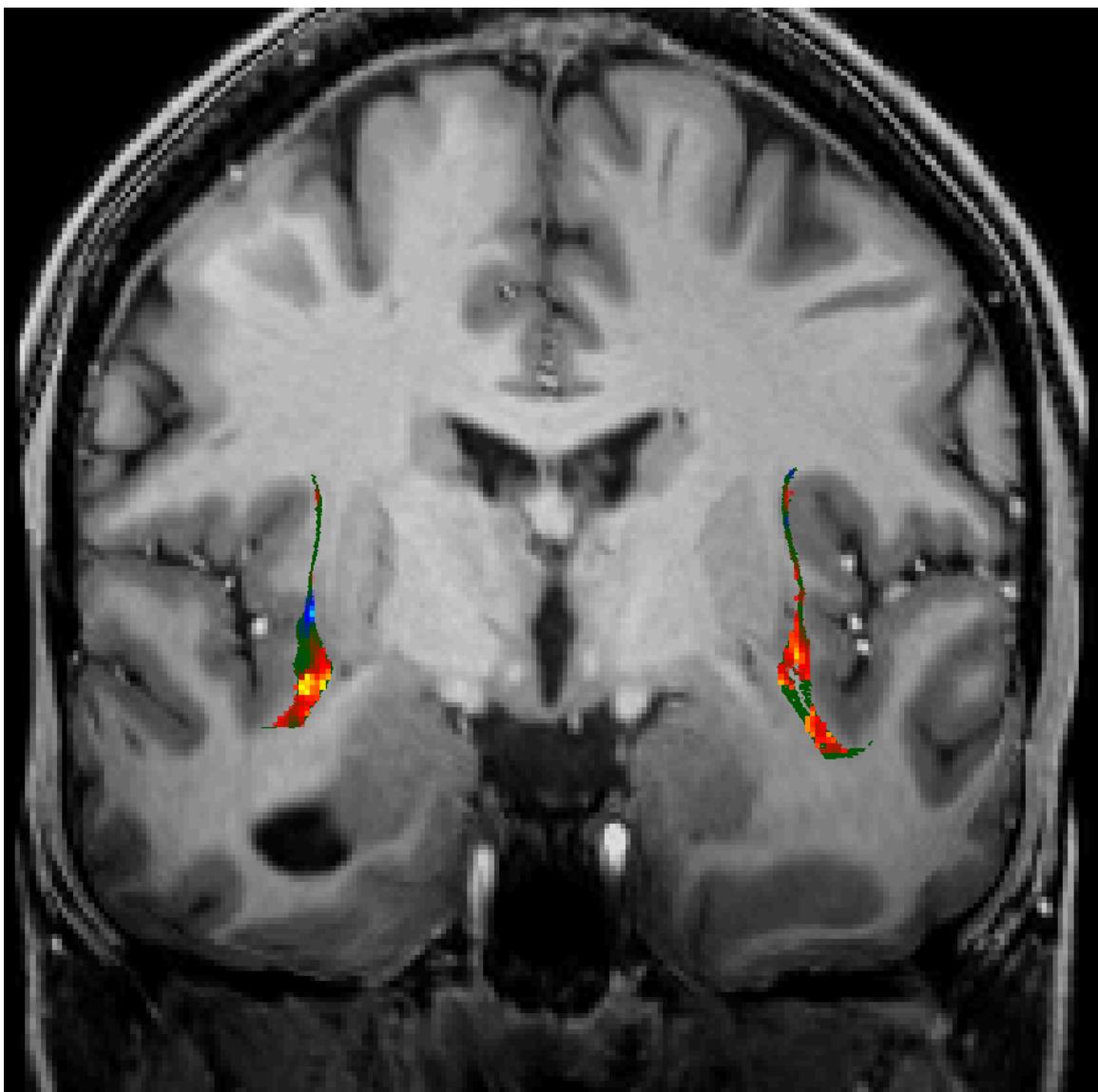




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Introduction to fMRI

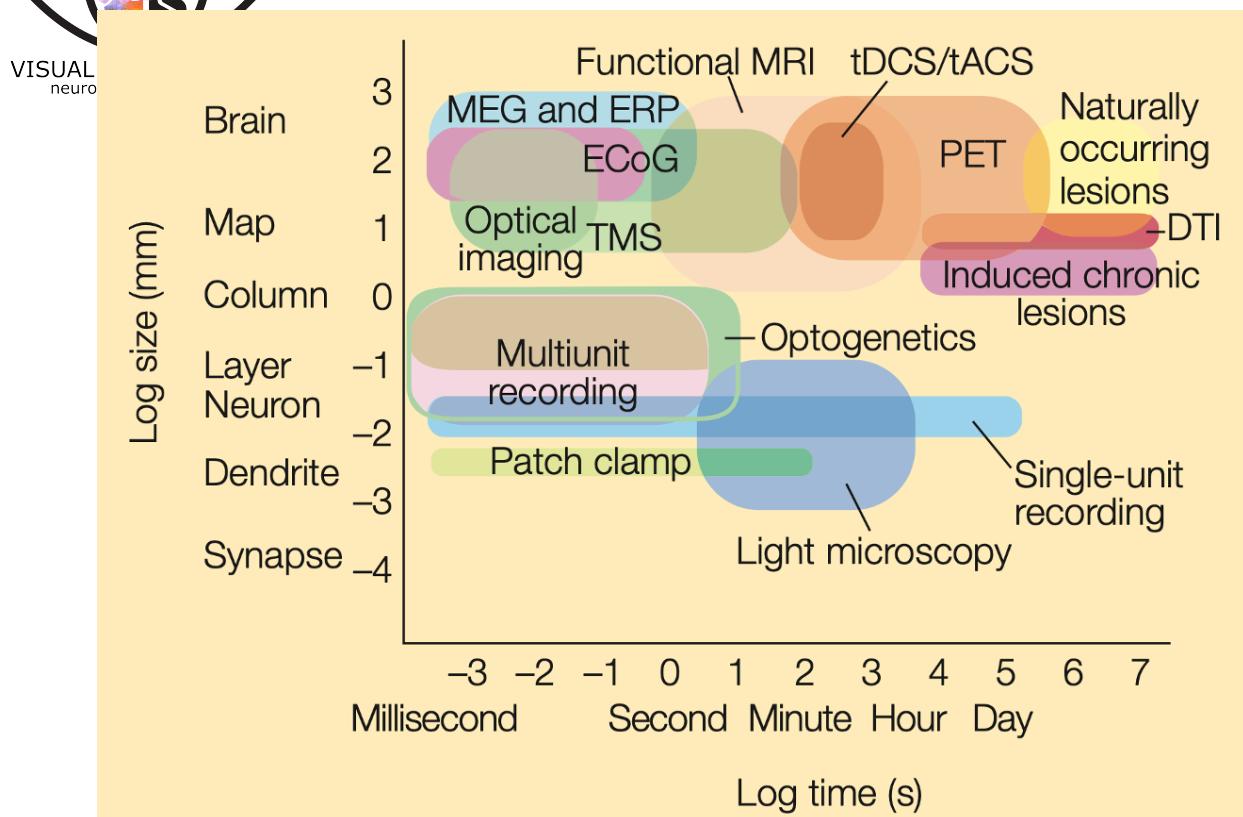


Visual activity in the human claustrum [1]

fMRI is a method that allows to non-invasively measure brain activity.



Brain comparison



Source: Gazzaniga 5th edition, Figure 3.45



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<https://mri-lab.uni-graz.at/>



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Image source: Medical University of Vienna



MRI scanner: 9.4 Tesla

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Image source: Max-Planck Institute for Biological Cybernetics, Tübingen

Types of MRI contrasts

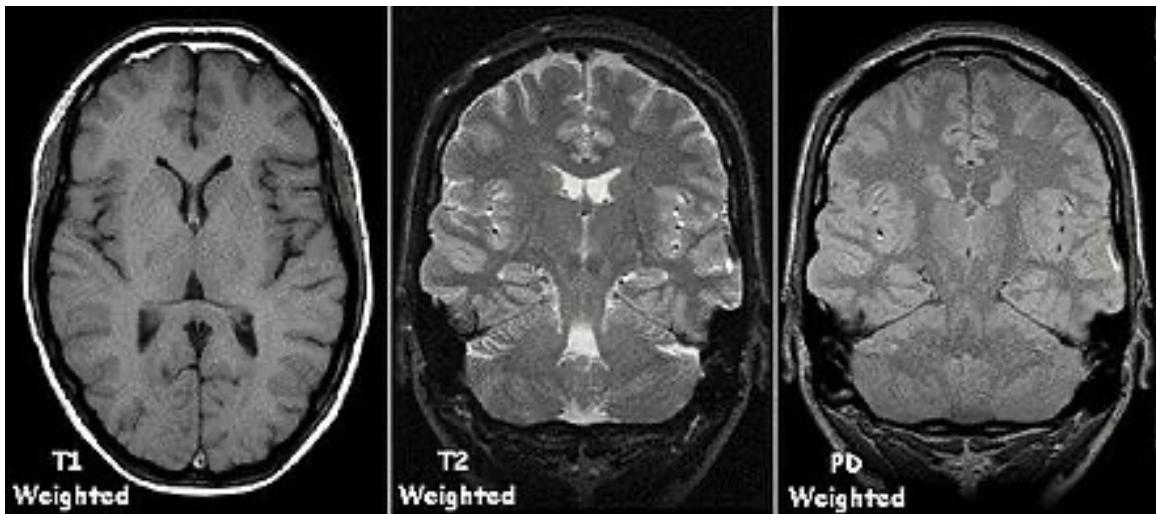
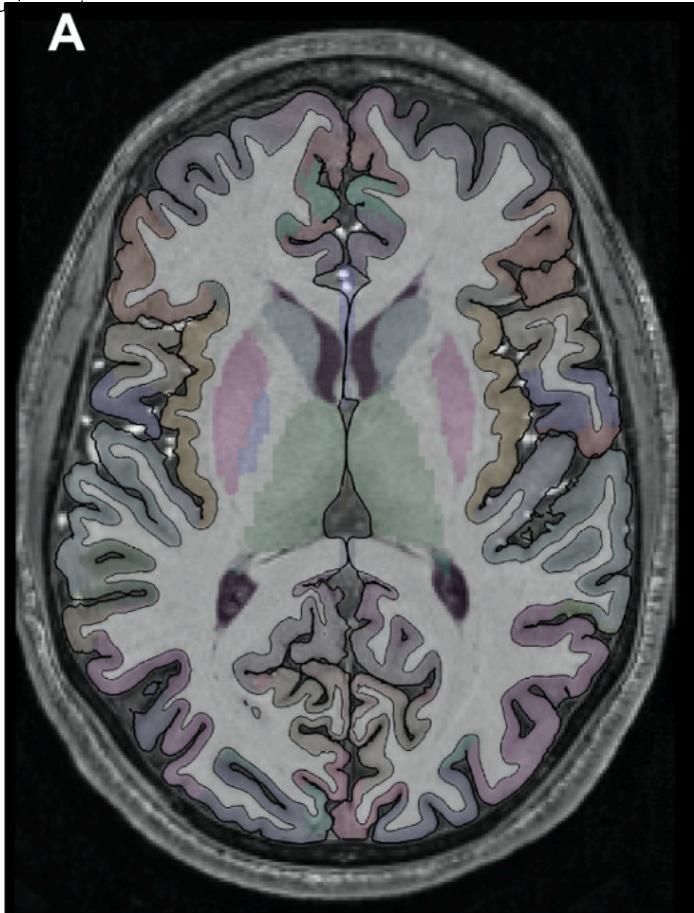




Image source: https://en.wikipedia.org/wiki/Magnetic_resonance_imaging

Brain in cognitive neuroscience

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Full Segmentation of a T1-weighted scan [2]

- Displaying activity on a high-resolution anatomical scan
- Quantitative morphometry
 - Aging
 - Neurodegeneration
 - Plasticity



