# Introduction to Functional Magnetic Resonance Imaging (fMRI)

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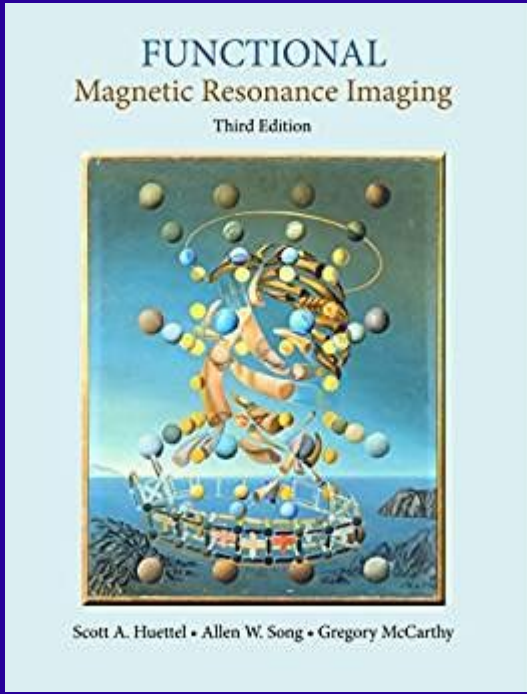
# Resources




Textbook on fMRI (3rd edition) by Huettel, Song & McCarthy

fMRI for Dummies

http://www.fmri4newbies.com/ by Jody Culham

MRC | Cognition and Brain Sciences Unit

http://imaging.mrc-cbu.cam.ac.uk/imaging/CbuImaging


http://www.fil.ion.ucl.ac.uk/spm/course

# A typical fMRI experiment

1. The volunteer is interviewed by a doctor.

2. s/he is installed in the scanner (pulse detection/respiration belt/eye tracker/...)

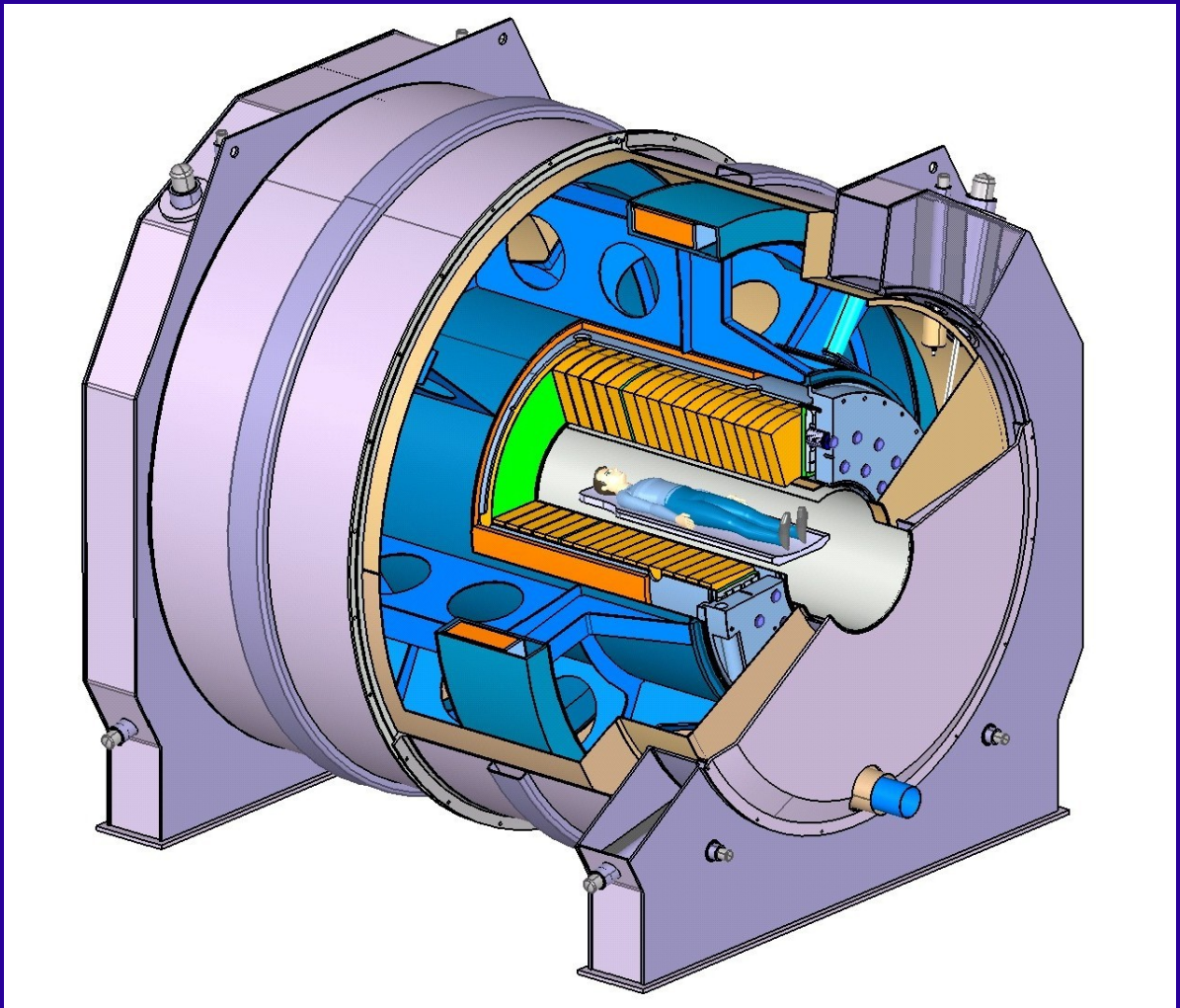
3. Data acquisition lasts about 1 hour:

 - One anatomical scan lasting 8 minutes

 - Series of functional scans (either whole brain, or only some slices.) each lasting ~ 2 seconds

Note: The subject can receive visual and auditory stimulation and move his hands and fingers. **But it crucial that s/he does not move the head.**

# Neurospin's 11.7T magnet for humans



Main Coil : 230 km of niobium-titanium wire assembled with a precision of a few micrometers.

45 tons

Current = 1400 A
Temperature = 1.8 K

http://irfu.cea.fr/Sacm/en/Phocea/Vie_des_labos/Ast/ast_visu.php?id_ast=3377

# After data acquisition

Brain images (typically a few GiB) are uploaded to a workstation or a computer cluster where they are :

1. **Preprocessed**, that is :
    - corrected for movements,
    - corrected for time-slice acquisition differences
    - (optionaly) spatially normalised to a standard template.

2. Submitted to **statistical analyses** with the aim to detect activations, that is transient changes in neural activity.

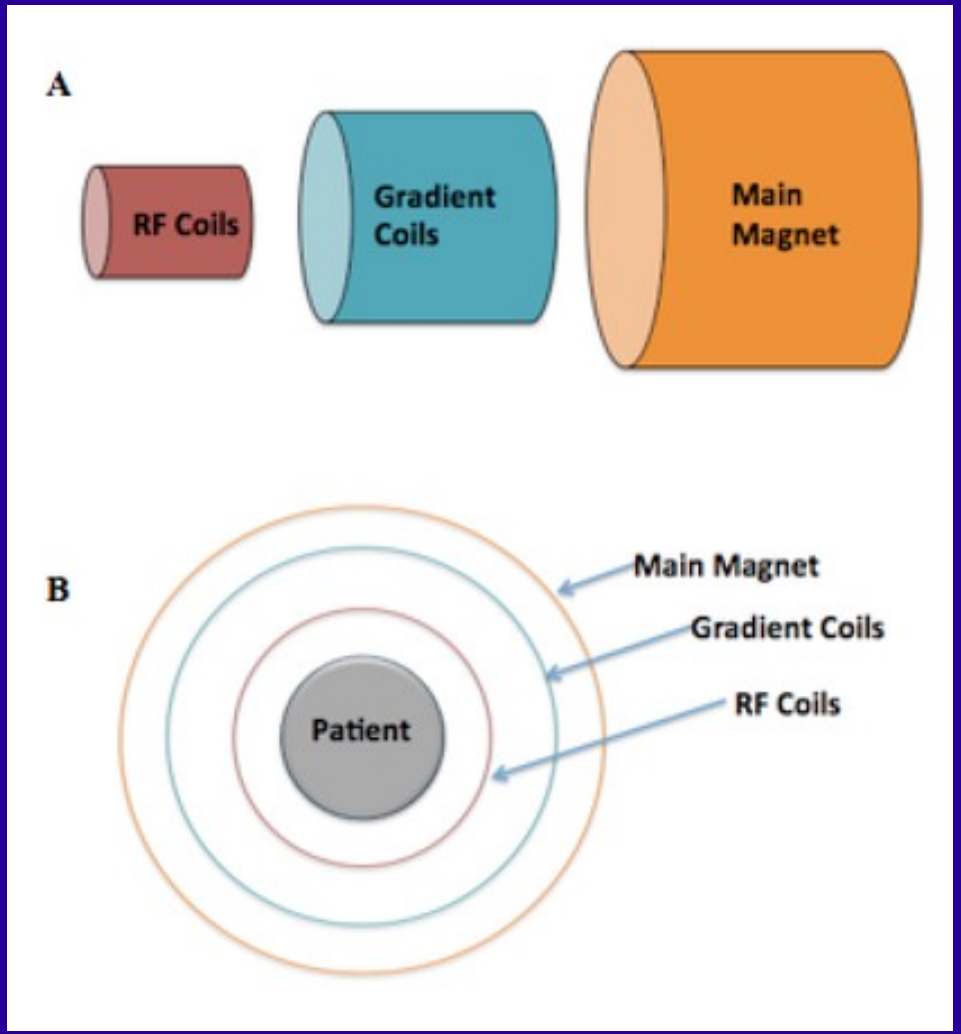
Remark: it is sometimes possible to perform « Real time analyses », simultaneously with data acquisition. This is useful for biofeedback experiments.

# Hardware of an MRI scanner

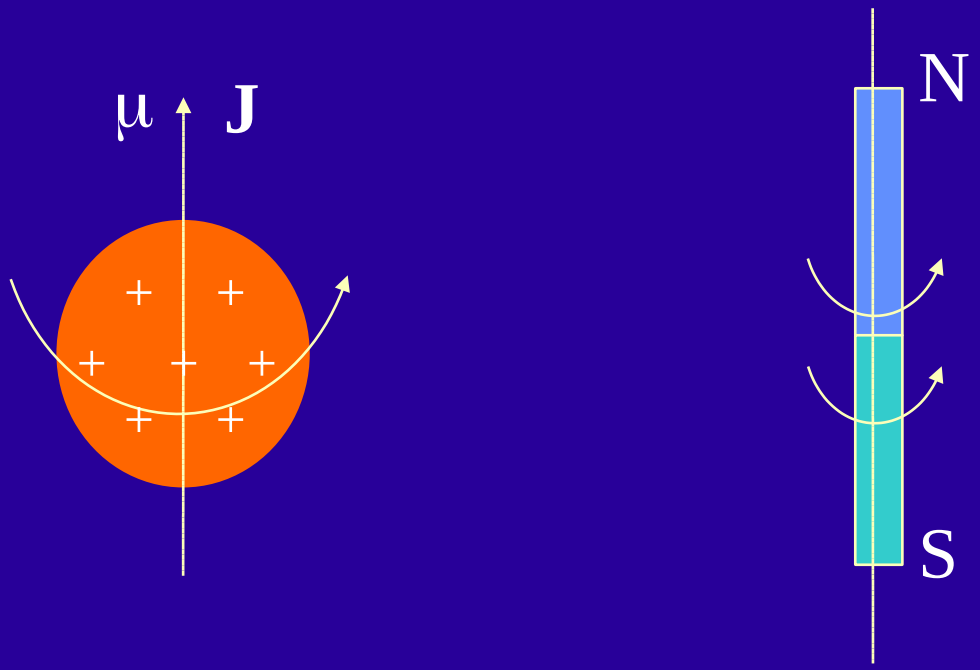
1) A main **magnet** generating a strong **static** field (a few Telsa)

2) **Gradient coils** generating small magnetic field varying in space (e.g. 50mT/m)

3) An **Antenna** (**Radio Frequency (RF) transmitter / receiver)** used to « excite » the protons in the brain and then measure the re-emitted signal.



# Similarity between a spinning proton and a spinning magnetic bar




Because a proton has an electric charge and is spining on itself, it has an *angular momentum* **J** and a *magnetic moment* **μ**.

$$\boldsymbol{\mu} = \gamma \mathbf{J}$$

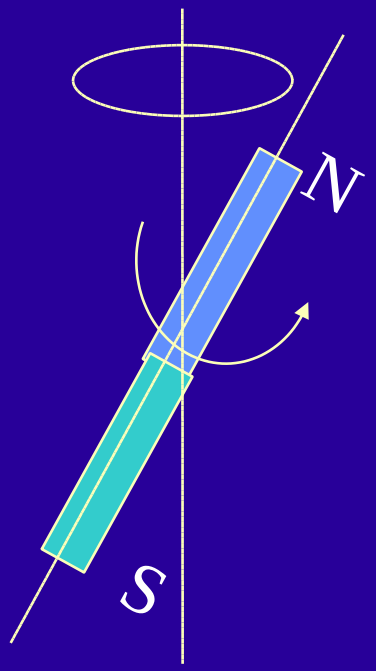
where $\boldsymbol{\gamma}$ is an experimental constant called the gyromagnetic ratio (which varies with the type of atomic nucleus)

# Behavior of a Magnetic Bar in a Magnetic Field


Magnetic field


Static magnetic bar

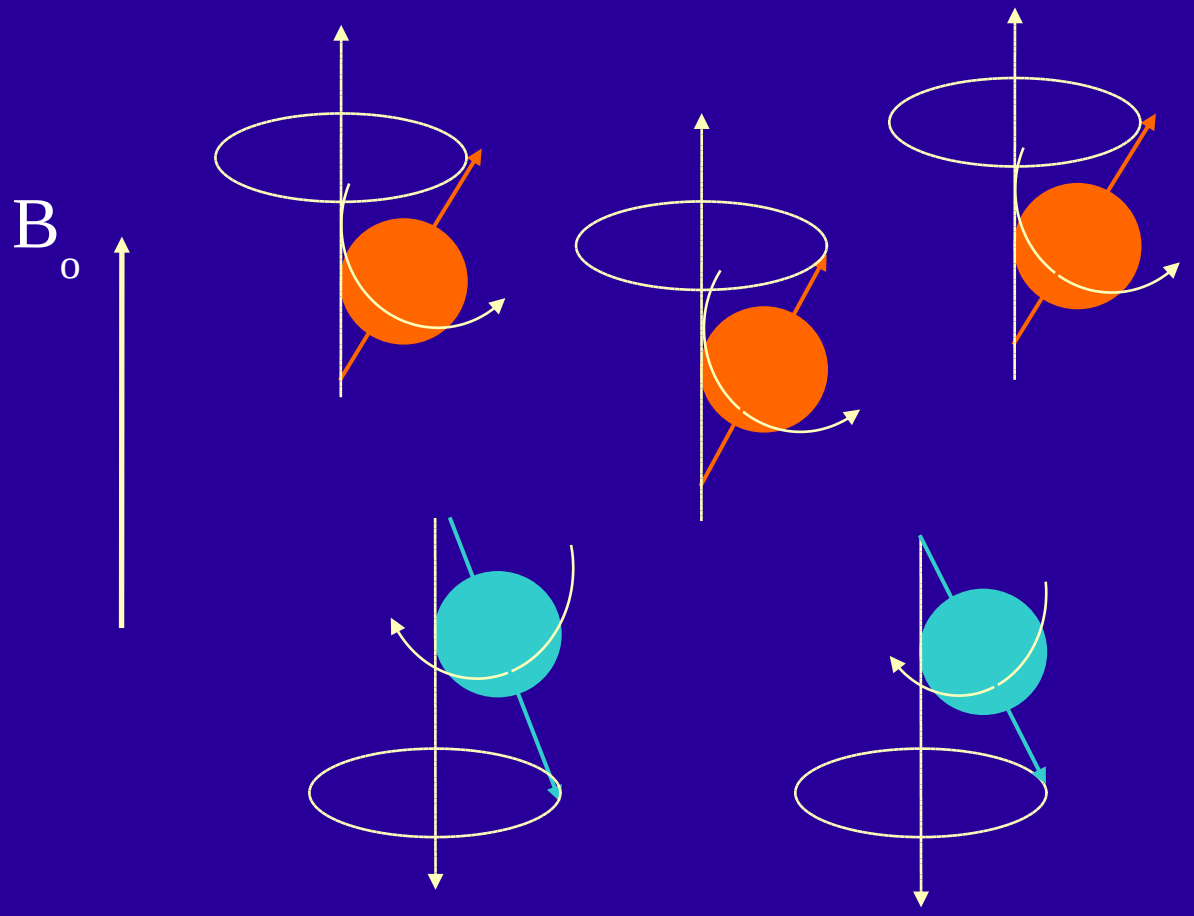
Orients itself
along the vector **B**




Spinning magnetic bar

Has a movement
of precession

# Protons in a Magnetic Field

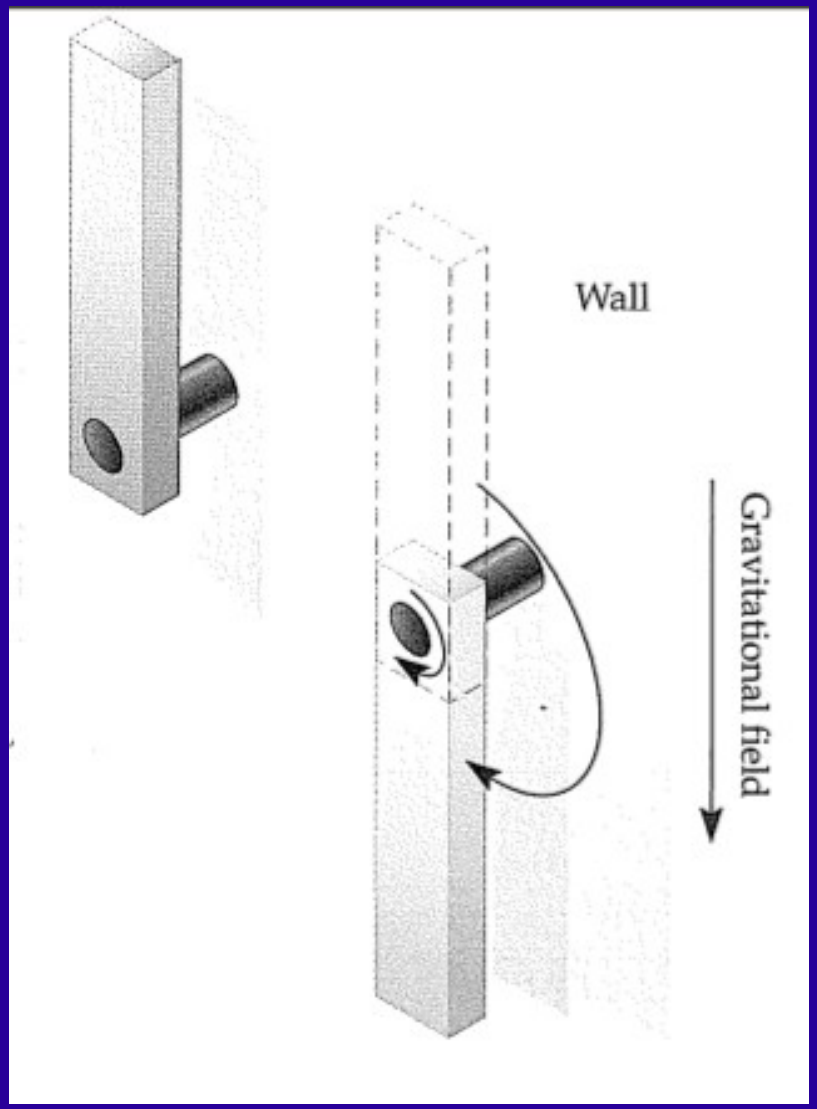



Parallel (low energy)

Anti-Parallel (high energy)

Spinning protons in a magnetic field will assume **two** states. (It is a quantum mechanics property: The angular momentum of protons is quantified, that is can only take 2 discrete values)

# Example of a discrete states system



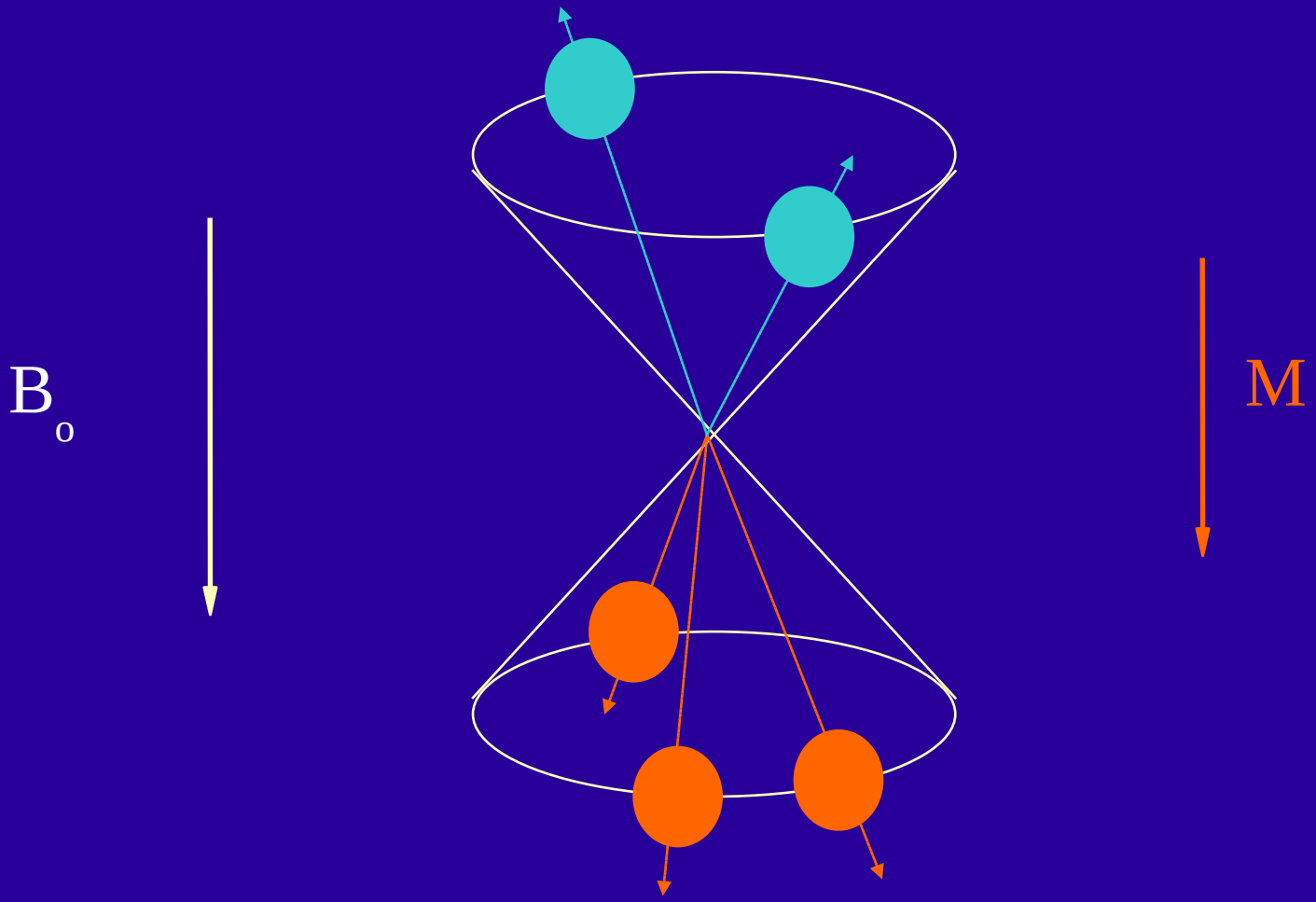

A handle bar within the earth gravitational field can assume two states :

The antiparallel state (up) with high potential energy

The parallel state (down) with low potential energy (but more stable)

There are more protons in the low energy state.

