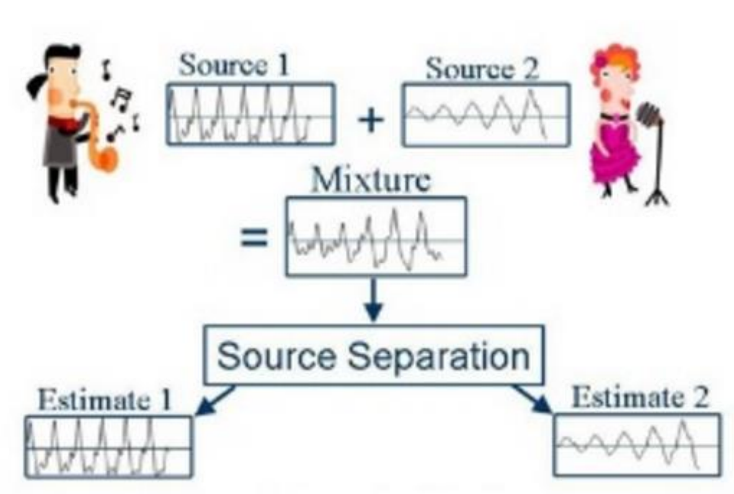
Independent Component Analysis (ICA)

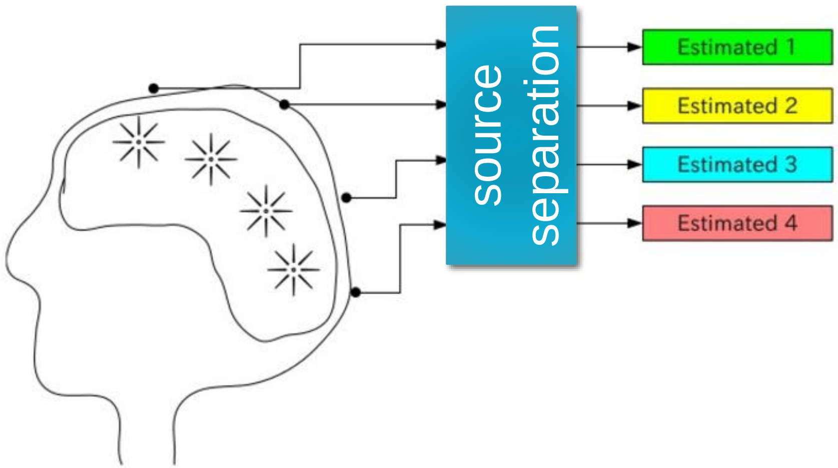
ICA decomposes a two-dimensional (time x space) data matrix into the time courses and associated spatial maps of the underlying ‘hidden’ signal sources

- Spatial ICA: a form of ICA that generates components that have minimal spatial redundancy

- Temporal ICA: a form of ICA that generates components that have minimal temporal redundancy

