

7.91 Functional MRI of the Human Brain



Analyzing fMRI data: The General Linear Model

Idan Blank



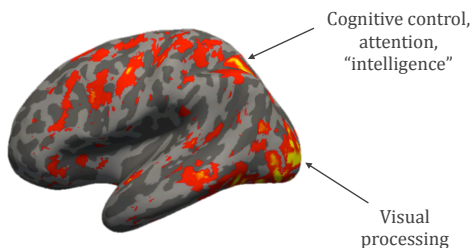
Finding the “language regions” in your brain

Question: which brain regions are engaged in high-level language processing?
which regions increase their activity in response to **sentences**?



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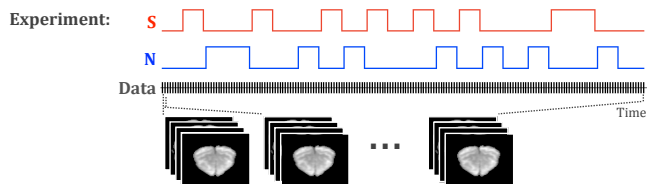
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which regions respond more to **sentences** than to **nonwords**?

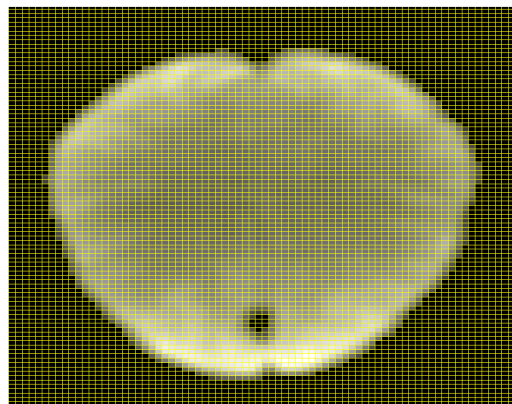
What do these two conditions have in common?
What do **sentences** have that **nonwords** do not?

The structure of our data

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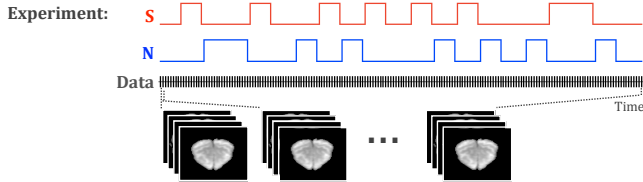


The structure of our data



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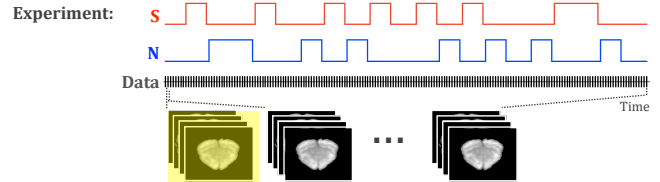
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- **Volume:** a 3D picture of a brain (a stack of 2D pictures, "slices")
- **Voxel:** the building block of a volume (a "cube", $\sim 1\text{mm}^3$ - 8mm^3)
- **Anatomical data:** a single volume of structural information
- **Functional data:** a series of volumes collected over time (brain activity throughout the task, measured via the BOLD signal)

The structure of our data

Question: which brain regions are engaged in high-level language processing?
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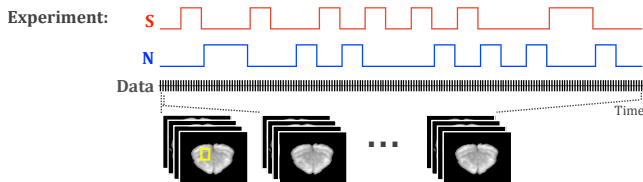


In MATLAB:

- **Volume:** a 3D matrix (a stack of slices, or 2D matrices)
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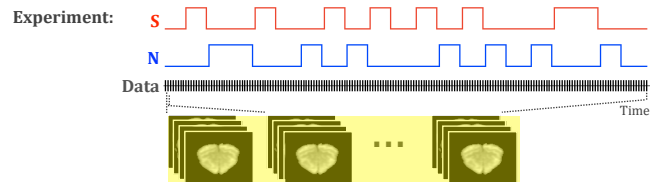


In MATLAB:

- **Volume:** a 3D matrix (a stack of slices, or 2D matrices)
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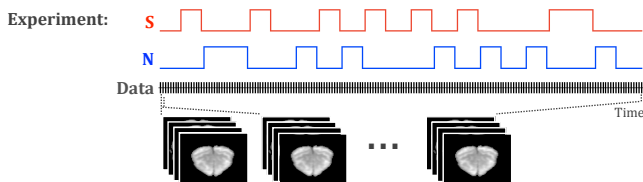


In MATLAB:

- **Volume:** a 3D matrix (a stack of slices, or 2D matrices)
- **Voxel:** a single entry $[x,y,z]$ in a volume
- **Anatomical data:**
- **Functional data:** a 4D matrix of BOLD signals (a "movie" of 3D matrices)
The entry $[x,y,z,t]$ stores the signal from voxel $[x,y,z]$ at time t .

