Vendredi 18 Décembre 13:30 – 15:30

MRI INT Technical Lecture

Part 2 : Brain functional MR Imaging

Brain activity and functional connectivity

Thanks to the organizers Nicolas WANAVERBECQ & Ivo VANZETTA

Thanks to the speakers and those who helped to prepare this session :
Jean-Luc ANTON, Pascal BELIN, Thierry CHAMINADE, David MEUNIER,
Bruno NAZARIAN, Julien SEIN & Sylvain TAKERKART

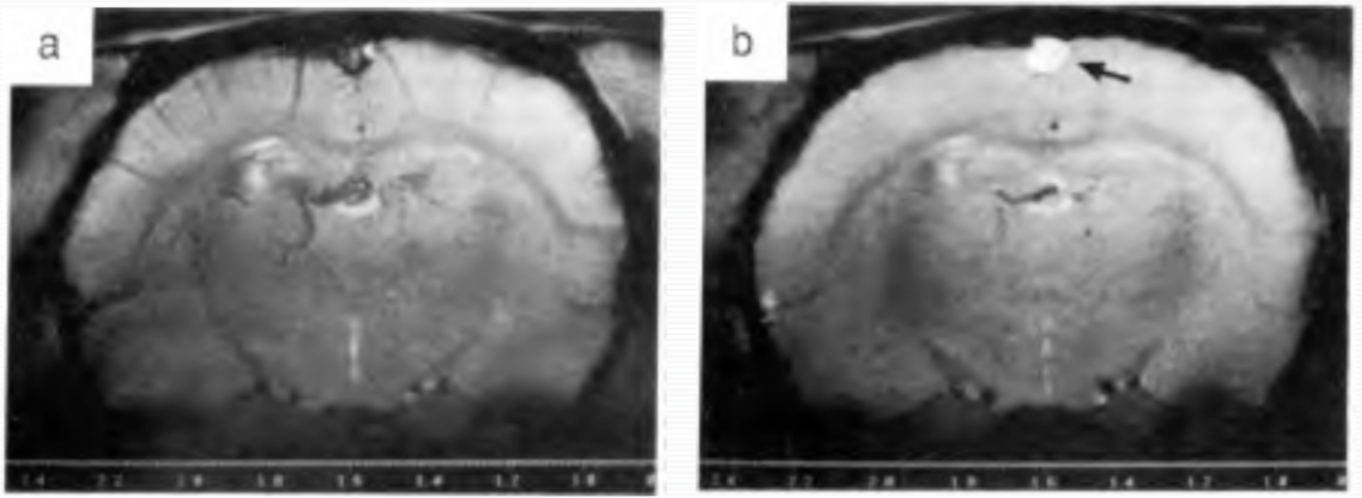
Institut de Neurosciences de la Timone (UMR 7289) & Centre IRM-INT@CERIMED

- Introduction & BOLD effect (Jean-Luc Anton)
- Functional MRI acquisition principles (Julien Sein)
- Instrumentation for fMRI experiment (Bruno Nazarian)
- Univariate fMRI data processing (Jean-Luc Anton)
- fMRI advanced processing (Sylvain Takerkart, Pascal Belin)
- Functional connectivity (David Meunier & Thierry Chaminade)

Modalities of the session :

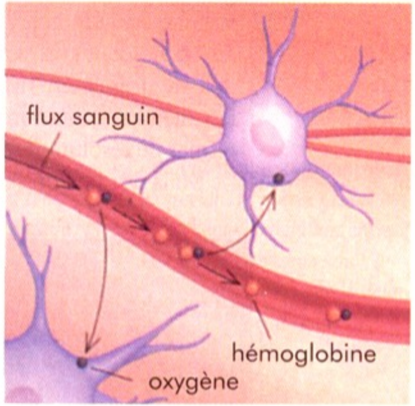
microphones off, questions in the chat, discussion at the end … ;-)

The Blood Oxygen Level Dependent effect



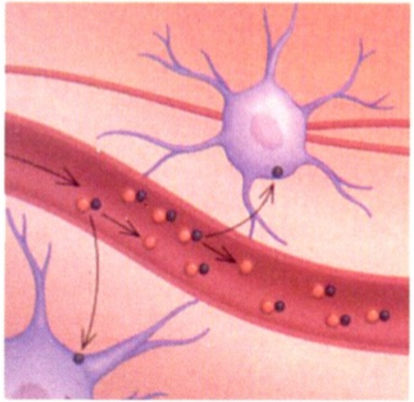
Effect of blood CO_2 level on BOLD contrast.
(*a*) Coronal slice brain image showing BOLD contrast from a rat anesthetized with urethane. The gas inspired was 100% O_2.
(*b*) The same brain but with 90% O_2/10%CO_2 as the gas inspired. BOLD contrast is greatly reduced.

S Ogawa, *et al.*,
PNAS, **87**(24):9868,1990



Increased local brain activity

→ Significant increase in blood flow
(> +30%) (expansion of the capillaries)
Small increase in O2 consumption
(< +5%)



→ Increasing the local Hb-O2 rate
→ Decrease of deoxy-Hb (paramagnetic)
→ Protons stay in phase longer
→ Increase in the local value of T2/T2*

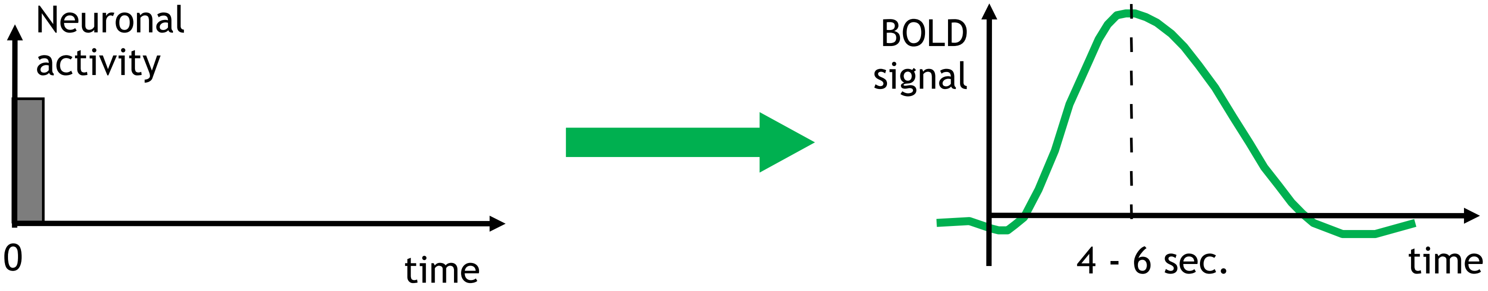
→ BOLD response : Blood Oxygen Level Dependent
Deoxy-Hb : Intrinsic Contrast Agent

Functional MRI : biophysical principles

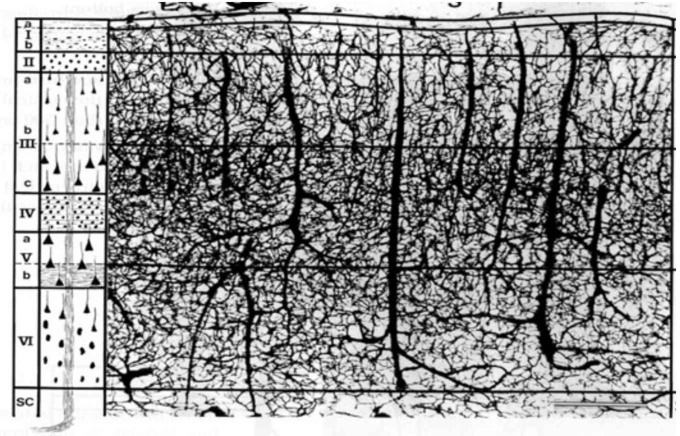
- Indirect measurement of brain activity
  (metabolic effects of the electrical activity of activated neurons)

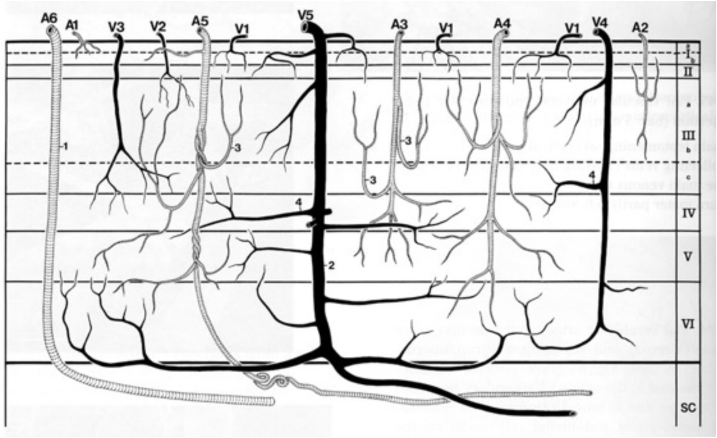
- Phenomenon measured in the blood vessels (capillaries, venules, etc.) that drain the activated cerebral territory

→ Precise spatial location (mm3) but to be considered with caution
→ Time course of the fMRI signal : smoothed and delayed by the haemodynamic function



Cerebral vasculature

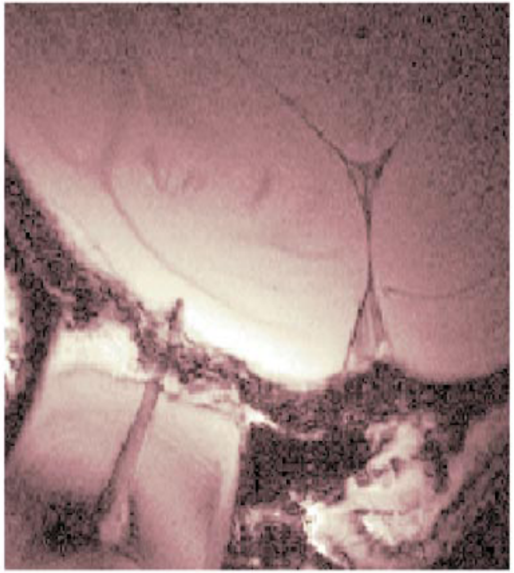


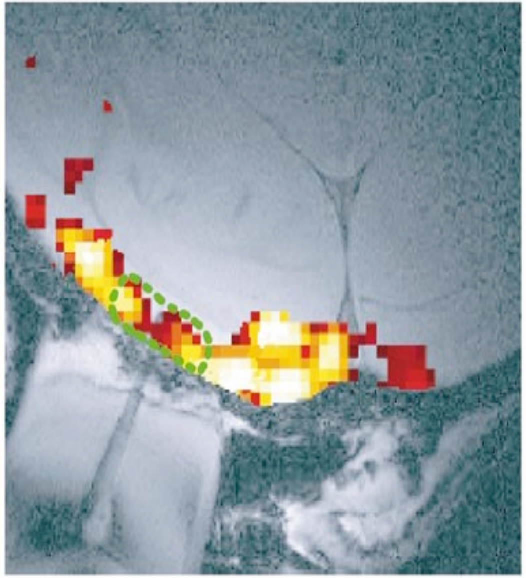


HM Duvernoy
The Human Brain - Surface, Blood Supply and Three-Dimensional Sectional Anatomy, Springer, 1999

- **In anaesthetised monkeys, joint recordings :**

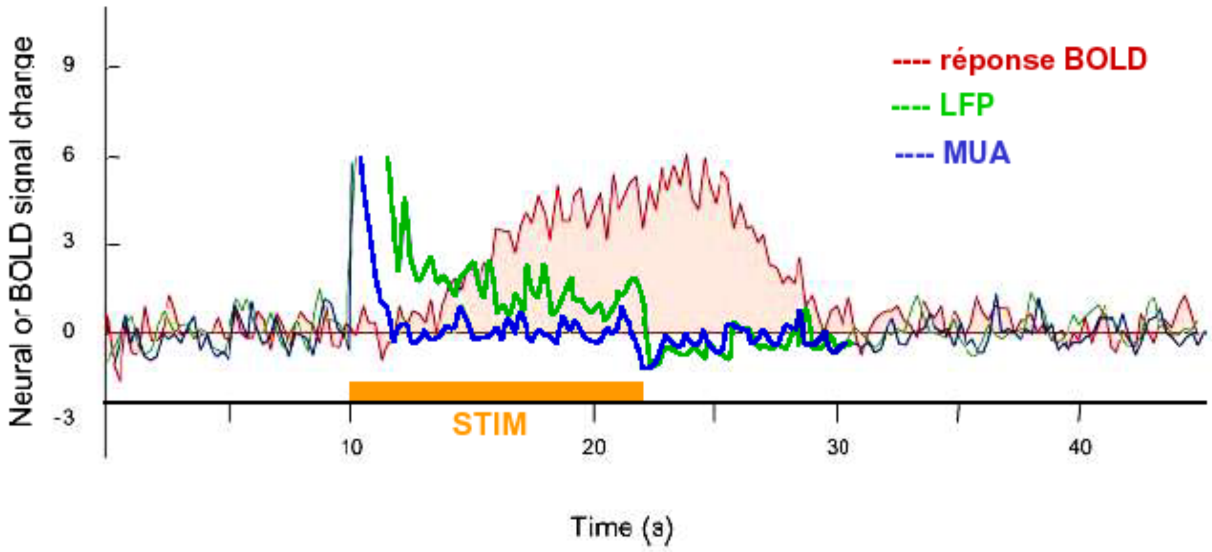
Neural electrical signals by microelectrode & fMRI signal





Logothetis et al.
Neurophysiological investigation of the basis of the fMRI signal. Nature. 2001

- **The BOLD response seems to correlate more with LFPs than with MUAs**
  → The BOLD would be more sensitive to dendritic and synaptic events than to the action potentials.



Logothetis et al.
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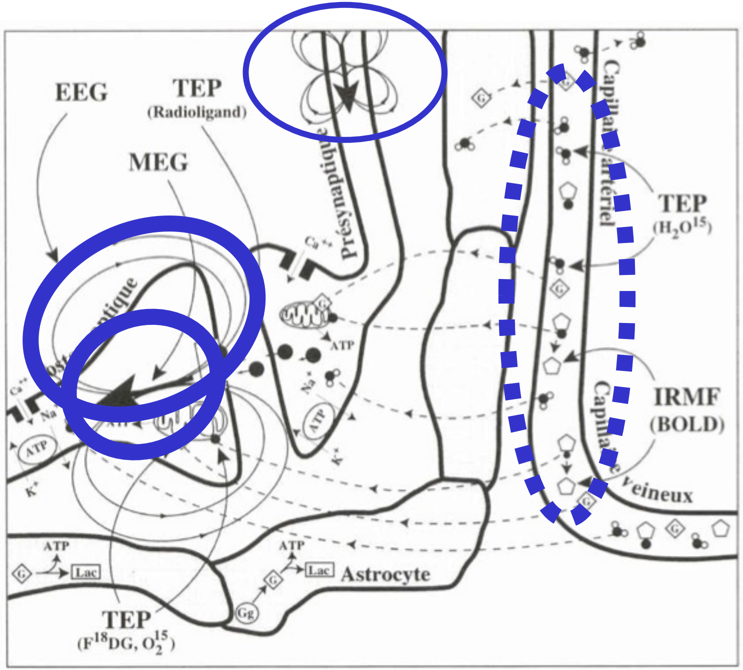
- The BOLD would be more sensitive to dendritic and synaptic events than to the action potentials

  → Caution in the interpretation of fMRI results and in their comparison with those from other brain activity recording techniques (EEG, MEG, electro-physiology, ...) !



From B. Mazoyer

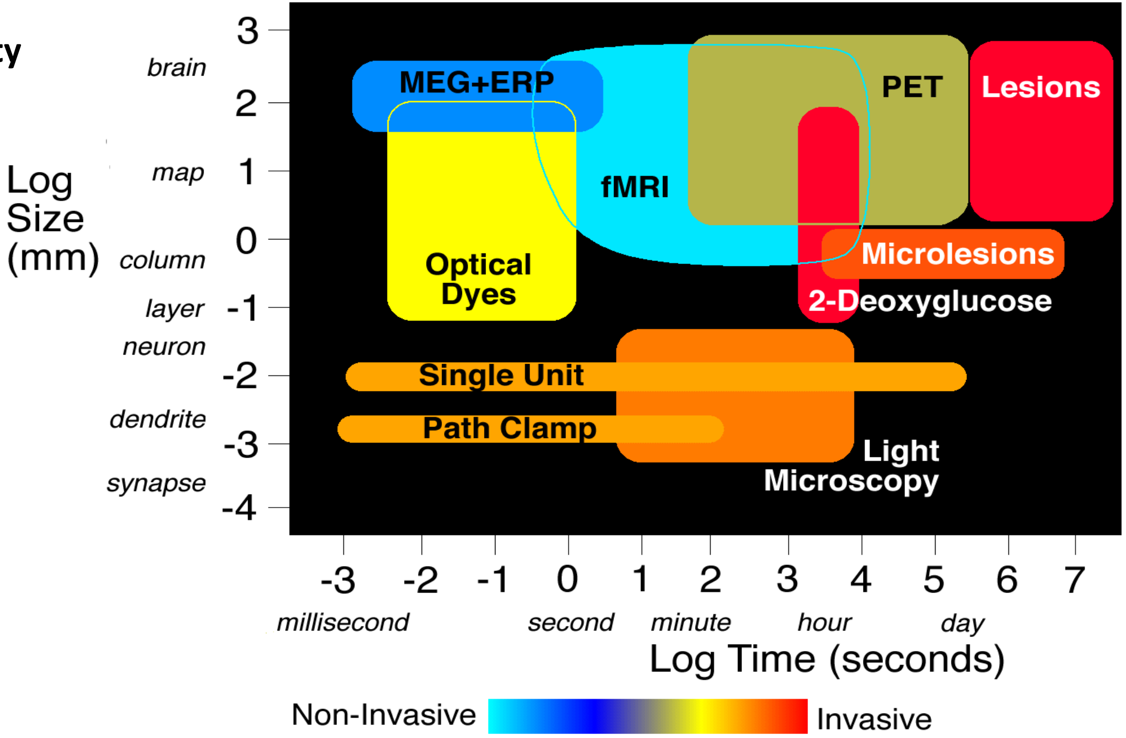
- **The BOLD would be more sensitive to dendritic and synaptic events than to the action potentials**

  → Caution in the interpretation of fMRI results and in their comparison with those from other brain activity recording techniques (EEG, MEG, electro-physiology, ...) !

- **New references on Coupling neuronal activity & BOLD effect :**

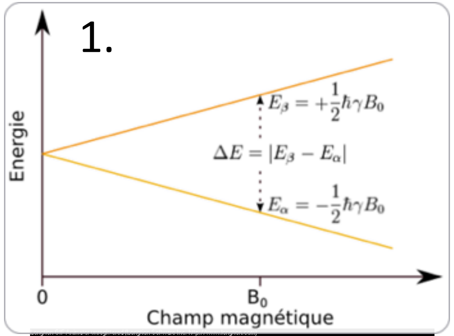
  Review from Lauritzen : https://pubmed.ncbi.nlm.nih.gov/15611729/
  Recent Special Issue : https://royalsocietypublishing.org/toc/rstb/2021/376/1815

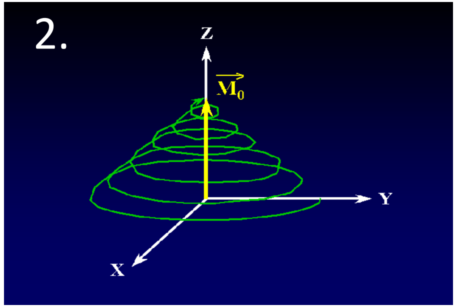
- Non-invasive (intrinsic signal of the organism)
- Good spatial resolution : ≈ millimetre
- Relatively poor temporal resolution : ≈ second
- Vascular phenomenon
- indirect measurement of brain activity

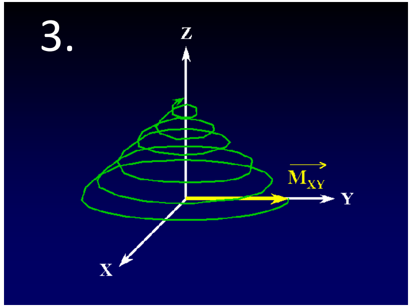


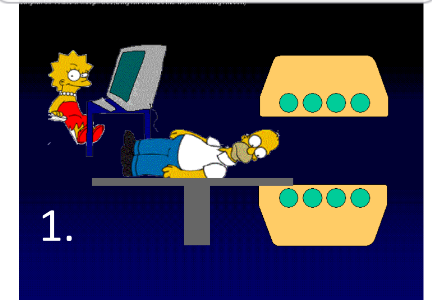
Signal:

1. Polarization
2. Resonance
3. Relaxation









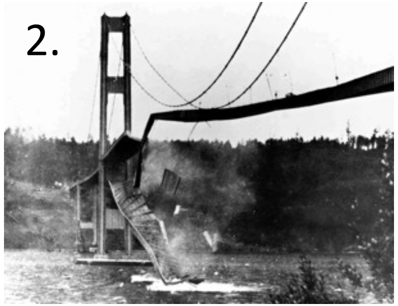
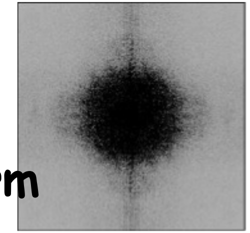


Image:

1. ADC
2. Fourier Transform

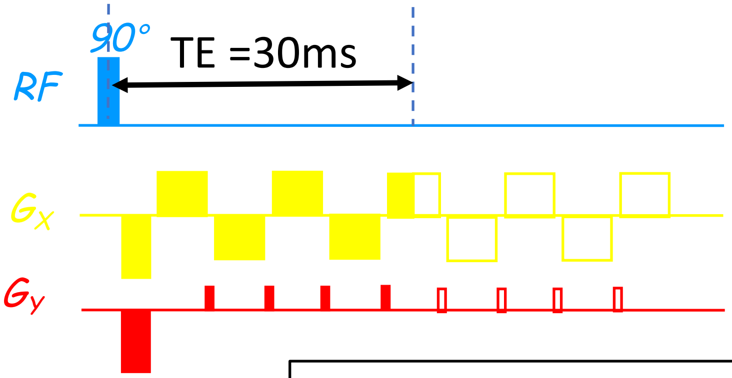


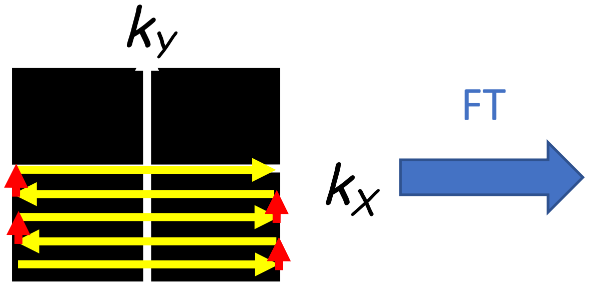
FT →

1. **fast**: high sampling rate, “freeze” motion to study rapidly changing physiological processes

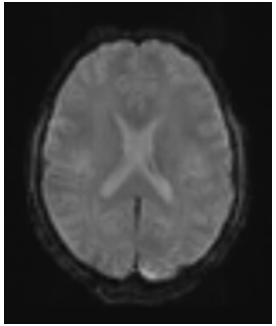
2. **sensitive to the BOLD** effect (= T2* weigted)

=> The workhorse for fMRI: Gradient echo (=T2* weighted) Echo Planar Imaging (=fast)





TA_{slice}= 68 ms



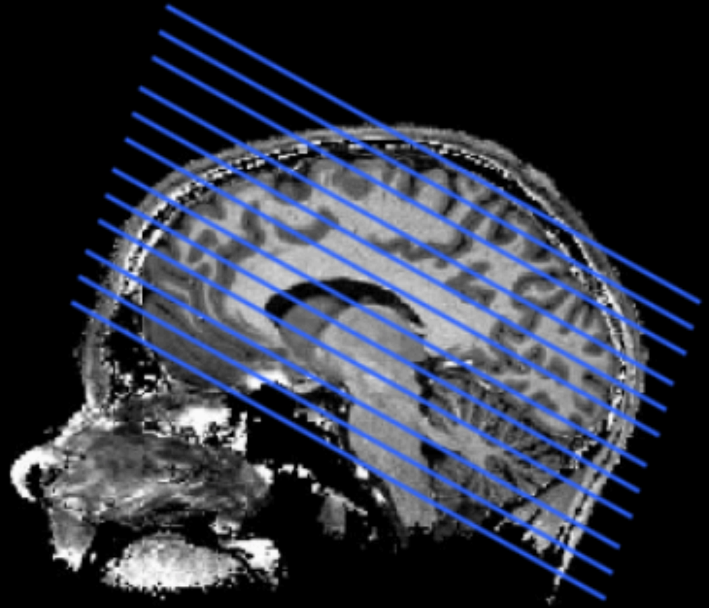
The k-space (slice) is acquired after one excitation

Voxel size = (2.5 mm)^3

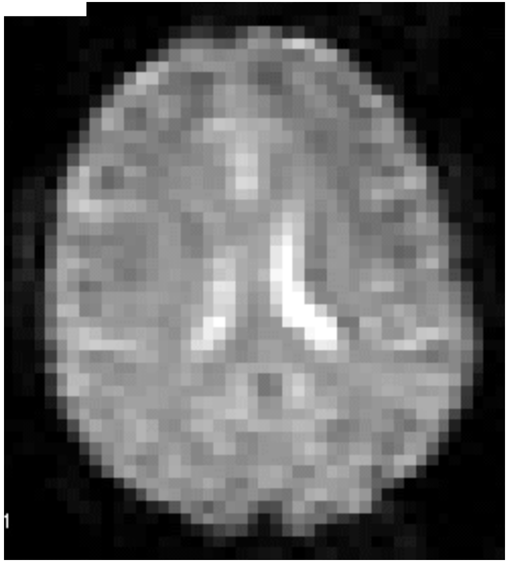
Conventional Multi-slice Imaging

Whole Volume TR

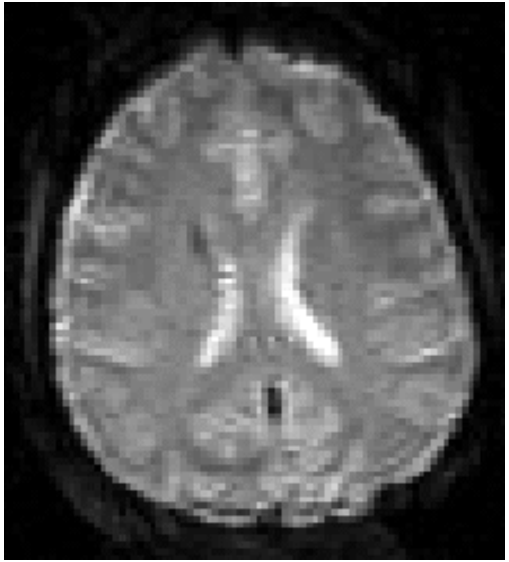
= N_{slice} x Time per slice



64 x 64 voxels of 3mm x 3mm



128 x 128 voxels of 1,5mm x 1,5mm

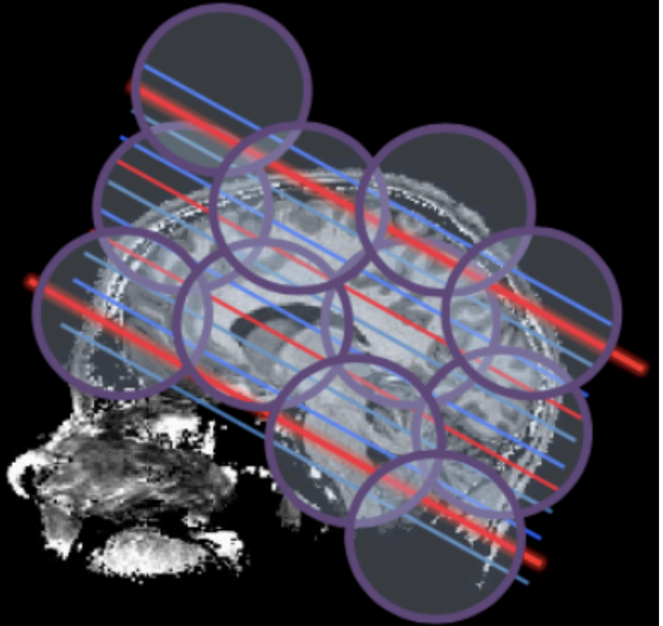


Nice! But higher isotropic resolution means higher number of slices to cover the whole brain => TR increases!

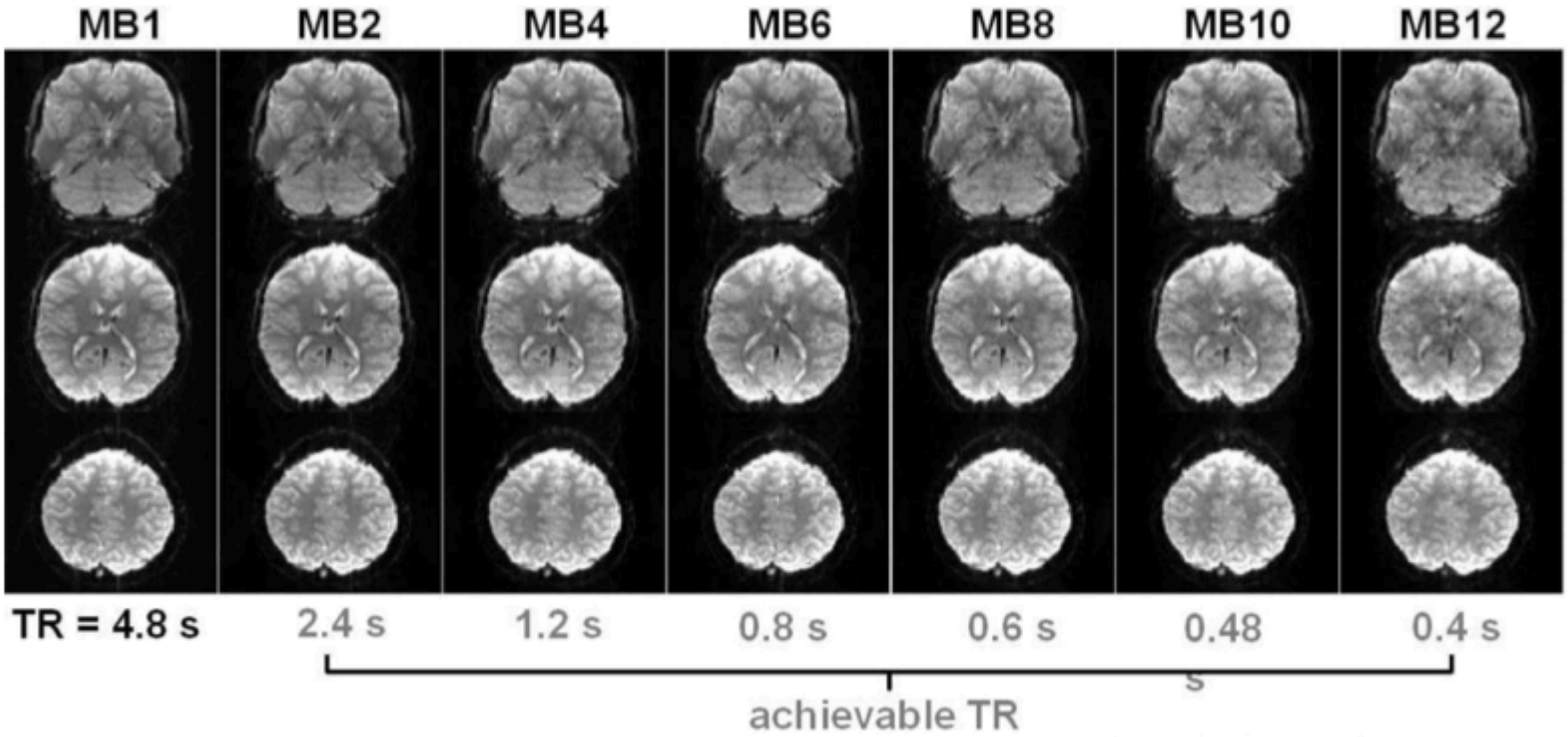
SMS, Multiband: simultaneous slices separated via multiple coils

- Larkman et al., JMRI, 2001
- Moeller et al., MRM, 2010
- Setsompop et al., MRM, 2012

- Excite ***multiple*** slices simultaneously
- Each coil yields a linear combination of signals from the different slices (weighted by sensitivity profiles)
- Matrix inversion provides a solution to separate slices

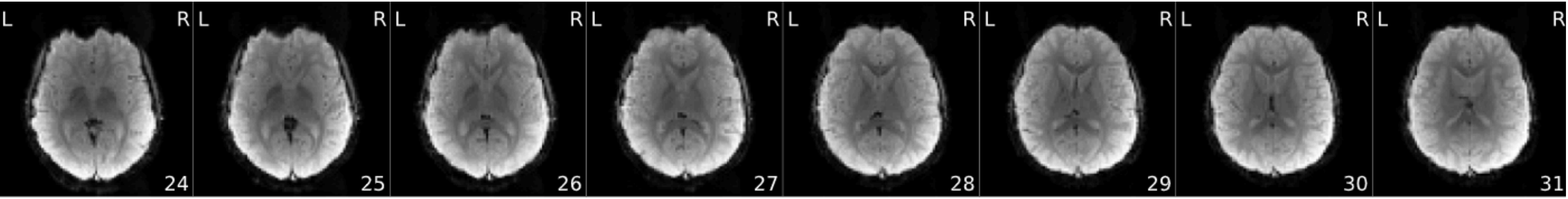


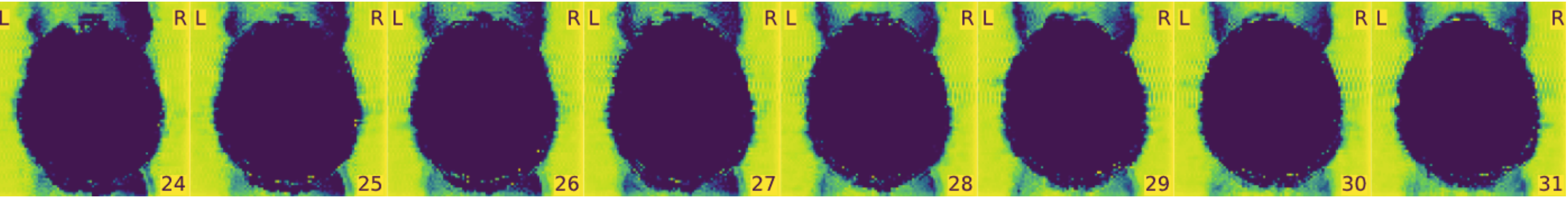
Simultaneous multi slice acquisitions



No free lunch ! (little dirty secrets of EPI)

