Functional MRI and data analysis
Encoding models

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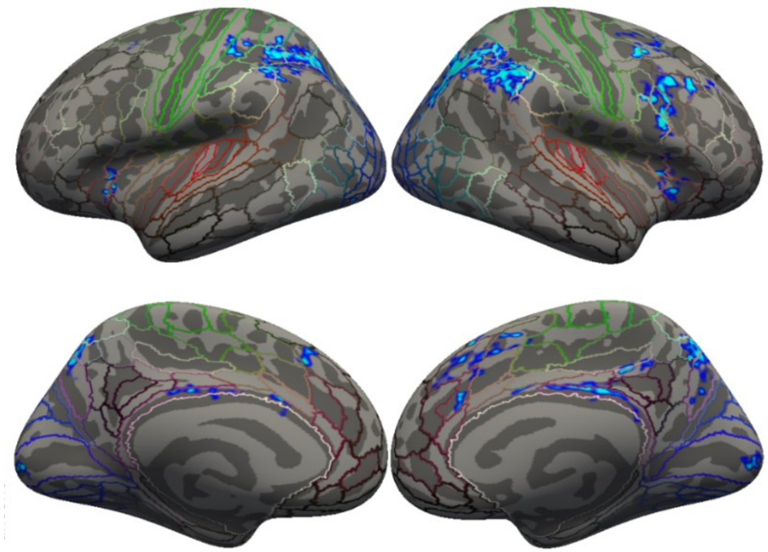
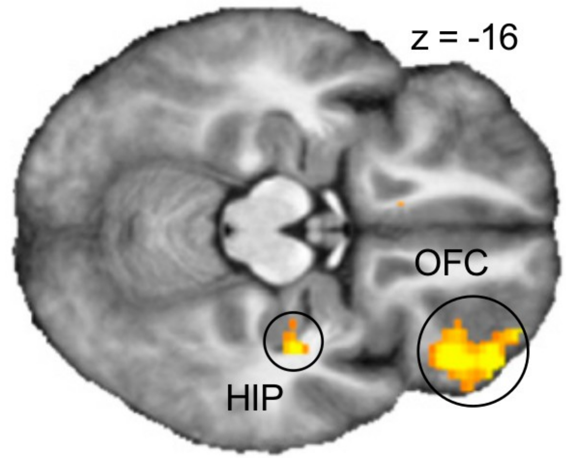


(…) brain regions where activity is significantly correlated with confidence.

Bounmy, Eger & Meyniel (2023)
NeuroImage



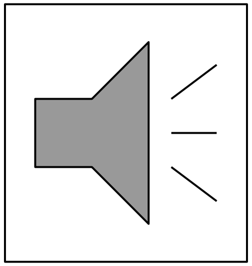
(…) searchlight decoding analysis [was] used to reveal identity-specific value codes

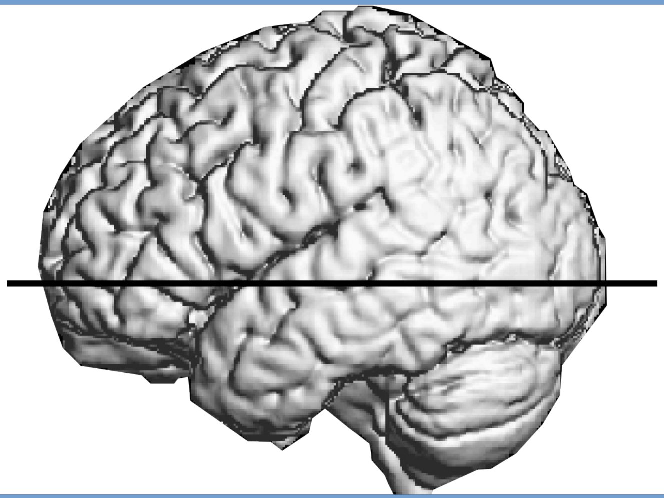
Howard, Gottfried, Tobler & Kahnt (2015)
PNAS

A general distinction: encoding vs. decoding

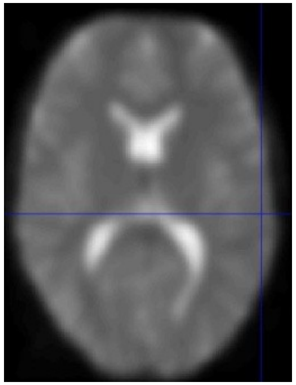
ENCODING
What are the brain responses triggered by this stimulus, task, emotion … ?
(related to: forward models, univariate analysis, GLM, …)

Task and stimuli





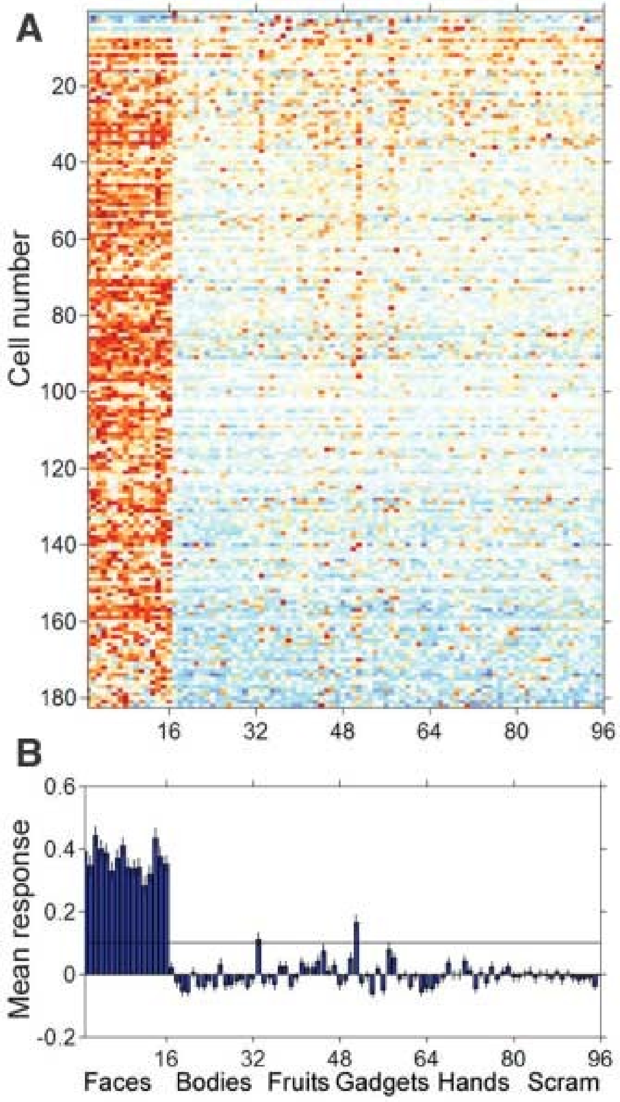
fMRI activity
(gray scale)

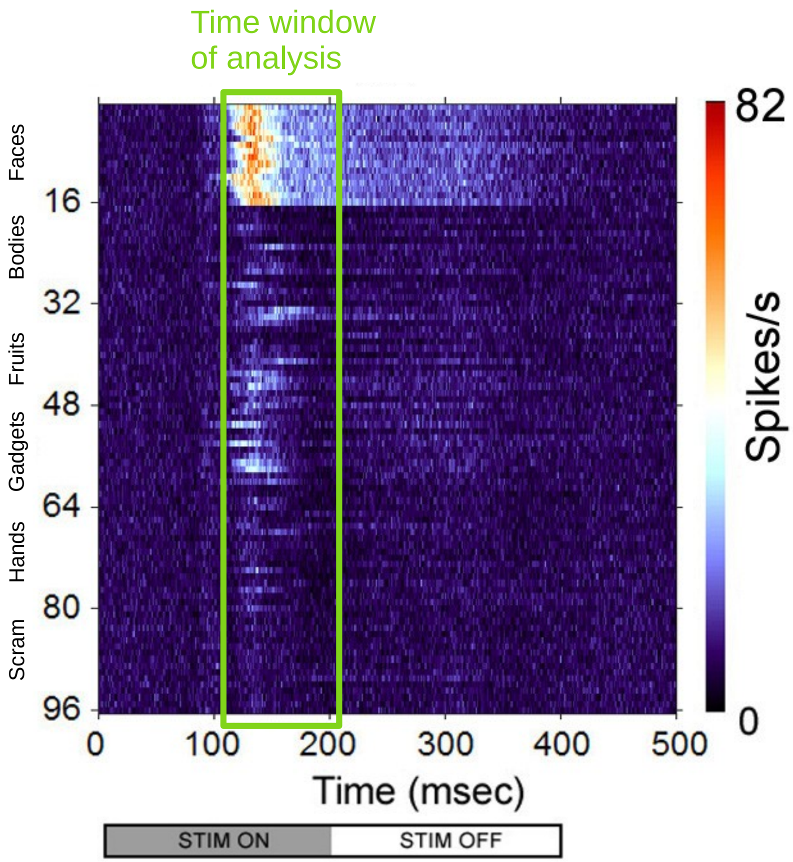


DECODING
What is the likely cause (stimulus, task, emotion …) of this brain response ?
(related to: multivariate pattern analysis, search light, SVM, …)

