Resting state fMRI (rsfMRI)

Methods & Models for fMRI Analysis 2019

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

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

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

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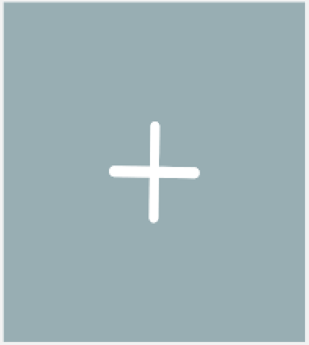
Resting state Acquisition

Duration: 5-10 min

Eyes open



With fixation cross

Without fixation cross

Eyes closed

Planning a resting state study

- Optimal data acquisition?
  - design?
  - phiysiological recordings?
  - sequence?
  - instructions?
- Optimal preprocessing pipeline?
- Optimal noise correction pipeline?
  - Movement
  - Physiological noise

Methods - GLM

$$Y \quad = \quad \beta \quad X \quad + \quad \varepsilon$$

fMRI time series = weighted sum of explanatory variables plus reiduals

BOLD data t.b.d *design* *errors/noise*

(pre-processed)

Task-based fMRI:

Data = Noise + Activation + Error

Resting-state fMRI:

Data = Noise + ~~Activation~~ + Error

no design!

Data = Noise *Model* + Signal + Error *Residuals*

not part of this lecture

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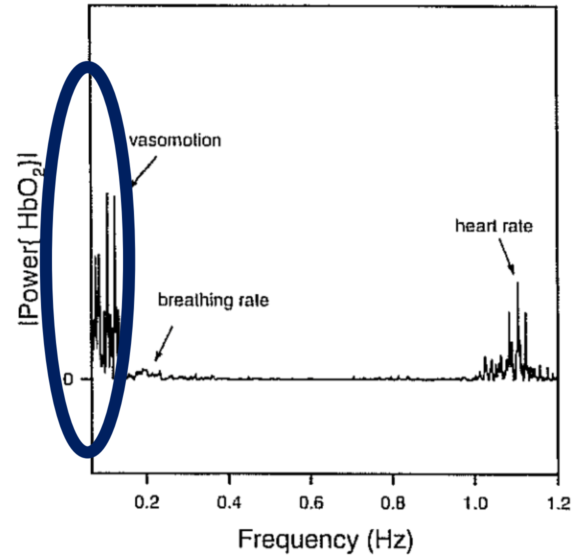
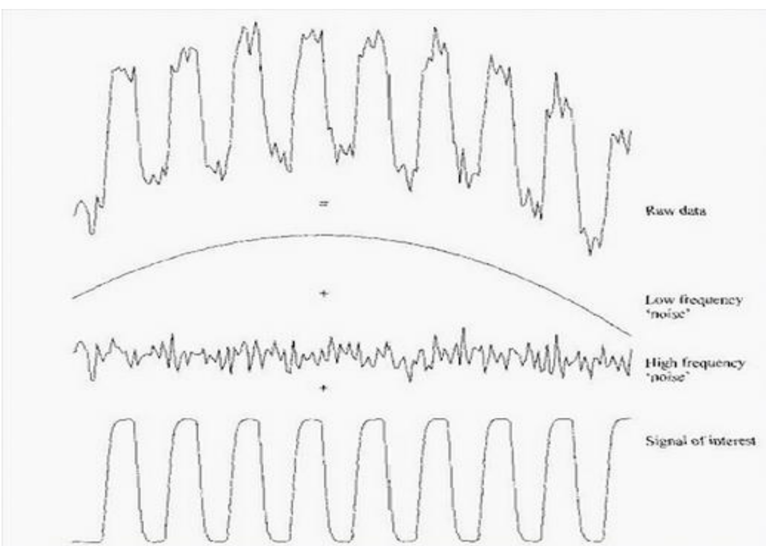
Spontaneous BOLD activity

- 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)

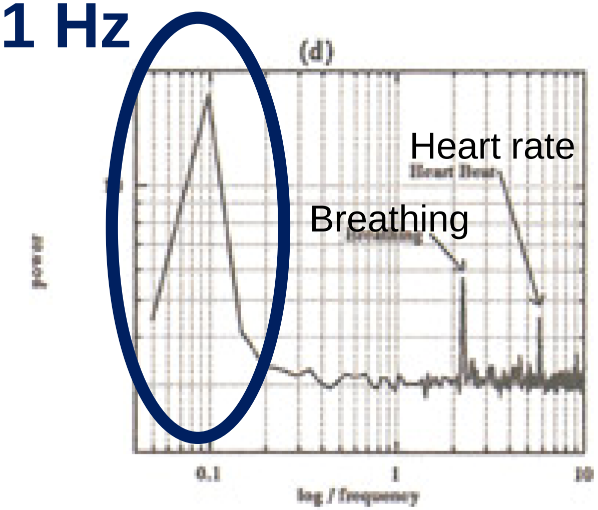


Elwell et al., 1999



Smith, 2001

< 0.1 Hz



Mayhew et al., 1996

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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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rsfMRI or R-fMRI → resting-state fcMRI

functional connectivity

correlated fluctuations

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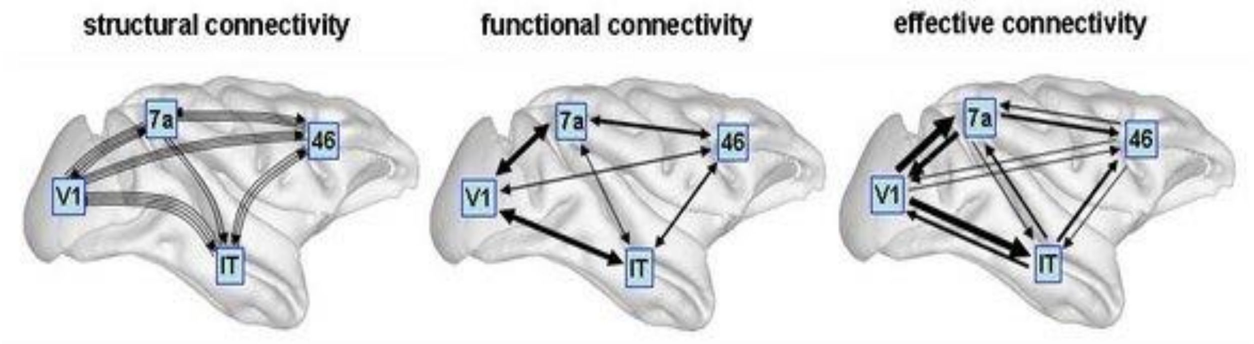
Structural, functional & effective connectivity



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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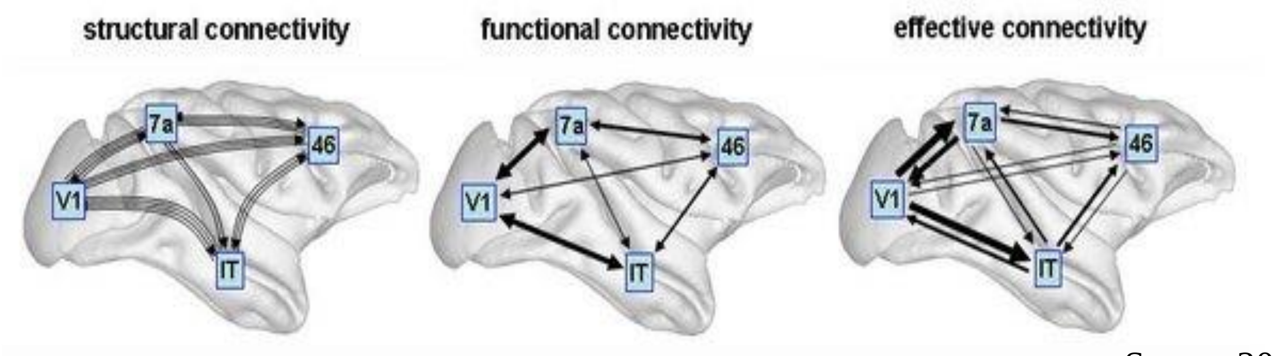
Structural, functional & effective connectivity