Average bold signal



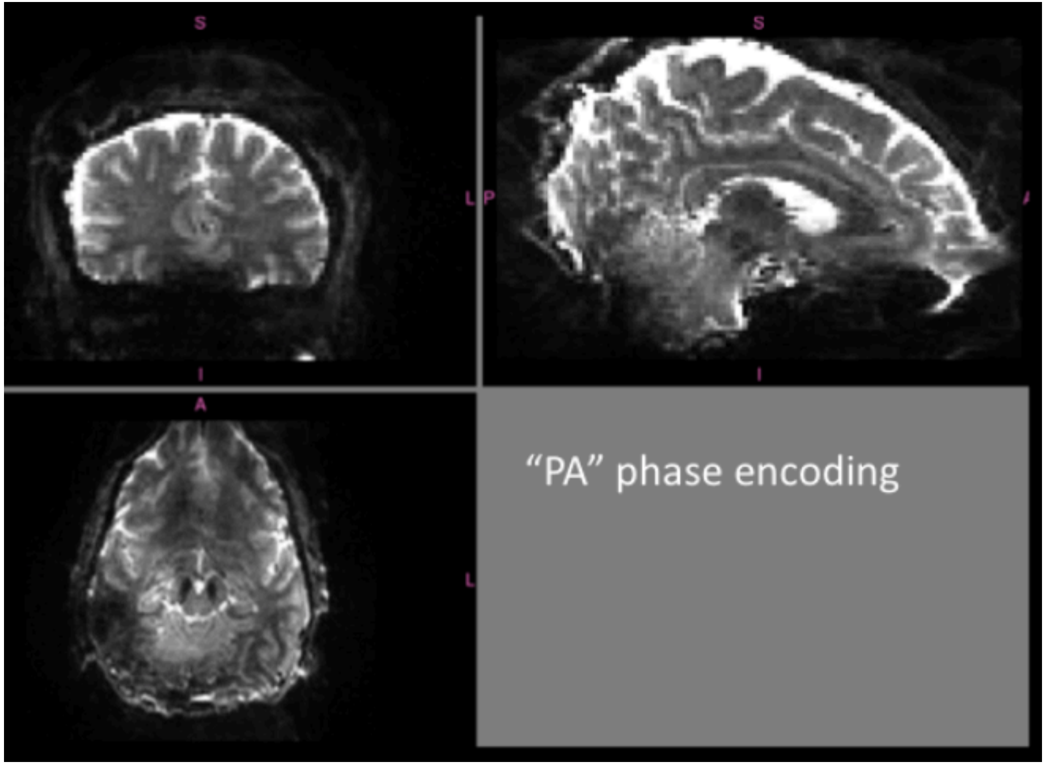


Average bold signal, with background enhancement

⇒ Nyquist ghost N/2

⇒ In general not a problem, but something to check in QC

Problem: large distortions due to magnetic susceptibility (especially at interfaces air/ tissue)



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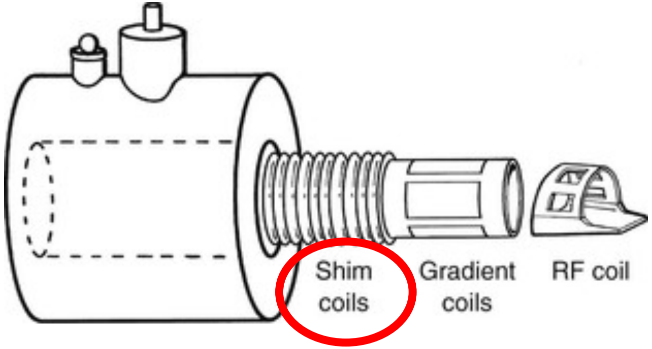
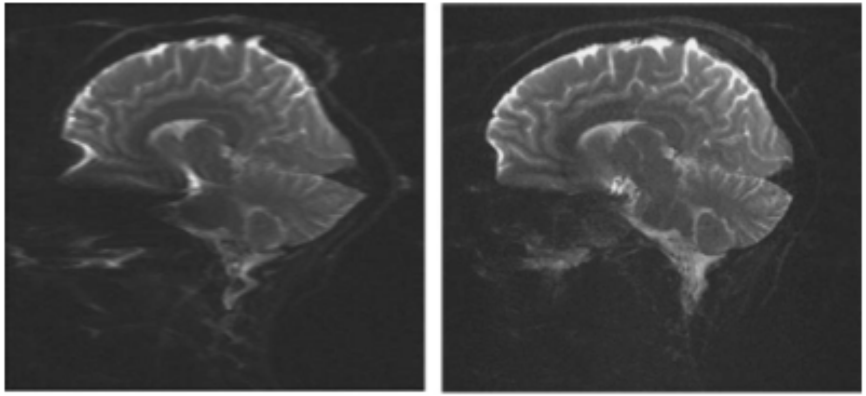


Solutions:

- **On the acquisition side:**

  - best shimming from the scanner
  - Possibility to use parallel excitation

No GRAPPA



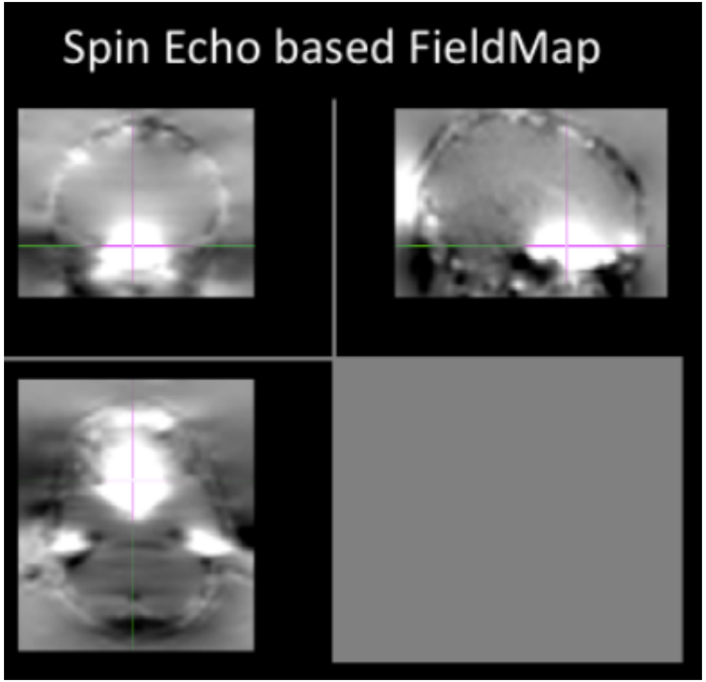
GRAPPA = 3

Problem: large distortions due to magnetic susceptibility (especially at interfaces air/ tissue)

Solutions:

- **On the acquisition side:**

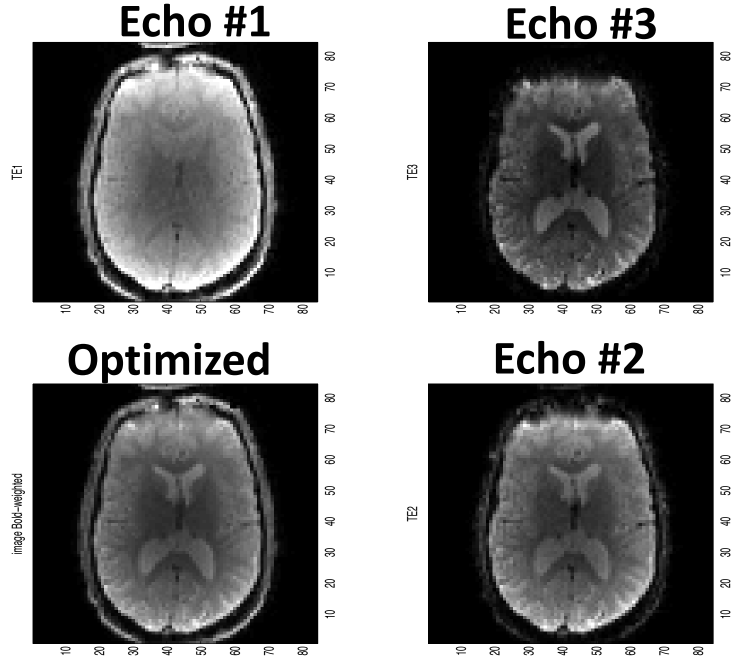
  - Acquire a B0 Fieldmap



=> to be used in preprocessing

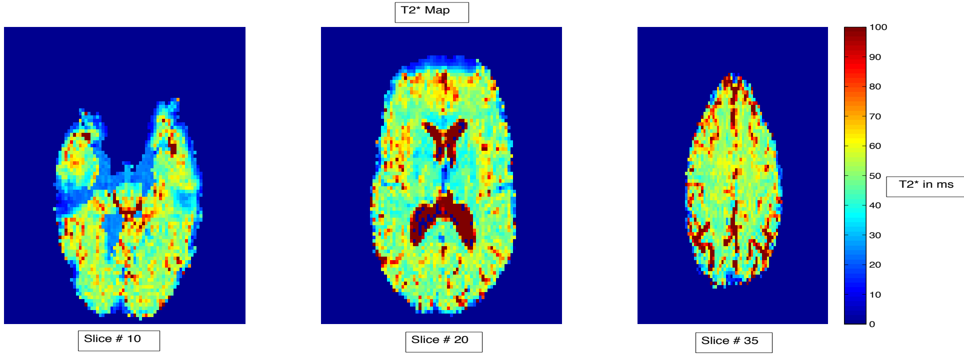
Alternative solutions

Multi-echo EPI

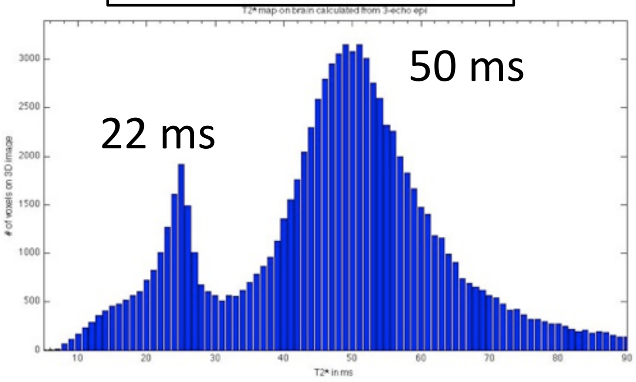


- More than 1 T2* in the brain
- Best BOLD sensitive when TE=T2*
- Which TE to use?

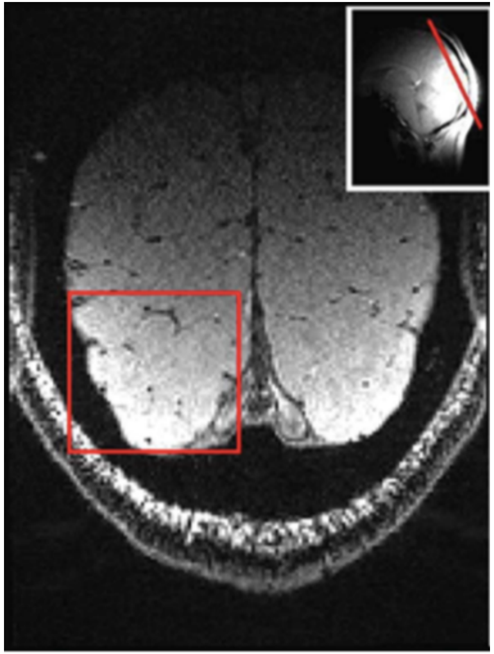
T2* Map

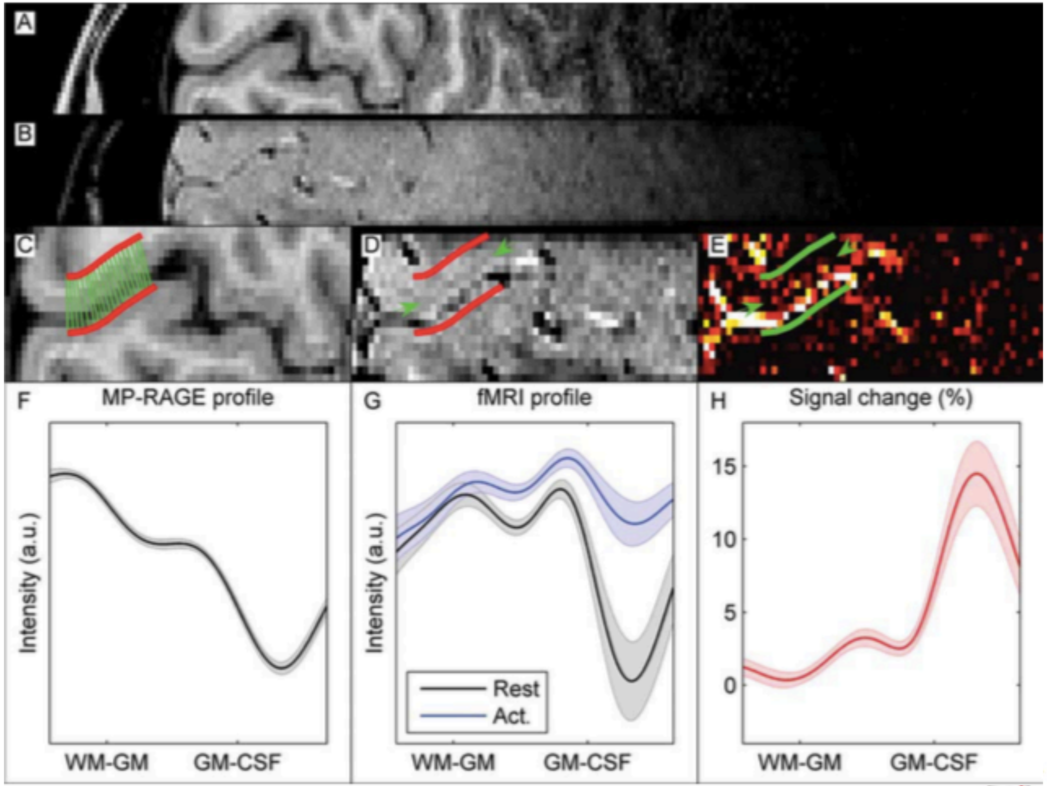


T2 * distribution



3D FLASH (Gradient Echo) sequence
for intra layer fMRI in V1
$0.75 \times 0.75 \times 0.75\ mm^3$ at 3T
20 slices

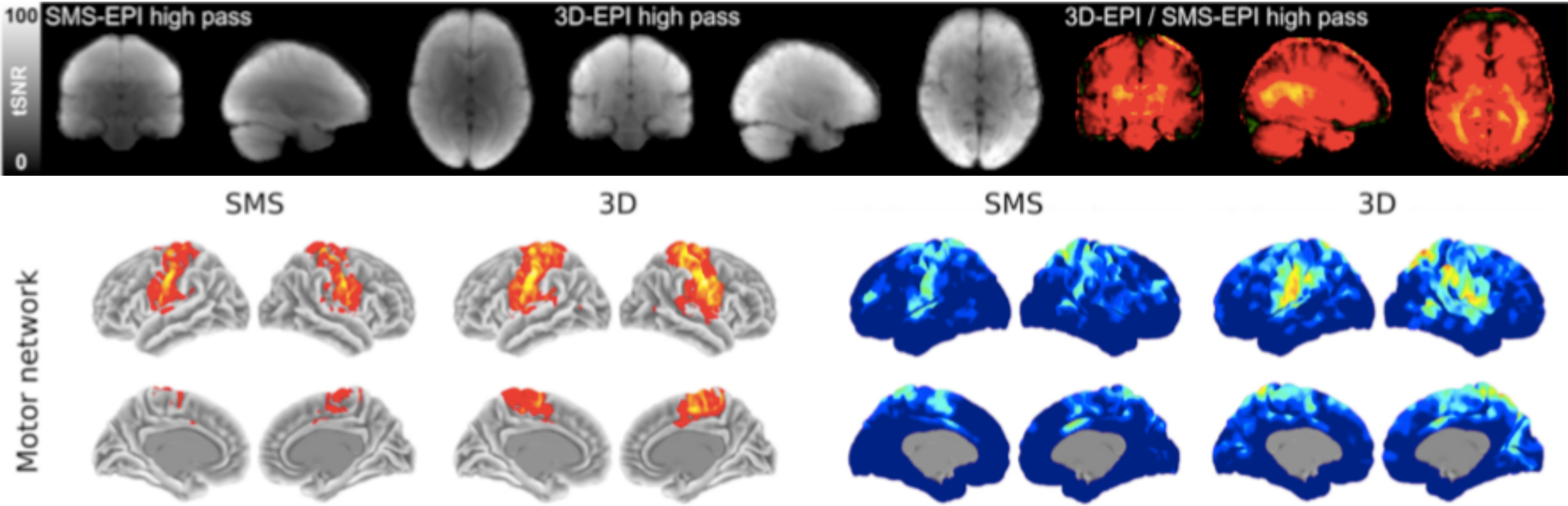




Koopmans, Barth, Norris. HBM (2010)

Not only 2D EPI: 3D EPI at 3T

3T



Average functional connectivity

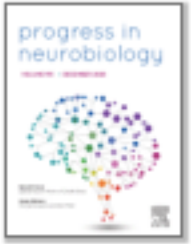
ICC

Stirnberg et al. NeuroImage (2017)

To go further

ELSEVIER

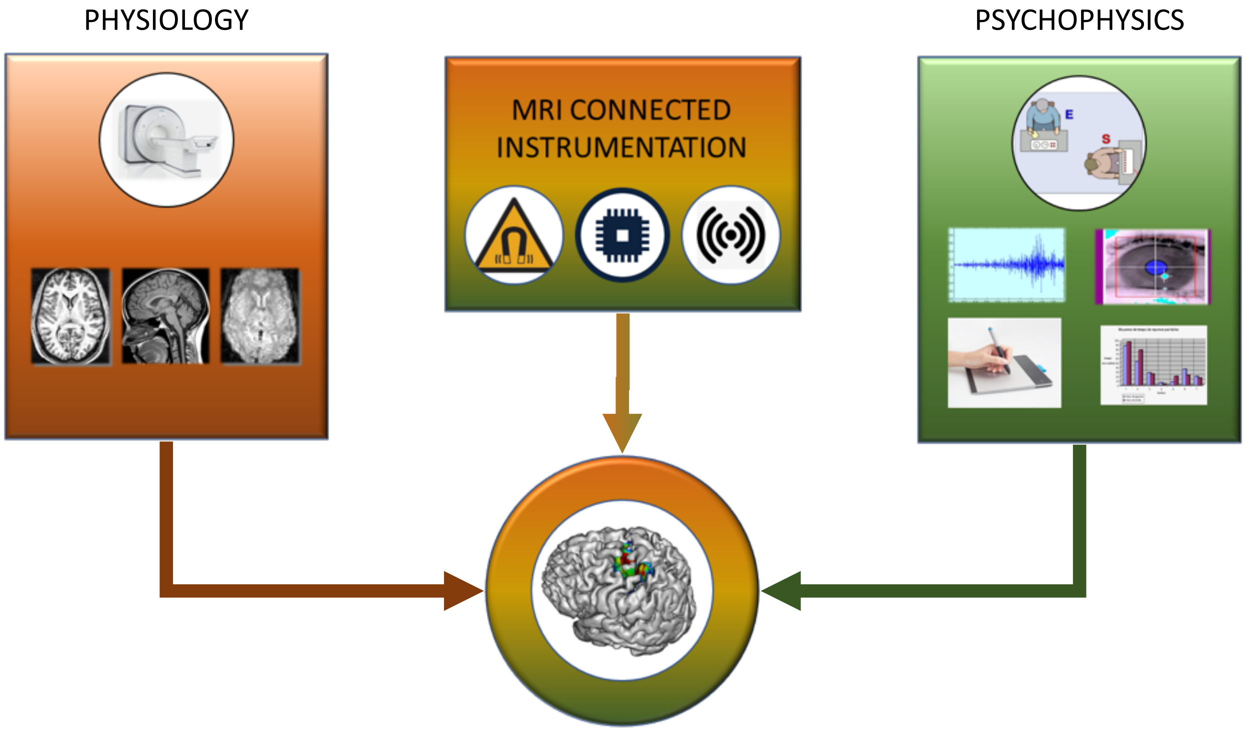
Progress in Neurobiology
Available online 23 October 2020, 101936
In Press, Corrected Proof



Review

New acquisition techniques and their prospects for the achievable resolution of fMRI ☆

Saskia Bollmann [a], Markus Barth [a, b, c]


PHYSIOLOGY
MRI CONNECTED
INSTRUMENTATION
PSYCHOPHYSICS
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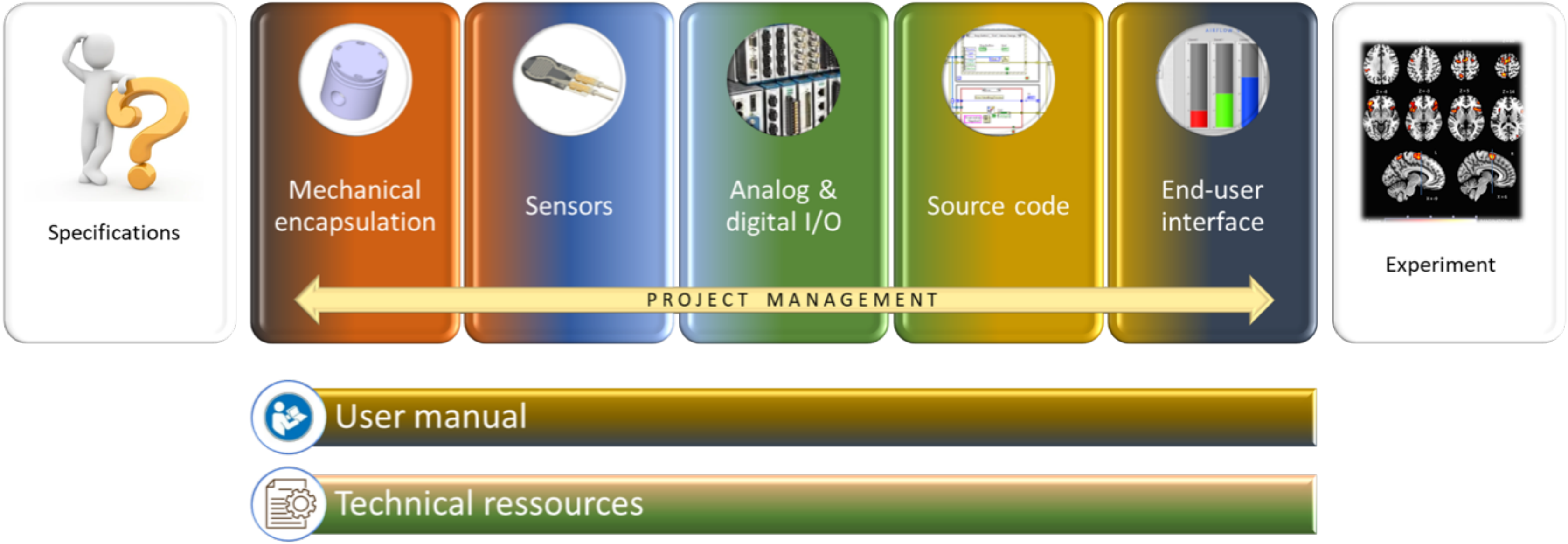
Instrumentation for fMRI – Global template



Instrumentation for fMRI – Hardware solutions

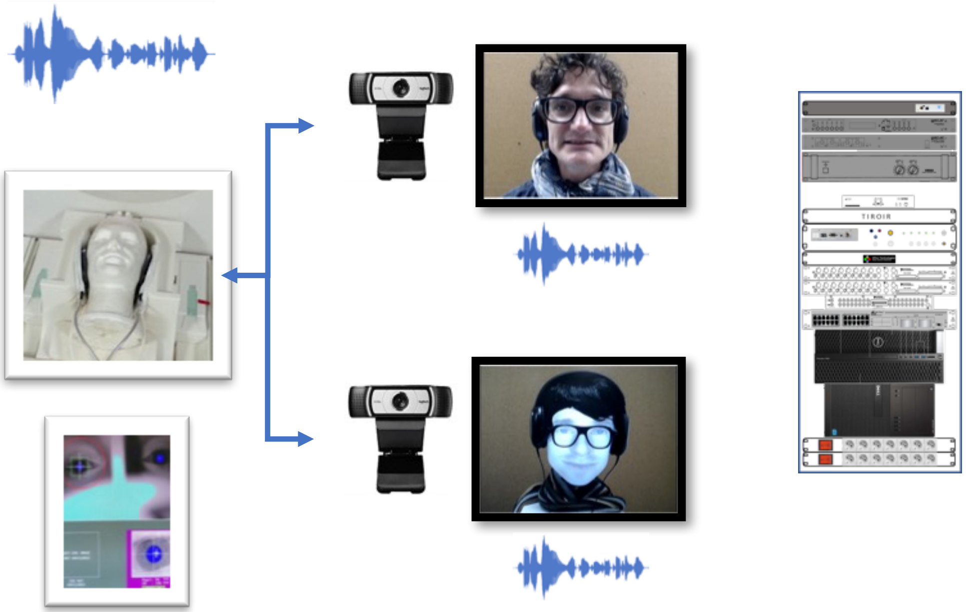
Instrumentation for fMRI – Devices

- Stimulation
  - Visual : 120-1440 Hz FullHD video-projector, LED Matrix stimulator
  - Audio : ANC OptoActive headphones / Passive piezo Sensimetrics earplugs
  - Tactile : regulated parametric airflow dispenser, electric stimulators
  - Proprioceptive : pneumatic vibrators
  - Olfactive : 4 channels smell difuser
  - Fluid dispenser

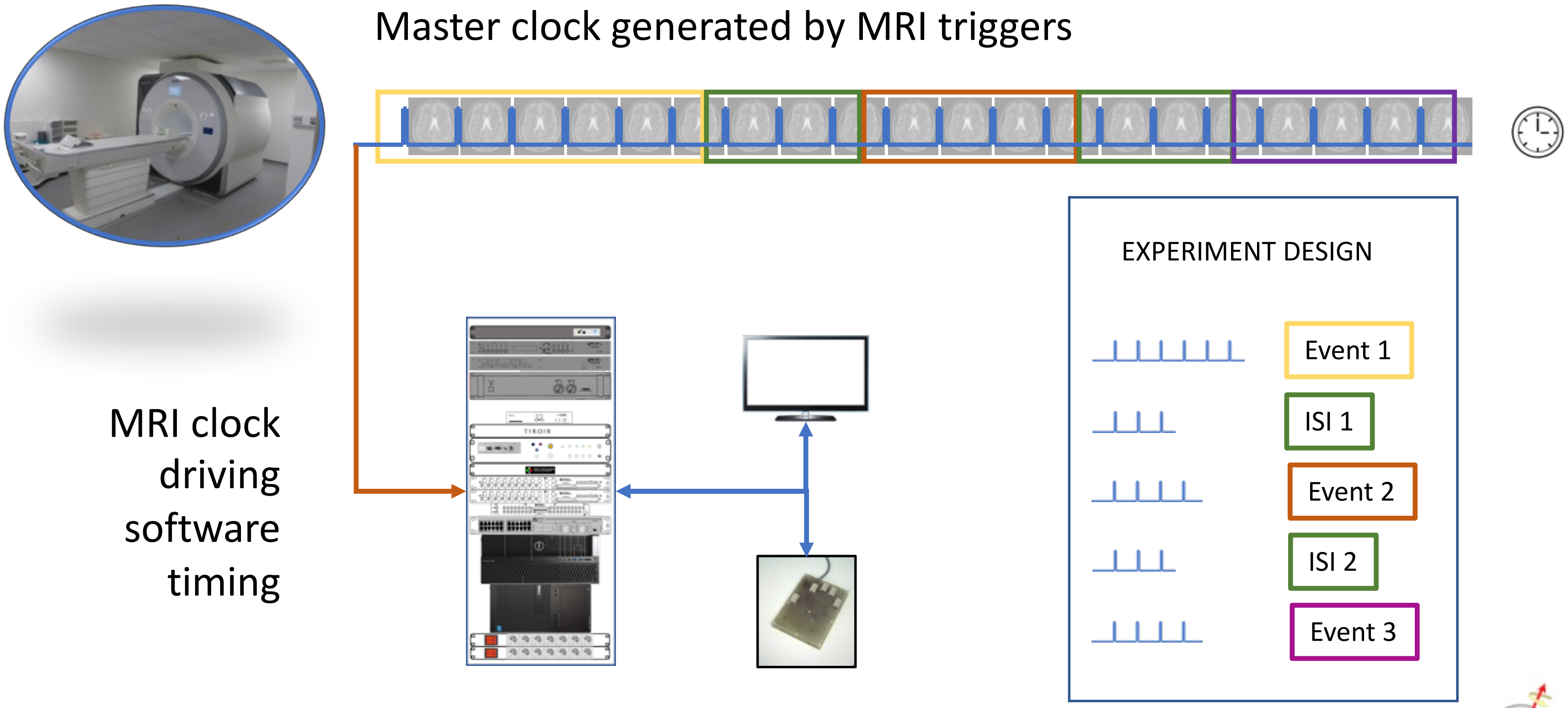
- Behavioral & physiological data recording
  - 5-fingers ergonomic keyboards, response button
  - Force & movement sensors, trackball, joystick
  - Eye movements & pupil size acquisition : 1000 Hz EyeLink from SR-Research
  - Resistive graphic tablet for writing task (100 Hz)
  - ANC optical microphon from OptoAcoustics
  - EMG acquisition
  - Physiological monitoring & acquisition (PPG / Respiratory belt / SPO2)

Instrumentation for fMRI – The Challenge

How to make several instruments working together and synchronously



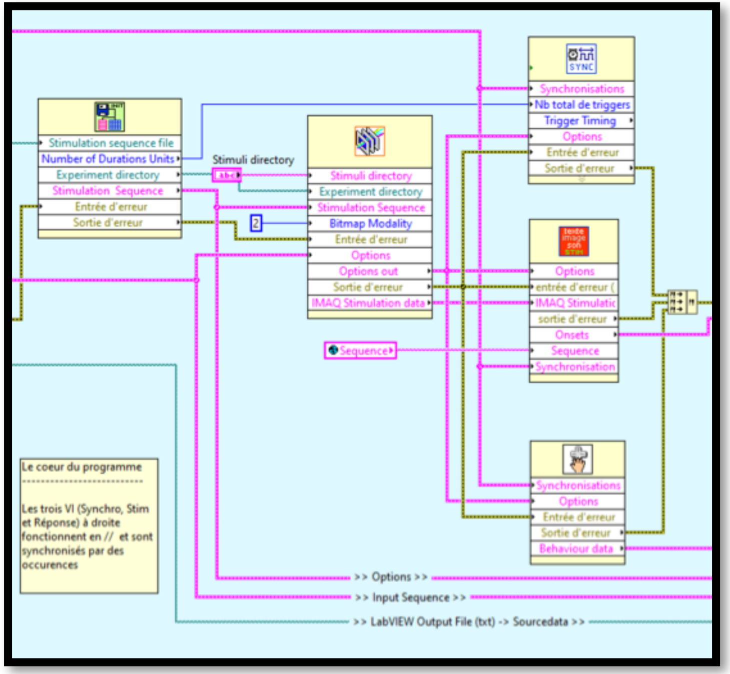
Instrumentation for fMRI – Master/Slave template

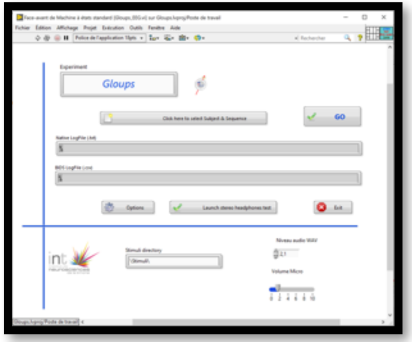


How to make several instruments working together and synchronously

- Multi-threading
- Parallel programming
- Real-time processing

NATIONAL INSTRUMENTS LabVIEW

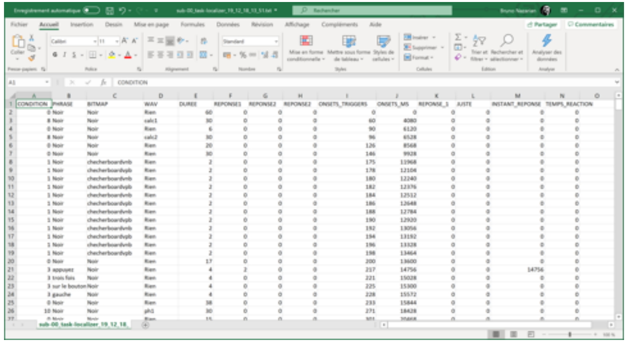


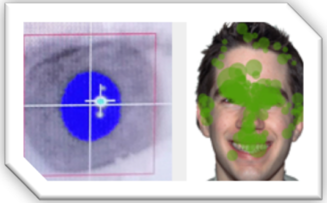


Instrumentation for fMRI – Outputs (Data)

