

# Resting-State fMRI (rsfMRI)

## Methods & Models for fMRI Analysis 2018

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## task-fMRI

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

vs.

## rsfMRI

- 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

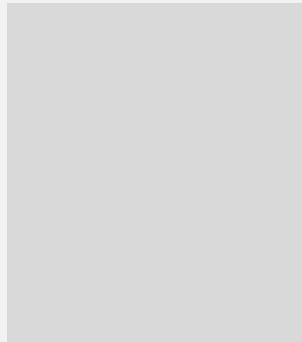
**Duration: 5-10 min**



**Eyes open**



**With fixation cross**



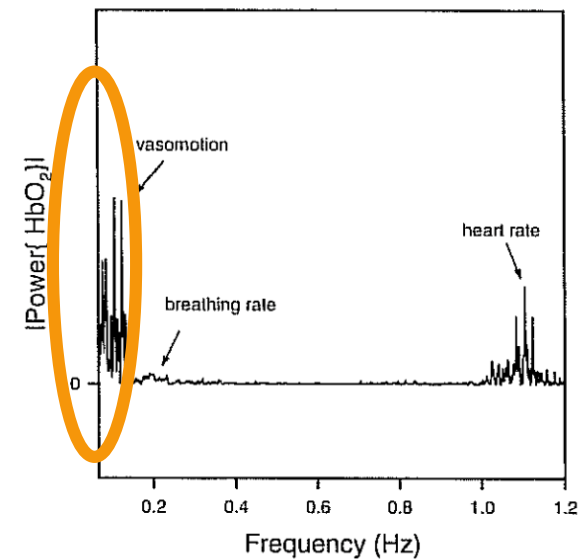
**Without fixation cross**



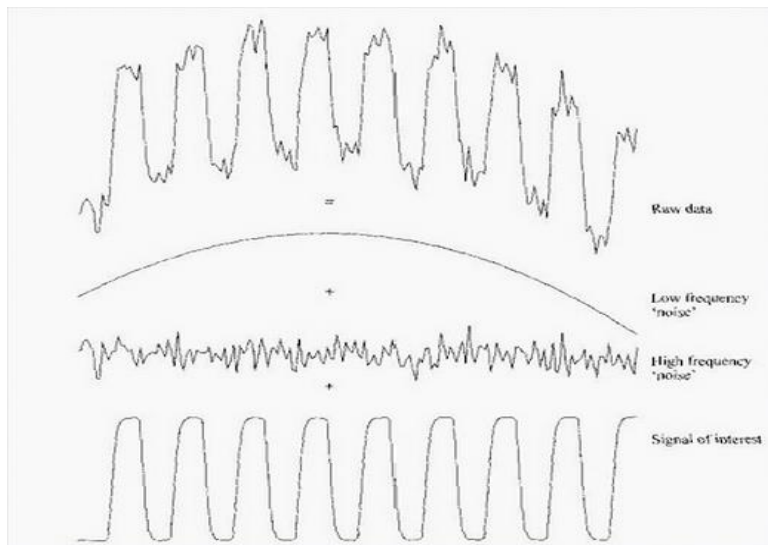
**Eyes closed**

# 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)

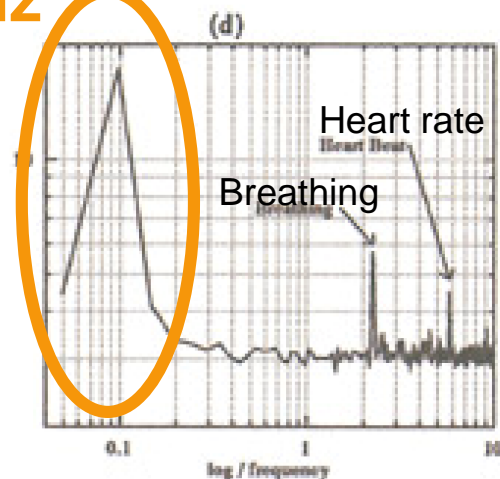


Elwell et al., 1999



Smith, 2001

< 0.1 Hz




Mayhew et al., 1996

**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>

**correlated fluctuations**



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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 → resting-state fcMRI

**functional connectivity**



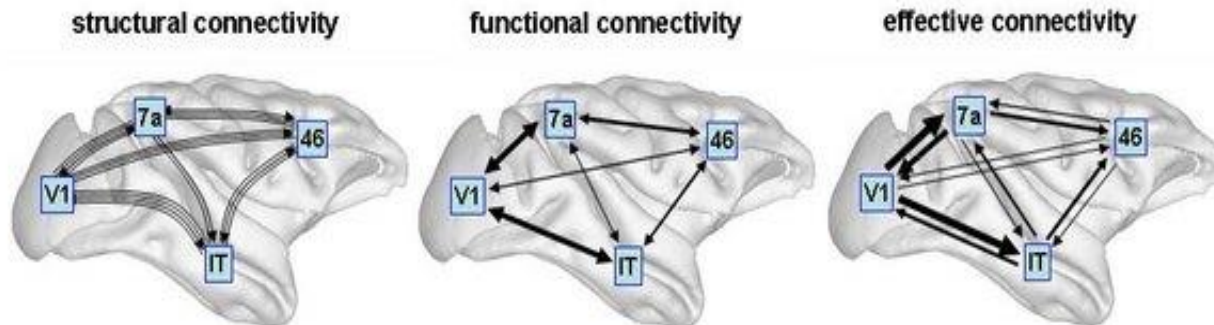
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# Structural, functional & effective connectivity

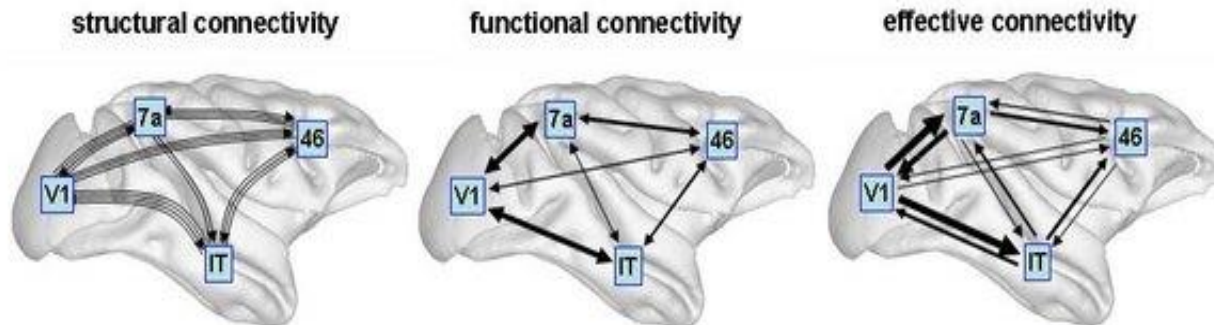


Sporns 2007, *Scholarpedia*

- **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



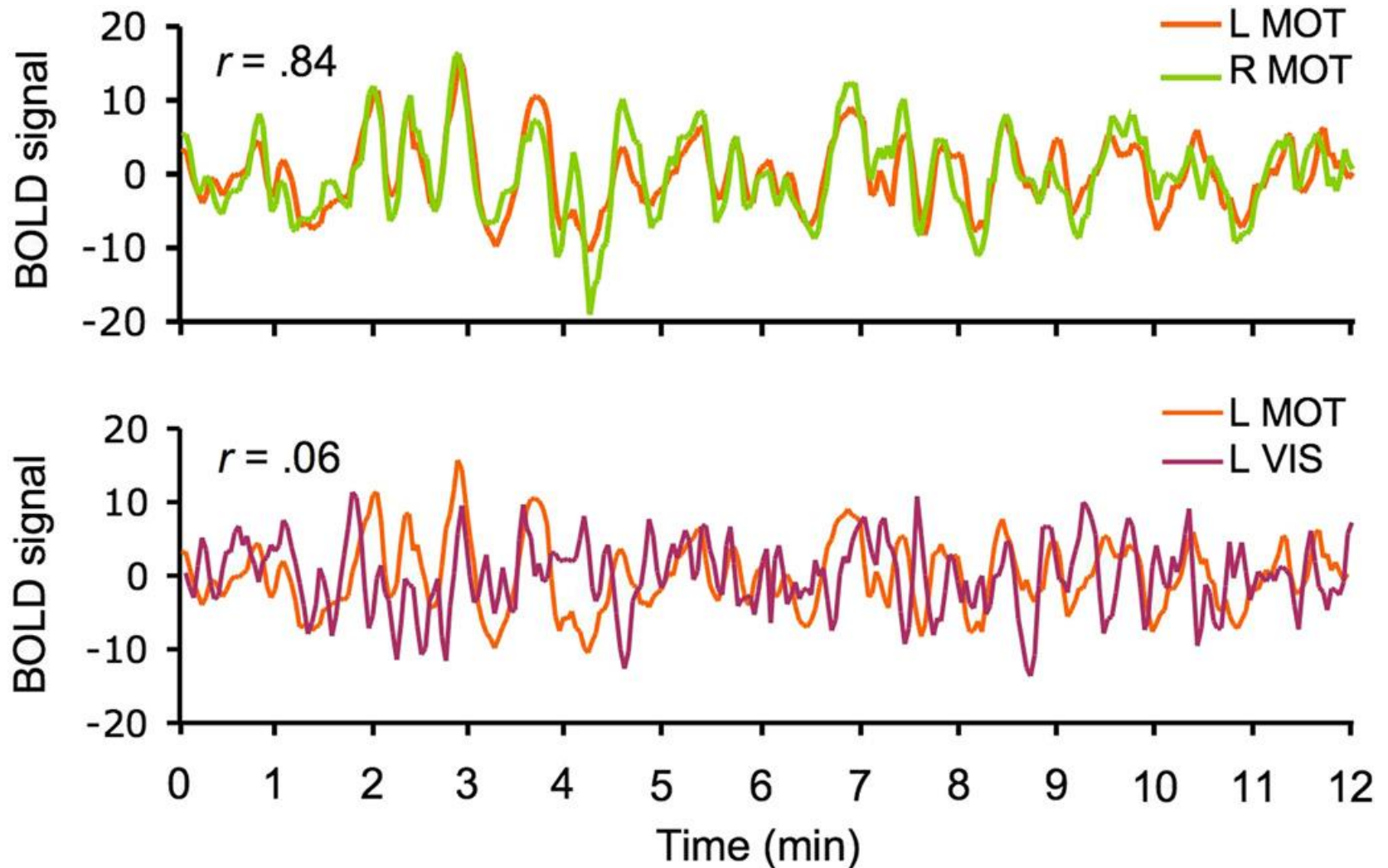
# Structural, functional & effective connectivity