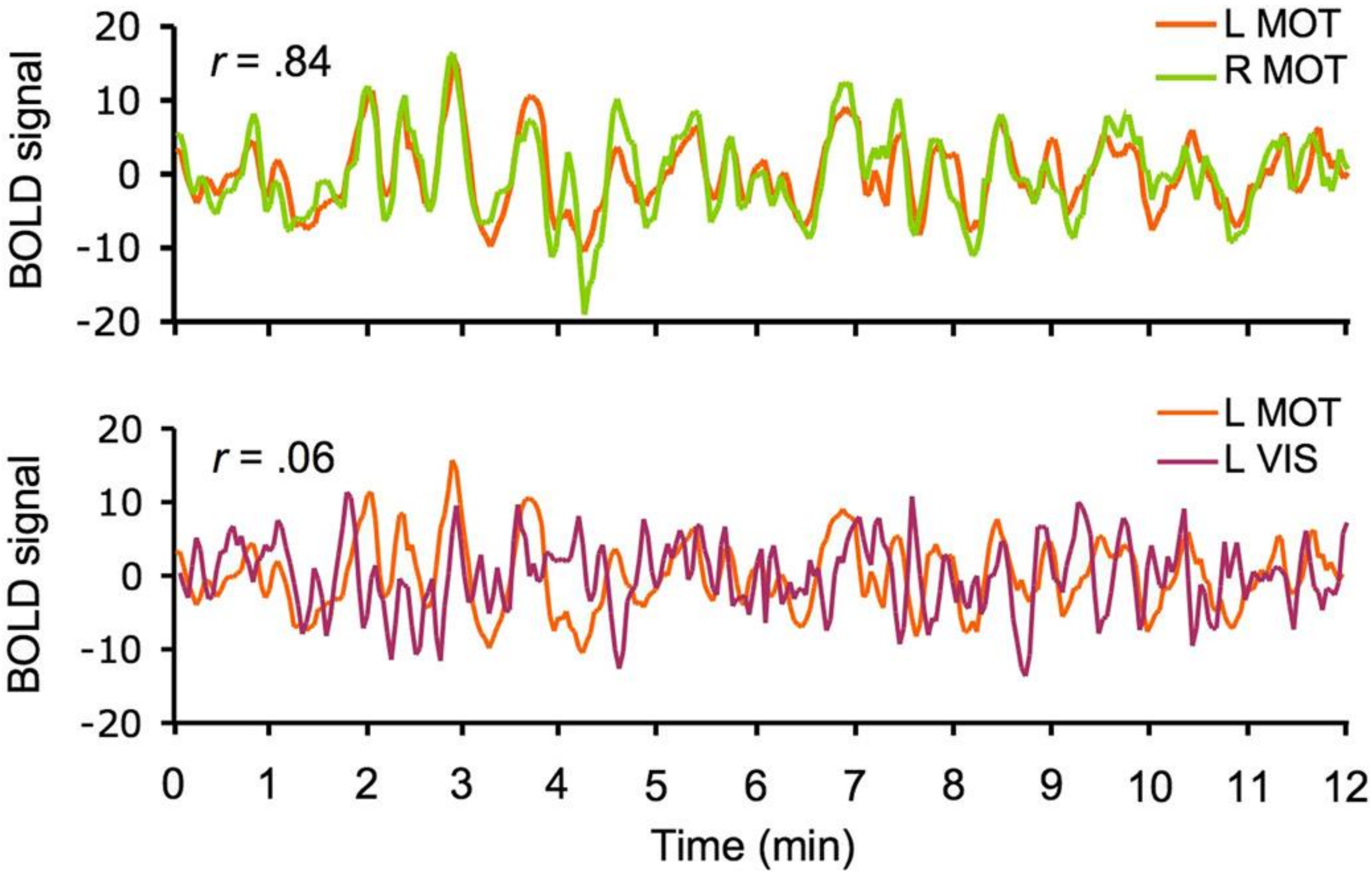
Sporns 2007, *Scholarpedia*

- **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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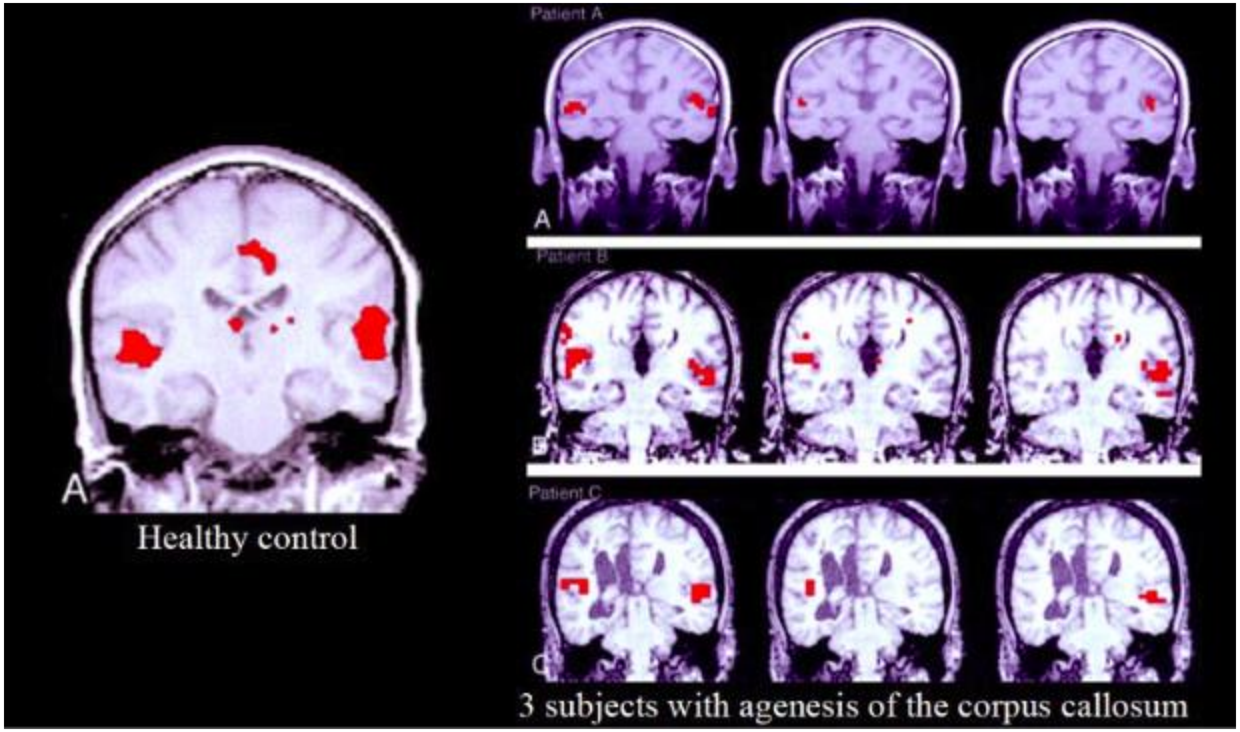
Functional connectivity = anatomical connectivity?

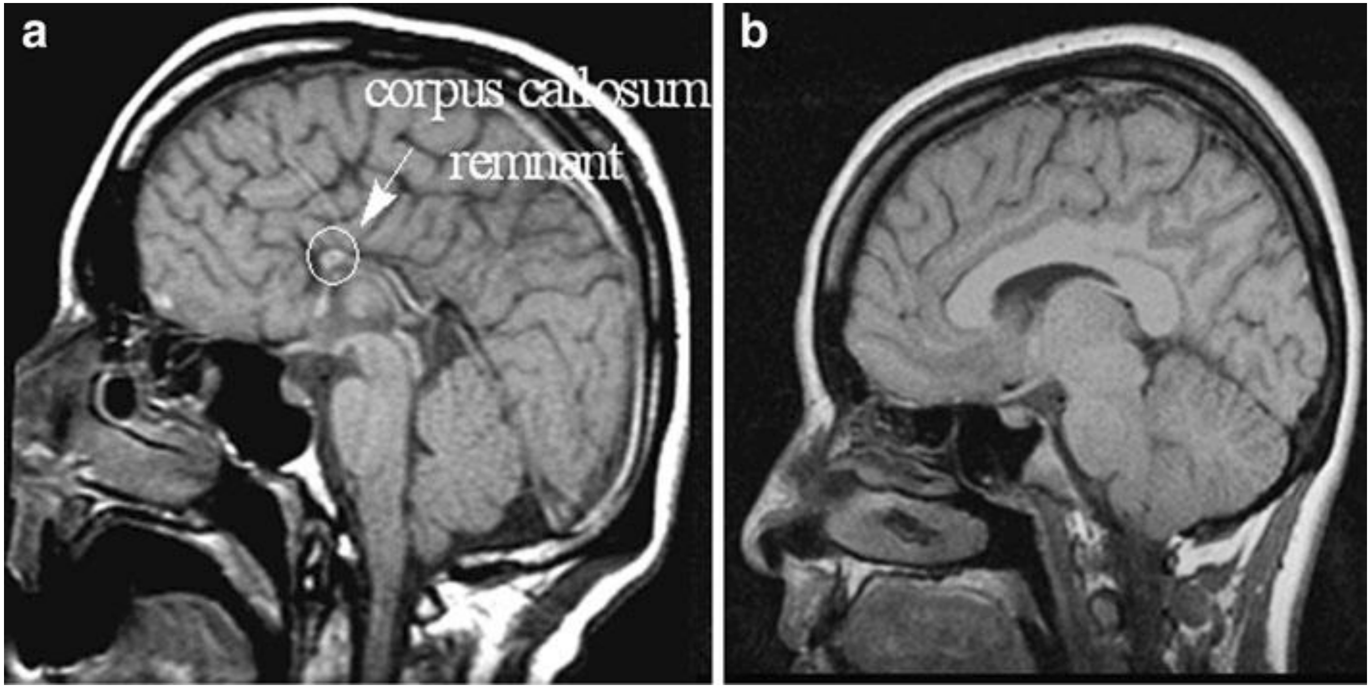
Healthy control: seed voxel from the right auditory cortex