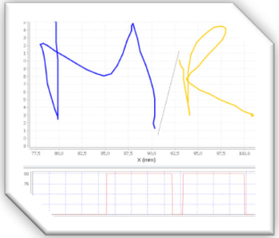
Stimulation timings and behavioral data

Onsets, digital responses, reaction times



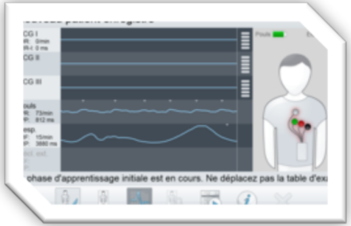


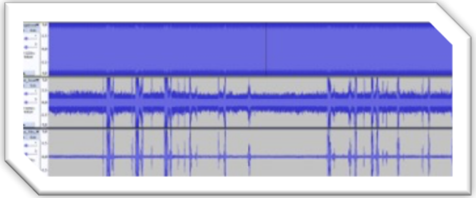
Eye movements



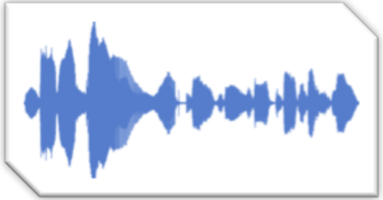
Complex tasks production

Physiology



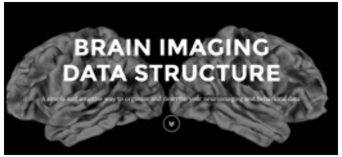


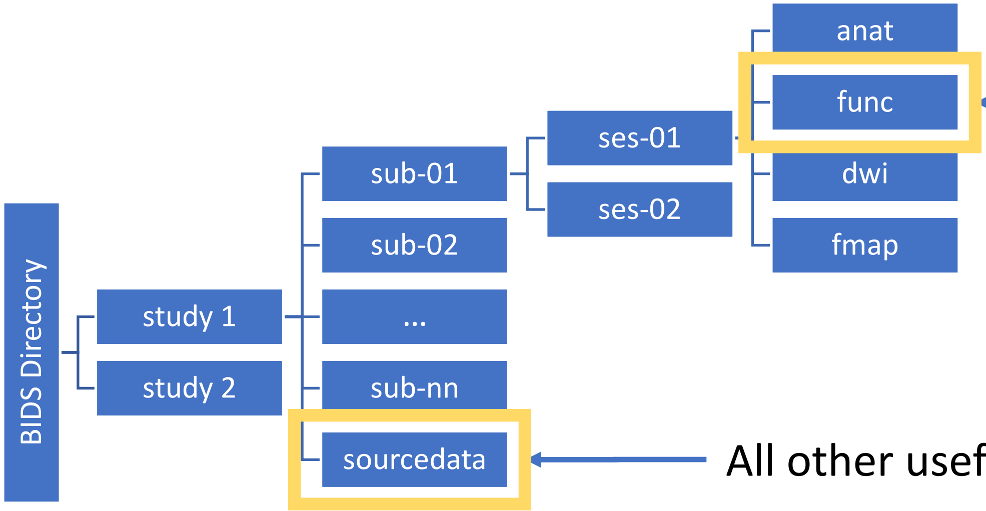
Electrophysiology



Vocal responses

Brain Imaging Data Structure : BIDS

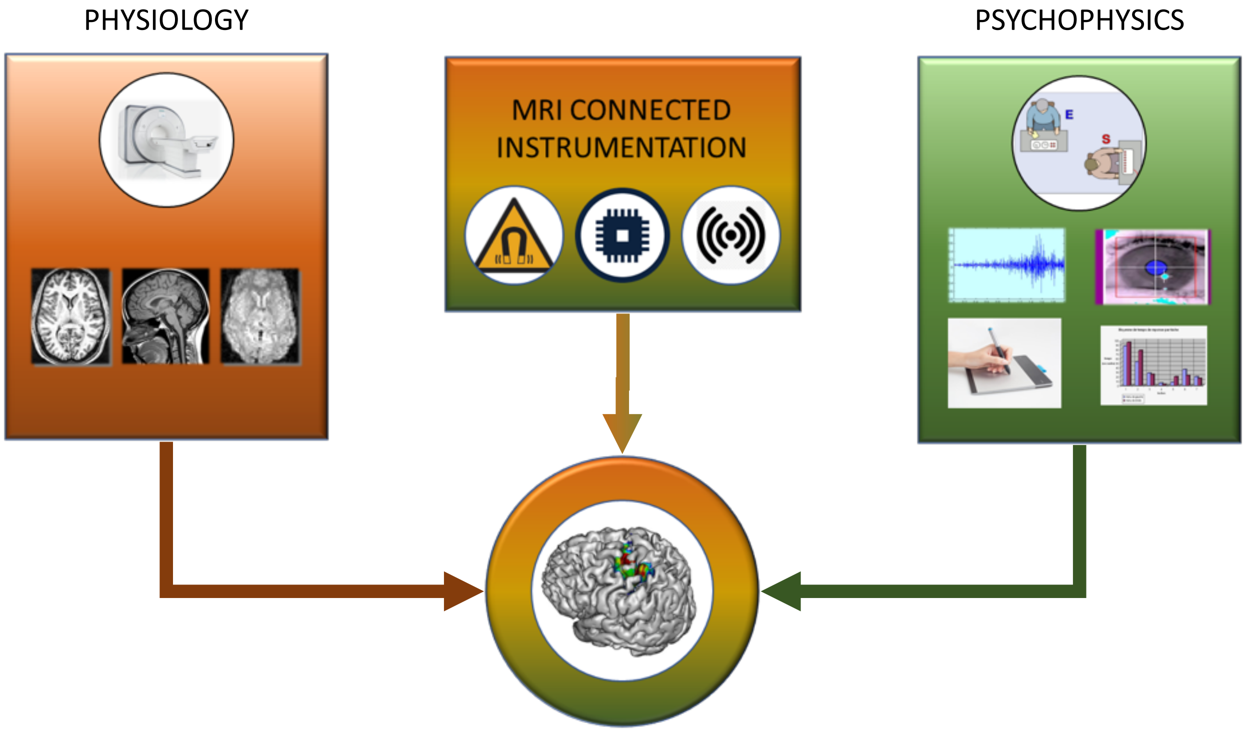




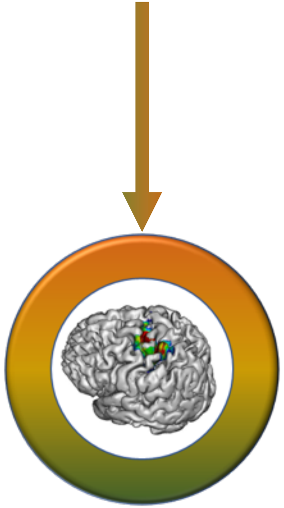
Basic « events » TSV files

All other useful ressource files (WAV, AVI, EDF, …)

Instrumentation for fMRI – Outputs (next step)

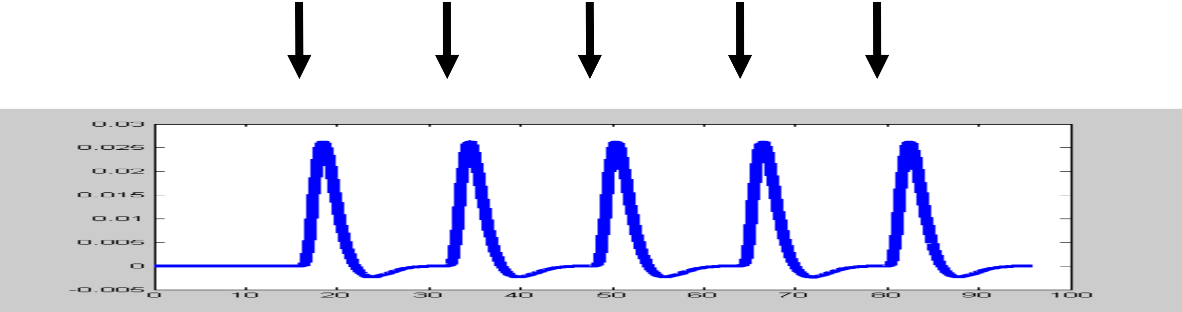


PROCESSING



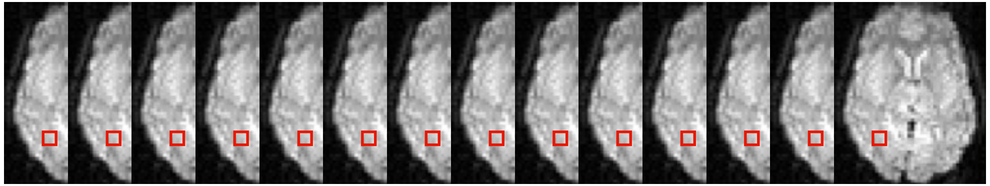
Experimental principle in summary

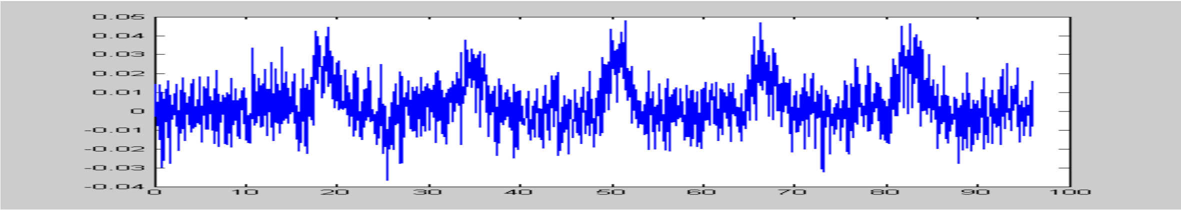
Simple example : one type of stimuli



expected
BOLD response

Concurrently, acquisition of numerous functional brain volumes





fMRI signal
recorded in a voxel

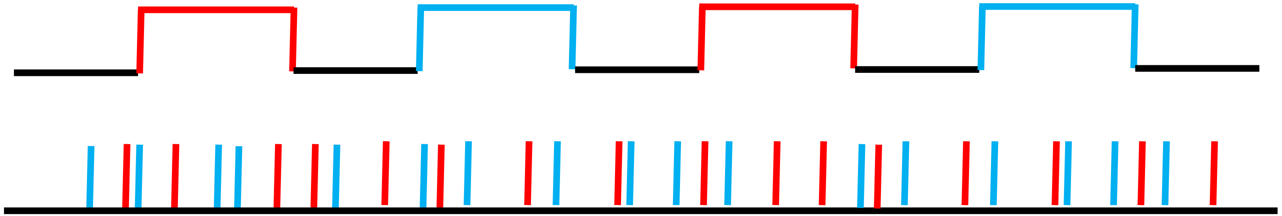
fMRI psychophysics protocols

Tasks design :

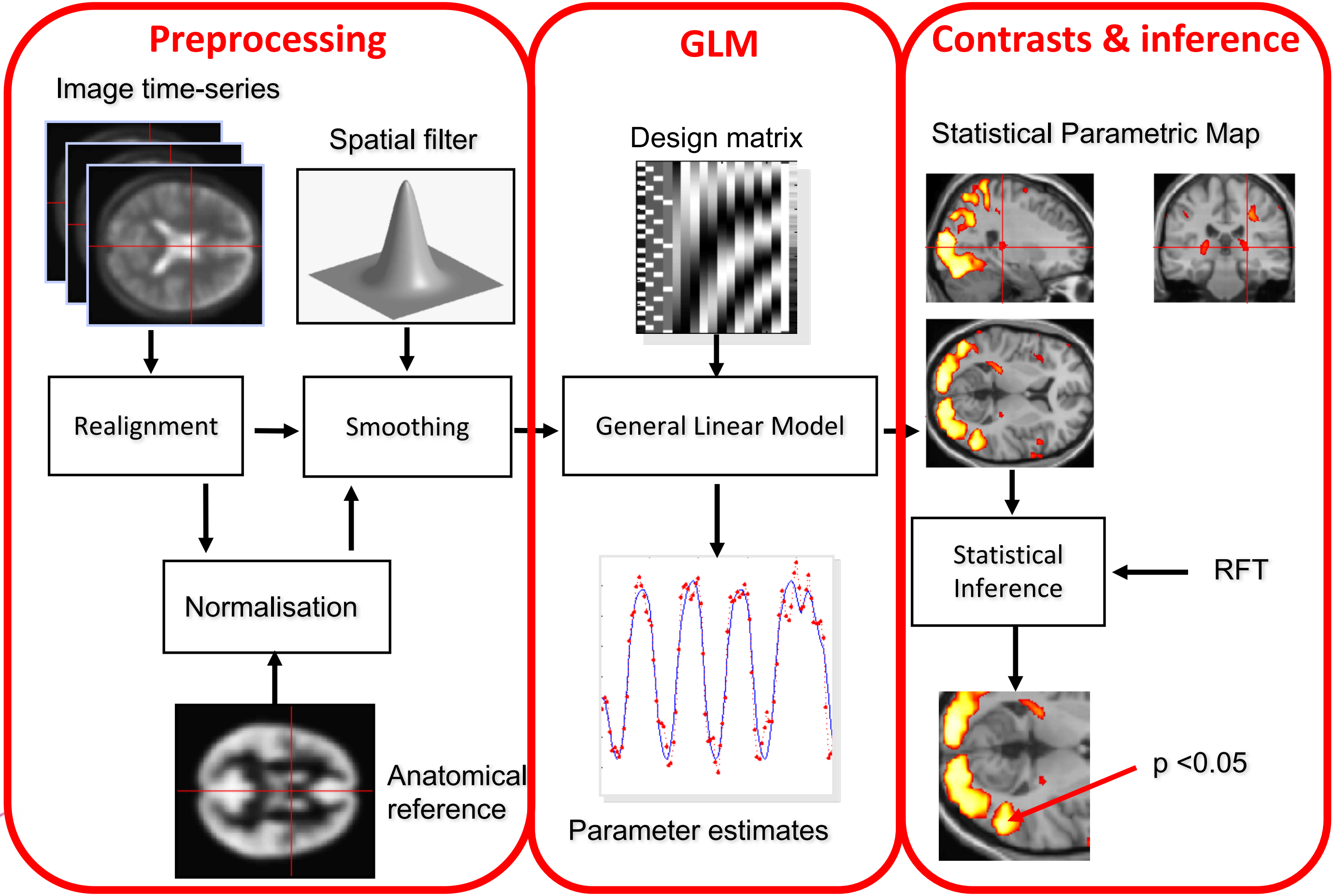
- Simple « cognitive subtraction » : task A versus task B
- Factorial design : e.g. 2 factors :
    - sensory modality (visual or tactile)
    - nature of stimulus (left or right)
- Parametrical : e.g. varying the intensity of the stimuli, the load of the Working Memory, …
- Repetition Suppression : the activation level depends on the similarity of two consecutive stimuli (priming effect)

Temporal design :

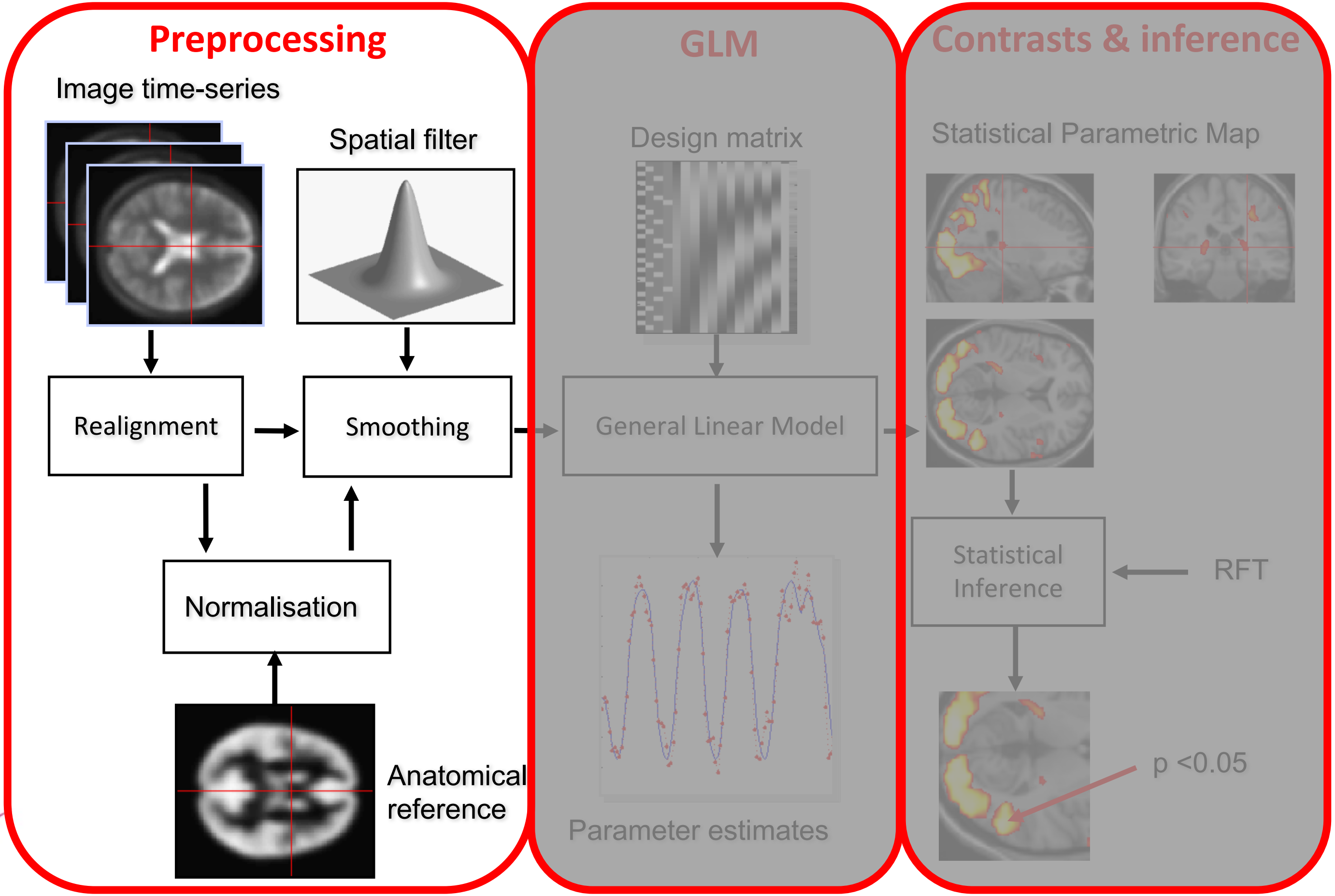
- Block design
- Event design



General fMRI processing scheme



General fMRI processing scheme



Preprocessing : data correction for artefacts

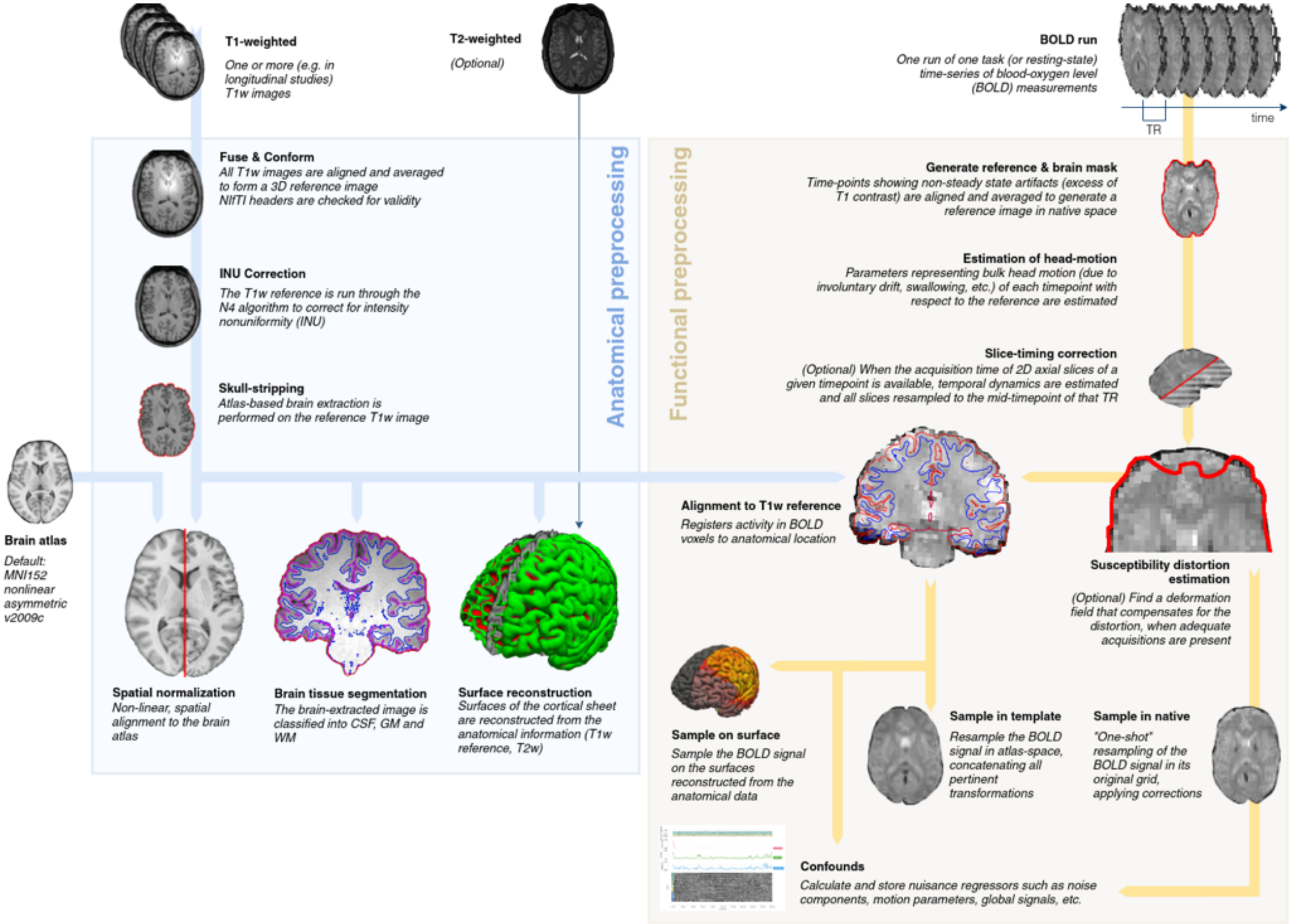
- Motion of subject's head → motion correction of EPI-BOLD volumes

Distorsion of EPI-BOLD volumes
(due to inhomogeneity of magnetic field) → susceptibility distorsion correction (based on fielmap)

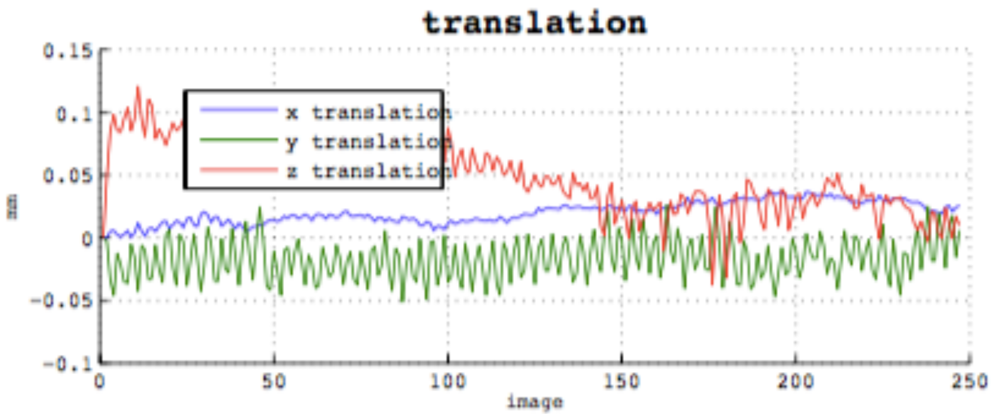
Motion / distorsion btw structural & functional → coregister the functional volumes onto structural one