ICA





$$X = AS$$

X: measured data

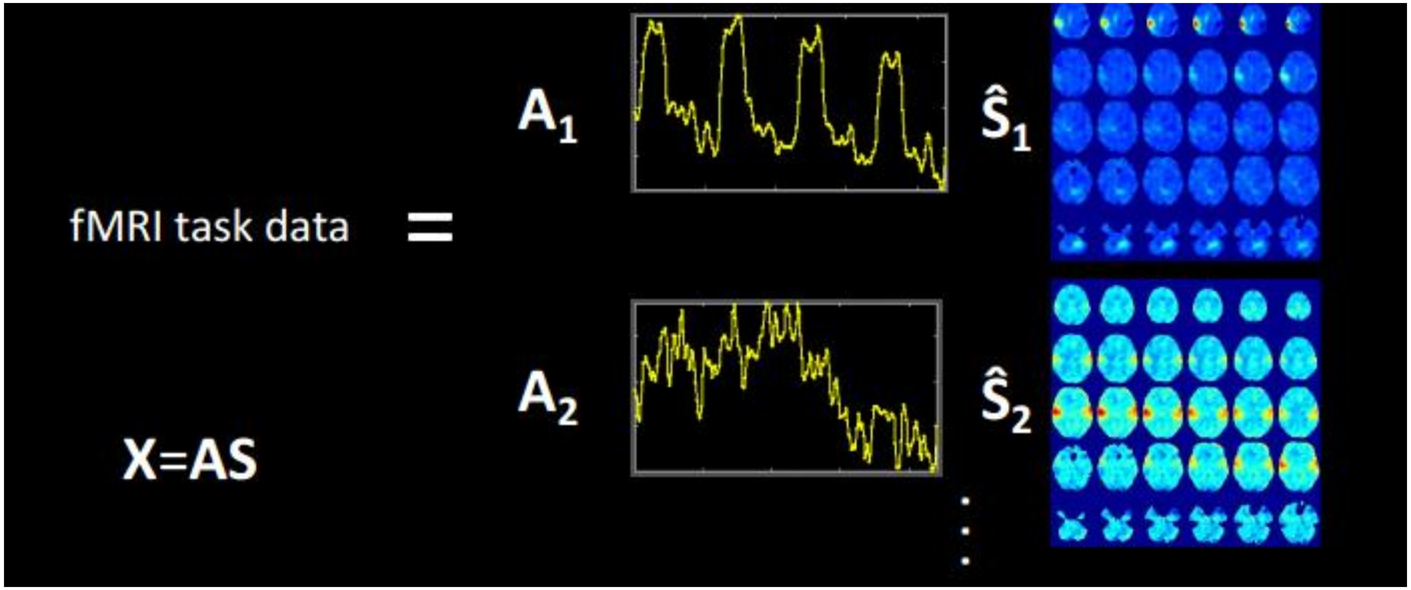
A: mixing matrix

S: the underlying (original) signal source (IC component)

ICA applied to fMRI

Spatial ICA

- the sources are maps that are maximally spatially independent (i.e. non-overlapping)
- the mixing matrix represents activation time courses of the sources



ICA applied to fMRI

→identifies stationary sets of voxels whose acivations vary together over time and are maximally distinguishable from other sets.

→assumes that fMRI data consist of a set of spatially overlapping components, each with an independent spatial pattern and different time course

→the term «independent» means that the algorithm minimizes the overlap between the components, but the components do not need to be orthogonoal with each other

→One common approach is to estimate maximally statistically independent, non-Gaussian components from fMRI data (by optimizing a measure of non-Gaussianity in the estimated spatial maps)

toolbox

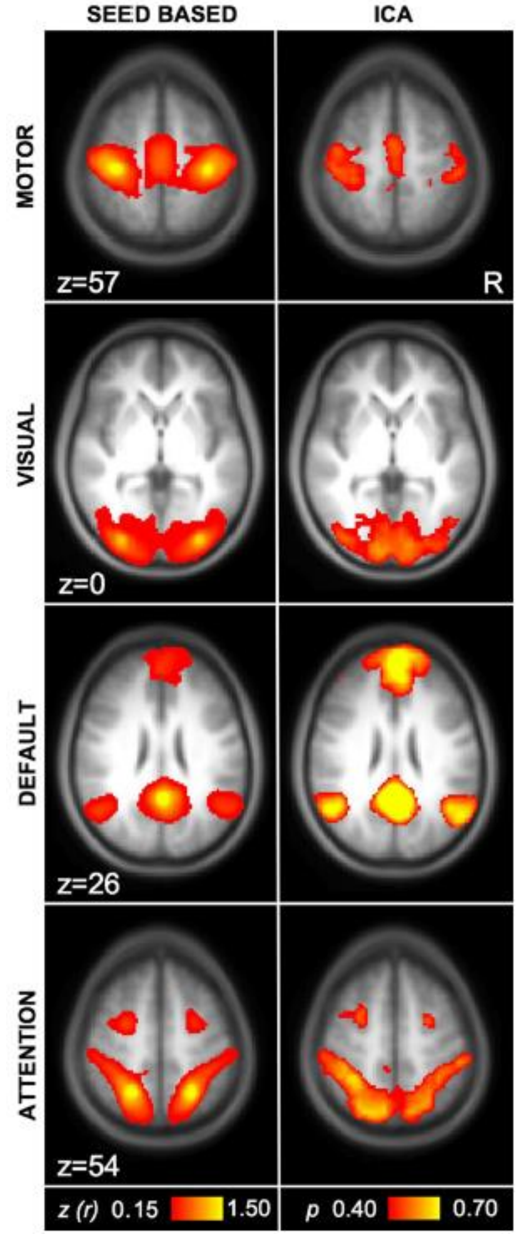
- MELODIC FSL
- GIFT (MIALAB; Vince Calhoun)
- REST and DPARSF SPM
- CONN Toolbox (http://www.nitrc.org/projects/conn/)