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*

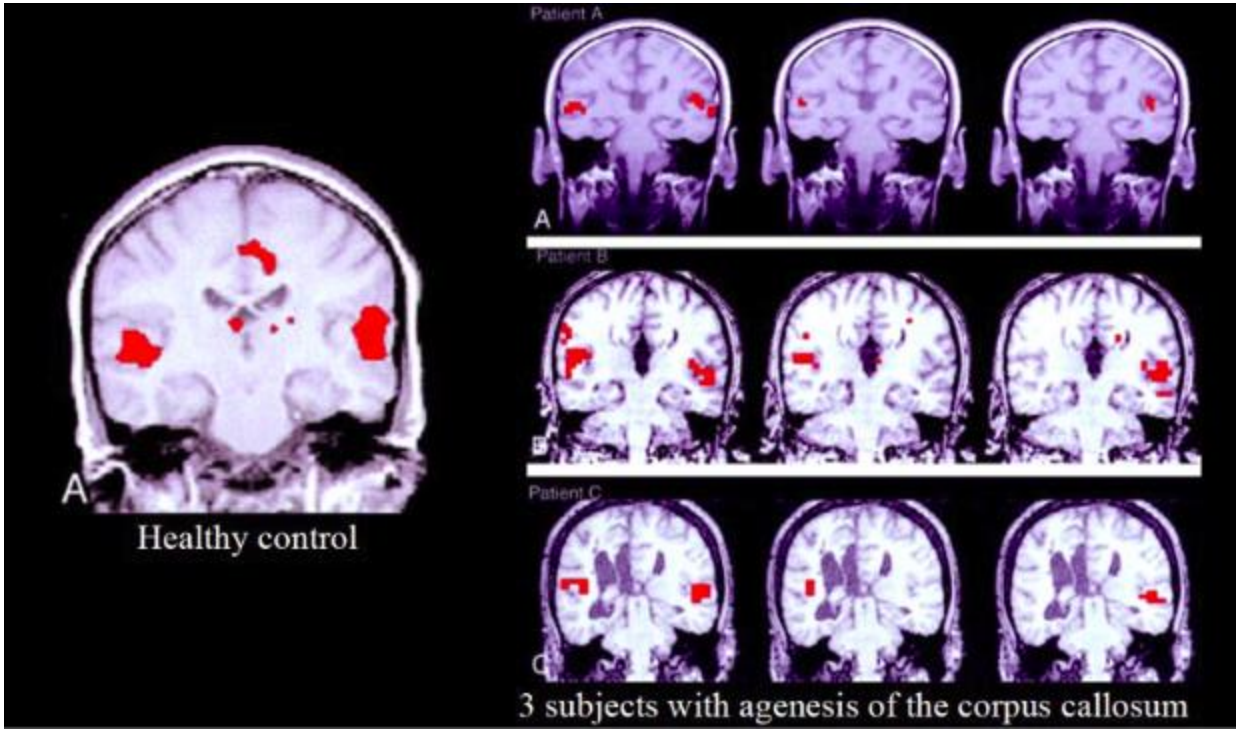
Corpus callosum



Lowe (2010), *Magn Reson Mater Phy*

Functional connectivity = anatomical connectivity ?

Healthy control: seed voxel from the right auditory cortex



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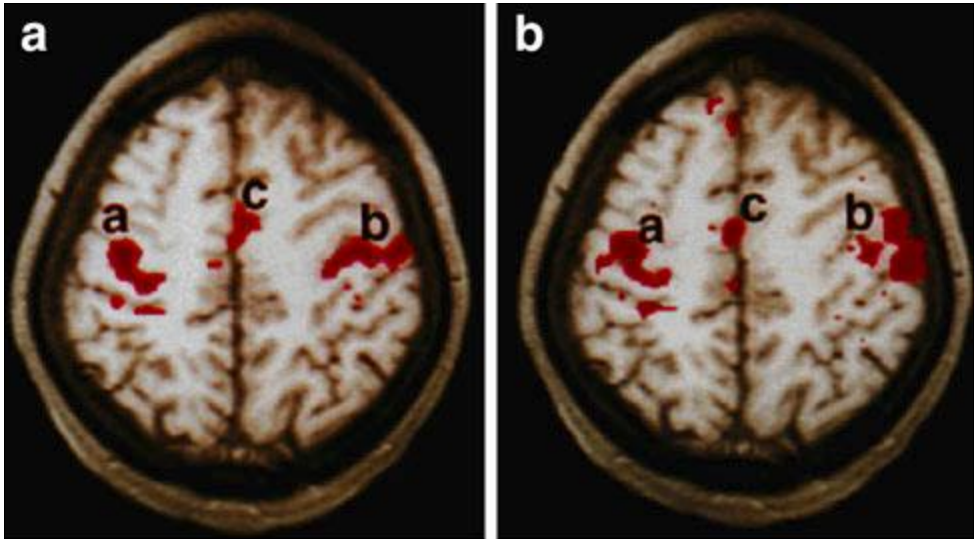
Quigley et al. (2003), *AJNR*

Early studies - fMRI



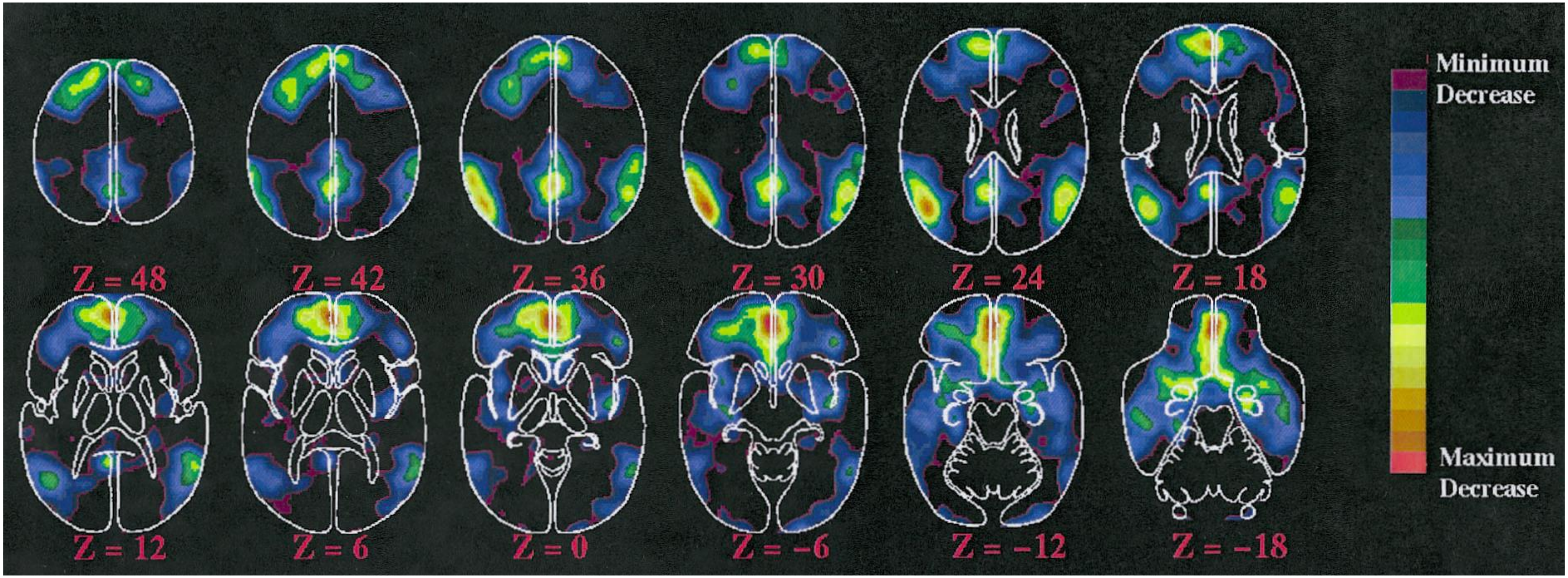
a) fMRI task-activation response to bilateral finger movement

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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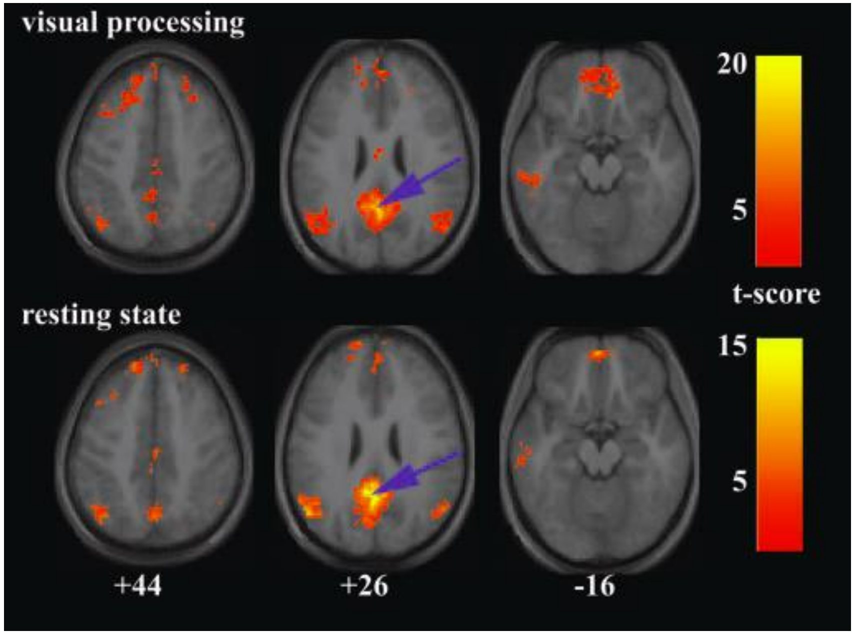
Early studies - fMRI