Typical encoding analysis in neuroscience

Cell responses (firing rate) for each image





Tsao et al, *Science* 2006

I/ Encoding: From neural activity to BOLD signal (forward model)

- The haemodynamic response function
- Predicting the BOLD signal during a simple experiment
- Convolution model for BOLD data

II/ Encoding: Testing effects with mass univariate analysis

- The regression approach: intuition and formalization
- Statistical parametric mapping with mass univariate analysis

III/ Encoding: General Linear Model

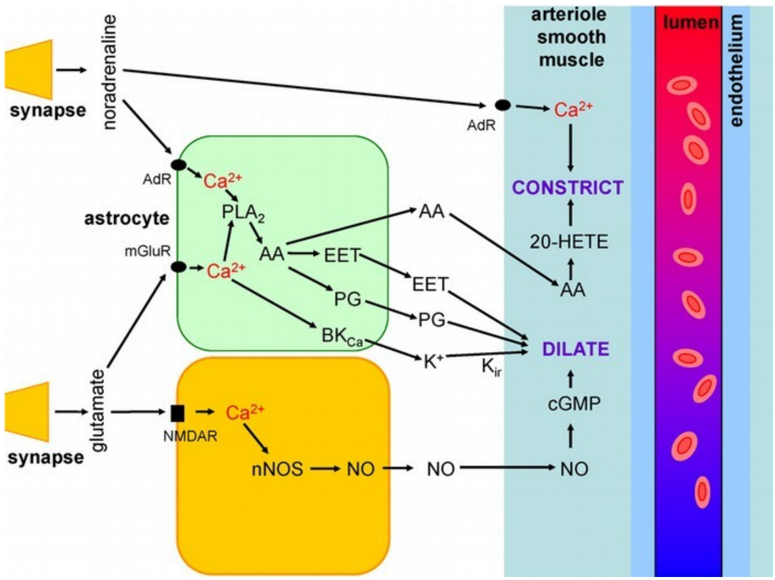
- General linear model (GLM) and design matrix
- Testing the effect of interest with “contrasts”
- Categorical and parametric regressors
- Subject and Group level analyses

IV/ The problem with multiple comparisons

- Multiple testing inflates the risk of having a false positive
- Statistical methods to correct for multiple comparisons

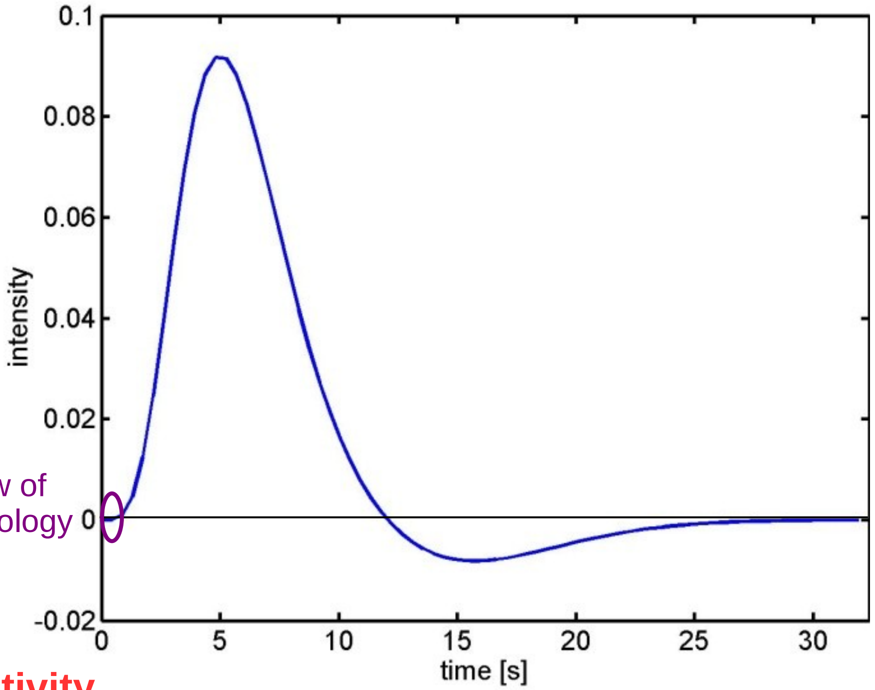
Applying encoding analysis to fMRI signal is difficult because the fMRI signal is slow and delayed

Stimulus → Neural activity → BOLD signal



Harris, Reynell, Attwell (2011)

BOLD response (a.k.a. *haemodynamic response function)*

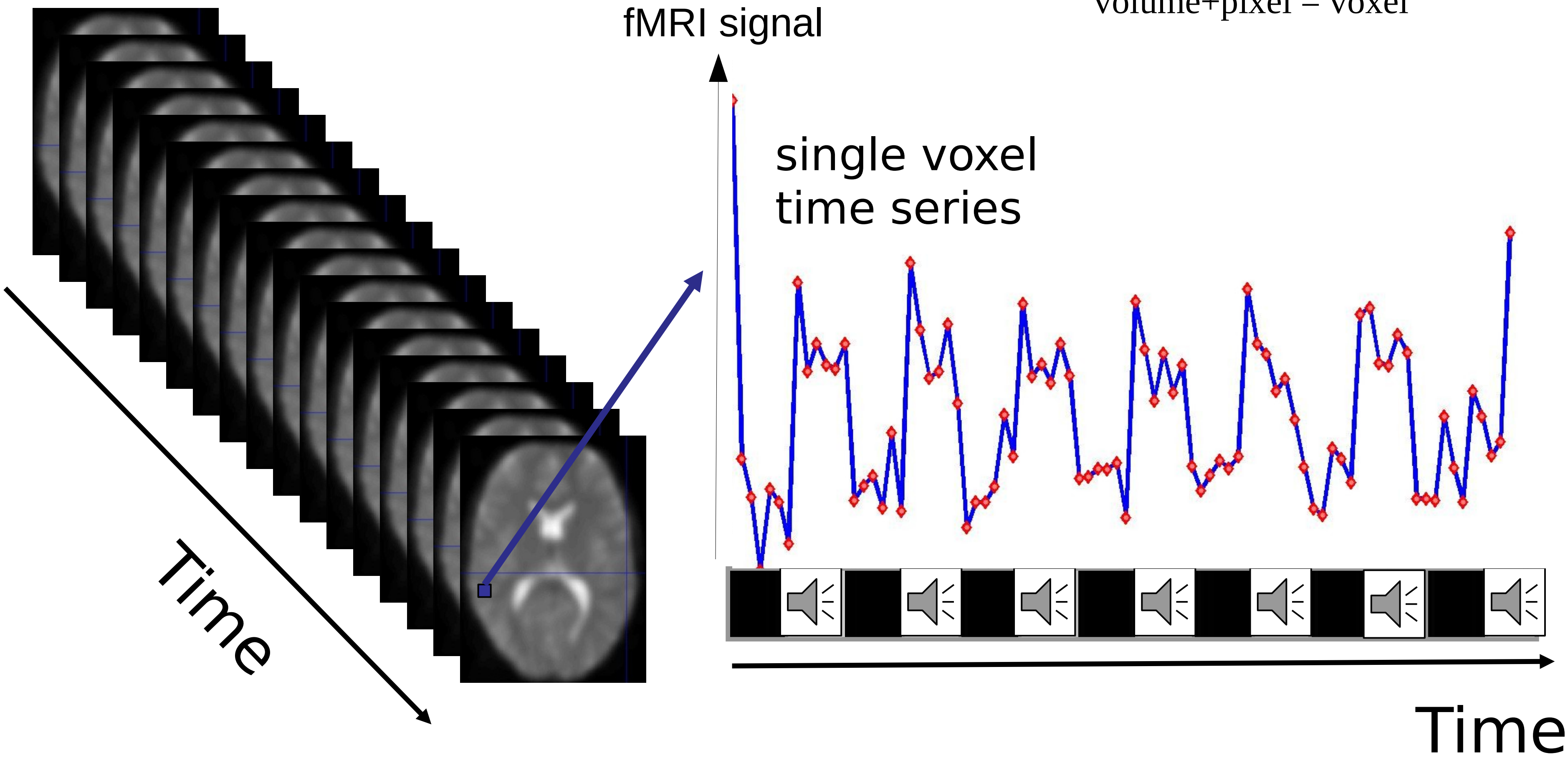


Neural activity

→ Encoding analysis of fMRI signal must be analysis of *timeseries*

Starting with an example

voxel = point in the MRI image
"volume+pixel = voxel"



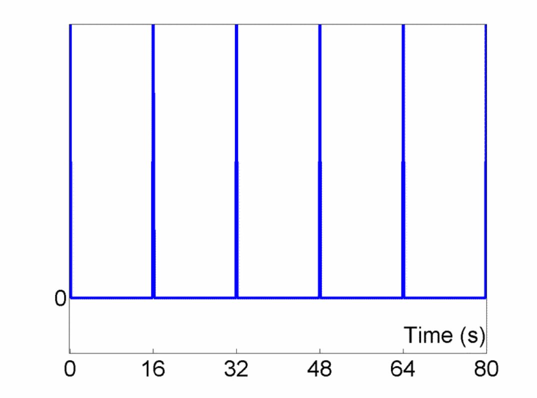
Example question: What are the brain regions (i.e. voxels) whose activity increase when a sound is played?
fMRI data are noisy timeseries, answering this question requires modeling and a statistical approach.