Methods: model-free

- Decomposition
  - ICA/ PCA
    - multivariate-approach

- Advantage:
  - Data-driven; explore fMRI data in search of systematic variation, without necessarily adopting an a priori model for that variation
  - Partition the four dimensional fMRI time series into a set of components that may reflect distinct aspects of brain functioning, and also sources of non-neuronal variance (related to movement, ventricles, WM, respiration)
- Weakness:
  - Poorly chosen models (e.g. how to select the number of components?)
  - Variability in the hemodynamic response
  - Loss of specificity in relation to a well-defined seed of interest, interpretation?

SCA vs. ICA



Van Dijk, 2010, *J Neurophysiol*

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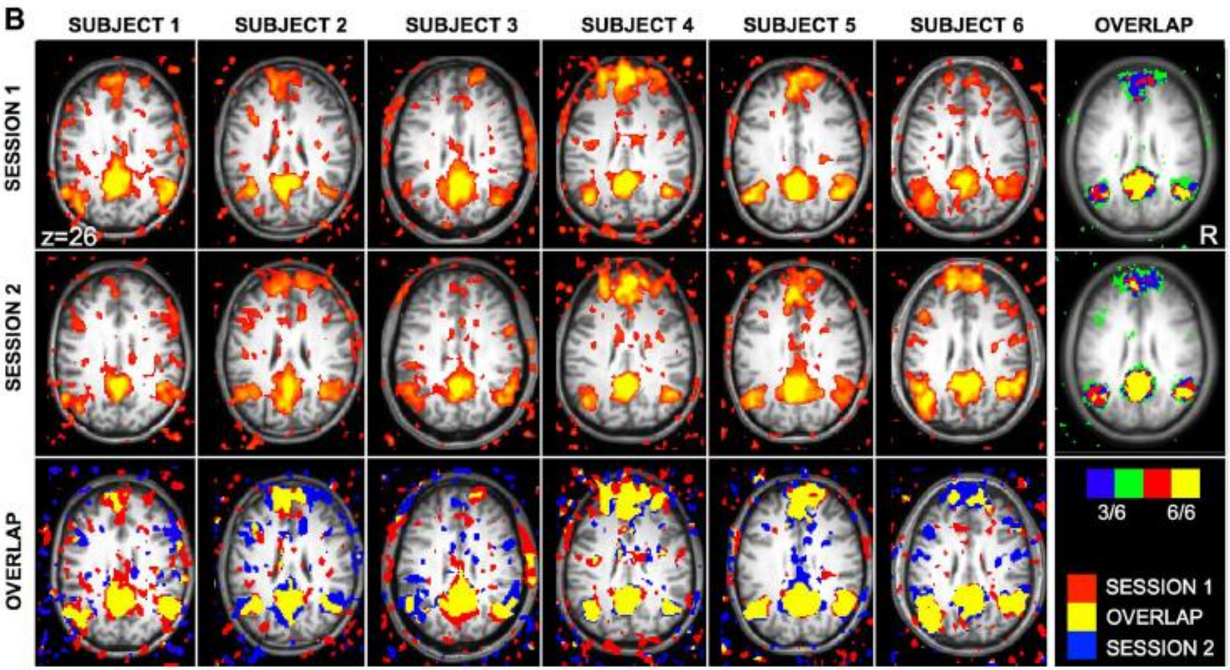
rsfMRI reliability

two sessions with a mean delay of 7.7 ± 5.5 (SD) days.