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

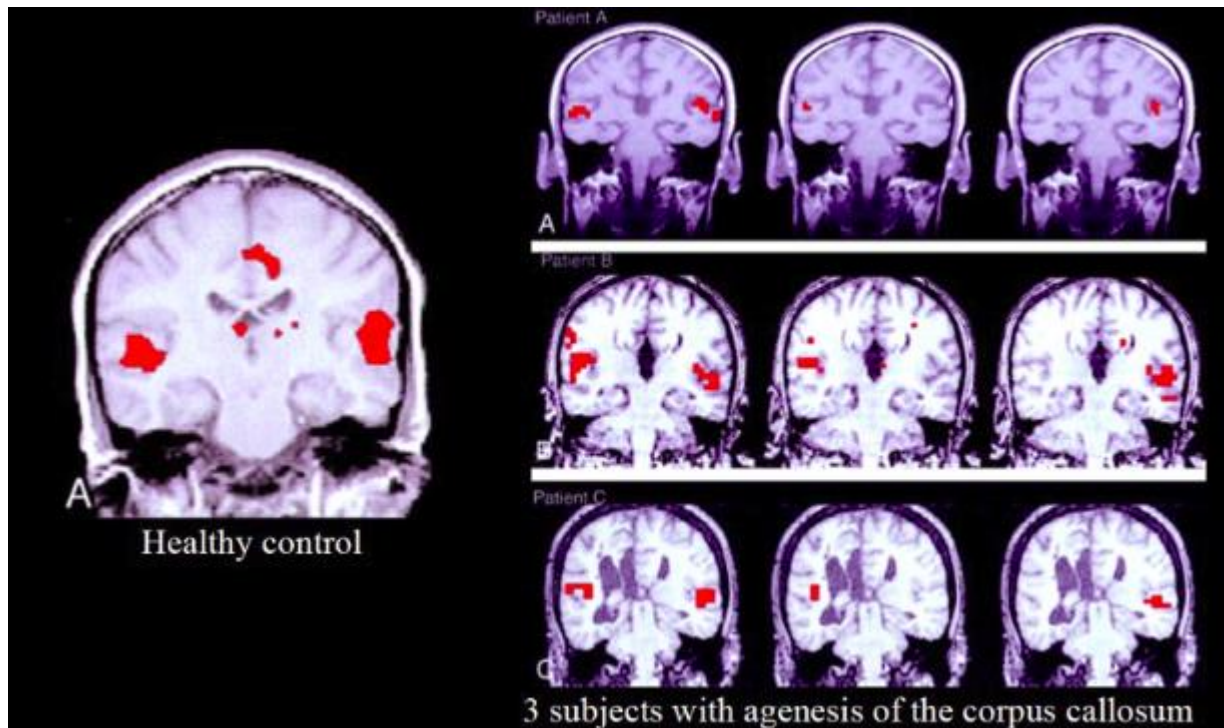
# Spontaneous BOLD activity



Van Dijk et al., 2009

# Functional connectivity = anatomical connectivity ?

Healthy control:  
seed voxel from  
the right auditory  
cortex



Patients:

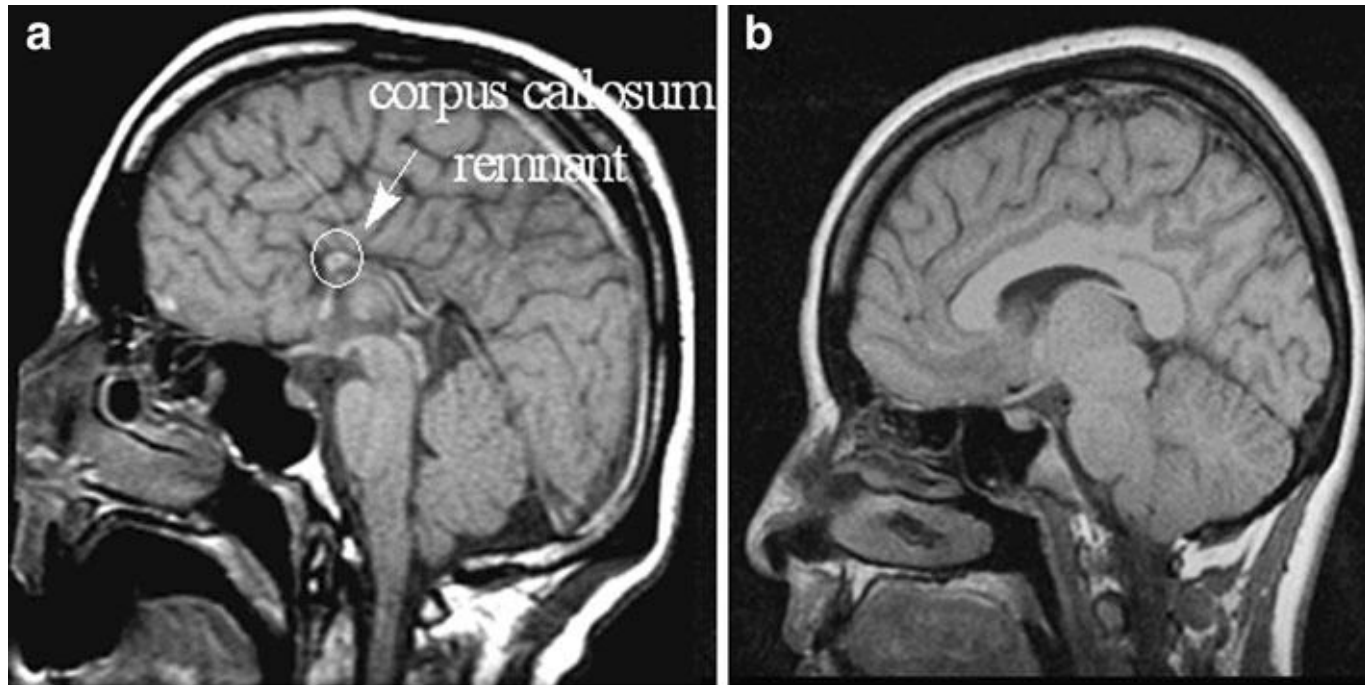
**Left:** activation data from the auditory cortex during a text-listening task.

**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

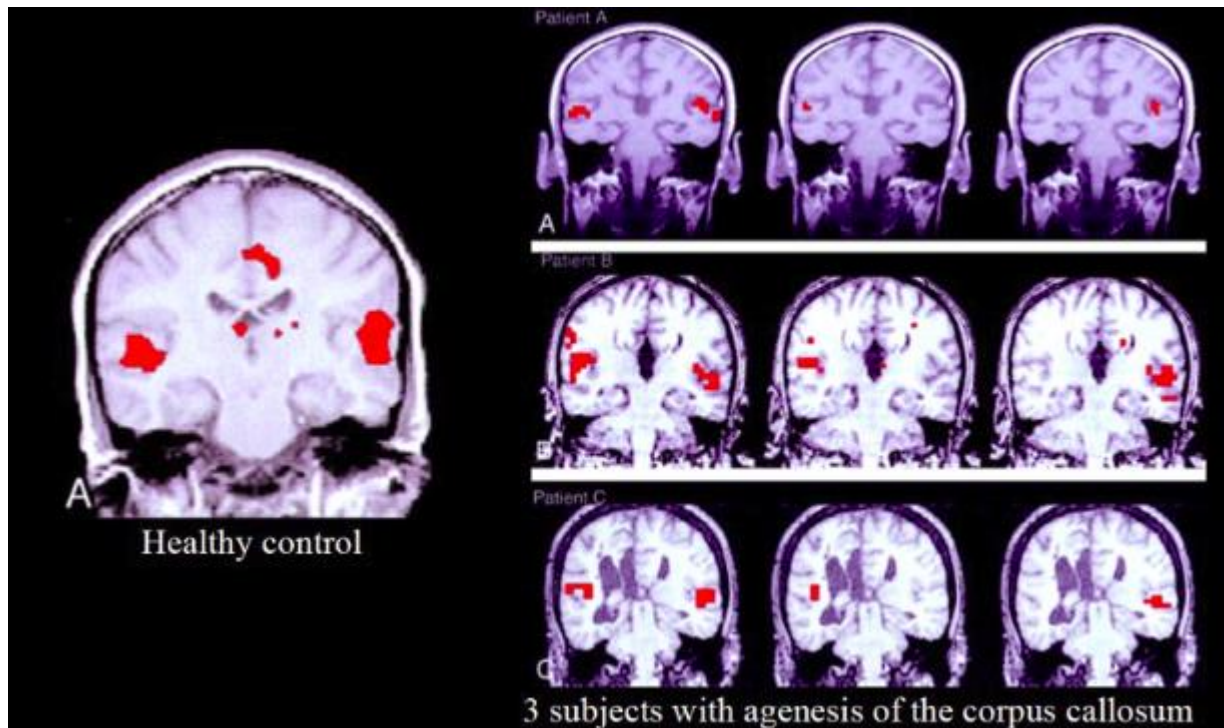


Lowe (2010), *Magn Reson Mater Phy*



# Functional connectivity = anatomical connectivity ?

Healthy control:  
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Patients:

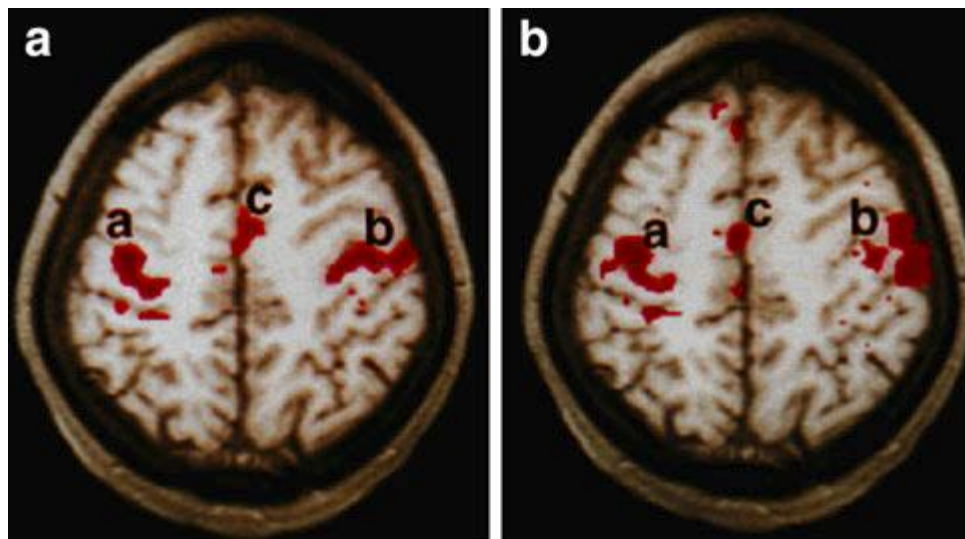
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# Early studies - fMRI



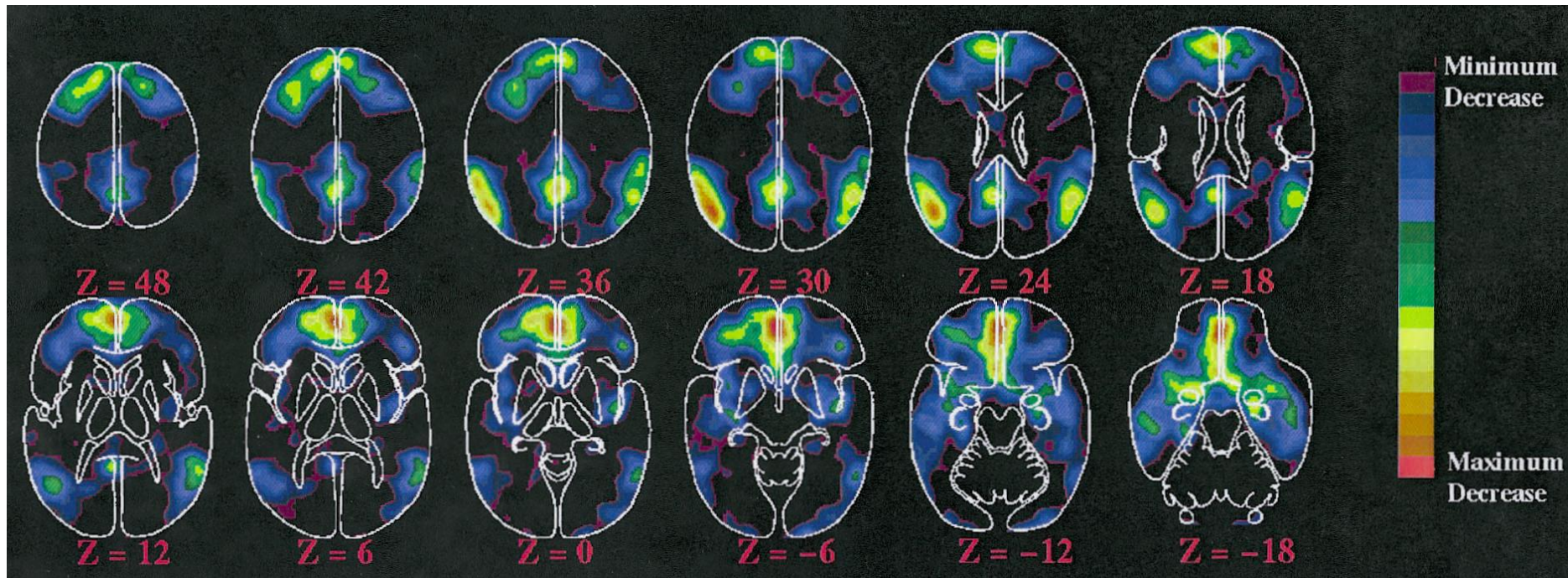
a) fMRI task-activation response to bilateral finger movement