Adapted from: SPM courses

Predicted BOLD responses in a simple experiment

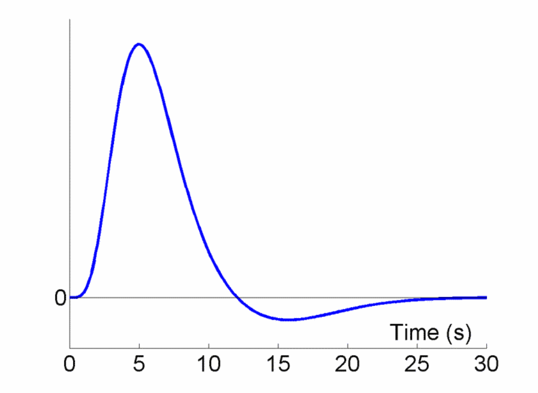
Task: every 16 s, a sound is played.

Expected neuronal activity
in the auditory cortex



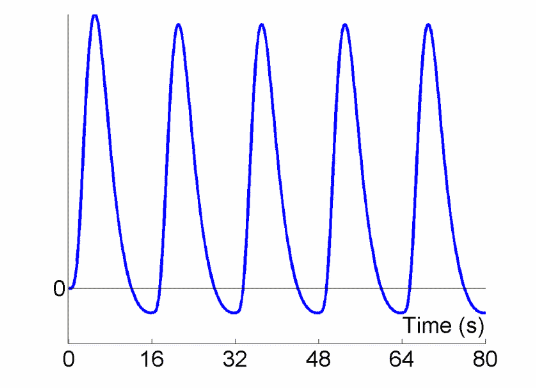
$\otimes$

Expected BOLD response for a
single, transient neural event



$=$

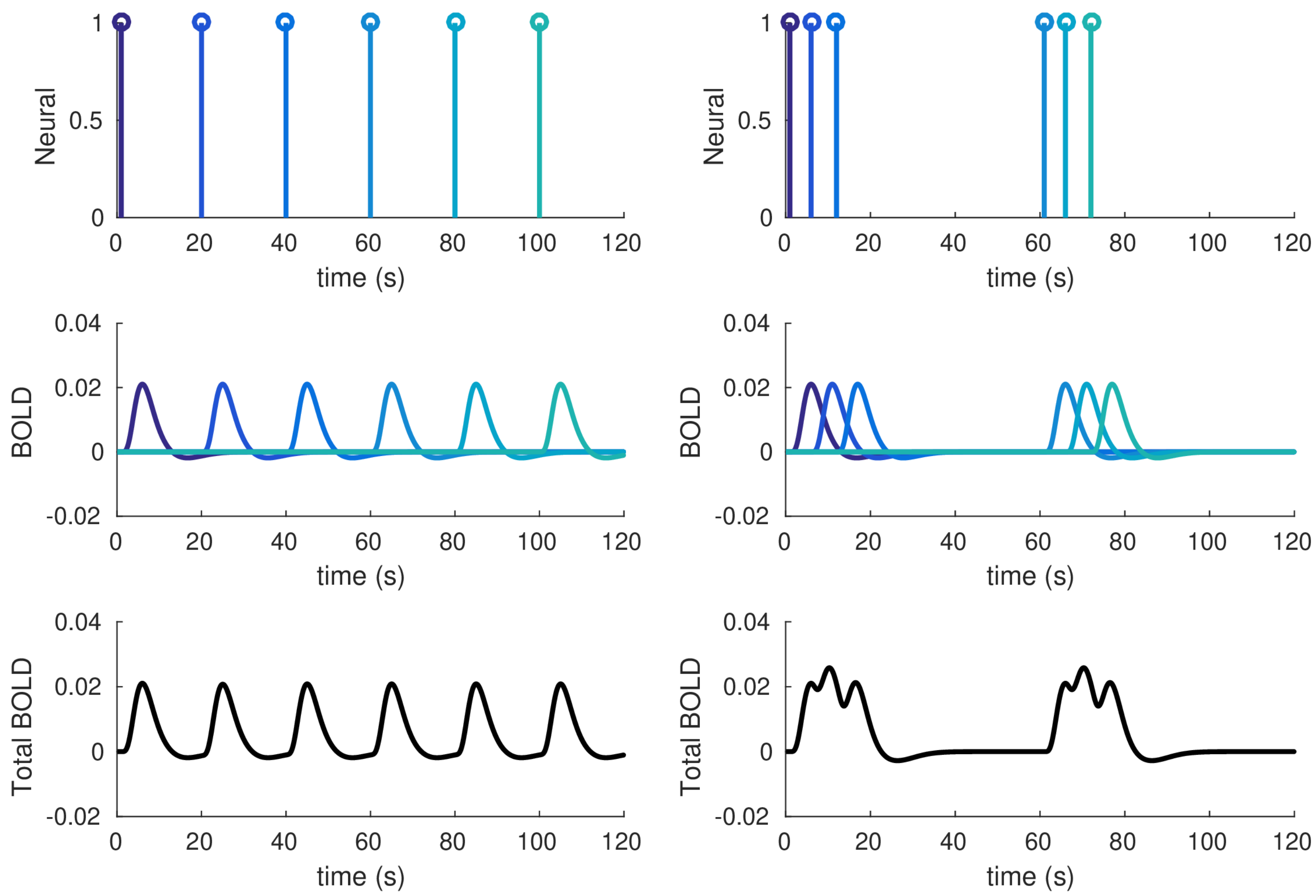
Expected BOLD timeseries in
the auditory cortex



In standard fMRI analyses, we assume that the observed BOLD signal is the superposition of (= the sum of) the BOLD responses evoked by every single neural event.

Mathematically, the expected BOLD signal is therefore the timeseries of neural activity convolved with the hemodynamic response function.

Overlap of BOLD responses in fast designs



Implications:

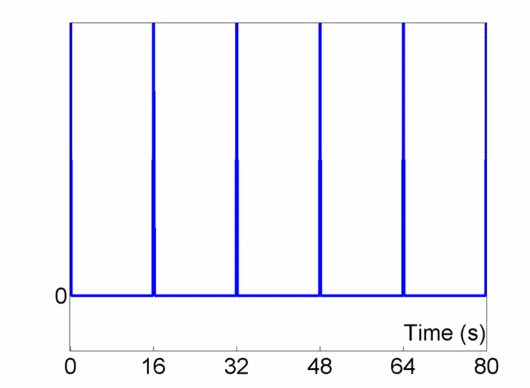
- some experimental designs are better than other (e.g. some neuronal effects may be completely smoothed out at the BOLD level)
- Even in very simple designs, events of interest generate time series of observations (sampled by each repetition of the fMRI measurement).

→ example #1 in the notebook

From neuronal effects to timeseries of BOLD data: The power of forward modelling

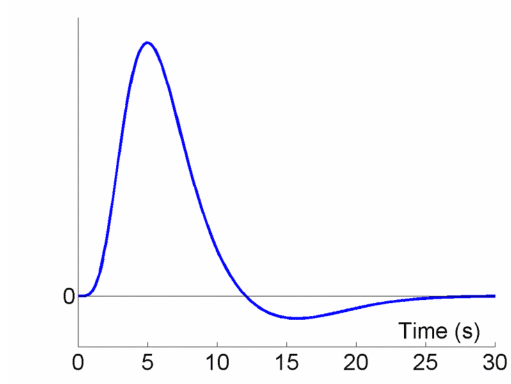
FORWARD MODEL OF OBSERVATIONS

Expected neuronal activity in the auditory cortex



$\otimes$

Expected BOLD response for a single, transient neural event



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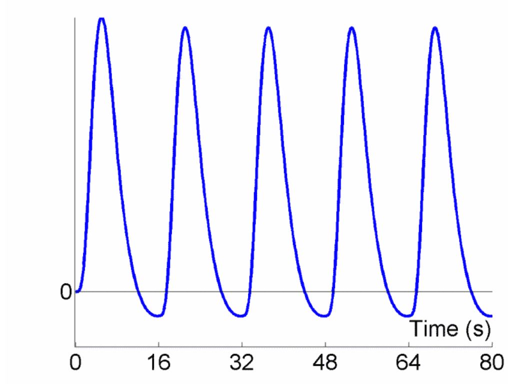
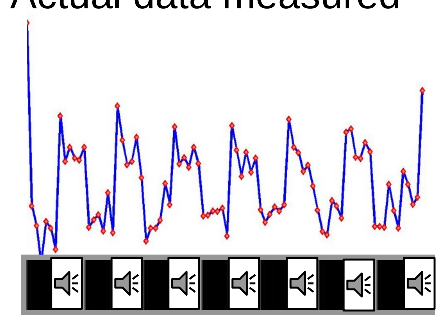
Expected BOLD timeseries in the auditory cortex



Match ???