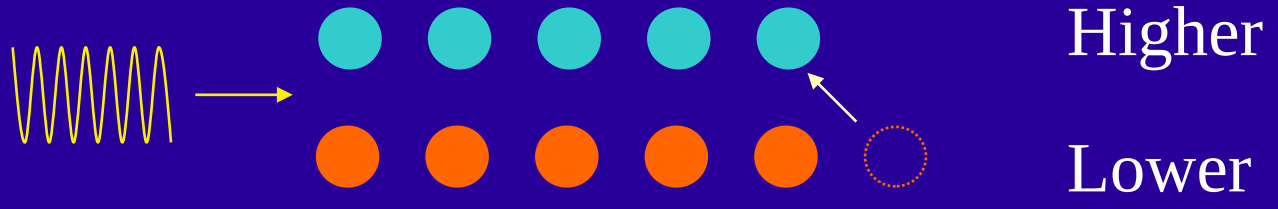
The sum of all magnetic moments create
a *net macroscopic magnetization* ‘M’ aligned with B0



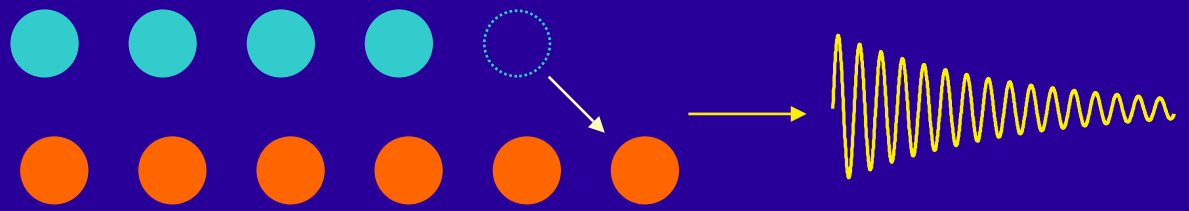
# Nuclear Magnetic resonance

1) Spin system before irradiation:


2) Transitions induced by electromagnetic field (EM)




3) Return to steady steady state after the end of irradiation



To induce transitions between the energy states, the electromagnetic wave must have a very precise frequency:

$$\nu = \gamma/2\pi \; . \; B_o$$

$\nu$ is known as the Larmor frequency (resonance frequency)

$\gamma/2\pi$ = 42.57 MHz / Tesla for **protons in H2O**

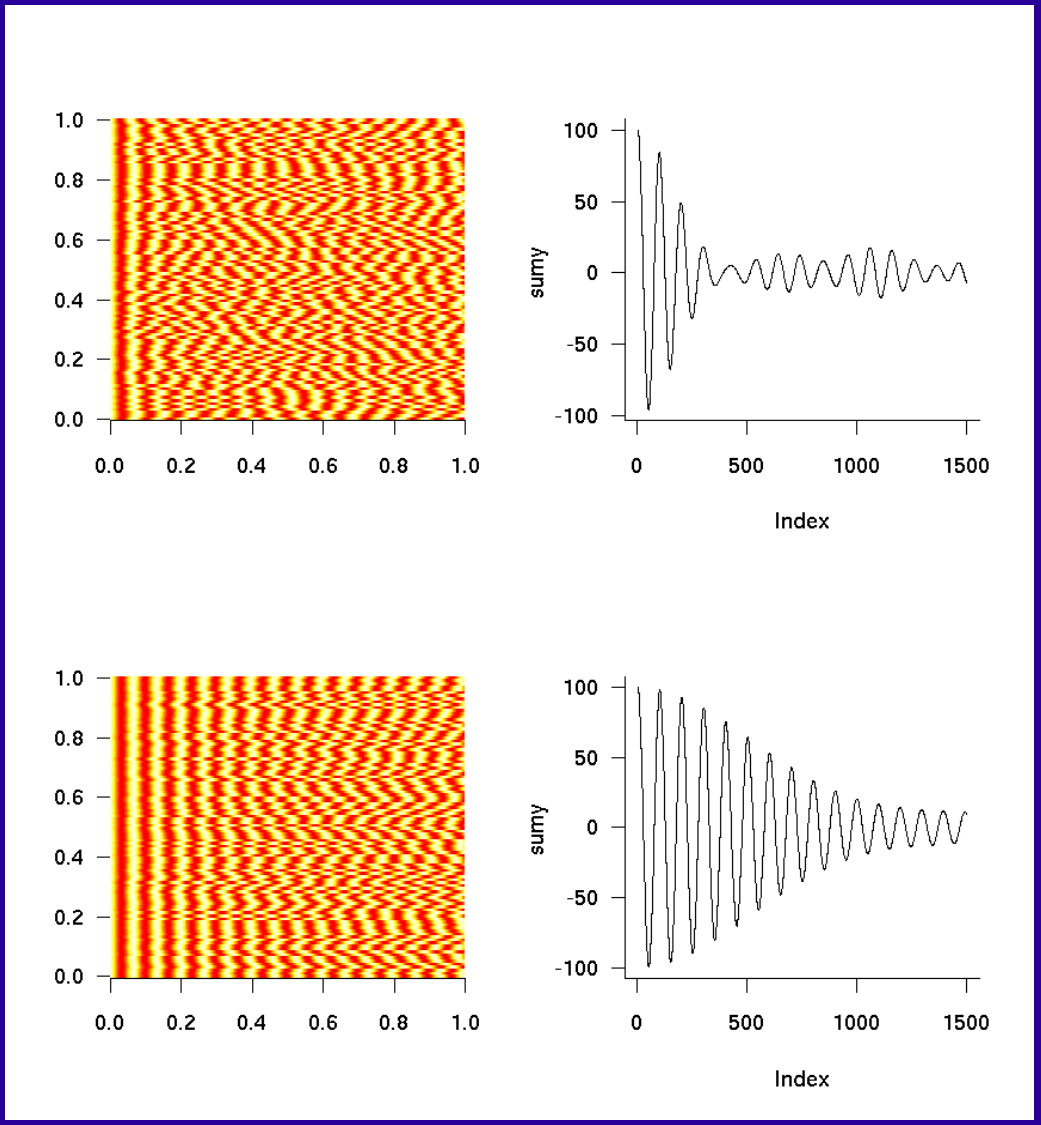
# T2* relaxation

T2* is the time of the decrease of the Free induced decay (FID).

It is related to the speed at which protons become *out of phase*.

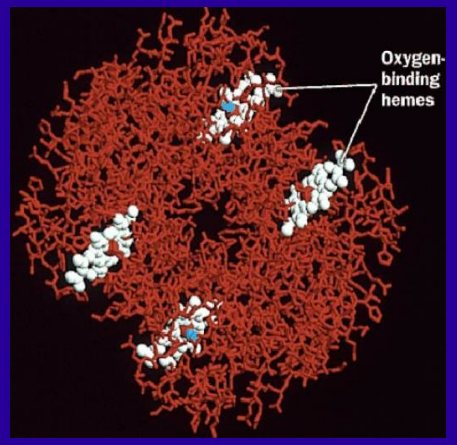
Protons become out of phase faster in presence of $B_0$ *inhomogeneities* (because they spin at different frequencies).

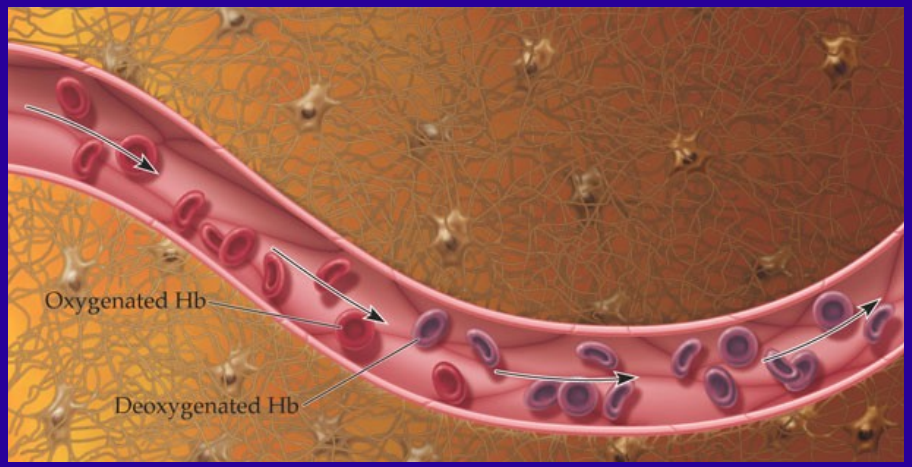
**The more inhomogenous the $B_0$ field is, the less signal you observe**.

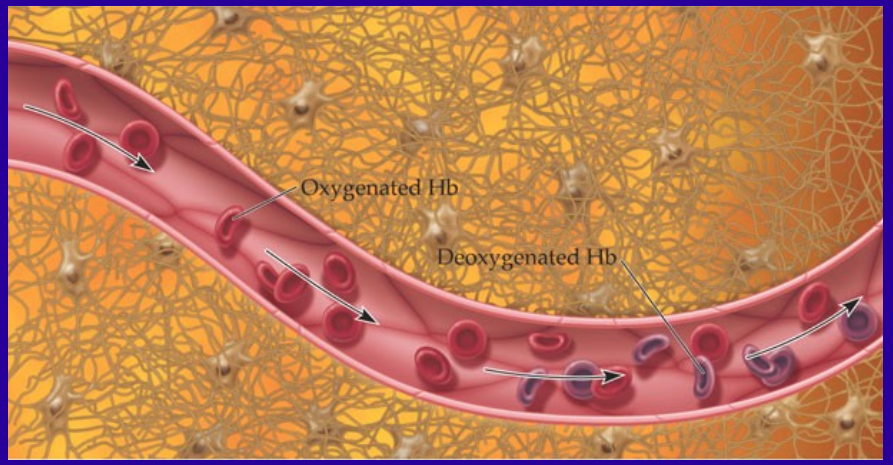


# The basis of functional MRI images

- Changes in neural activity alter the local concentrations of oxyhemoglobin (carrying $O_2$) and deoxyhemoglobin



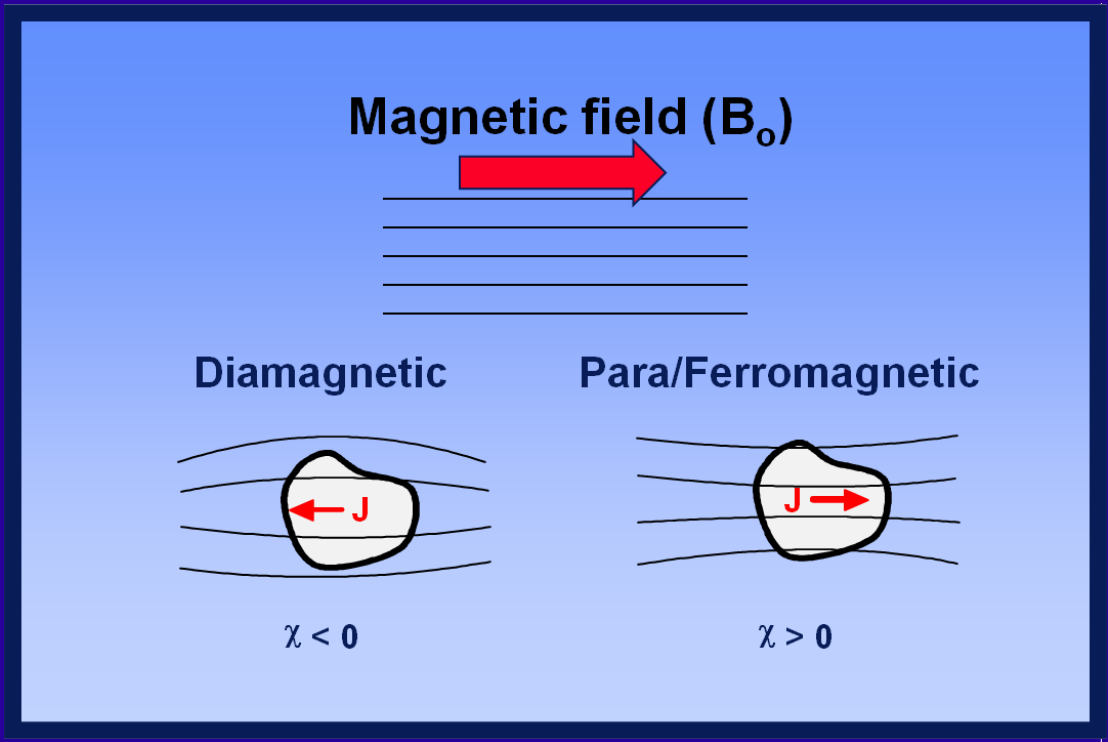



# The basis of functional MRI images

Oxyhemoglobin and Deoxy-hemoglobin have different magnetic properties :

- OxyH is diamagnetic (it repels magnetic field)

- DeoxyH is paramagnetic (it attracts magnetic field).




A change in the local concentrations of oxy/deoxy haemoglobin creates **local distortions** of the magnetic field.

Increase in deoxy-Hb => smaller T2*

Increase in oxy-Hb => larger T2*

# The basis of fMRI: the BOLD signal (Ogawa, 1990)

The BOLD signal ("*Blood Oxygen Level Dependent*" contrast)

=

changes in T2*

(typically due to a stimulation)

=> SHOW an example of an 4D fMRI scan

# Relationship between the BOLD signal and neural activity

- Contrary to electrical or optical imaging methods which can directly tap neural activity (spiking or presynaptic potentials), the *BOLD signal is a indirect measure of neural activity.*

- Changes in concentration of oxy/de-oxy hemoglobin are linked to :

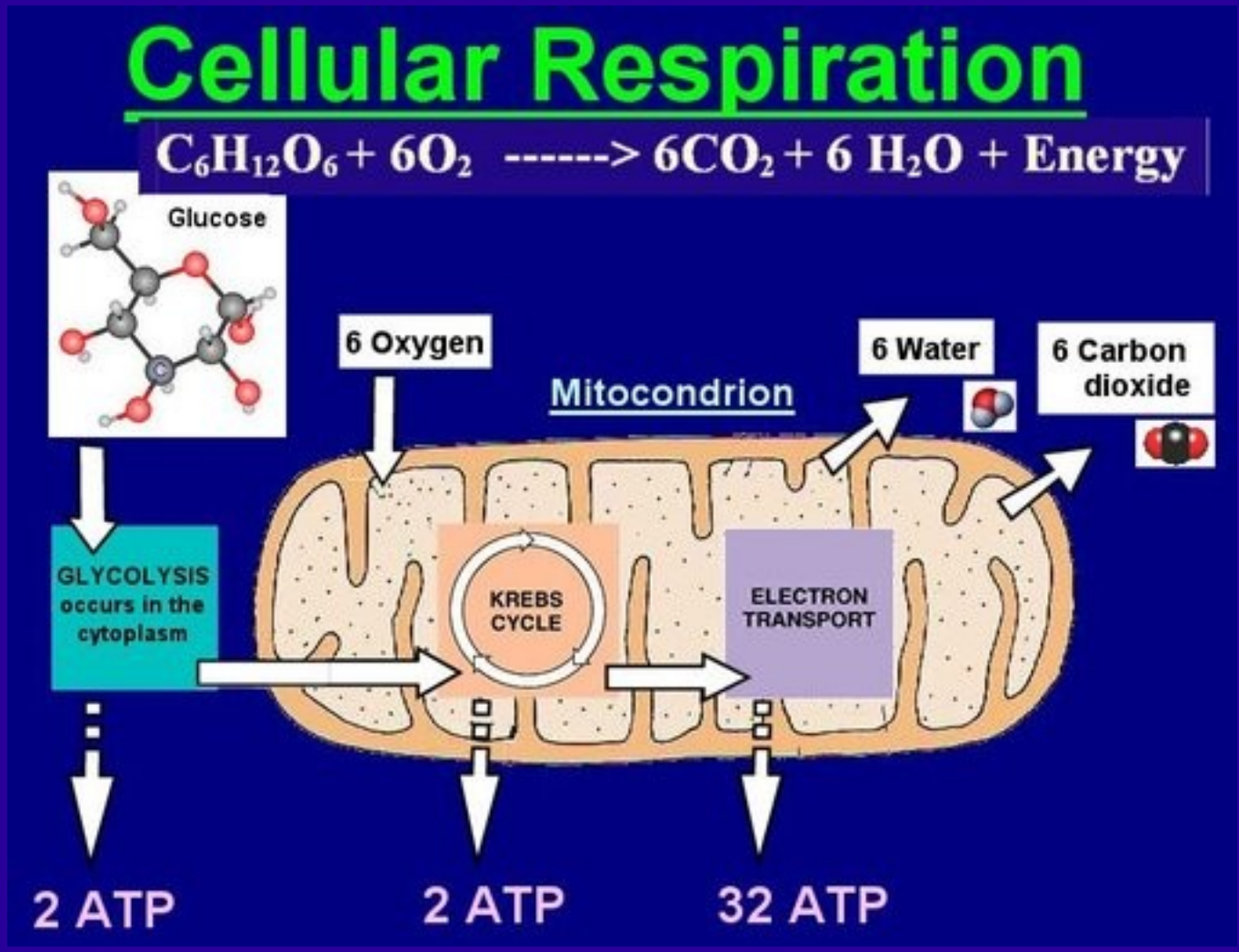
  - *Metabolism* (consumption of oxygen) in neurons AND glials cells.
  - Changes in *Blood Volume* (dilation of capillaries) and *Blood Flow*.

# Metabolism

The fuels of the cells are **oxygene** and **glucose.**

Increases of neuronal activity leads to increased consumptions of glucosis and oxygene.

**The cerebral metabolic rates of glucose (CMRglu) and oxygene (CMRO2) are markers of neural activity.**



# Positron Emission Tomography (PET scan)

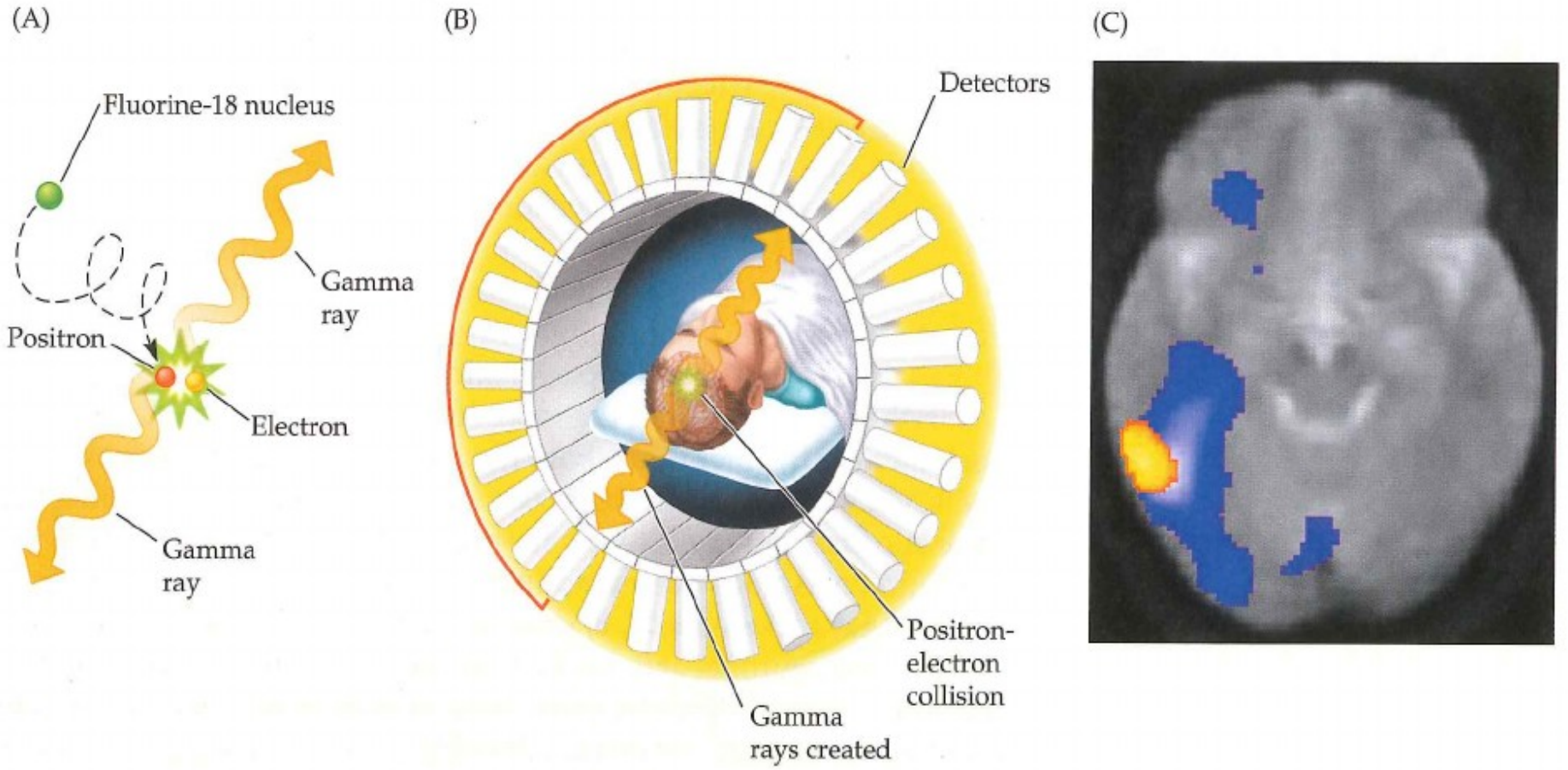



**Figure 1** Positron emission tomography (PET) imaging. Until the mid-1990s, the most common functional neuroimaging technique was PET, which relies on the injection of a radioactive tracer into the bloodstream. As the tracer decays, it emits positrons, which travel a short distance before colliding with an electron (A). The collision results in a pair of emitted gamma rays that travel in opposite directions. The PET scanner (B) consists of a series of coincidence detectors that record the simultaneous arrival of these gamma rays. Depending on the tracer used, PET can be sensitive to several aspects of brain metabolism, including blood flow or oxygen consumption. The output of a PET scan indicates the number of events measured from each voxel during a long time period. (C) These numbers can be converted to statistical maps, which can then be overlaid on anatomical images, often from MRI. (C courtesy of Dr. David Madden, Duke University.)