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*



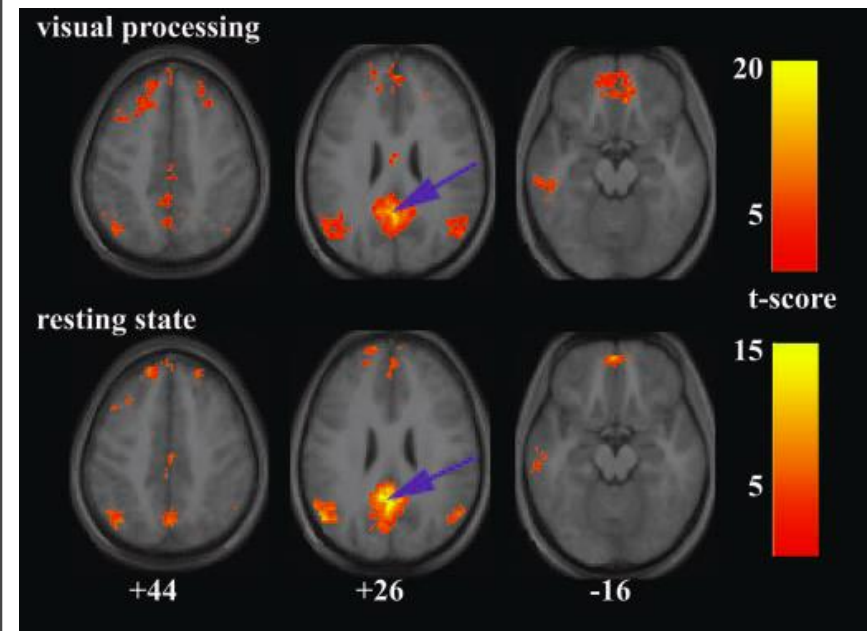
# Early studies - fMRI

## 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]

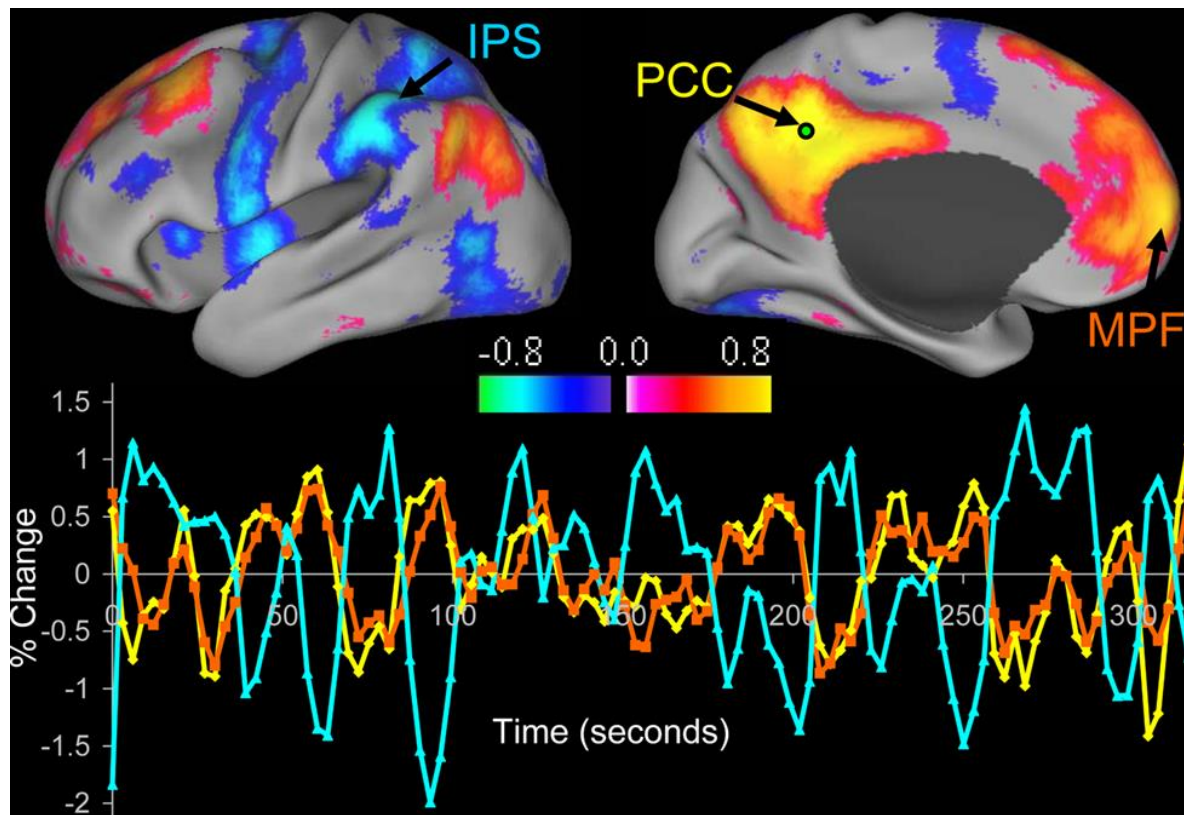


Greicius et al. (2003), *PNAS*



# 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*

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

*Niazy et al., 2015*

# 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)

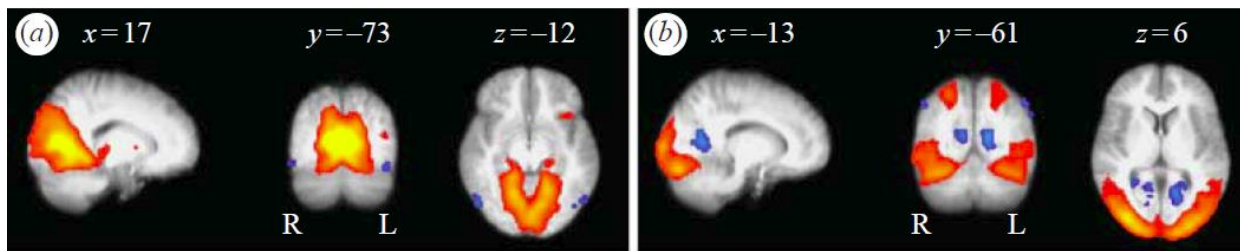
- Temporal

- 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)

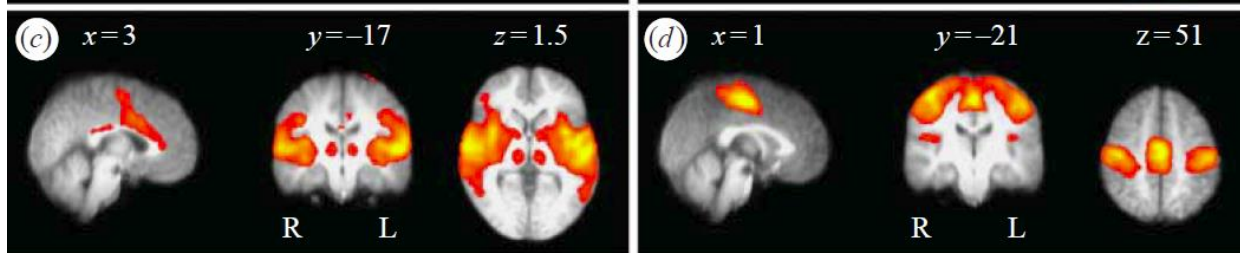
# Spatial characteristics - Networks

## RSNs

a) & b) Visual

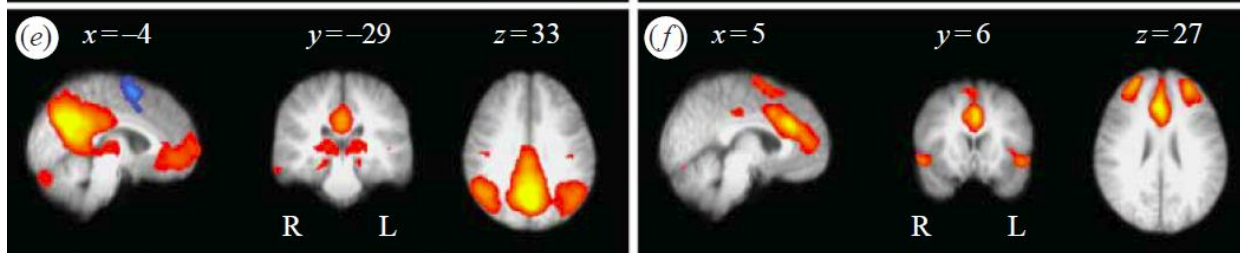


c) Sensory



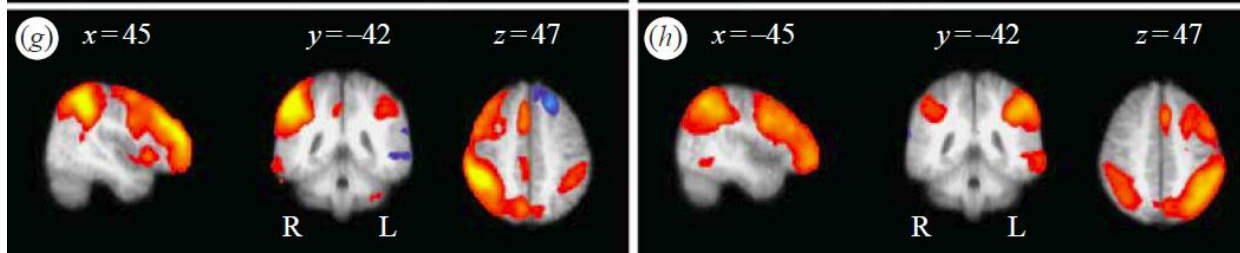
d) Motor

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*

# What is so interesting about 'rest'?

- Usefulness?

- Not a measure of structural connectivity
- Not a measure of effective connectivity

- Interpretability?

- Confounds

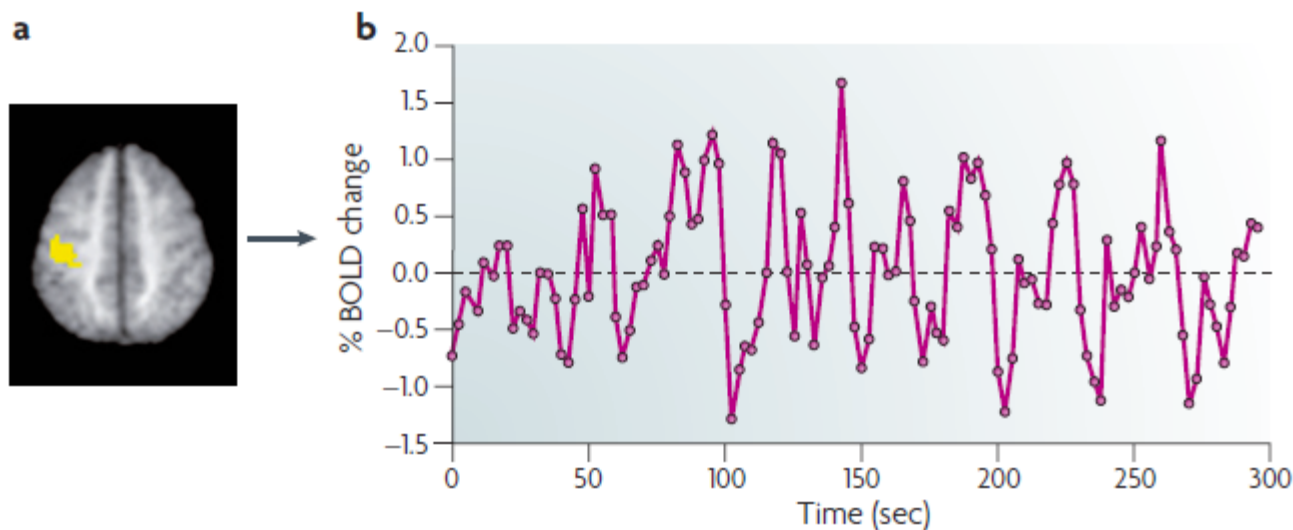
- RSNs reflect artifacts, i.e. cardiac and respiratory effects (Krüger and Glover, 2001, Birn et al., 2006)
- vascular processes (unrelated to neuronal function) (Wise et al., 2004)
- participants might fall asleep, be planning what to do next, or might be thinking about the previous task ...