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

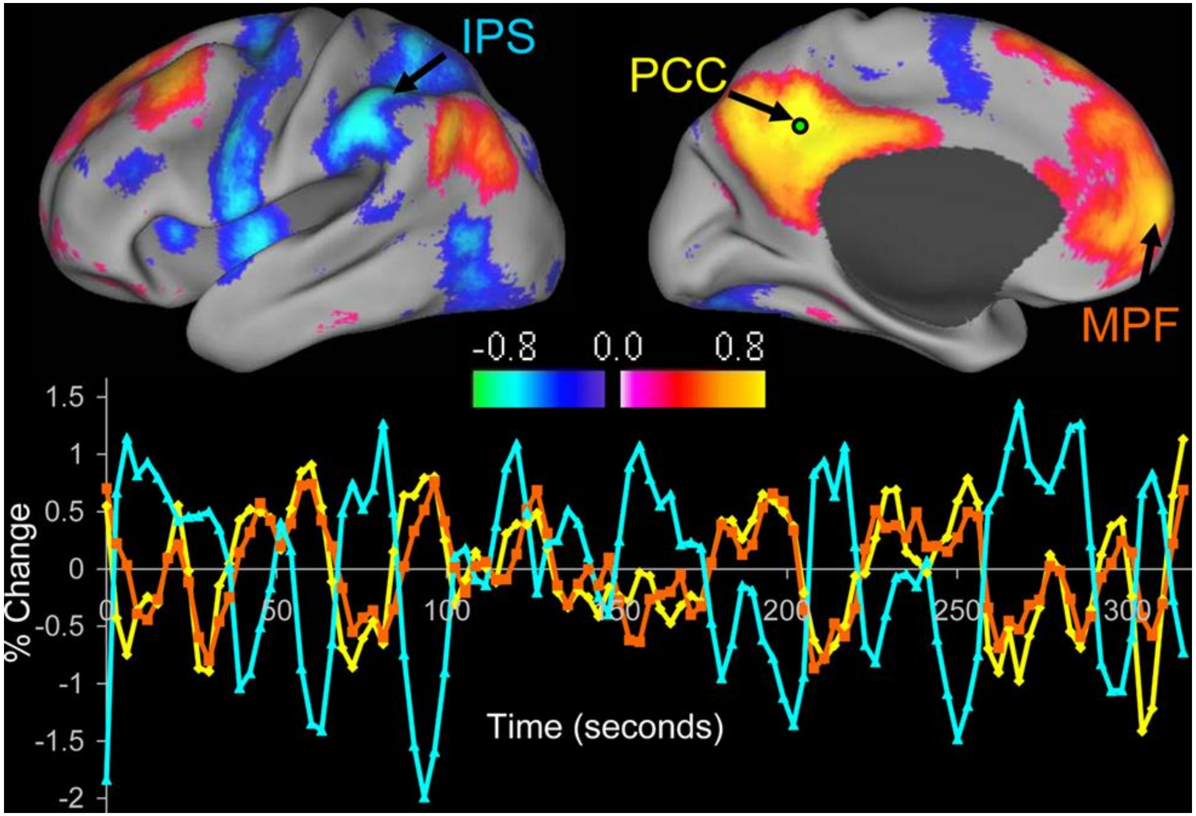
[-2 -51 27]



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)

Spatial characteristics - Networks

RSNs

a) & b) Visual

c) Sensory

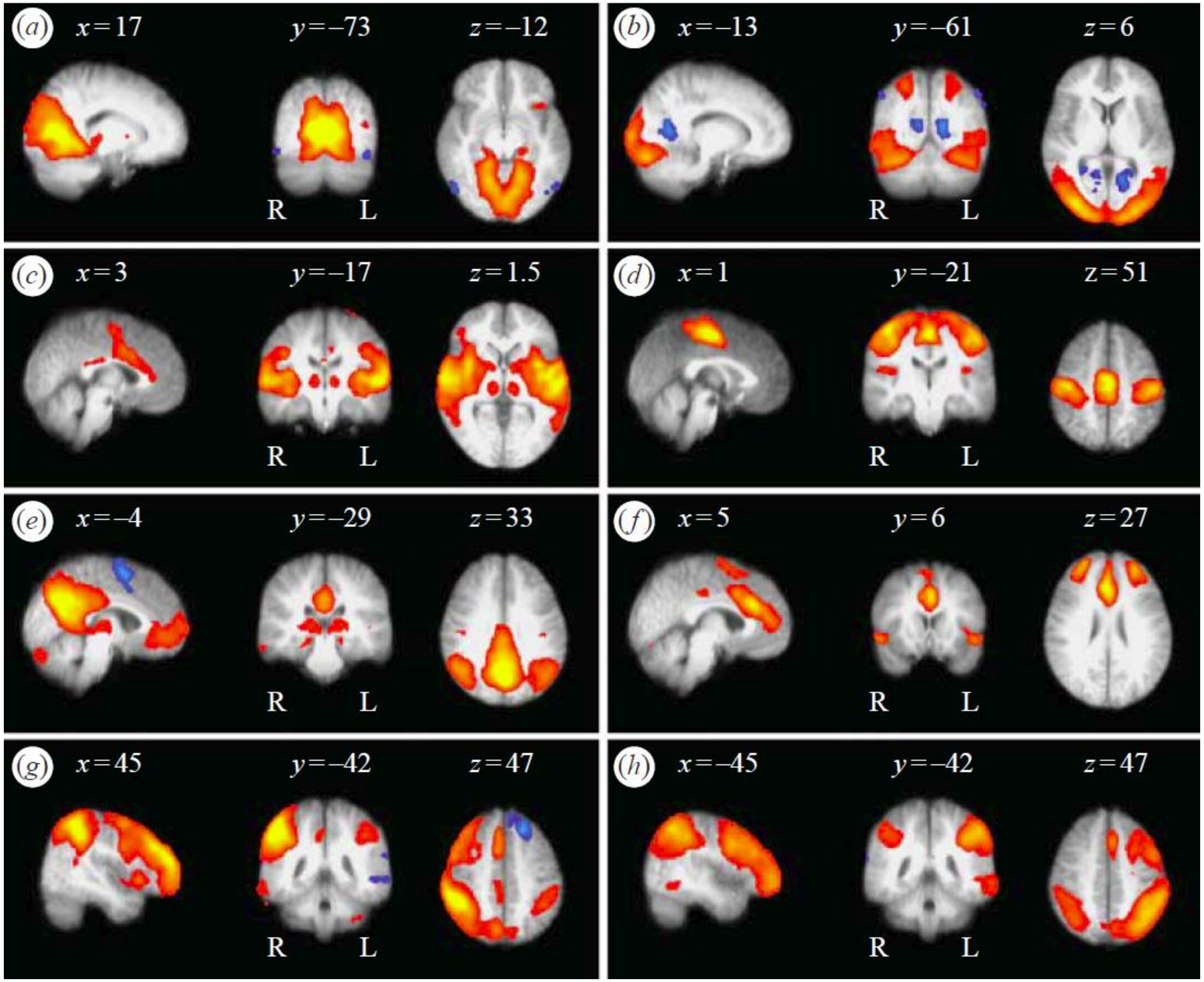
d) Motor

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*

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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

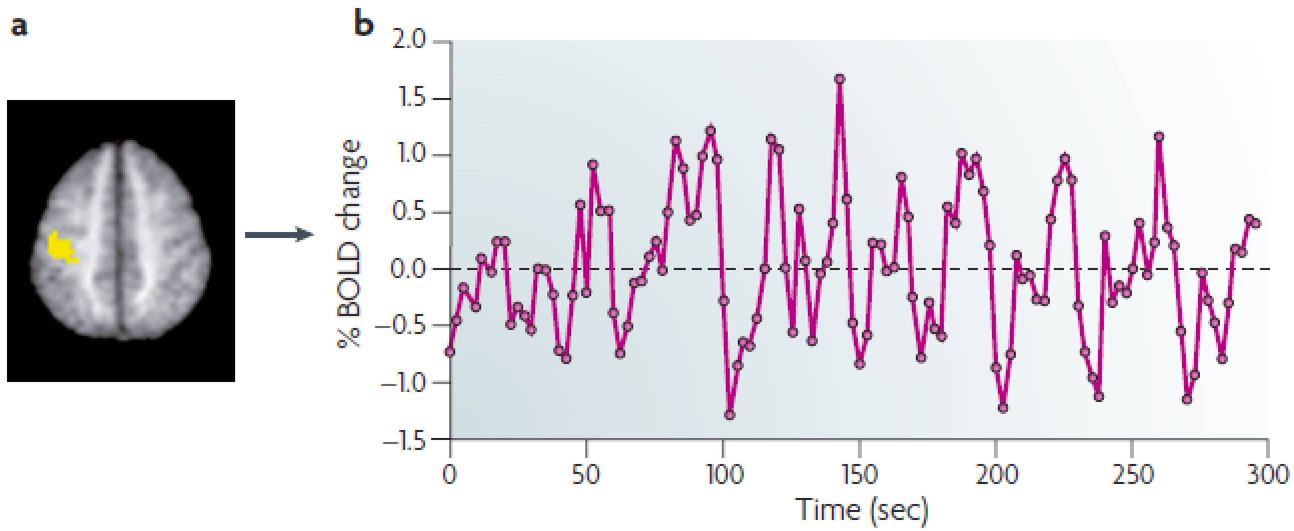
- Model-based
  - Seed based correlation analysis
- Model-free
  - Decomposition
    - Independent component analysis (ICA), principal component analysis (PCA)
  - Clustering
    - Fuzzy clustering analysis (FCA), hierarchical clustering analysis (HCA)