# With a PET scan, one can

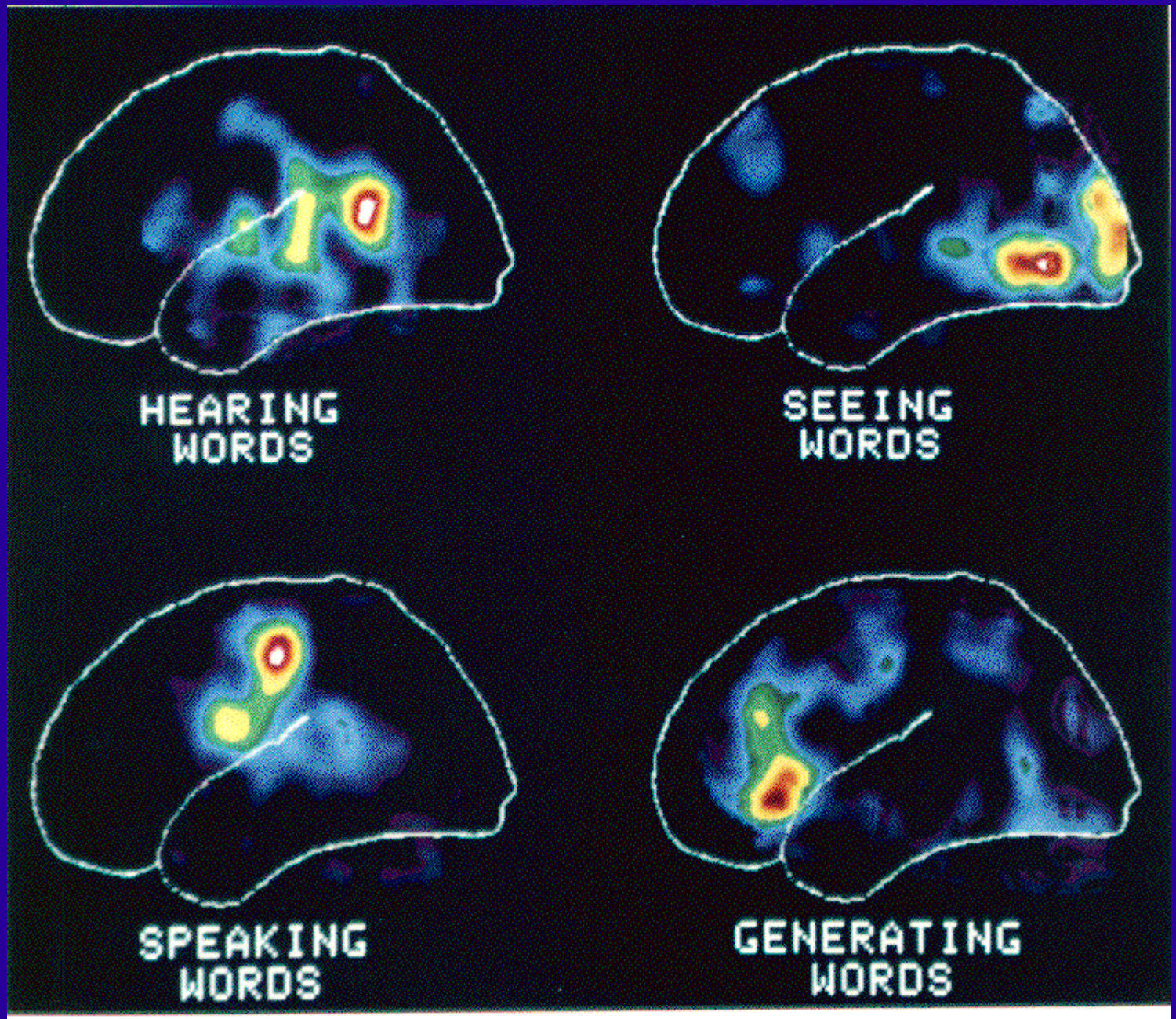
- mark glucosis => measure metabolism
- mark $H_2O$ => measure Blood Flow

Remark : Regional **cerebral blood flow (rCBF)** is tighly coupled to cortical metabolism of glucose (**CMRglu**).

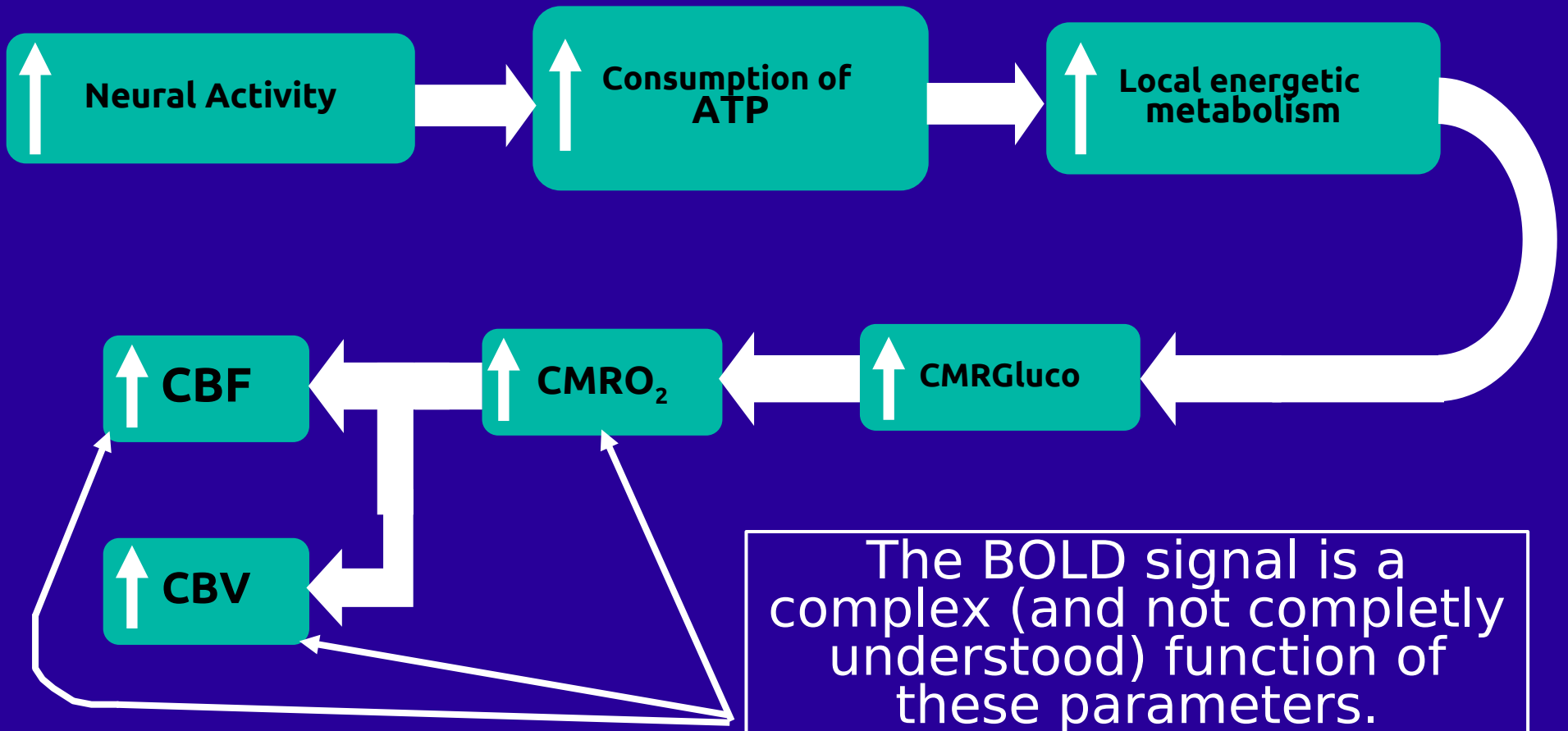
# $H_2O^{15}$ PET experiment

- A typical experiment consists of 12 runs of 90 seconds each, separated by 8~10 minutes.
- Result = 12 scans with a spatial resolution around 8x8x8 millimeters
- In comparison, a typical fMRI experiment can yield more 3000 scans with a 2x2x2mm resolution, in less than one hour.

Positron emission tomographic studies of the processing of single words. Petersen et al. (1989) *J. Cognitive Neuroscience*



# To Recap

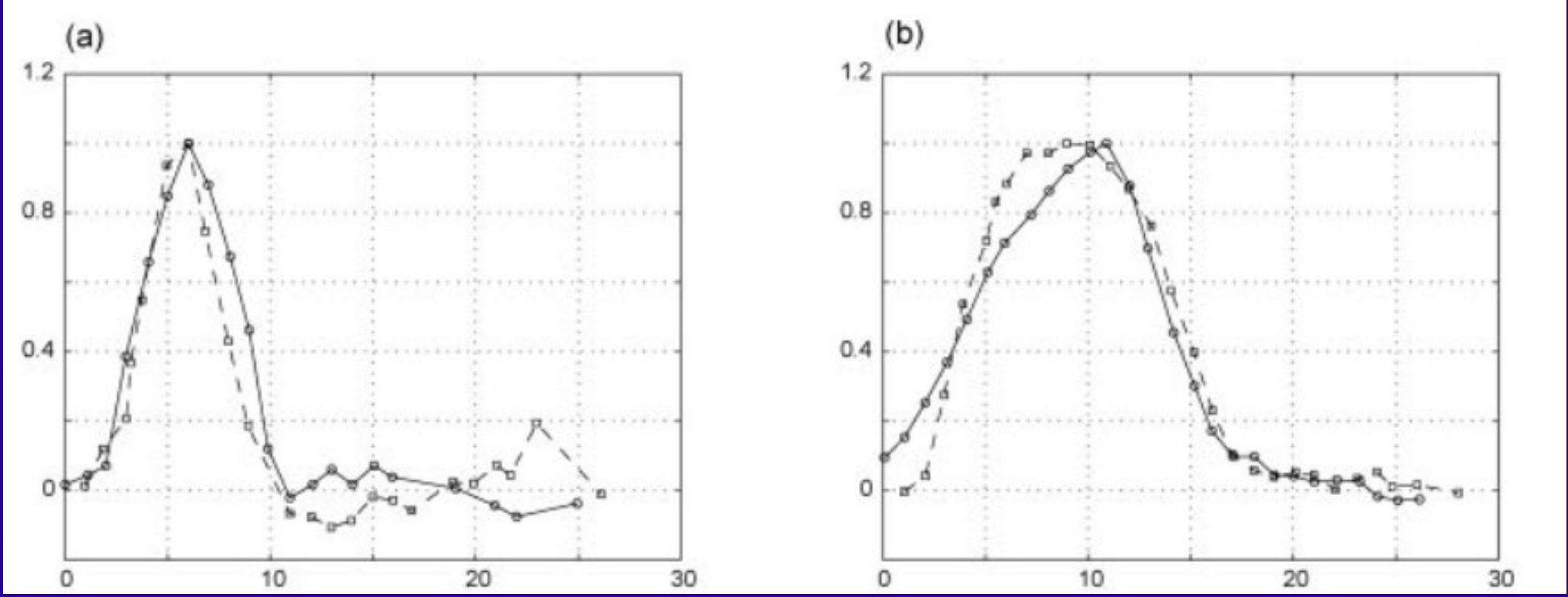



The BOLD signal is a complex (and not completly understood) function of these parameters.

See Drew (2019) “Vascular and Neural Basis of the BOLD Signal.” *Current Opinion in Neurobiology* 58: 61–69. https://doi.org/10.1016/j.conb.2019.06.004.

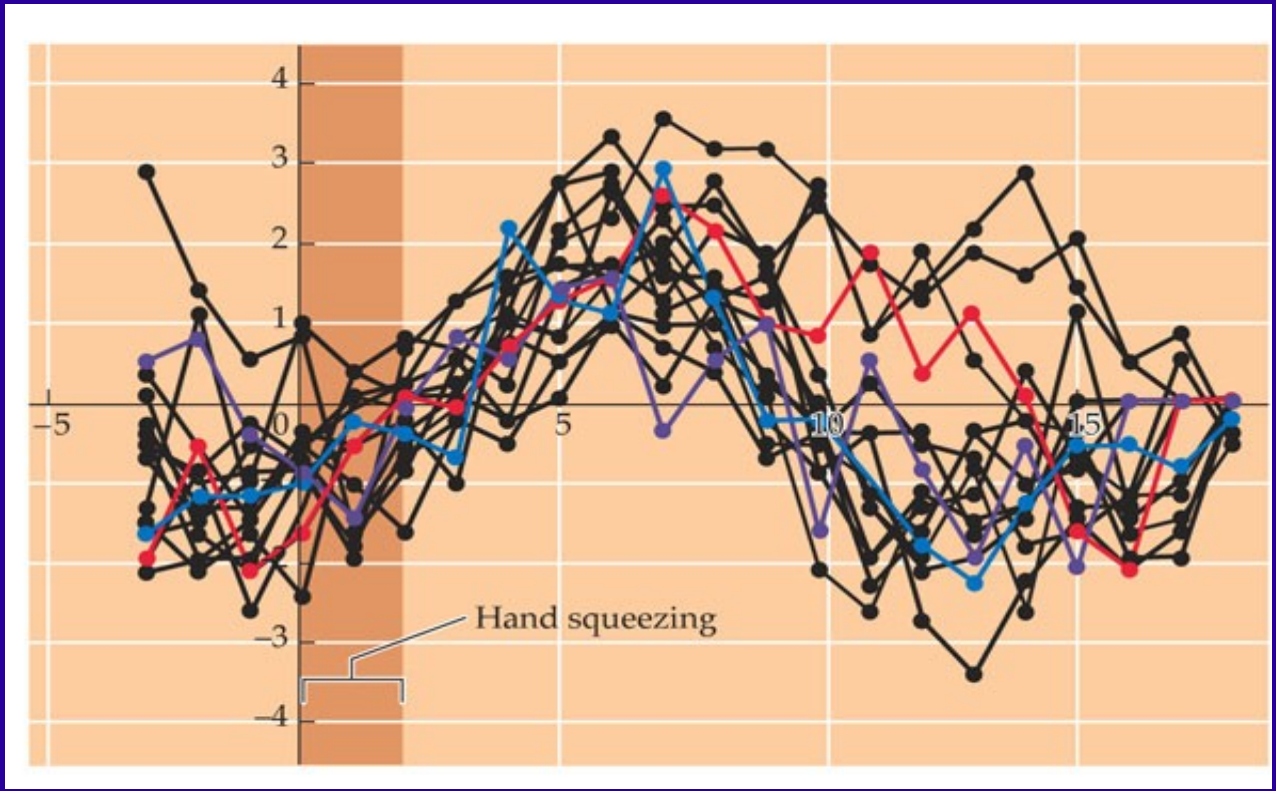
# The BOLD response to sensory events

Time course of the BOLD response.
Data from experiments in motor cortex (open circles) and visual cortex (open squares). The two panels show measurements in response to a **visual stimulus** or **movement** of 2 s (a) or 8 s duration (b).




Logothetis (2004) *Ann. Rev. Neurosci*

# Trial to Trial Variability




*Huettel, Song & McCarthy, 2004, Functional Magnetic Resonance Imaging*

From trial to trial, the measured signal varies.

You need several trials to make sure that variation is not due to random fluctuations of the signal.

The number of trials depends on the amplitude of the effect.

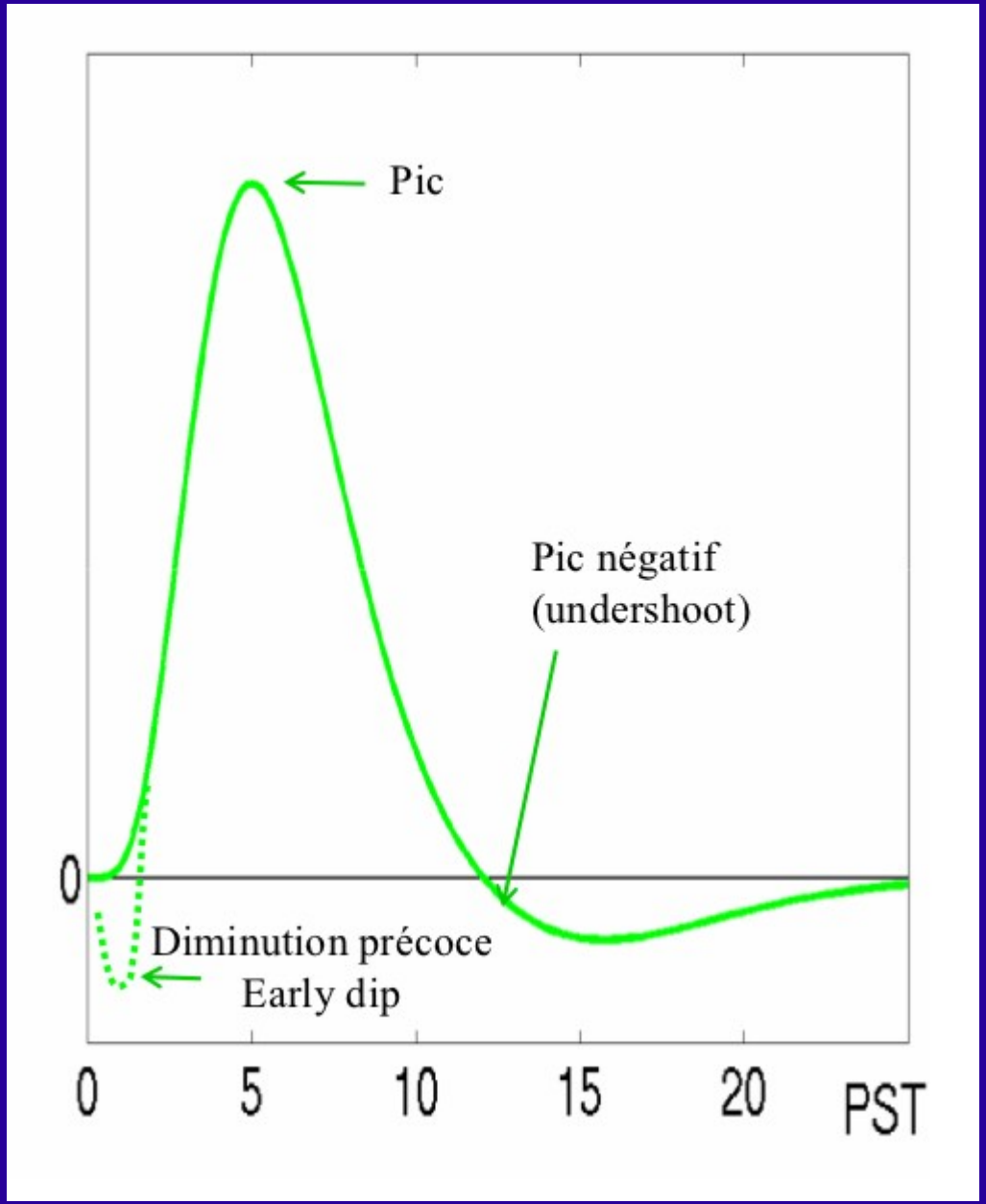
need of statistical tools...