- 
- 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)

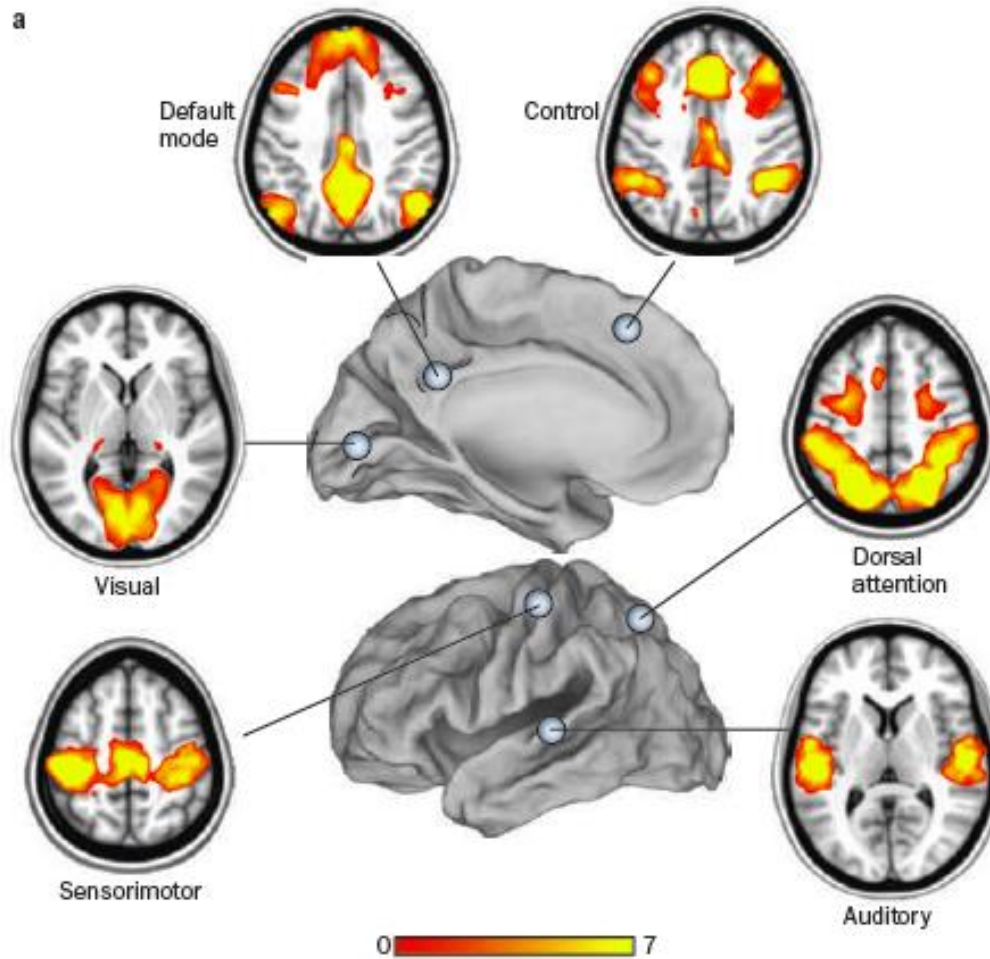
- Model-based
  - Seed based correlation analysis
- Model-free
  - Decomposition
    - Independent component analysis (ICA), principal component analysis (PCA)
  - Clustering
    - Fuzzy clustering analysis (FCA), hierarchical clustering analysis (HCA)

# 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



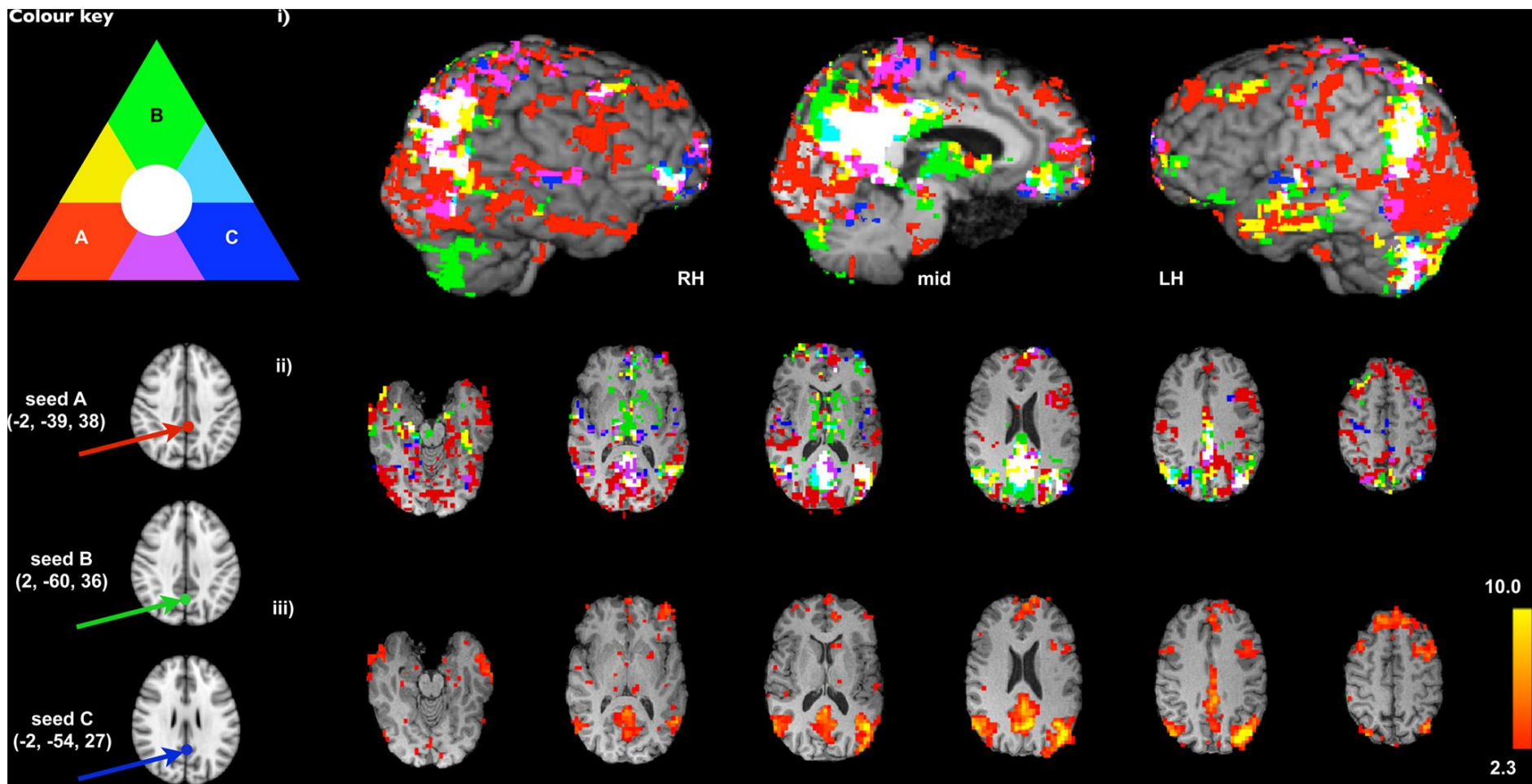




Zhang & Raichle, 2010, *Nature Reviews, Neurology*



# DMN versions using 3 different seed voxels



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

# 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

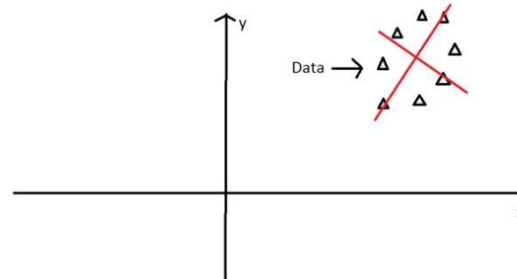
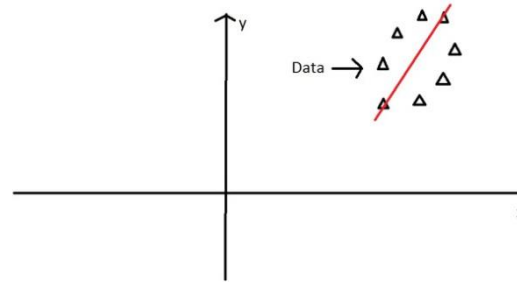
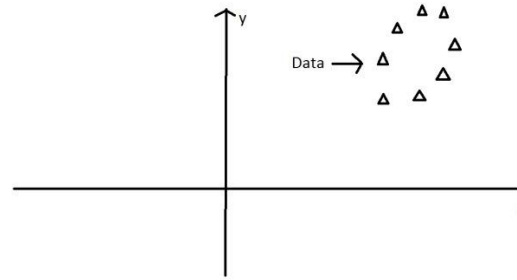
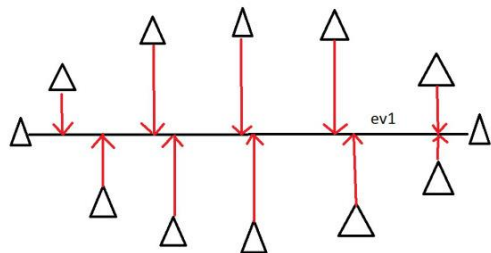
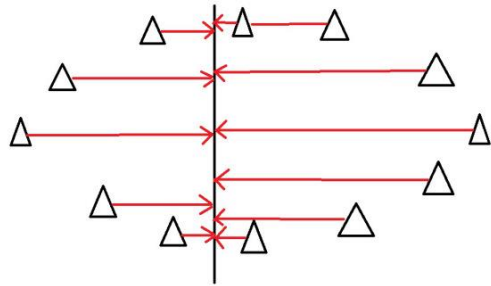
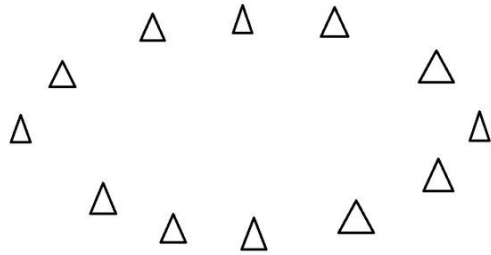
- Decomposition
  - Independent component analysis (ICA), principal component analysis (PCA)
    - multivariate-approach
- The signal in fMRI data is composed out of different sources of variability:
  - machine artefacts
  - physiological pulsation
  - head motion and
  - Spontaneous fluctuations in 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