The structure of our data

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The structure of our data: Exercises 1-4

FMRI DATA STRUCTURE

The data collected with fMRI are 3D pictures of the brain, called **volumes**. Each entry in such a 3D picture is called a **voxel** (similar to the entries of a 2D picture, called "pixels").

Each time we "run" the MRI scanner we collect a volume, or multiple volumes, of the brain. There are two common types of such **runs**:

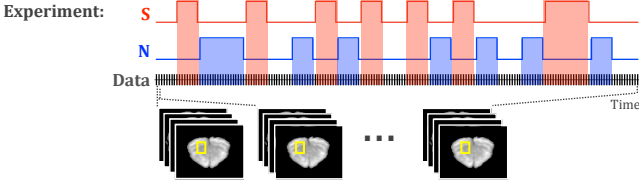
- An **anatomical run** collects a single volume of the brain, while the subject is resting. We collect an anatomical volume in order to see the structure of the brain.
- A **functional run** collects a series of volumes, one after the other, while the subject is performing some tasks. We collect these functional volumes to see how the activity in the brain changes over time, according to the tasks being performed.

The brain slices we have studied so far are mainly used for visualization purposes. The actual analysis of functional MRI data is concerned with how brain activity changes throughout our experiment, and it therefore focuses on **signal time-series**: a voxel's signal from all functional volumes, collected across the entire run.

HOW DO YOU CONSTRUCT SIGNAL TIME-SERIES?

Finding the "language regions" in your brain

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

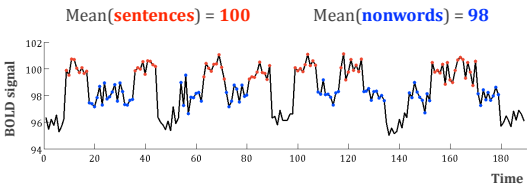
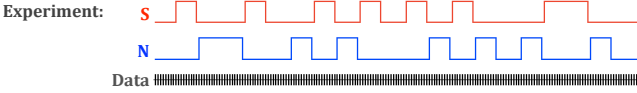


Analysis: an intuitive approach

- 1. For each voxel, look at its signal time-series (activity across time)
- 2. Average the signal across volumes collected while reading **sentences**
- 3. Average the signal across volumes collected while reading **nonwords**
- 4. Compare the two averages: does the voxel show a **S > N** pattern?

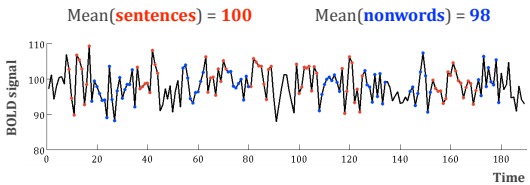
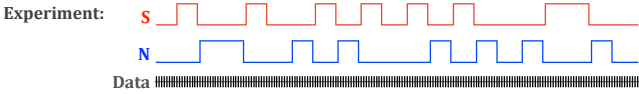
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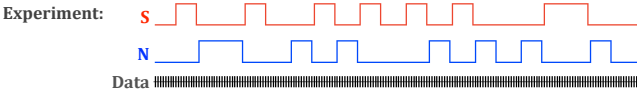
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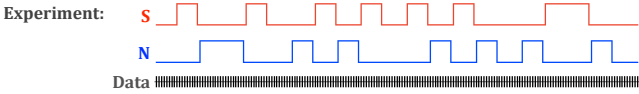
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BOLD signal = task-related activity changes + noise (other changes)
explained variations unexplained variations

Finding the "language regions" in your brain

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Analysis: a somewhat better approach

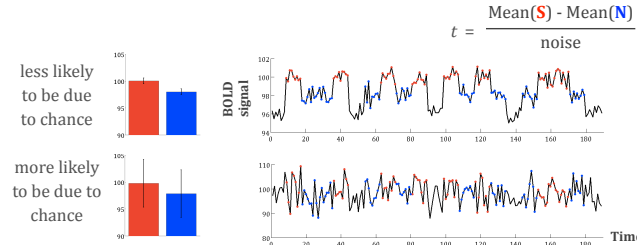
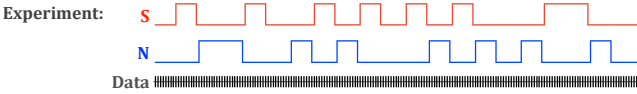
- The difference in response to **S** and **N** might be due to chance (not real)
- To test how likely the difference is to be real, we take noise into account
- The simplest way is to compute a **t-value**:

$$t = \frac{\text{Mean(S)} - \text{Mean(N)}}{\text{noise}} = \frac{\text{explained variations}}{\text{unexplained variations}}$$

- We know how likely it is to get different **t-values** by chance. To believe our results are real, we want a **t-value** that is very unlikely to get by chance.