Normalize each subject data to a standard space for group study

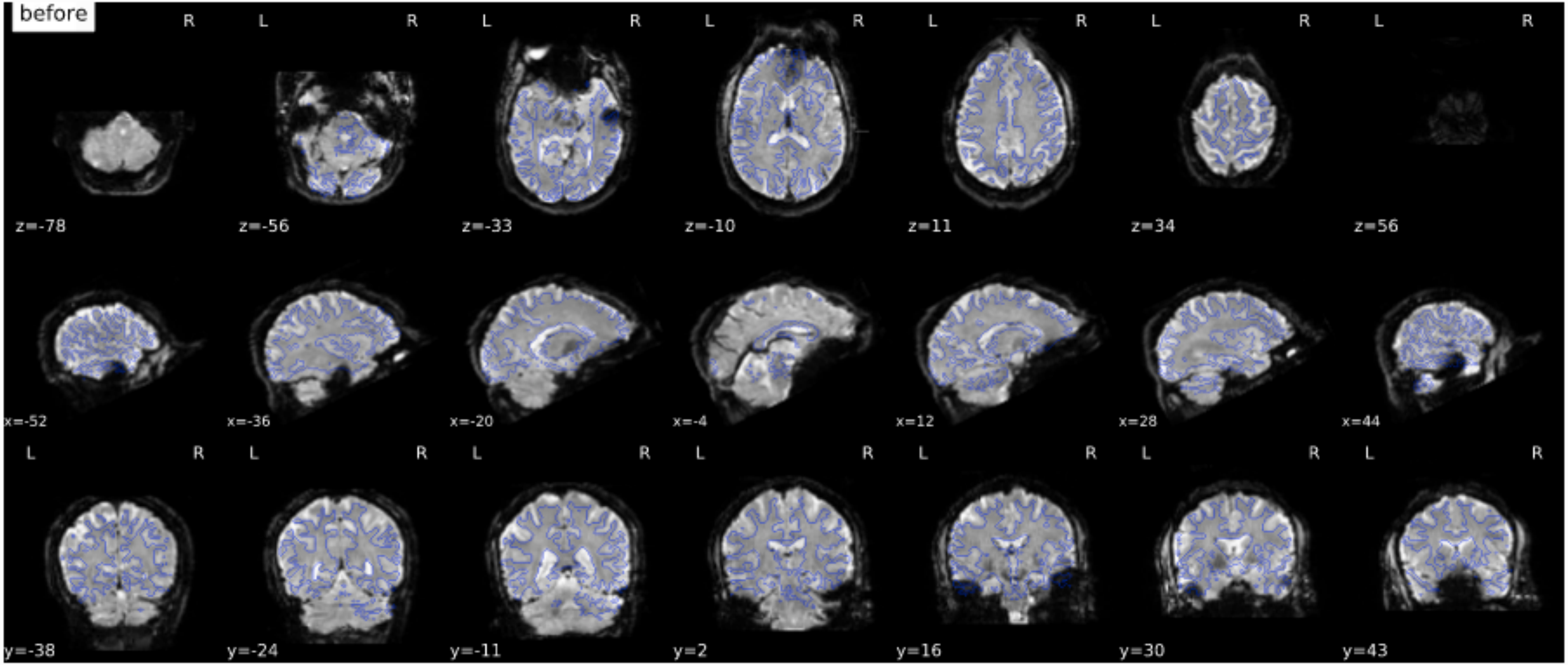
FMRI-PREP preprocessing pipeline



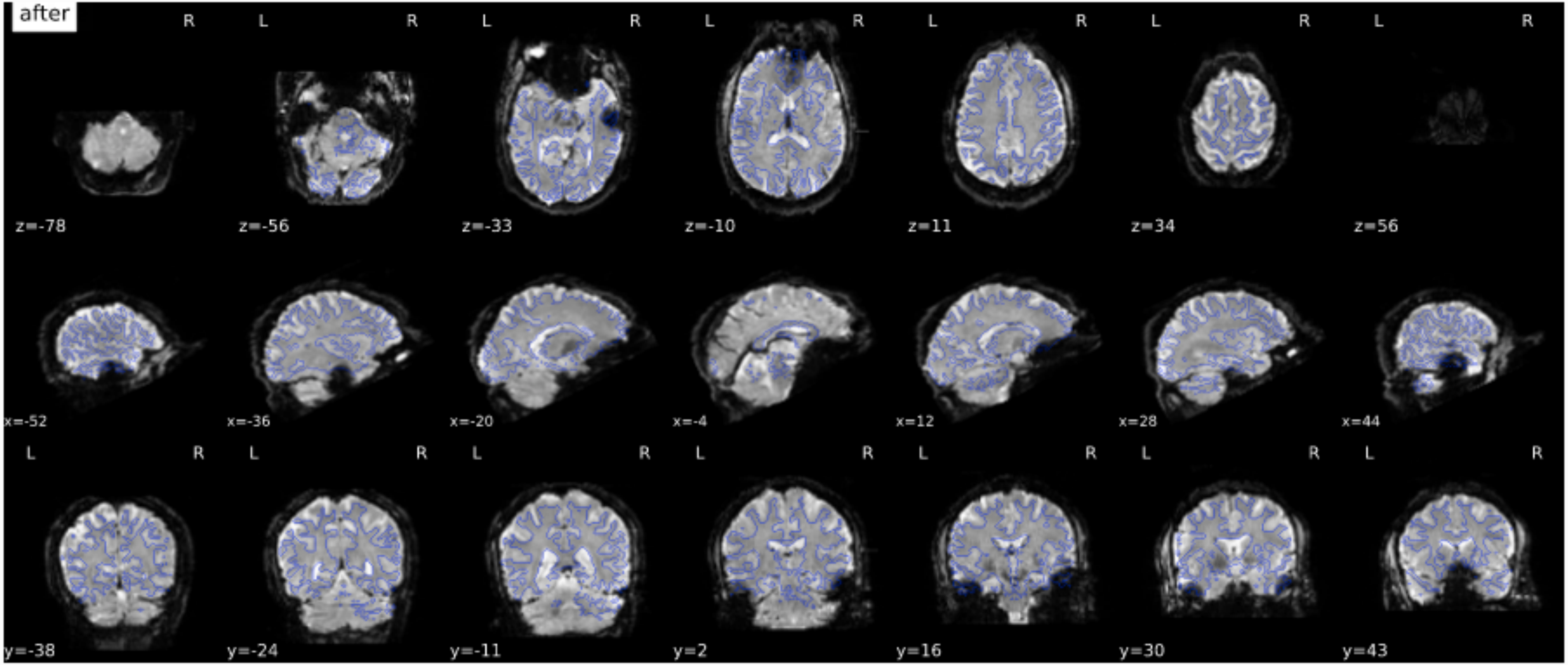
Motion correction of EPI-BOLD volumes



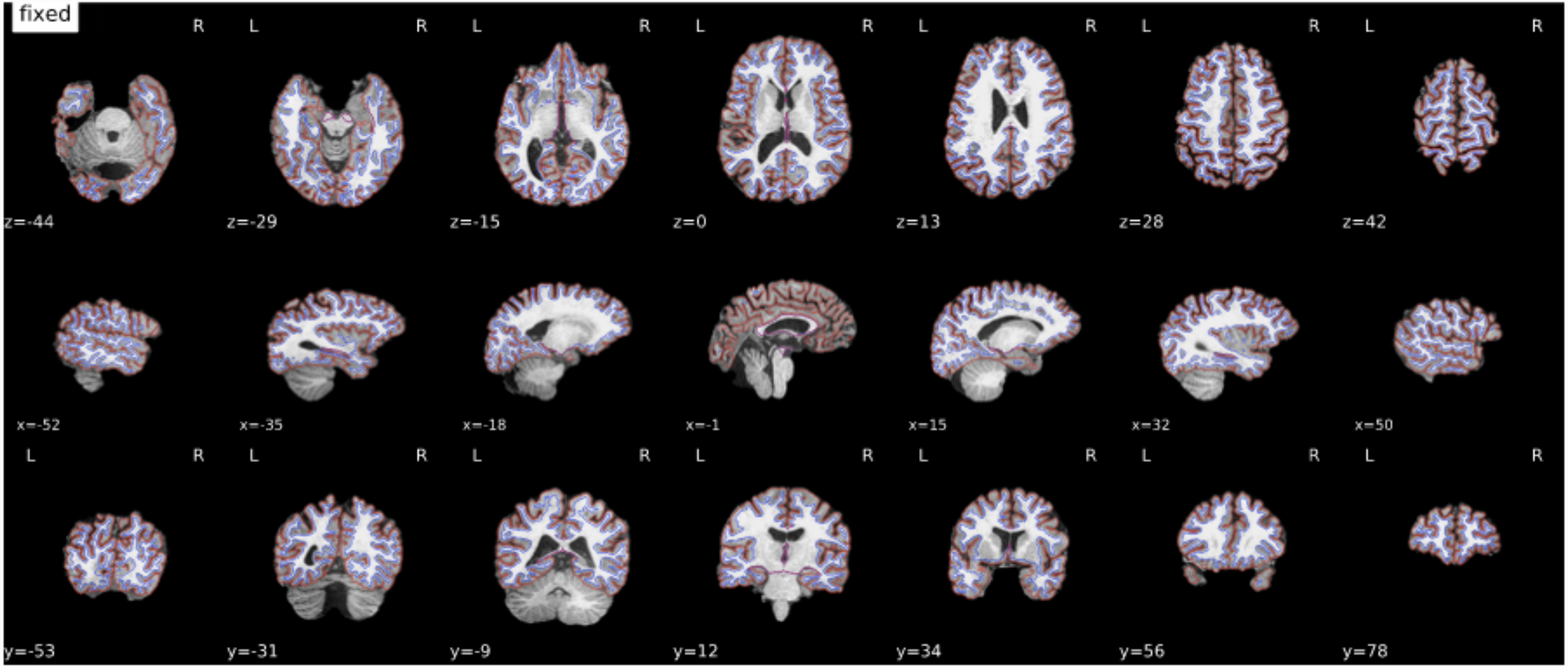
Susceptibility distorsion correction



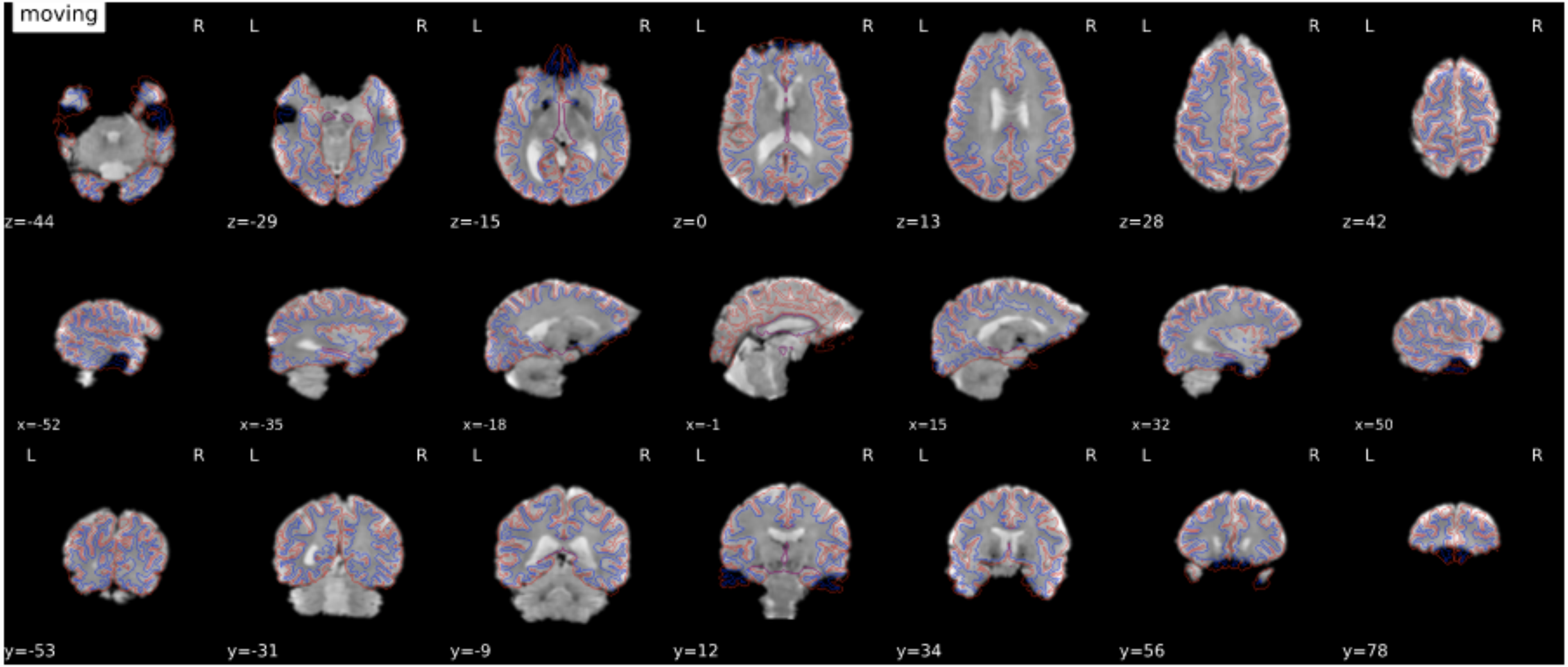
Susceptibility distorsion correction



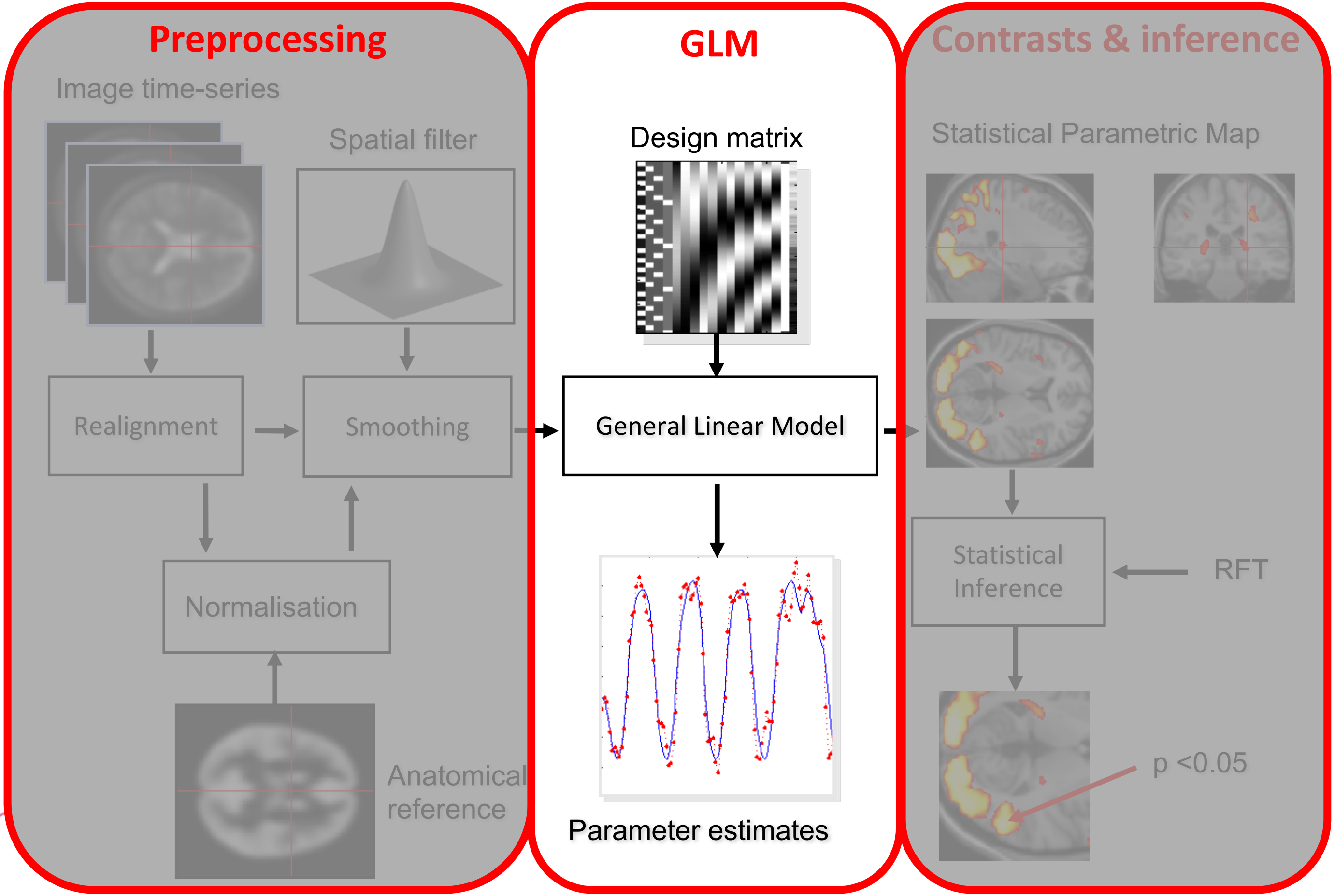
Coregister functional & anatomical data



Coregister functional & anatomical data



General fMRI processing scheme



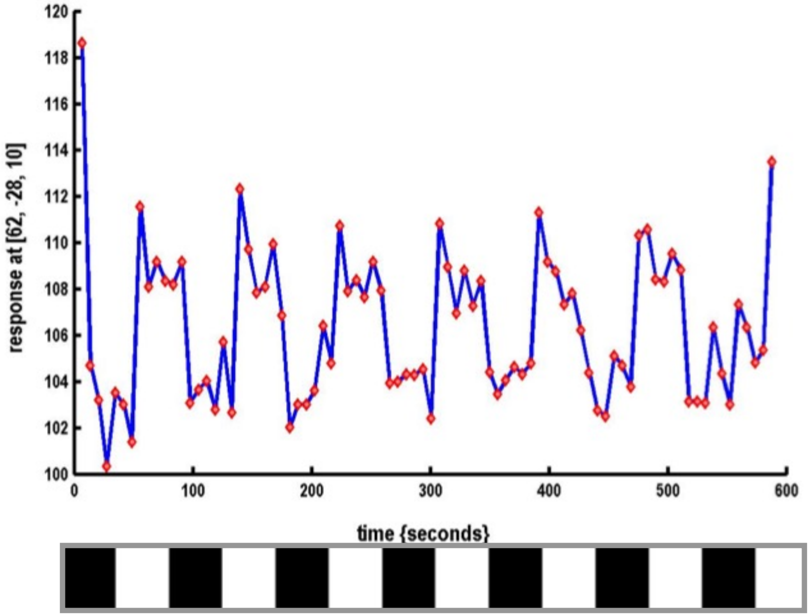
A very simple fMRI experiment

One session

Passive word listening versus rest

7 cycles of rest and listening

Blocks of 6 scans with 7 sec TR

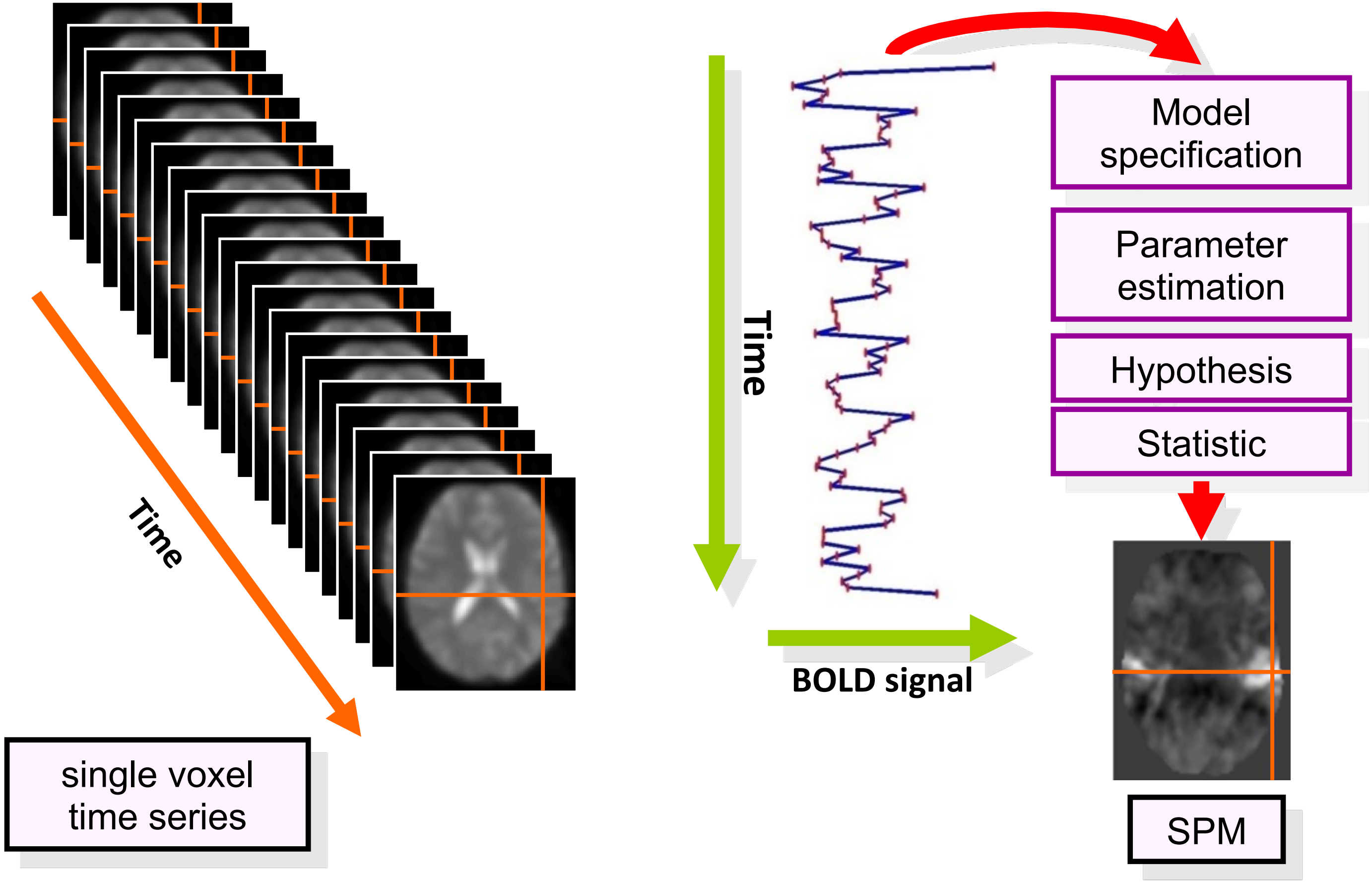


Stimulus function

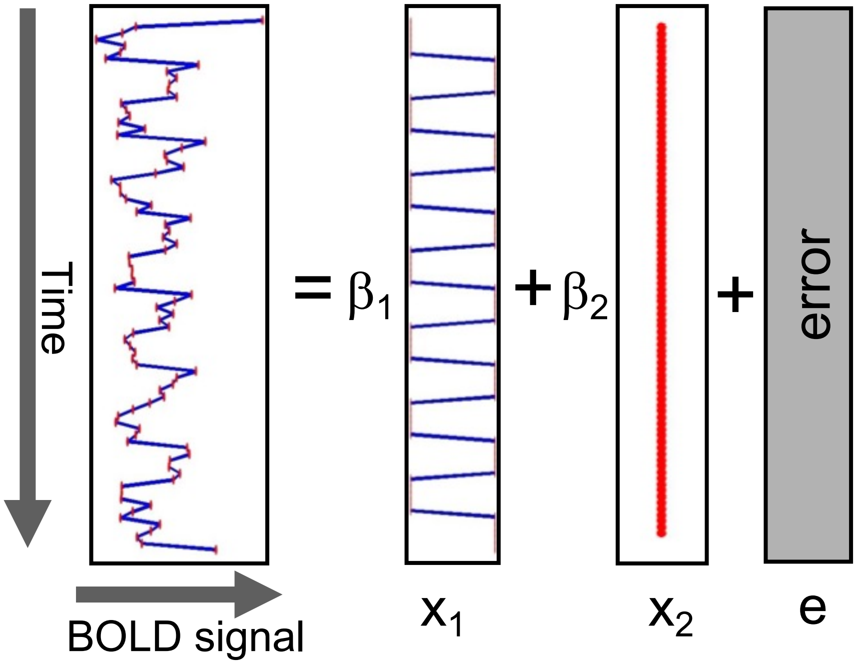
Question: Is there a change in the BOLD response between listening and rest ?

General Linear Model (GLM)

Voxel-wise time series analysis

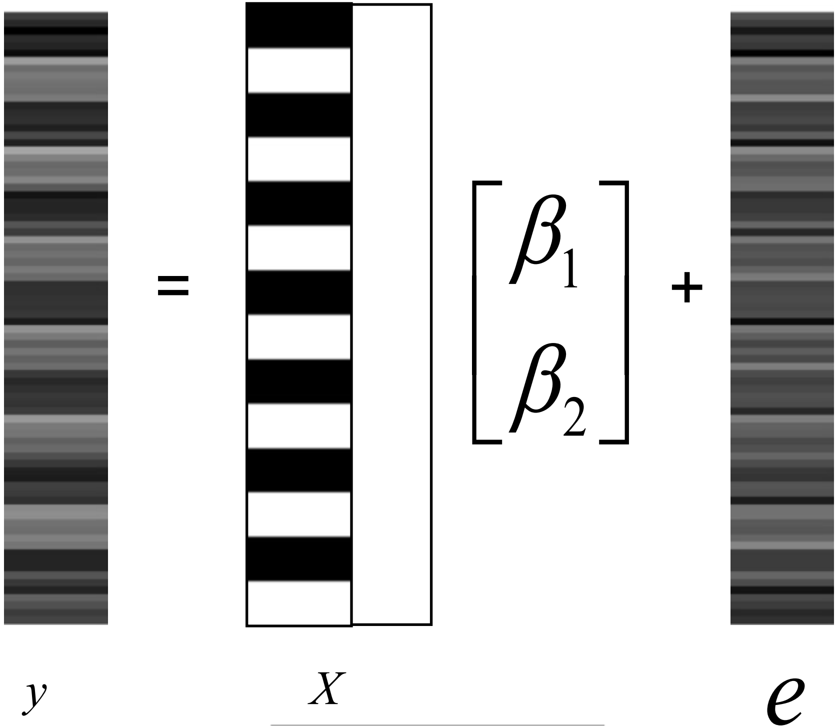


Single voxel regression model



$$y = x_1\beta_1 + x_2\beta_2 + e$$

Parameter estimation



$$y = X\beta + e$$

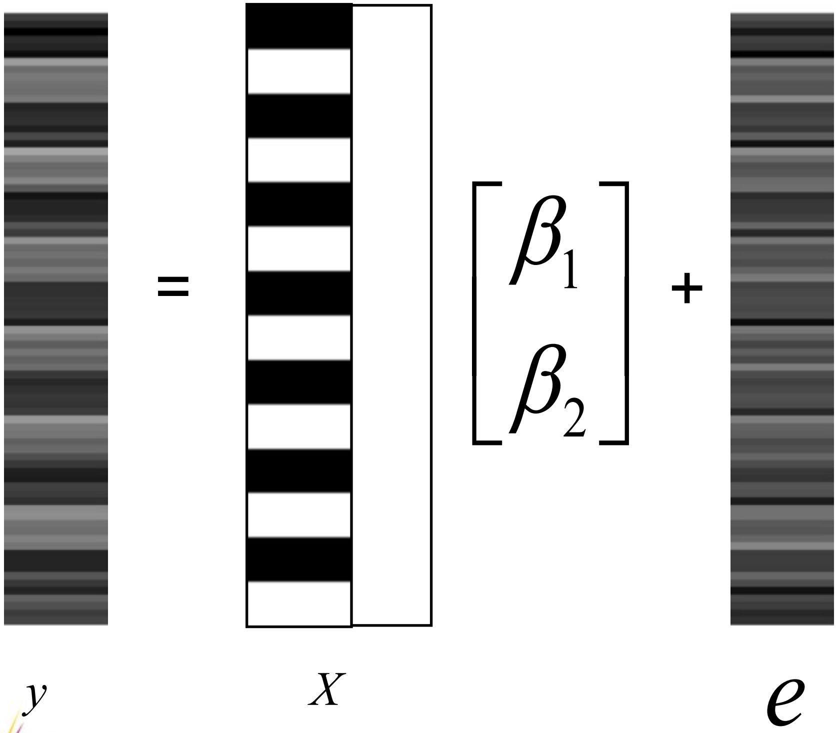
Estimate parameters β to minimize : $\sum_{t=1}^{N} e_t^2$

Ordinary least squares estimation (OLS) (assuming i.i.d. error):

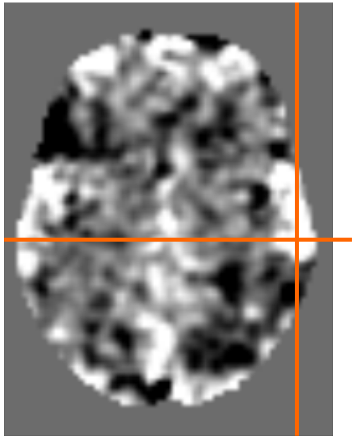
$$\hat{\beta} = (X^T X)^{-1} X^T y$$

$$\hat{\beta} \sim N(\beta, \sigma^2 (X^T X)^{-1})$$

Mass-univariate analysis



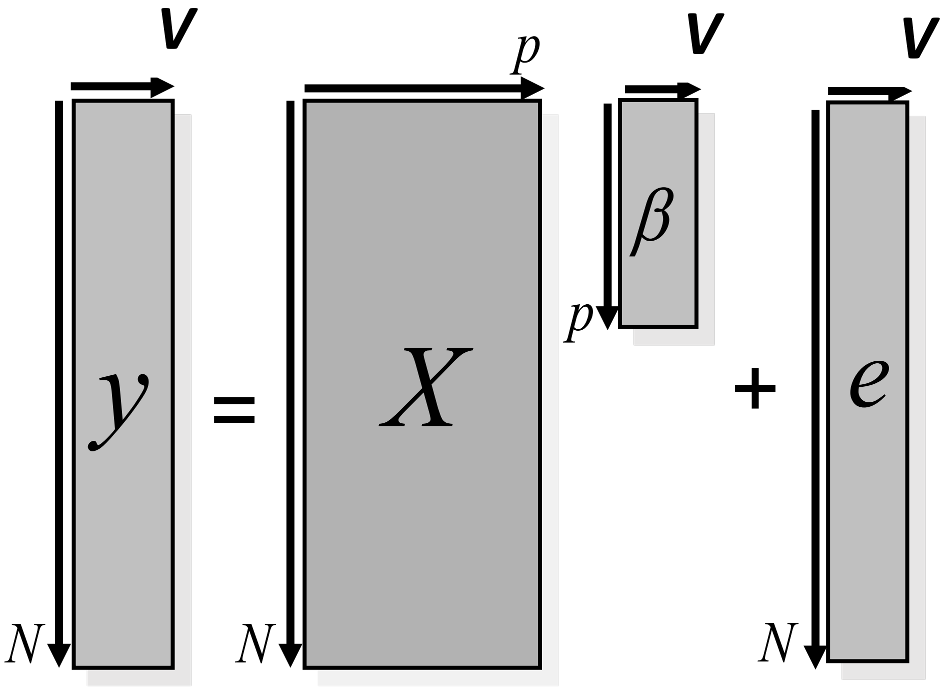
for each voxel



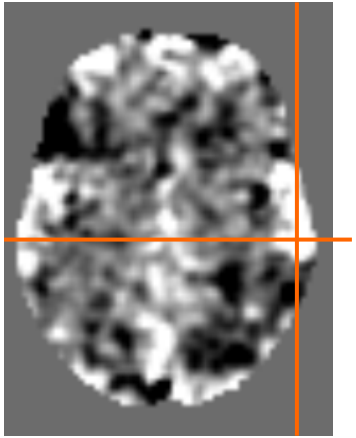
2 beta maps
1 error map

$$y = X\beta + e$$

Mass-univariate analysis



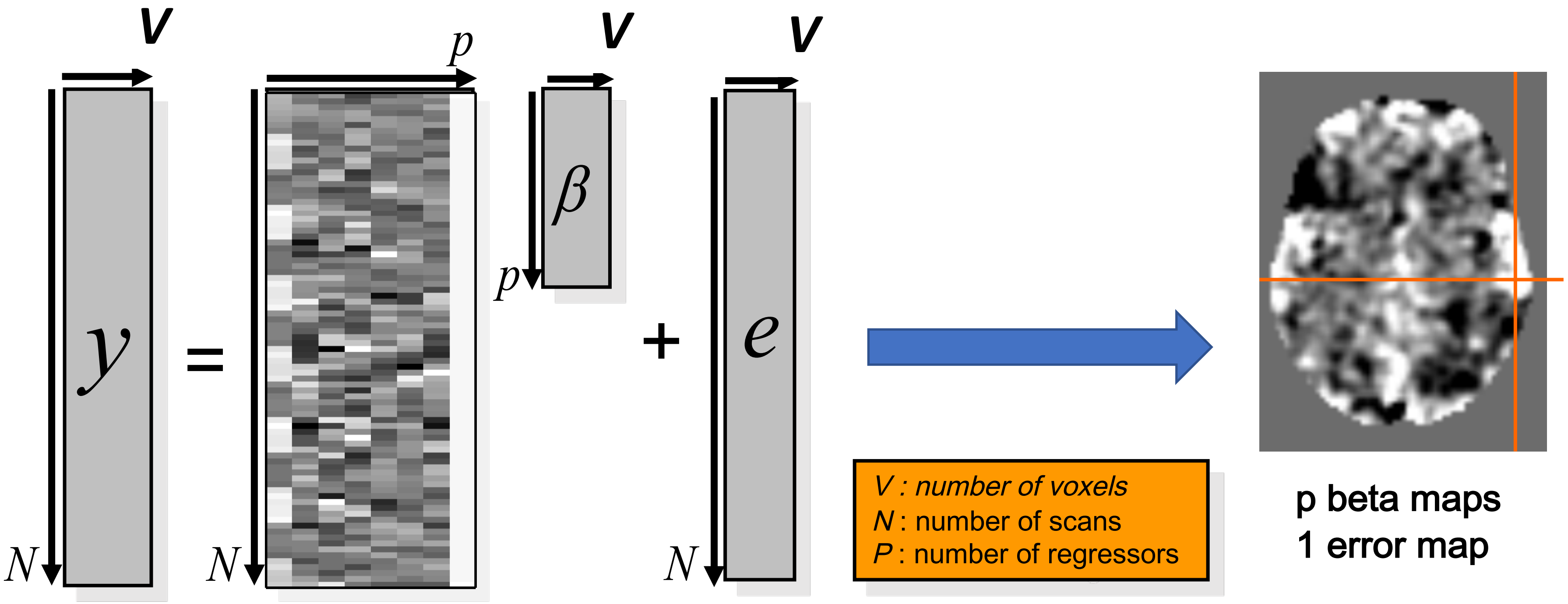
V : number of voxels
N : number of scans
P : number of regressors



p beta maps
1 error map

The design matrix X embodies all available knowledge about experimentally controlled factors and potential confounds.

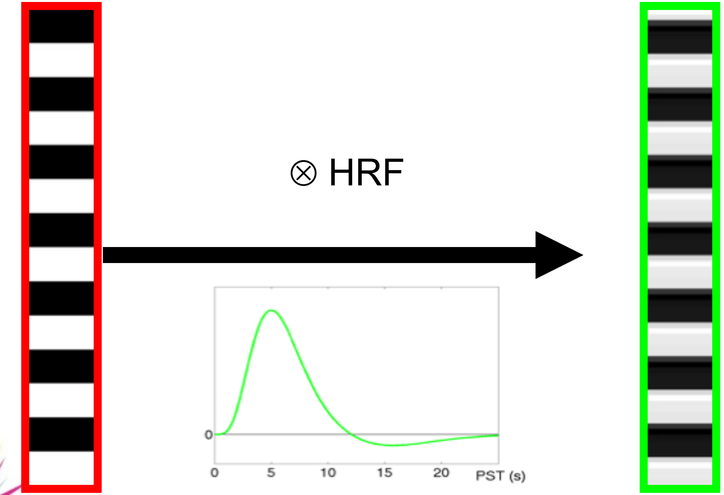
Mass-univariate analysis

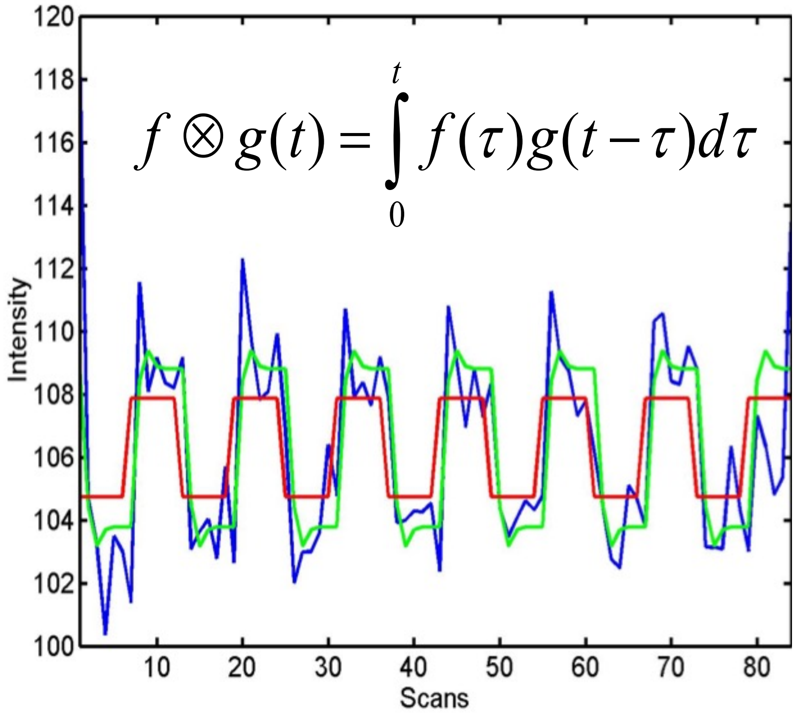


The design matrix X embodies all available knowledge about experimentally controlled factors and potential confounds.

Convolution model of the BOLD response

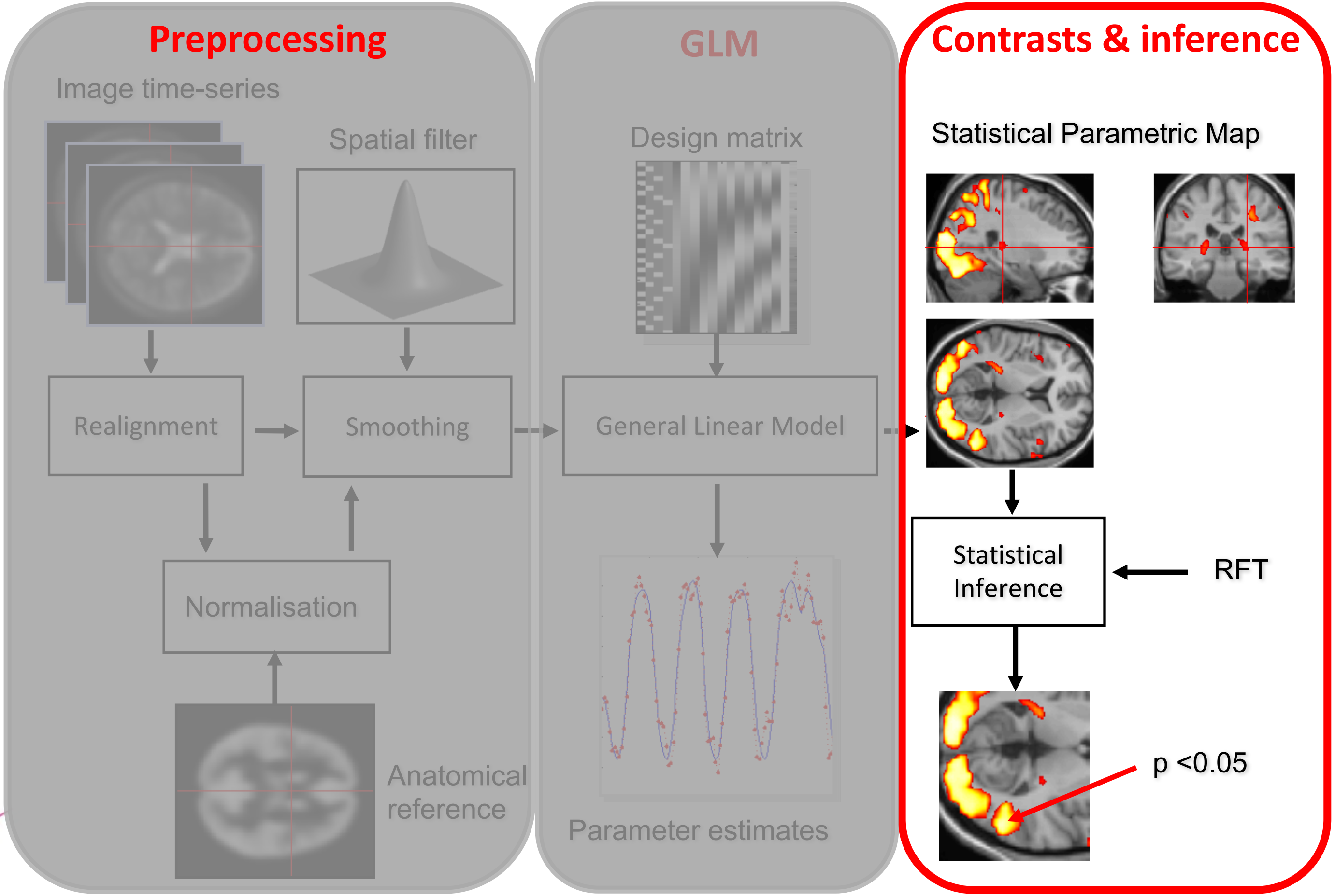
Convolve stimulus function with a << canonical>> hemodynamic response function (HRF):





$$f \otimes g(t) = \int_0^t f(\tau)g(t-\tau)d\tau$$

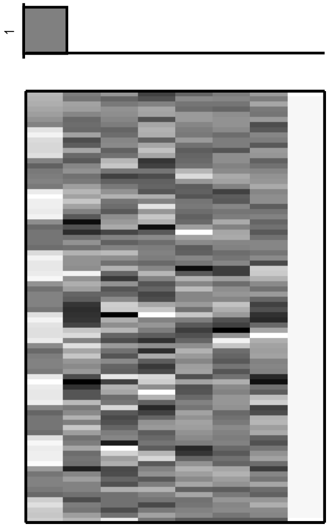
General fMRI processing scheme



T-test: a simple example

- Passive word listening versus rest

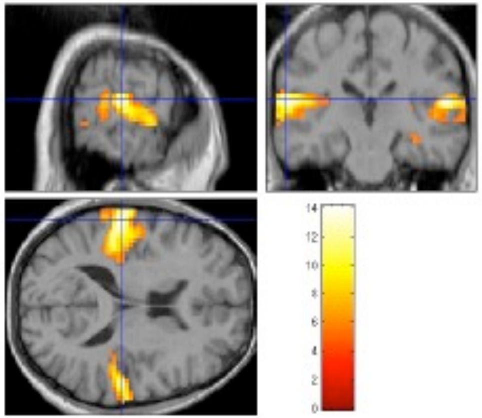
c^T = [1 0 0 0 0 0 0 0]



Q: activation during listening ?

Null hypothesis: $\beta_1 = 0$

$$t = \frac{c^T \hat{\beta}}{\sqrt{\mathrm{var}(c^T \hat{\beta})}}$$



SPMresults:

Height threshold T = 3.2057 {p<0.001}

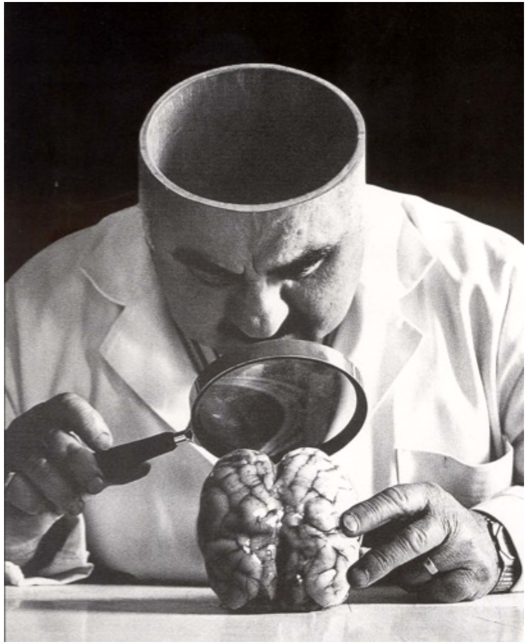
voxel-level

T	(Z)	$p_{uncorrected}$	mm	mm	mm
13.94	**Inf**	**0.000**	**-63**	**-27**	**15**
12.04	Inf	0.000	-48	-33	12
11.82	Inf	0.000	-66	-21	6
13.72	**Inf**	**0.000**	**57**	**-21**	**12**
12.29	Inf	0.000	63	-12	-3
9.89	7.83	0.000	57	-39	6
7.39	**6.36**	**0.000**	**36**	**-30**	**-15**
6.84	**5.99**	**0.000**	**51**	**0**	**48**
6.36	**5.65**	**0.000**	**-63**	**-54**	**-3**
6.19	**5.53**	**0.000**	**-30**	**-33**	**-18**
5.96	**5.36**	**0.000**	**36**	**-27**	**9**
5.84	**5.27**	**0.000**	**-45**	**42**	**9**
5.44	**4.97**	**0.000**	**48**	**27**	**24**
5.32	**4.87**	**0.000**	**36**	**-27**	**42**

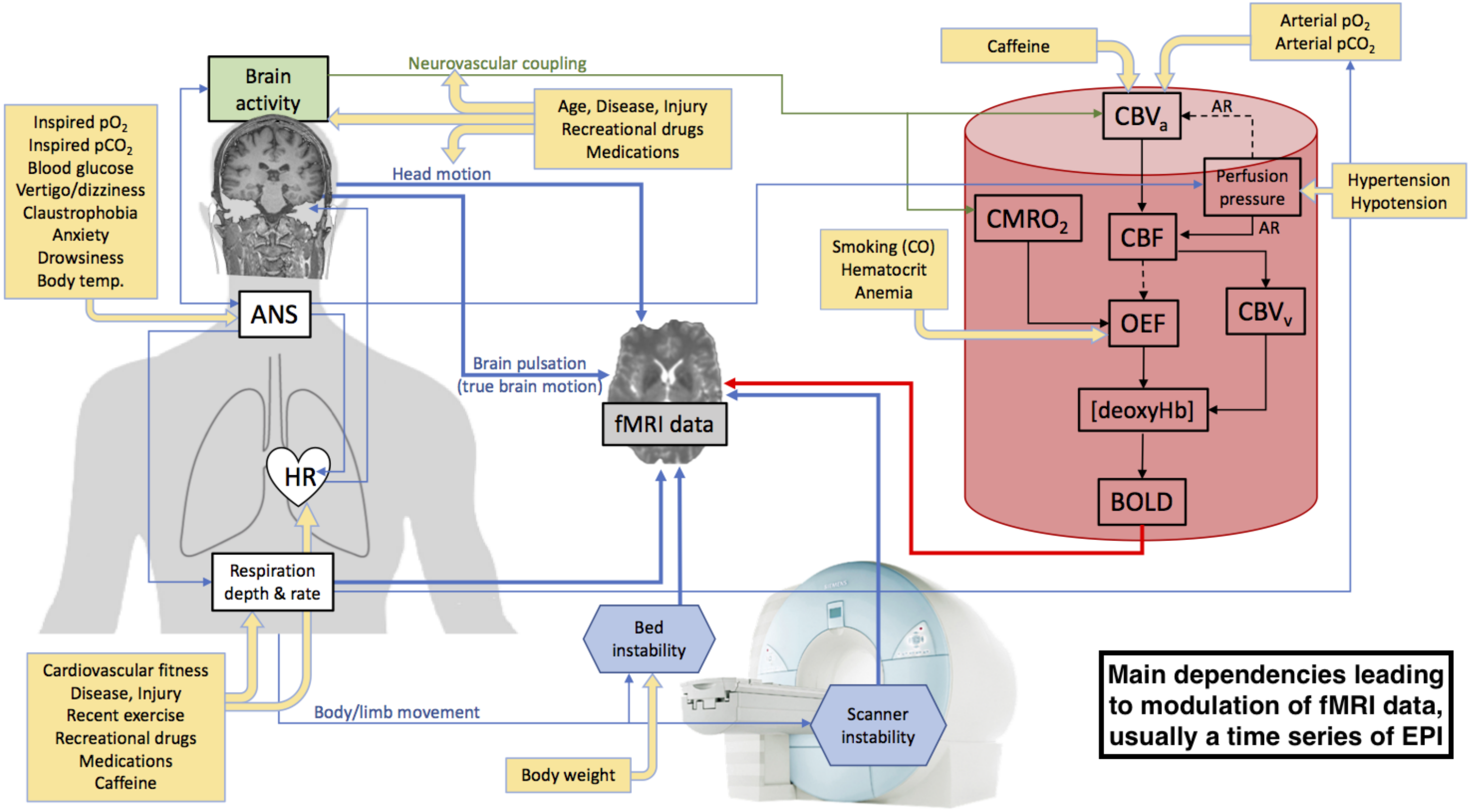
- **Even after good preprocessing, there still remain artefactual fluctuations of the BOLD signal due to motion or physiological influences**