The principle of fMRI

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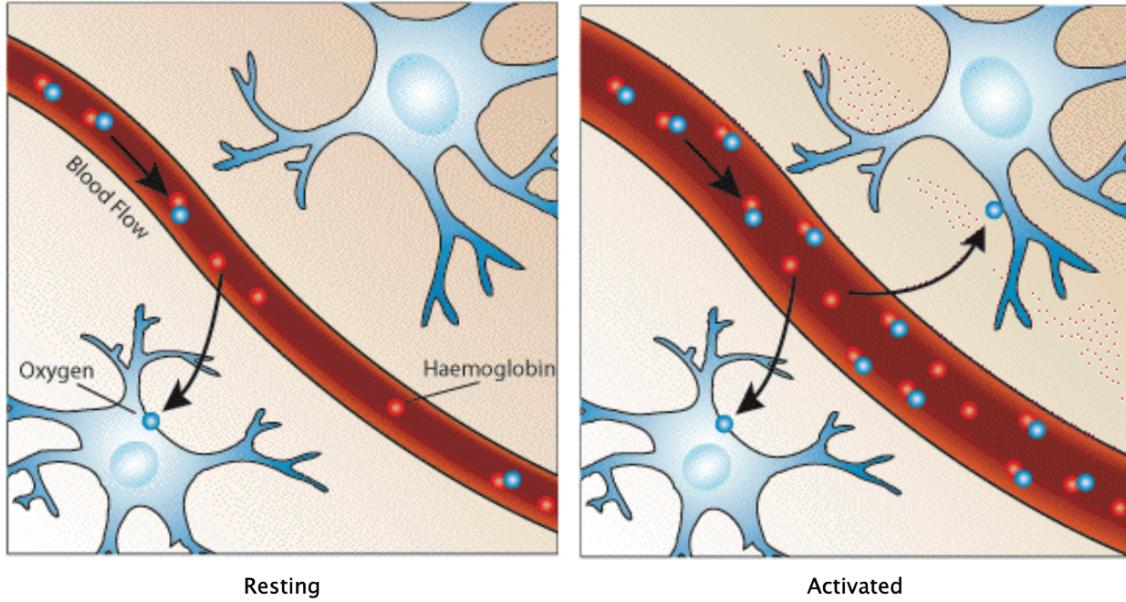
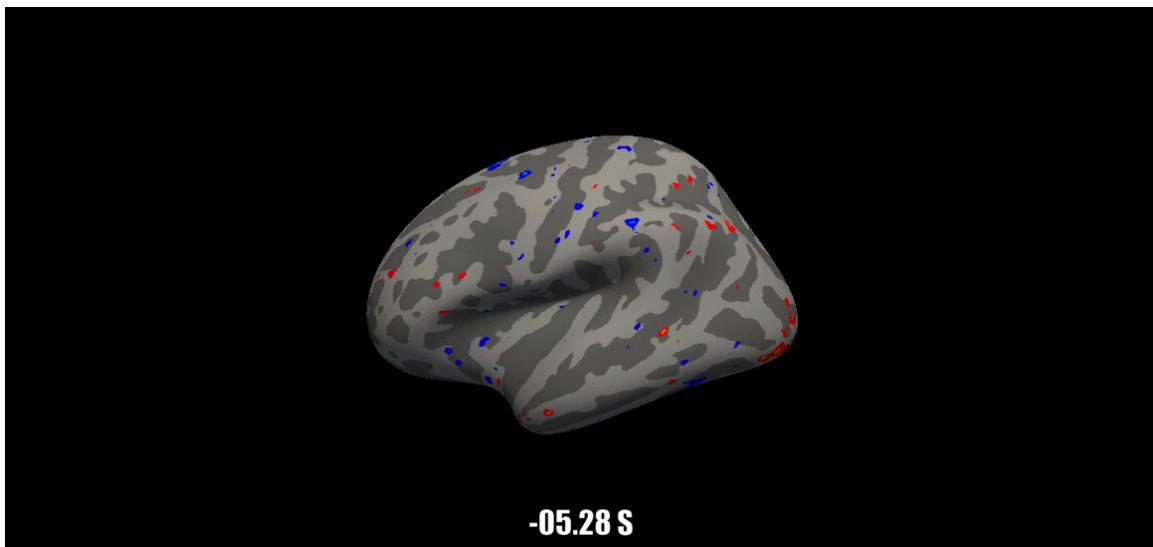


Image source: https://www.nature.com/scitable/blog/brain-metrics/what_does_fmri_measure

Hemodynamic changes: - increase in blood flow - increase in blood volume - increase in tissue CMRO₂

Hemodynamic response



Source: Visual Neuroscience Lab

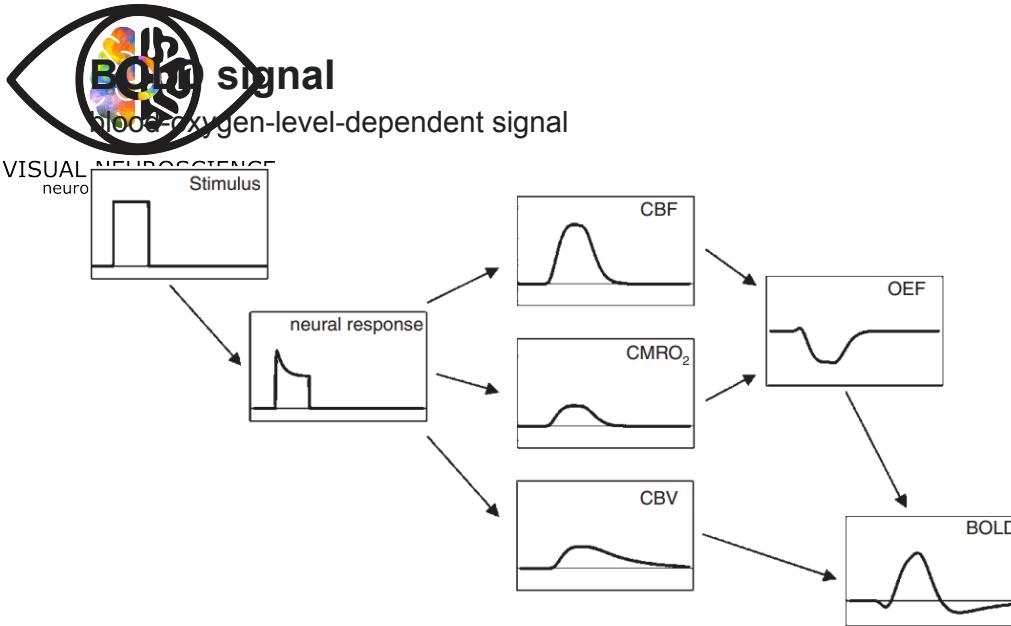
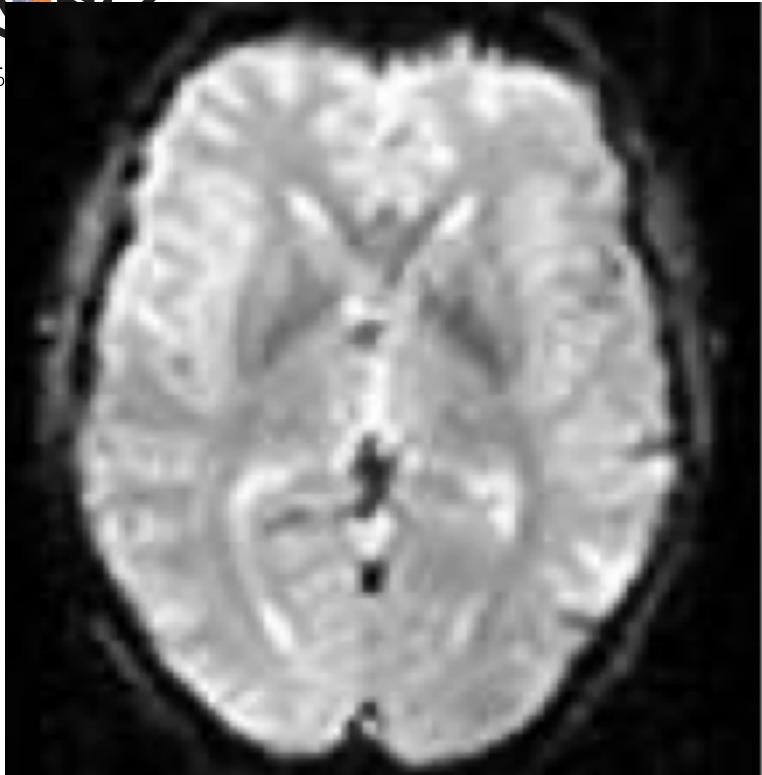


Fig. 16.2. The chain of events leading to the BOLD signal. A stimulus triggers local neural activity, which in turn triggers metabolic activity in the form of a large increase of cerebral blood flow (CBF), a small increase of cerebral metabolic rate of O_2 ($CMRO_2$), and a moderate increase of cerebral blood volume (CBV). The combined changes in CBF, $CMRO_2$ and CBV create the BOLD signal change. The response curves at each stage suggest ways in which the stimulus shape is altered in the progression to the BOLD response. A key aspect of this chain of events is that CBF and $CMRO_2$ are driven in parallel, rather than in series, and potentially by somewhat different aspects of the neural activity. OEF, O_2 extraction fraction.

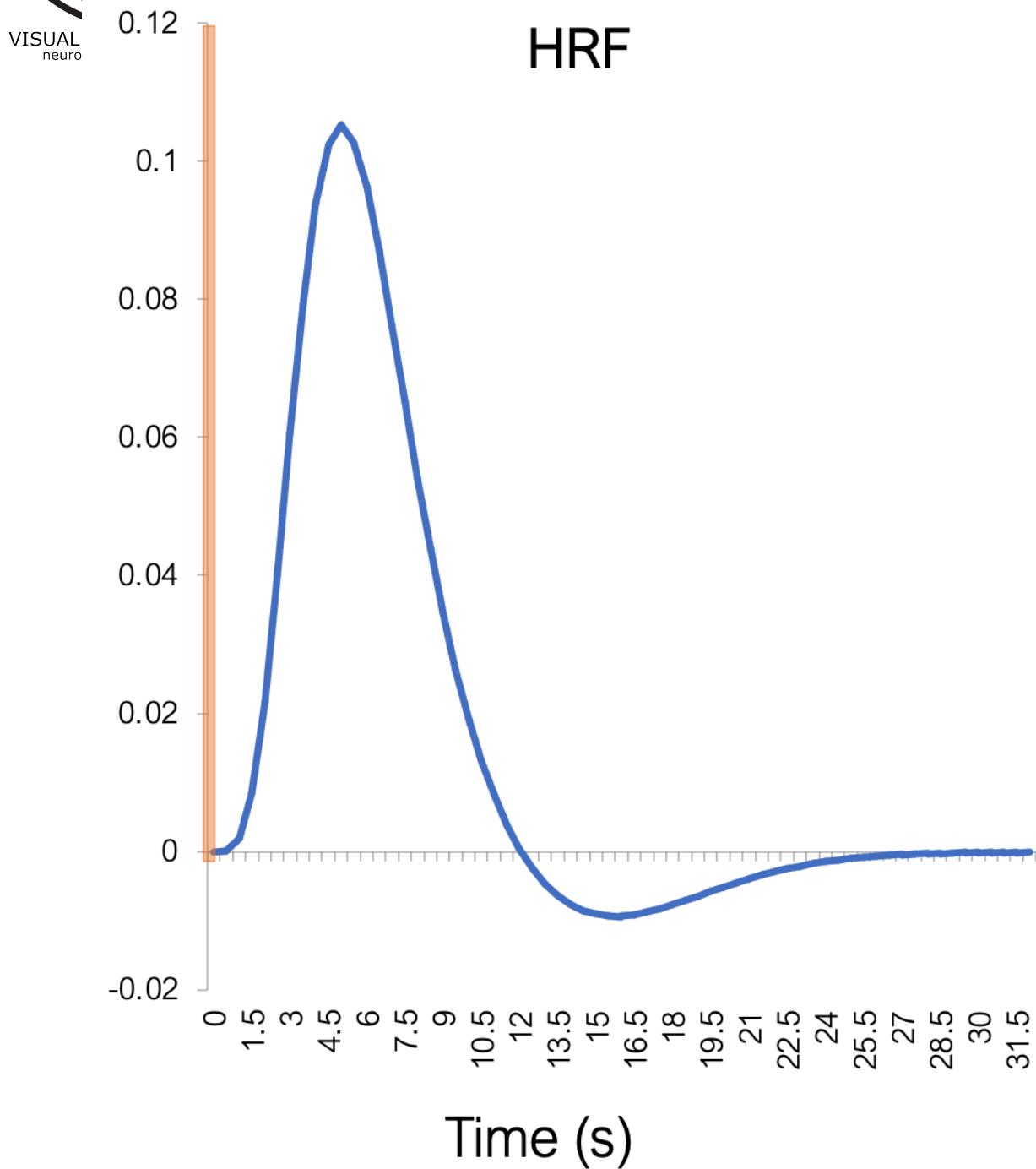
Hemodynamics leading to the BOLD signal [3]