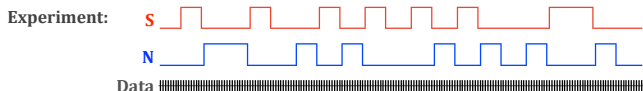
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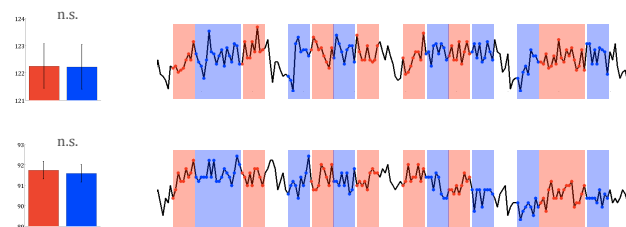
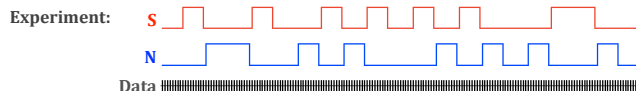


The difference between the response to **sentences** and to **nonwords** might be due to chance.
The more noisy our data are, the _____ this difference should be in order for us to believe that it is real.

A. Bigger
B. Smaller
C. I don't know

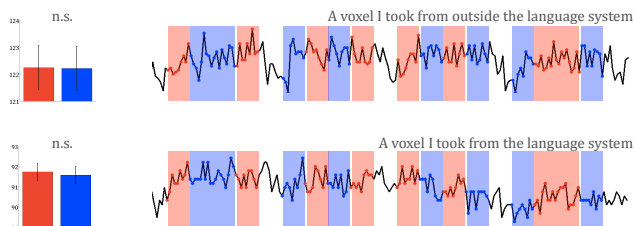
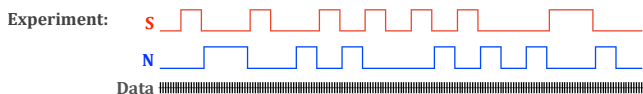
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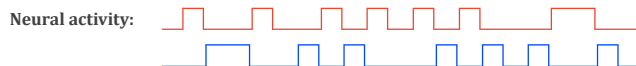
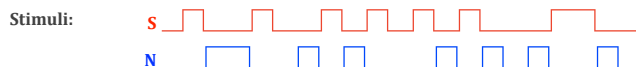


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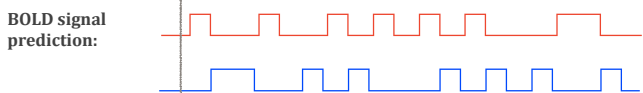
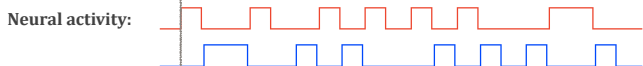
What do we know about fMRI data?



BOLD signal prediction: **When neurons are active, the fMRI BOLD signal will rise...**

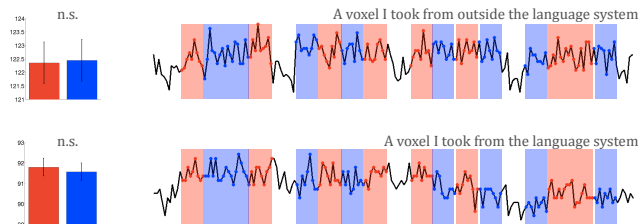
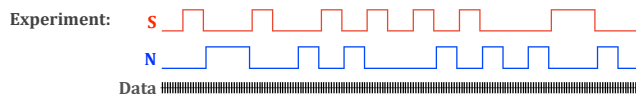
A. immediately
B. 1-3 seconds after the neural activity
C. 6-12 seconds after the neural activity
D. 25-30 seconds after the neural activity

What do we know about fMRI data?

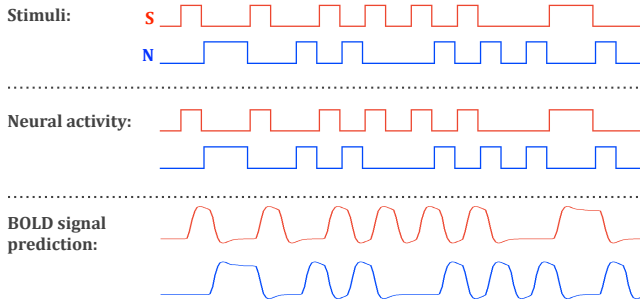


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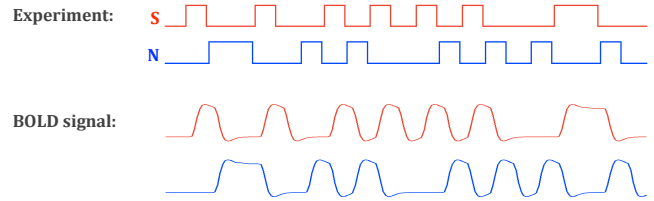


What do we know about fMRI data?