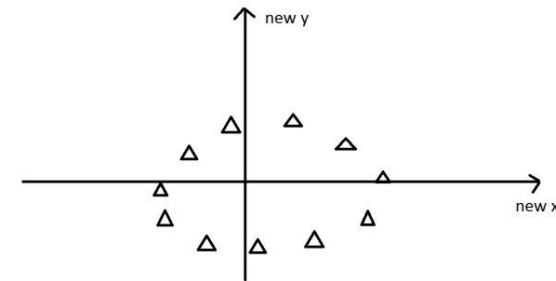
# PCA example

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*

# SVD: an example using simulated data

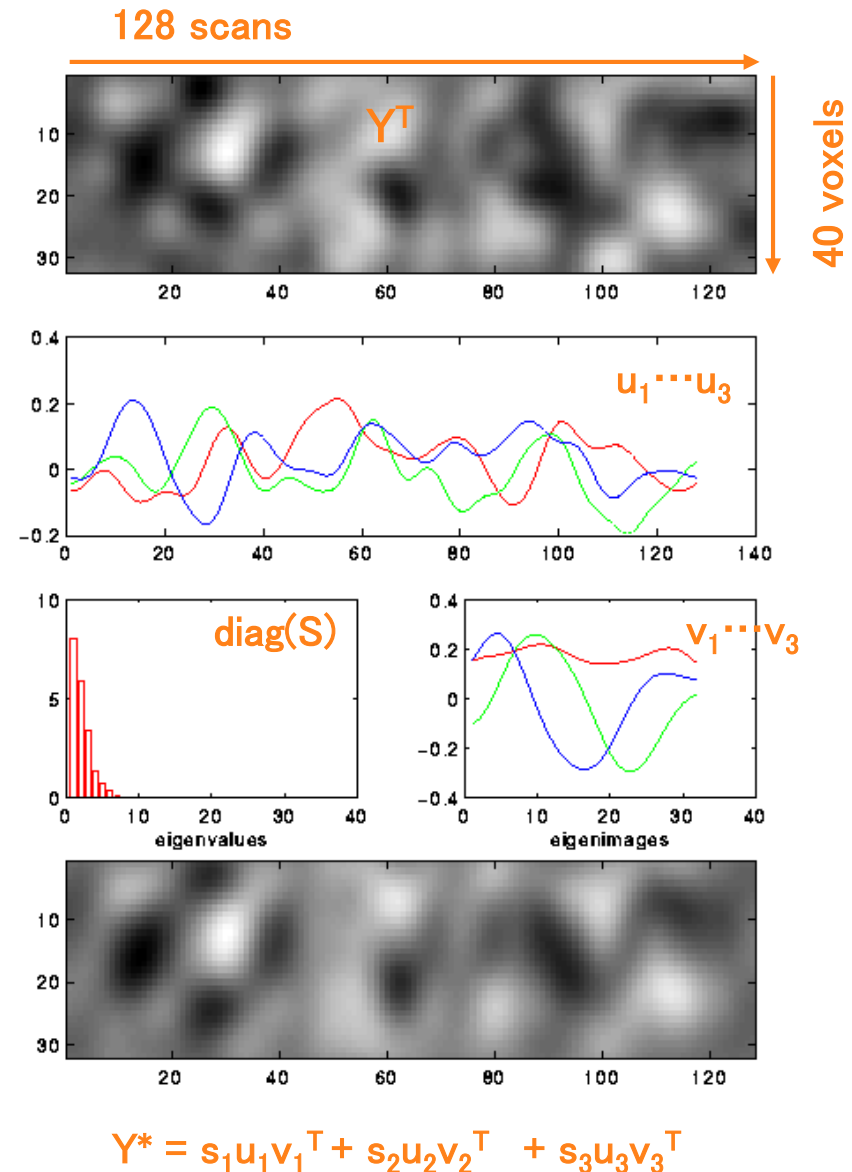
A time-series of 1D images:  
128 scans of 40 “voxels”

(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

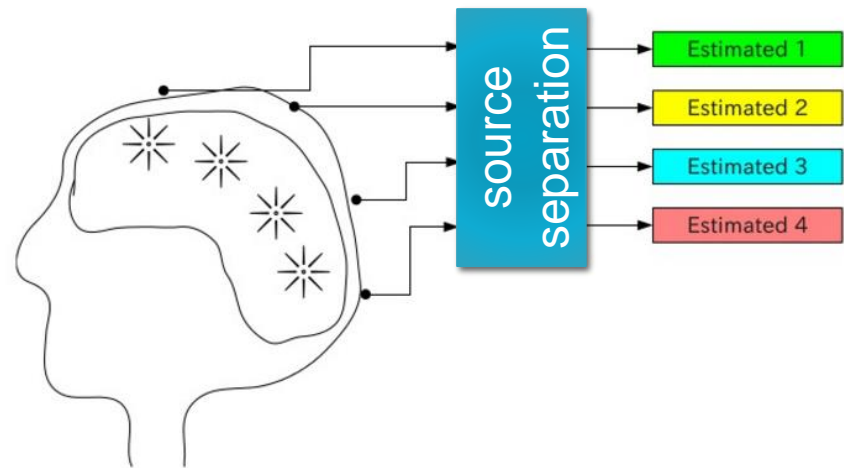
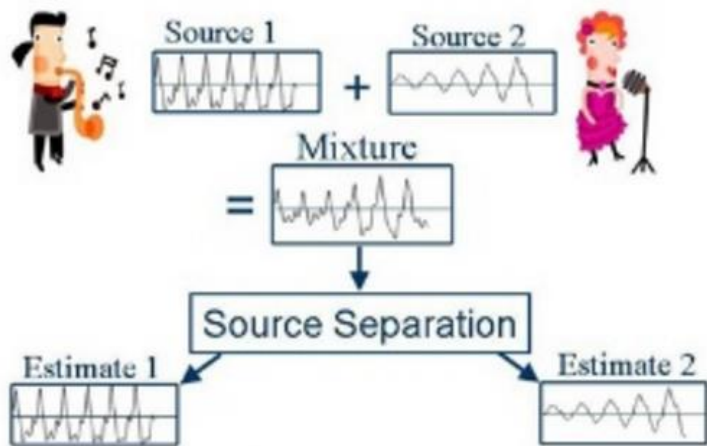


# Independent Component Analysis (ICA)

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





$$X = AS$$

$X$ : measured data

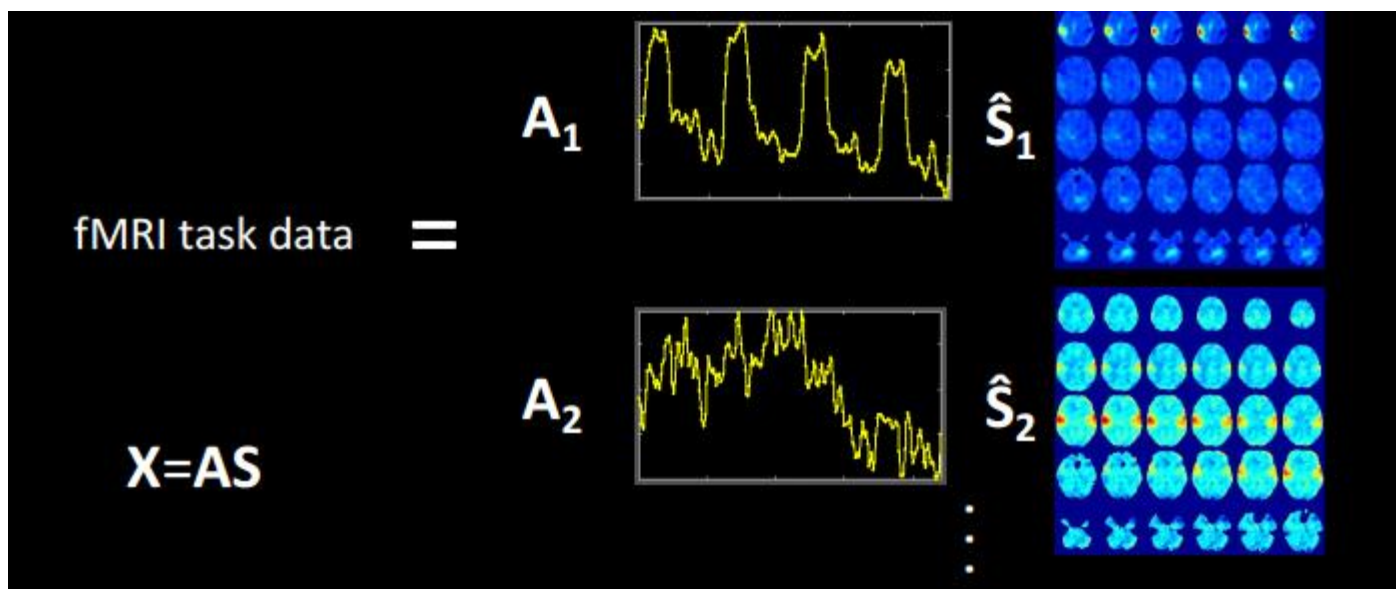
$A$ : mixing matrix

$S$ : 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 activations 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 orthogonal 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)