# The “impulse” BOLD response (response to a very short event)

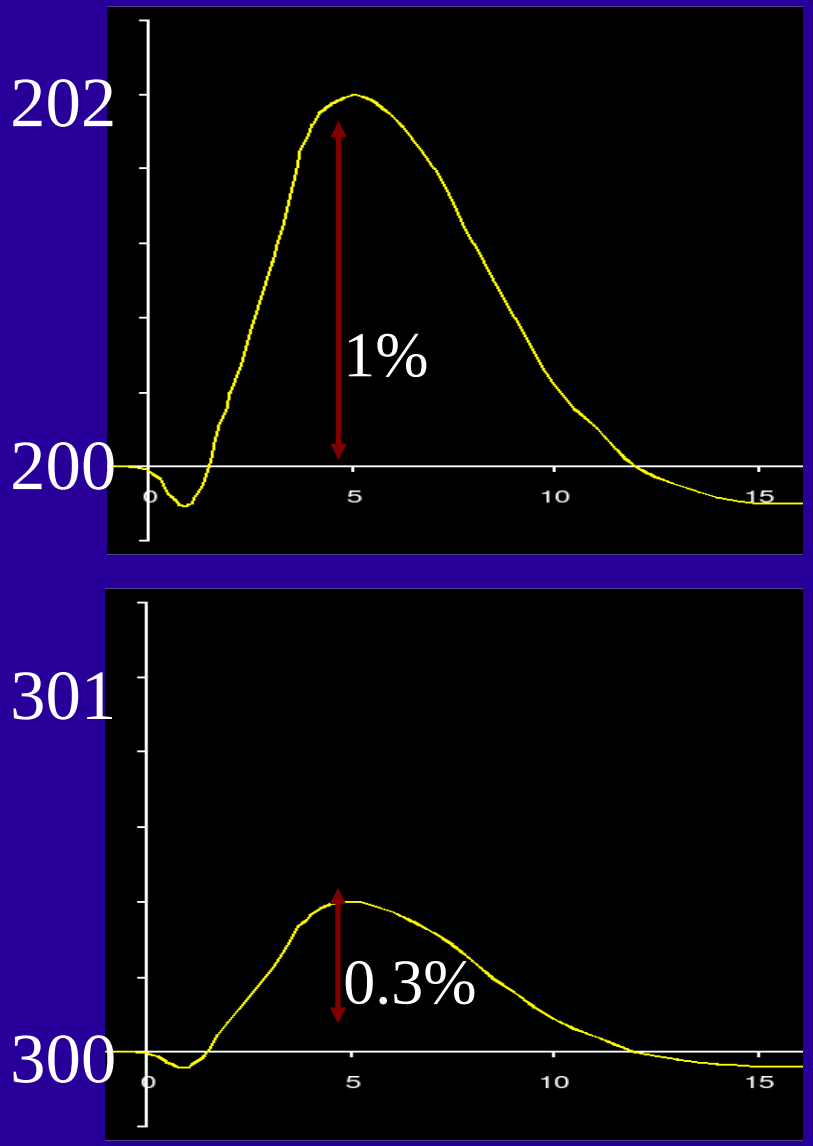
Reaches a peak 4~6 seconds after the event then goes back to baseline (in ~20 sec)

Sometimes, it is possible to detect an 'early dip'

It is similar, but varies, across brain regions and individuals

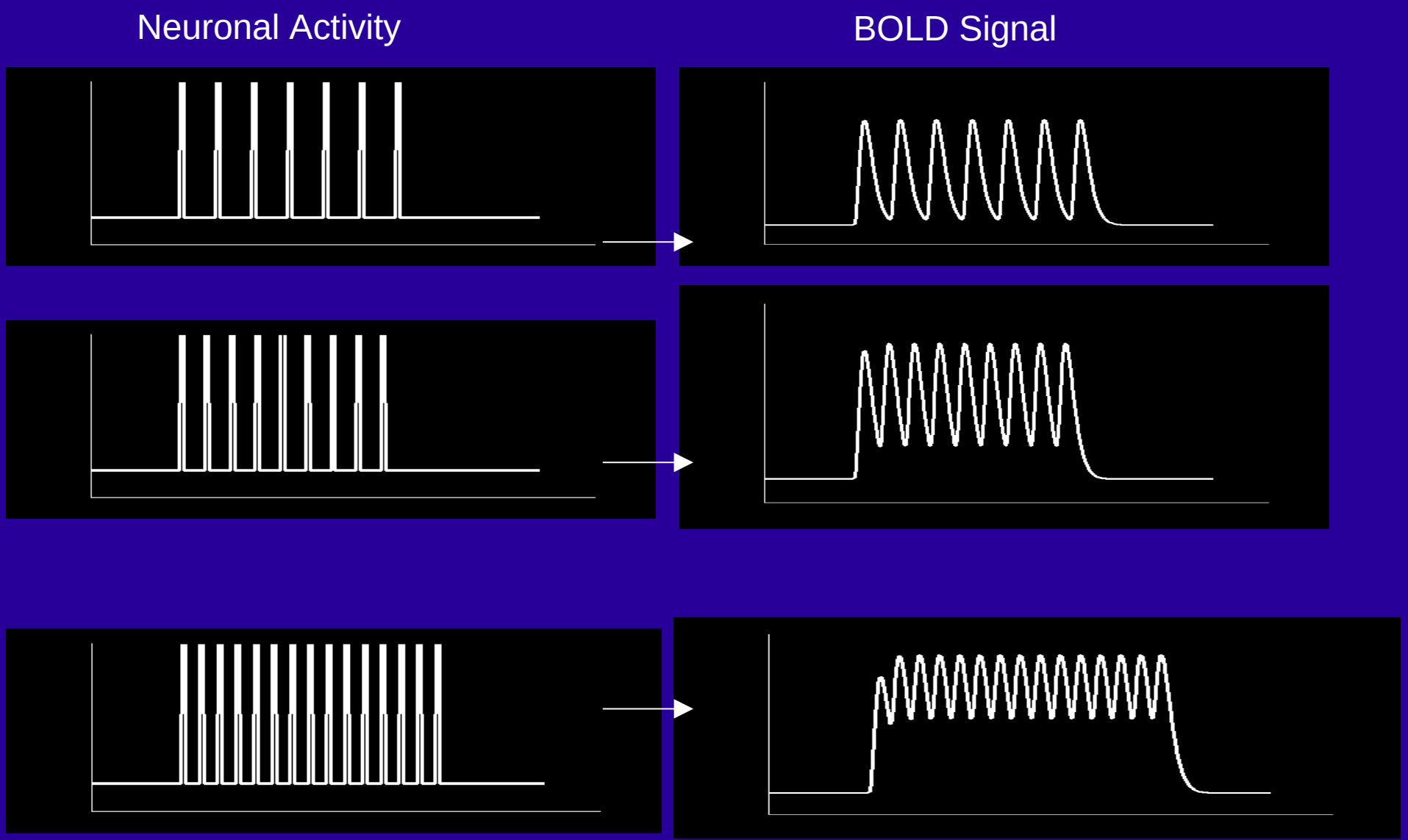


# Percent Signal Change




- Peak / mean(baseline)
- Often used as a basic measure of “amount of activity”
-
- To compare two experimental conditions one compares the signal changes.

# BOLD Summates

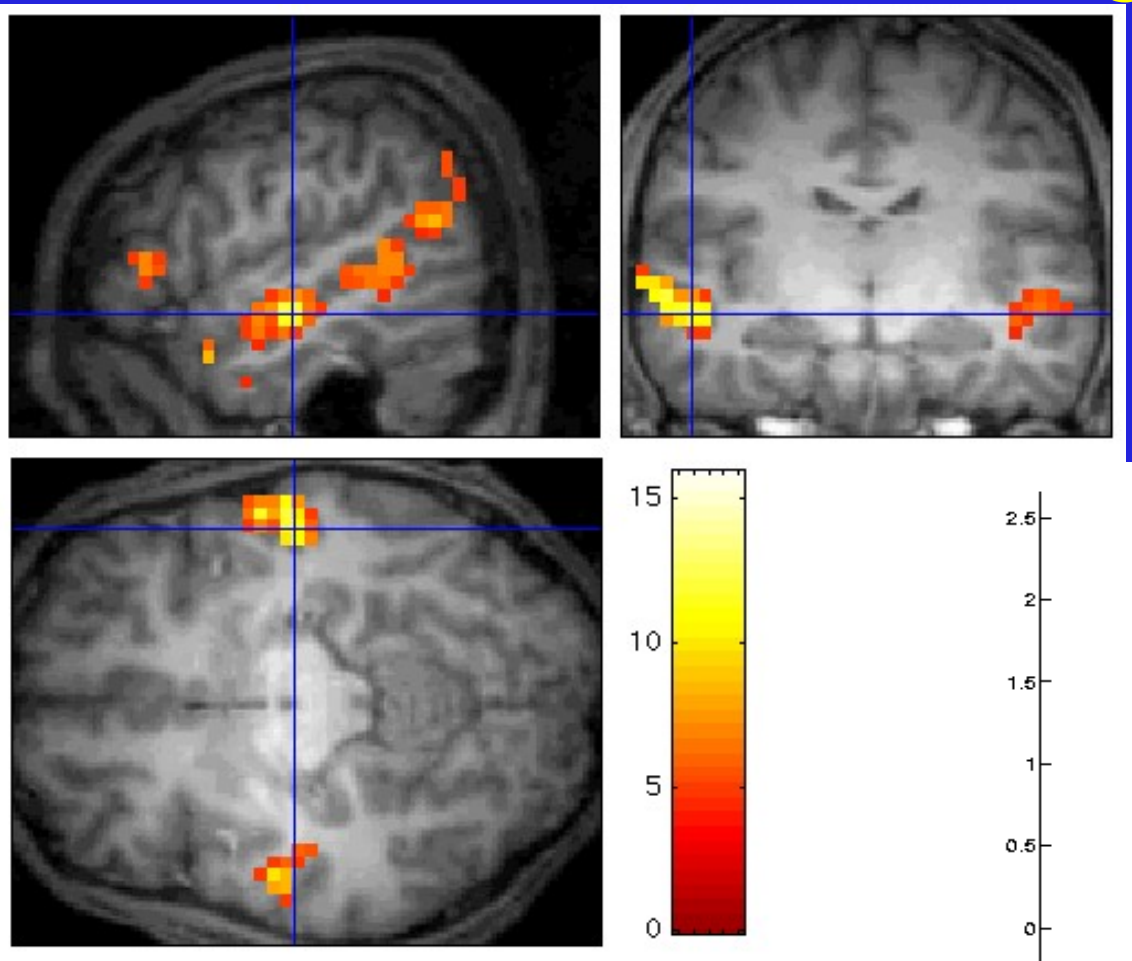



*Slide from Matt Brown*

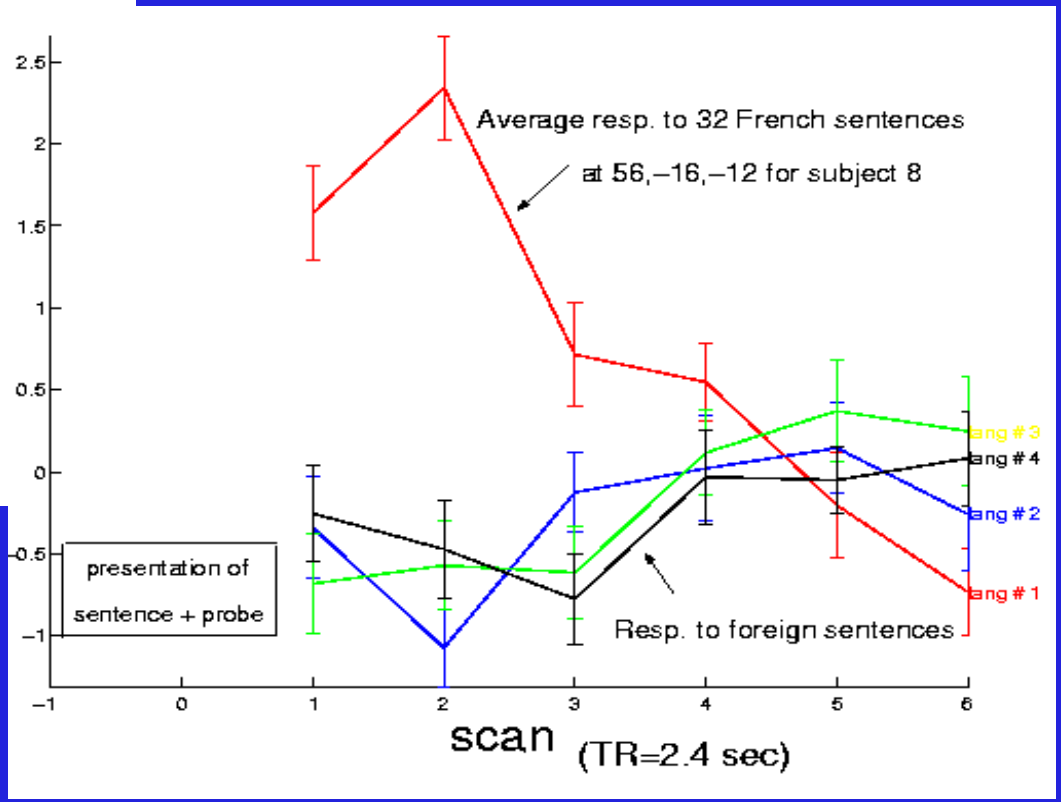
# The delay is good news for auditory fMRI:

- The scanner makes a lot of noise when an image is being taken.
- As the haemodynamic response is delayed, it is possible to present auditory stimuli in **silent periods between scans.**

# Example of data in one French subject: areas showing more activation following French sentences than foreign sentences.



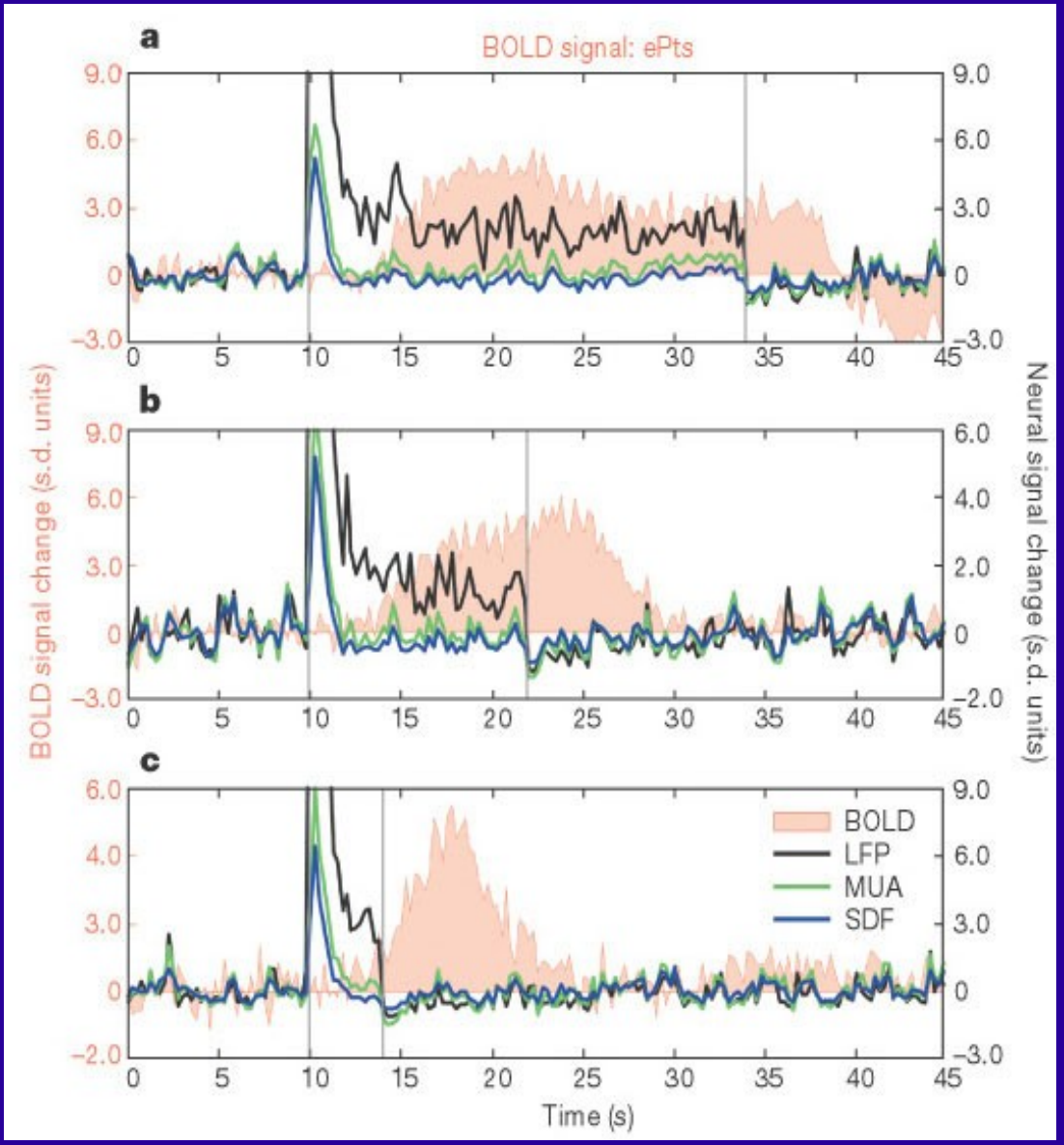

(threshold: p<0.05 FWE-corrected)



# Relationship between neural activity and the BOLD signal

Simultaneous recordings of fMRI and electrical activity (!!!) in cells of monkey visual cortex revealed that fMRI correlates more with Local Field Potentials (LFP), than with spiking activity.

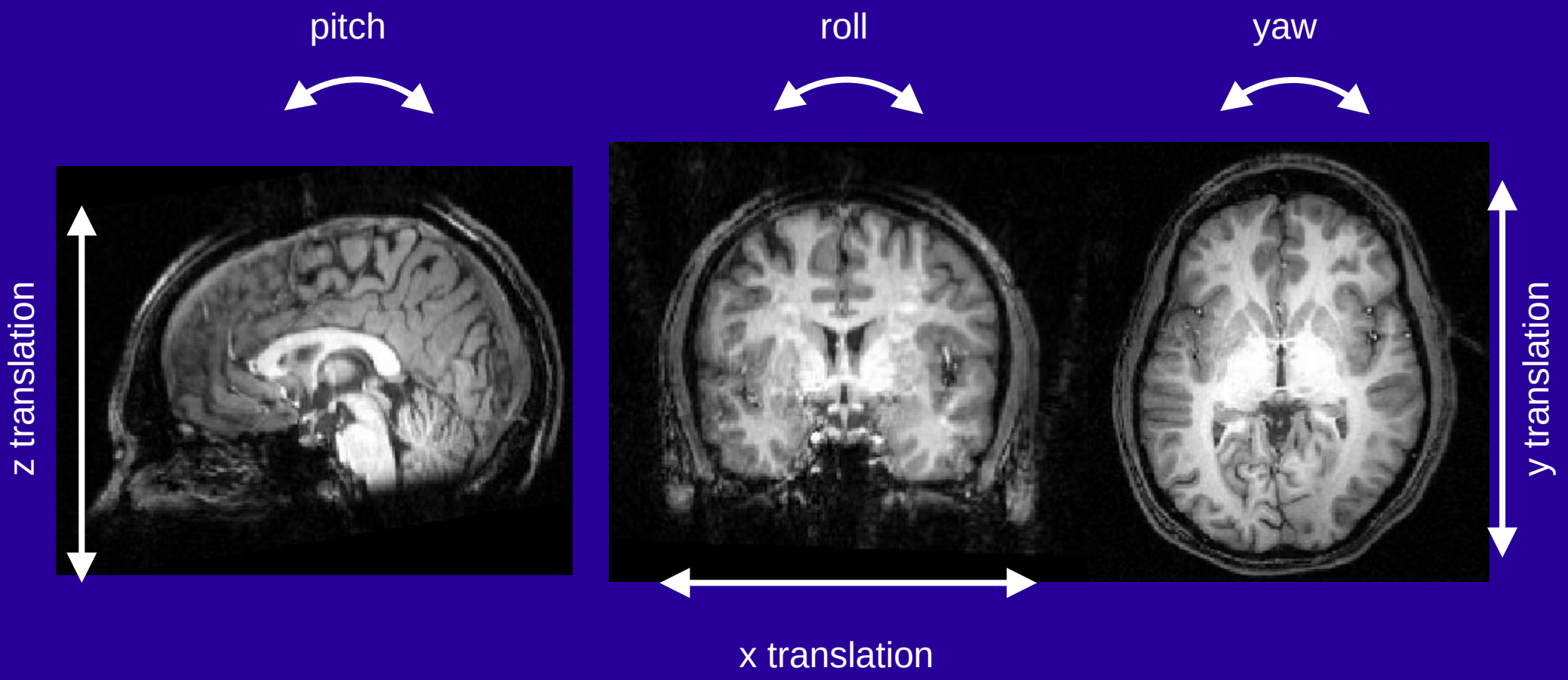
FMRI mostly reflects postsynaptic activity (like EEG/MEG).