Finding the “language regions” in your brain

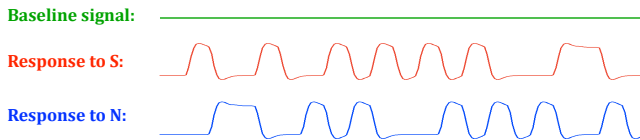
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The time series of language voxels should look like a combination of the two signals above, with the upper (**S**) having more weight than the lower (**N**)

(de)Constructing BOLD signals

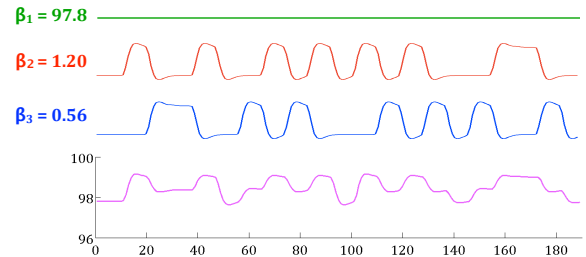
We can approximate the signal time-series of a voxel by combining these 3 signals:



MATLAB demonstration
 (classDemoLinearCombinations.m)

(de)Constructing BOLD signals

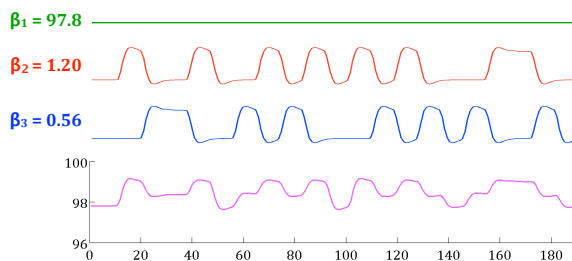
We can approximate the signal time-series of a voxel by combining these 3 signals:



- These signals we use to construct the approximation are called **predictors**.
- Each predictor is associated with a weight called a **beta-weight**.
- To create a **linear combination** of predictors, which approximates a true signal, we multiply each predictor by its beta-weight and then sum the results.

(de)Constructing BOLD signals

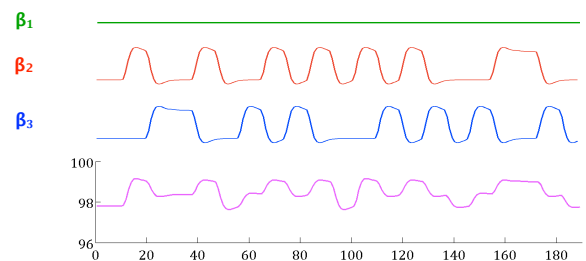
We can approximate the signal time-series of a voxel by combining these 3 signals:



- β_2 estimates a voxel's increase in activity in response to reading **sentences**
- β_3 estimates a voxel's increase in activity in response to reading **nonwords**

(de)Constructing BOLD signals

We can approximate the signal time-series of a voxel by combining these 3 signals:

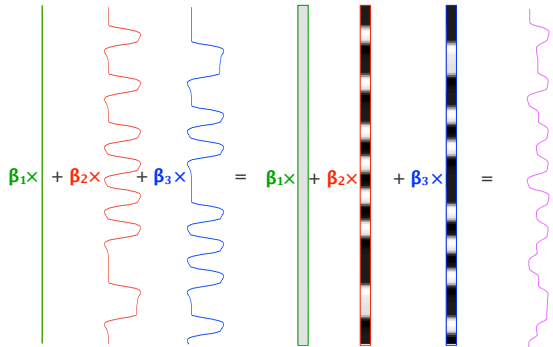


In MATLAB:

- predictors are column vectors: **x1**, **x2**, **x3**
- Beta-weights are scalars (numbers)
- An approximation is created by simple multiplication and addition

(de)Constructing BOLD signals

We can approximate the signal time-series of a voxel by combining these 3 signals:



(de)Constructing BOLD signals: Exercises 5-9

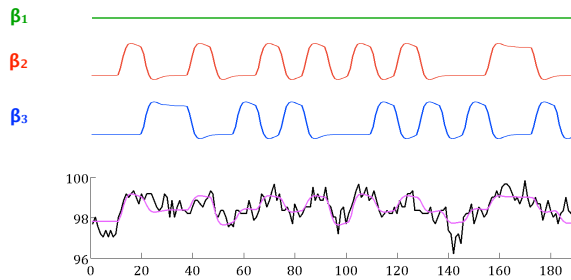
LINEAR COMBINATIONS AS APPROXIMATIONS OF REAL SIGNALS

You will now try to construct approximations of some signals. These signals simulate the activity measured in a voxels throughout the experiment, but they have much less noise than the actual signals recorded from real voxels (in order to make this exercise simpler).

