# Statistical Machine Learning and Optimisation Challenges for Brain Imaging at a Millisecond Timescale

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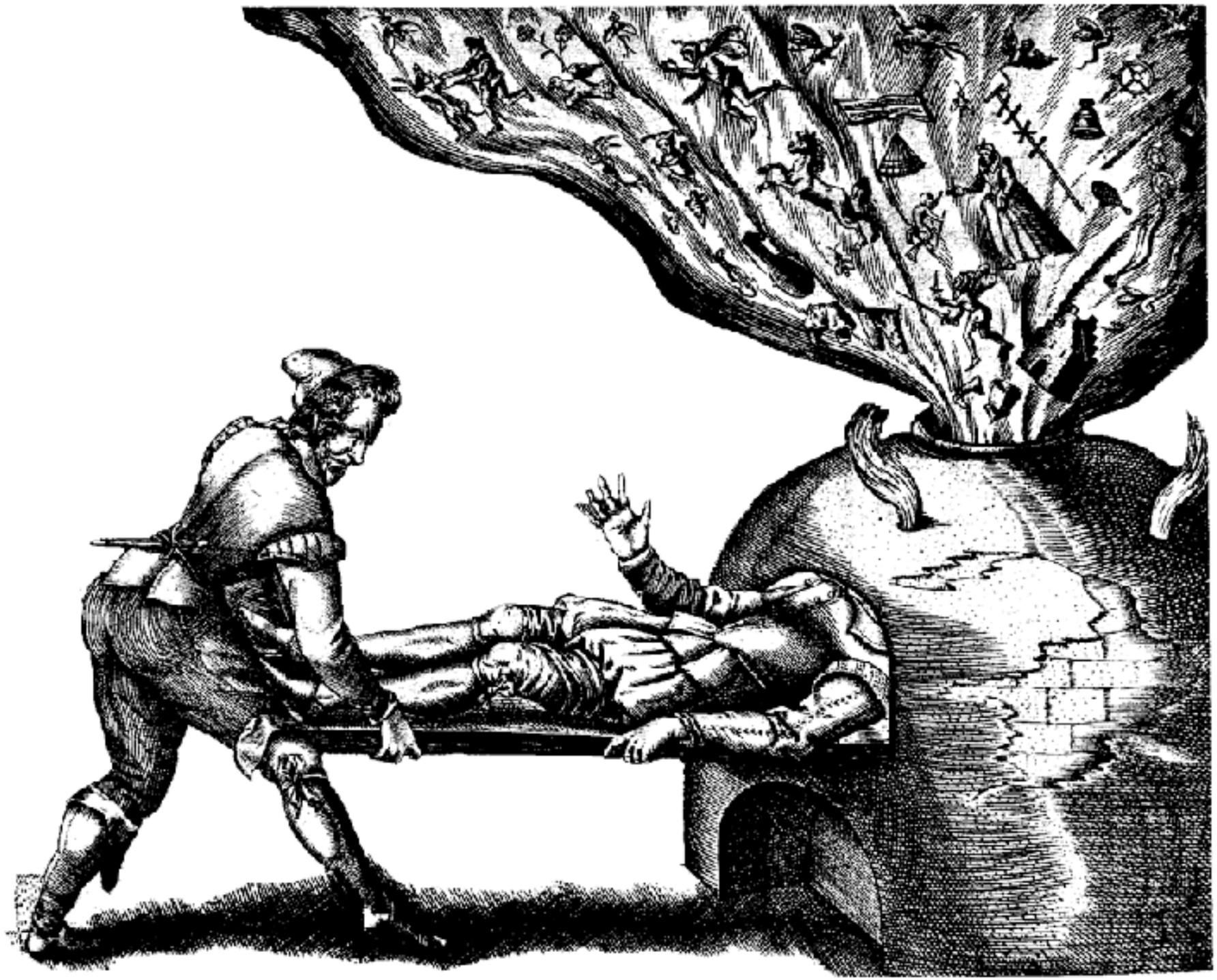
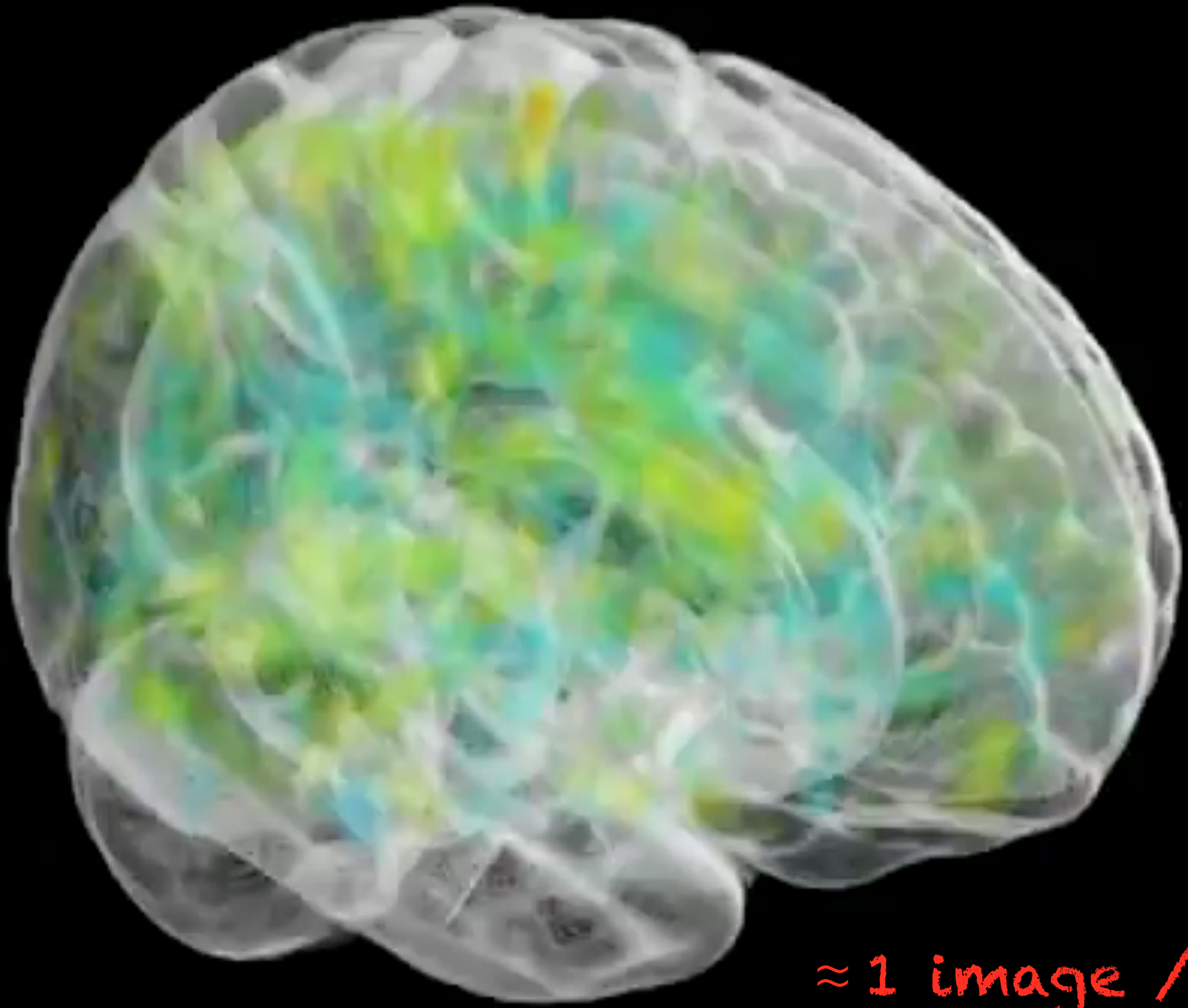
http://alexandre.gramfort.net