Actual data measured



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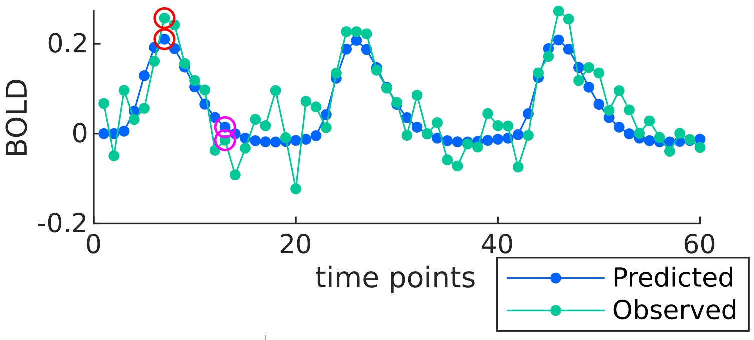
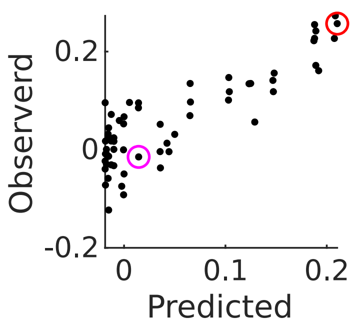
From neuronal effects to timeseries of BOLD data: The regression approach

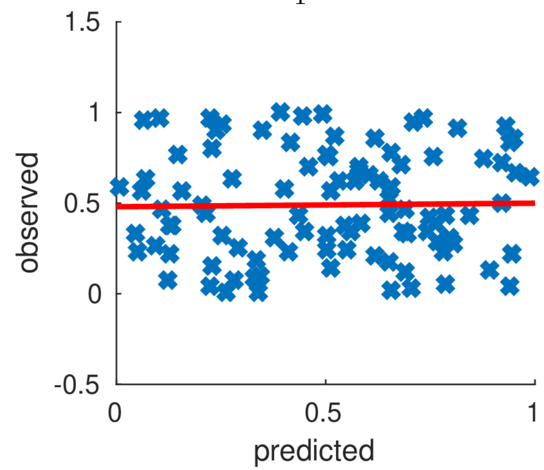
Compare predicted and observed time series



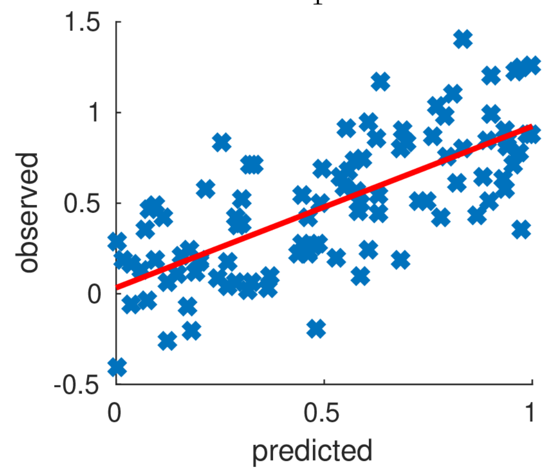
Re-plot X(t) and Y(t)
As X vs. Y



Example: no effect
($\beta_1 \approx 0$)



Example: an effect!
($\beta_1 \neq 0$)



Observed data

Predicted value

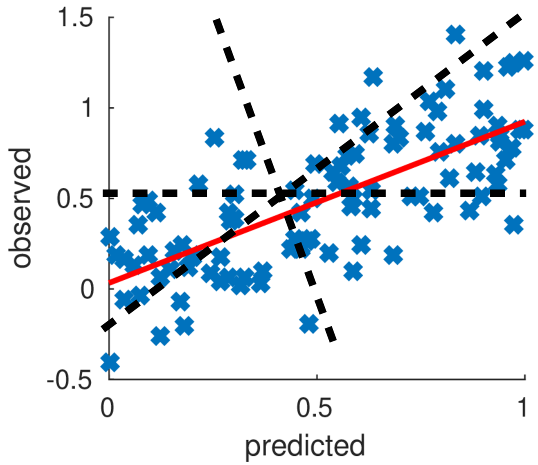
Error (what is not captured by the prediction)

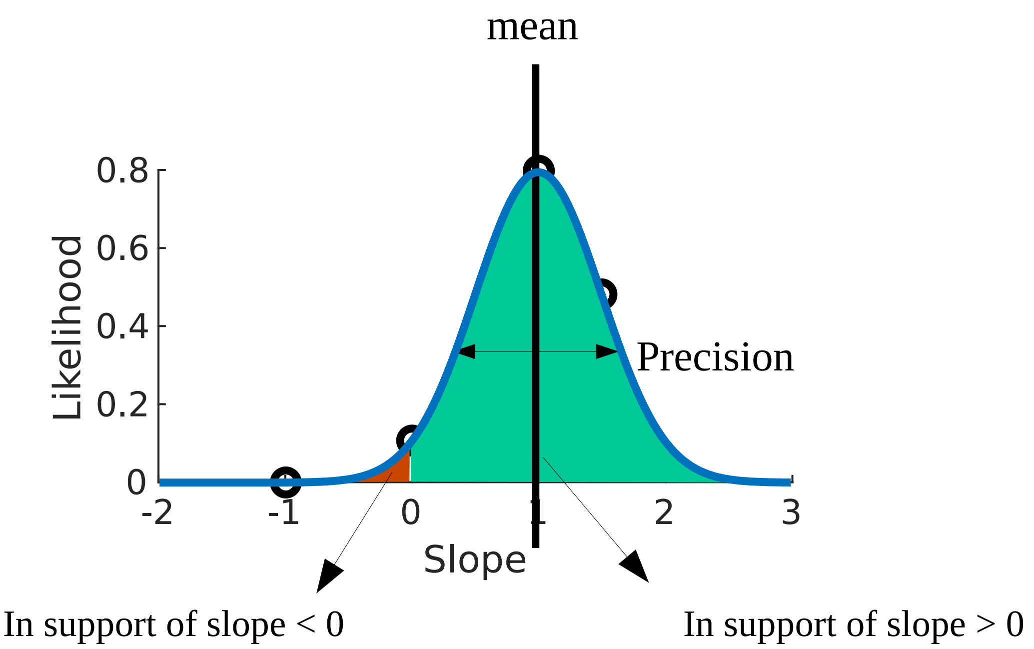
$$y = \beta_0 + \beta_1 x_1 + \varepsilon$$

“intercept”

“slope”

Quantifying the significance of a regression
The Student T-test: a signal-to-noise measure to quantify “Is β different from 0 ?”





The Student T-test tests whether the (central) value of a noisy variable, observed through a limited number of data points (X), is non-zero.

T-value = β / SE[β] : more extreme values indicate that mean(X) ≠ 0

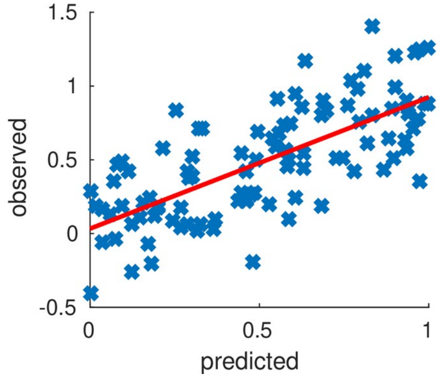
estimated slope

standard error of the slope
= ratio of standard deviations of residuals and predictor, weighted by the number of observations

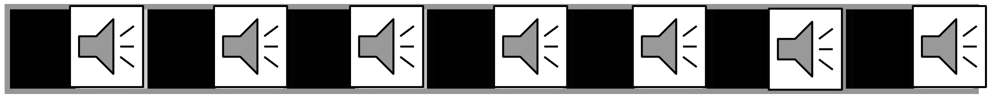
$$\frac{1}{\sqrt{n-2}}\frac{\sigma_{res}}{\sigma_{predictor}}$$

The regression approach applied to the entire brain: statistical parametric mapping and the mass univariate approach