- 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

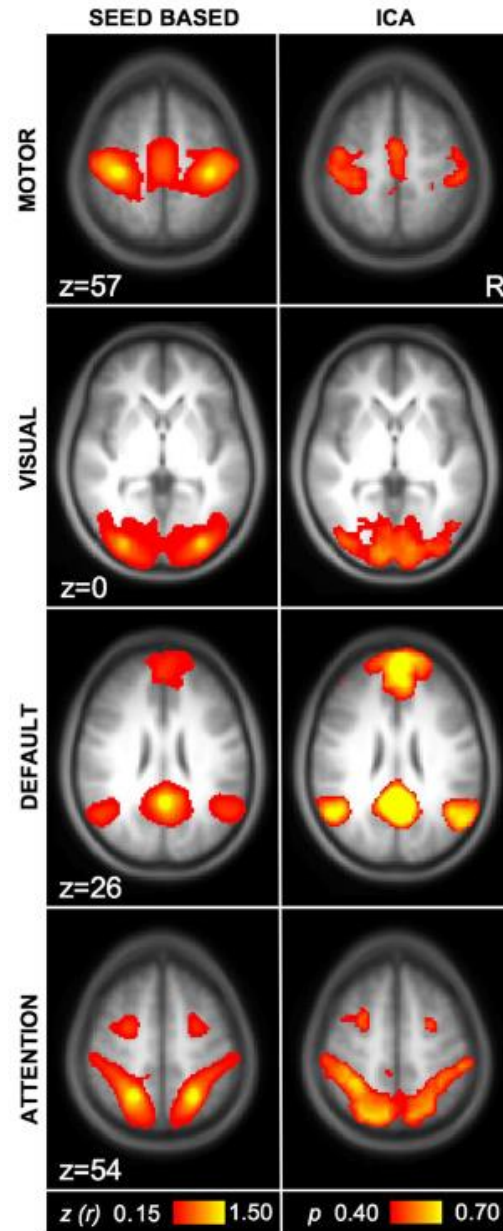
- Advantage:

- 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)

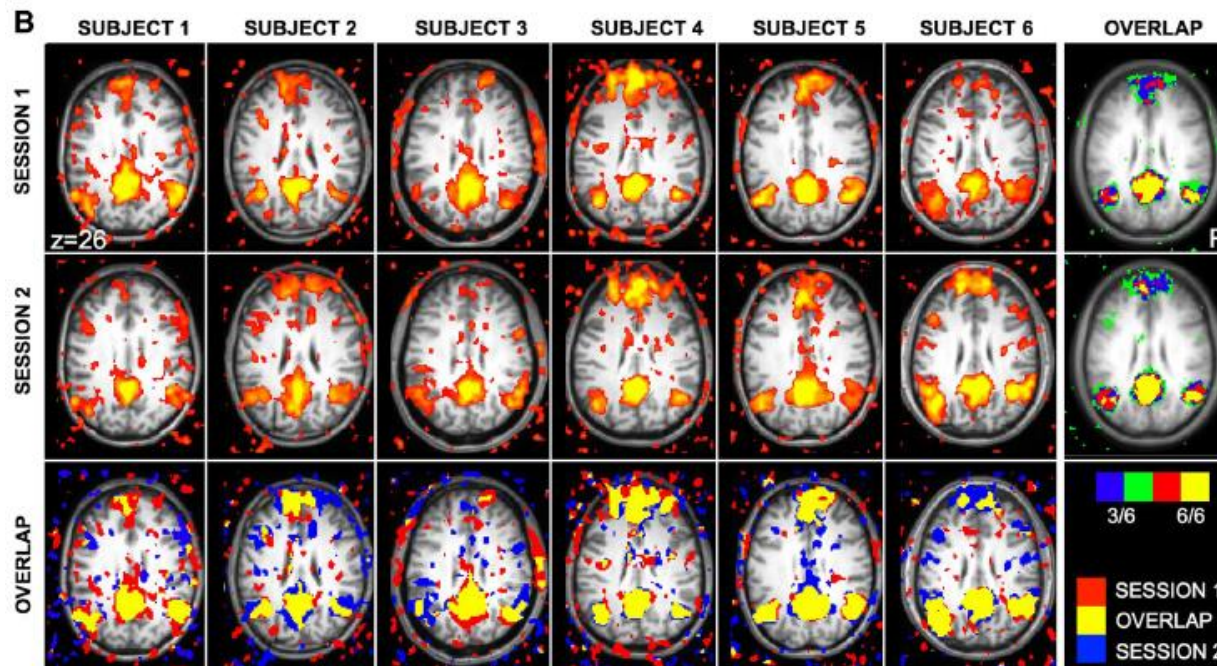
- Weakness:

- 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



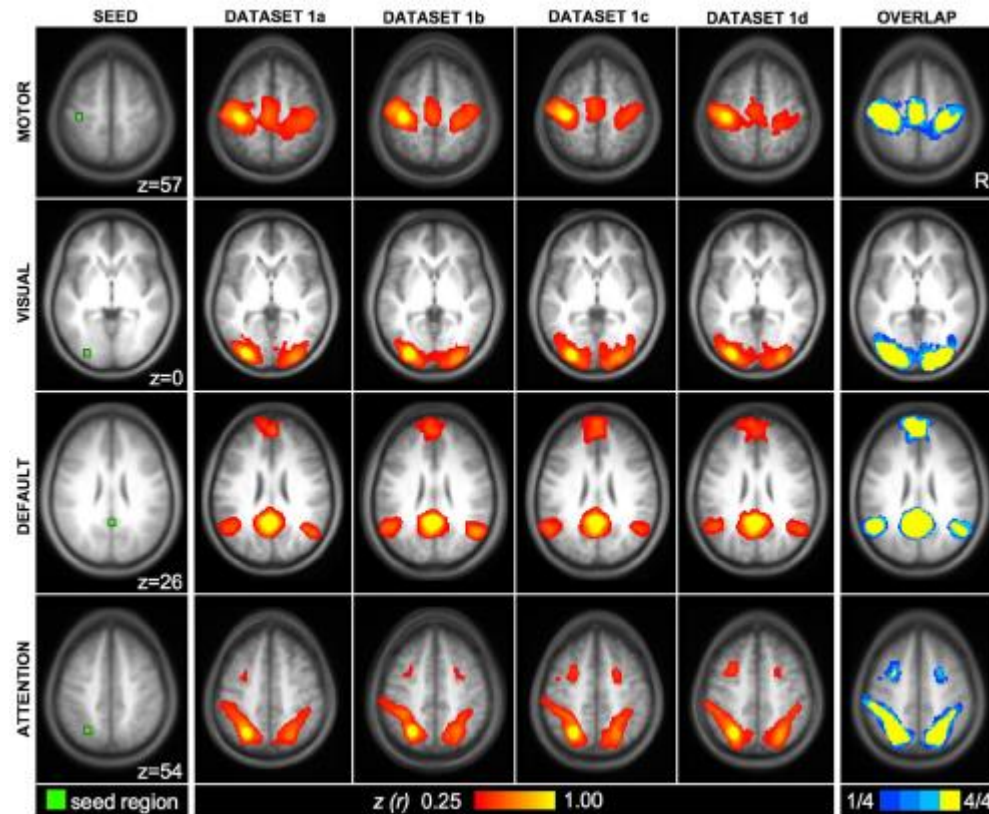
two sessions with a mean delay of  $7.7 \pm 5.5$  (SD) days.





## Dataset 1:

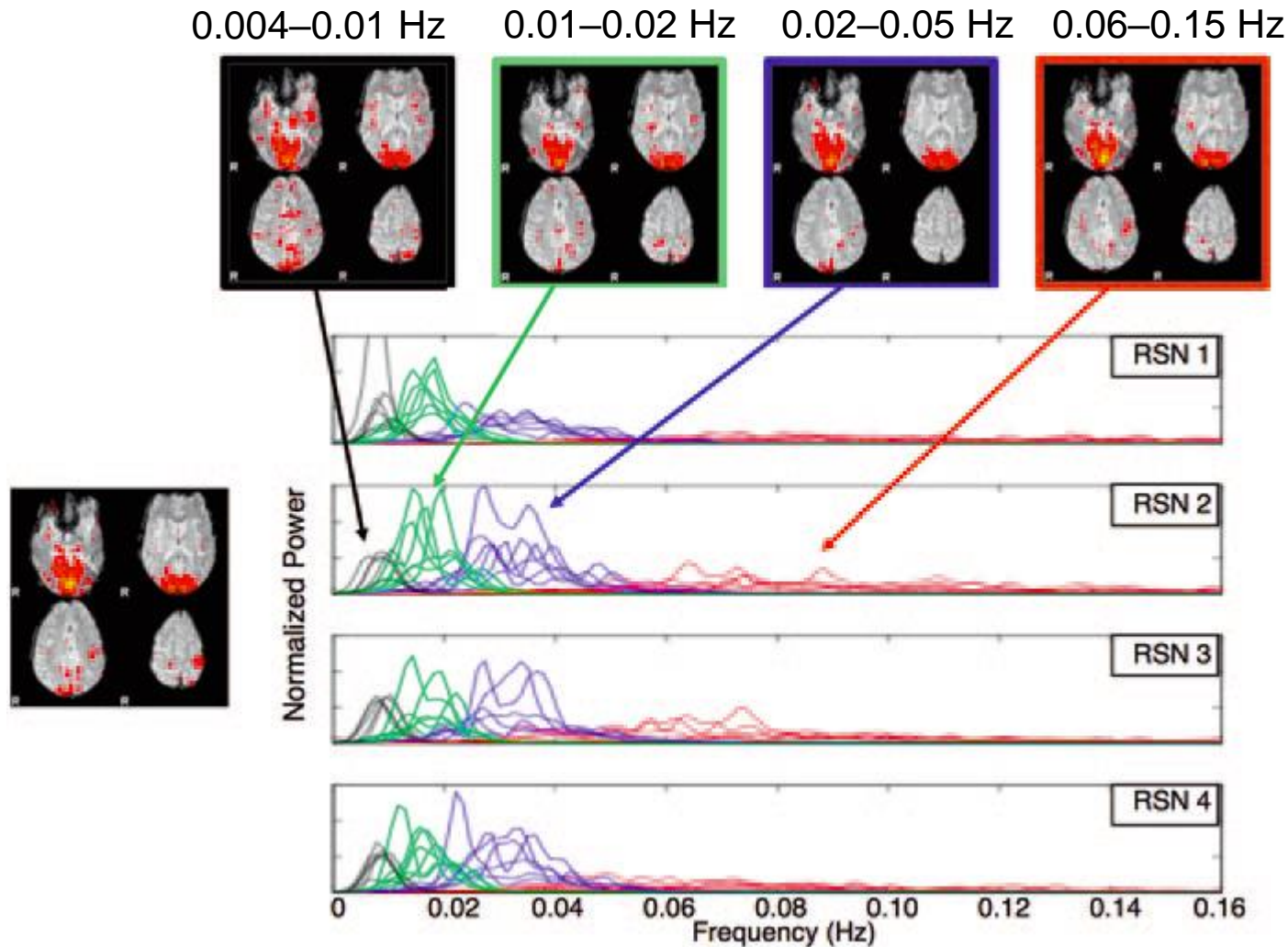
- N=48; 6 min fixation, TR: 2.5s, 3x3x3mm
- The 48 subjects from a dataset were divided into four independent groups of 12 subjects