Hemodynamic response function

HRF



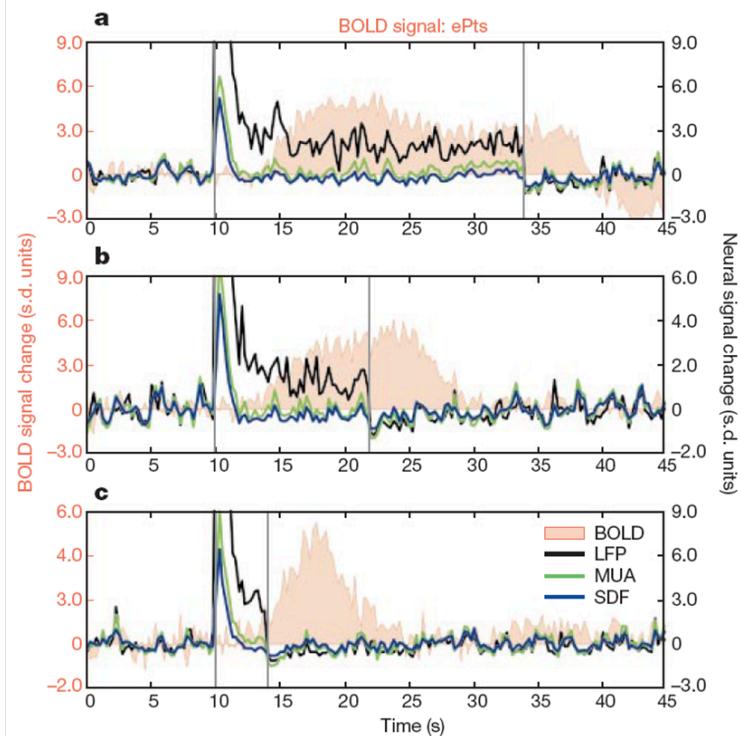
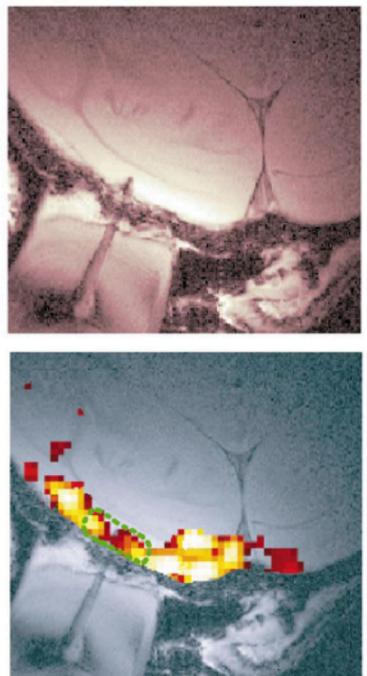
This curve describes the measured signal in response to a brief stimulus.

The response is heavily delayed, and has a relatively complex temporal structure, described by the so called hemodynamic response function (HRF).



After a brief stimulus that lasts less than a second, the response lasts for seconds. It has a delayed rise phase, a peak, and a subsequent undershoot. The fact that the response is so slow is the main constraint of the temporal resolution of fMRI. It constrains the kind of questions you can ask in your experiment and also puts some constraints on your experimental design.

Neural activity and BOLD



BOLD signal correlates better with LFP than with MUA [4]

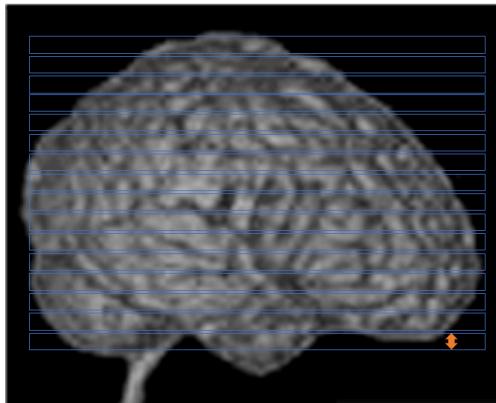
LFP = Local Field Potentials (dendritic currents)

MUA = Multiunit Activity (action potentials)

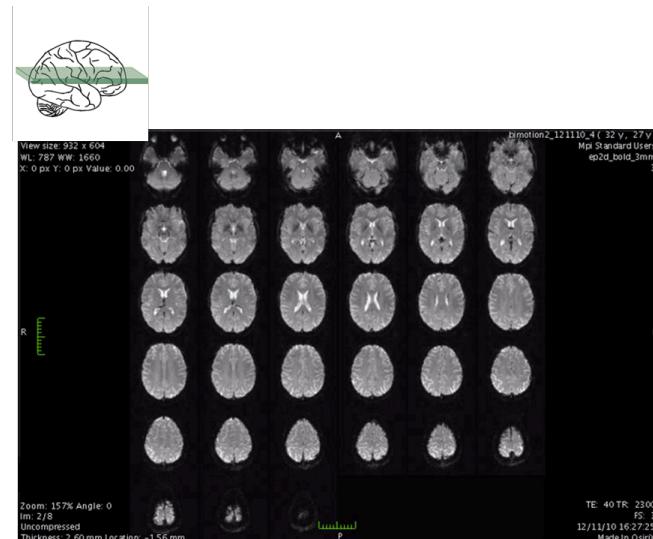
SDF = Spike-density function (action potentials)



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In-plane resolution 3x3mm
Slice thickness 3mm

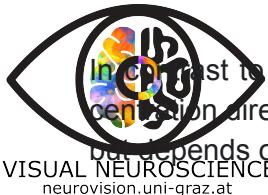


→ Voxel size 3x3x3mm

The functional volume is usually acquired slice-by-slice; this is why when you are acquiring the data you see an image like this on the monitor. A functional sequence is characterized by the in-plane matrix size and resolution, as well as by the slice thickness.

Experimental design

	Condition of interest	Control
Checkerboard		
Finger tapping		
Faces		
Cola		



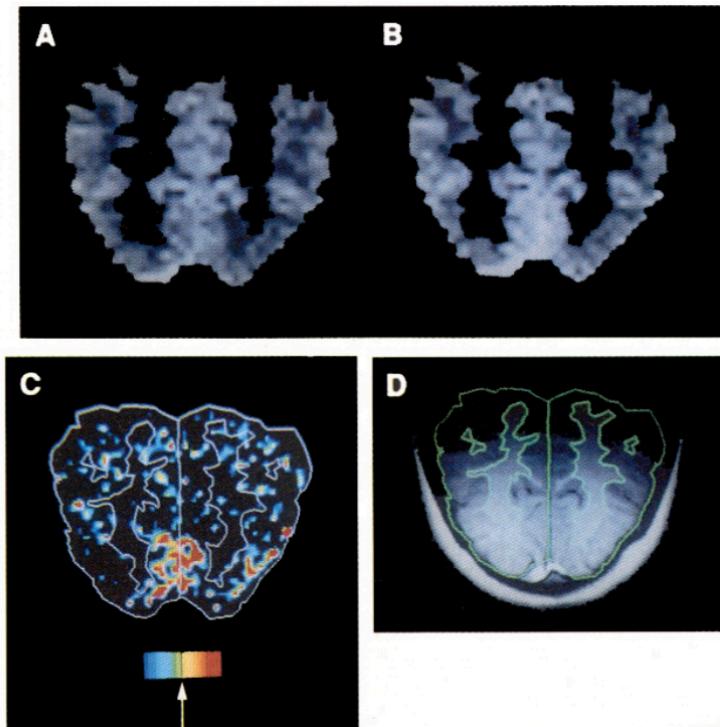
In contrast to e.g. fNIRS, the BOLD-fMRI does not measure the deoxyhemoglobin concentration directly. It is a measure that is weighted by the deoxyhemoglobin concentration, but depends on many other factors like scanner, sequence, participant, and brain area.

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This is why any measure of fMRI experiment has to contain at least two conditions, a baseline, and condition of interest. The activation is always computed relative to some baseline. For instance a checkerboard vs gray background, finger tapping versus rest; faces versus houses, etc. And a typical analysis will compare the BOLD signal during condition of interest with rest.

First fMRI experiment

Fig. 3. Magnetic resonance CBV maps of the brain during darkness (**A**) and during 7.8-Hz photic stimulation (**B**). Image intensity is proportional to CBV. All images are aligned along the calcarine fissure (Fig. 1), with the occipital pole at the bottom. (**C**) Subtraction image of changes in CBV induced by photic stimulation ($C = B - A$). A linear color scale was used, with red equivalent to greatest activity. The arrow points to the $+2$ SD threshold. (**D**) An anatomic (T1-weighted) image was used to segment the gray and white matter (20). This outline was applied to the CBV subtraction image. A marked area ($\sim 600 \text{ mm}^2$) of increased blood volume ($\sim 24\%$) is localized in the anatomically defined primary visual cortex (C). We acquired these CBV images using a 3 by 3 by 10 mm voxel.



Brain images and statistical analysis [5]

The first experiment was not a BOLD, but a blood volume signal measurement.



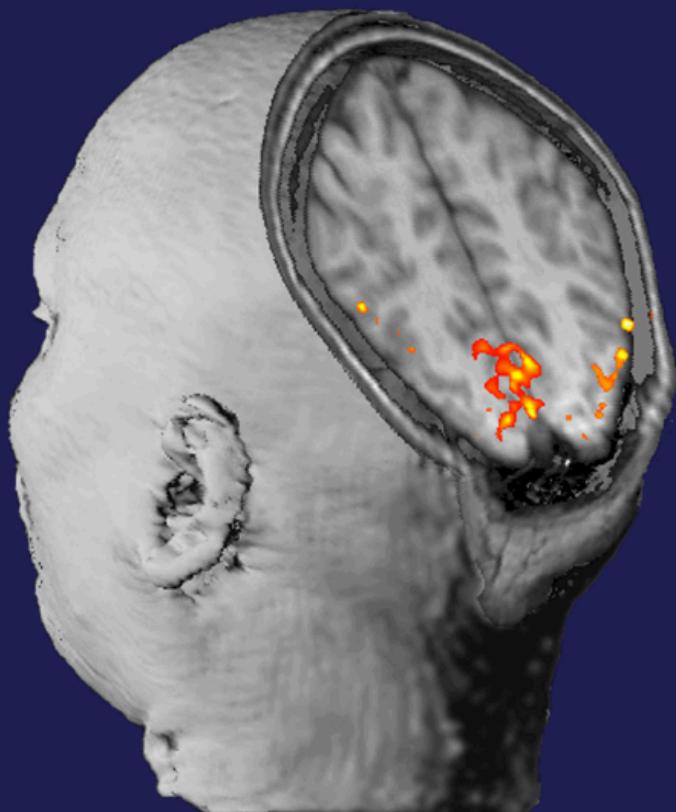
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AMERICAN
ASSOCIATION FOR THE
ADVANCEMENT OF
SCIENCE

SCIENCE

1 NOVEMBER 1991
VOL. 254 ■ PAGES 621-768

\$6.00



Cover of the science magazine where the paper was published [5]