For each of the following four exercises 5-8, you will be presented with the signal that should be approximated. To construct the approximation, you will use a MATLAB code that combines three three predictors: a constant predictor (x_1), a predictor for the response to **sentences** (x_2), and a predictor for the response to **nonwords** (x_3) (the three predictors are already given in the code). Your task is to find the three beta weights (one for each predictor) that give the best approximation of the given signal.

(de)Constructing BOLD signals

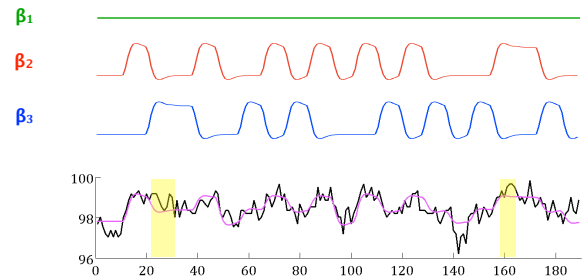
We can approximate the signal time-series of a voxel by combining these 3 signals:



For every point in time: $\text{signal}(t) - \text{prediction}(t) = \text{error}(t)$

(de)Constructing BOLD signals

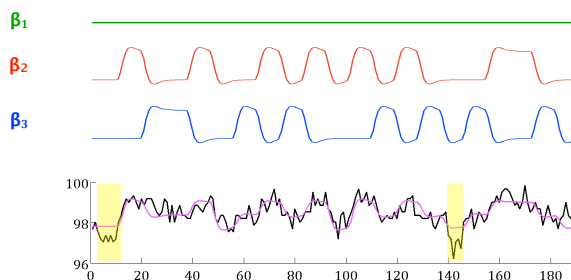
We can approximate the signal time-series of a voxel by combining these 3 signals:



For every point in time: $\text{signal}(t) - \text{prediction}(t) = \text{error}(t)$
 Example: $\text{signal}(t) > \text{prediction}(t)$ $\text{signal}(t) - \text{prediction}(t) > 0$ $\text{error}(t) > 0$

(de)Constructing BOLD signals

We can approximate the signal time-series of a voxel by combining these 3 signals:



For every point in time: $\text{signal}(t) - \text{prediction}(t) = \text{error}(t)$
 Example: $\text{signal}(t) < \text{prediction}(t)$ $\text{signal}(t) - \text{prediction}(t) < 0$ $\text{error}(t) < 0$

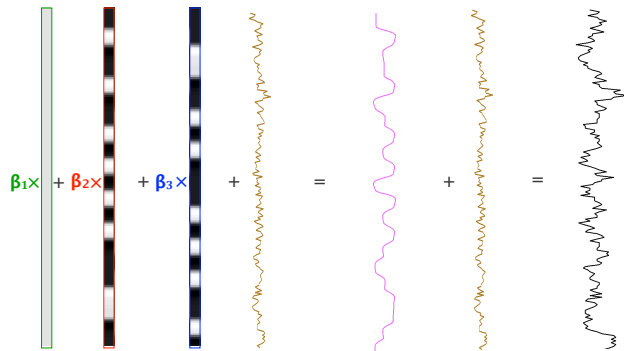
(de)Constructing BOLD signals

In the analysis we demonstrated, what is the input (things we know) and what is the output (things we are looking for)?

- INPUT: a voxel's true BOLD signal
 OUTPUT: predictors and beta weights that best approximate the signal
- INPUT: a voxel's true BOLD signal and our predictors
 OUTPUT: beta weights that combine with the predictors to give the best approximation of the true signal
- INPUT: a voxel's true BOLD signal and beta weights
 OUTPUT: predictors that combine with the beta weights to give the best approximation of the true signal

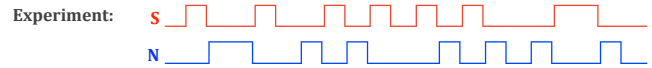
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We can approximate the signal time-series of a voxel by combining these 3 signals:



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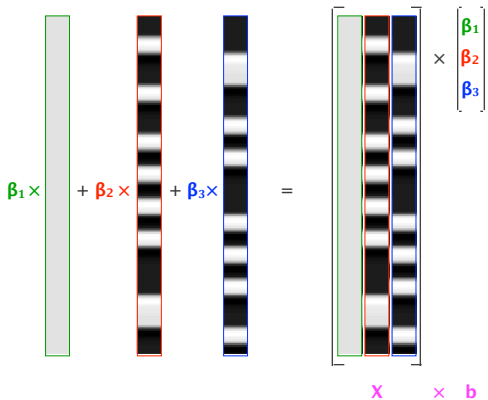


Analysis: the approach that works

- Find the beta weights that best approximate a voxel’s signal time-series. The best approximation is the one with the least errors.
- Compare the beta-weight for (estimated response to) **sentences** to the beta-weight for (estimated response to) **nonwords**.