Van Dijk, 2010, *J Neurophysiol*

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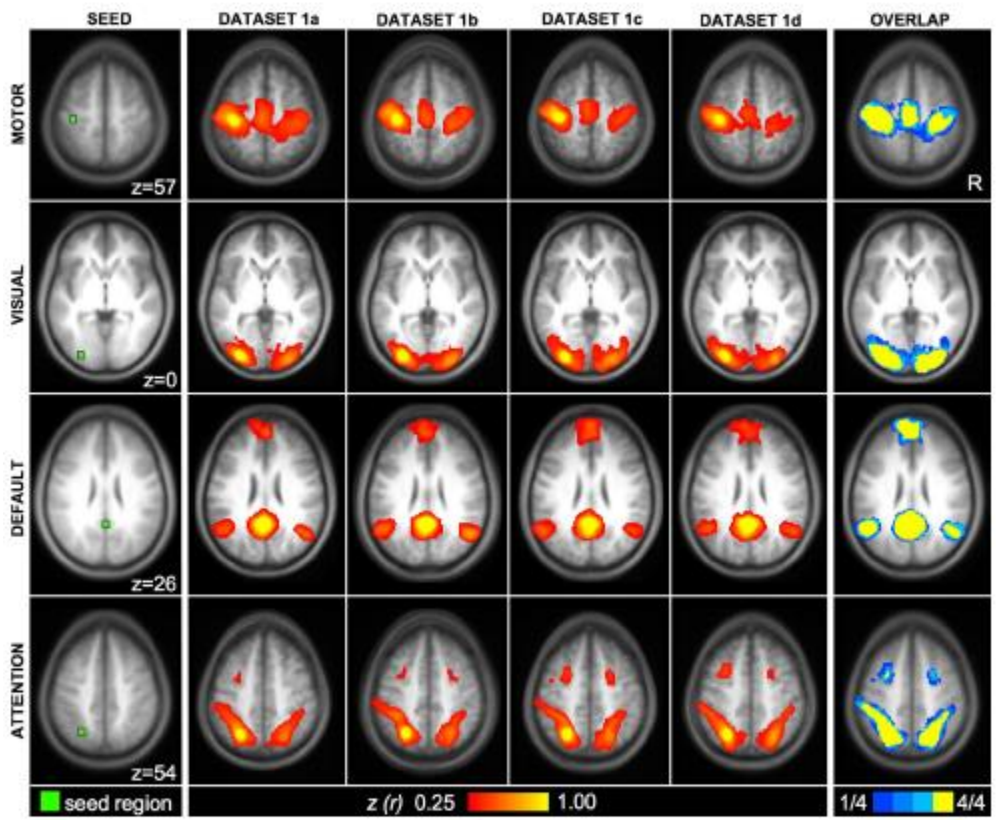
rsfMRI stability