This rendering was produced specifically for the cover



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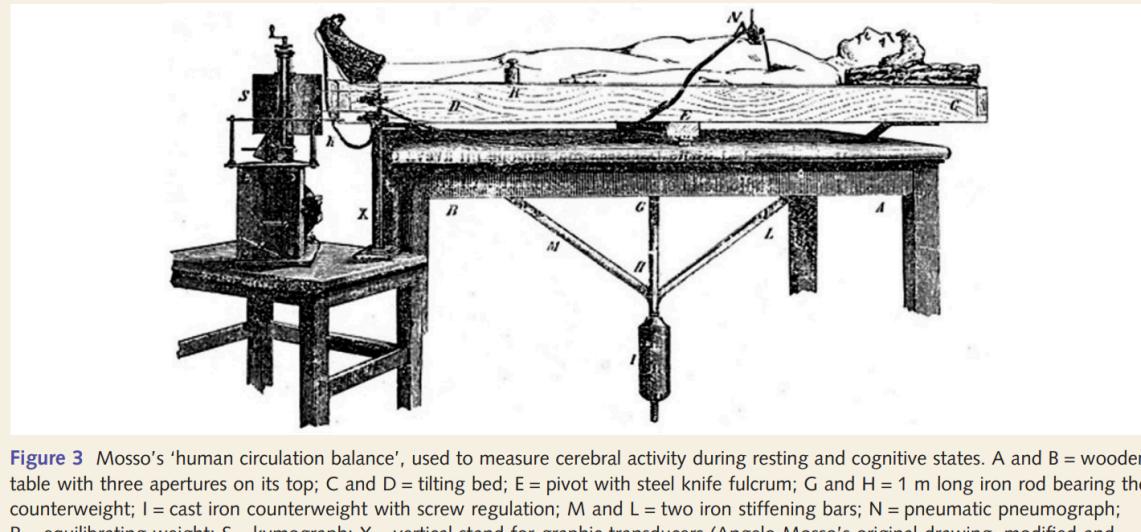
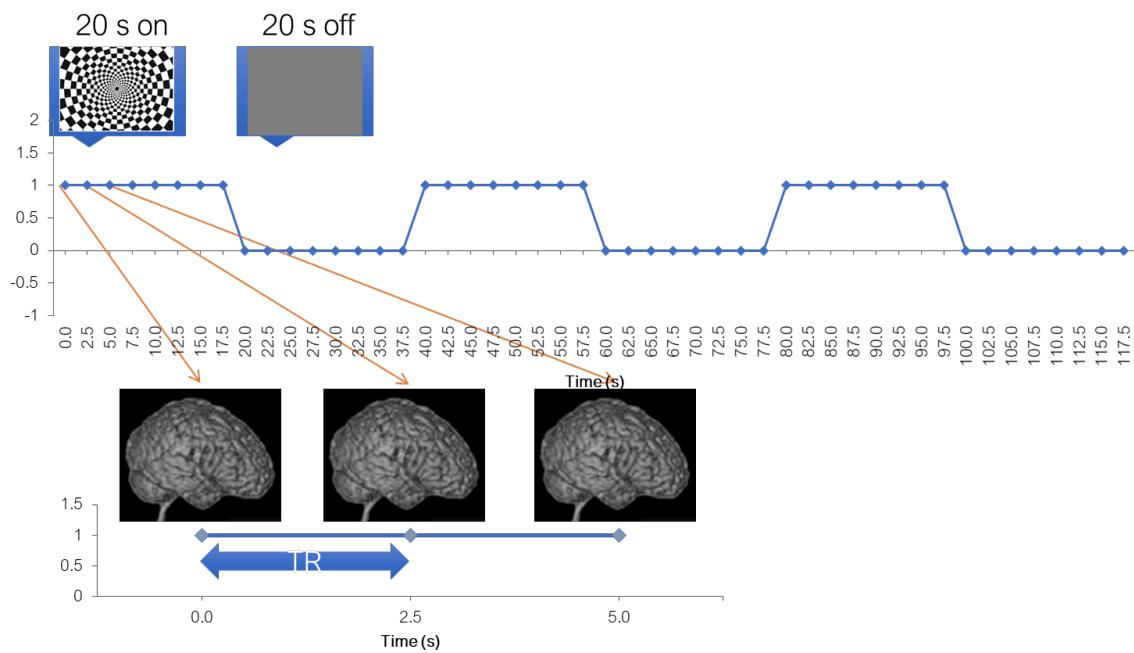


Figure 3 Mosso's 'human circulation balance', used to measure cerebral activity during resting and cognitive states. A and B = wooden table with three apertures on its top; C and D = tilting bed; E = pivot with steel knife fulcrum; G and H = 1 m long iron rod bearing the counterweight; I = cast iron counterweight with screw regulation; M and L = two iron stiffening bars; N = pneumatic pneumograph; R = equilibrating weight; S = kymograph; X = vertical stand for graphic transducers (Angelo Mosso's original drawing, modified and adapted from Mosso, 1884, Atti della Reale Accademia dei Lincei).

Experimental setup of Angelo Mosso [6]

A typical experiment



To help us better understand the analysis steps, let's use an example. Let's say we have conducted a classical experiment in the visual system, a flickering checkerboard. In this experiment, we want to find out which brain areas are active when subjects view a flick-

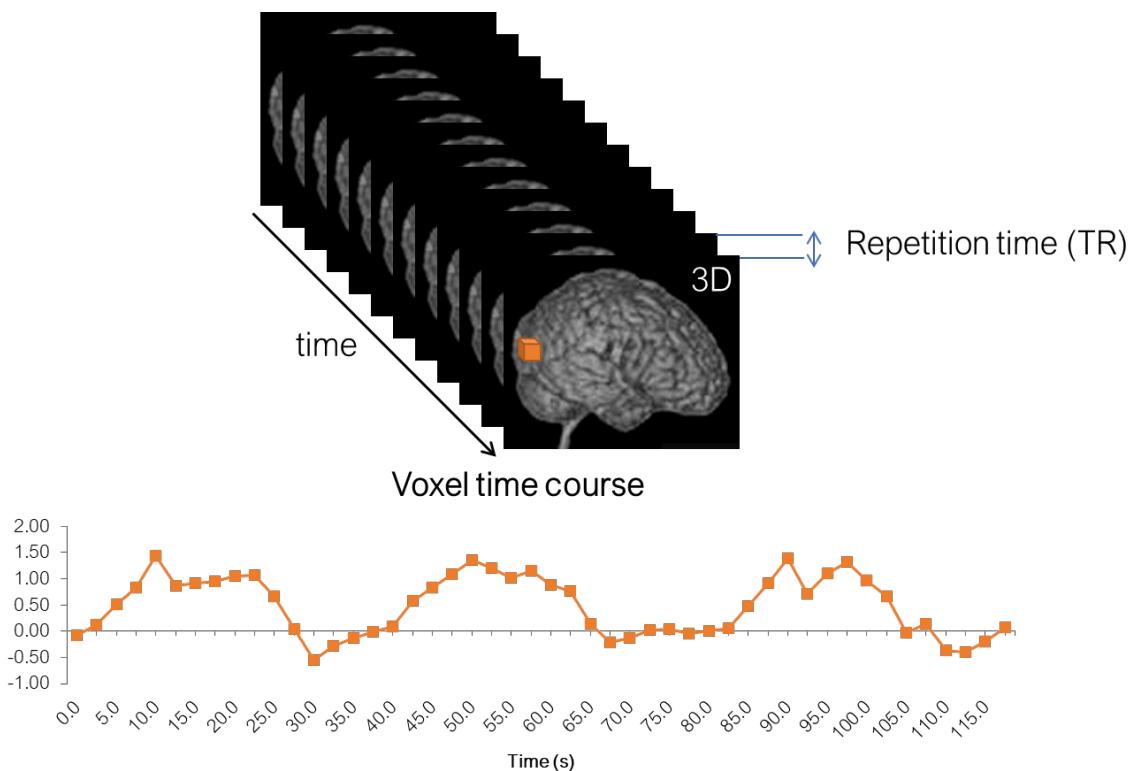


every volunteer a checkerboard compared to when they view a gray background. We have shown to measure a whole brain volume every 2 seconds, for e.g. to minutes or so.

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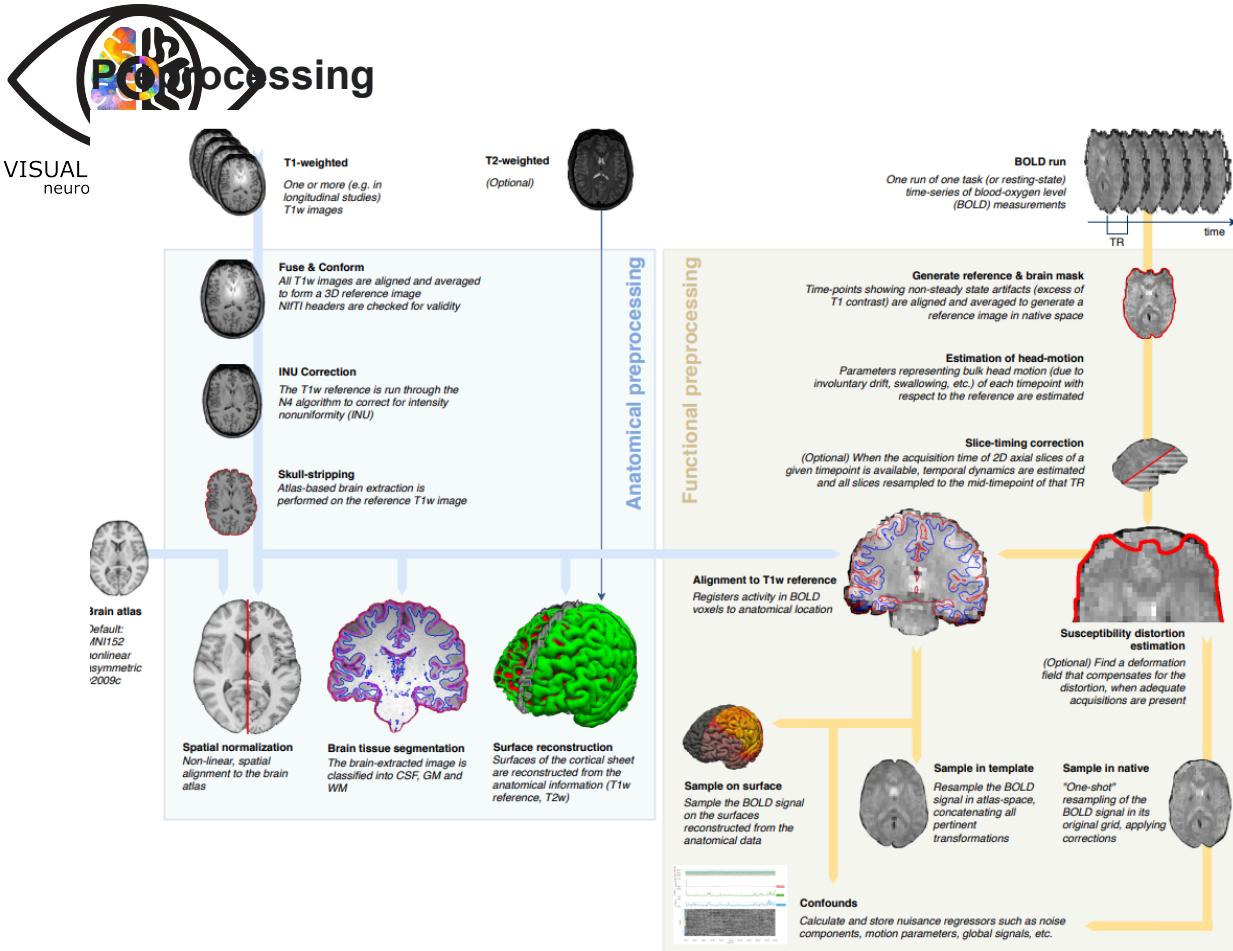
Matlab code to generate stimulus, BOLD and shifted BOLD X = [1 1 1 1 1 1 1 1 1 0 0 0 0 0
0 0 0 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 0 0 0 0 0 0 0]; bf = spm_get_bf; % indicated a tr of 2.5 Y = conv(X,bf.bf); Ye = Y+randn(size(Y)).*0.2;

4D dataset



In a functional experiment we usually measure brain activity across the whole volume over extended periods of time, so it is comfortable to think about each functional dataset that we acquire as a 4D dataset, which consists of 3D brain volumes and time as a 4th dimension. This is how the data is typically stored.