BOLD signal = task-related activity changes + noise (other changes)
 explained variations + unexplained variations
 linear combination of predictors (approximation) + errors

Matrix notation



(de)Constructing BOLD signals: Exercises 10-11

EXERCISE 10: ERRORS

You will now explore errors between a linear combination of predictors and the actual signal that they try approximating. For this purpose, you will use the code Q10.m. This code already has some variables that are given to you:

- `allBetas`: a 2D matrix, where each column contains a set of beta weights (this time you do not have to create this matrix, the code already has it).
- `x1`, `x2`, `x3`: the same predictors used in exercises 5-9.
- `signal1`: a column vector with the true brain-signal of voxel B from exercise 9.

Fill in the code (lines **18-23**) to loop through the 3 sets of beta weights, constructing a linear combination `p` based on each set, and computing the errors between the resulting approximations and `signal1`. When you run the code, it will generate figures of the errors. Inspect these figures and answer the question that follows.

EXERCISE 11: MATRIX NOTATION

This short exercise does not require any MATLAB code. Simply answer the questions below.

(de)Constructing BOLD signals

A voxel’s BOLD signal at rest is 100.
 When the participant is reading **sentences**, the signal increases to 120.
 When the participant is reading **nonwords**, the signal increases to 110.
 When approximating the voxel’s BOLD signal using our three predictors, what should the beta weights for **sentences** and **nonwords** be?

- Sentences:** 120; **Nonwords:** 110
- Sentences:** 0.2; **Nonwords:** 0.1
- Sentences:** 20; **Nonwords:** 10
- Sentences:** 1.2; **Nonwords:** 1.2

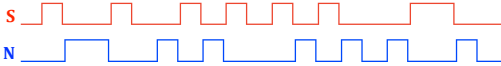
(de)Constructing BOLD signals

At the beginning of the experiment, when the participant is not reading anything, the predictors that contribute to the approximation are ____.
 Twelve seconds after the participant has started reading **nonwords**, the predictors that contribute to the approximation are ____.

- baseline + sentences + nonwords; nonwords
- baseline; nonwords
- baseline + sentences + nonwords; baseline + nonwords
- baseline; baseline + nonwords
- baseline + sentences + nonwords; baseline + sentences + nonwords
- baseline; baseline + sentences + nonwords

Finding the “language regions” in your brain

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

Experiment: 

Analysis: the approach that works

- Find the beta weights that best approximate a voxel’s signal time-series. The best approximation is the one with the least errors.
- Compare the beta-weight for (estimated response to) **sentences** to the beta-weight for (estimated response to) **nonwords**.

Instead of trial and error: **The General Linear Model**

The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

GLM:

BOLD signal = $X \times b$ + **error**
 explained variations + unexplained variations
 task-related activity changes + noise (other changes)

What we know:

- BOLD signal: we collect this from the brain (functional data).
- X: design matrix (each column is a predictor that we built ourselves).

What we want to find:

- b: vector of beta-weights (one weight per predictor in X) that give the best approximation of the BOLD signal.

How we find it:

- By minimizing the sum of squared errors. In practice, the GLM has a formula, which guarantees to find these beta-weights.

The General Linear Model (GLM)

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GLM:

BOLD signal = $X \times b$ + **error**
 explained variations + unexplained variations
 task-related activity changes + noise (other changes)

In MATLAB:

`b = regress(BOLD_signal, X)`

What to do when we get b:

Is $\beta(\text{sentences}) > \beta(\text{nonwords})$?

The comparison takes the **sum of squared errors (SSE)** into account:

- Big errors (poor approximation): $\beta(S) > \beta(N)$ probably due to chance
- Small errors (good approximation): $\beta(S) > \beta(N)$ is a real difference

The General Linear Model (GLM)

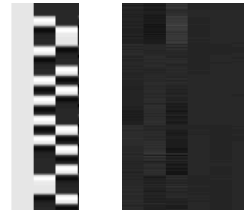
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GLM:

Any predictor that can help approximate the BOLD signal will decrease SSE.

Therefore, we include additional predictors:

- 6 head-motion predictors: 3 translations and 3 rotations



The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
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GLM:

Any predictor that can help approximate the BOLD signal will decrease SSE.