(Logothetis et al. 2001 *Nature*)

# Processing of Images

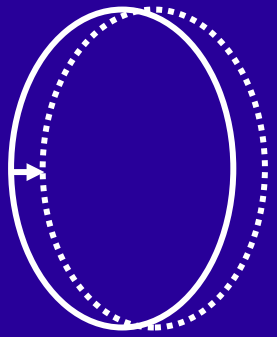
# Motion Correction Algorithms

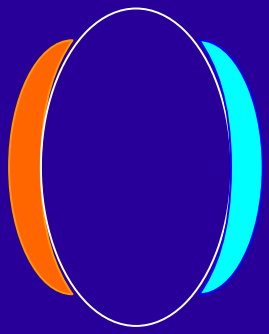



- Align each volume of the brain to a target volume using six parameters: three translations and three rotations
- Target volume: the functional volume that is closest in time to the anatomical image

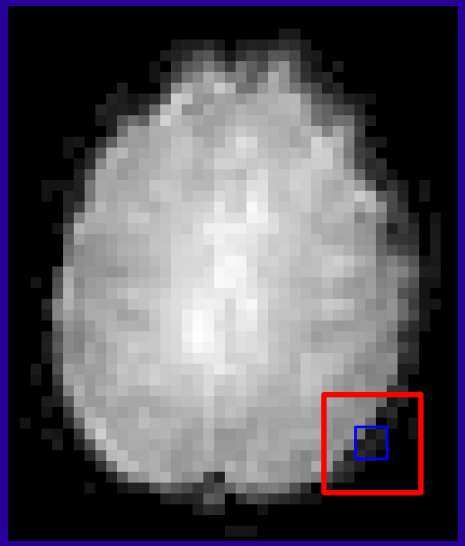
# Spurious Activation at Edges

time1 → time2

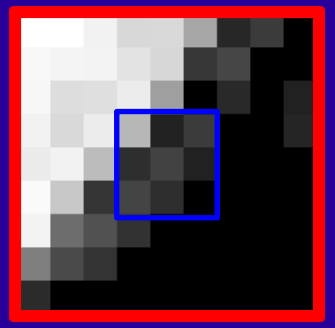




A

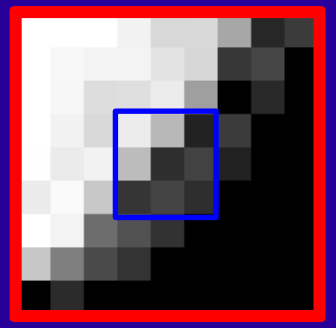


B



| | | |
|---|---|---|
| 507 | 89 | 154 |
| 119 | 171 | 83 |
| 179 | 117 | 53 |

C



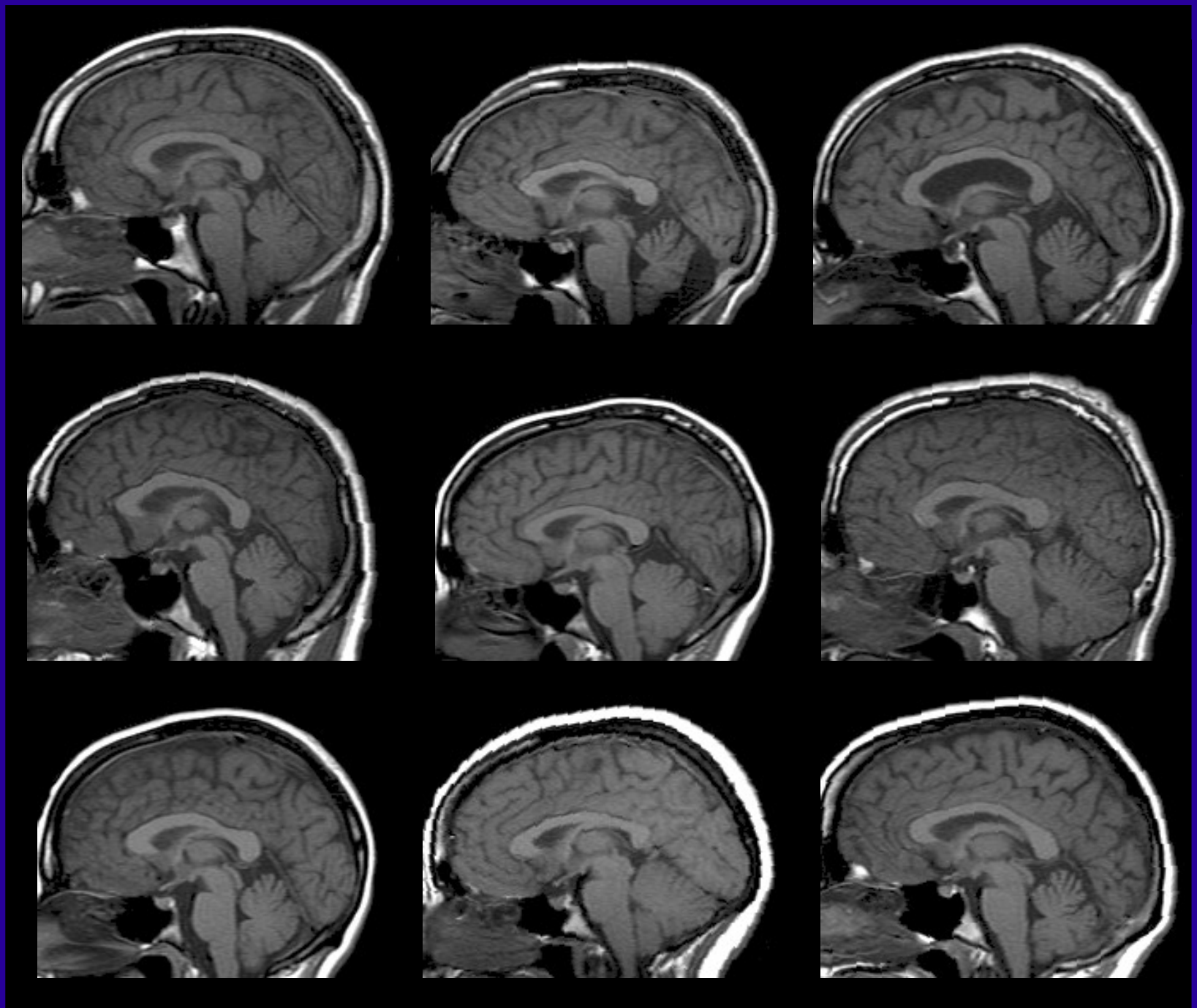
| | | |
|---|---|---|
| 663 | 507 | 89 |
| 520 | 119 | 171 |
| 137 | 179 | 117 |

*Slide modified from Duke course*

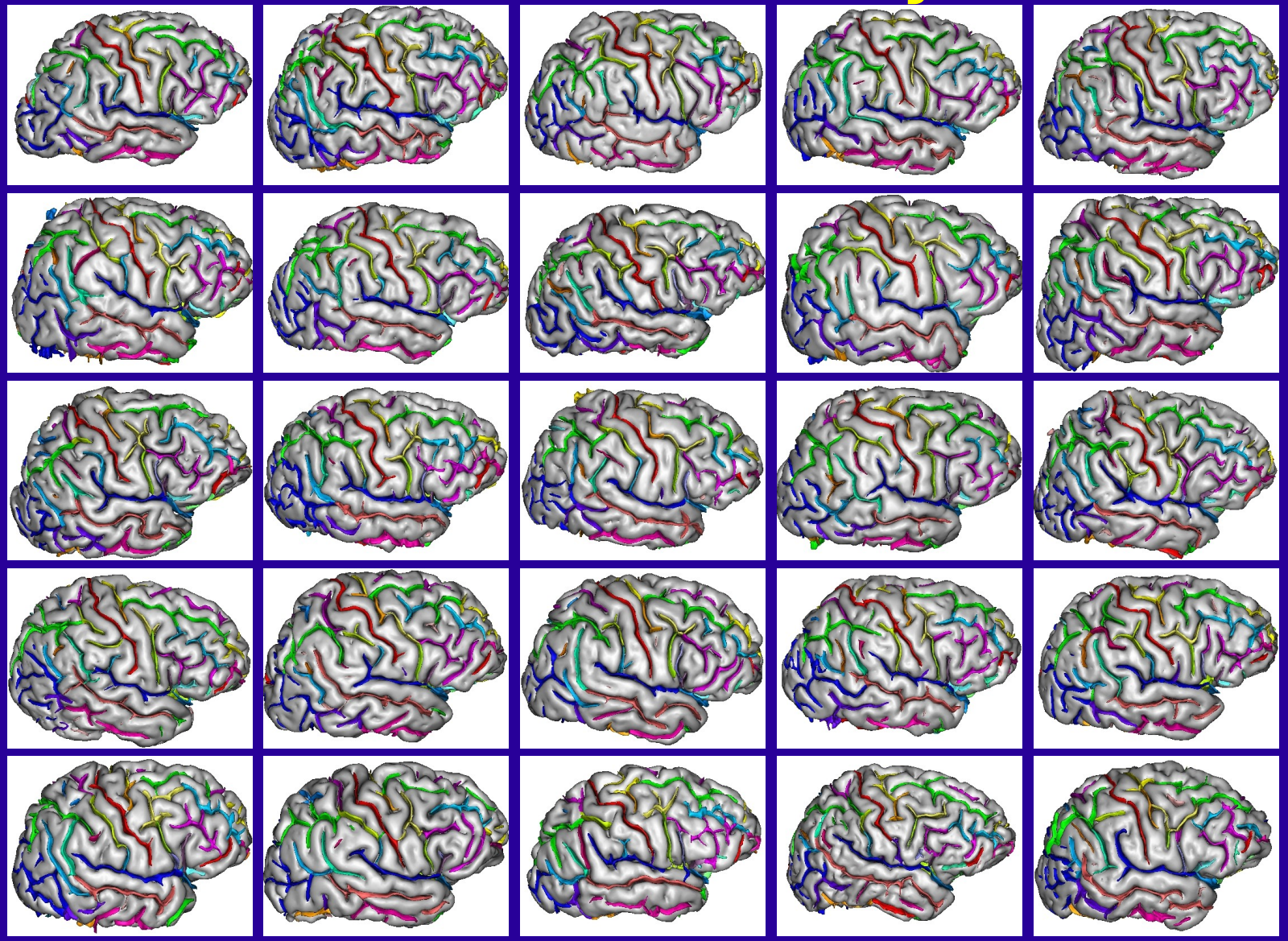


# Spatial normalisation

# Inter individual variability in brain anatomy is not negligeable



# A database of manually labelled

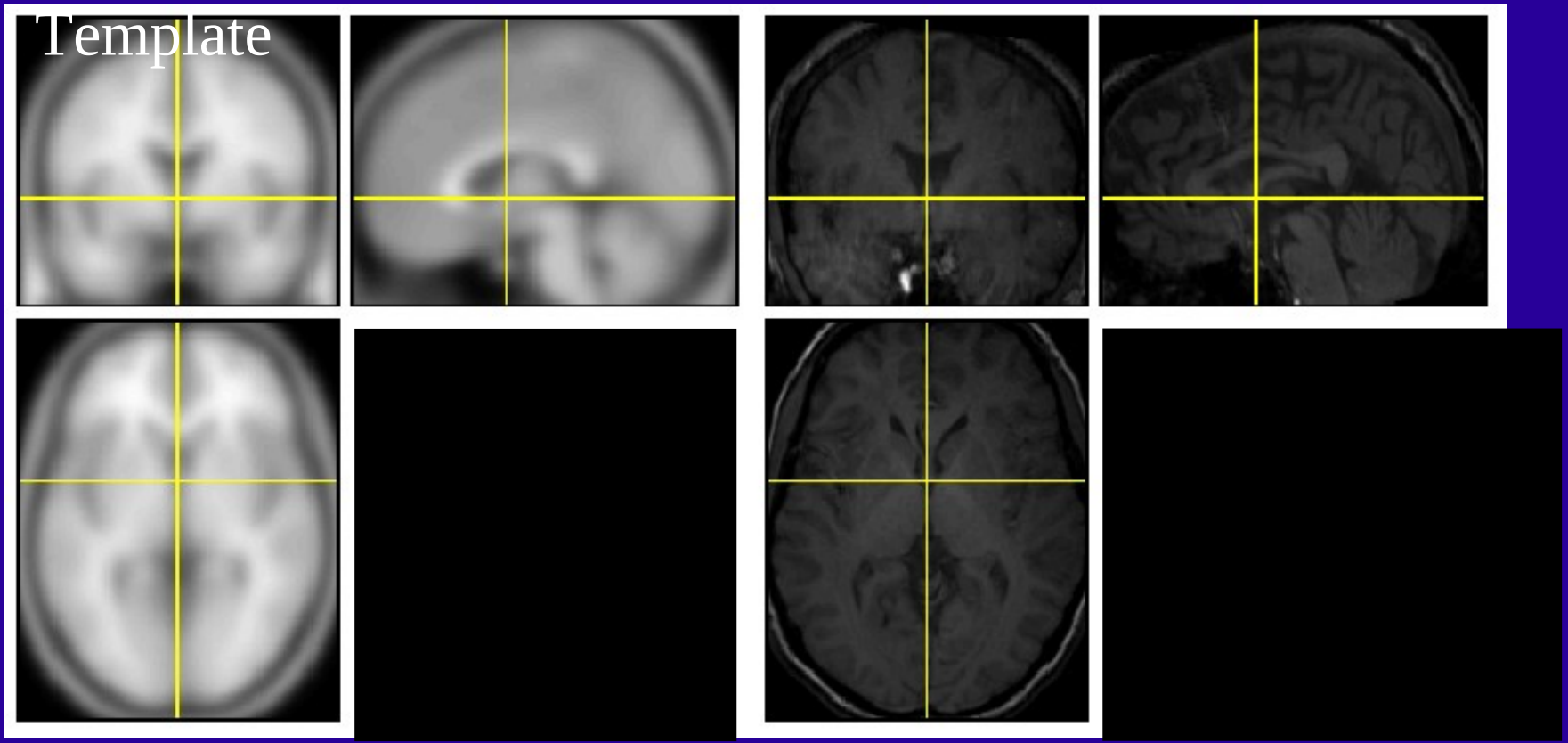


Jean-Francois Mangin & Denis Riviere, SHFJ, Orsay

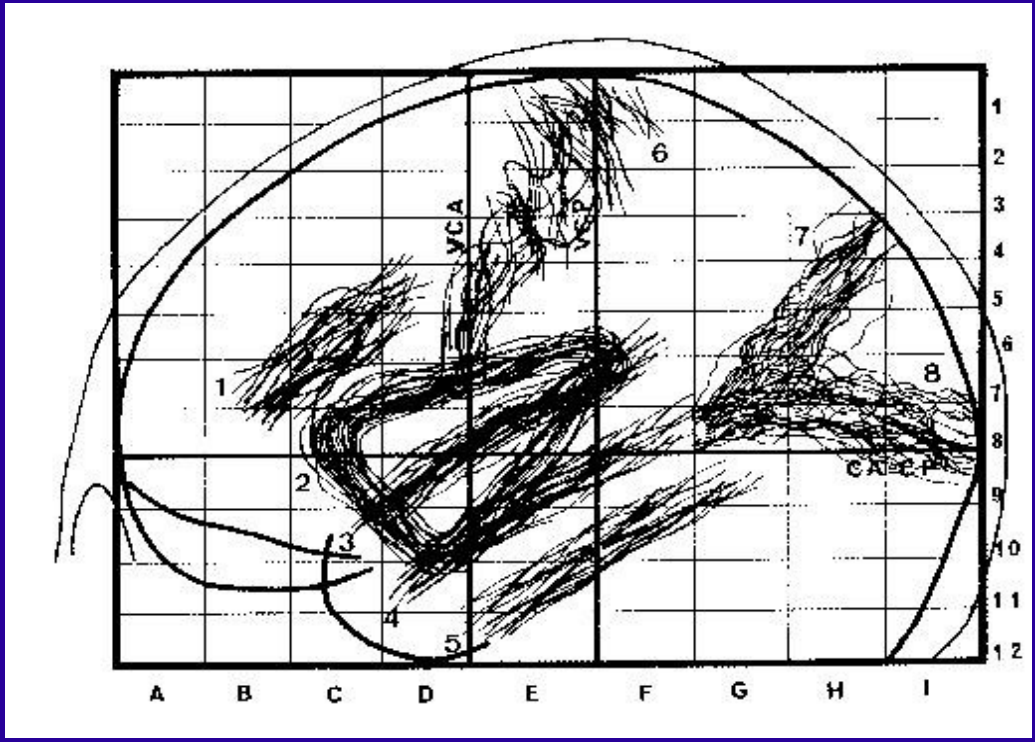
# Normalization to Template

Normalization Template

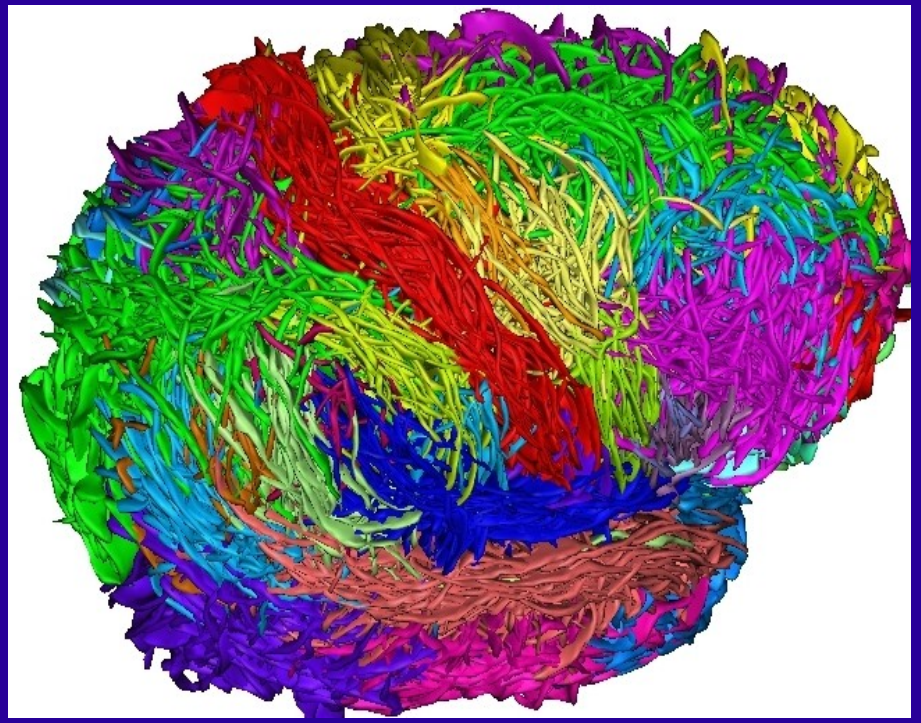
Normalized Data



# Variability of Sulci




*Source: Szikla et al., 1977 in Tamraz & Comair, 2000*



# Spatial normalization

- Provides coordinate space for reporting results
- Enables averaging across subjects
- Allows generalization of results to larger population
- Improves comparison with other studies

- But
  - Reduces spatial resolution

# Statistical Analyses

# Analysis? What Analysis?

The are several ways ways to analyze the spatio-temporal signal contained in fMRI data:

- **Activation detection**
  to detect task-related activations in each voxel. This is done by examining temporal correlations between behavior/stimulation and the signal in voxels (univariate analyses)

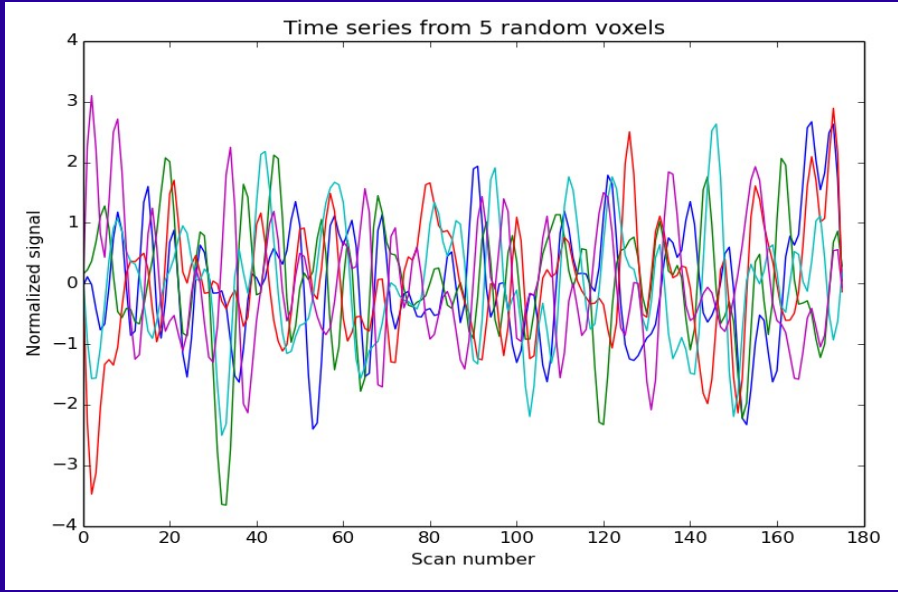
- **Brain decoding**
  seeks to associates spatial patterns of activation to stimuli (Multivariate pattern classification & Representational Similarity Analysis).

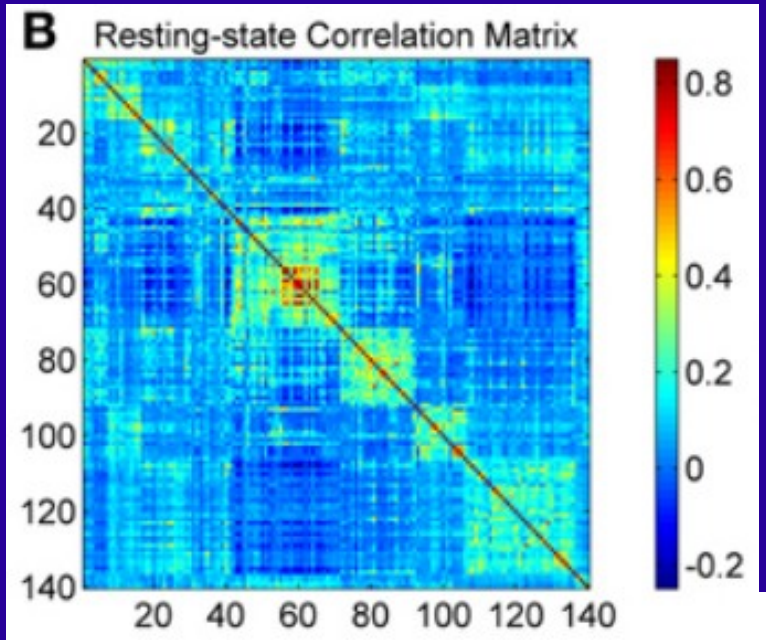
- **Functional connectivity**
  search for temporal correlations between the signals in different voxels in the same brain

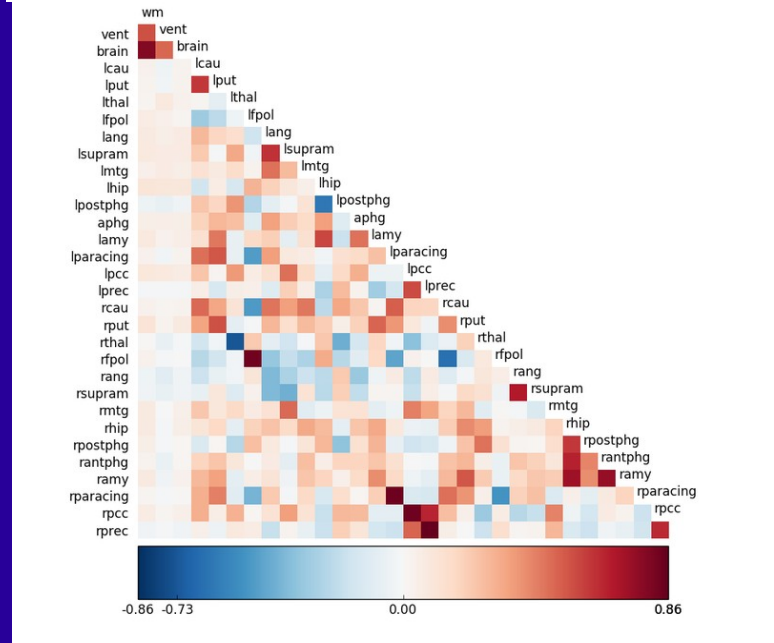
- **Inter-subject correlations** (correlations between different brains (!))