A further important parameter is the repetition time (TR). It is the time passes between the acquisition times of two adjacent volumes.



Summary of preprocessing steps [7]

The data quality of modern scanners is typically good enough to skip this step, if your subject is compliant. But it is nevertheless very much advisable and is **ALWAYS** performed. We will therefore dedicate a whole session to preprocessing. See [course schedule](#) for the date.

Analysis

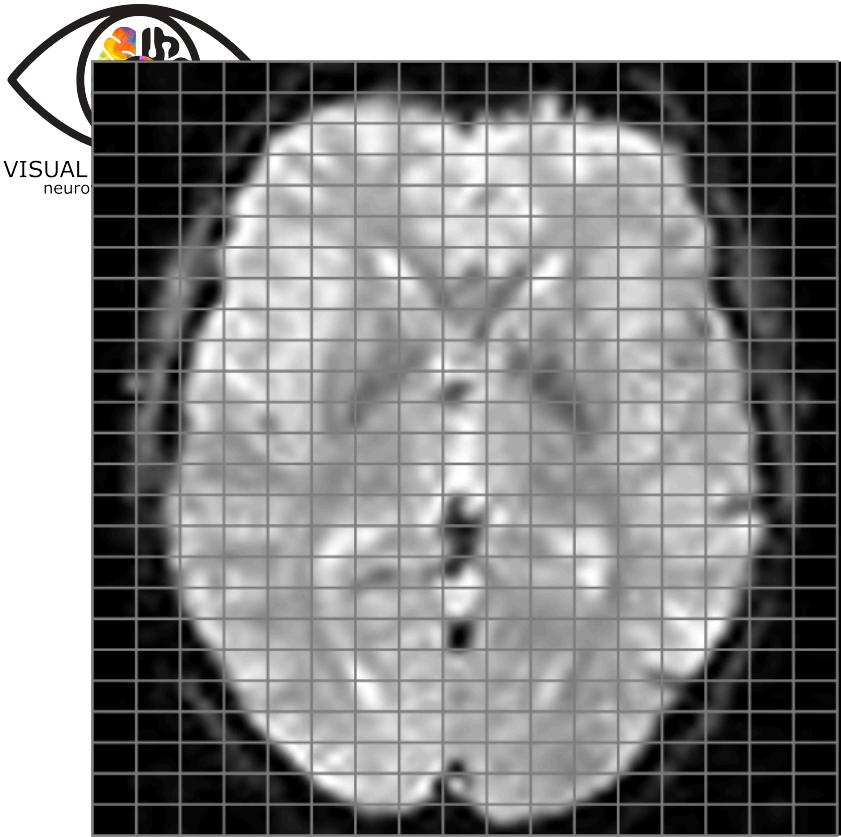
- Single-subject - first level - fixed effects analysis (FFX)
- Group - second-level - random effects analysis (RFX)

This is equivalent to e.g. conducting many trials per subject to measure reaction time, and then compute a subject-specific mean per condition, after which you would perform the actual statistical inference

Multilevel modelling is also possible (for small datasets), but less frequent.

Single-subject (first-level) analysis

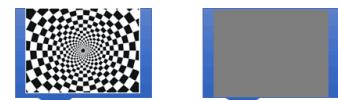
Univariate/voxel-wise analysis



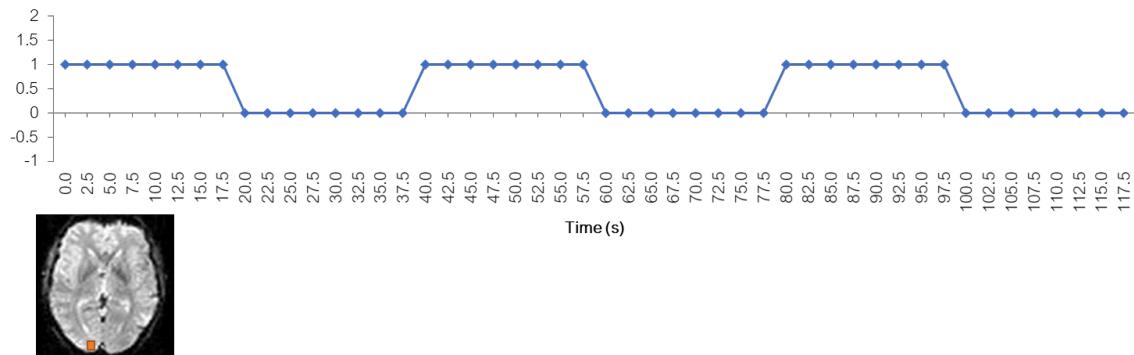
Question: Which areas are activated by the flickering checkerboard?

Remember that an image is 4d and consists of little 3D cubes called voxels, with the 4th dimension being time. A classical analysis is done over time for every voxel in the brain independently.

Stimulus function



Stimulus function





Let's recall our checkerboard experiment where participants viewed either a checkerboard or a grey screen. Let's also create a function, called "stimulus function", which is one where the checkerboard was on, and zero where the checkerboard was off

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Side-note on terminology

Trial

Continuous presentation of 1 experimental condition, usually 1-20 seconds

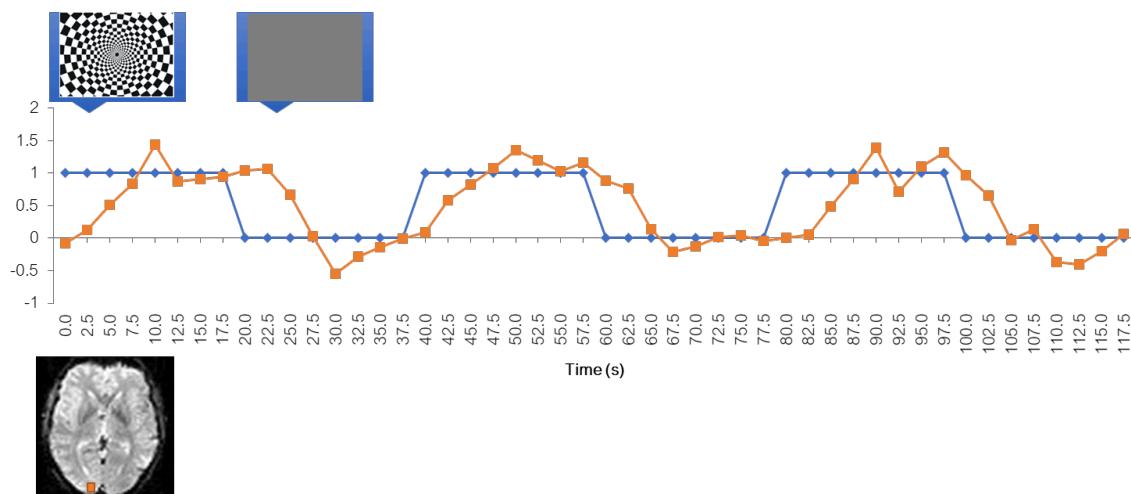
Run

Block of trials separated by interruption of a scanner acquisition, usually 5-10 minutes

Session

Block of runs, separated by subject going out of the scanner and going in again, usually at least one day

Voxel time course

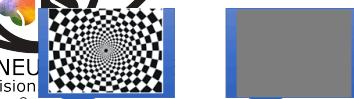


Let's now look at the time course of a voxel in the visual cortex. You see that it is noisy and delayed, but it kind of follows the stimulus.

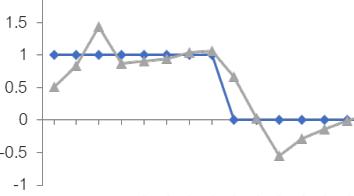


Simpler analysis: temporal alignment

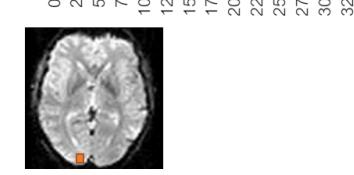
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Stimulus sequence



BOLD time course

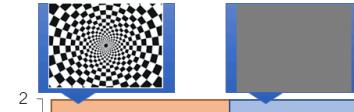


Brain scan image

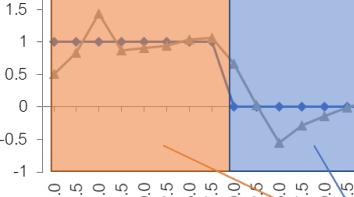
Time(s)

The simplest analysis would be to realign the BOLD time course with the stimulus time course

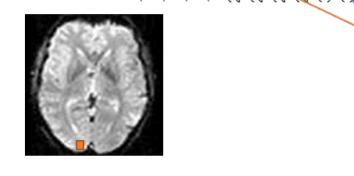
Simplest analysis: statistical inference



Stimulus sequence



BOLD time course



Brain scan image

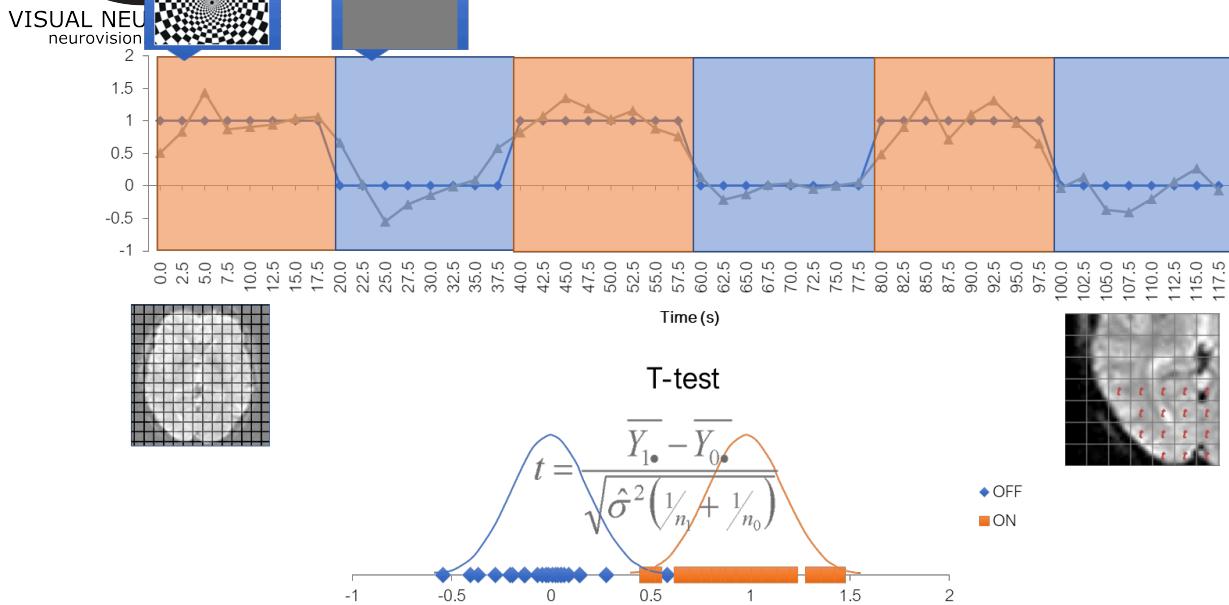
Time(s)

$$t = \frac{\bar{Y}_1 - \bar{Y}_0}{\sqrt{\hat{\sigma}^2 \left(\frac{1}{n_1} + \frac{1}{n_0} \right)}}$$

Then label each value according to when it was acquired, stimulus or baseline. Collect two types of data points into two big piles and do a statistical comparison via a t-test



Samples analysis: statistical map



If you do it for every voxel, you can get a new volume, which consists of t-statistics