*Functional connectivity networks are reliable across independent subject groups*

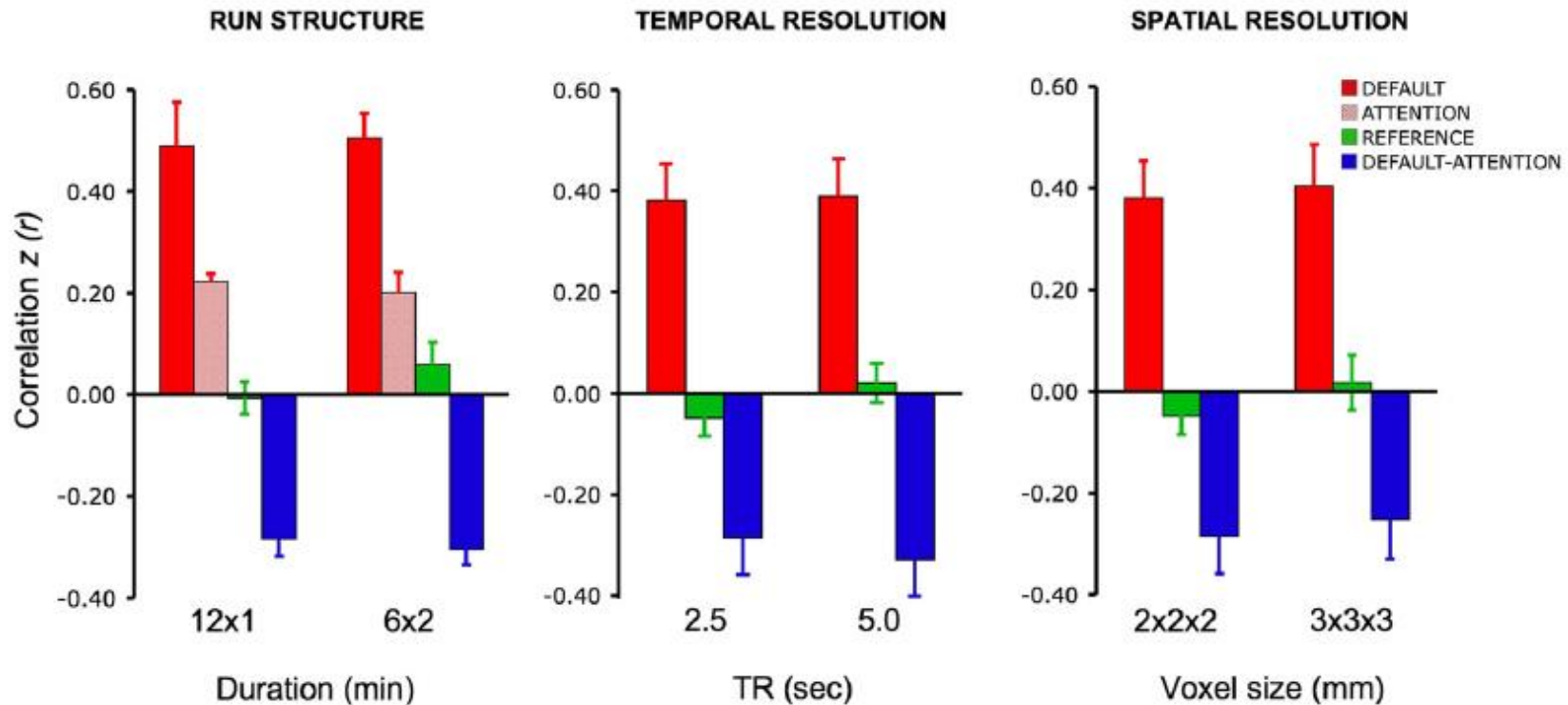


# Temporal characteristics



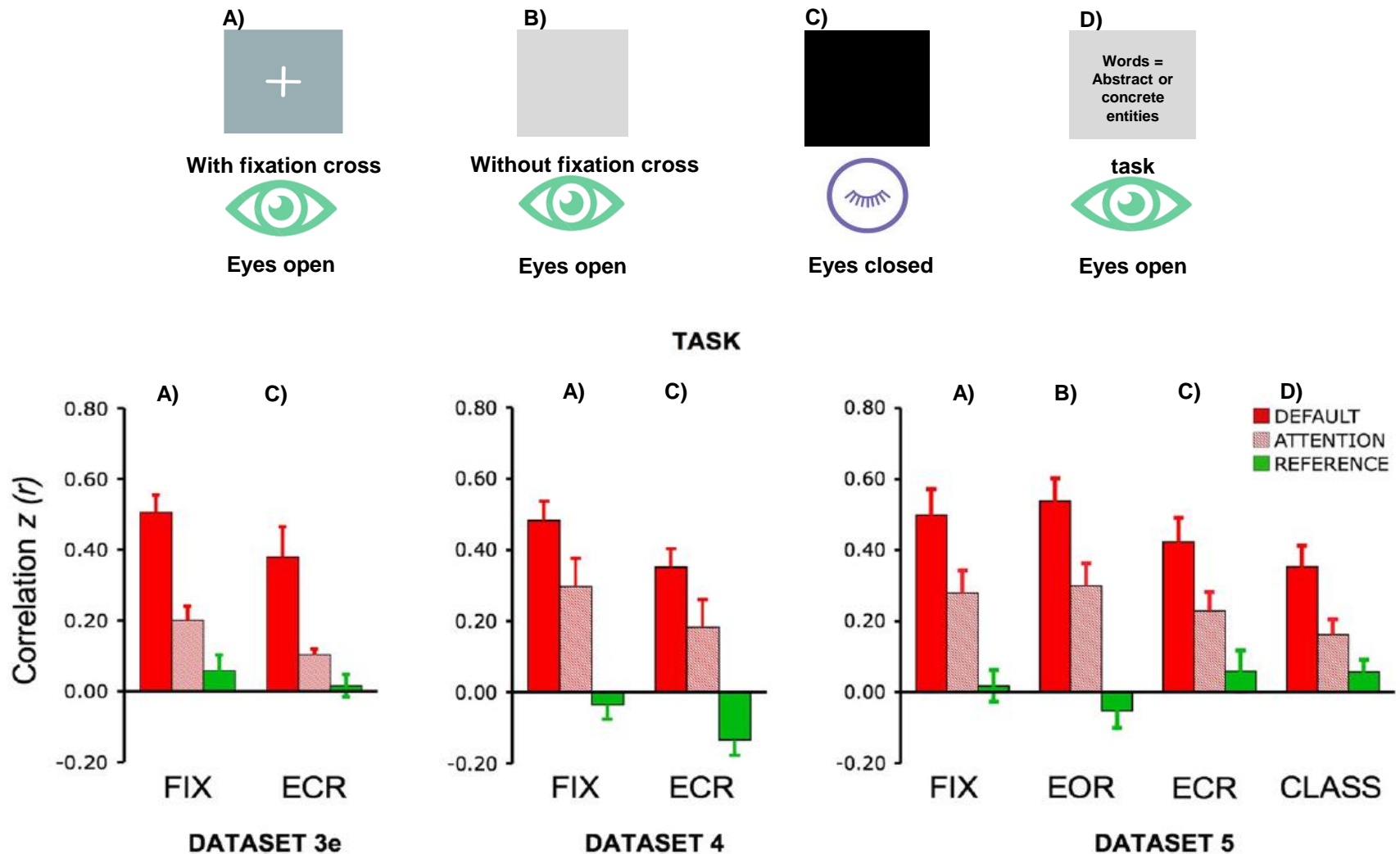
RSNs reproduced using ICA in different frequency bands of the power spectrum from the same data

# Effects of structure & resolution on rsfMRI



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

# Effects of design on rsfMRI



*Functional connectivity strength is influenced by task*

# Application resting-state fMRI

- 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?

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