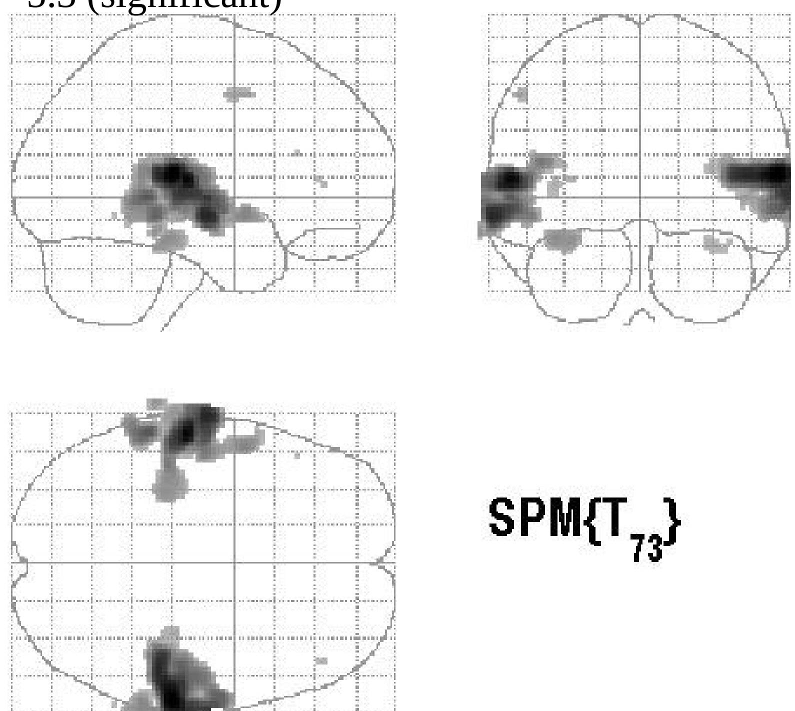
1 voxel

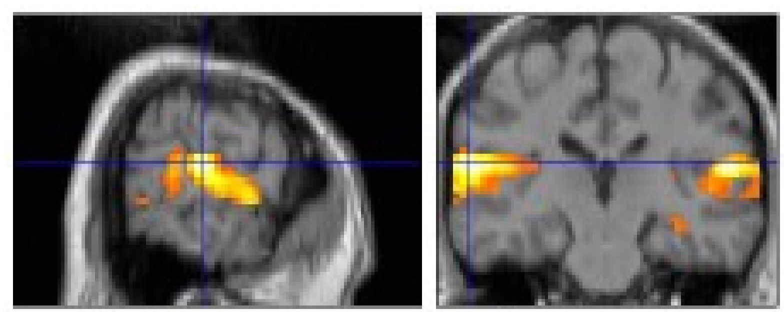


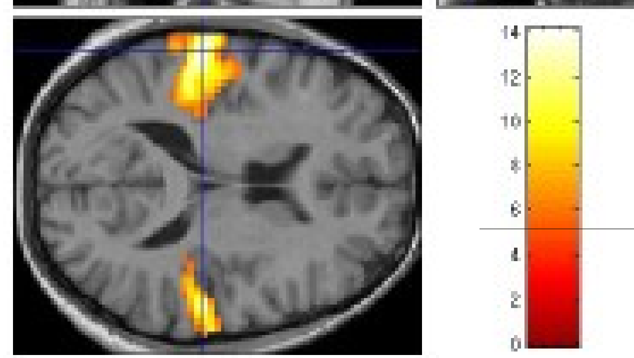
The sound modulates activity
T=5.3 (significant)



What are the brain regions whose activity is modulated by the sound?
→ Repeat the same analysis for all voxels (mass univariate approach).







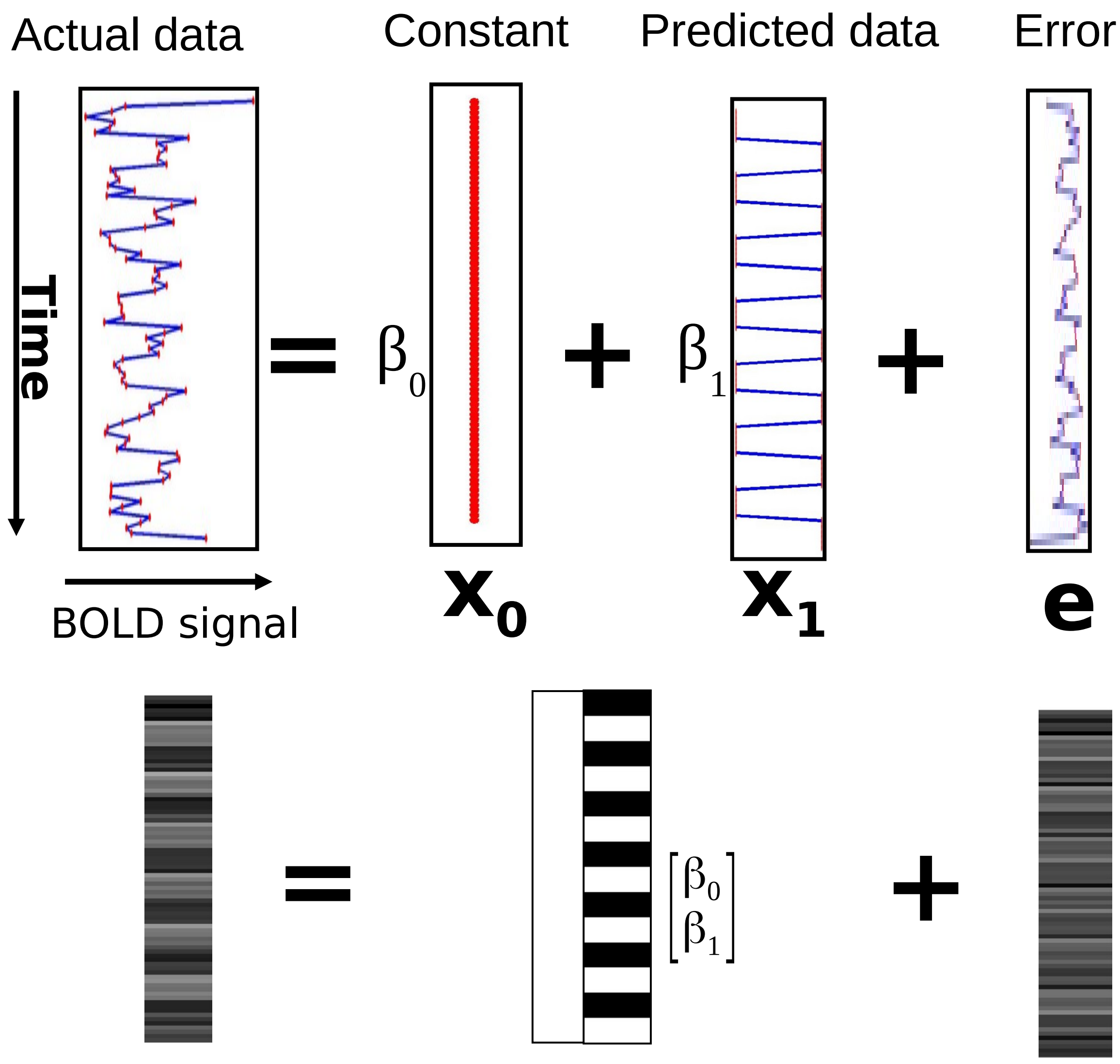
Visualization is thresholded for significance (only the most significant voxels are shown)

→ examples #2, #3 in the notebook

Adapted from: SPM courses

Modelling BOLD response in a task: Matrix notations for regression and the General Linear Model (GLM)

$$y = \beta_0 + \beta_1 x_1 + \varepsilon$$

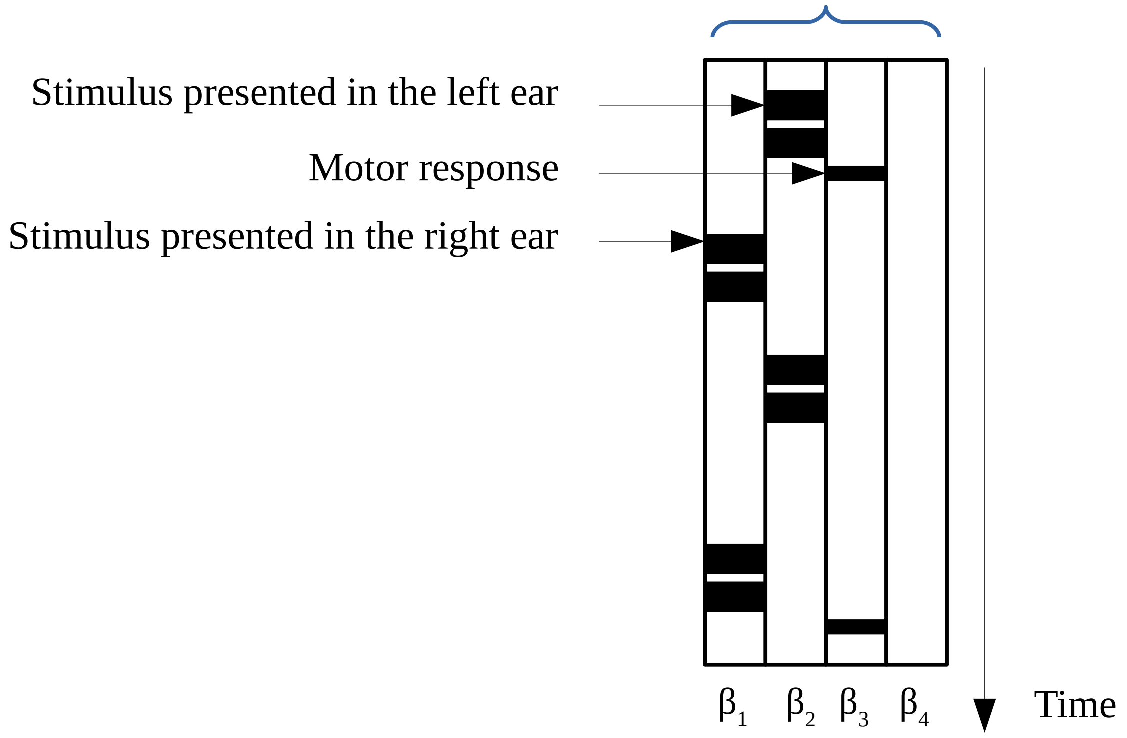


$$Y = X\beta + \varepsilon$$

Adapted from: SPM courses

Modelling BOLD response in a task: The “design matrix” models observations as a linear combination of factors (multiple regression)