Methods: model-based

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

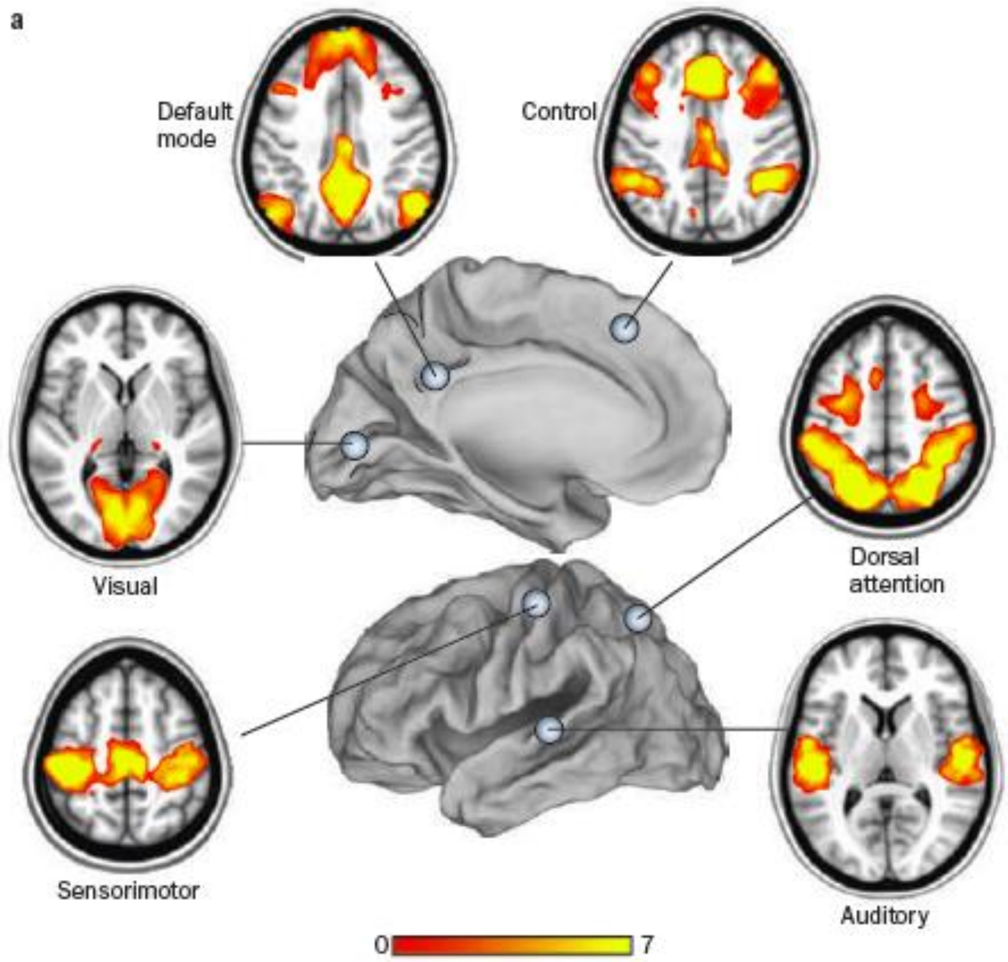
→ Temporal correlation between the time course of every voxel in the brain and the time course from a seed voxel

- 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



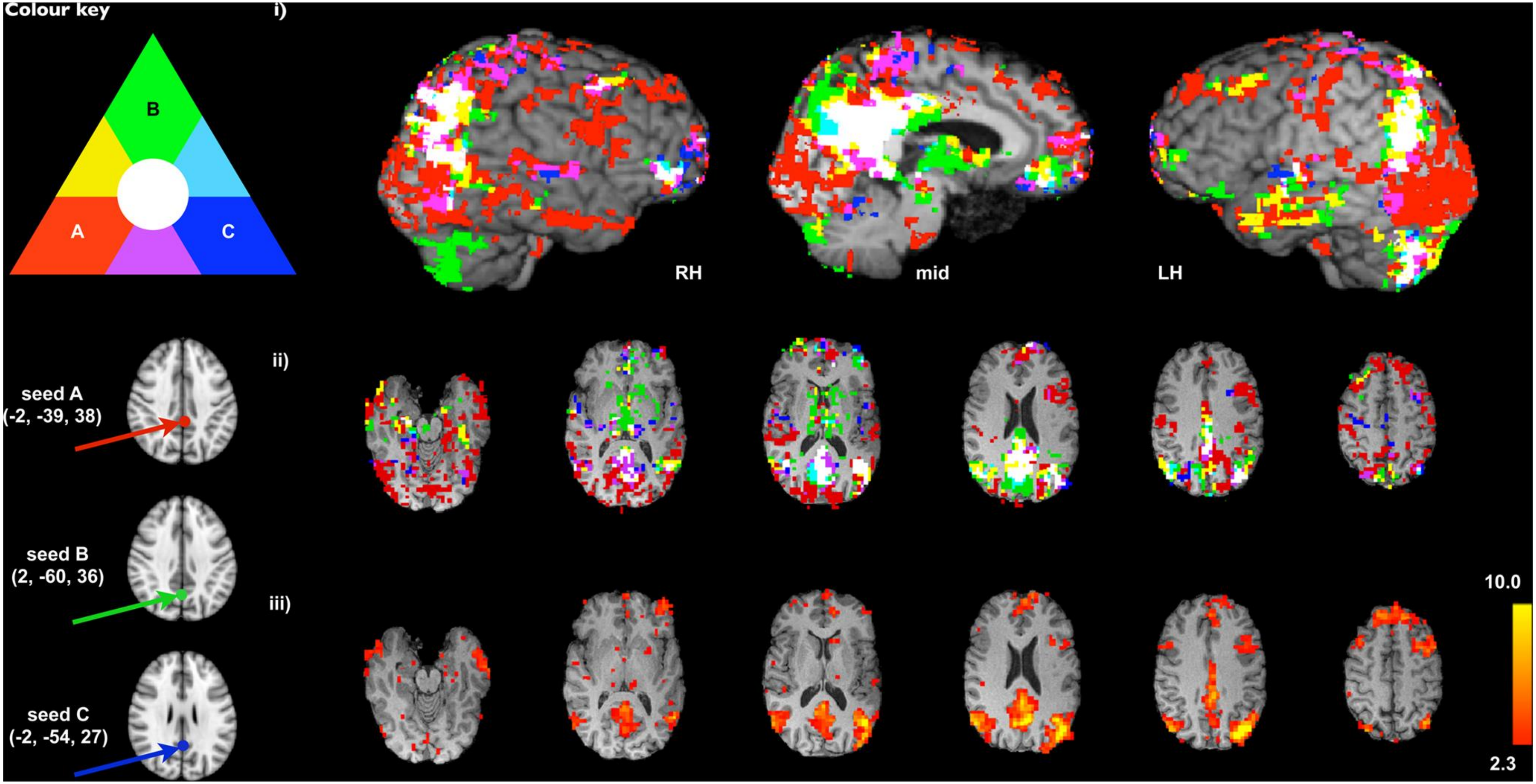
Fox & Raichle, 2007, *Nature Reviews, Neuroscience*

SCA



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

DMN versions using 3 different seed voxels



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

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

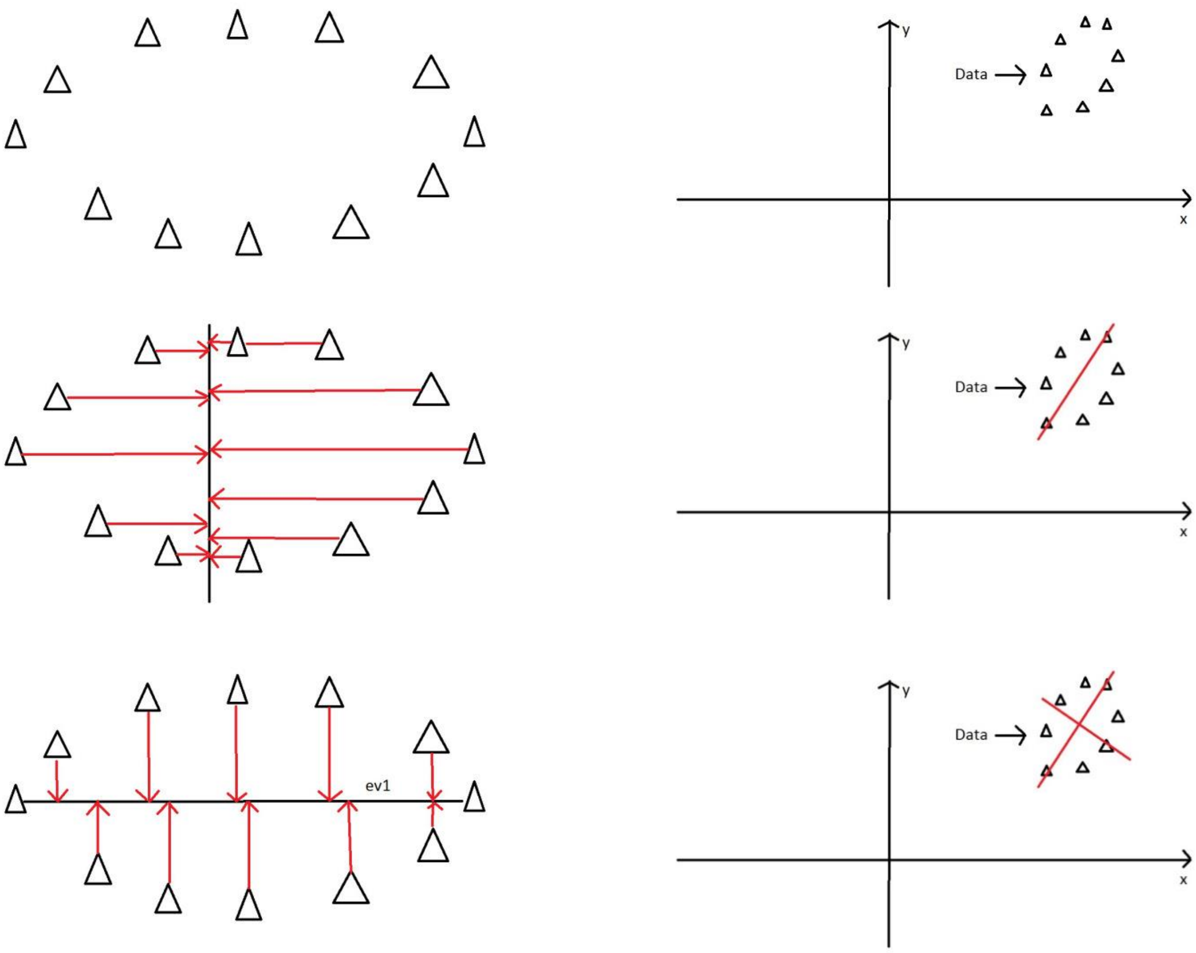
- Goal: to express the original fMRI dataset as a linear combination of basis vectors (PCA) or statistically independent components (ICA)