# Functional connectivity in “resting” state

In the absence of task, the signals measure ‘spontaneous fluctuations of brain activity’.
For any two voxels, or two brain regions, compute their temporal correlation.



# Using Independent Component Analysis (ICA), to identify networks in resting state data

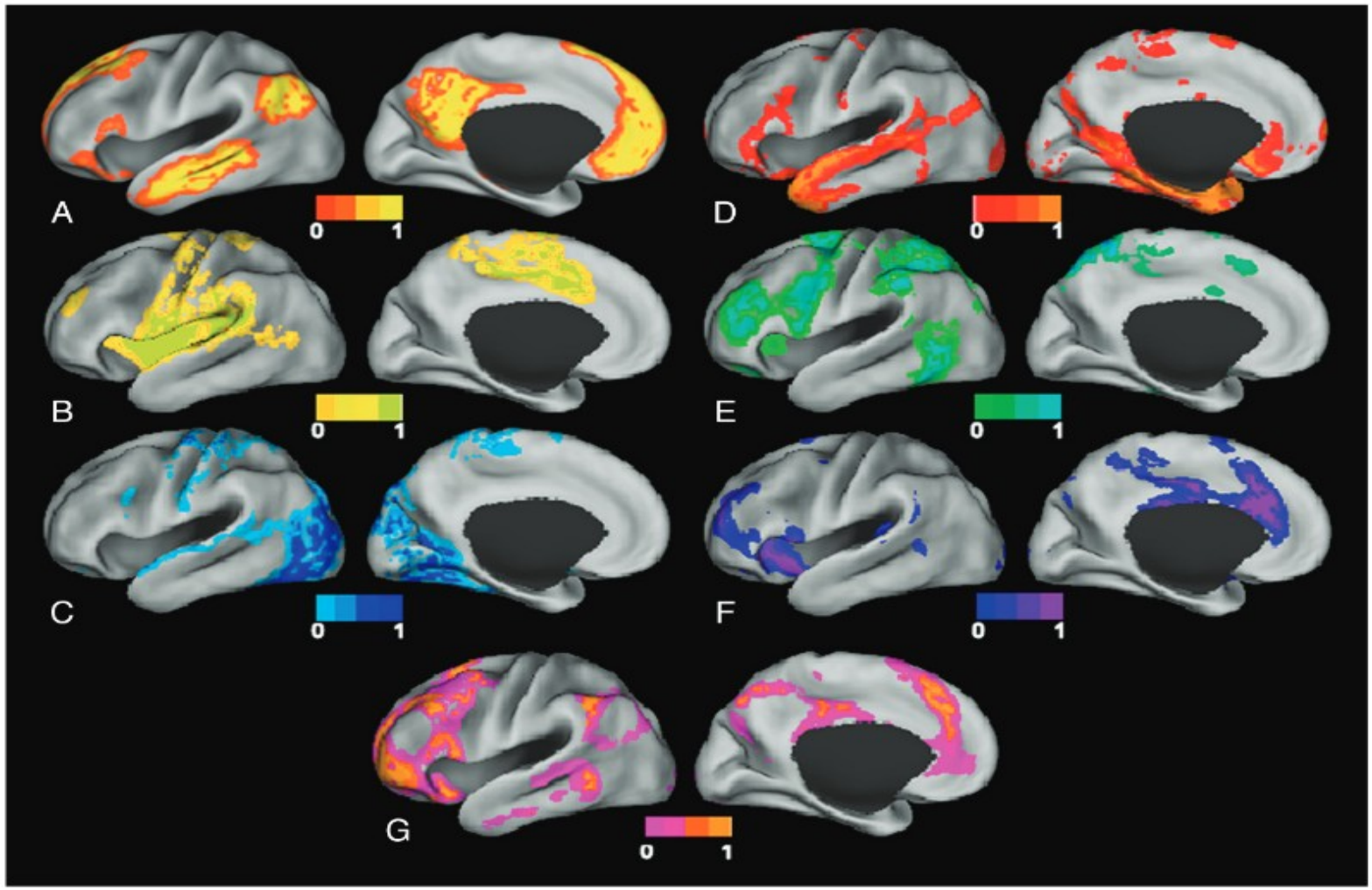
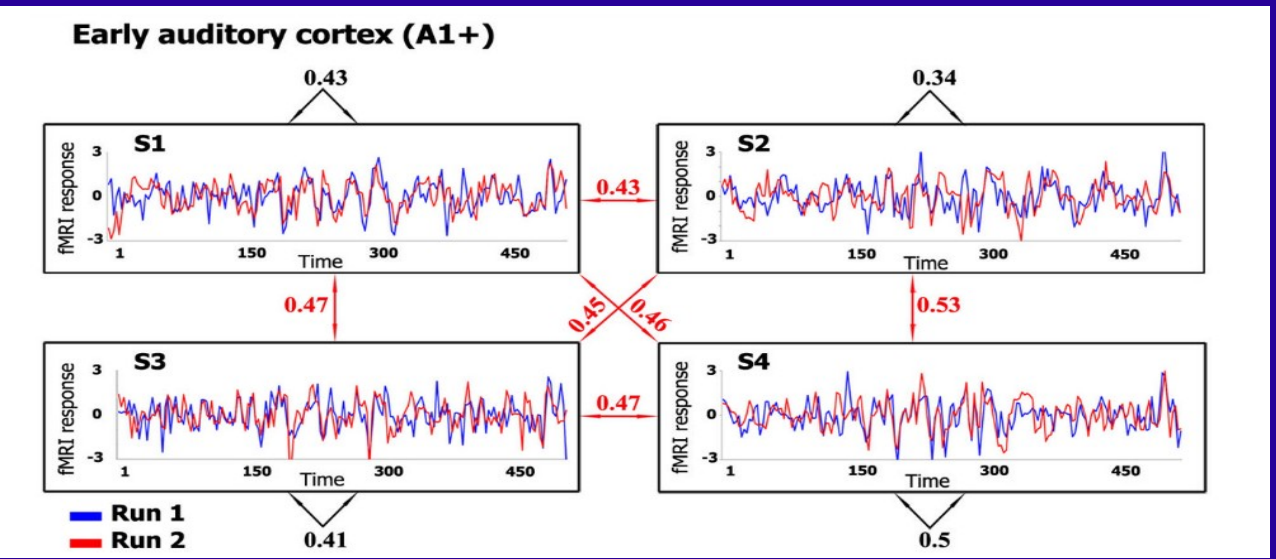


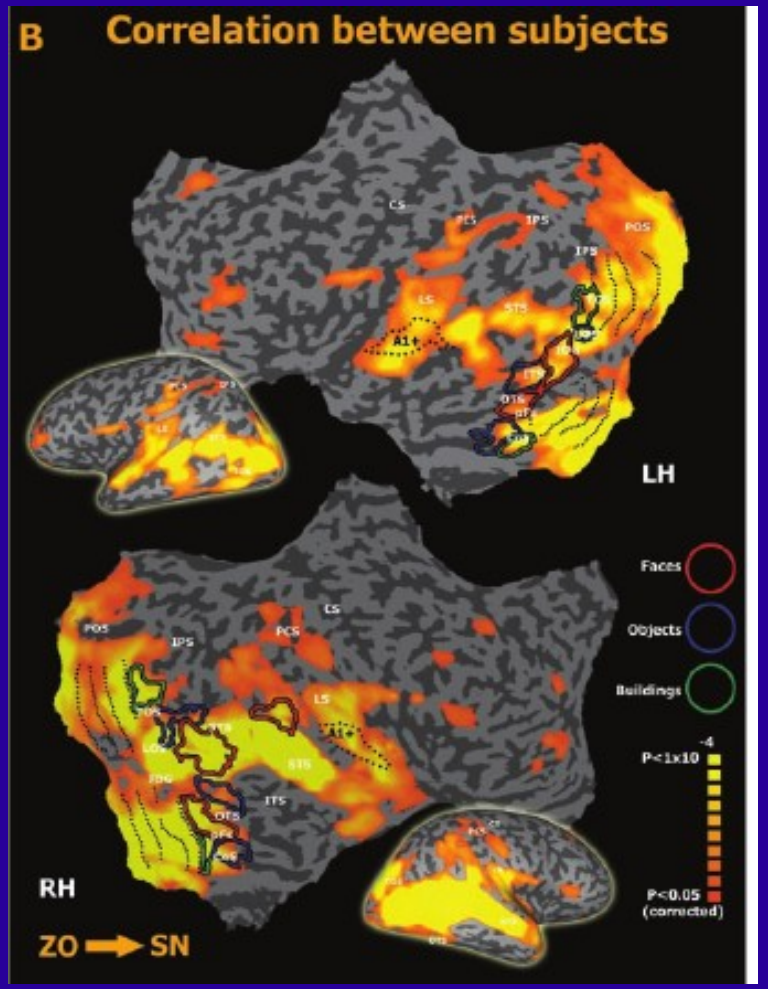

**FIG 1.** Surface plots of RSNs. *A*, Default mode network. *B*, Somatomotor network. *C*, Visual network. *D*, Language network. *E*, Dorsal attention network. *F*, ventral attention network. *G*, Frontoparietal control network.

See Damoiseaux, et al. 2006. “Consistent Resting-State Networks across Healthy Subjects.” *PNAS*, 103 (37): 13848–53. https://doi.org/10.1073/pnas.0601417103.

# Inter-subjects Correlations (ISC)

Hasson, U. 2004. “Intersubject Synchronization of Cortical Activity During Natural Vision.” *Science* 303 (5664): 1634–40.



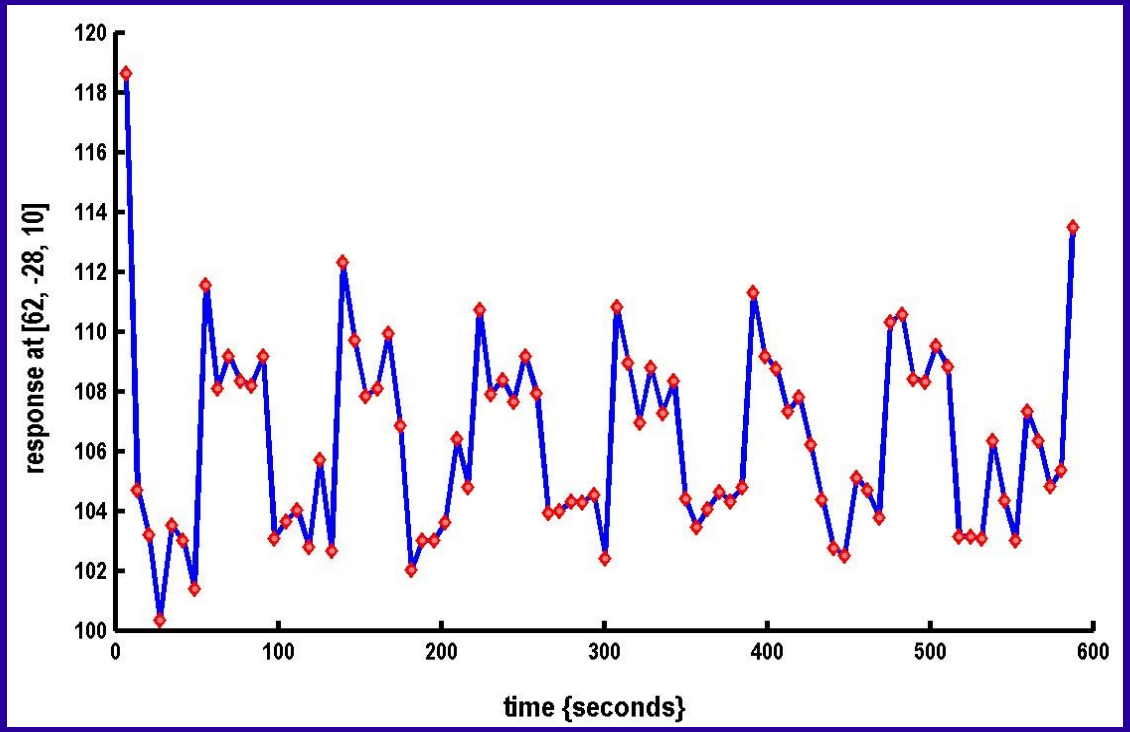

Beware: these are not “activations”, but maps of significance (pvalues) of correlations

# Detection of task-related activations

(this represents the vast majority of the studies)

Example:

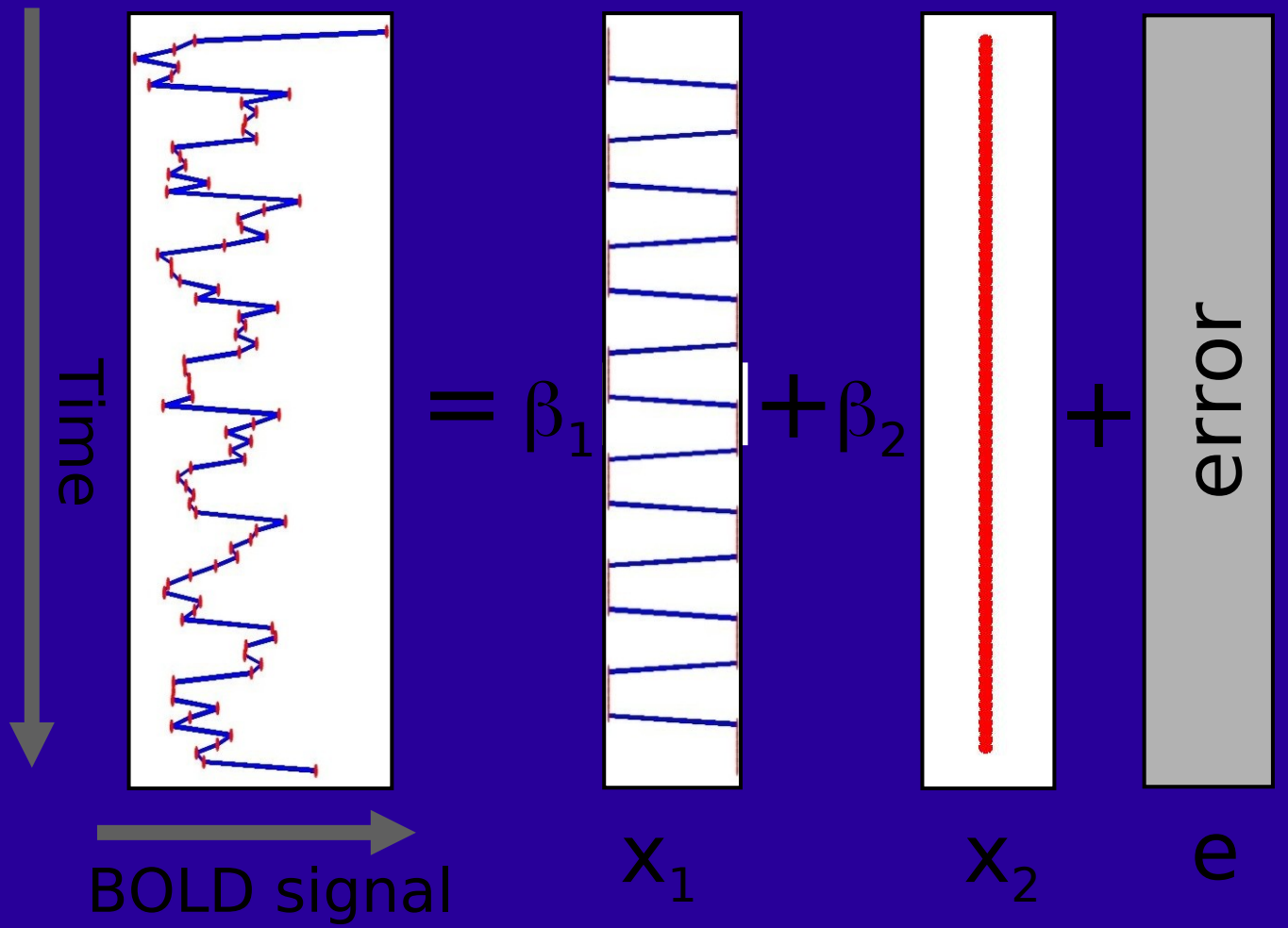
Participants passively listened to words or silence




7 cycles of rest and listening

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

# Regression model

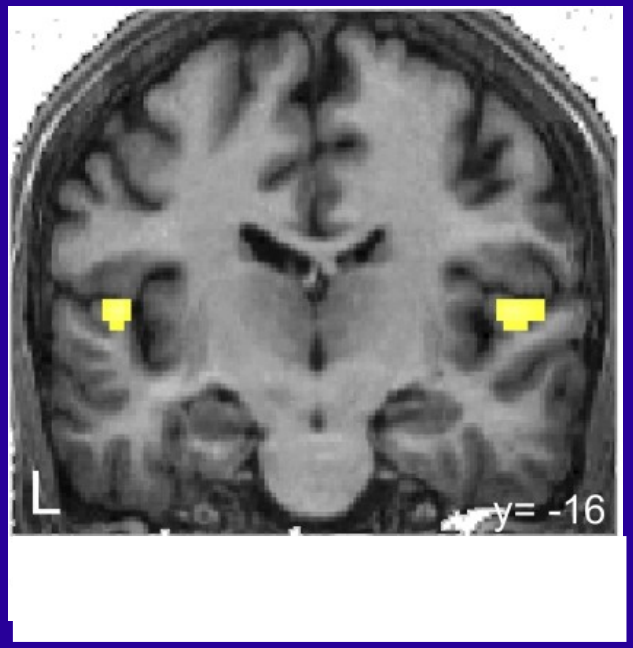



$$y = x_1\beta_1 + x_2\beta_2 + e$$

# Statistical Parameter Maps

At each voxel, a T (or p, or Z) value is computed.
It can by used to test if the effect of interest ($\beta_1$ coefficient) is significantly larger than 0.

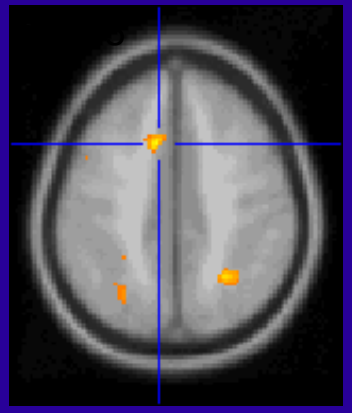
A brain map of p-values is obtained, which is thresholded at a given *alpha level* (e.g. $p < 0.0001$) and displayed overlaying an anatomical scan.



# Visualizing Statistical Maps

*Where's the signal?*

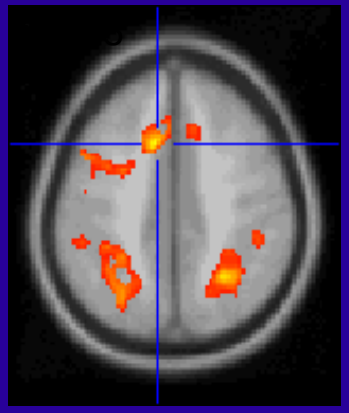
High Threshold



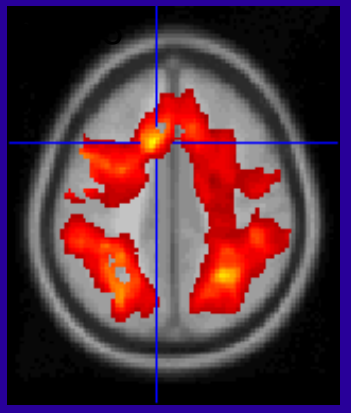
Good Specificity

Poor Power
(risk of false negatives)

Med. Threshold



Low Threshold



Poor Specificity
(risk of false positives)

Good Power

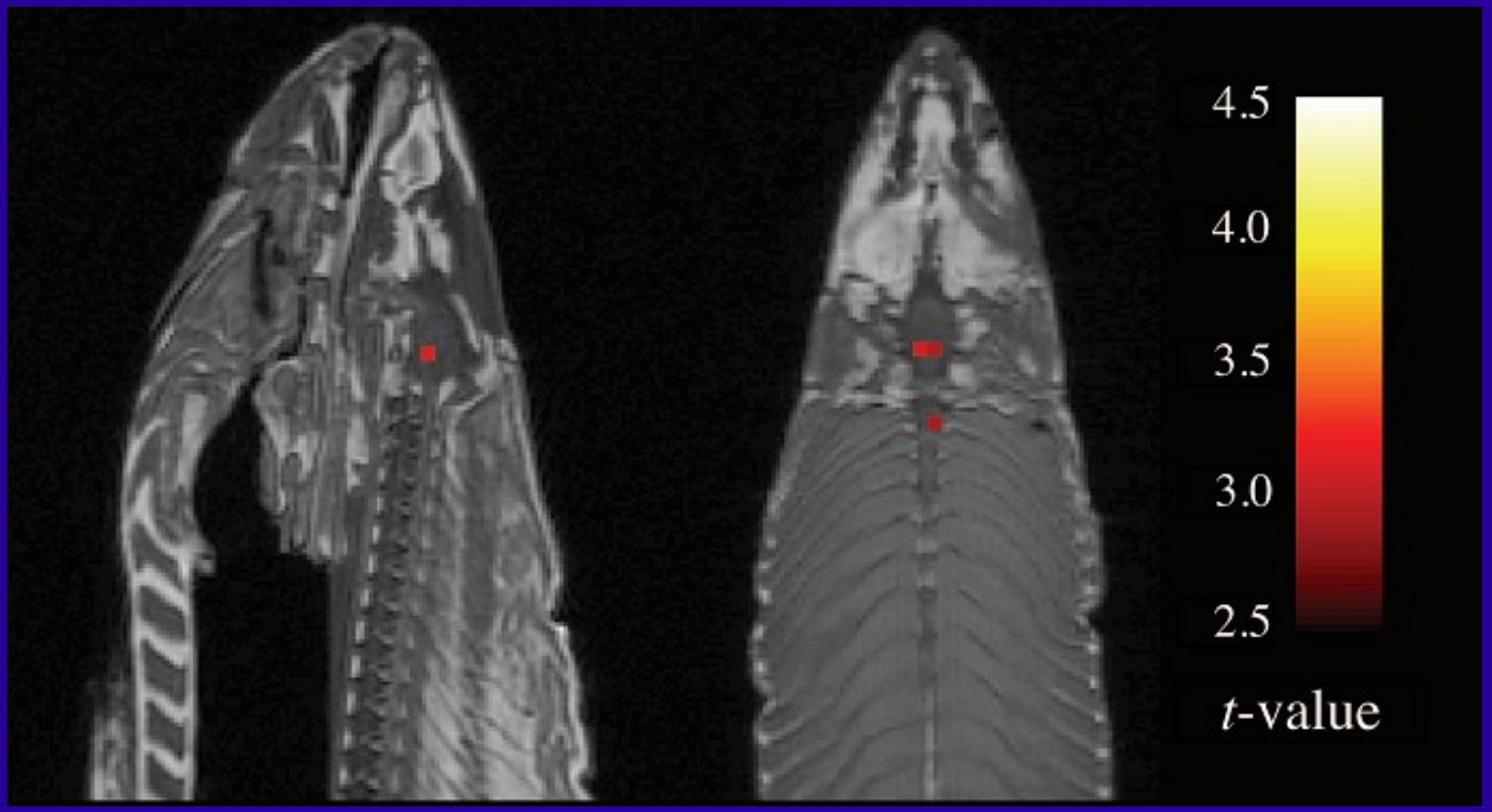
*…but why threshold?!*

# The problem of multiple comparisons

Probability that an event with p=5% is observed at least once in 'N' trials.

# Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon (Bennett et al. 2009)

In this study, the salmon was shown images of people in social situations, either socially inclusive situations or socially exclusive situations.



# Addressing the Multiple Comparison Issue

**Reduce the number of tests by using *a priori* Regions of interest**

## Family-Wise-Error threshold (FWE)

Given the variance in the image and its spatial correlation, this procedure estimates a threshold that enforces a error rate at the whole brain level. P(FWE)<.05 means there is 0.05 % probability that one voxel at least is detected under the null hypothesis.

## False Discovery Rate threshold (FDR)

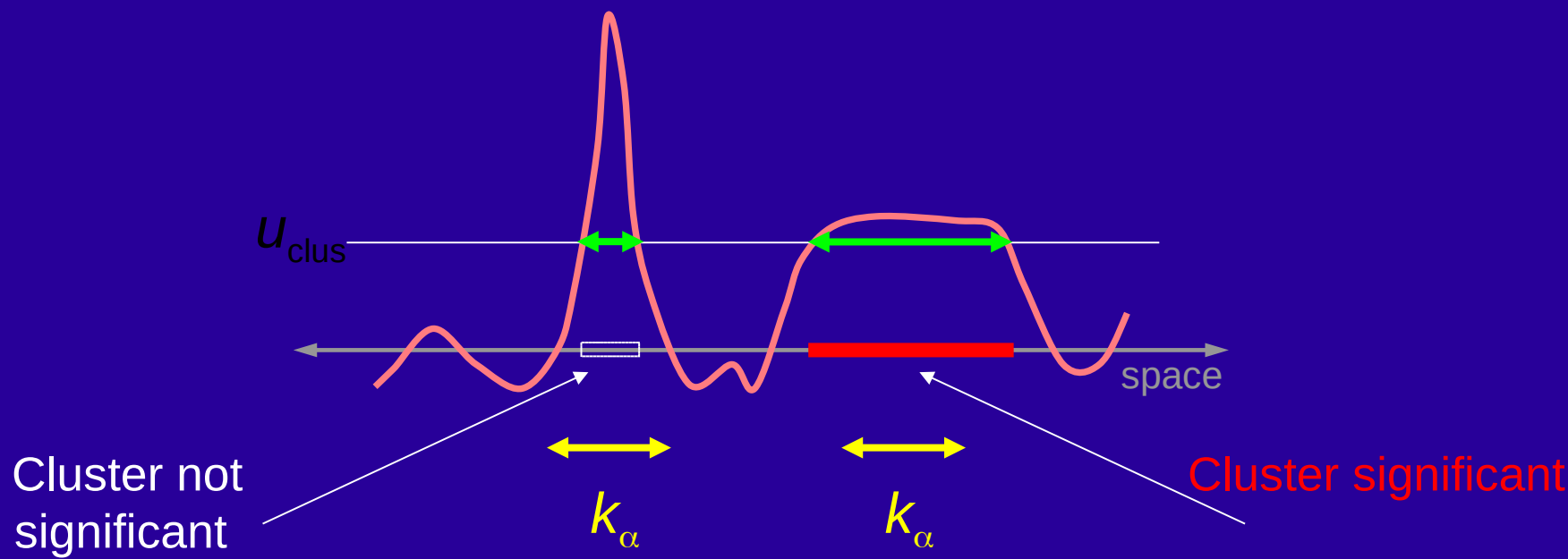
Controls the relative number of false alarms in an image (i.e P(FDR) < 0.05 means 5% of the voxels in the mans are False alarms)

## Cluster-based thresholding

A cluster is a set of contiguous voxels. Given a voxel threshold and the smoothness of the data, one can compute the distribution of cluster sizes under the null hypothesis of no activation.

# Cluster-level Inference

- Two step-process
  - Define clusters by arbitrary threshold $u_{clus}$
  - Retain clusters larger than $\alpha$-level threshold $k_\alpha$



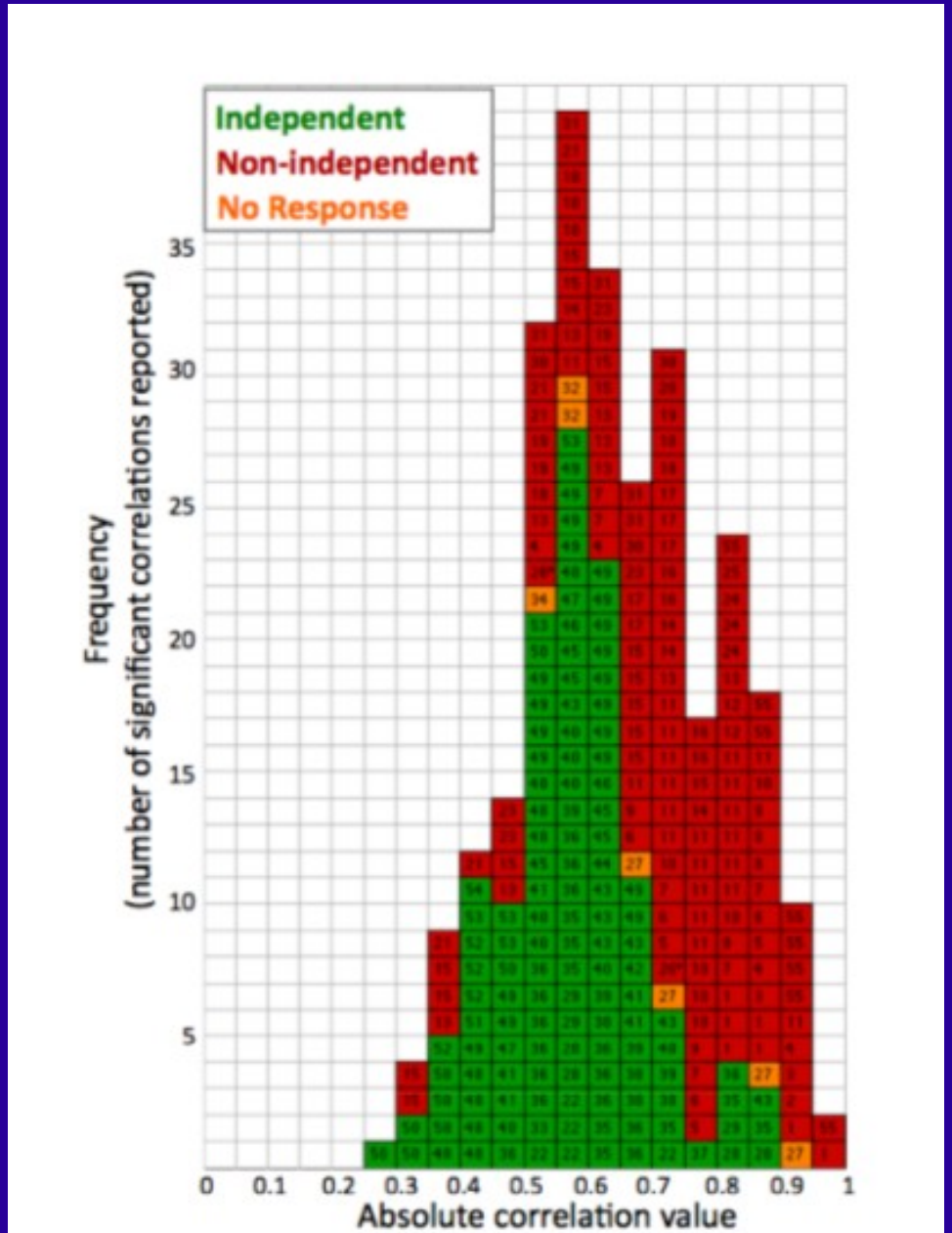
# “Voodoo correlations”

**(Vul et al (2009) Puzzlingly high correlations in fMRI studies of emotion, personality, and social cognition. *Psych. Sci.)***

In the Social neuroscience, many studies have reported very high correlations (r>.8) between self-reported measures (of presonality...) and BOLD signal.

These values are implausible given the reliability of the measures.

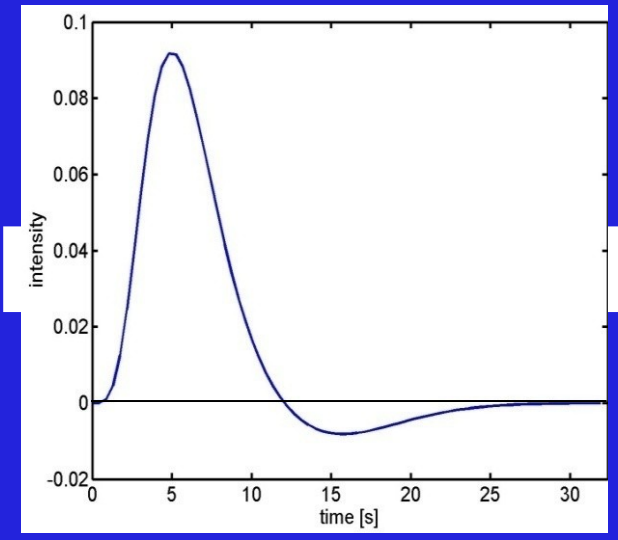
It is due to the *non-independent selection* of voxels where the correlations were computed.



# IMPROVING THE MODEL

# What are the problems of this model?

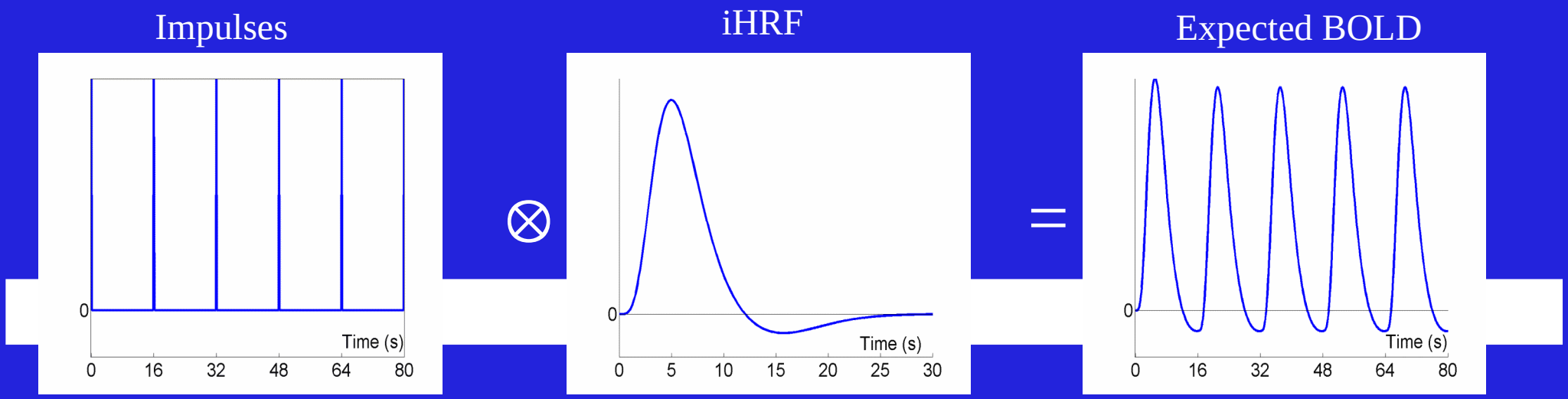
1. BOLD responses have a delayed and dispersed form.




2. The BOLD signal includes substantial amounts of low-frequency noise (eg due to scanner drift).

3. Due to breathing, heartbeat & unmodeled neuronal activity, the errors are serially correlated. This violates the assumptions of the noise model in the GLM

# Solution: Convolution by iHRF




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

= input function ⊗ impulse response function (HRF)

Design Matrix
BOLD Timeseries
Regressors of Interest
Nuisance Regressors
Amplitude parameter (unknown)
Error Term
time
=
x
+

# Statistical modeling with the General Linear Model

- For each experimental condition (i), create a theoretical neural activation profile.
- Convolve this by a theoretical hemodynamic impulse response function.
- Use the resultant profile as a regressor ($X_i$) in a multiple regression with the observed signal ($Y_{vox}$) as the dependent variable, that is find a set of $a_i$ such that :

$$Y_{vox} \cong \sum a_i . X_i$$

- Interpretation : ai represents the amplitude of response to condition 'i'

# Group analyses

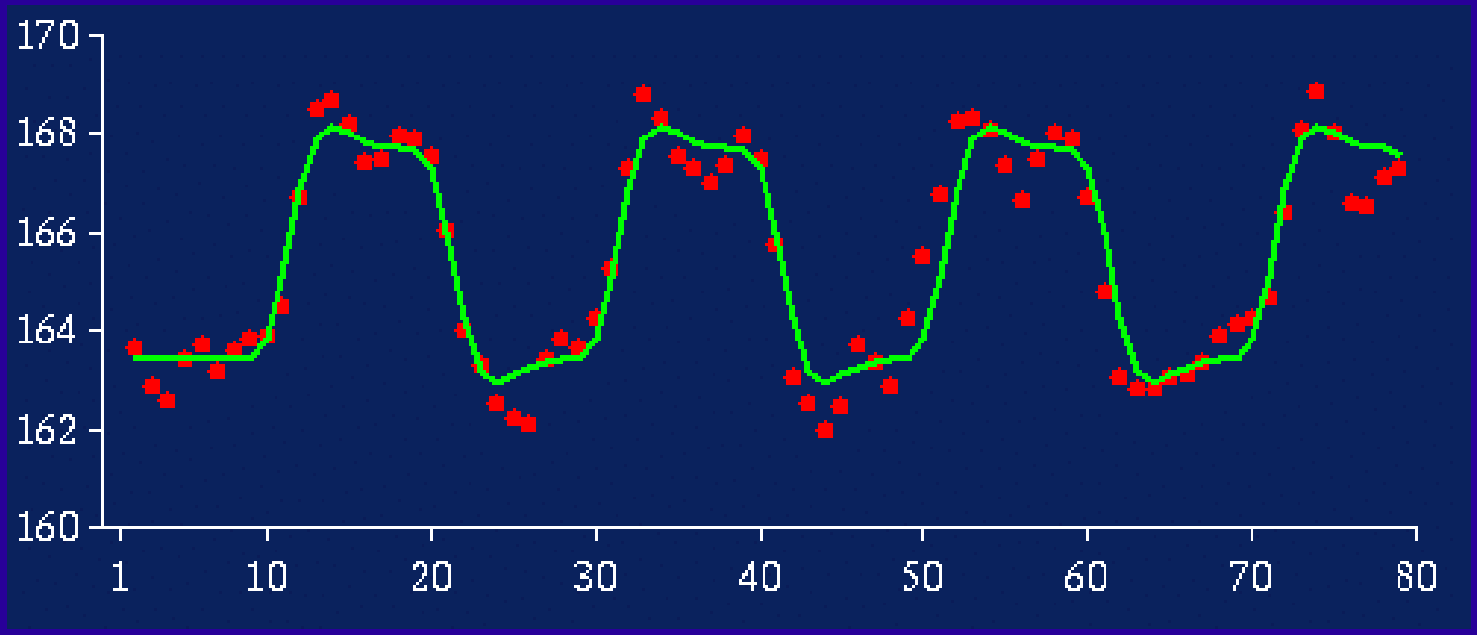
At this stage, you have obtained, for a single participant, maps that assess *the effect size for each condition* in your experiment.

You can then perform statistical tests to detect which conditions produce **statistically significant effects**, or compare them, ***for this particular participant***.

Yet science requires reliability between subjects and you must therefore conduct a **group analysis** (or « between participants ») to make inference at the population level.

# Subject 1

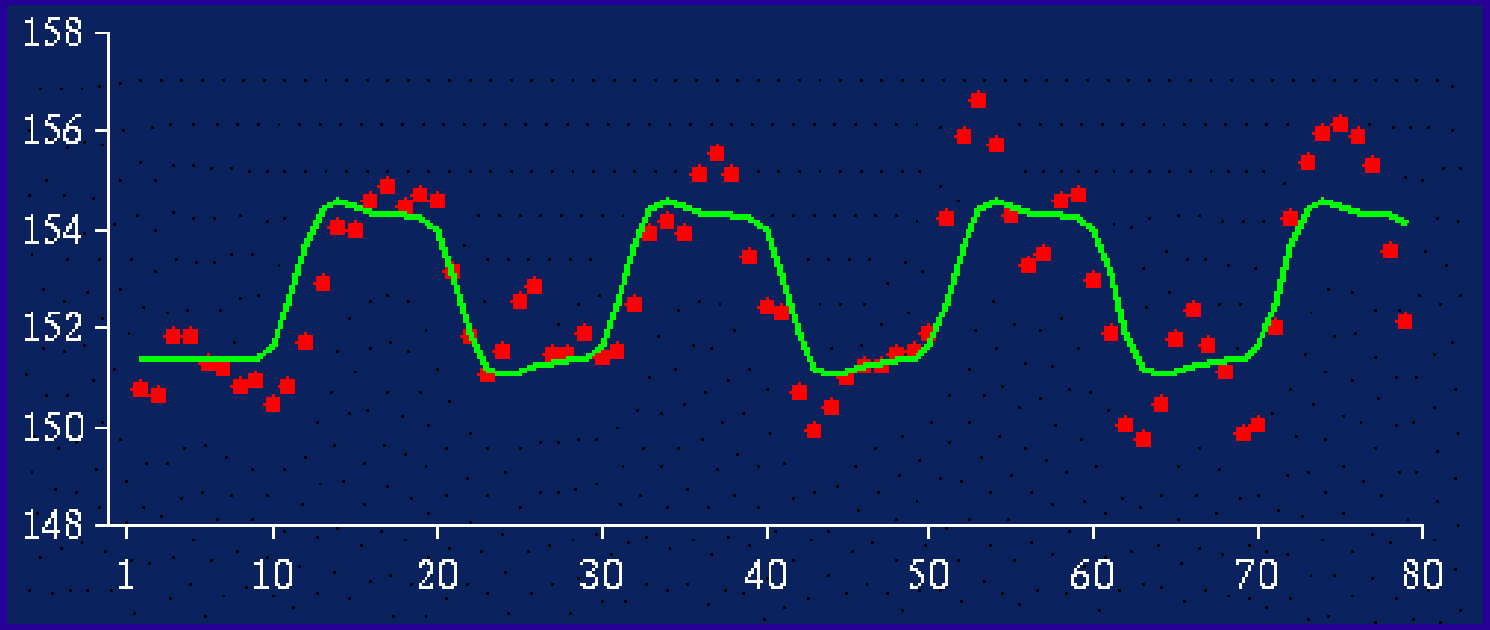
For voxel v in the brain




Effect size, c ~ 4

# Subject 2

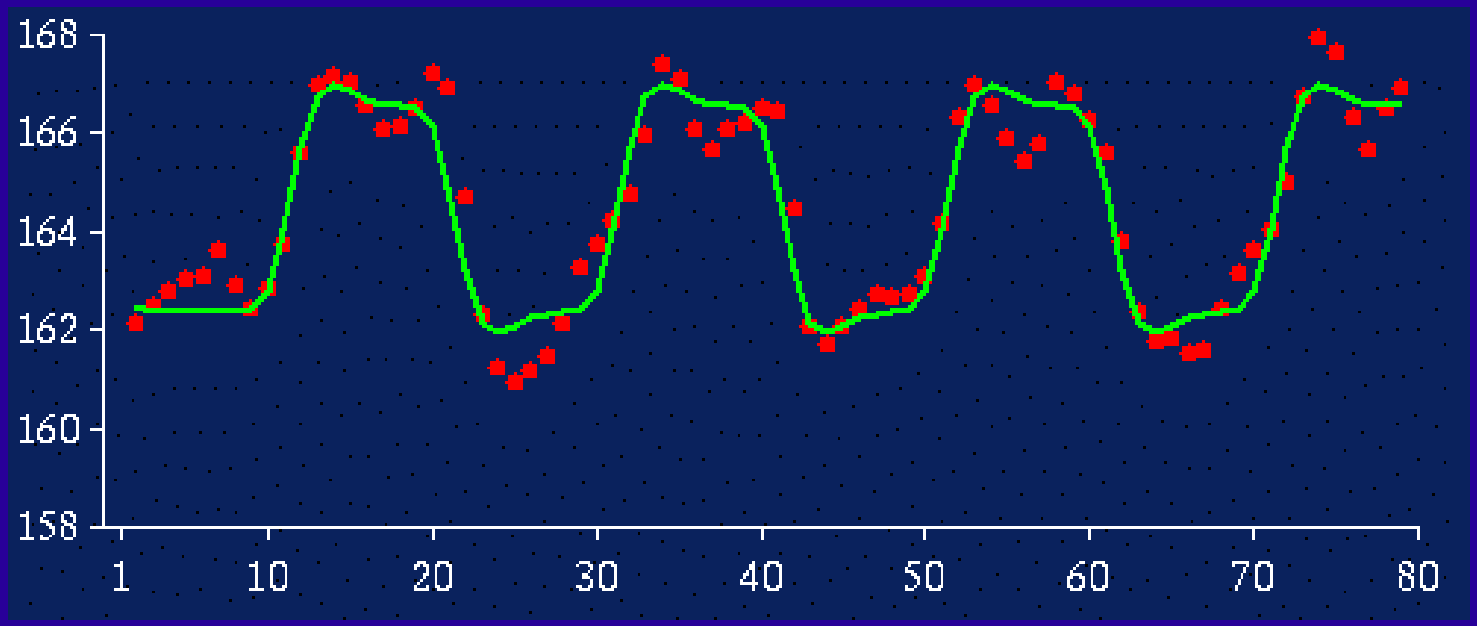
For voxel v in the brain




Effect size, c ~ 2

# Subject 3

For voxel v in the brain




Effect size, c ~ 4

# RFX: Summary Statistic

First level

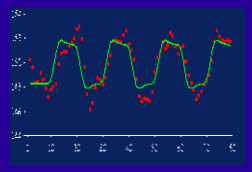
Second level

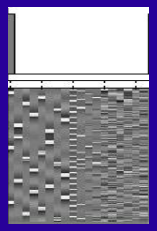
$$t = \frac{c^T \hat{\alpha}}{\sqrt{V\hat{a}r(c^T \hat{\alpha})}}$$