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



The model of observations is estimated by finding the best-fitting values for the β parameters.
The least-square estimates (those that minimize the residual sum-of-square):

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

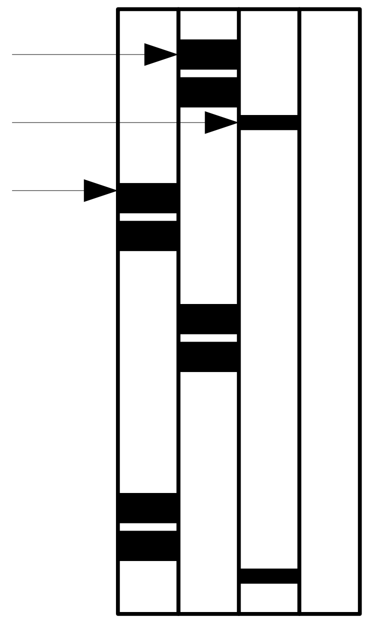
NB: the error should be normally, identically and independently distributed

→ data are spatially smoothed (it improves many aspects, including the issue of normal errors)

→ data must be “whitened” to remove the temporal autocorrelation of the data (which is inherent given the BOLD response)

From neuronal effects to timeseries of BOLD data: Testing effects with linear contrast

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



$C^T = [0 \quad 0 \quad 1 \quad 0\ ]$ Contrast testing for more activity when there is a motor response (is $\beta_3 > 0$?).

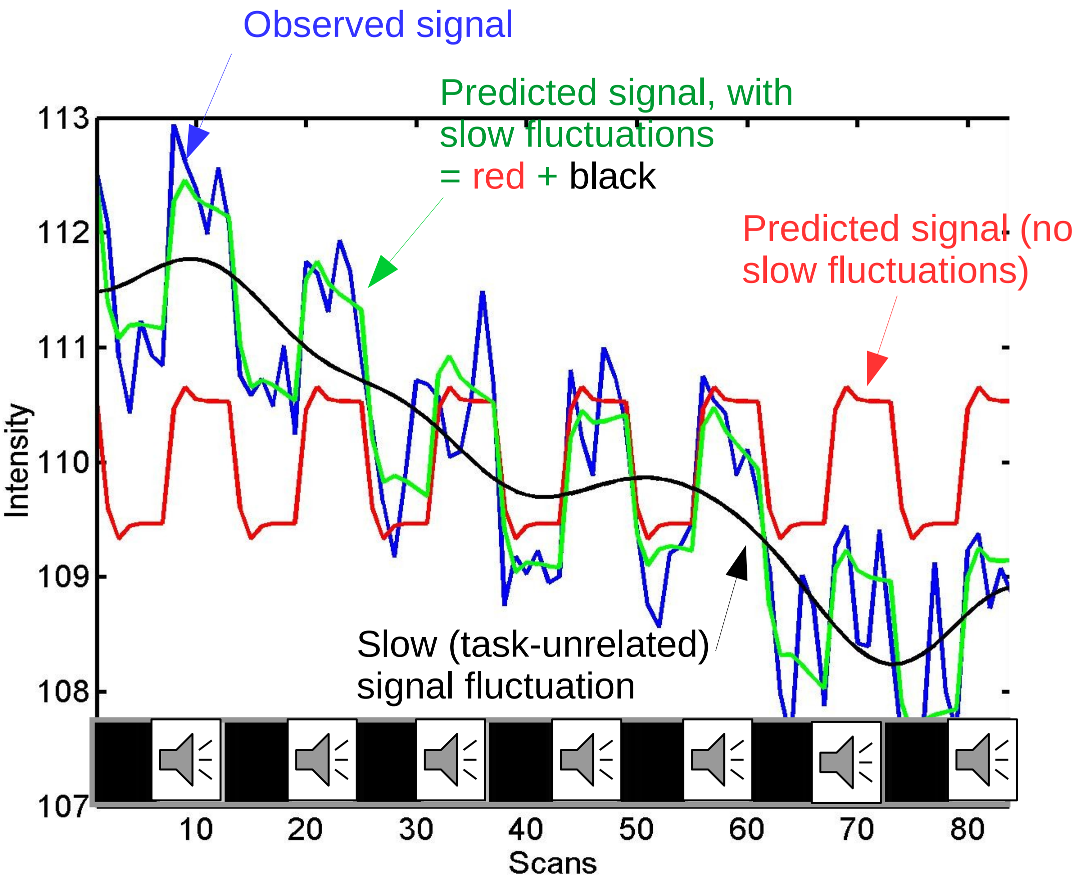
$C^T = [1 \quad -1 \quad 0 \quad 0\ ]$ Contrast testing for more activity when the stimulus is presented on the right compared the to left (is $\beta_1 > \beta_2$?)

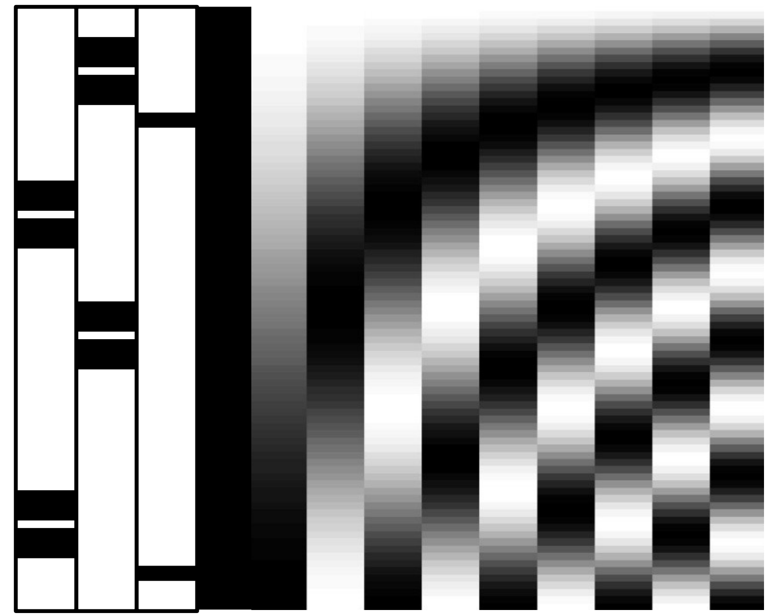
Statistical test: is $c^T\beta \neq 0$?
→ Use a Student T-test.

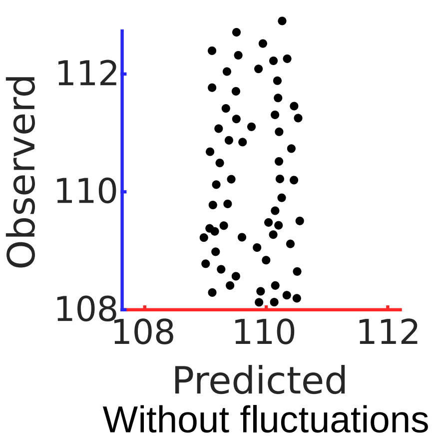
$$T = \frac{c^T \hat{\beta}}{\sqrt{\hat{\sigma}^2 c^T (X^T X)^{-1} c}}$$

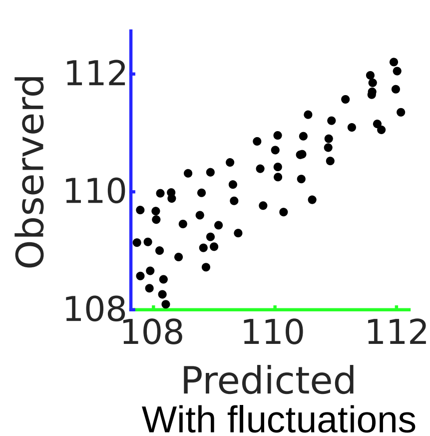
NB: σ^2 is the residual variance
→ any effect that can be accounted for should be included in the design matrix