Inria, Parietal Team

*Cambridge - Sept. 2017*

# What is functional brain imaging?

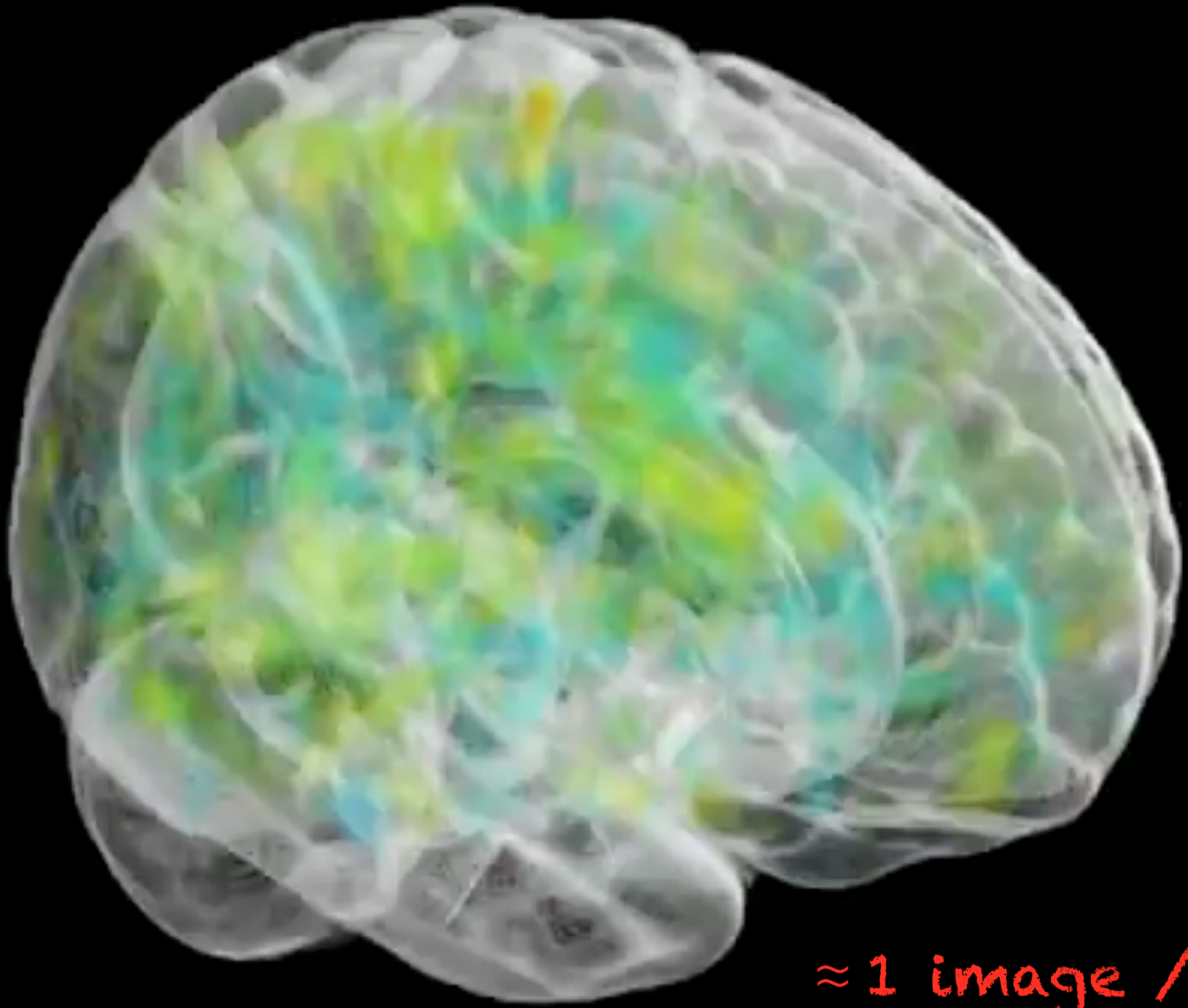




≈ 1 image / 2s

http://www.youtube.com/watch?v=uhCF-zlk0jY