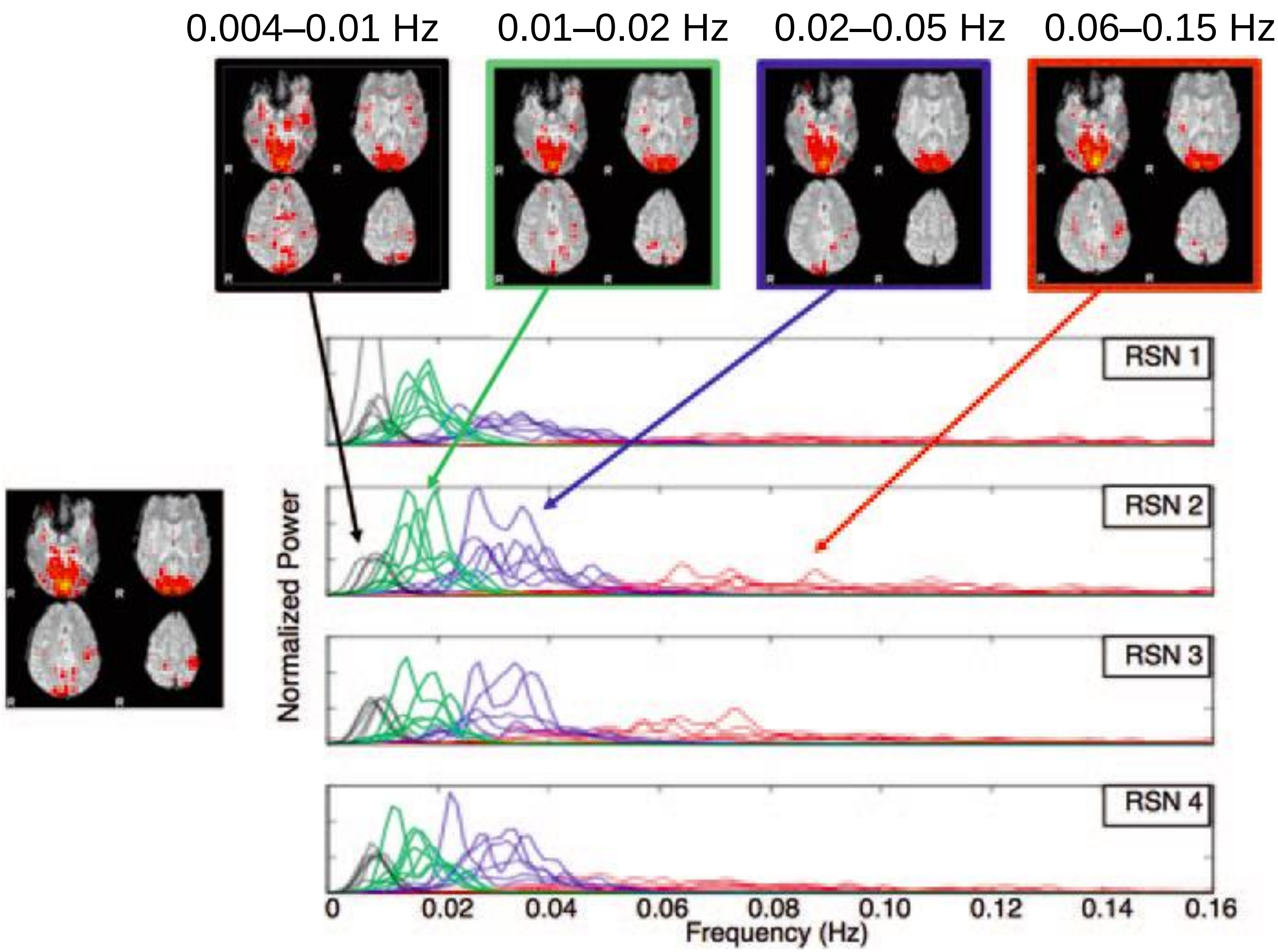
Dataset 1:

- N=48; 6 min fixation, TR: 2.5s, 3x3x3mm
- The 48 subjects from a dataset were divided into four independent groups of 12 subjects