From neuronal effects to timeseries of BOLD data: Include covariates in the design matrix





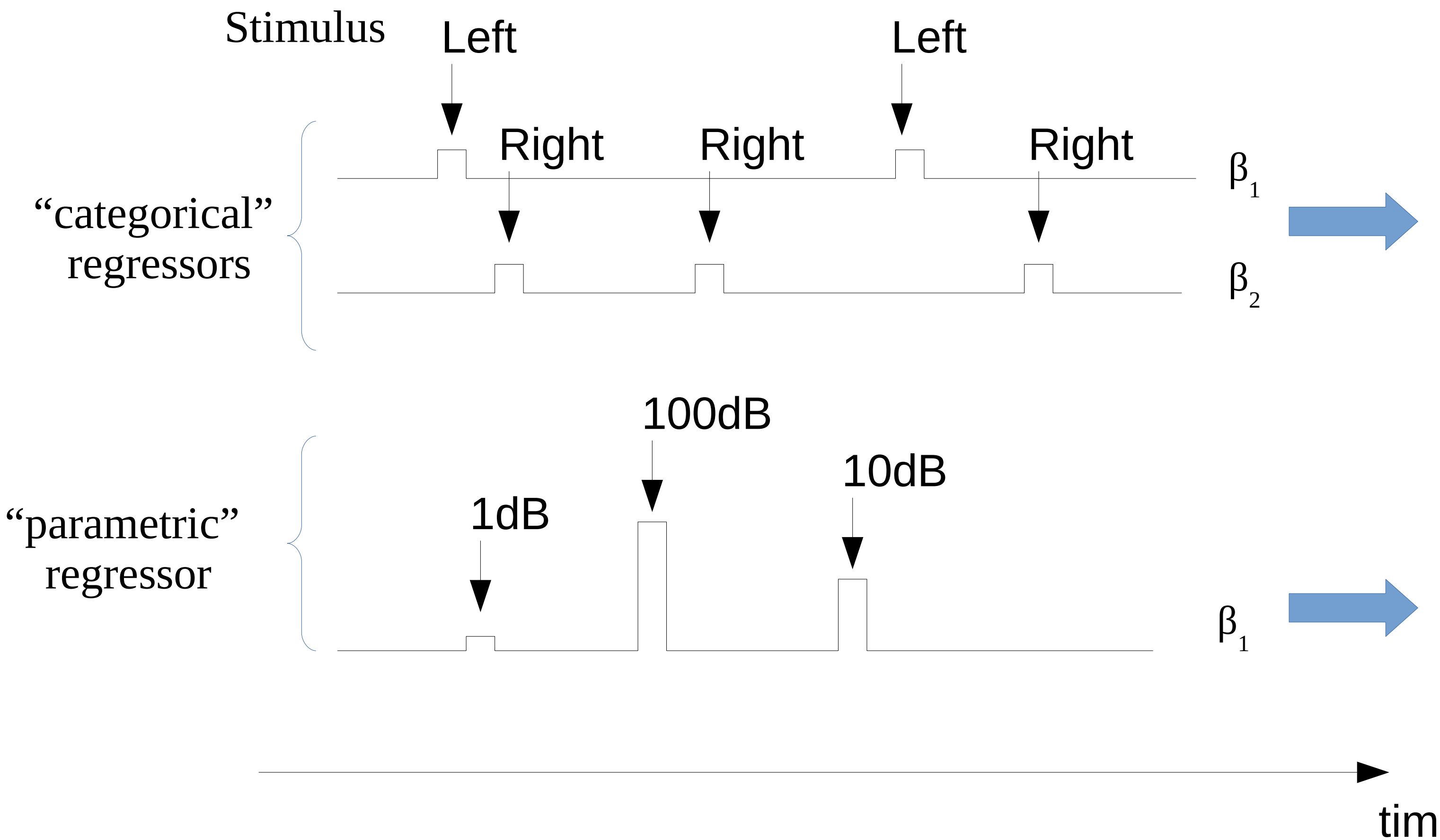




The fMRI signal is often corrupted by slow drifts (instability of the scanner)

Other “confound” variables typically included: subject's motion parameters

GLM: A conceptual distinction between categorical regressors and parametric regressors



Example question

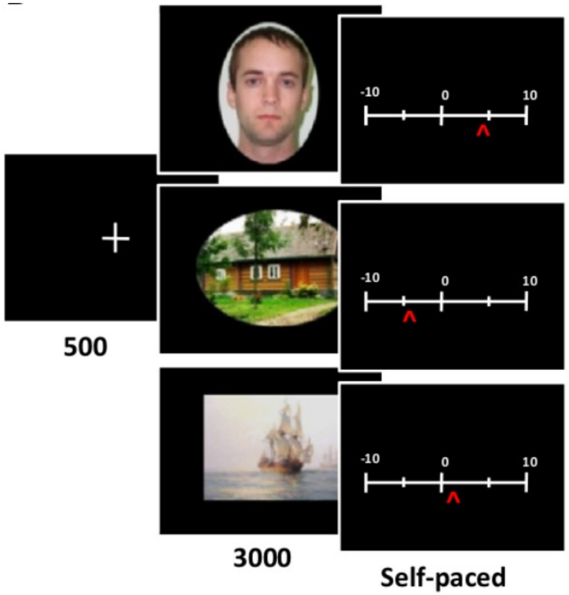
Which brain regions are more activated by sound coming from the left than coming from the right? $\beta_1 > \beta_2$

Which brain regions are more activated by louder sounds? $\beta_1 > 0$

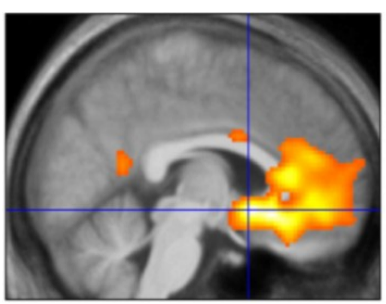
In the end, both types boil down to a regression of time-series in the GLM...

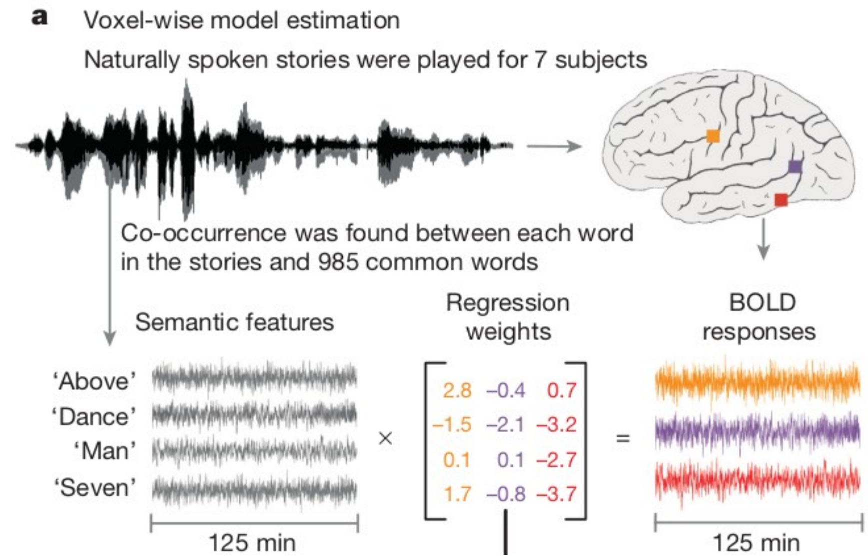
"Parametric" regressors may reflect a property of the stimulus,
or some variable computed from a model of cognitive function

Simple vs. sophisticated parametric regressors

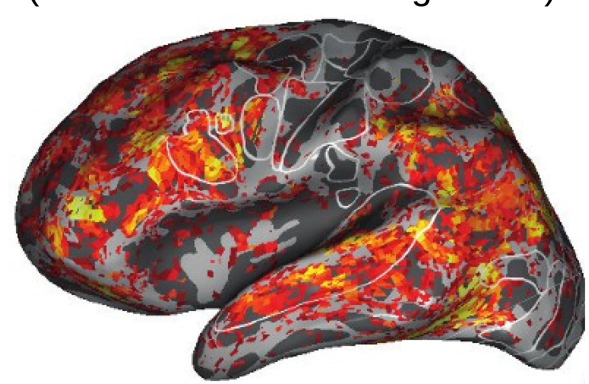


Parametric regressor: value rating





Parametric regressors: semantic features (from a word embedding model)