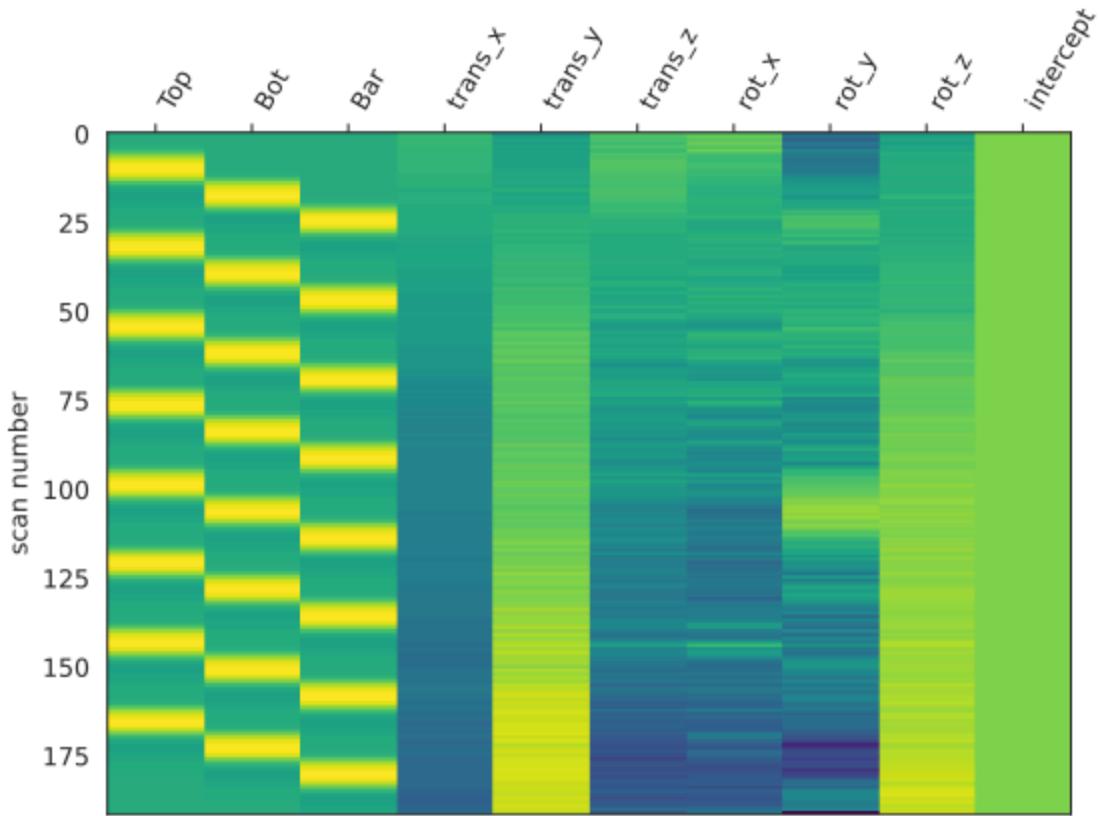
General Linear Model (GLM)

Multiple regression with ingredients:

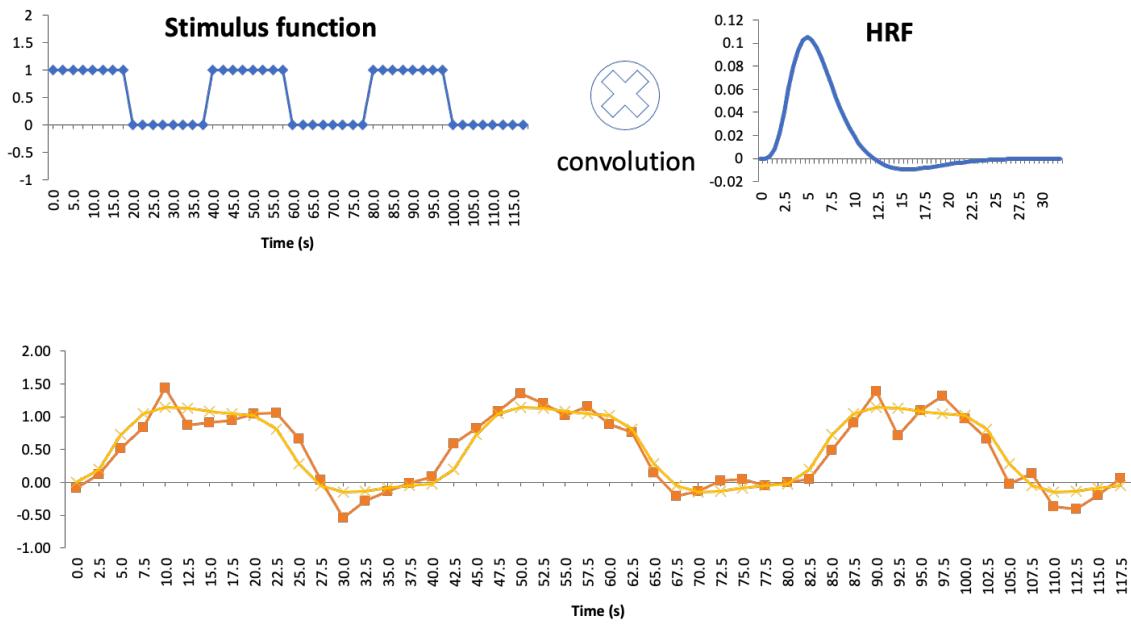
- Predictor(s): stimulus function convolved with the HRF (see [Building regressors](#))
- Nuissance regressors



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Buidling regressors



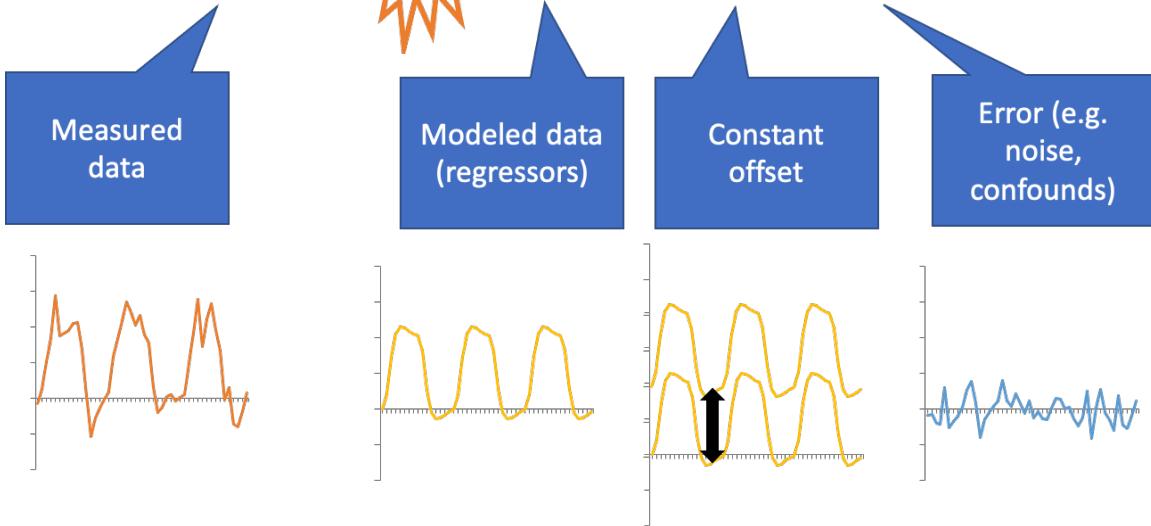


Some convolution examples can be found here [8]

General linear model

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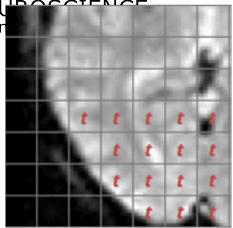
$$Y(t) = \beta^* X(t) + c + e(t)$$





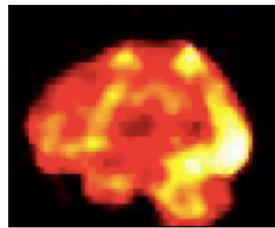
Statistical inference in whole-brain analysis

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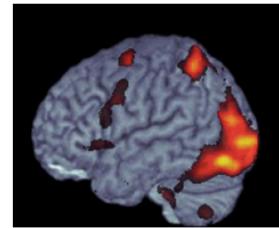
Voxel-wise t-statistic

$$t = \beta / \text{SE}(\beta)$$



3D t-statistic map

72,221 voxels

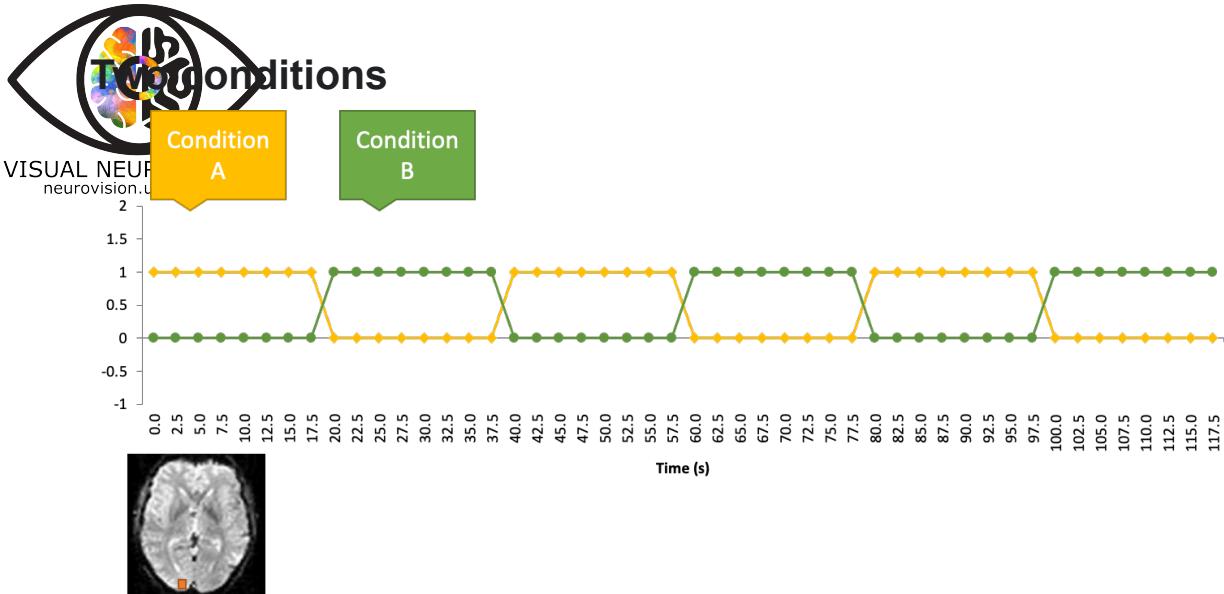


Final result

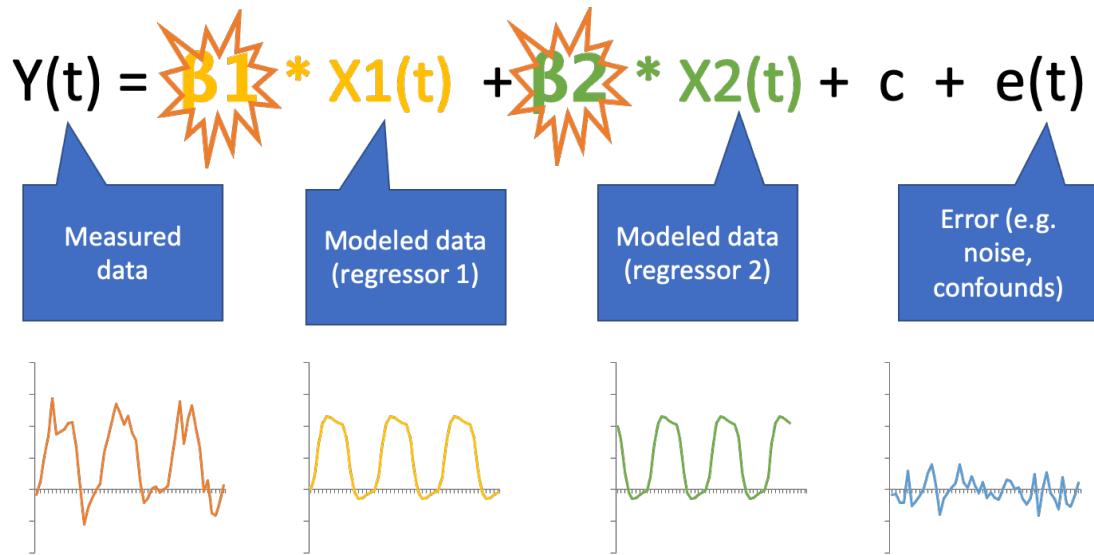
Thresholding:
deal with multiple
comparison
problem!