- **Different sources of noise :**

- Head motion
- Cardiac pulsatility → motion (global) & inflow (local)
- Respiratory induced changes → change of B0 in the head
- Draining veins
- Slow drifts
- Hardware related instabilities



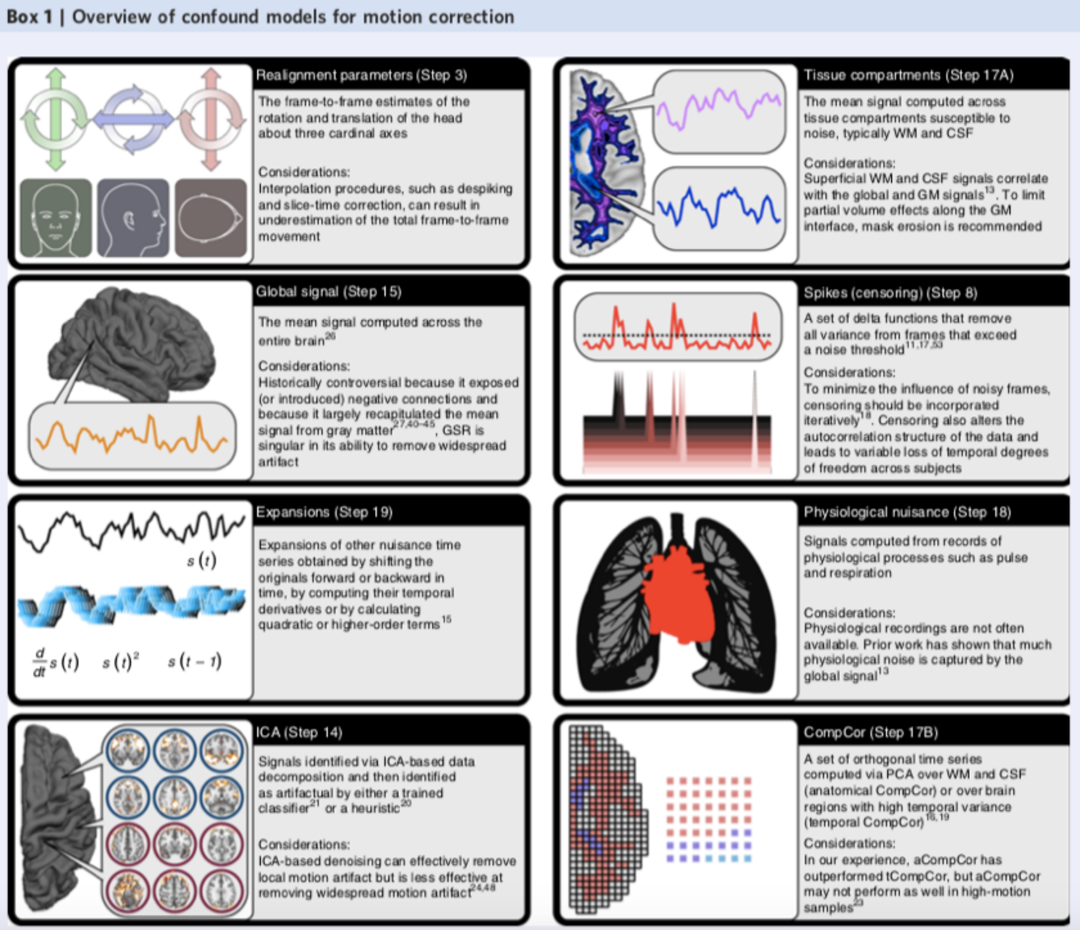
Signal fluctuations or noise …



Main dependencies leading to modulation of fMRI data, usually a time series of EPI

Krainik & al, 2013

Denoising motion & physiological-related noise



Box 1 | Overview of confound models for motion correction

Realignment parameters (Step 3)

The frame-to-frame estimates of the rotation and translation of the head about three cardinal axes

Considerations:
Interpolation procedures, such as despiking and slice-time correction, can result in underestimation of the total frame-to-frame movement

Tissue compartments (Step 17A)

The mean signal computed across tissue compartments susceptible to noise, typically WM and CSF

Considerations:
Superficial WM and CSF signals correlate with the global and GM signals[13]. To limit partial volume effects along the GM interface, mask erosion is recommended

Global signal (Step 15)

The mean signal computed across the entire brain[26]

Considerations:
Historically controversial because it exposed (or introduced) negative connections and because it largely recapitulated the mean signal from gray matter[27,40–45], GSR is singular in its ability to remove widespread artifact

Spikes (censoring) (Step 8)

A set of delta functions that remove all variance from frames that exceed a noise threshold[11,17,53]

Considerations:
To minimize the influence of noisy frames, censoring should be incorporated iteratively[18]. Censoring also alters the autocorrelation structure of the data and leads to variable loss of temporal degrees of freedom across subjects

Expansions (Step 19)

$s(t)$

$\frac{d}{dt}s(t)$ $s(t)^2$ $s(t-1)$

Expansions of other nuisance time series obtained by shifting the originals forward or backward in time, by computing their temporal derivatives or by calculating quadratic or higher-order terms[15]

Physiological nuisance (Step 18)

Signals computed from records of physiological processes such as pulse and respiration

Considerations:
Physiological recordings are not often available. Prior work has shown that much physiological noise is captured by the global signal[13]

ICA (Step 14)

Signals identified via ICA-based data decomposition and then identified as artifactual by either a trained classifier[21] or a heuristic[20]

Considerations:
ICA-based denoising can effectively remove local motion artifact but is less effective at removing widespread motion artifact[24,48]

CompCor (Step 17B)

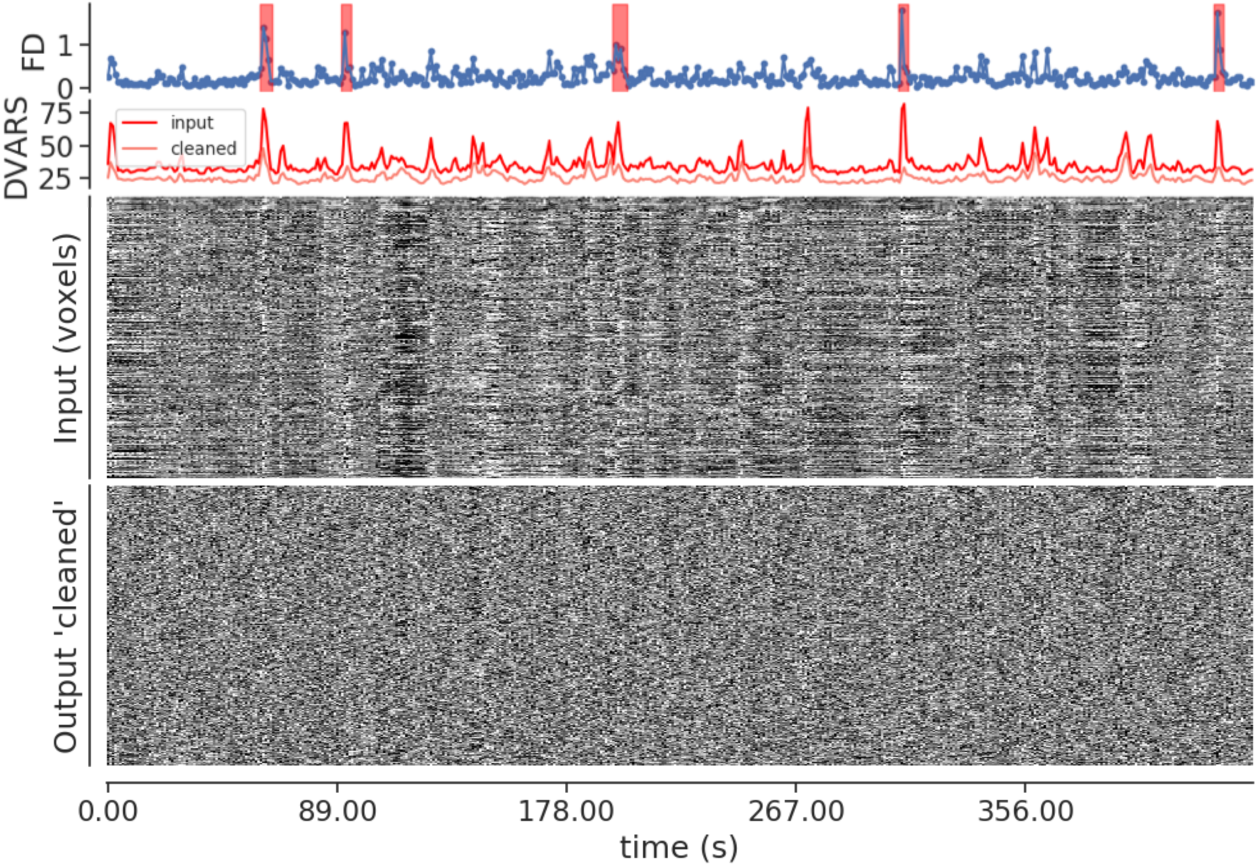
A set of orthogonal time series computed via PCA over WM and CSF (anatomical CompCor) or over brain regions with high temporal variance (temporal CompCor)[16,19]

Considerations:
In our experience, aCompCor has outperformed tCompCor, but aCompCor may not perform as well in high-motion samples[23]

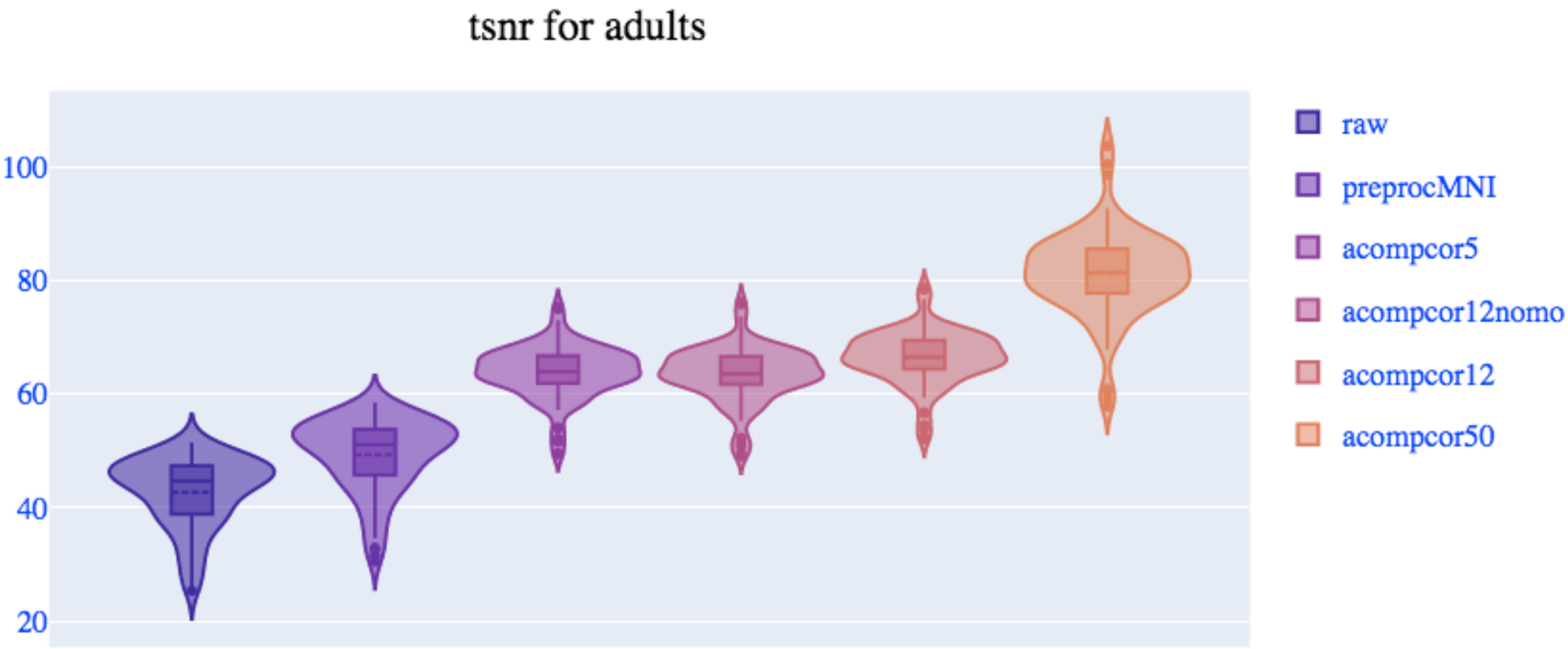
Ciric & al

Improvement of data quality

- **Framewise Displacement**
- **DVARS**
- **Carpet Plot (before)**
- **Carpet Plot (after)**



Improvement of data quality



Improvement of data quality

- **It's crucial to well denoise for connectivity analysis, but also for activation studies**

Loss of ventricular noising activity

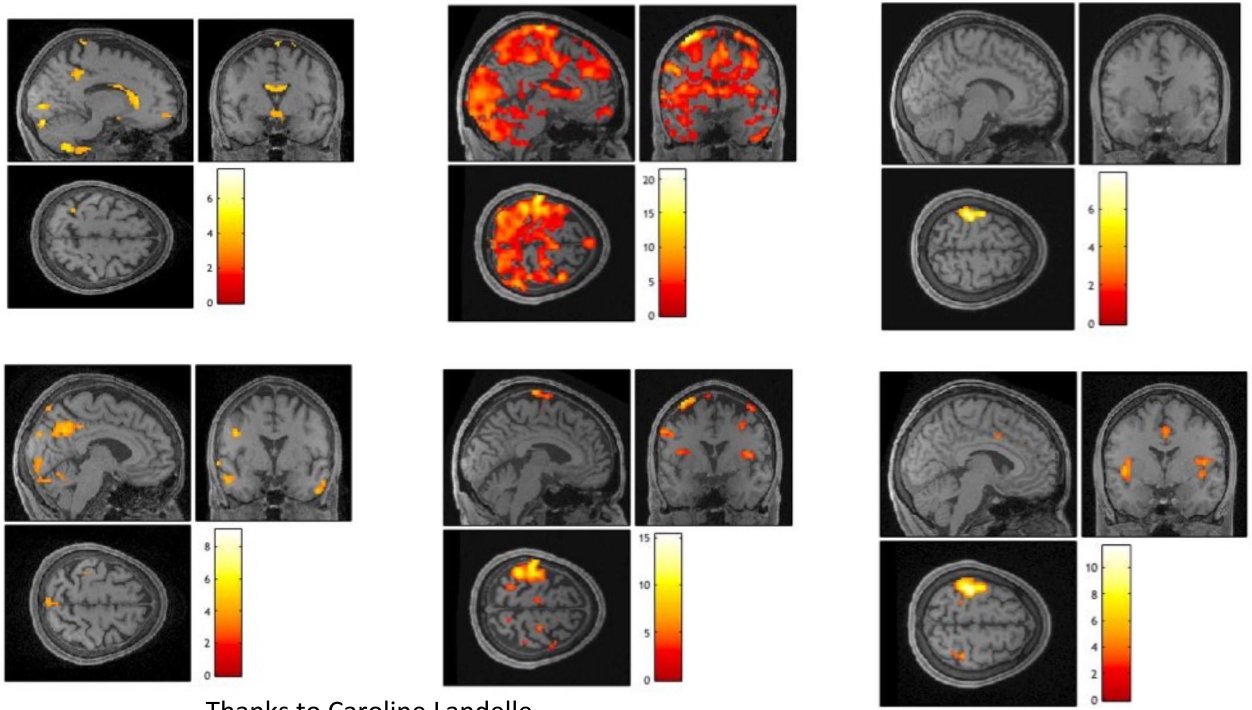
Loss of all brain noising activity

Greater statistical values

Before

Denoising

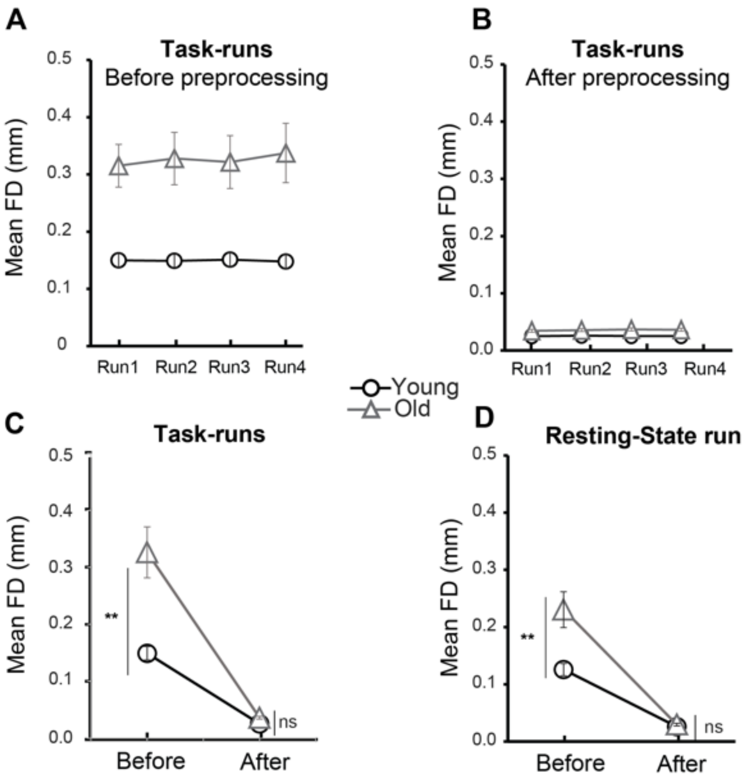
After



Thanks to Caroline Landelle

Improvement of data quality

- **It's crucial to well denoise for connectivity analysis & activation studies, when comparing groups**



Landelle & al, 2020

Group study : Random Effect (RFX)

First level

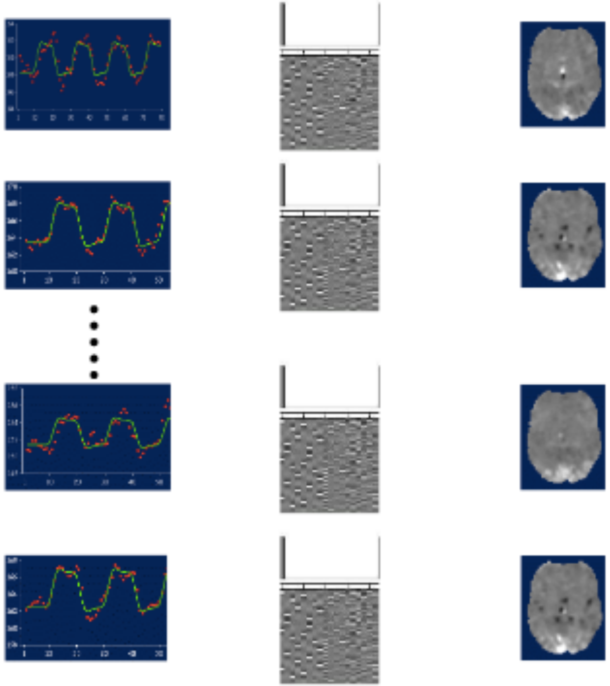
Data (per voxel) | Design Matrix | Contrast Image

S1

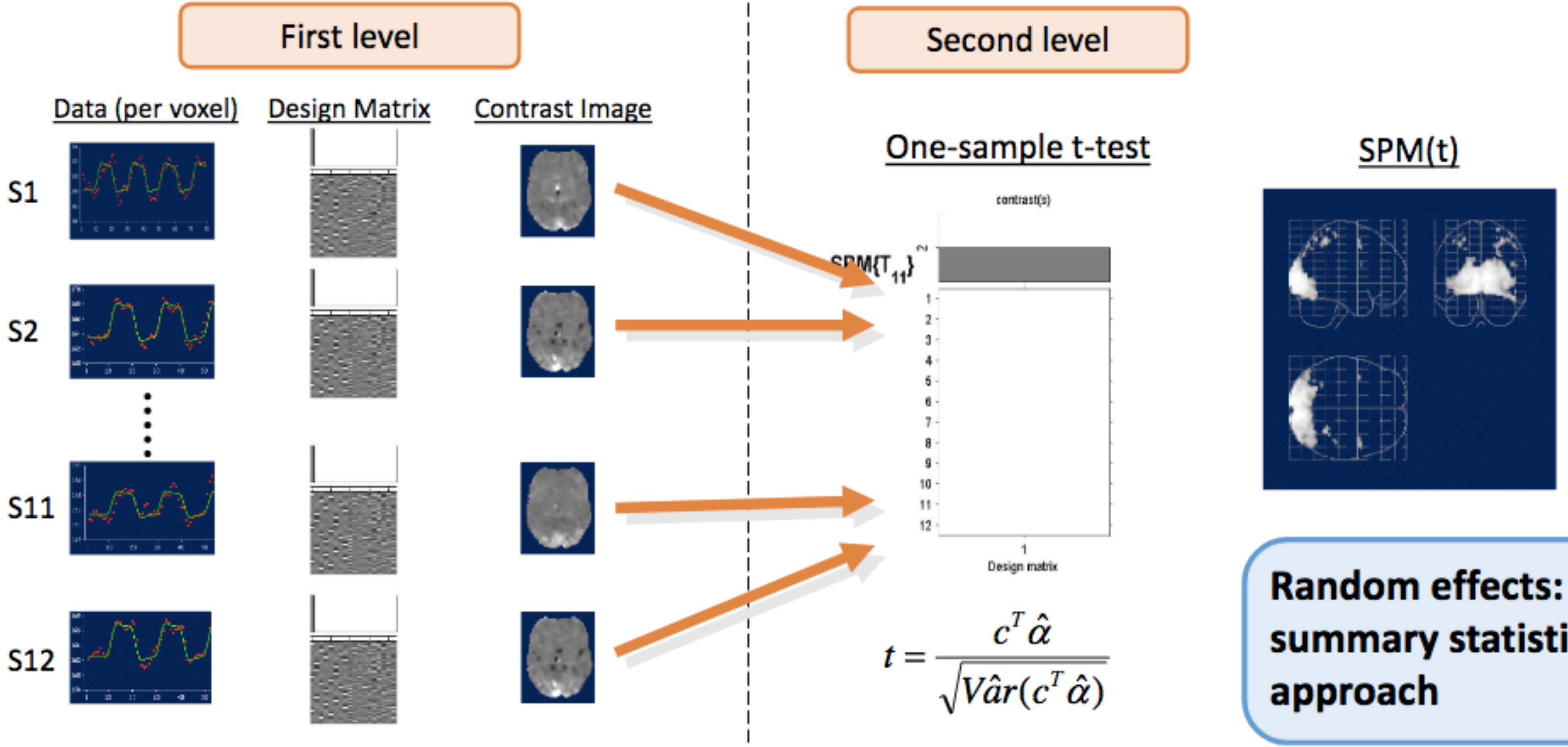
S2

S11

S12



Group study : Random Effect (RFX)



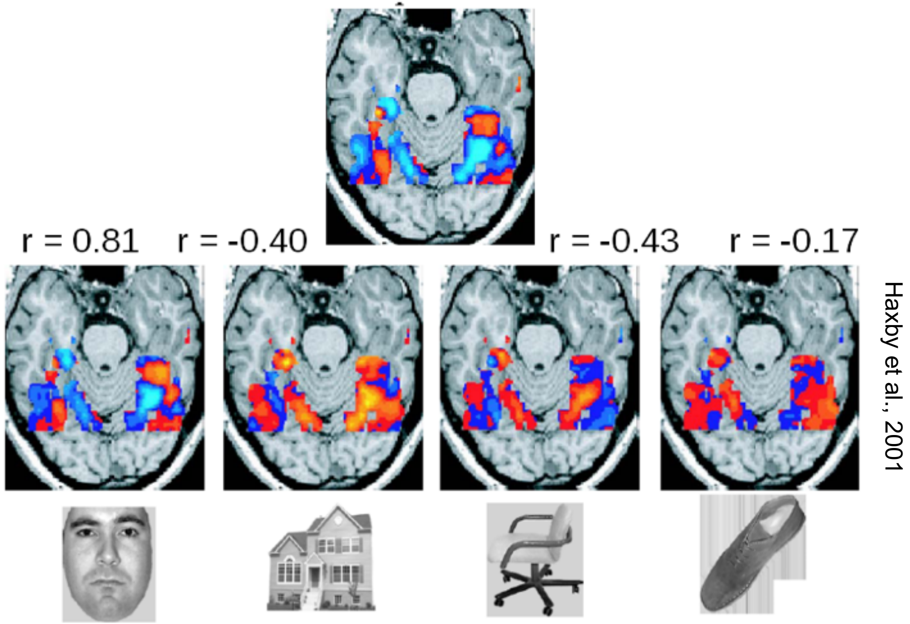
$$t = \frac{c^T \hat{\alpha}}{\sqrt{\hat{Var}(c^T \hat{\alpha})}}$$

Random effects: summary statistic approach

From Univariate to MultiVariate Pattern Analysis

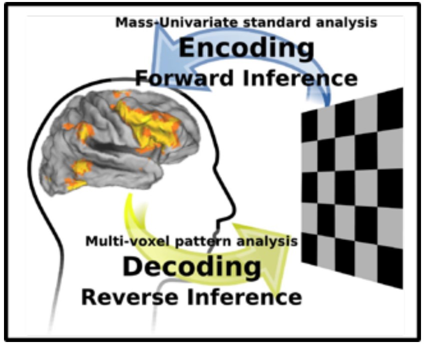
1. Concepts
2. Methods
3. Applications

Let's try something…



Congratulations !!!

Univariate GLM : *f(X)* = *Y*
X = the design (experimental paradigm)
Y = the data (timeseries of ONE voxel)
f = a multiple regression
« encoding »



Varoquaux et al., 2014

Multivariate pattern analysis : *f(X)* = *Y*
X = the data (spatial pattern of SEVERAL voxels)
Y = a variable related to brain *states* (stimulus category, reaction time etc.)
f = a model (can be anything, linear or not, etc.)
« decoding »

MultiVariate Pattern Analysis (MVPA) – Decoding
(Brain reading - Reverse inference)

Where is the **Machine Learning ?**
Fitting model = learning the function *f*

What's magic with Machine Learning ?
Supervised learning = providing examples of the relations between x & y
Training the model on these examples to learn *f*

In computer vision, machine learning models (e.g for object recognition) are trained on millions of labelled examples… In MVPA studies, we have a few 100s…

MVPA fMRI magics : stimulus reconstruction
Supervision + A dedicated generative model + More data than usual

Defining *f, X, y* in the equation *f(X) = Y*

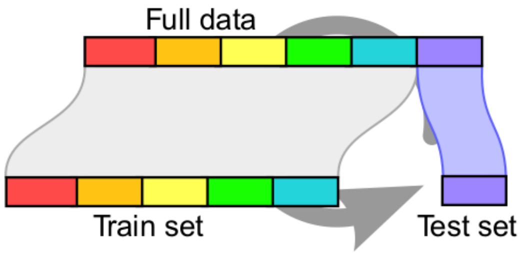
1. choosing *X* and *y* defines your scientific question
e.g *X* = full brain and *y* = category of stimulus
e.g *X* = ROI1 and ROI2 and *y* = reaction time

2. preprocessing matters… *X* should « represent » the response to one trial

3. *y* defines the machine learning problem
e.g *y* discrete : classification task
e.g *y* continuous : regression task

4. which model *f* ? (e.g which classifier amongst tens of existing classifiers)
In general, they all perform similarly (if well used)
If you see a large difference, it's probably because you misused some

Evaluation of the generalization performance (of predictive models) :



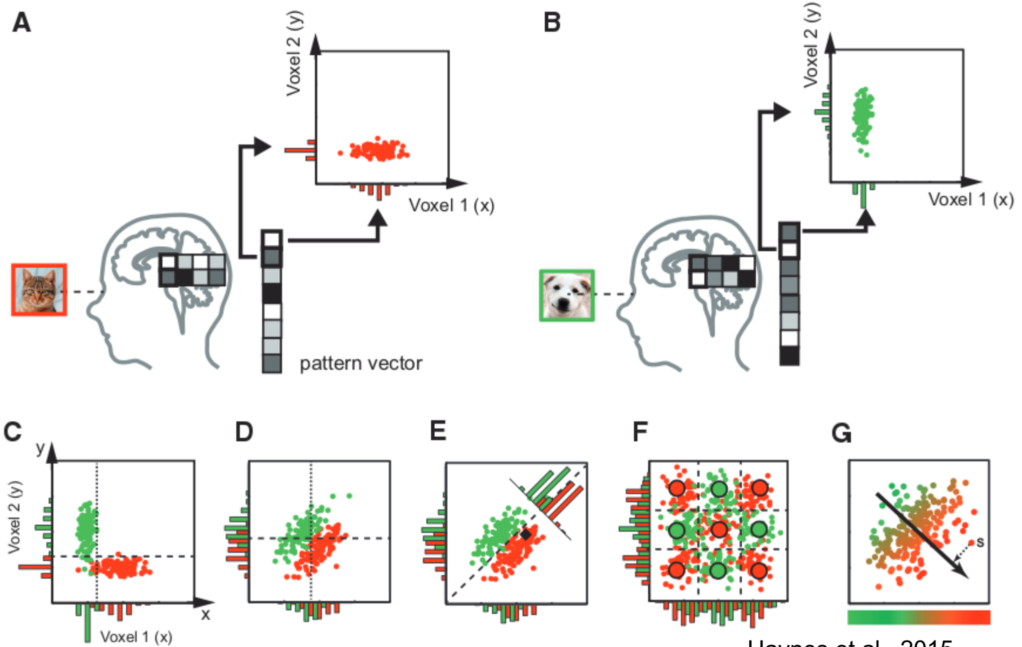
Varoquaux et al., 2017

1. train on data ; test on **independent data**
e.g on different runs, on different subjects

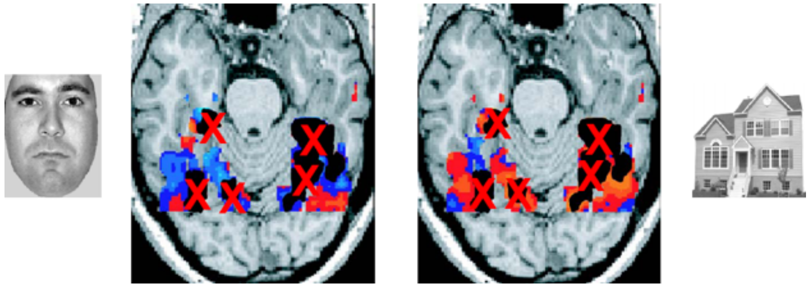
2. with few data, split data in several pieces and **cross-validation**
Each split should have the same *P(X,Y)* distribution

3. assess significance with **non-parametric statistics**

1. study small **distributed effects** (representations...)

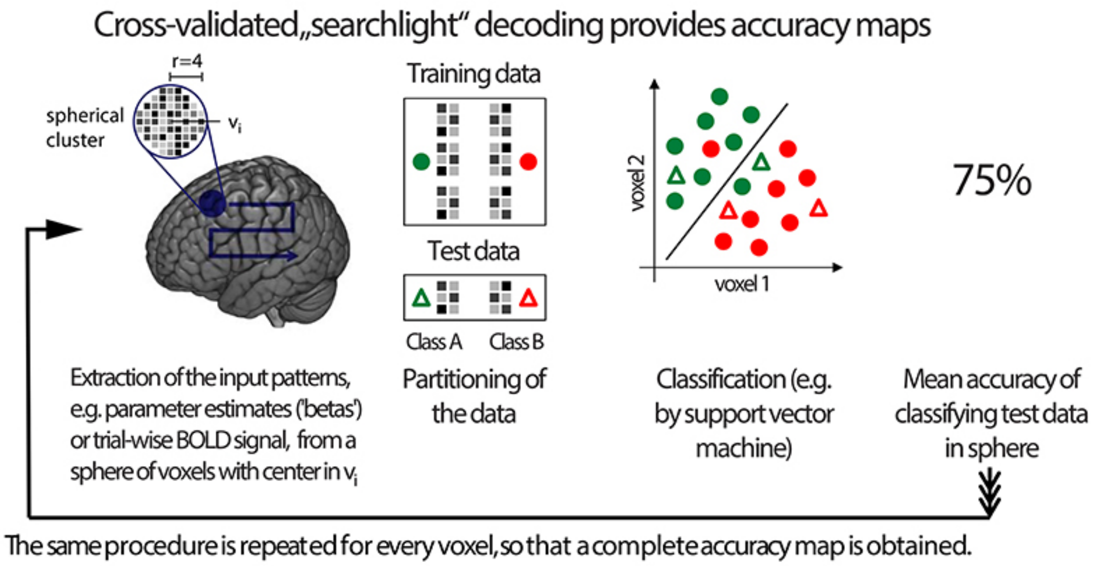


Haynes et al., 2015

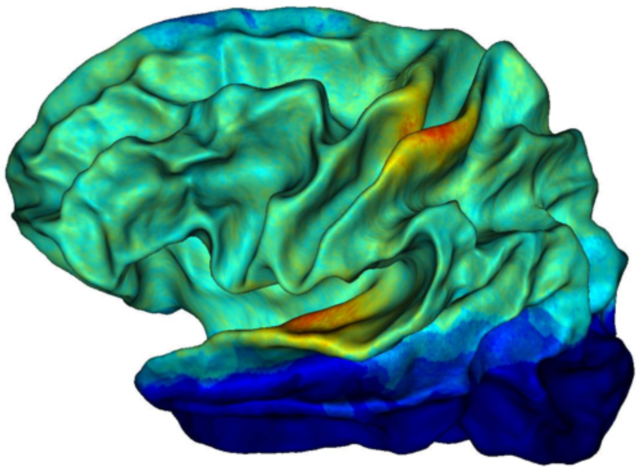


Haxby et al., 2001

2. brain **mapping** : the searchlight approach (sliding window)

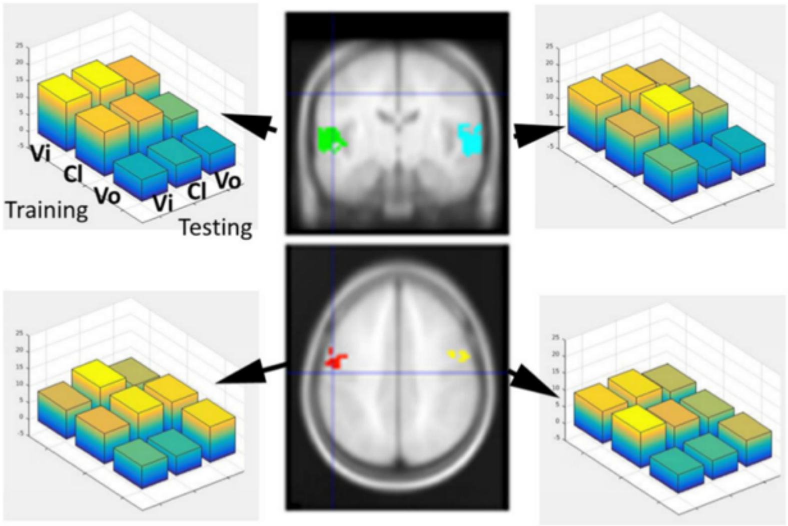


Hebart et al., 2015



Schön and Takerkart

3. probing for **generalization across contexts** (tasks, regions, populations...)