Therefore, we include additional predictors:

- 6 head-motion predictors: 3 translations and 3 rotations
- Time derivatives: slight time-shifts of the original **S** and **N** predictors



The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

GLM:

Any predictor that can help approximate the BOLD signal will decrease SSE.

Therefore, we include additional predictors:

- 6 head-motion predictors: 3 translations and 3 rotations
- Time derivatives: slight time-shifts of the original **S** and **N** predictors



$\times \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \dots \\ \beta_{11} \end{bmatrix}$

Design matrix (X)

MATLAB
demonstration
(classDemoLinearCombinations2.m)

The General Linear Model (GLM)

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Therefore, we include additional predictors:
- 6 head-motion predictors: 3 translations and 3 rotations
 - Time derivatives: slight time-shifts of the original **S** and **N** predictors

Why stop there?
Why not add a gazillion more predictors?

The General Linear Model (GLM): Exercises 12-14

EXERCISE 12: DO-IT-YOURSELF GLM

You will now implement a GLM in MATLAB, analyzing the signals from the six voxels you have worked with earlier (three of these are voxels A, B and C from exercise 9):

voxel 1: (67, 63, 35)
voxel 2: (45, 68, 24)
voxel 3: (33, 60, 51)
voxel 4: (12, 52, 20)
voxel 5: (48, 60, 30)
voxel 6: (28, 41, 42)

You will use the three predictors you have been working with (constant, **sentences**, **nonwords**) to find, for each voxel, beta weights that produce the best approximation of the voxel's true signal.

EXERCISE 13: THE SSE MEASURE

To study the behavior of errors and the SSE measure, let us focus on voxel number 2: (45, 68, 24). The code Q13.m creates 5,001 linear combinations to approximate the signal from this voxel. One linear combination uses the beta weights found with a GLM (those you found in the exercise 12). The other 5,000 linear combinations use random beta weights.

The General Linear Model (GLM): Exercises 12-14

EXERCISE 14: A GLM WITH 11 PREDICTORS

Here, you will test whether additional predictors - modeling head-motion and time-shifts in the BOLD signal - change the results of the GLM. The code Q14.m runs two models - one with only 3 predictors (similar to what you have done previously), and one with 11 predictors. The following variables in the code are given to you:

- `signals`: a 2D matrix where every column is the signal of one of our 6 voxels.
- `x1, x2`: two design matrices, one with 3 predictors and the second with 11 predictors.

The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

GLM: Is $\beta(S) > \beta(N)$?

$$t = \frac{\beta(S) - \beta(N)}{\text{error(ish)}} = \frac{\text{explained variations}}{\text{unexplained variations}}$$

$$\begin{aligned} \beta(S) &= 0.4 \\ \beta(N) &= 0.2 \\ \text{SSE} &= 22.82 \end{aligned}$$

highly unlikely to get these results by chance!

$$\begin{bmatrix} y_1 \\ y_2 \\ \dots \\ y_n \end{bmatrix} = \begin{bmatrix} x_{11} & x_{12} & \dots & x_{1k} \\ x_{21} & x_{22} & \dots & x_{2k} \\ \dots & \dots & \dots & \dots \\ x_{n1} & x_{n2} & \dots & x_{nk} \end{bmatrix} \times \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \dots \\ \beta_{11} \end{bmatrix} + \text{error}$$

$$t = \frac{\text{Mean}(S) - \text{Mean}(N)}{\text{noise}} \quad \text{n.s.}$$



The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

GLM: A comparison of beta-weights is called a **contrast**.

Formally, a contrast is a vector indicating which beta-weights we are testing:

$$\begin{aligned} \beta(S) &> \beta(N) \\ \beta(S) - \beta(N) &> 0 \\ [0 \quad 1 \quad -1 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0] \end{aligned}$$

$$\begin{bmatrix} y_1 \\ y_2 \\ \dots \\ y_n \end{bmatrix} = \begin{bmatrix} x_{11} & x_{12} & \dots & x_{1k} \\ x_{21} & x_{22} & \dots & x_{2k} \\ \dots & \dots & \dots & \dots \\ x_{n1} & x_{n2} & \dots & x_{nk} \end{bmatrix} \times \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \dots \\ \beta_{11} \end{bmatrix} + \text{error}$$

The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

GLM: A comparison of beta-weights is called a **contrast**.

Formally, a contrast is a vector indicating which beta-weights we are testing

- We can compare one set of beta-weights to another set of beta-weights

Example: some model with 5 predictors; are β_1, β_2 bigger than β_3, β_4 ?

$$\frac{\beta_1 + \beta_2}{2} > \frac{\beta_3 + \beta_4}{2}$$

$$\frac{\beta_1 + \beta_2}{2} - \frac{\beta_3 + \beta_4}{2} > 0$$

$$\frac{1}{2}\beta_1 + \frac{1}{2}\beta_2 - \frac{1}{2}\beta_3 - \frac{1}{2}\beta_4 > 0$$

$$[0.5 \quad 0.5 \quad -0.5 \quad -0.5 \quad 0]$$

The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

GLM: A comparison of beta-weights is called a **contrast**.
Formally, a contrast is a vector indicating which beta-weights we are testing

- We can compare one set of beta-weights to another set of beta-weights
Note: the sum of all positive entries should be 1; the sum of all negative entries should be -1.