How do we get from beta estimates to making statistical inference? As in a typical regression, beta estimate divided by its standard error is a t-statistic with a t-distribution. So to know whether an activation in one voxel is significant is relatively straightforward.

If we had just one voxel, we would have computed the t-statistic, and then depending on the degrees of freedom determined if it exceeds the critical value. However, we are doing the same statistical test for MANY voxels. SO the probability that we find a significant voxel simply by chance increases. This is the multiple comparison problem that is encountered anywhere in statistics. In fMRI it is particularly prominent, because the number of single tests is enormous. There are several ways and philosophies for dealing with it, I won't go into details right now. The important thing is that any voxel-wise analysis MUST deal with this problem in some way.

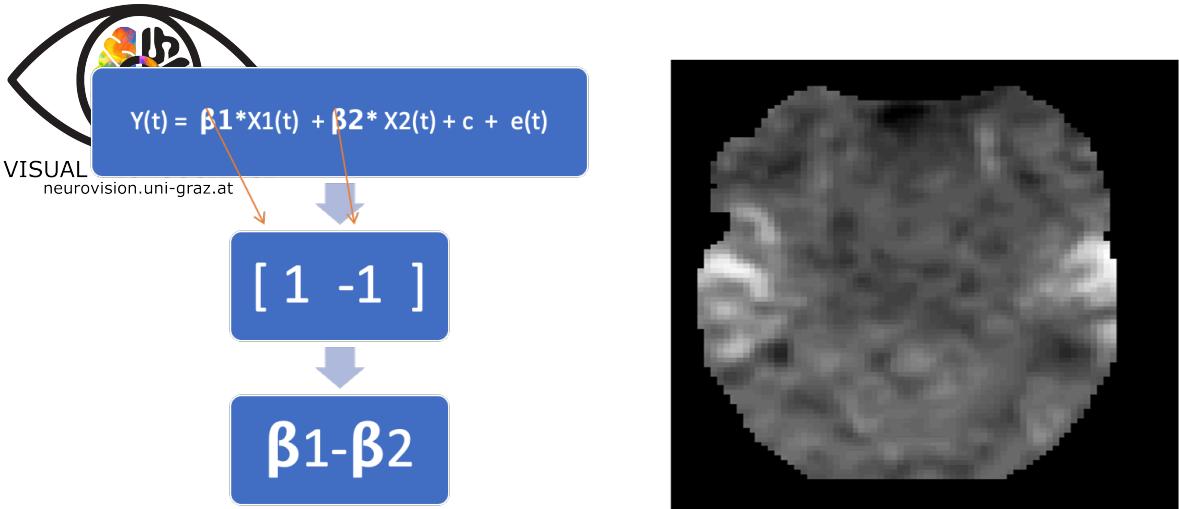


General linear model with two conditions

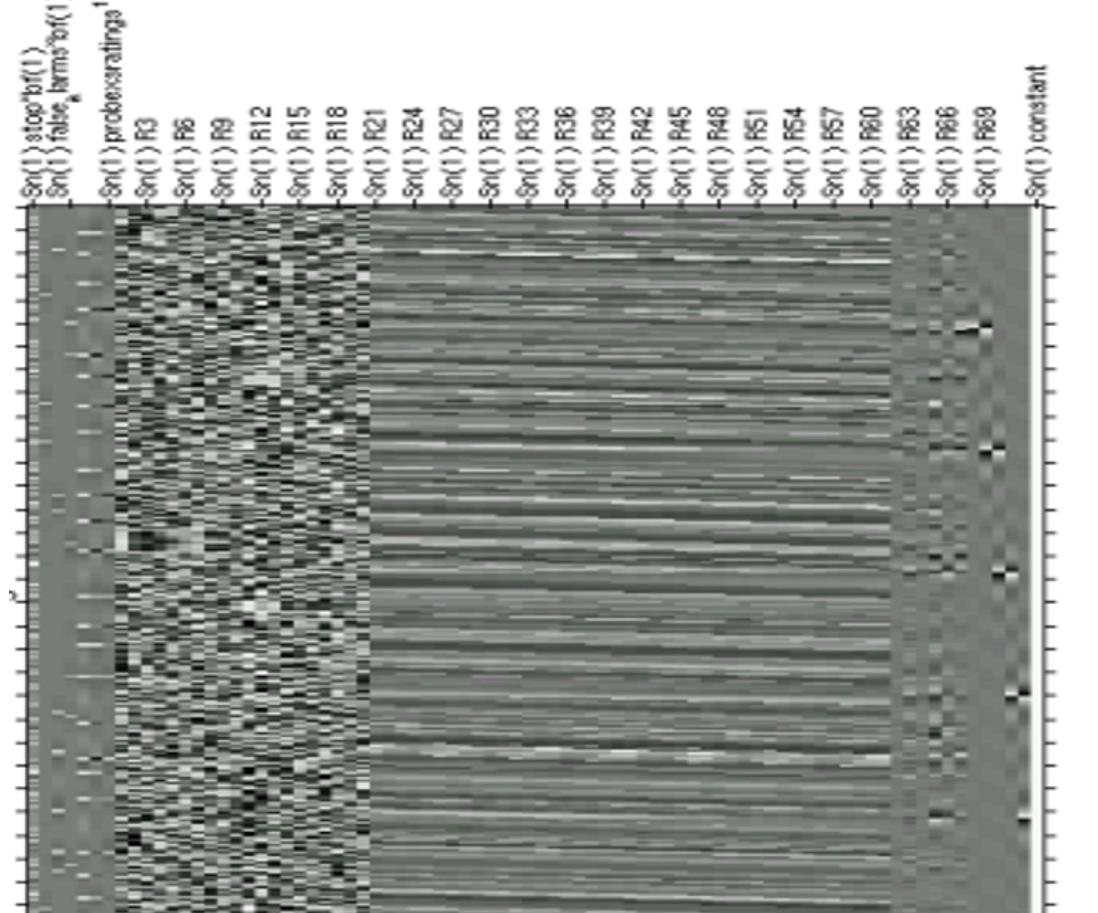


Contrast

A linear combination of beta estimates



GLM advantages

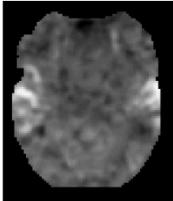




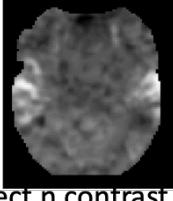
Group analysis

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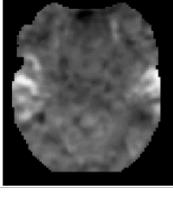
Subject 1 contrast image



Subject 2 contrast image

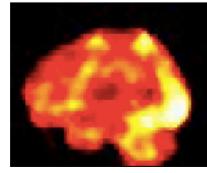


Subject n contrast image

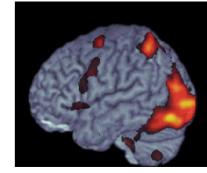


Voxel-wise
one-sample
t-test

Is our
combination
of betas
different from
zero?



3D t-statistic
map

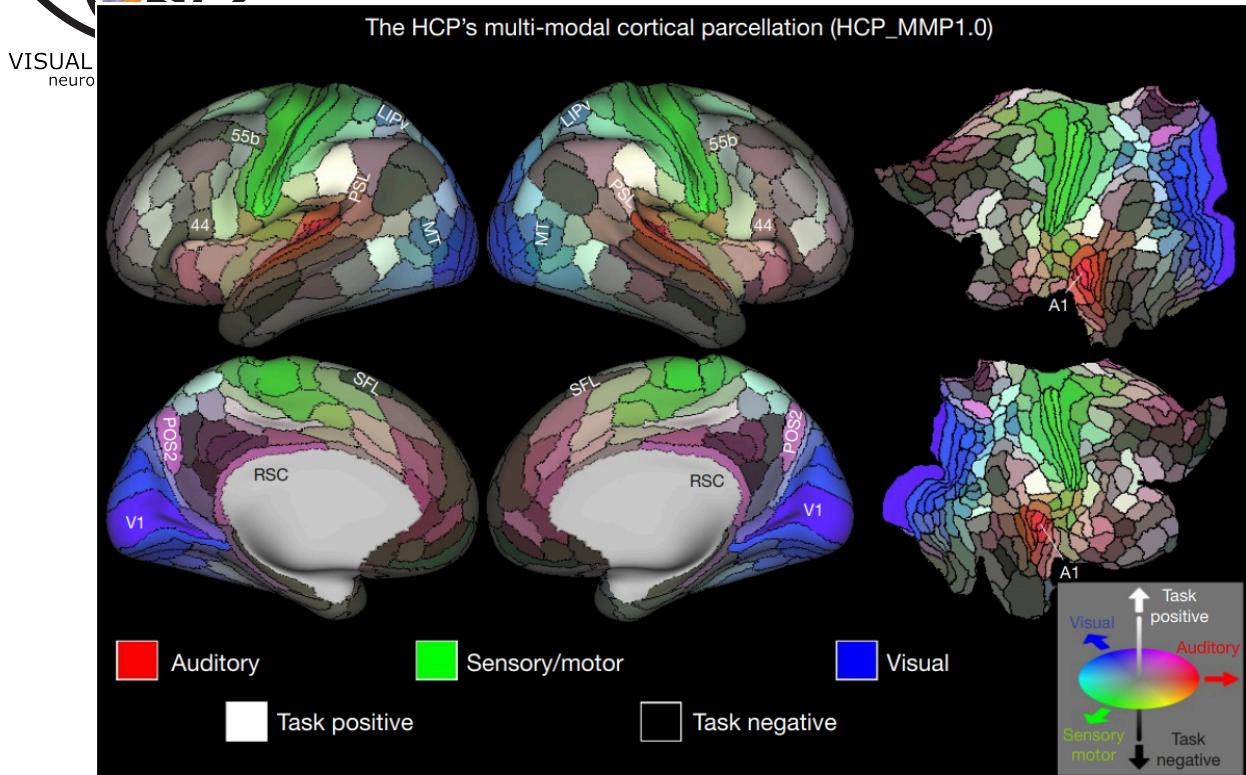


Final result

Thresholding:
deal with multiple
comparison
problem!



Region-of-interest (ROI) analysis



Question: Does the primary visual cortex respond to flickering checkerboards?

HCP cortical parcellation ("Glasser atlas") [9]

ROI analysis is a way to deal with multiple comparison problem. But it requires an a priori and independent definition of an ROI.