Paquette et al., 2018

e.g : studying the coding of emotions in voice and music

BEHAVIORAL AND BRAIN SCIENCES (1998) **21**, 449–498
Printed in the United States of America

Representation is representation of similarities

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frontiers in
SYSTEMS NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 24 November 2008
doi: 10.3389/neuro.06.004.2008

Representational similarity analysis – connecting the branches of systems neuroscience

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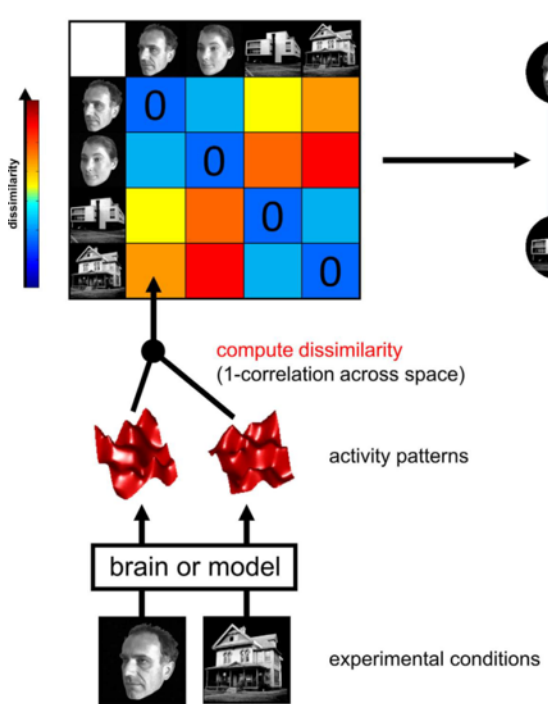
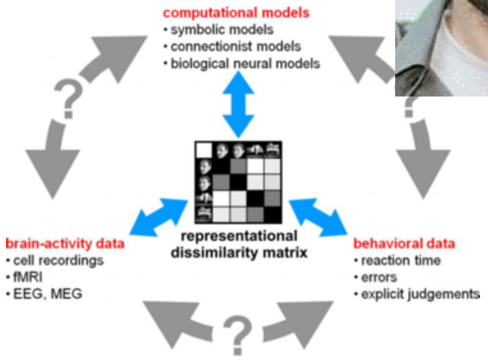
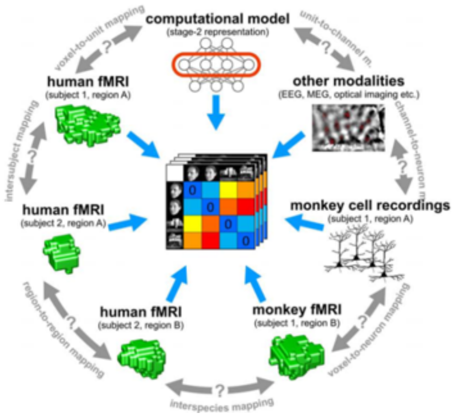
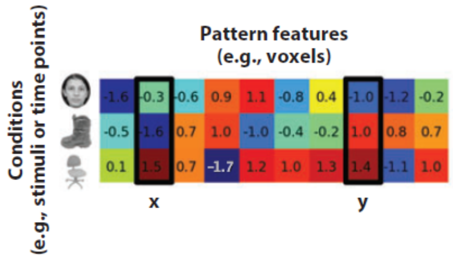
[1] *Section on Functional Imaging Methods, Laboratory of Brain and Cognition, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA*
[2] *Department of Cognitive Neuroscience, Faculty of Psychology, Maastricht University, Maastricht, The Netherlands*







Representational similarity analysis



re

Figure 4

Representational similarity analysis examines the patterns of distances between vectors in the high-dimensional vector space. Measures of angular similarity such as cosine and Pearson product-moment correlation are standard measures that are most sensitive to the relative contributions of feature dimensions. These similarity measures are transformed into dissimilarities by subtracting them from 1. Another standard measure of the distance between vectors is Euclidean distance, which is more sensitive to overall differences in vector length or magnitude.

Haxby et al (2014) *Ann Rev Neurosci*

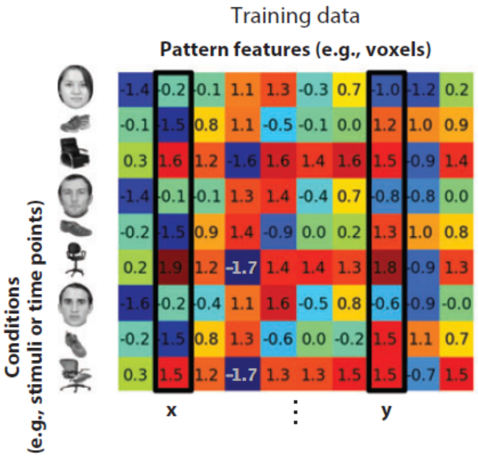
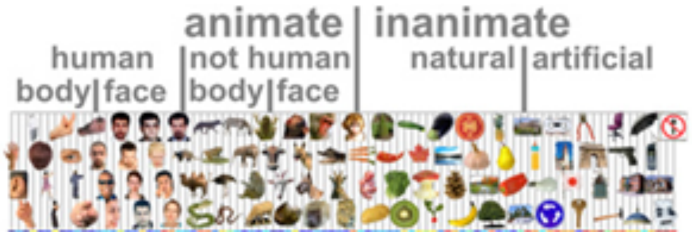
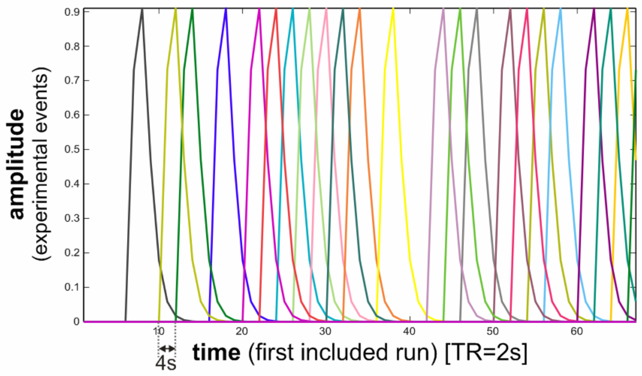


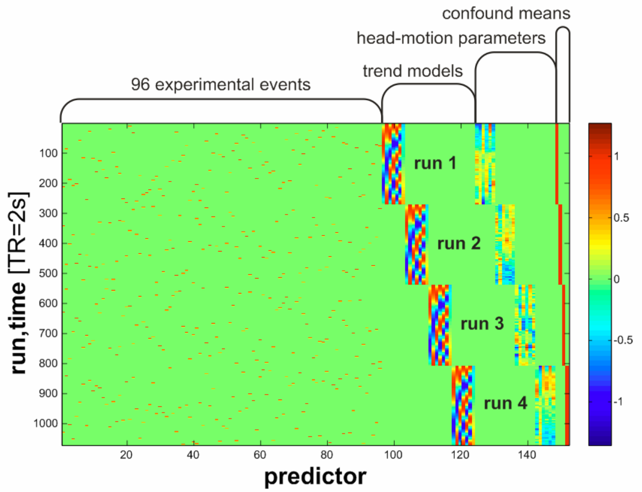
Figure 2

MVP classification analyses involve partitioning data matrices into different sets for training and testing a pattern classifier. A classifier is trained to designate sectors of the vector space to the labels provided for the samples in the training set. Test samples are then classified as belonging to the labeled class associated with the sector in which they reside. Classification accuracy is measured as the proportion of predicted labels that match the actual label (target) for each test item. A confusion matrix provides information about the patterns of correct classifications (on the diagonal) and misclassifications (off diagonal).

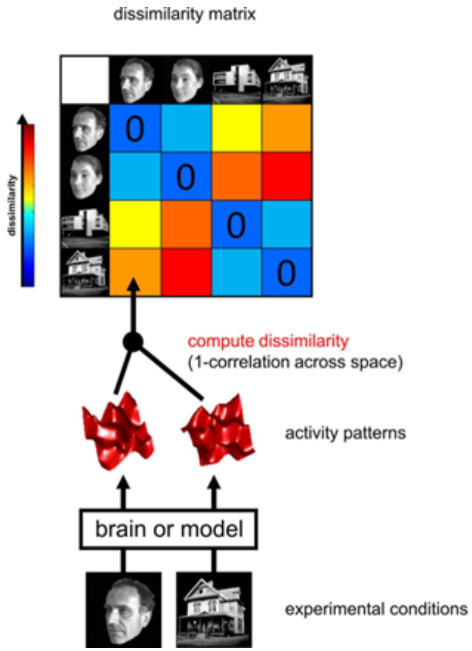
Haxby et al (2014) *Ann Rev Neurosci*

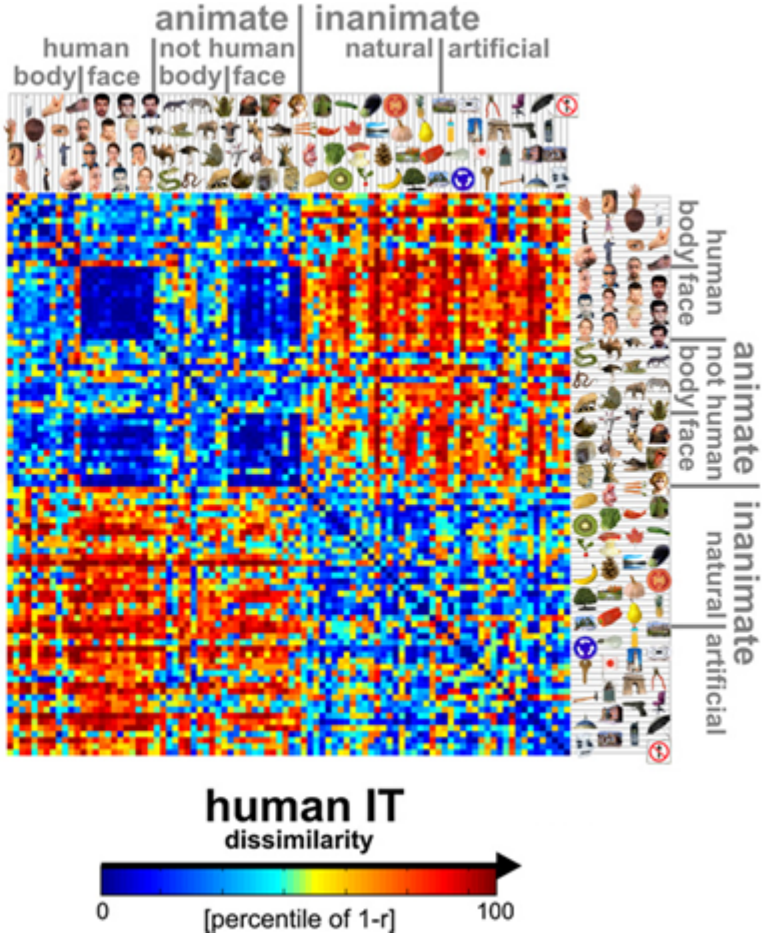




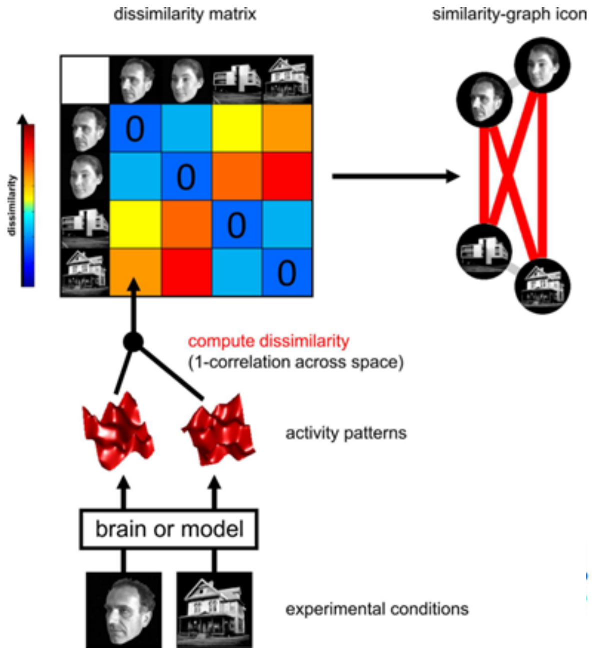


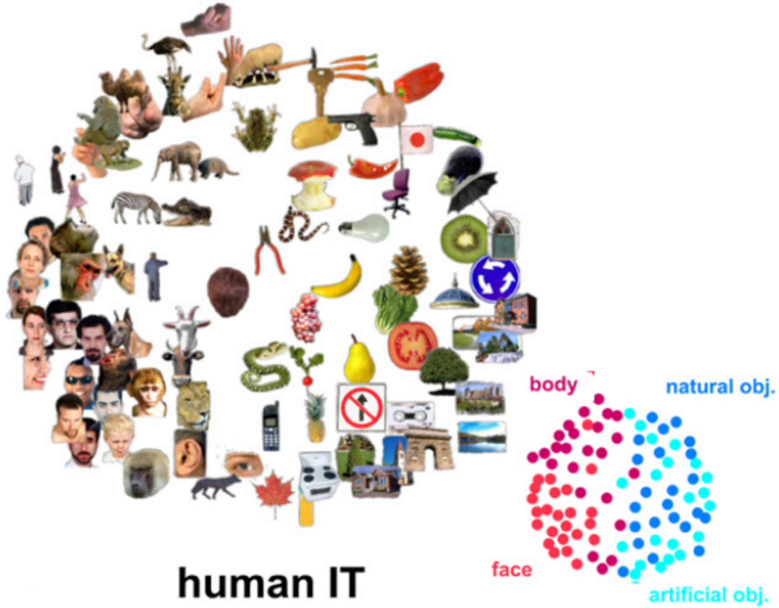
Kriegeskorte et al (2009) *Front Human neurosci*





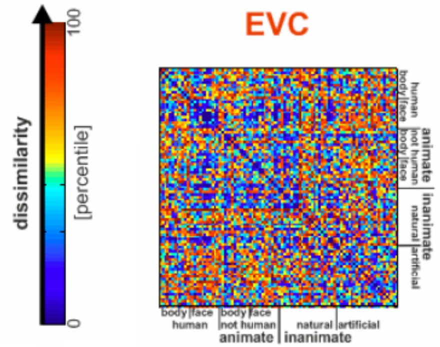
Kriegeskorte et al (2009) *Front Human neurosci*





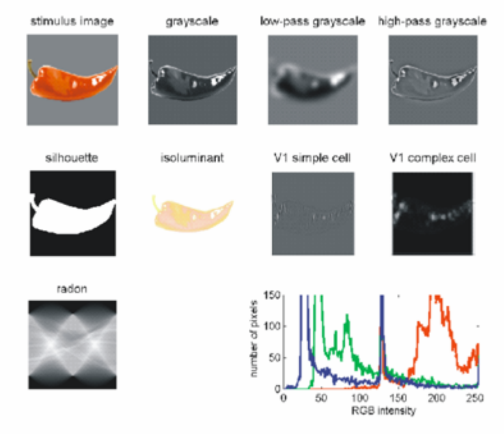
Kriegeskorte et al (2009) *Front Human neurosci*

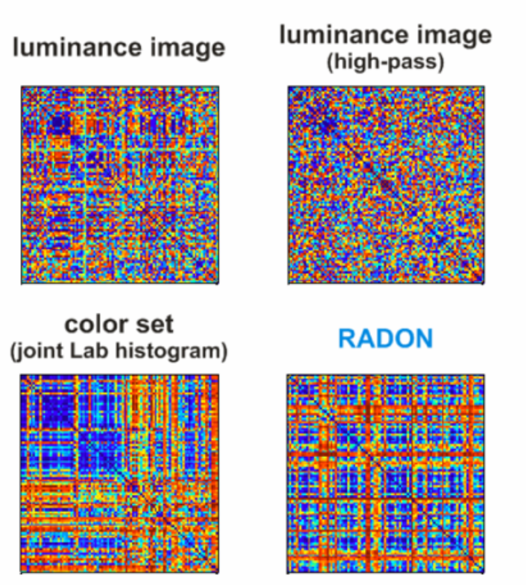
Brain-based RDMs



Kriegeskorte et al (2009) *Front Human neurosci*

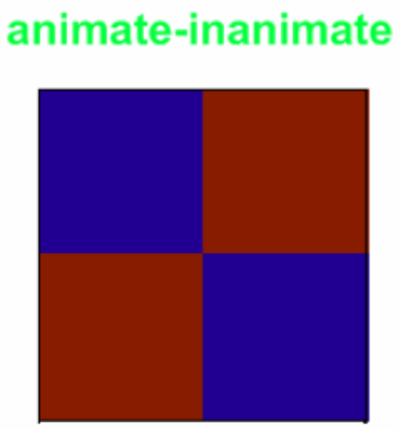
Computation-based RDMs





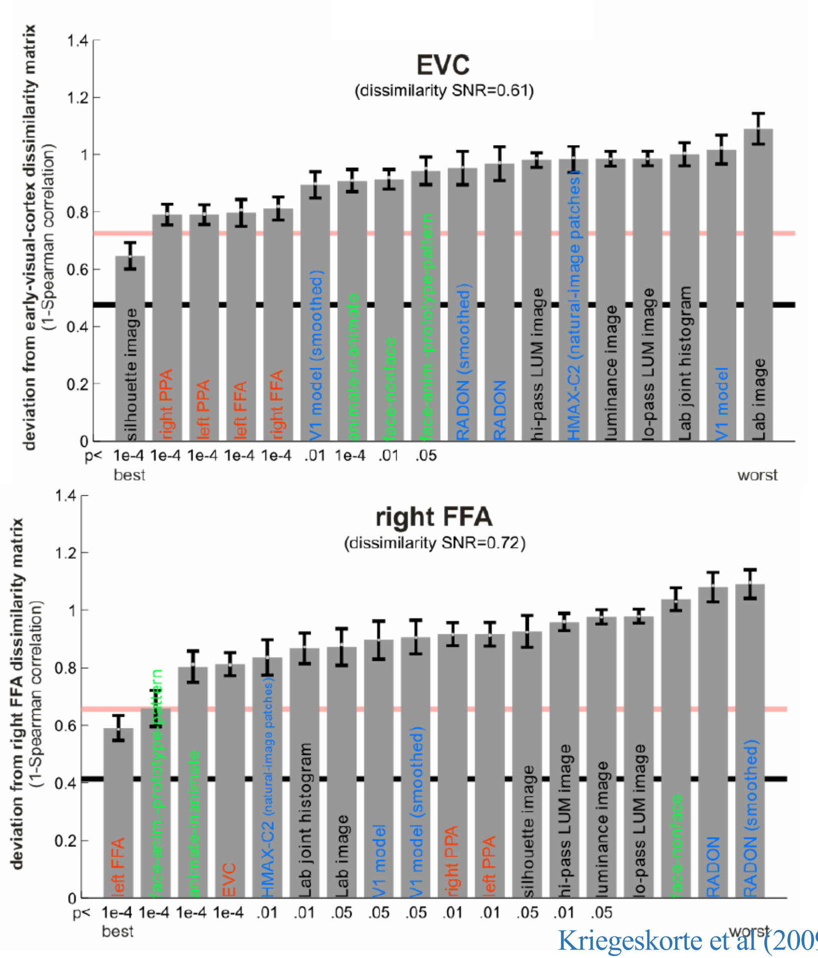
Kriegeskorte et al (2009) *Front Human neurosci*

Theory-based RDMs



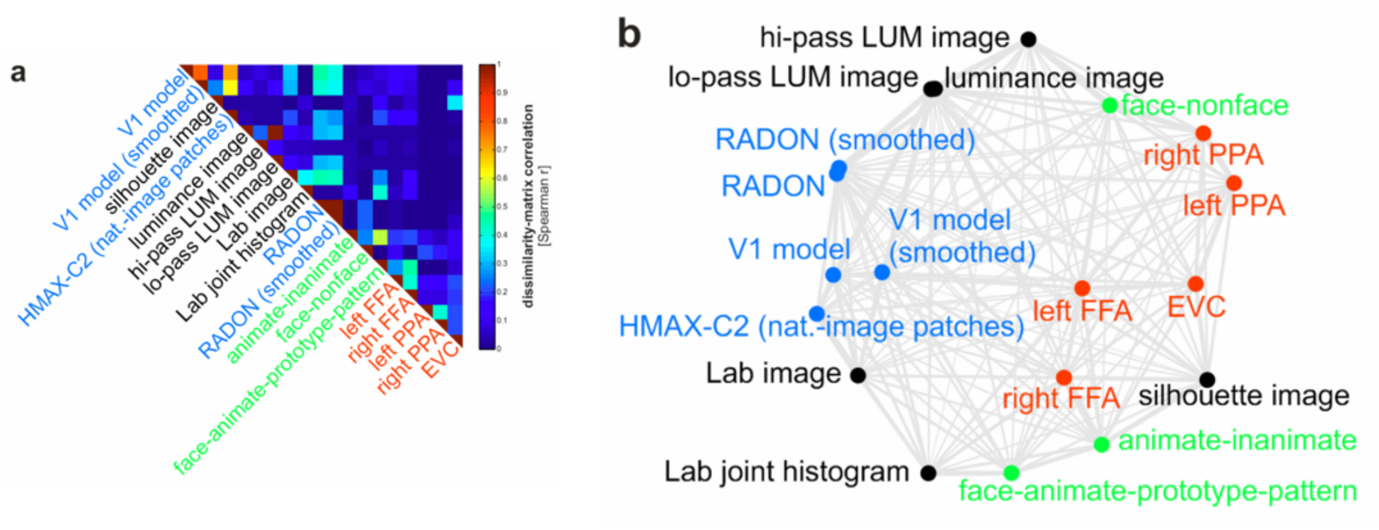
Kriegeskorte et al (2009) *Front Human neurosci*

Interpreting Brain-based RDMs



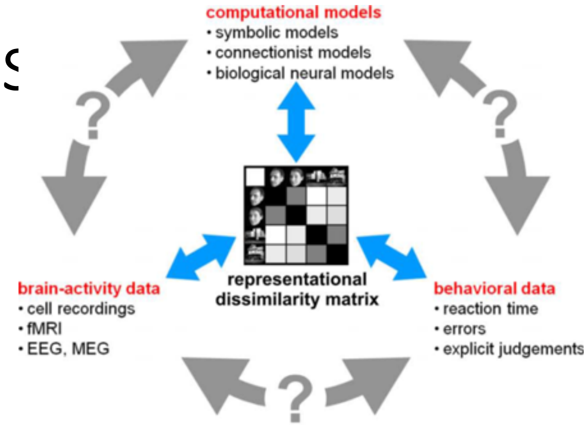
Kriegeskorte et al (2009) *Front Human neurosci*

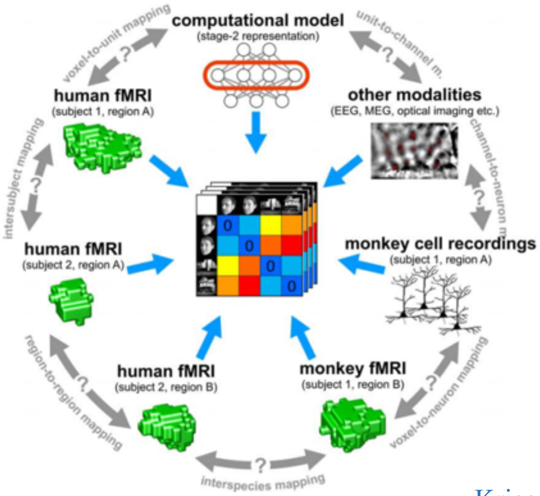
Interpreting Brain-based RDMs

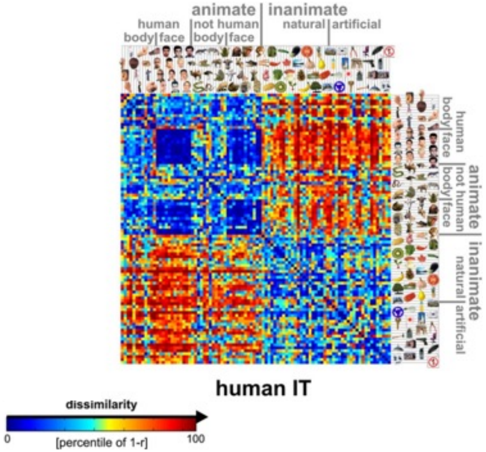


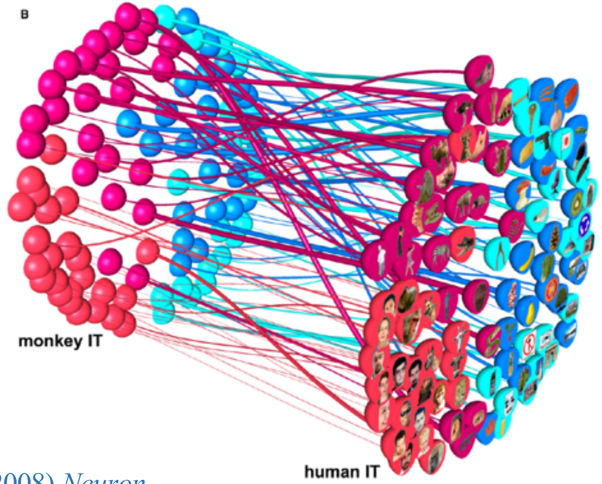
Kriegeskorte et al (2009) *Front Human neurosci*

Cros



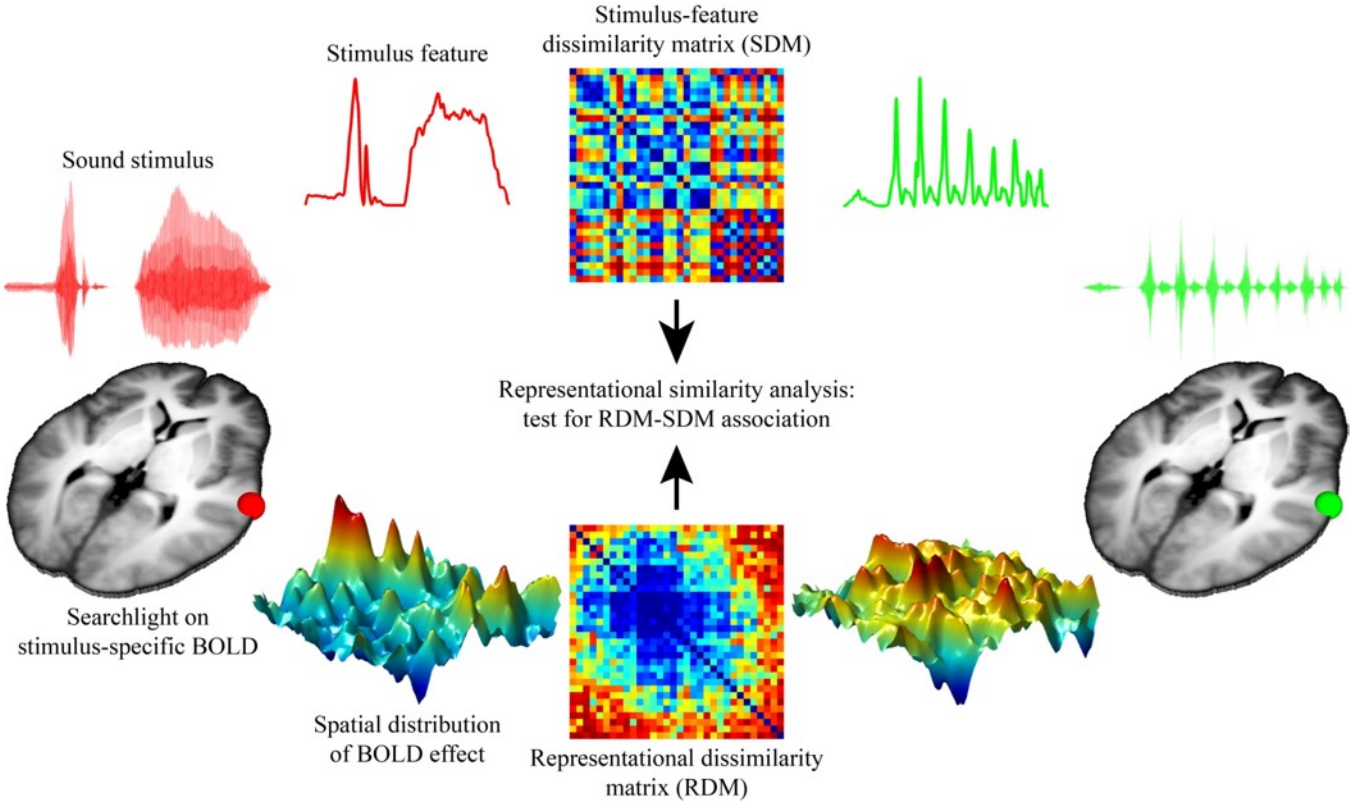






Kriegeskorte et al (2008) *Neuron*

RSA with auditory stimuli

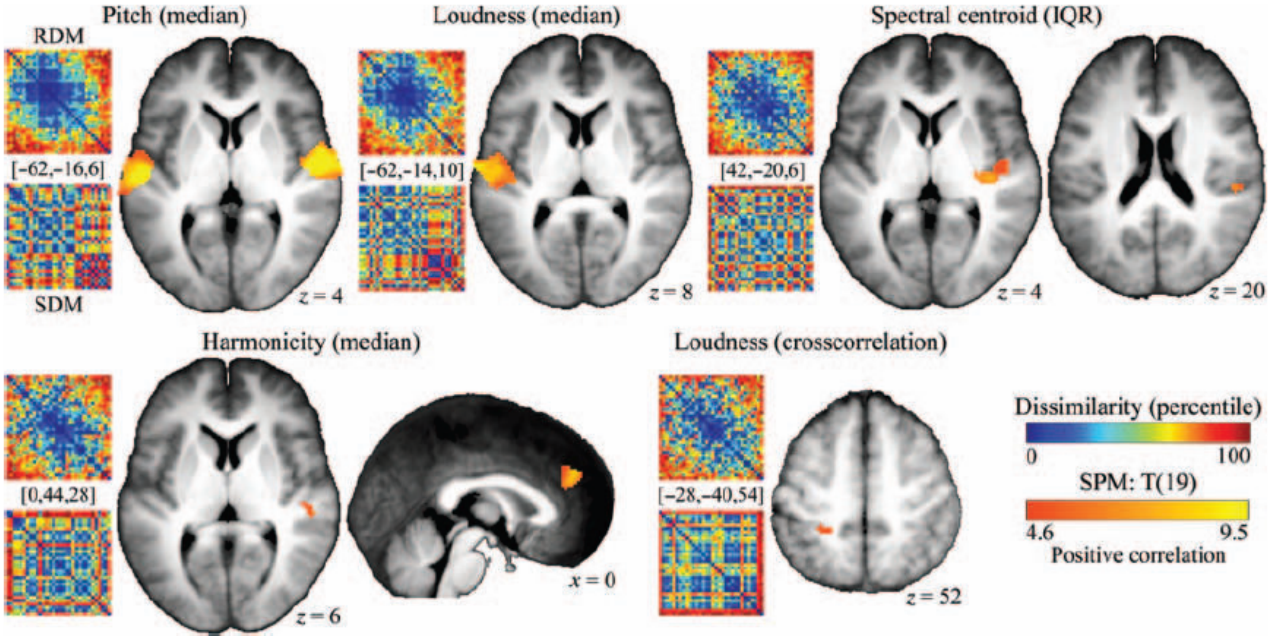


Giordano et al (2009) *Cerebral cortex*

Cerebral Cortex
doi:10.1093/cercor/bhs162

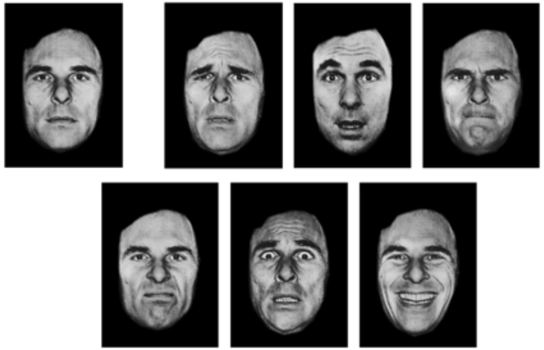
Abstract Encoding of Auditory Objects in Cortical Activity Patterns

Bruno L. Giordano[1,2], Stephen McAdams[2], Robert J. Zatorre[3], Nikolaus Kriegeskorte[4] and Pascal Belin[1,5]

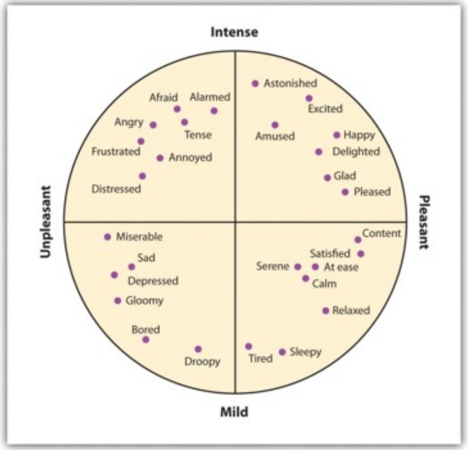


Giordano et al (2009) *Cerebral cortex*

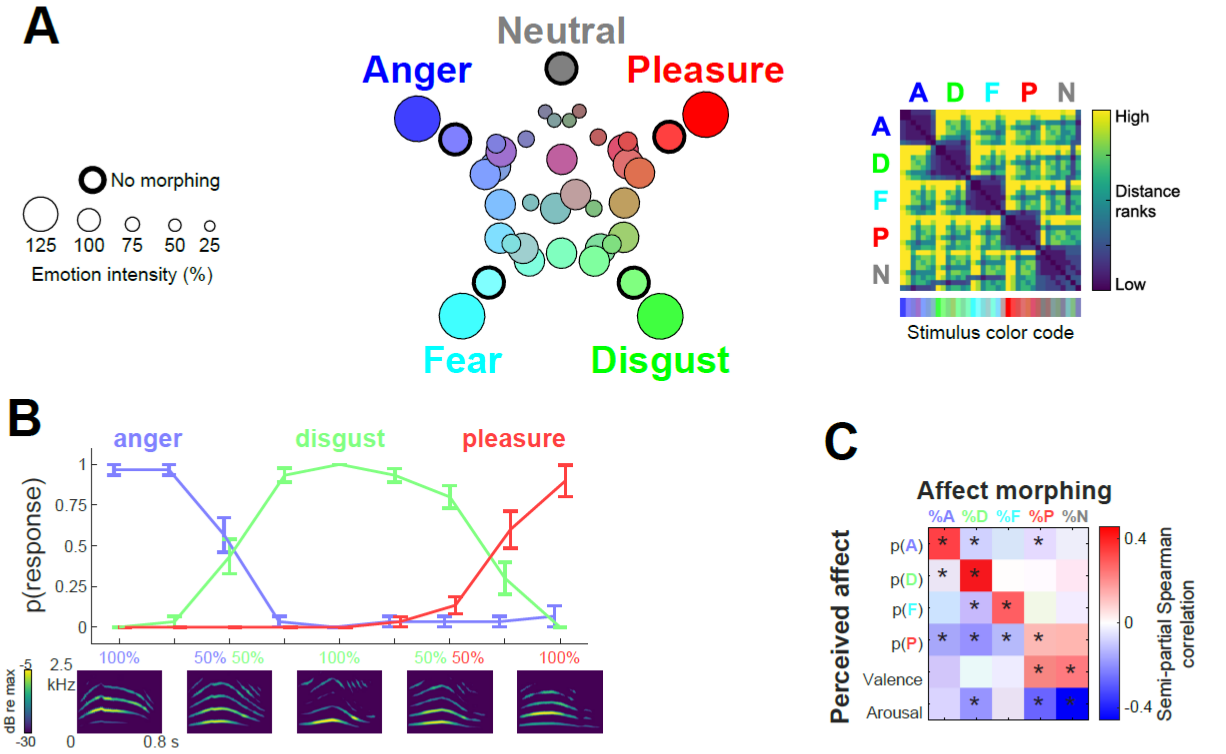
Continuous vs Discrete Emotions



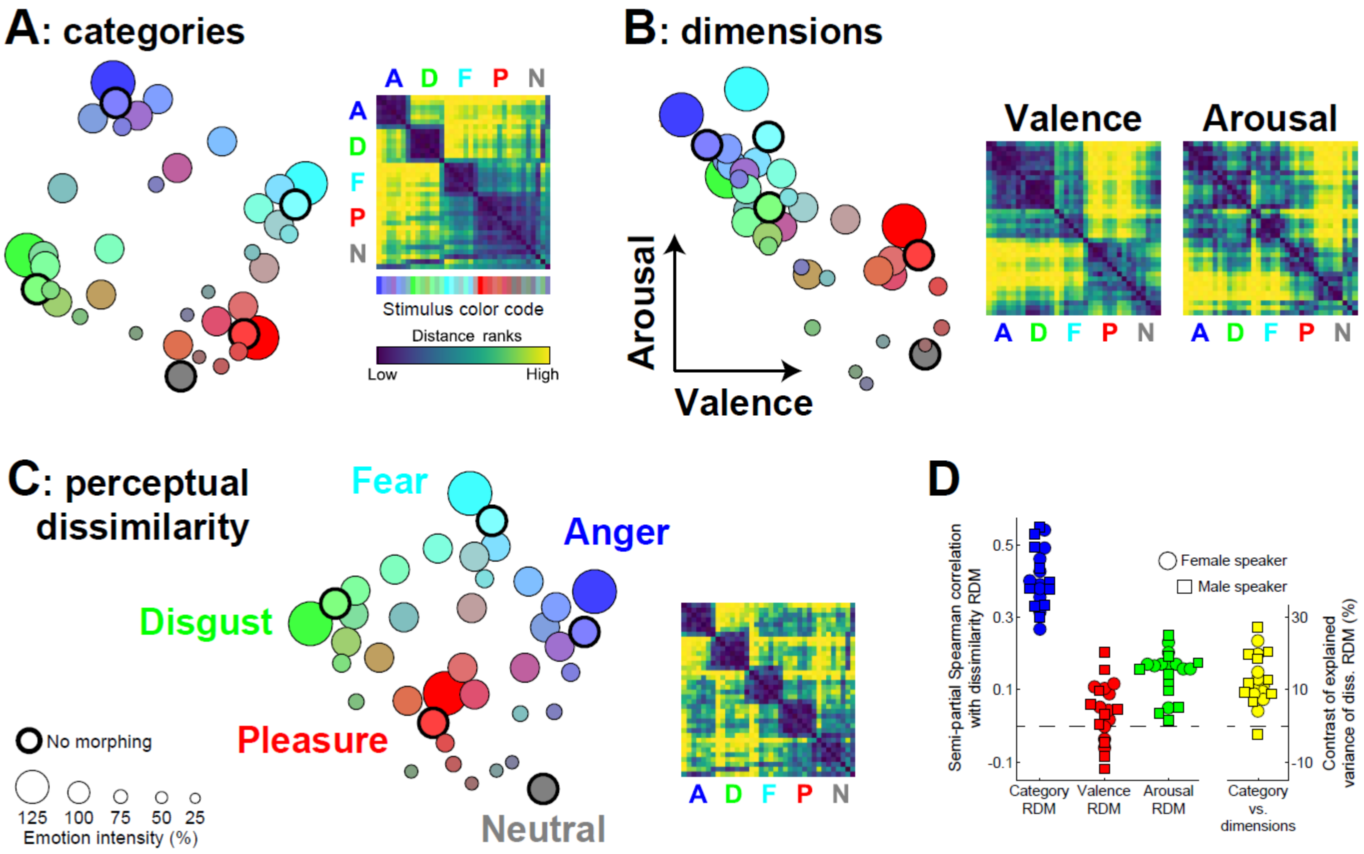
?