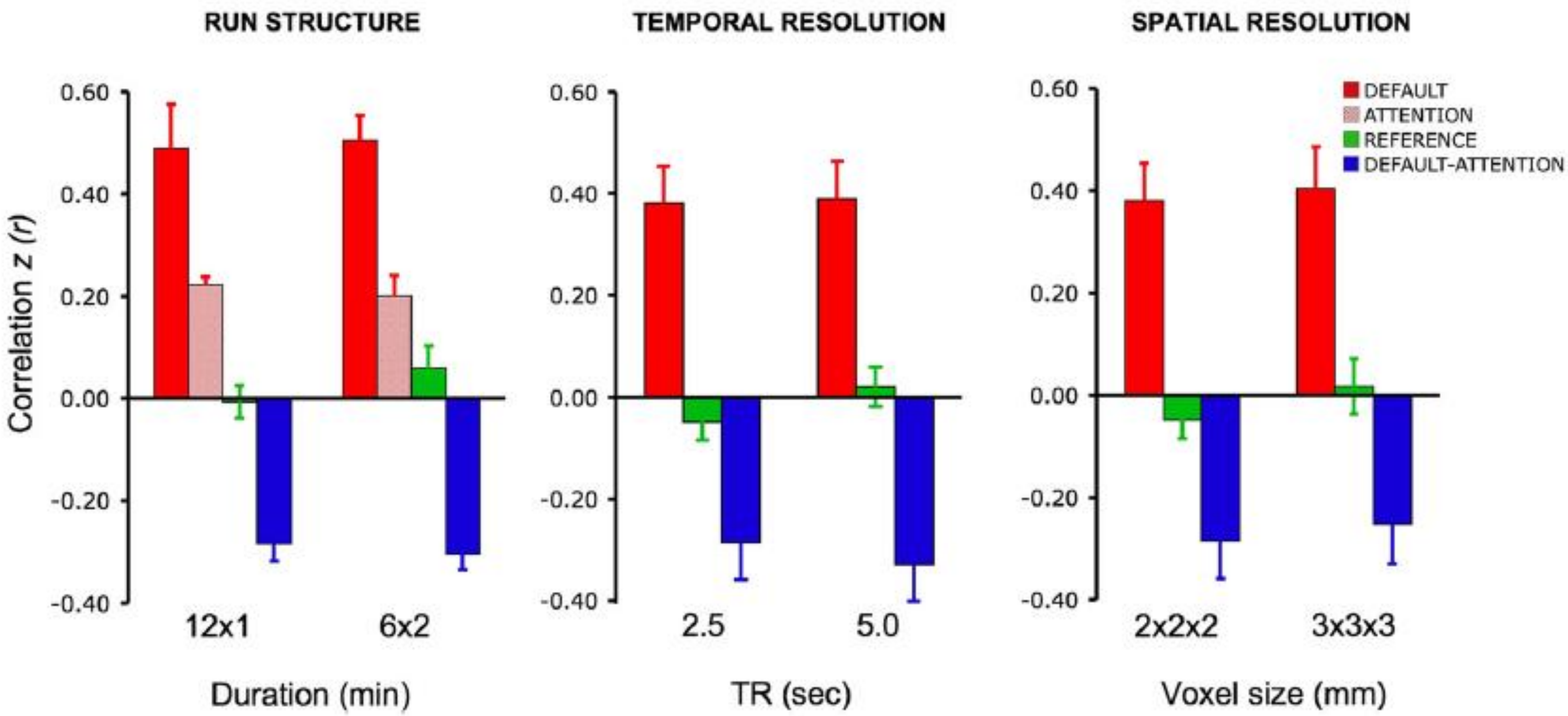
Functional connectivity networks are reliable across independent subject groups

Temporal characteristics



RSNs reproduced using ICA in different frequency bands of the power spectrum from the same data

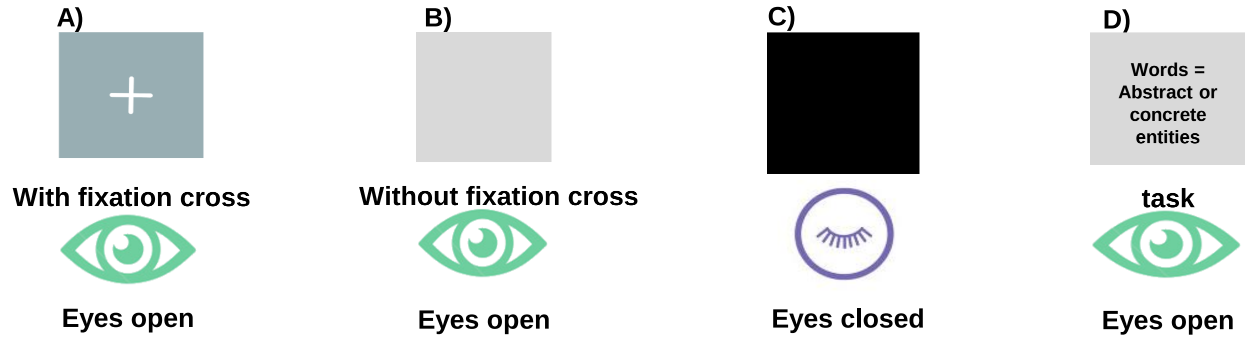
Effects of structure & resolution on rsfMRI