The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

GLM: A comparison of beta-weights is called a **contrast**.
Formally, a contrast is a vector indicating which beta-weights we are testing

- We can compare one set of beta-weights to another set of beta-weights
Note: the sum of all positive entries should be 1; the sum of all negative entries should be -1.

- We can compare a single beta-weight (or a single set) to 0.

Example: some model with 5 predictors; is β_2 bigger than 0?

$$\beta_2 > 0$$

$$[0 \ 1 \ 0 \ 0 \ 0]$$

The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

- GLM:**
- Extract the signal time-series from a given voxel
 - Run a GLM (the signal and your design matrix are the input) to find beta-weights that best approximate the true signal
 - Compute the **Sum of Squared Errors (SSE)**
 - Define your contrast and test it: $[0 \ 1 \ -1 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0]$

Repeat for all voxels.
Significant voxels are those that have t -values that are highly unlikely to get by mere chance.

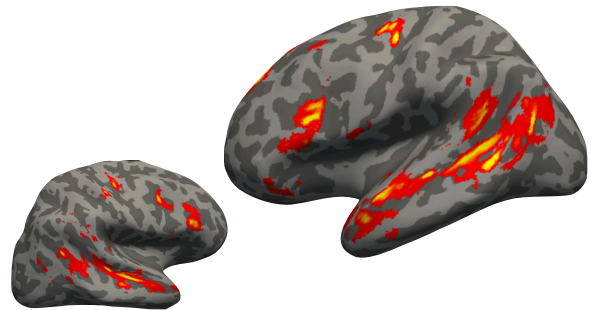
$$t = \frac{\beta(S) - \beta(N)}{\text{error(ish)}}$$

$$\begin{matrix}
 \beta_1 \\
 \beta_2 \\
 \beta_3 \\
 \beta_4 \\
 \dots \\
 \beta_{11}
 \end{matrix}$$

The General Linear Model (GLM)

Question: which brain regions are engaged in high-level language processing?
which regions respond more to **sentences** than to **nonwords**?

Answer:

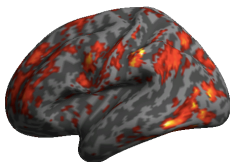


The General Linear Model (GLM)

You can also use the same data to ask other questions, using other contrasts:

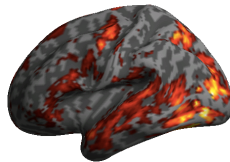
Which regions respond more to **nonwords** than to **sentences**?

$$\beta(N) > \beta(S)$$



Which regions respond to **sentences**?

$$\beta(S) > 0$$



The General Linear Model (GLM): exercise 15

EXERCISE 15: DEFINING CONTRASTS

When we localize someone's language system using fMRI, we usually include two runs of the experiment (i.e., two runs of reading both **sentences** and **nonwords**). Therefore, our full design matrix usually includes:

- A constant predictor for the **first** run
- A predictor for the response to **sentences** in the **first** run
- A predictor for the response to **nonwords** in the **first** run
- A constant predictor for the **second** run
- A predictor for the response to **sentences** in the **second** run
- A predictor for the response to **nonwords** in the **second** run

Summary

- **Predictor:** a “mock signal” indicating the expected change in brain activity throughout the experiment caused by a hypothesized process (cognitive, physiological, etc.)
- **Beta-weight:** a weight indicating how much a predictor contributes to the true BOLD signal, i.e., how much the signal changes due to the hypothesized process, holding everything else in the model constant.
- **Error:** the difference between the true BOLD signal and the combination of predictors that best approximates it. These are changes (variations) in the true signal that we cannot explain with the predictors.
- **Contrast:** the difference between two (groups of) betas
- **Contrast t-value:** the number which results from dividing the contrast value by a measure of error (“taking the error into account”).

$$t = \frac{\beta(S) - \beta(N)}{\text{error(ish)}}$$

BOLD signal = $X \times b$ + e
 explained variations + unexplained variations
 task-related activity changes + noise (other changes)

Final Exercise

PUTTING IT ALL TOGETHER

You are now ready to find the language system in the brain!

It's time to use everything you've learned in this workshop and implement a GLM from start to finish.

This exercise will be run through the code `FinalExercise.m`. The following pages describe the code and give some instructions about the exercise. After you run the code, answer the questions on the last page.