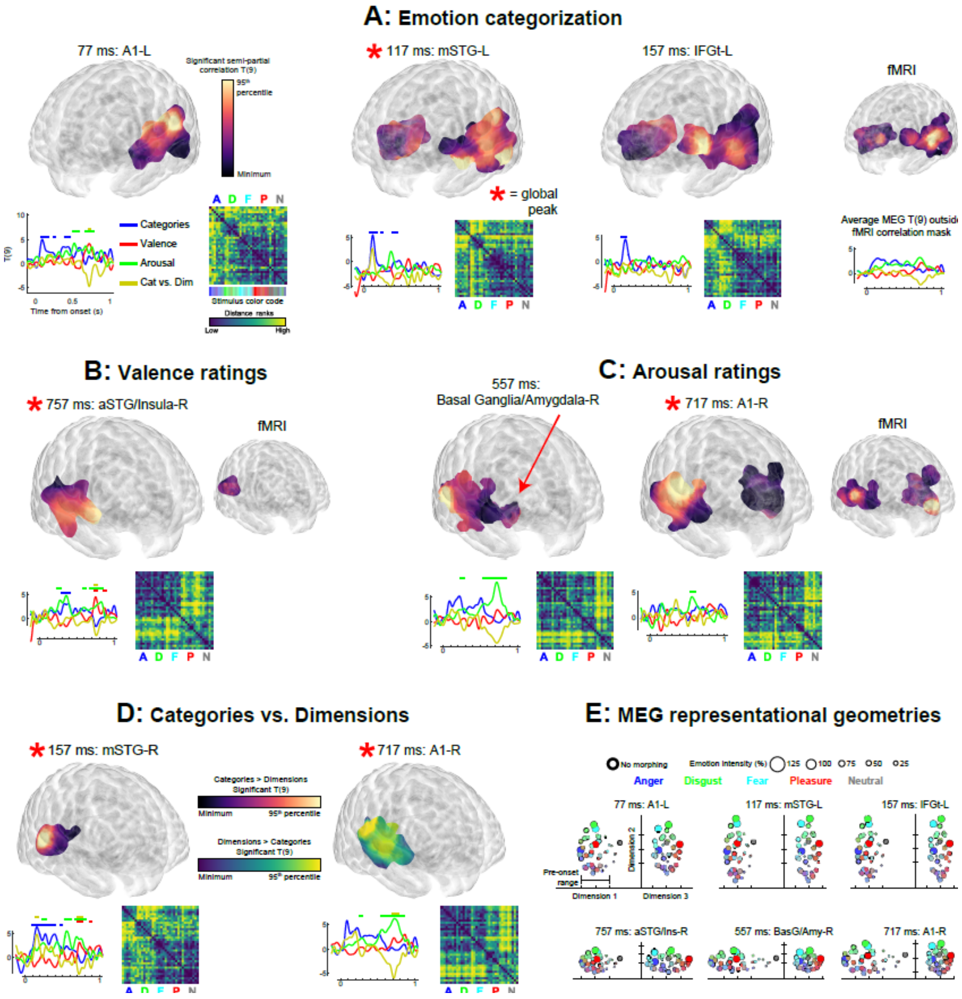
Giordano et al (in press) *Nature Human Behaviour*



Giordano et al (in press) *Nature Human Behaviour*



Giordano et al (in press) *Nature Human Behaviour*



Giordano et al (in press) *Nature Human Behaviour*

From Friston (1994) definition :

<u>Functional connectivity</u>

- co-activation of areas may be related to a functional link between the areas

→ study the **correlation** of signals

→ undirected relation (only strength)

<u>Effective connectivity</u>

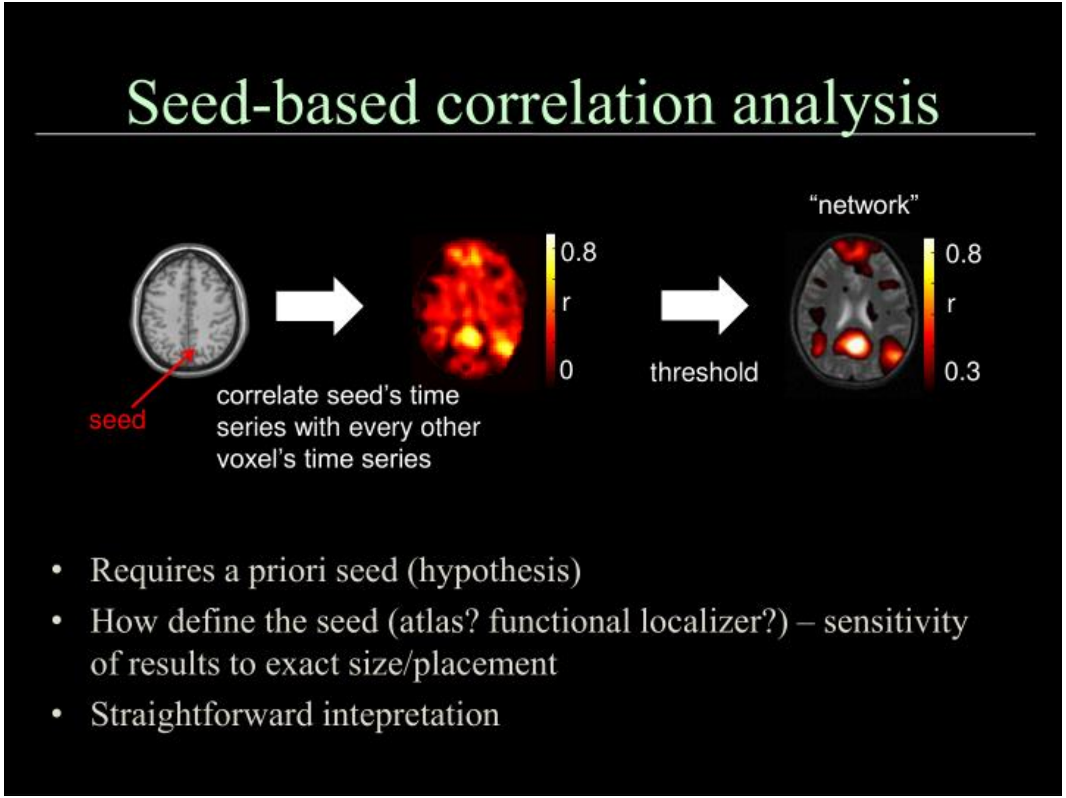
- causal link between 2 areas : the signal in one area influences the signal in the other

→ based on model fit (~ considering A→B, what results are expected?)

→ directed relation

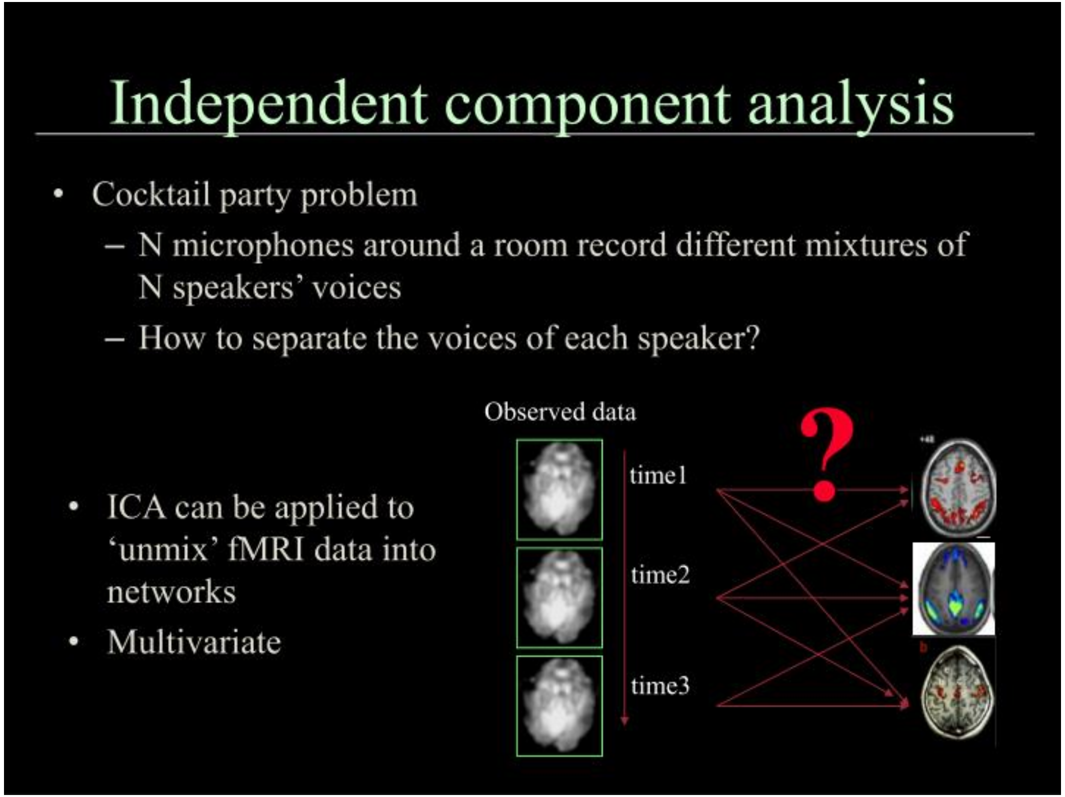
Different techniques (but ~ looking at the same properties):

<u>Seed-based connectivity</u>



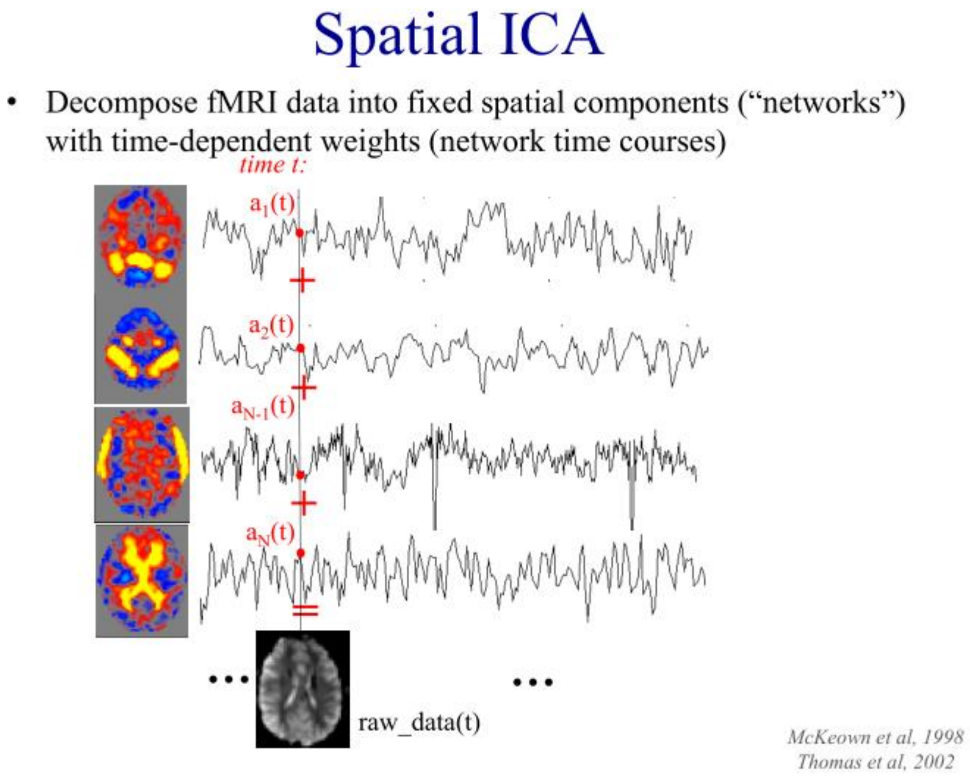
Different techniques (but ~ looking at the same properties):

<u>Spatial ICA</u>



Different techniques (but ~ looking at the same properties):

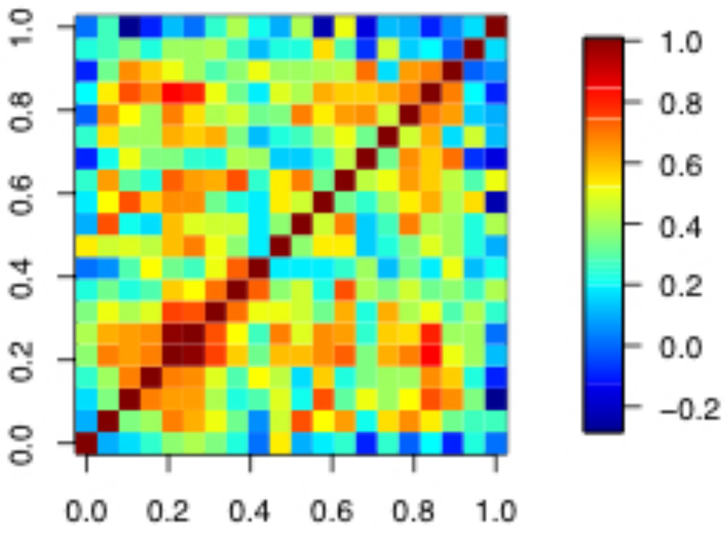
<u>Spatial ICA</u>



Different techniques (but ~ looking at the same properties):

<u>Graph-based based :</u>

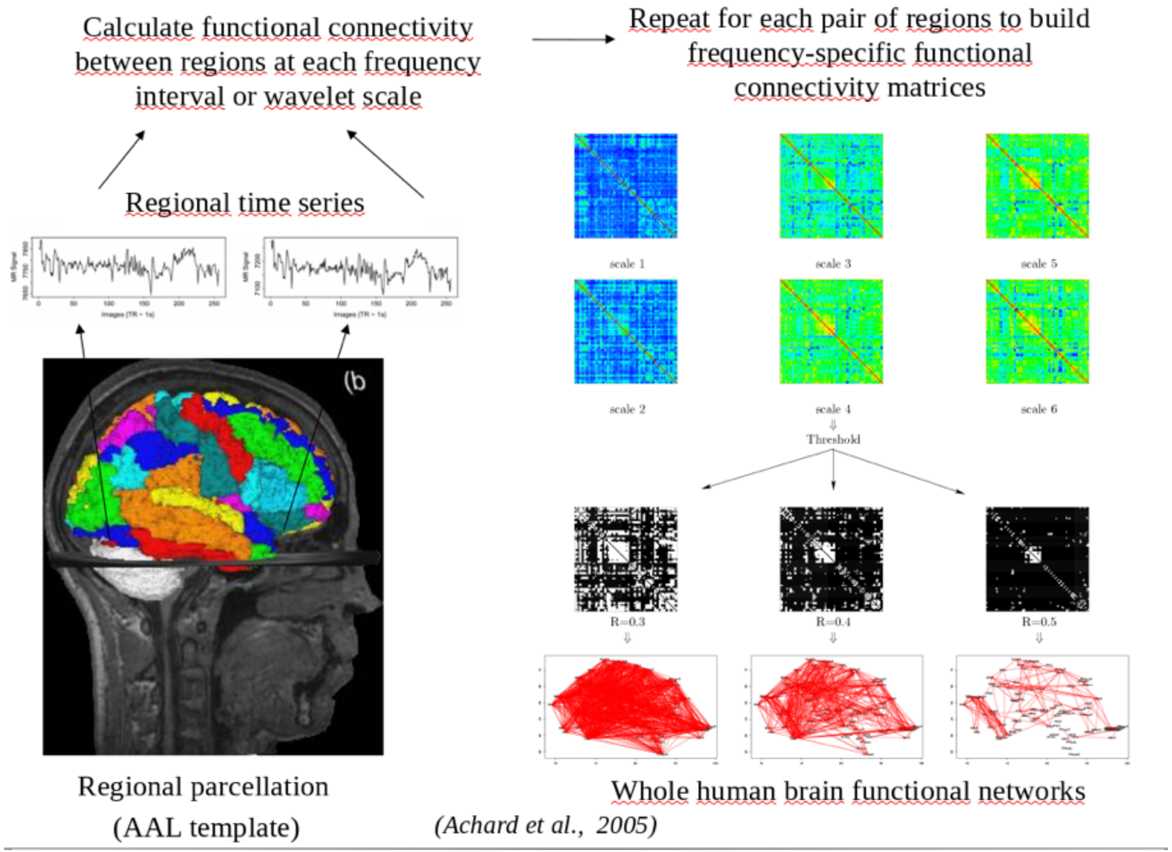
- All-to-all seed based correlations
- Requires the definition of « regions »
a priori (i.e. an atlas/template)



Functional connectivity

Different techniques (but ~ looking at the same properties):

Graph-based based :



Defaut mode network

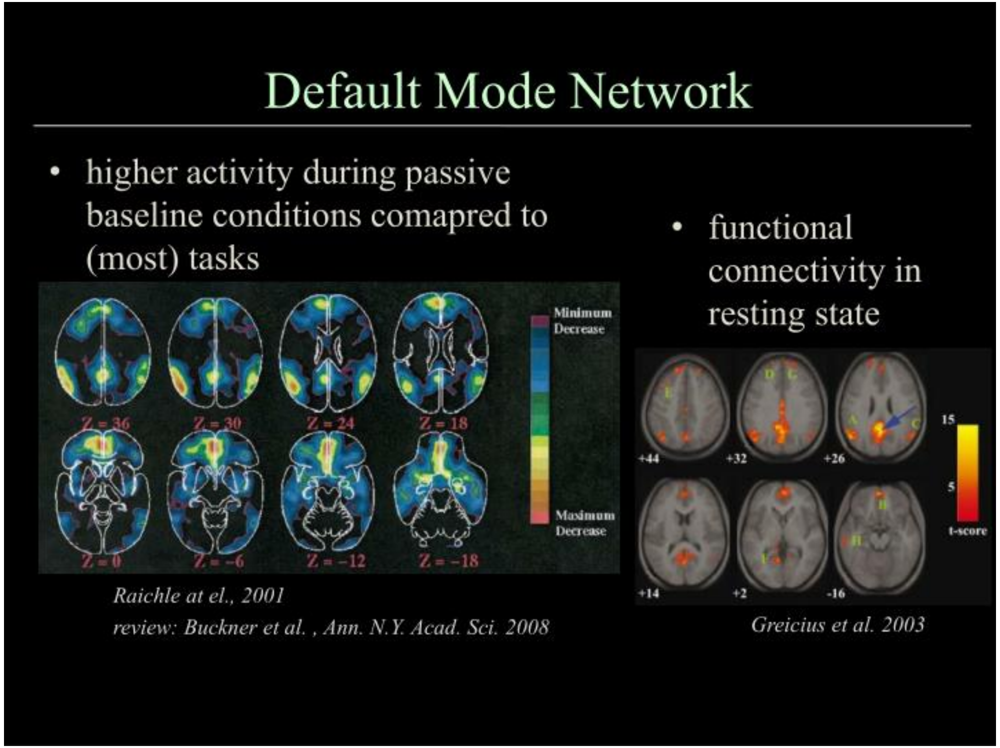
Originally :

- what happens when looking at regions more « active » during baseline than during ANY task in task activation fMRI

- Resting state : The subject stays at rest, eyes open, not falling asleep

Defaut mode network

A very unique pattern :
medial prefrontal cortex, posterior cingulate cortex, precuneus, inferior parietal lobules, and medial temporal regions
→ contrarily to what one may expect , VERY reliable across individuals



Effective Connectivity

(ie Task modulation of functional connectivity)

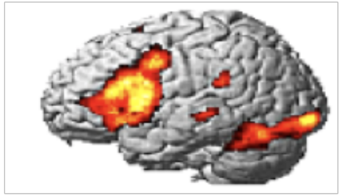
- Functional segregation = Localize tasks effects *versus*
  Functional integration = How networks interact during tasks

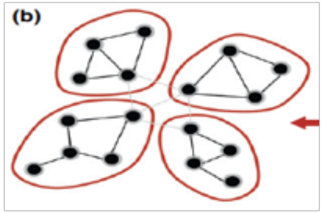
Functional Integration
Networks of interactions among specialised areas

- Analysis of how different regions in a neuronal system interact (coupling).
- Determines how an experimental manipulation affects coupling between regions.

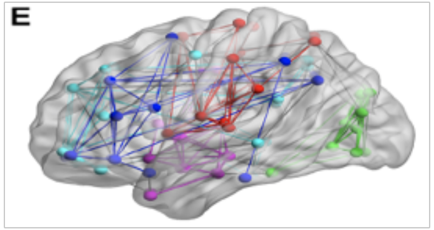
Functional connectivity **Effective connectivity**

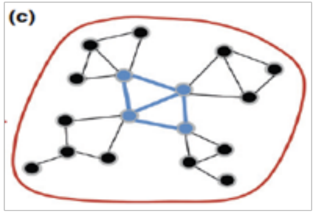
Functional segregation





Functional integration





'Connectivity' analysis

Gitelman, 2011; Friston, 2011

- Functional integration

FUNCTIONAL connectivity
"Statistical temporal correlations between spatially remote brain areas"

- MODEL-FREE
- Exploratory
- Data Driven
- No Causation
- Whole brain

- PCA/ICA
- Pairwise ROI Correlations
- Whole brain seed driven connectivity
- Graph analyses

EFFECTIVE connectivity
"Influence one area exerts on another area"

- MODEL-BASED
- Confirmatory
- Hypothesis driven
- Causal directions
- Reduced set of regions

PsychoPhysiological Interactions
PPI
Structural Equation Models
SEM
Dynamic Causal Models
DCM
Granger Causality ...

- Functional integration

FUNCTIONAL connectivity
"Statistical temporal correlations between spatially remote brain areas"

- MODEL-FREE
- Exploratory
- Data Driven
- No Causation
- Whole brain

- PCA/ICA
- Pairwise ROI Correlations
- Whole brain seed driven connectivity
- Graph analyses

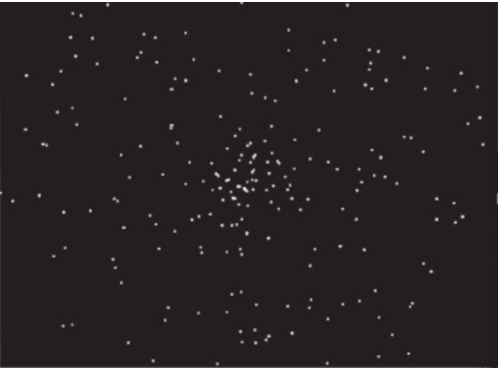
Mainly resting-state connectivity
rs-fcMRI

EFFECTIVE connectivity
"Influence one area exerts on another area"

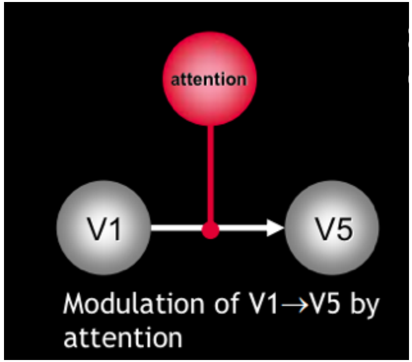
- MODEL-BASED
- Confirmatory
- Hypothesis driven
- Causal directions
- Reduced set of regions

PsychoPhysiological Interactions
PPI
Structural Equation Models
SEM
Dynamic Causal Models
DCM
Granger Causality ...

- PsychoPhysiological Interaction (PPI) analysis concerns task-specific changes in the relationship between different brain areas' activity
- PPI aims to identify regions whose activity depends on an interaction between a Physiological factor (BOLD time course of a region of interest) and a Psychological factor (the task)

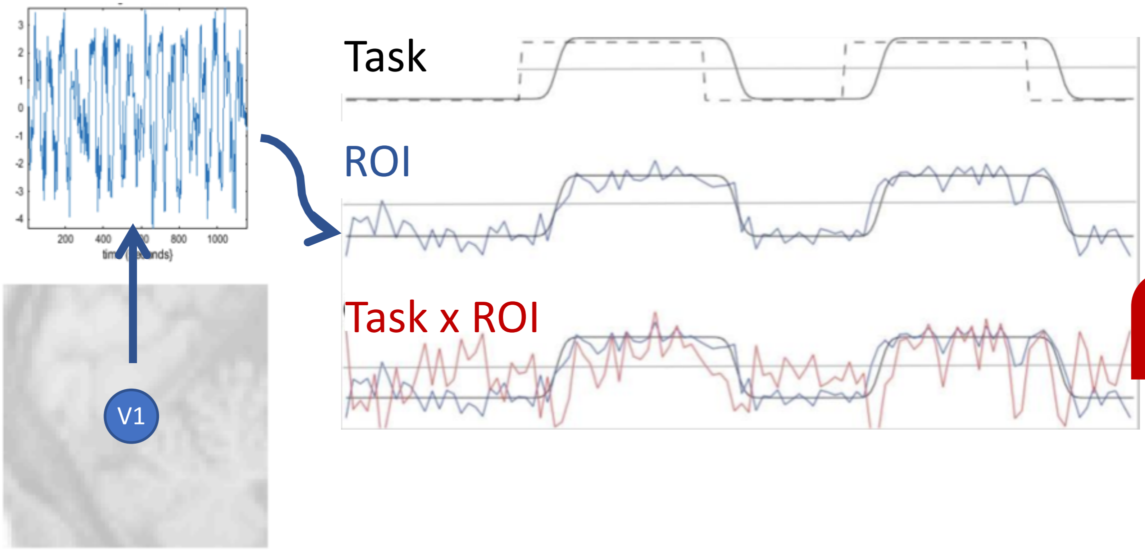


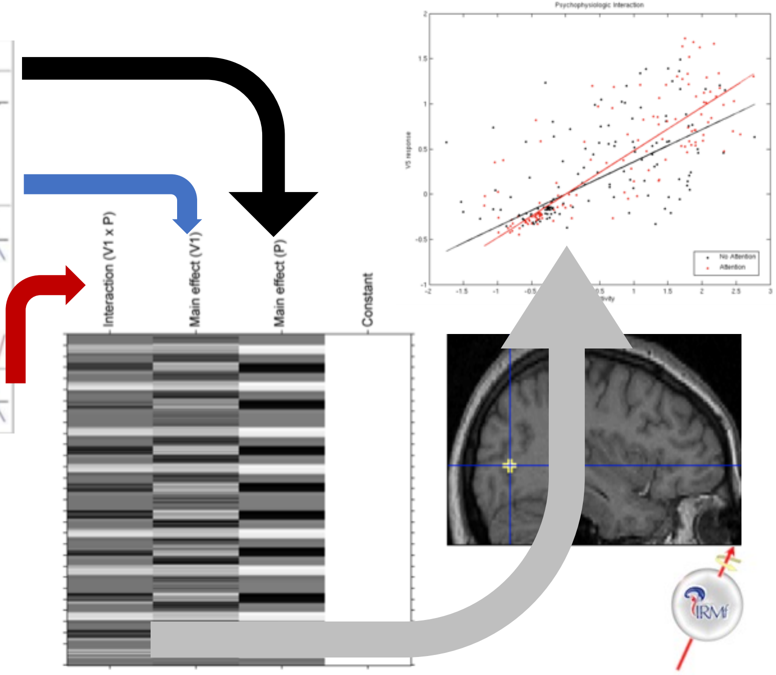
In this case study, the goal is to use PPI to examine the change in effective connectivity between V1 and V5 while the subject observes visual motion instructed to attend vs. not attend to dots' speed. The PPI attempts to find a significant difference in the regression slopes of V1 vs V5 activity under the influence of attention



Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage. 1997 Oct;6(3):218-29. doi: 10.1006/nimg.1997.0291.

- PsychoPhysiological Interactions (PPIs) analysis concerns task-specific changes in the relationship between different brain areas' activity
- PPI aims to identify regions whose activity depends on an interaction between Psychological factors (the task) and Physiological factors (the time course of a region of interest)

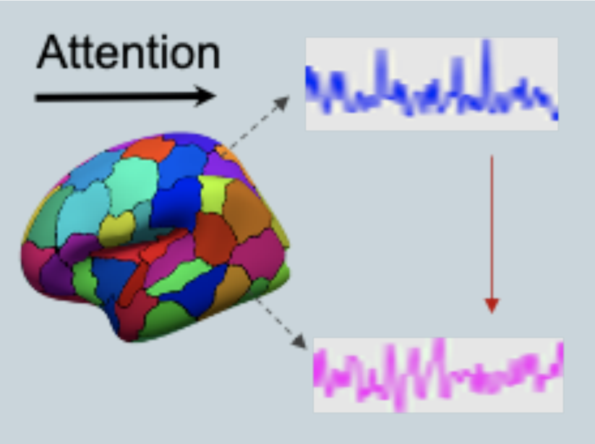


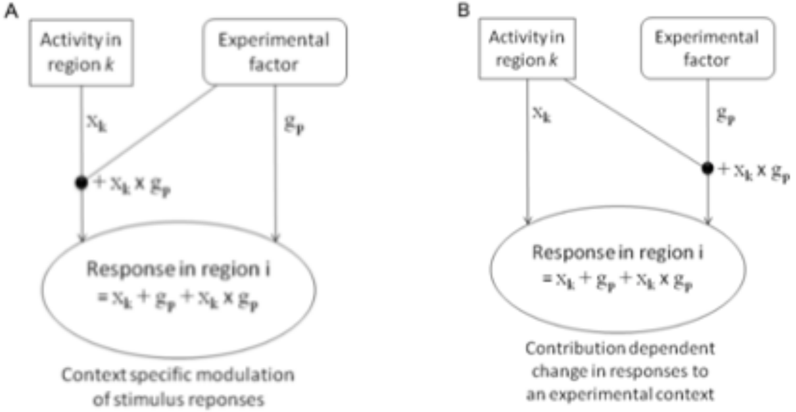


Limitation: Low statistical power !