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

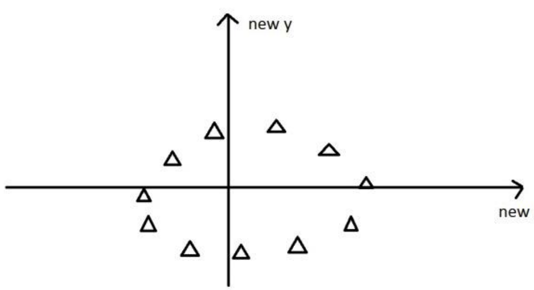
PCA example

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



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https://georgemdallas.wordpress.com/2013/10/30/principal-component-analysis-4-dummies-eigenvectors-eigenvalues-and-dimension-reduction/comment-page-4/#comment-900

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

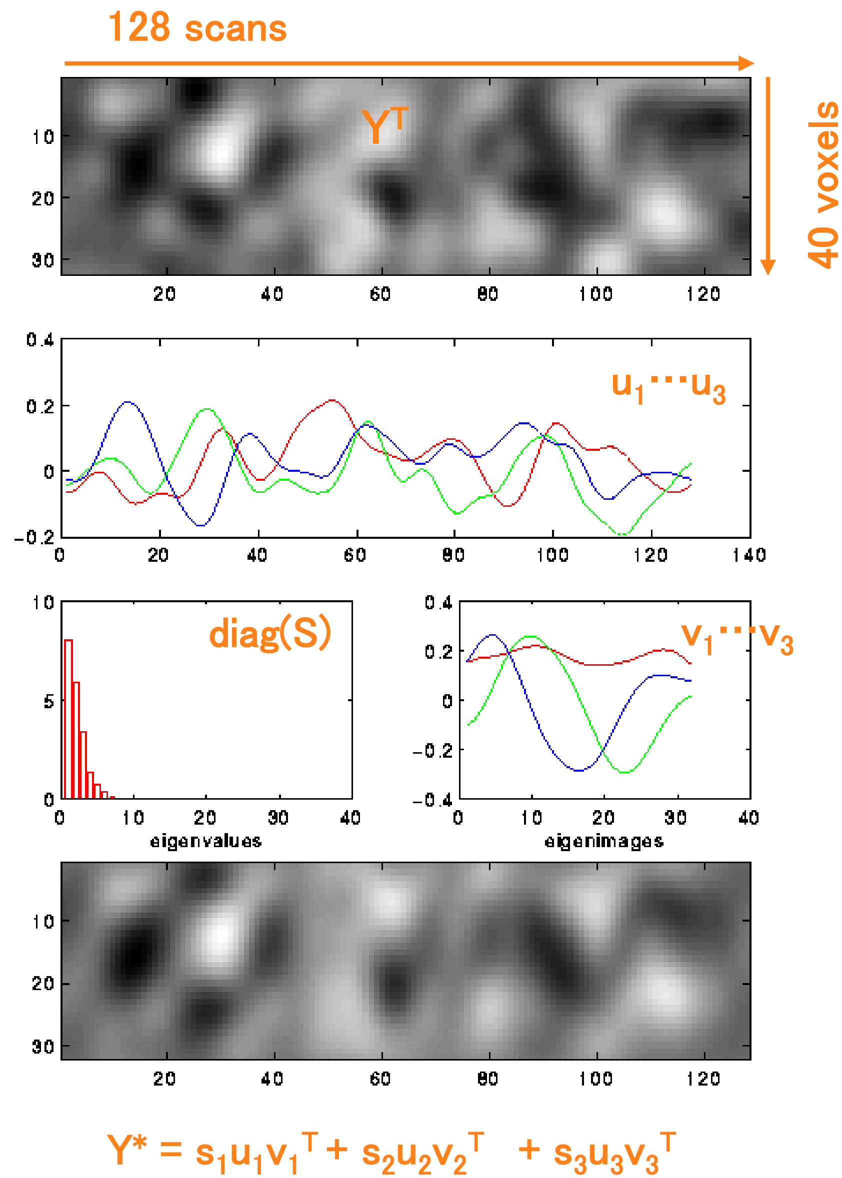
A time-series of 1D images:
128 scans of 40 "voxels"

(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

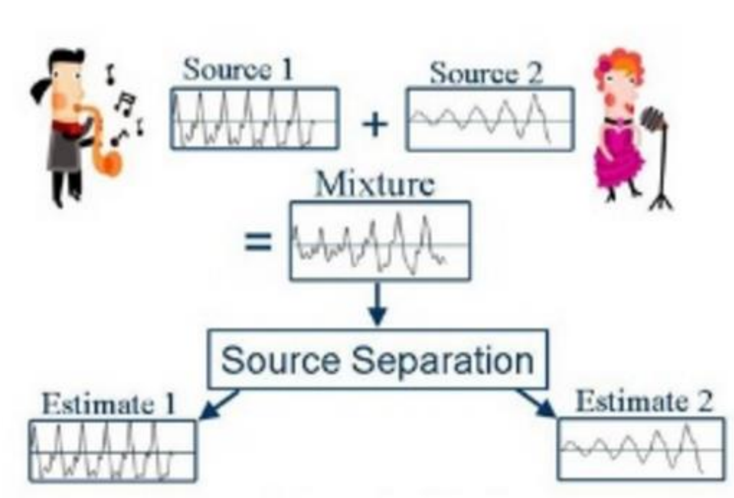


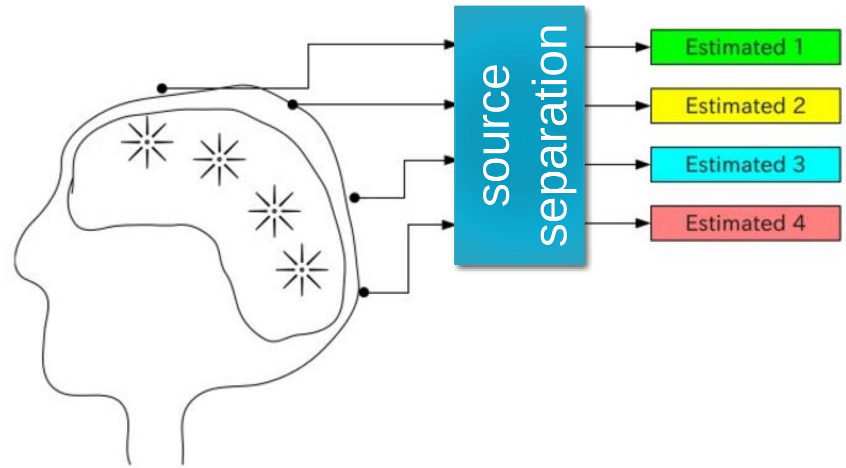
Independent Component Analysis (ICA)