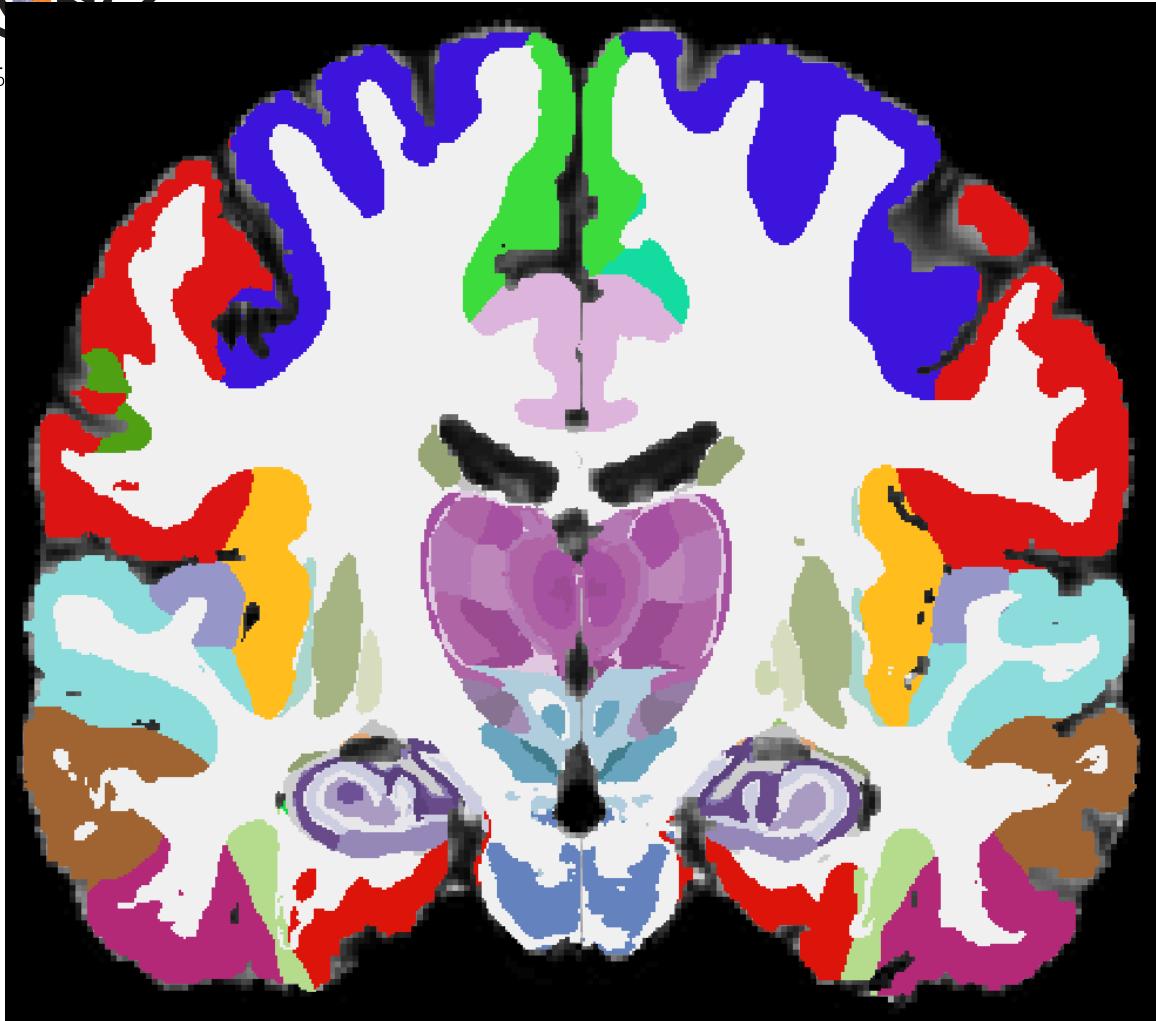
There are two ways to define ROIs:

- From an anatomical scan
- From an additional (separate) functional experiment



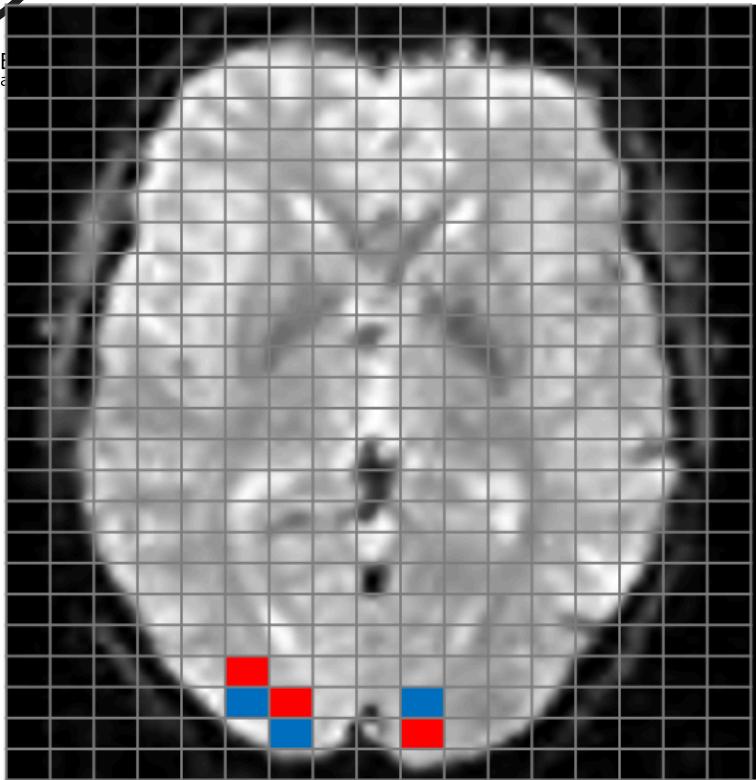
Subcortical ROIs

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NextBrain parcellation containing 333 anatomical structures [10]

This is the state-of-the-art for anatomically-based ROI definition based on deep learning



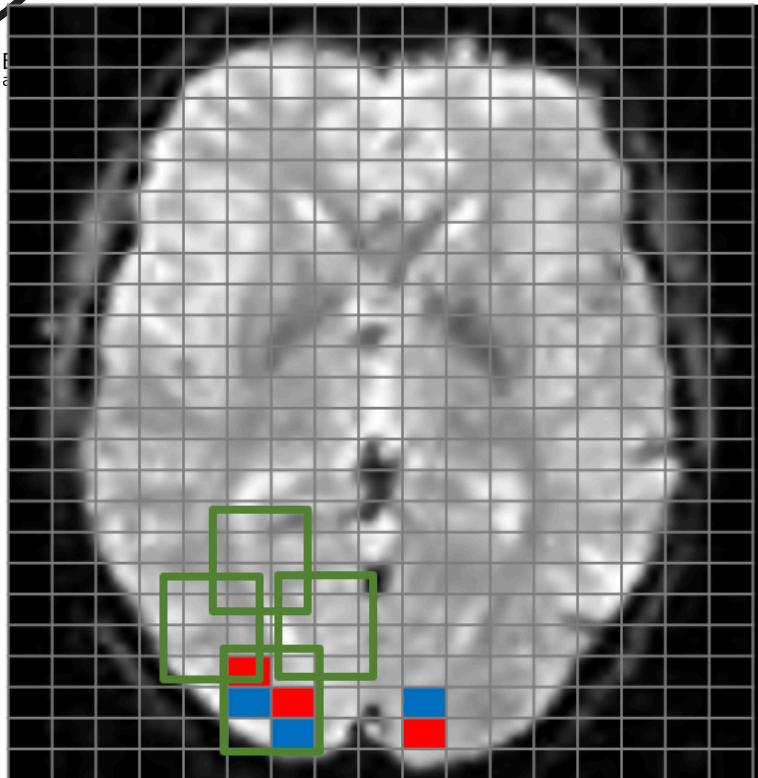
Question: Is the voxel response *pattern* different in condition A and B?

Remember that an image is 4d and consists of little 3d cubes called voxels, with the 4th dimension being time. A classical analysis is done over time for every voxel in the brain independently. In a multivariate analysis we first perform a univariate analysis and then look at response patterns of multiple voxels at a time.

In this example, both coca cola and pepsi activate the same 6 voxels in the visual cortex. But the red ones are activated more by cola than by pepsi, and the blue ones the other way around. If you just look at the average response over 6 voxels, you will not see a difference.



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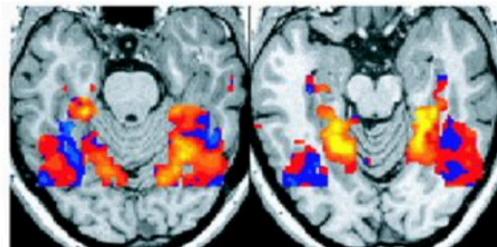
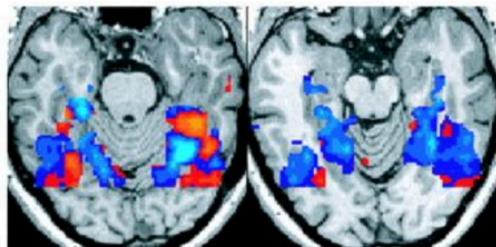
MVPA can be done for a region of interest, or for the entire brain. In the latter case, the brain is subdivided into multiple ROIs, and the relevant analysis is performed for each of them. This procedure is called “searchlight”. In this case, MCC is as relevant as it is in a univariate analysis.



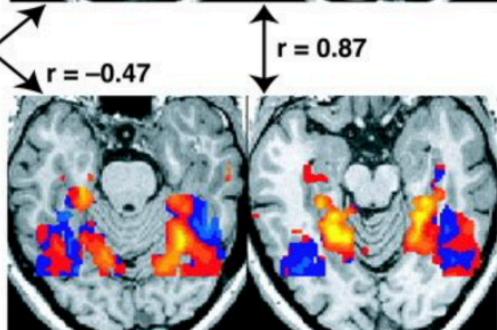
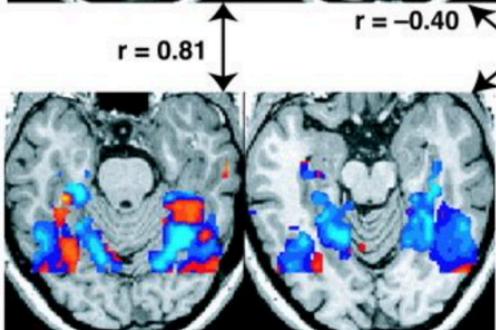
FCMVPA paper

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Even
Runs



Odd
Runs



Response
to Faces



Response
to Houses



Representation similarity analysis [11]

Machine learning

ARTICLES

nature
neuroscience

Decoding the visual and subjective contents of the human brain

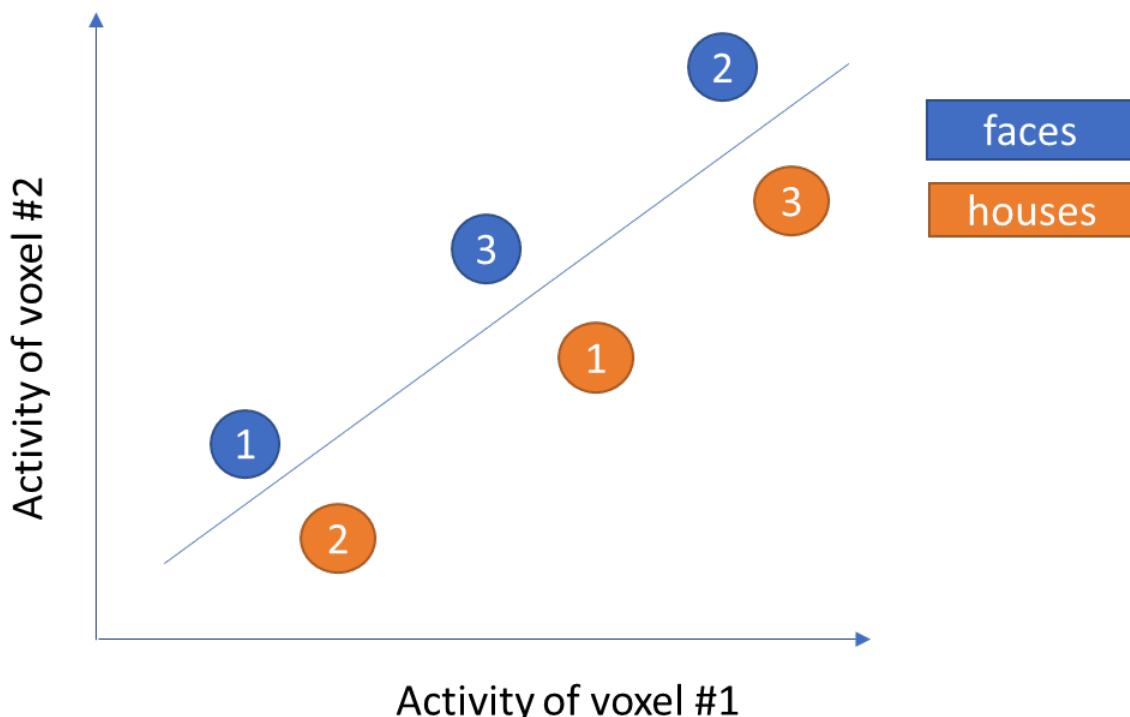
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Predicting the orientation of invisible stimuli from activity in human primary visual cortex

John-Dylan Haynes^{1,2} & Geraint Rees^{1,2}

First MVPA papers, both appeared in 2005 [12], [13]

SVM classifier



Toy example for 2D feature space. Further reading in e.g. Cohen et al. 2017

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