Interpretation of PPI

- Two possible questions:
  A. How contribution of one region to another is influenced by the experimental context
  B. How an area's response to an experimental context is modulated by input from another region
- Mathematically equivalent! But… one may be more **neurobiologically** plausible





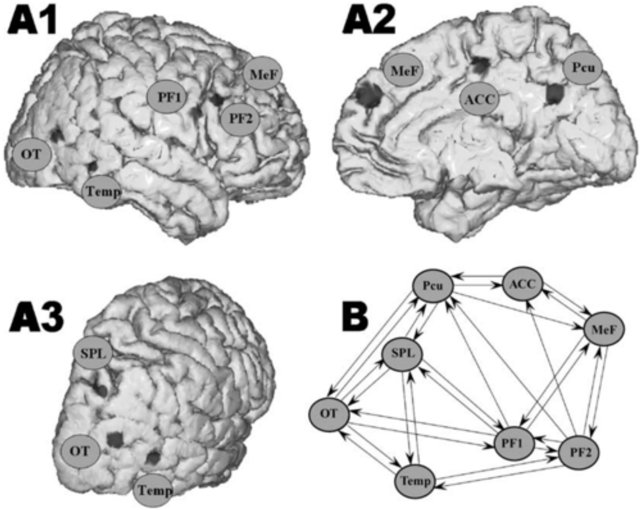
Limitation: Only allows modeling contributions from a single area (nb: generalized PPI)

- Based on a graphical model representing "neuroscience hypothesis generation":

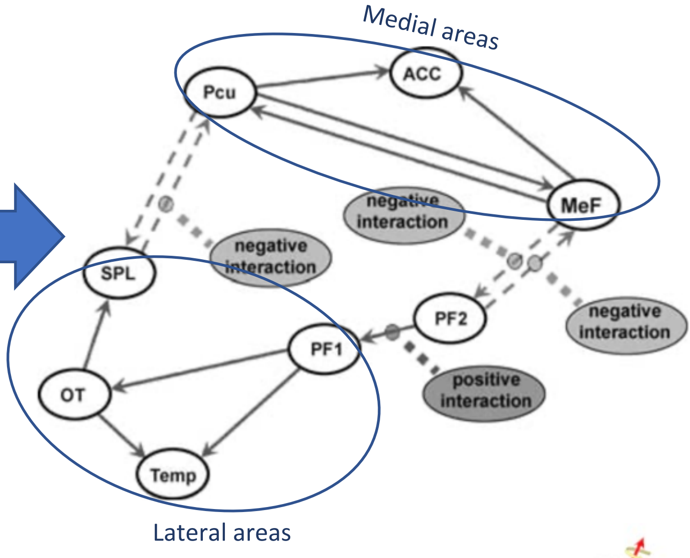
" How does attention load modifies connectivity in a network of areas activated during a visual task"

Chaminade, T. and Fonlupt, P. (2003), Changes of effective connectivity between the lateral and medial parts of the prefrontal cortex during a visual task. European Journal of Neuroscience, 18: 675-679.

- Based on a graphical model representing "neuroscience hypothesis generation":
  - (A) selecting regions or nodes of the network
  - (B) obtaining the anatomical model or edges of the network
  - (C) calculating the interregional covariance or correlations matrix from the *f*MRI data
  - (D) estimating the parameters and verifying the model's fit

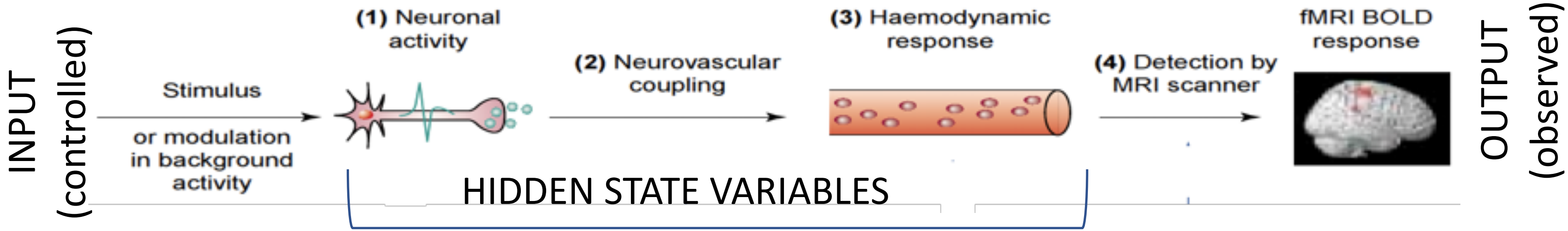


	Path coefficient
OT → Temp	0.392
Pcu → ACC	0.422
MeF → ACC	0.287
PF1 → Temp	0.316
SPL → Pcu	−0.138
MeF → Pcu	0.269
Pcu → MeF	0.269
Pcu → SPL	−0.138
PF2 → PF1	0.626
PF2 → MeF	−0.210
MeF → PF2	−0.210
OT → SPL	0.661
PF1 → OT	0.791
Interaction	
Attention × MeF → PF2	−0.289
Attention × PF2 → MeF	−0.231
Attention × SPL → Pcu	−0.246
Attention × PF2 → PF1	0.198



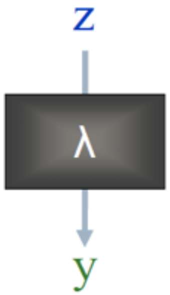
Limitation: Linear statistics, no generative model.

- Generic Bayesian framework for inferring hidden neuronal states from measured brain activity
  - Dynamic: linear and non-linear differential equations describe hidden neuronal dynamics
  - Causal: describe how dynamics in one area cause dynamics in another area, and modulation by experimental manipulations
  - Bayesian: each parameter is constrained by prior distribution
  - Neurophysiologically interpretable: Hypotheses are constrained by the underlying biological hemodynamic model

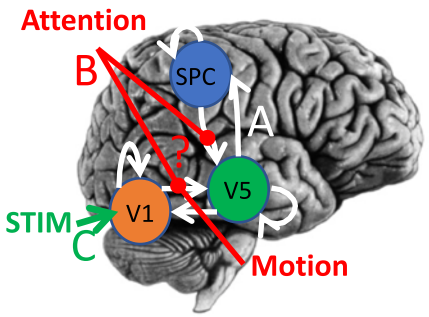


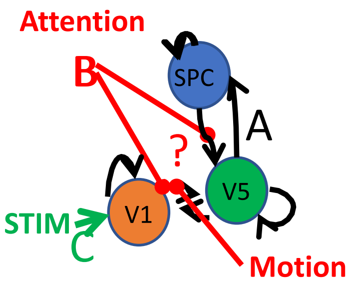
Hemodynamic model

Neuronal dynamics (Z) transformed into BOLD-signal (Y) via hemodynamic response function (λ)



DCM: Equations





Z is the underlying **Neuronal** state

What is modeled is Z evolution through time

$$dZ/dt = F(Z, u, \theta)$$

Z: current state

$(Z_{V1}, Z_{V5}, Z_{SPC})$

u: external input

STIM (C): influences of inputs on regional activity

Motion, Attention (B): change in coupling due to input

θ: intrinsic connectivity (A)

$$\boxed{\dot{z} = \left(A + \sum_{j=1}^{m} u_j B^{(j)}\right) z + Cu}$$

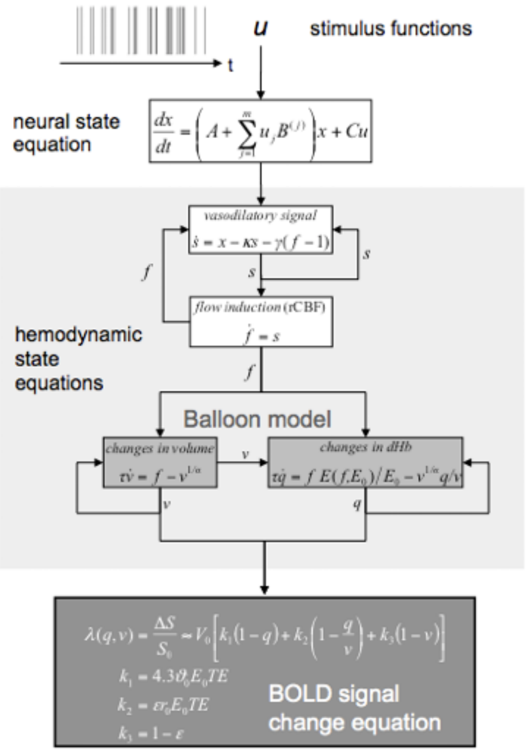
Neural state (Z)

Change in vasodilatory signal

Change in blood flow

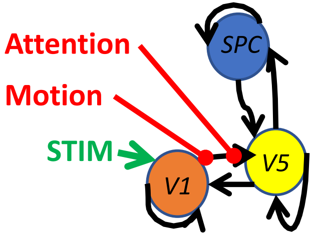
Change in blood volume and desoxyhemoglobin volume

Bold signal (Y)

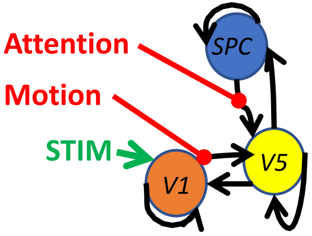


Example of DCM analysis and results

Model 1: Attention modulates forward

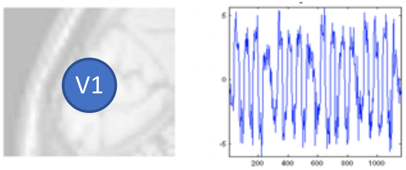


Model 2: Attention modulates backward

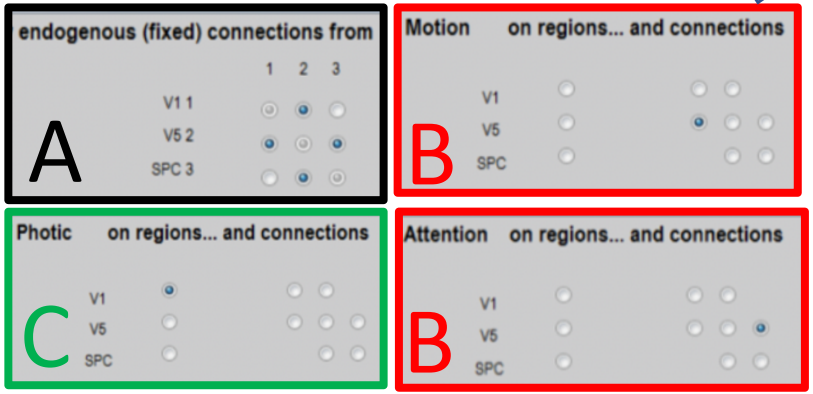


Hypotheses:
Attending to motion influences response to motion stimulus by affecting Forward (V1-->V5) or Backward (SPC-->V5) connections

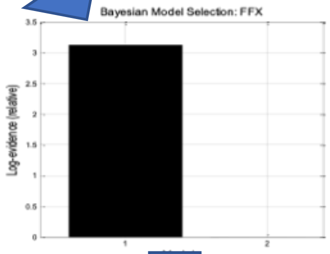
Extract local activity



Define the models (Here: model 2)



Models evaluation and comparison



Model 1 wins

Connectivity toolbox

- Many toolbox have been proposed to investigate connectivity
- Conn is becoming a standard given its large number of possible corrections during preprocessing and large amount of possible analyses

Brain Connectivity Toolbox[1]	Graph-theoretical analyses of functional connectivity	Matlab
Brain Modulyzer [2]	Explore Hierarchical Processes of the functional brain networks	Python
BrainNet viewer[3]	Brain network visualization tool	Matlab
Brainwaver[4]	Brain connectivity extraction and analysis	R
C-PAC[5]	Functional connectivity analysis pipeline	Python
CONN[6]	Functional connectivity analysis and display tool	Matlab
Connectome workbench	Visualization and discovery tool	Python
cPPI[7]	Task-related functional connectivity analysis	Matlab
DCM[8]	Dynamic Causal Modelling analysis	Matlab
FATCAT[9]	Functional and tractographic connectivity analysis	C
FSFC[10]	Seed-based functional connectivity analysis	Shell
Fubraconnex[11]	Tool for visual analysis of functional connectivity	C
GIFT[12]	Independent component analysis	Matlab
gPPI[13]	Task-related functional connectivity analysis	Matlab
Graph Theoretic GLM Toolbox[14]	Graph theory analysis and fMRI preprocessing pipeline	Matlab
Graphvar[15]	Graph-theoretical analysis tool	Matlab
MELODIC[16]	Independent component analysis	C

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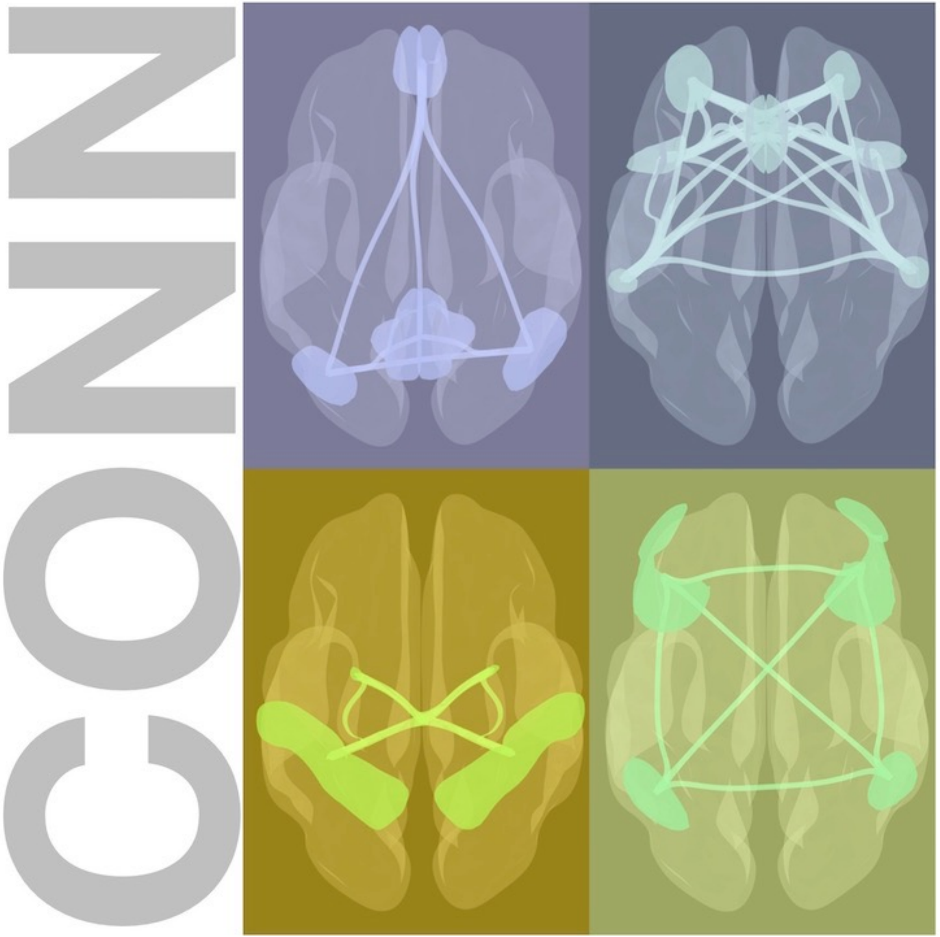
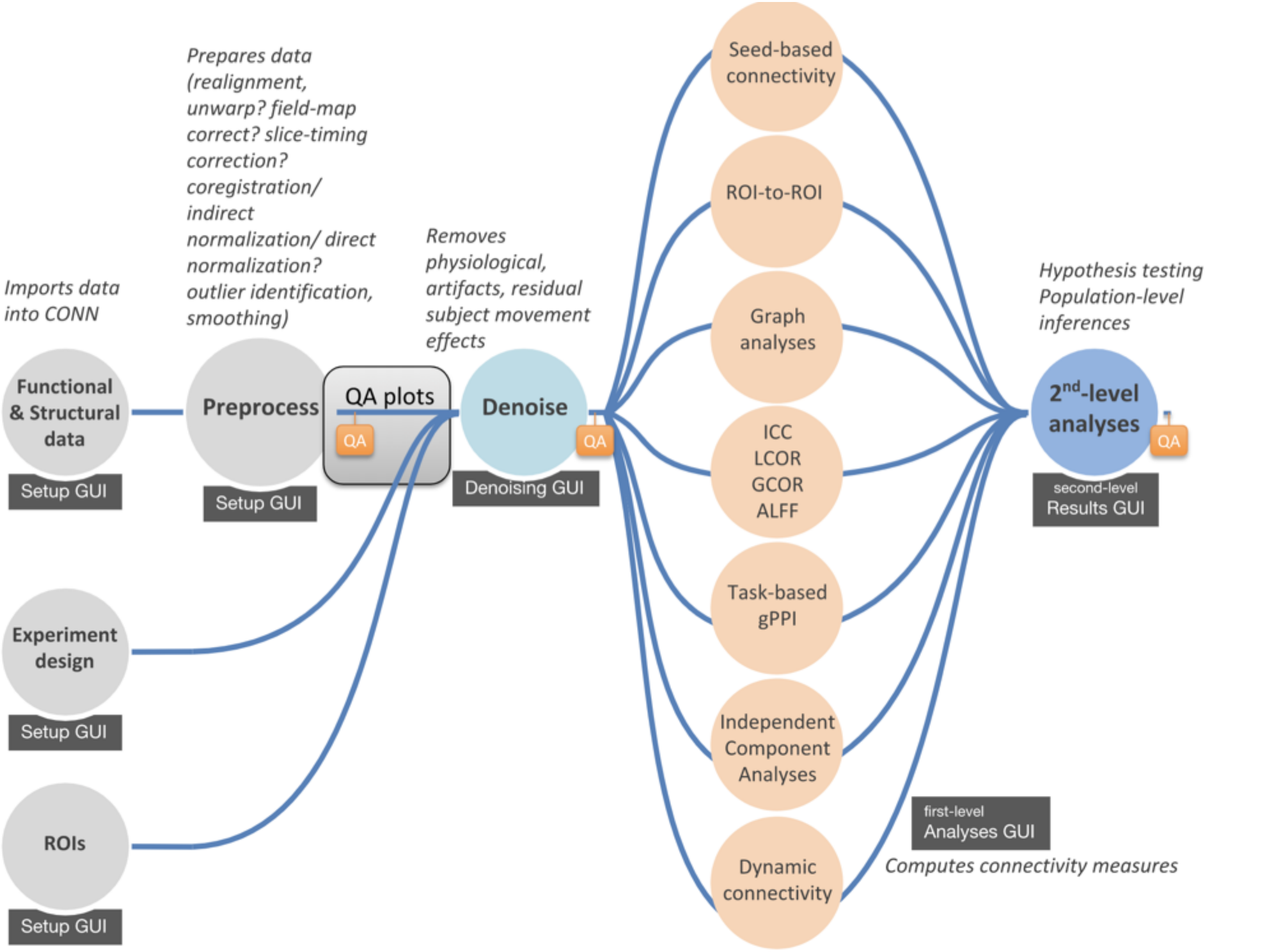
Conn toolbox, a swiss knife for connectivity analyses



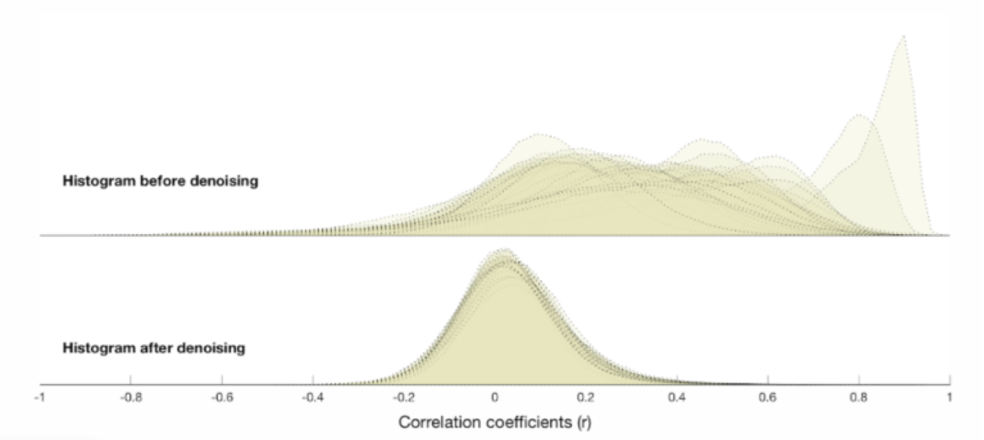
- Developed since 2010 and regularly updated and improved (12/2020)
- Full pipeline for import (automatic for BIDS datasets and fMRIPrep outputs), preprocessing, denoising, and quality assessment
- Several implementations of connectivity measures
- Several second-level inferences available

Whitfield-Gabrieli, S; Nieto-Castanon, A (2012). "Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks". *Brain Connect*. **2**: 125–41. doi:10.1089/brain.2012.0073

Conn Toolbox processing pipeline

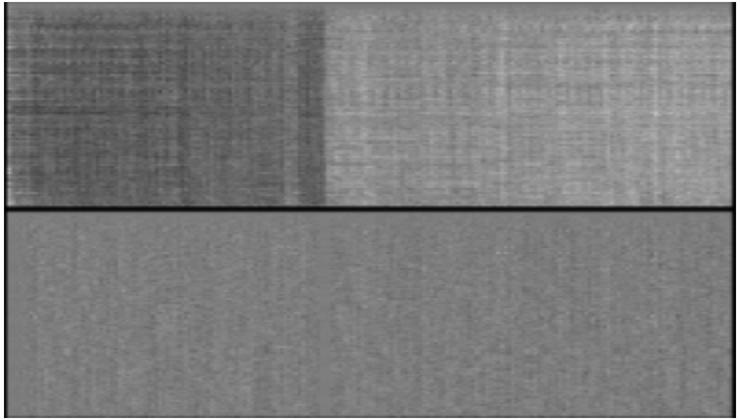


Denoising voxel-to-voxel correlations



- Histograms centered and overlapping

Denoising BOLD time-series



- No visible global effects

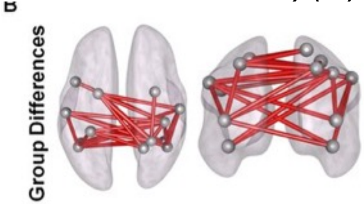
SEED-BASED CONNECTIVITY MEASURES

- *Seed-Based Connectivity (SBC) maps*
- *Multivariate Seed-Based Connectivity (mSBC) maps*
- *Weighted Seed-Based Connectivity (wSBC) maps*
- *Generalized Psycho-Physiological Interactions (gPPI) maps*

NB: similar can be done with target ROI instead of voxels providing ROI-to-ROI Connectivity (RRC) matrices

NETWORK MEASURES (VOXEL-LEVEL)

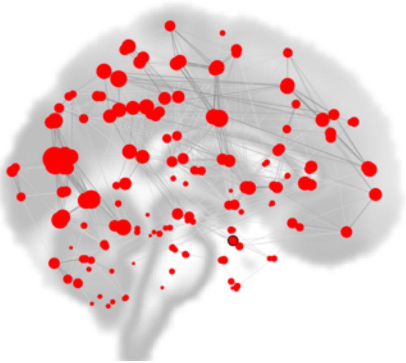
- *Intrinsic Connectivity (IC)*



- *Global Correlation (GCOR)*
- *Local Correlation (LCOR)*
- *Multivariate Correlation (MCOR) (group-MVPA)*
- *Independent Component Analyses (group-ICA)*
- *Principal Component Analyses (group-PCA)*

GRAPH MEASURES (ROI-LEVEL)

nodes = ROIs, and edges = supra- threshold connections

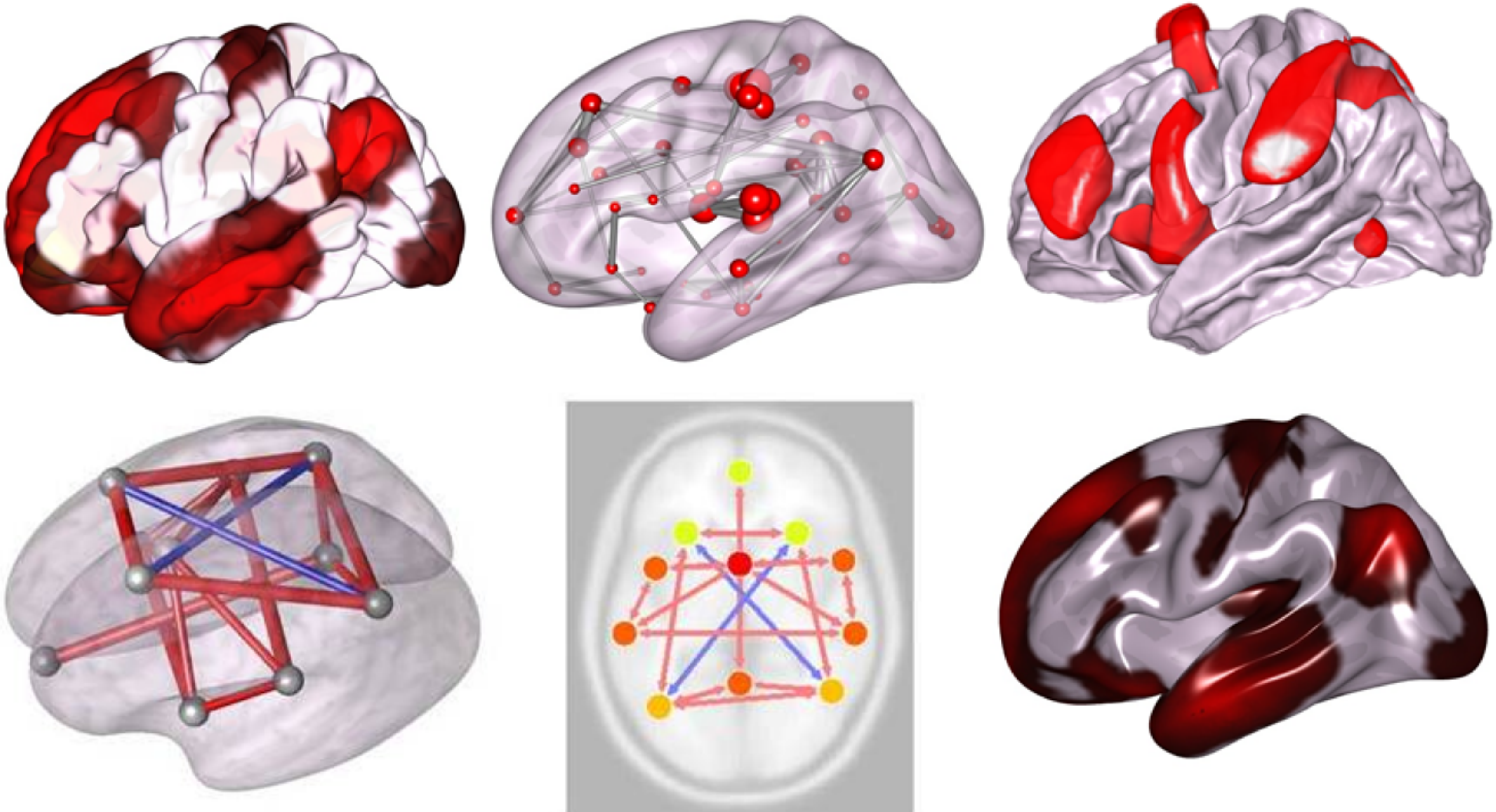


- *Degree & Cost*
- *Average path distance*
- *Clustering Coefficient*
- *Local Efficiency*
- *Betweenness Centrality*

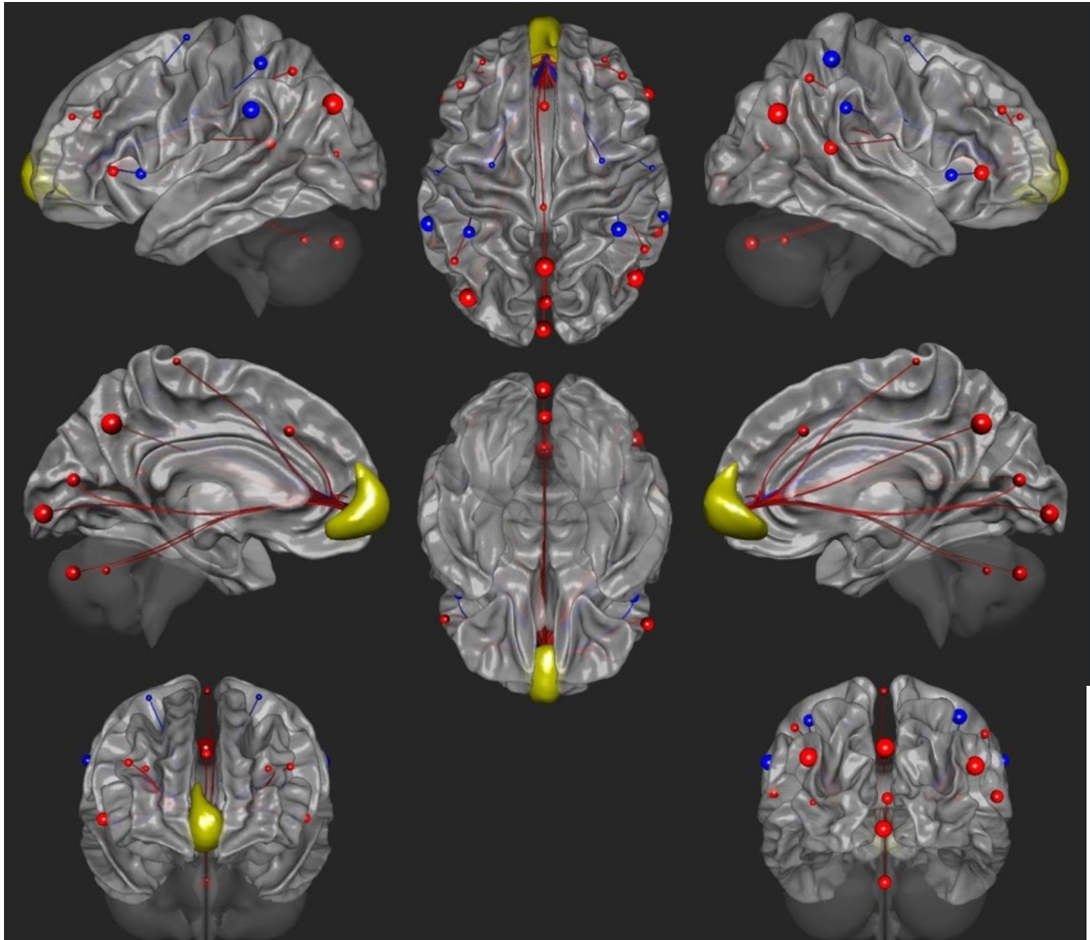
DYNAMIC CONNECTIVITY MEASURES

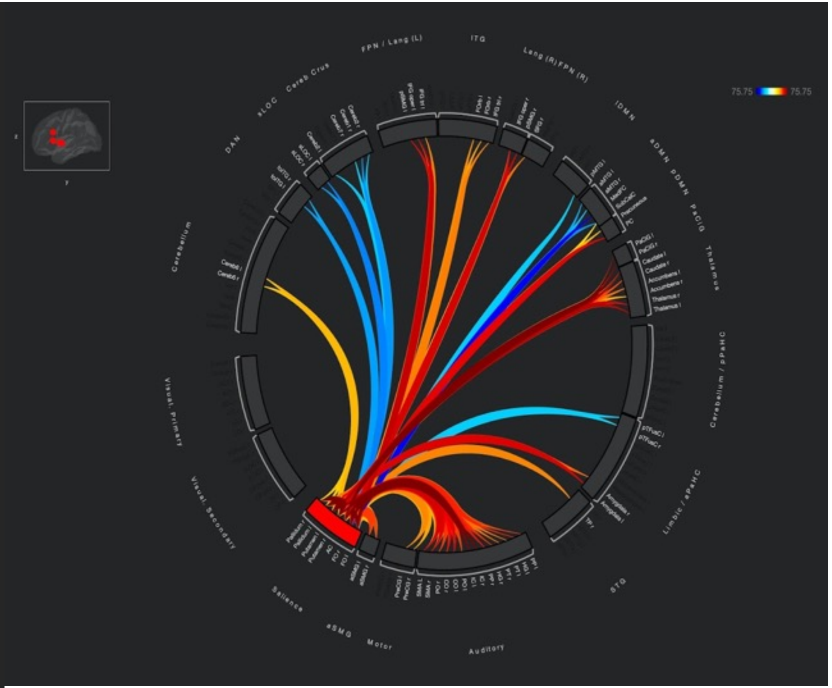
- *Dynamic Independent Component Analyses (dyn-ICA)*

Conn Connectivity rendering



Conn Connectivity rendering

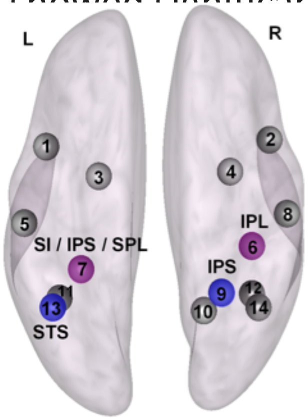


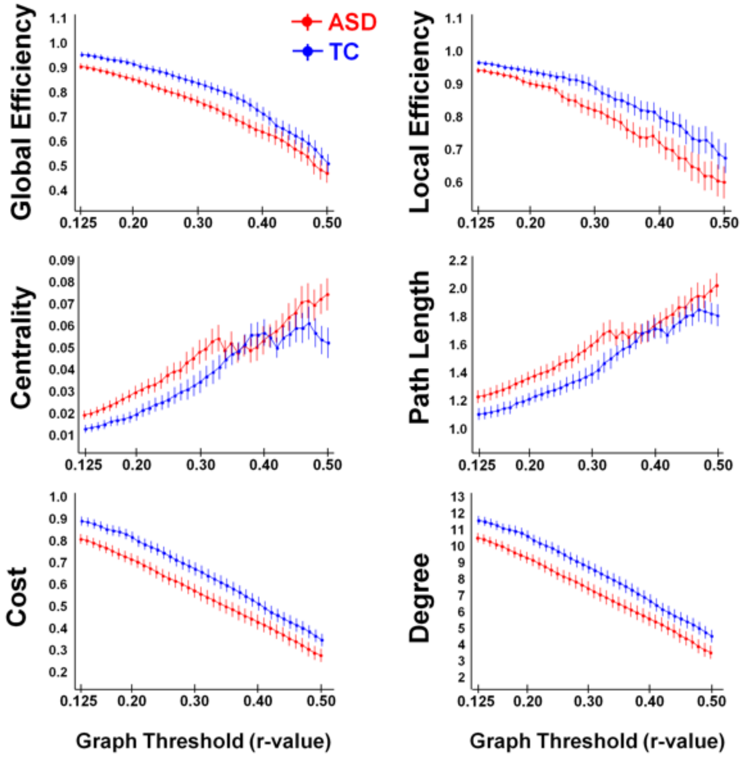


Conn Application: Graphs Theory measurements

- functional connectivity analysis of resting-state fMRI-data from adolescents and young adults with ASD and typical controls (TC)
- graph theory analyzes provide convergent evidence that the network integrity of the Action Observation Network is altered in ASD
- Compared to TC, individuals with ASD showed significant reductions in network efficiency and i
path lengths and centrality

ROIs in the Action Observation Network





Kaat Alaerts et al., PLOS One, 2015

- Despite its potential interest, Effective Connectivity analyzes are scarcely used because of:

    1) controversies about interpretations,

    2) low statistical power leading to Type 2 errors (false positive).

- These analyzes are prone to artifacts in the form of spurious correlations (Type 1 error) caused by:

    1) Participants **movements.**

    2) Physiological fluctuations (**cardiac** or **respiratory** activity).

    3) Main **effect of tasks**.

    4) **Global signal** fluctuations.

    5) Signals emerging in **areas likely to produce physiological artifacts** (eg ventricles).

➢ Preprocessing of the data is crucial, but still improving (eg Conn)

➢ Caution is required at all levels of analysis and interpretation


Thank you !
Some questions ?
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