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

ICA





$$X = AS$$

X: measured data

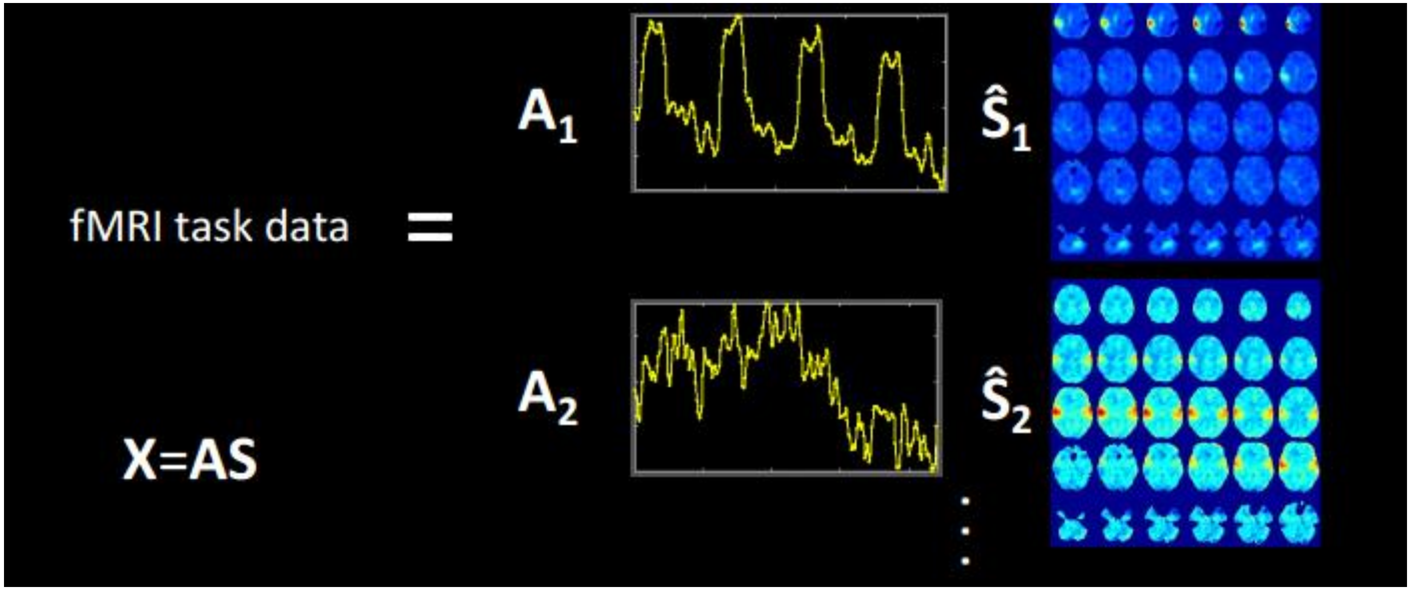
A: mixing matrix

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

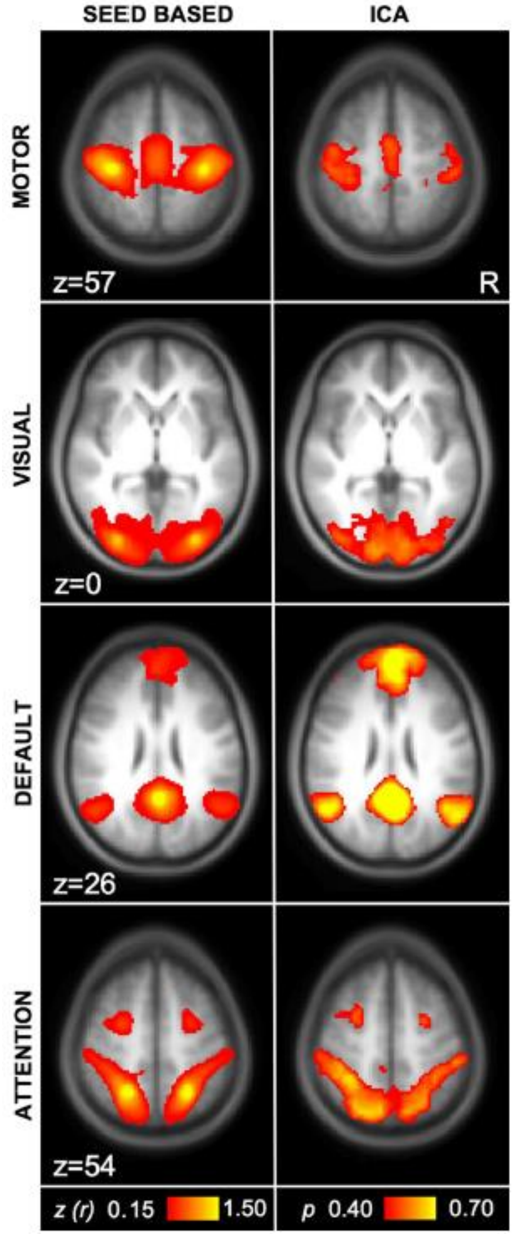
- MELODIC FSL
- GIFT (MIALAB; Vince Calhoun)
- REST and DPARSF SPM
- CONNN Toolbox (http://www.nitrc.org/projects/conn/)

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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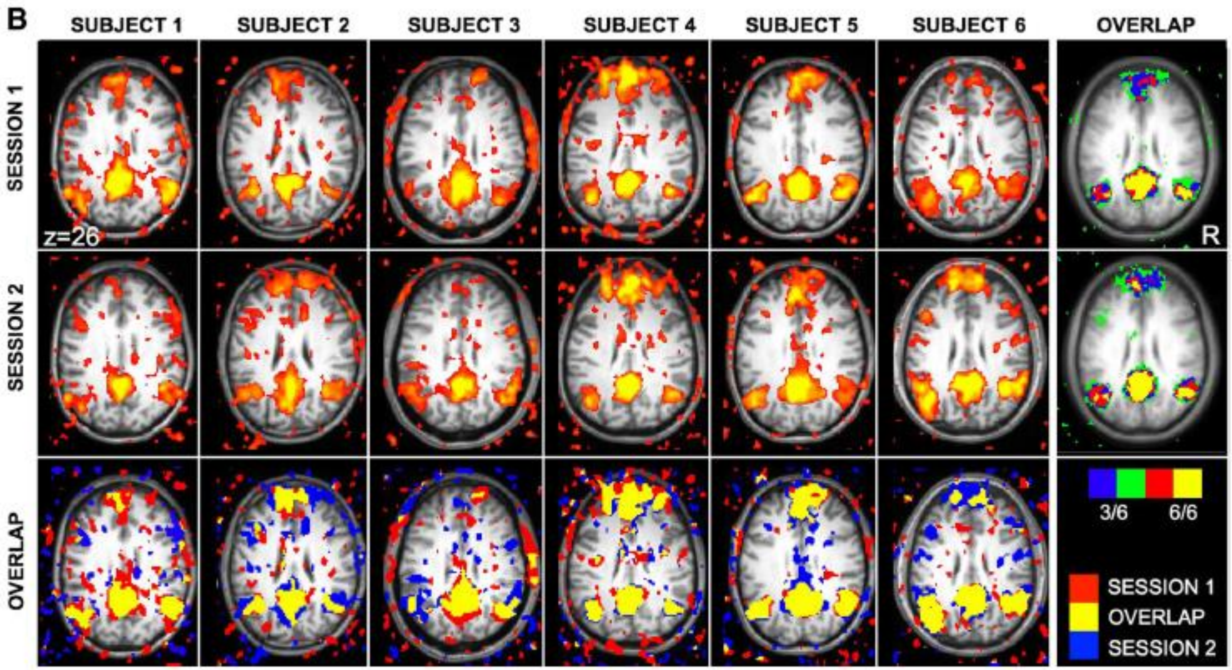
rsfMRI reliability

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



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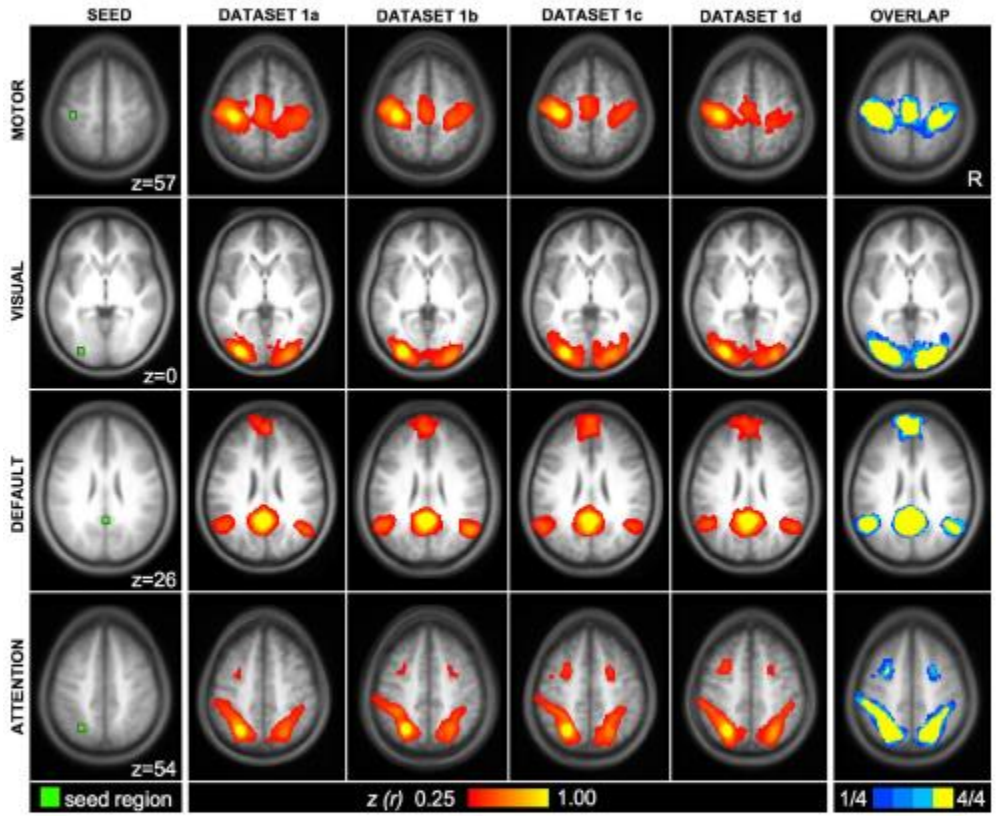
Van Dijk, 2010, *J Neurophysiol*

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

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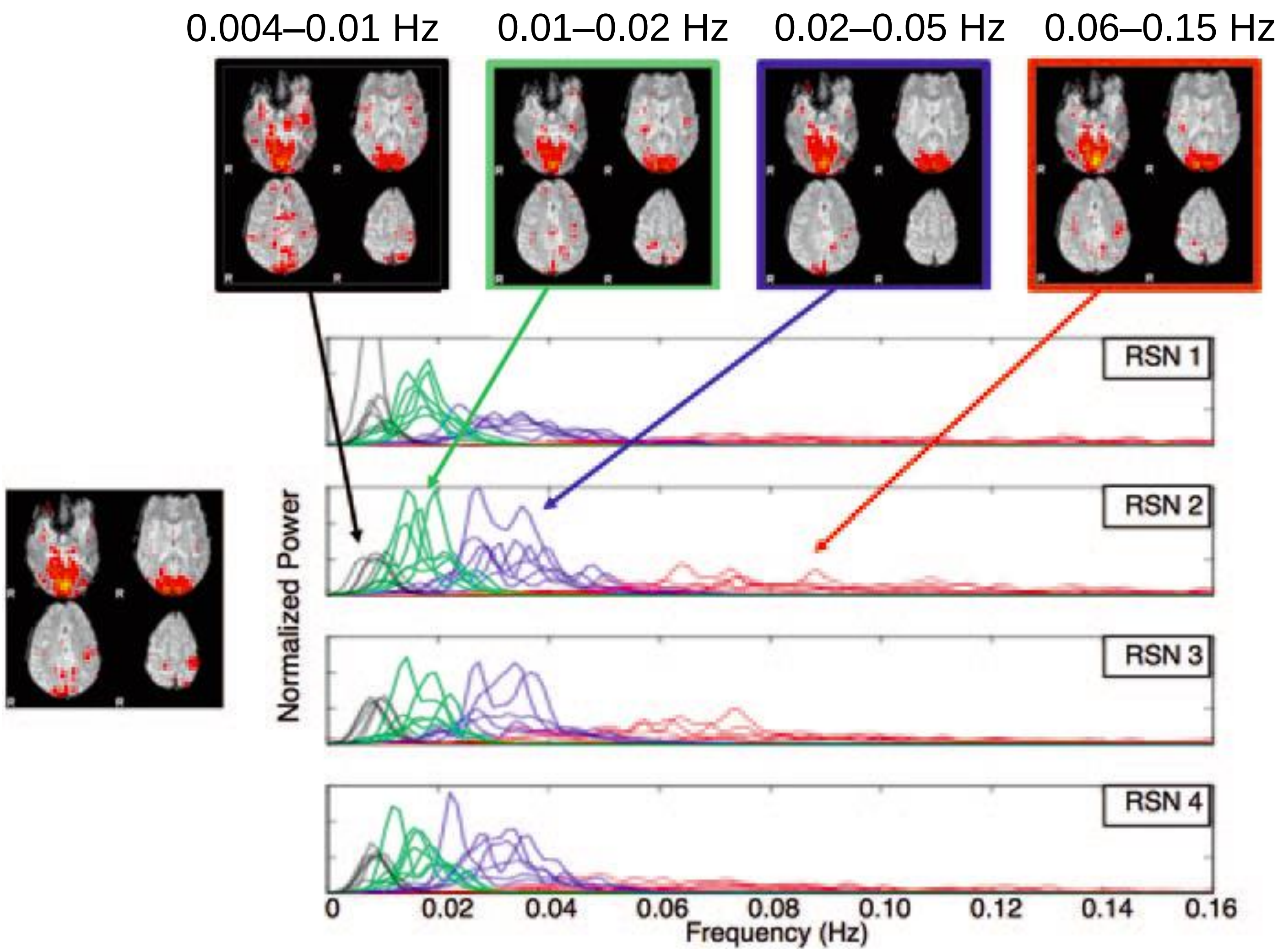
Van Dijk, 2010, *J Neurophysiol*