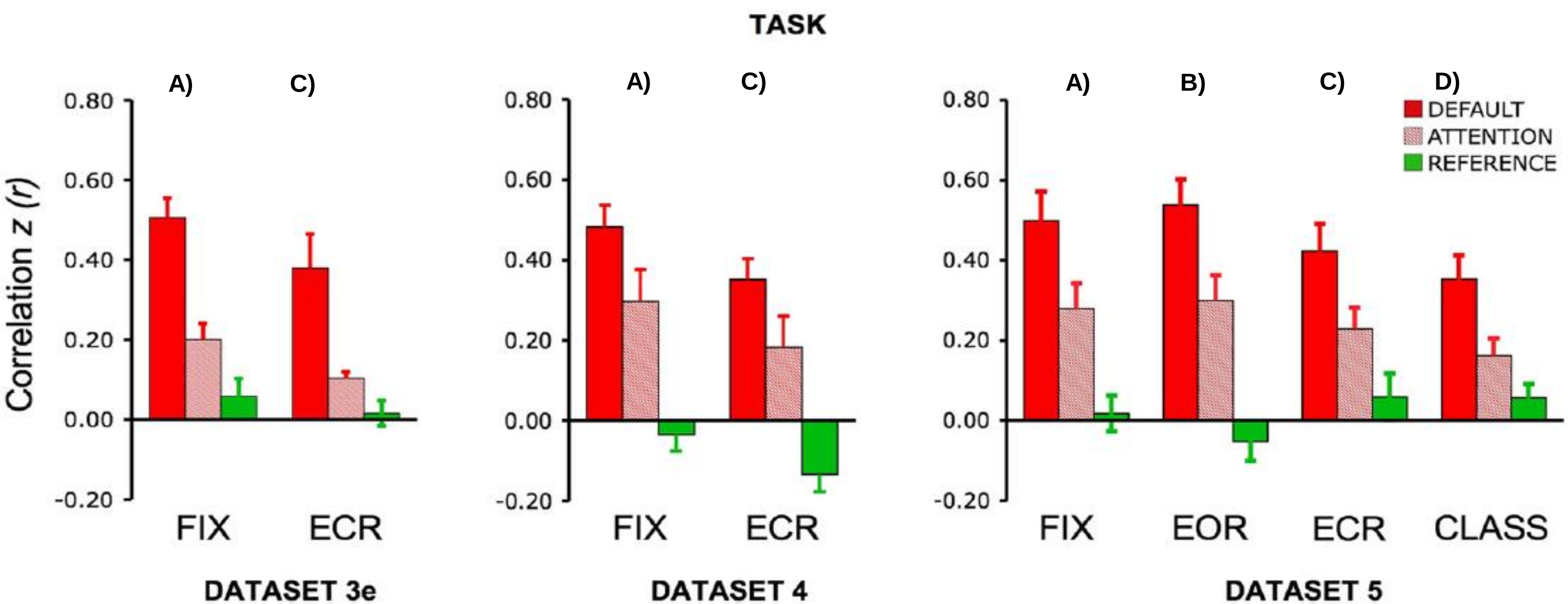


Functional connectivity strength depends minimally on run structure, temporal resolution, and spatial resolution

Van Dijk, 2010, *J Neurophysiol*

Effects of design on rsfMRI





Functional connectivity strength is influenced by task

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Van Dijk, 2010, *J Neurophysiol*

Application resting-state fcfMRI

- RSNs are reliable across subjects, sessions and replicable across independent subject groups → may be appropriate phenotypes for exploring individual and group differences

- Clinical application
  - Patients unable to perform tasks
  - rsfMRI can be collected during sleep, sedation, anaesthesia
  - Finding group differences resulting from pathologies
  - Used as biomarkers for obtaining diagnostic and prognostic information in single patients
  - Used to explore the brain's functional organization and if the brain is altered in neurological or psychiatric diseases

Questions?