Lebreton et al, *Neuron* 2009

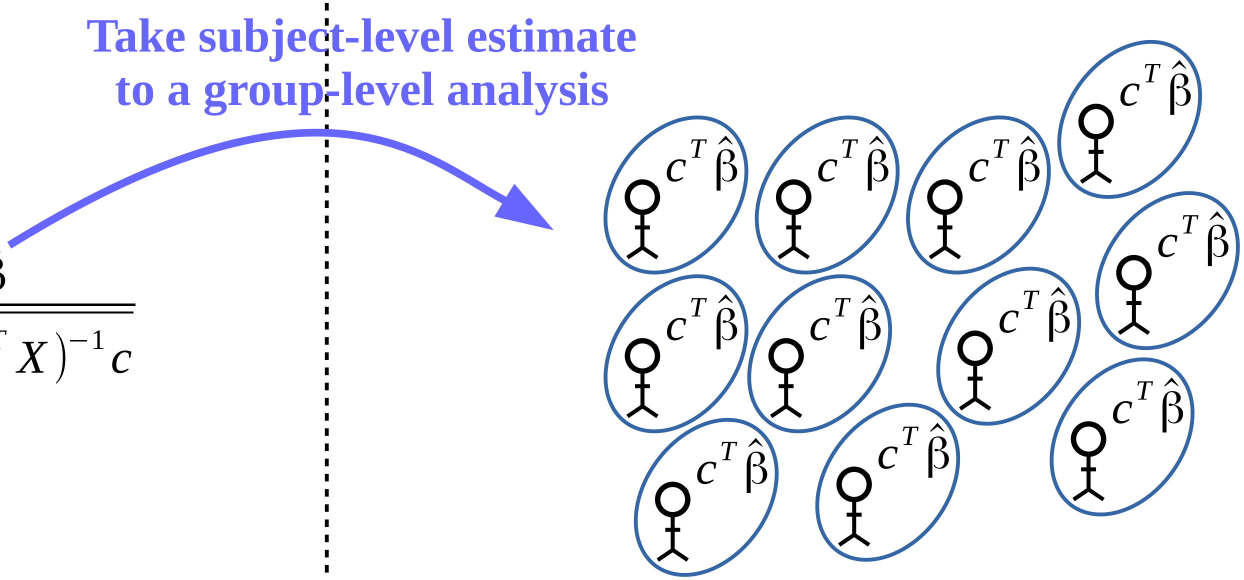
Huth et al, *Science* 2016

Subject-level and group-level analyses

Subject Level

$$T = \frac{c^T \hat{\beta}}{\sqrt{\hat{\sigma}^2 c^T (X^T X)^{-1} c}}$$

Group Level



$$T = \frac{MEAN\,(c^T \hat{\beta}_i)}{SEM\,(c^T \hat{\beta}_i)}$$

Is the effect consistently different from 0 across subjects?

NB1: This method ignores the variance (σ) of the parameters from different subjects. Mixed-models and hierarchical models can take into account the subject-level variance for the group-level inference.

NB2: To compare different subjects voxel-wise, the anatomy first needs to be “**normalized**”, i.e. aligned with one another. Usually, they are realigned to a standard anatomical space (e.g. MNI) so that a given voxel can be compared across studies. “functional alignment” is an alternative (e.g. Haxby et al, 2020 *eLife*)

The flexibility of General Linear Models

The GLM approach allows different statistical methods:

- Student T-test: Is my effect $E_1 \neq 0$? Is effect $E_1 > E_2$?
- Categorical variables and continuous variables
- F-test (ANOVA): Is there a difference between any level of factor E_1 (one-way ANOVA)? Is there a difference between any level of factor E_1 while controlling for the effects of E_2 , … E_N (N-way ANOVA)
- T-test and F-test can be performed at the subject-level and at the group-level.

→ This is why we say *General* linearl models

Comparison of the multivariate and univariate approaches

Univariate / encoding	**Multivariate / decoding**
Look at voxels independently from one another	Look at the information conveyed jointly by multiple voxels
Look for spatially smoothed signal	Look for spatially structured signals
Based on a regression approach	Based on a classification approach (+ extension for continuous variables)
One must fully specify the type of representation looked for	The classification automatically extracts the relevant features
Statistics: T-test, F-test (parametric or not)	Statistics: classification/prediction accuracy
Computationally cheap. Parametric tests suffice	Computationally expensive. Requires permutation, cross-validation

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It is likely that a rare event occurs if you try multiple times

Bet 1

You throw a pair of dice.
I give you 10€ if you have a double 6.
You give me 10€ otherwise.

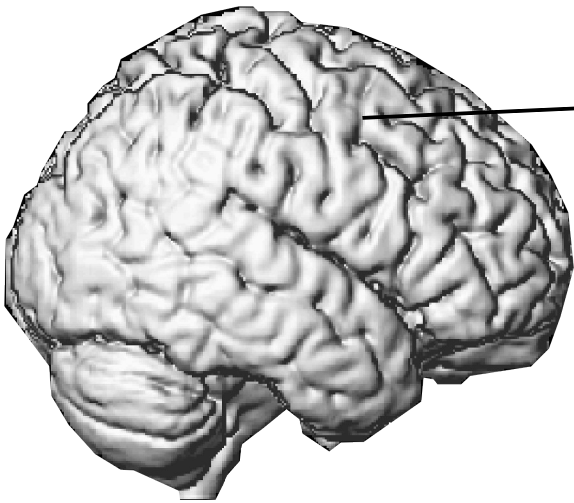
Probability that I win:
$1-(1/6)^2=97\%$

Bet 2

You throw a pair of dice 100 times.
I give you 10€ if you have a double 6 at least once. You give me 10€ otherwise.

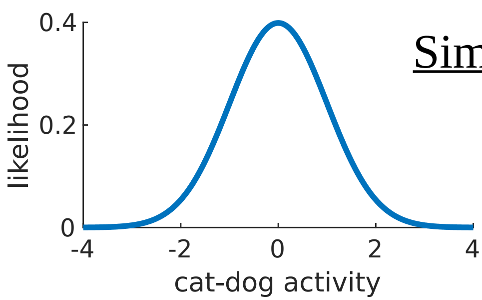
Probability that I win:
$[1-(1/6)^2]^{100}=6\%$

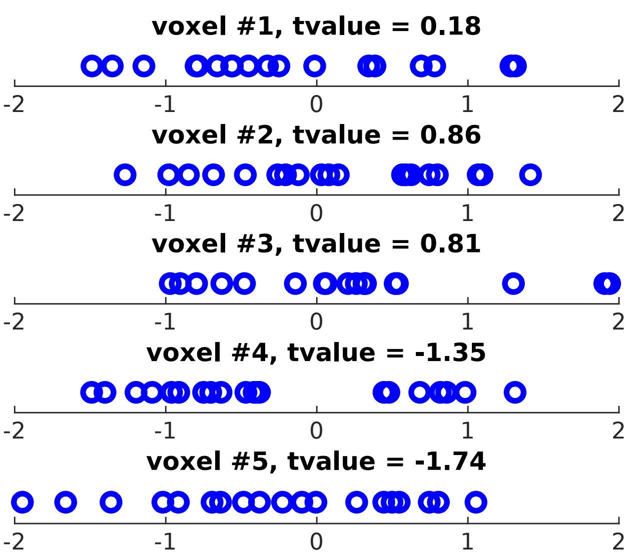
The problem of multiple testing across voxels



You find a voxel with different activity for “tone” and “no tone” in 20 subjects, at t=2.3 (p=0.016, one-tail t-test)!

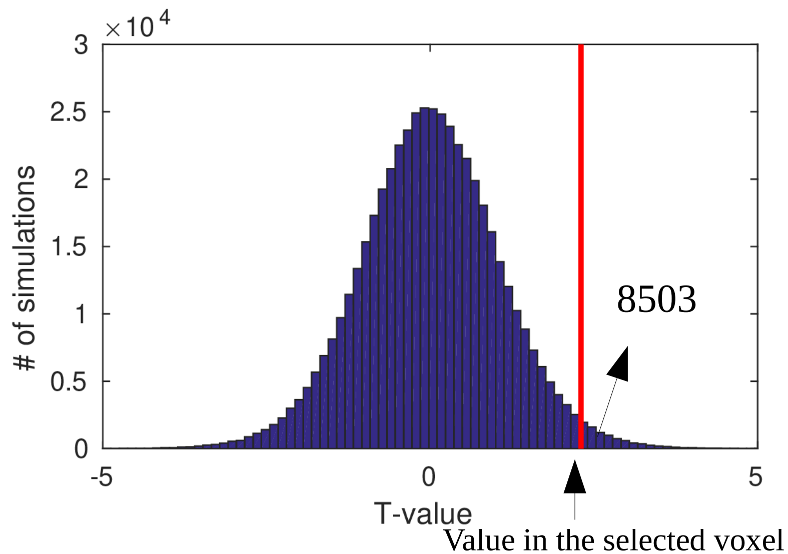
Number of voxels that can be considered as grey matter after smoothing, at a resolution of 1.5 mm: ~ 500 000.





… 500 000 times.

<u>Simulation of the chance level (null effect) in that experiment</u>



8503 simulations / 500000 yield the same (or a higher) t-value as the one found.
NB: using the parametric distribution:
500000*0.016=8000.

→ we need to correct for the inflation of false positives.

Corrections (See Thomas Nichols 2003 for a review):

- Family wise error (Bonferroni, Gaussian random fields)
- False discovery rate