Temporal characteristics



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

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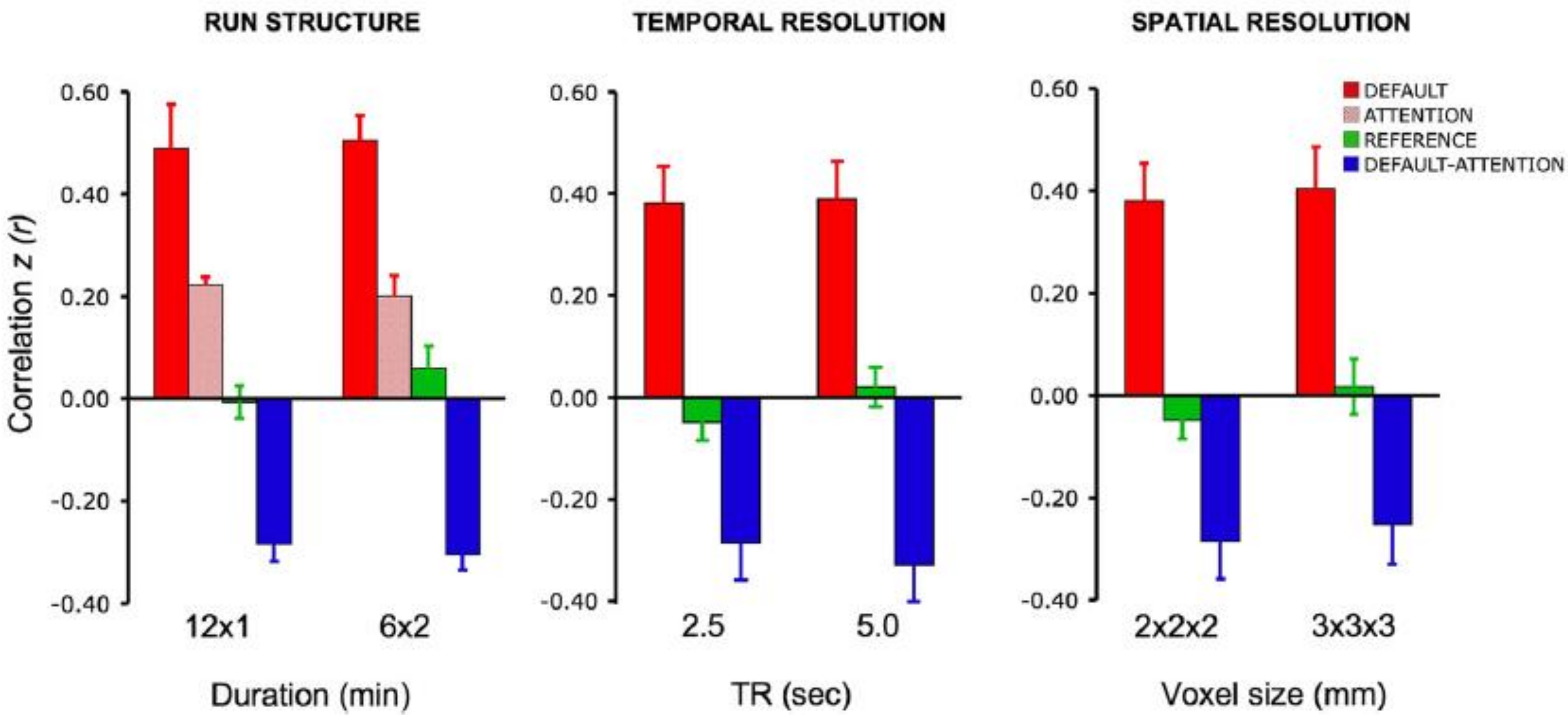
Effects of structure & resolution on rsfMRI



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

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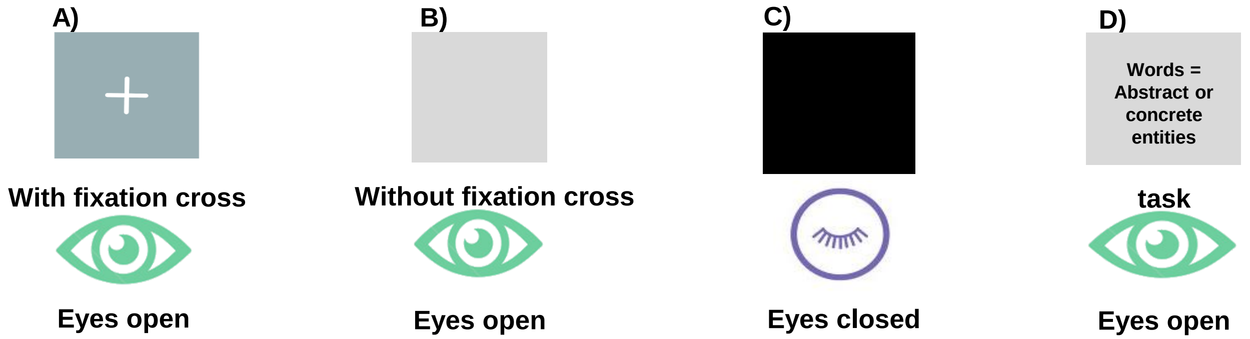
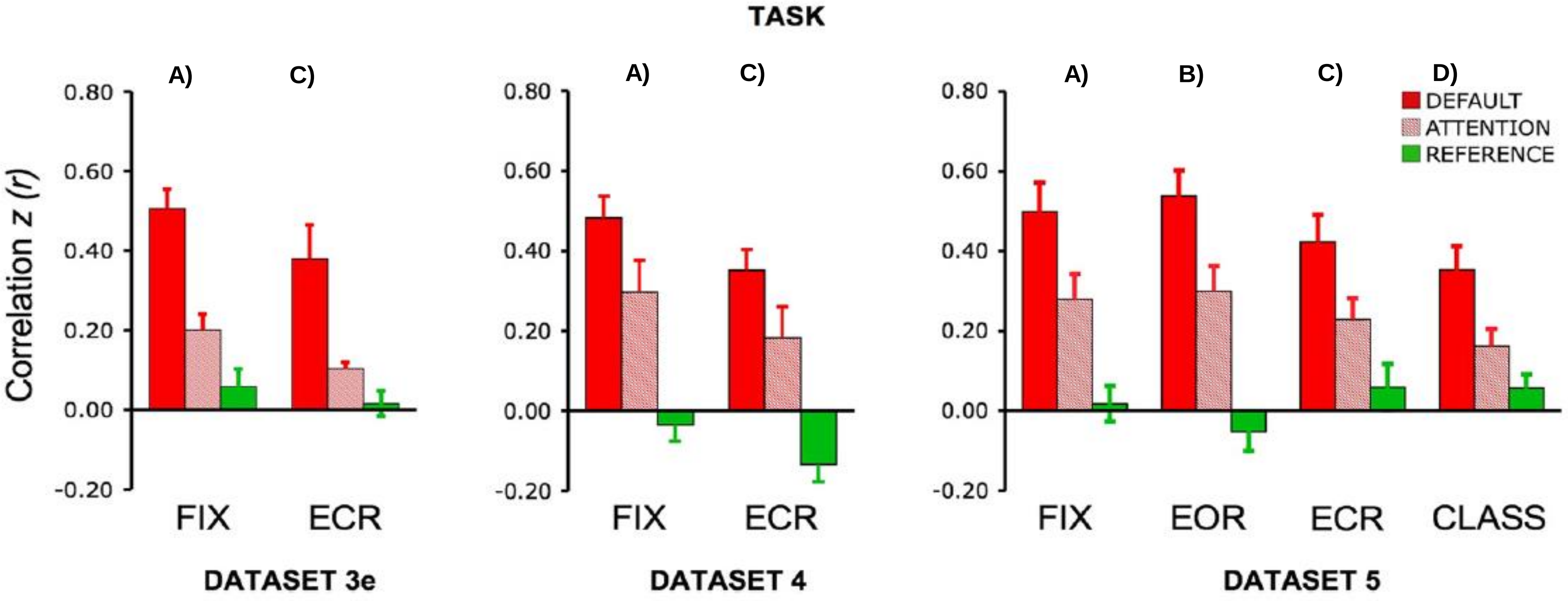
Van Dijk, 2010, *J Neurophysiol*

Effects of design on rsfMRI





Functional connectivity strength is influenced by task

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?

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