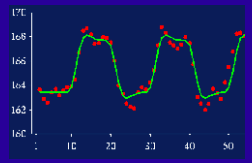
Data

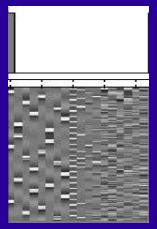
Design Matrix

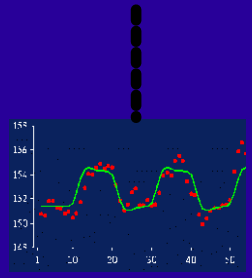
Contrast Images

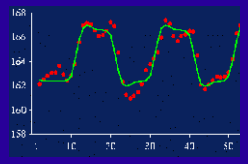


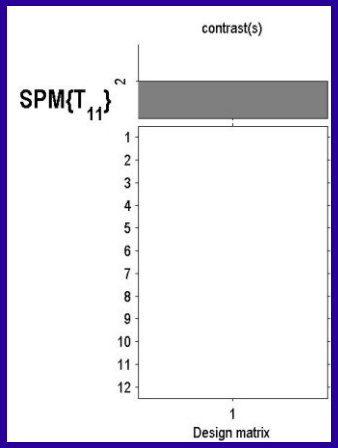




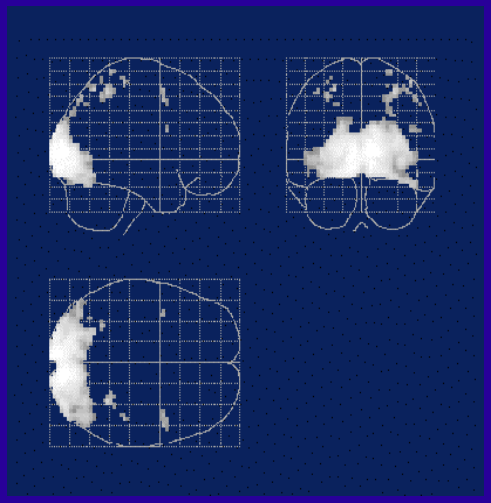


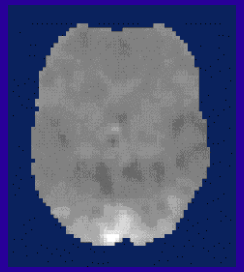







SPM(t)



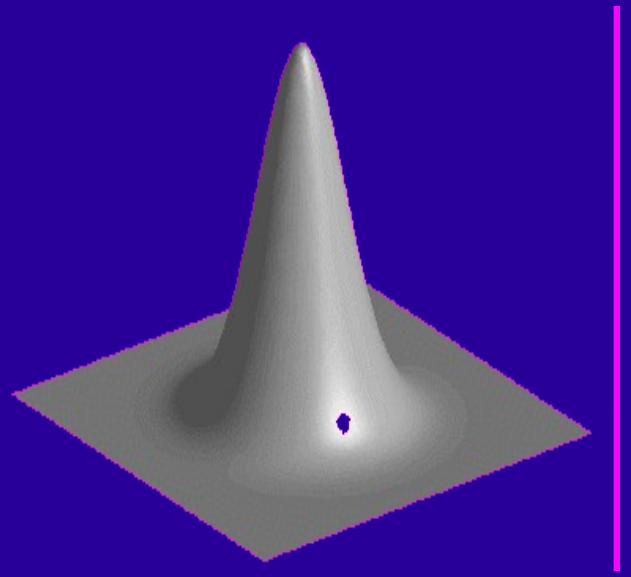


One-sample
t-test @ 2nd level

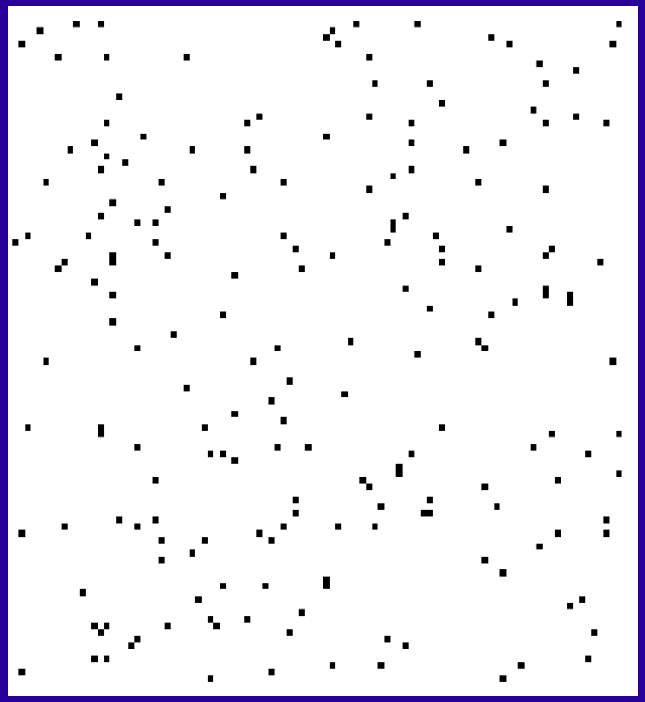
# Smoothing

Smoothing is done by convolution.

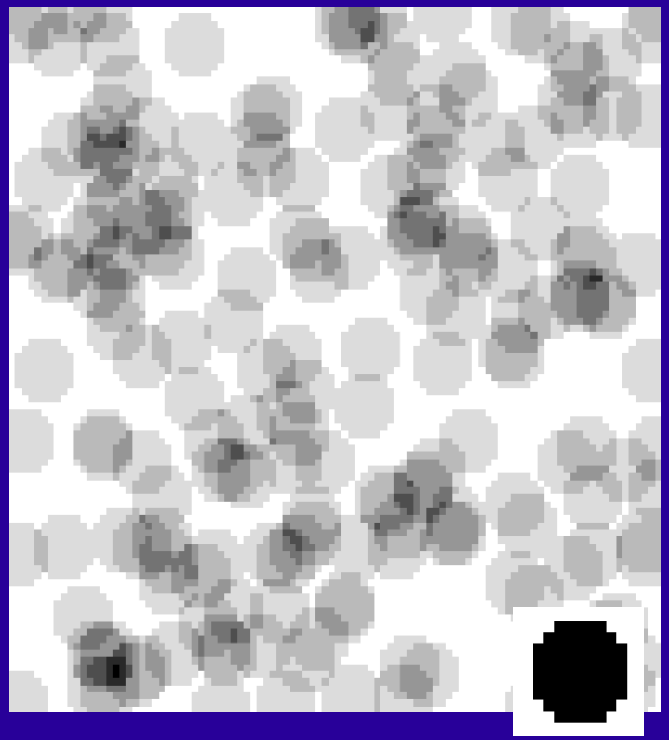
Each voxel after smoothing effectively becomes the result of applying a weighted region of interest (ROI).



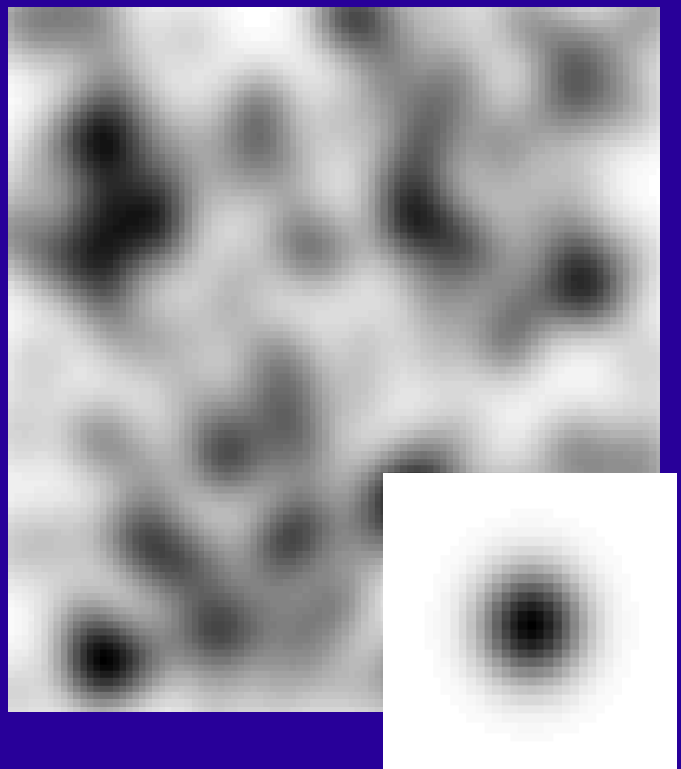
Before convolution



Convolved with a circle

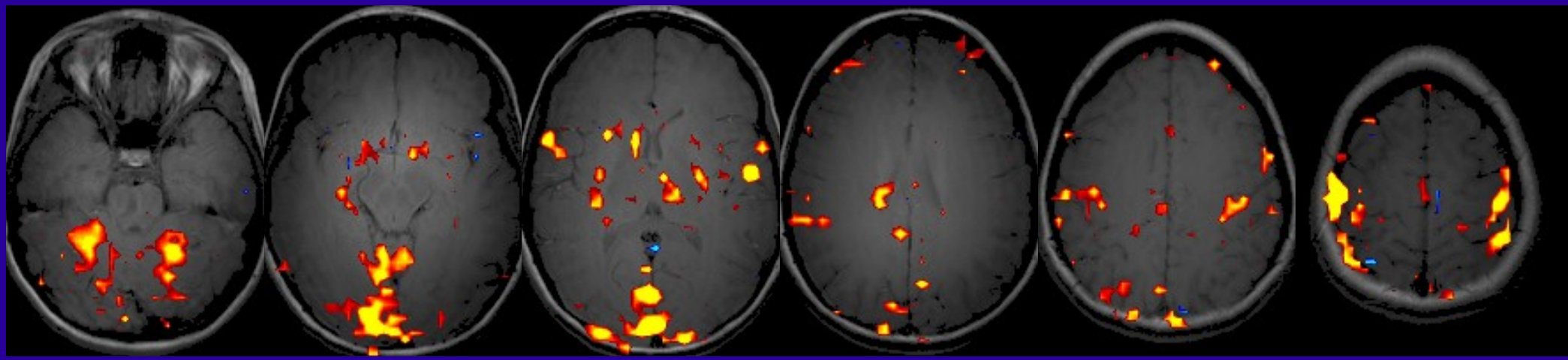


Convolved with a Gaussian

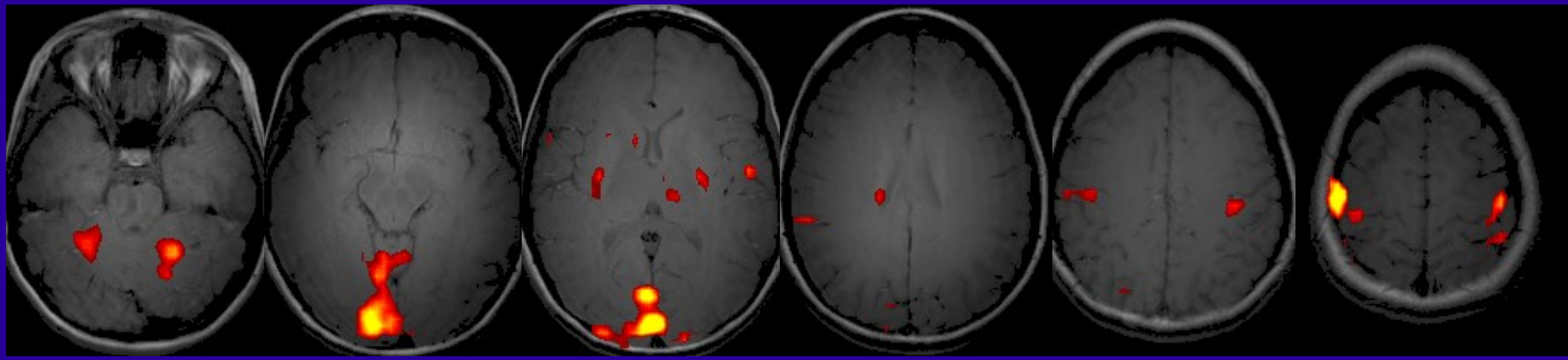


# Effects of Spatial Smoothing on Activity

Unsmoothed Data



Smoothed Data (kernel width 5 voxels)



*Slide from Duke course*

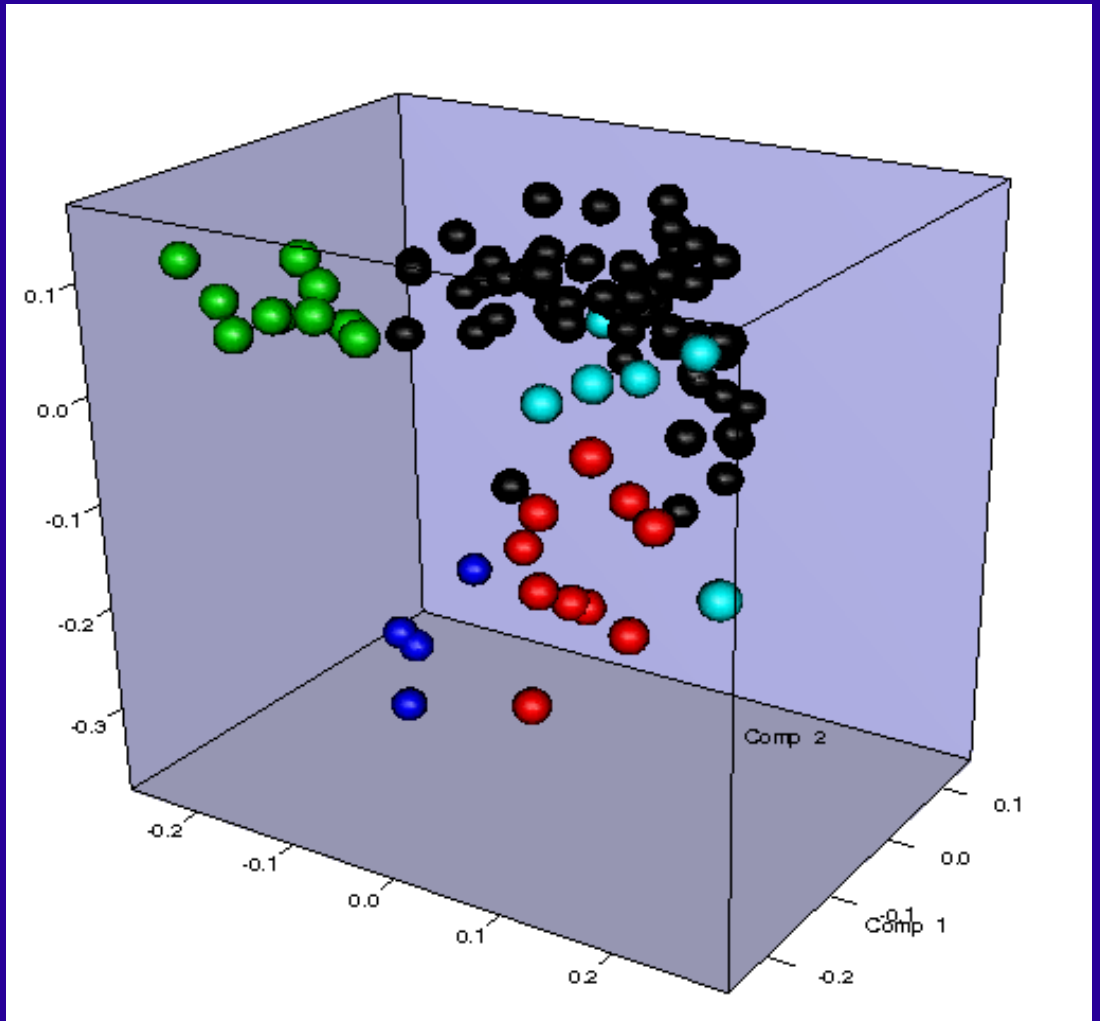
# Multivariate analyses

The massive **univariate** approach to analyse fMRI data described earlier compare activity independently at each voxel.

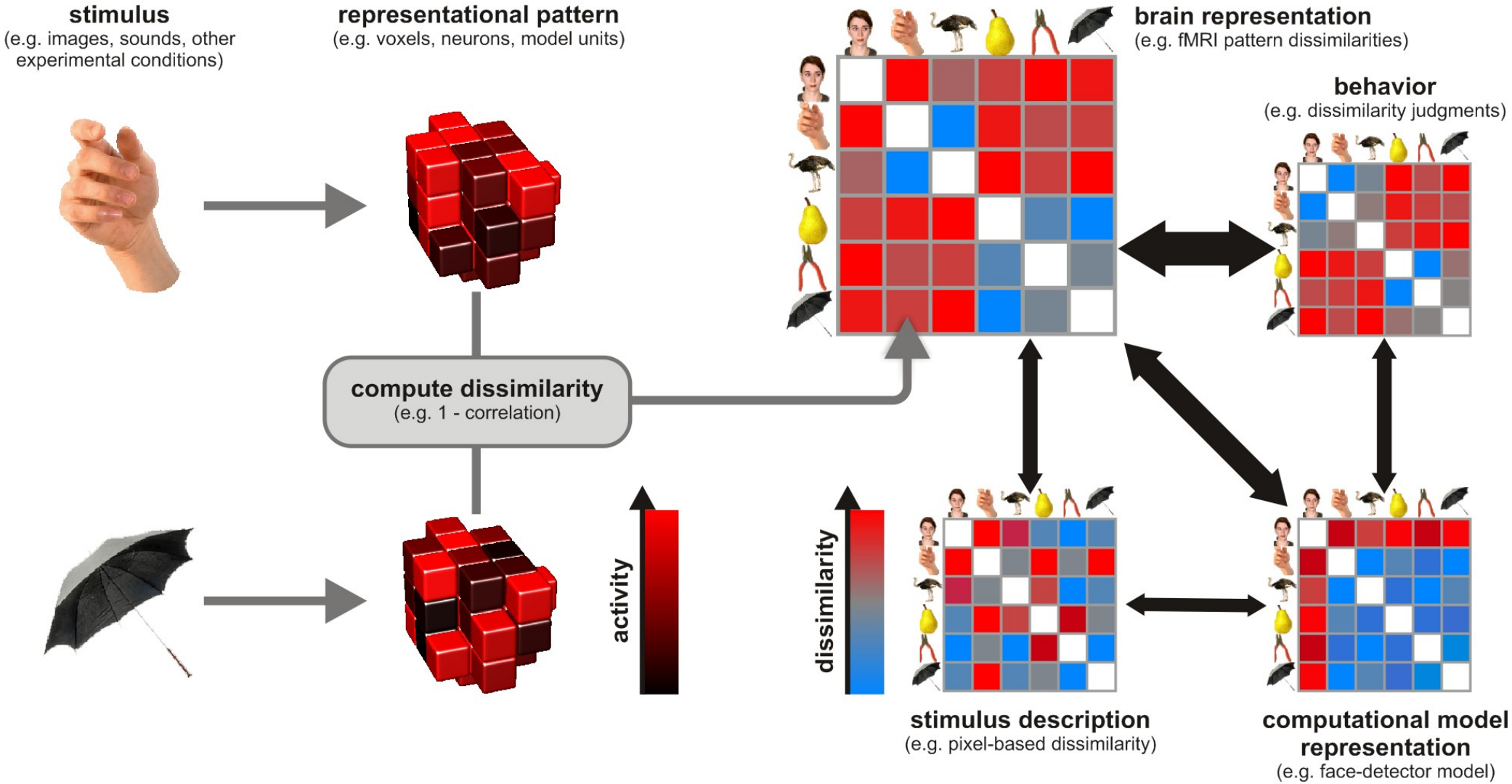
**Multivariate** analyses rely on activity patterns from several voxels (the whole brain or, more typically, Regions of Interest).

Classification algorithms:

* Linear Discriminant Analysis (LDA),
* neural networks
* support vector machine (SVM)
* Penalized Logistic Regression



# Representational Similarity Analysis (RSA)




See Kriegeskorte and Kievit. (2013) “Representational Geometry: Integrating Cognition, Computation, and the Brain.” *Trends in Cognitive Sciences*

# Visual stimulus reconstruction from fMRI activation in the visual cortex

(Miyawaki et al. 2008. *Neuron*)

Activity was measured in early visual cortex (V1-V4) for numerous 10×10 binary patterns of visual stimuli. The authors looked at correlations in bins of voxel activity to hundreds of visual test patterns.

Then they displayed novel visual input and used a linear combination of the local image element responses to predict the visual input from the brain activity alone.