courtesy of Gael Varoquaux



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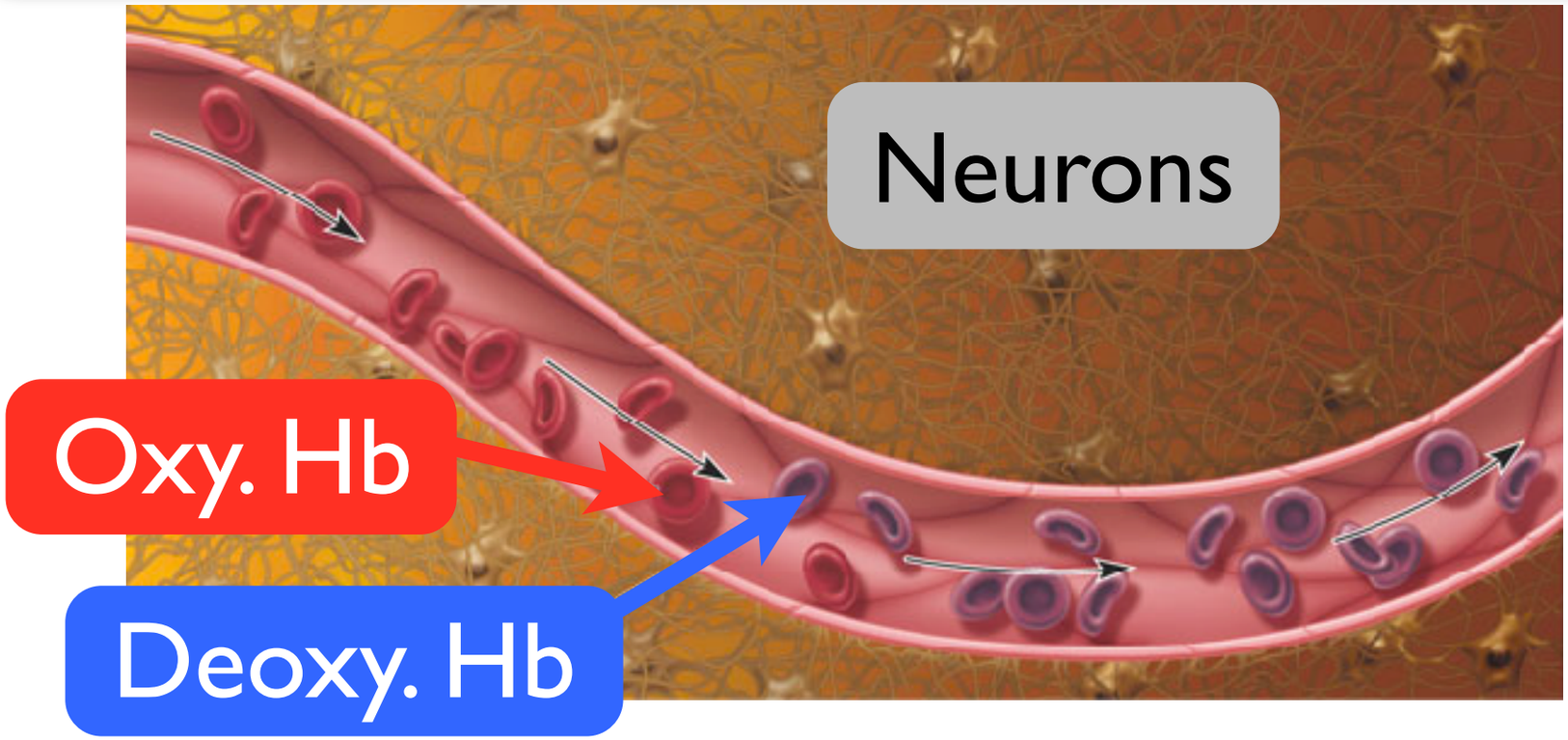
# Functional MRI (fMRI)



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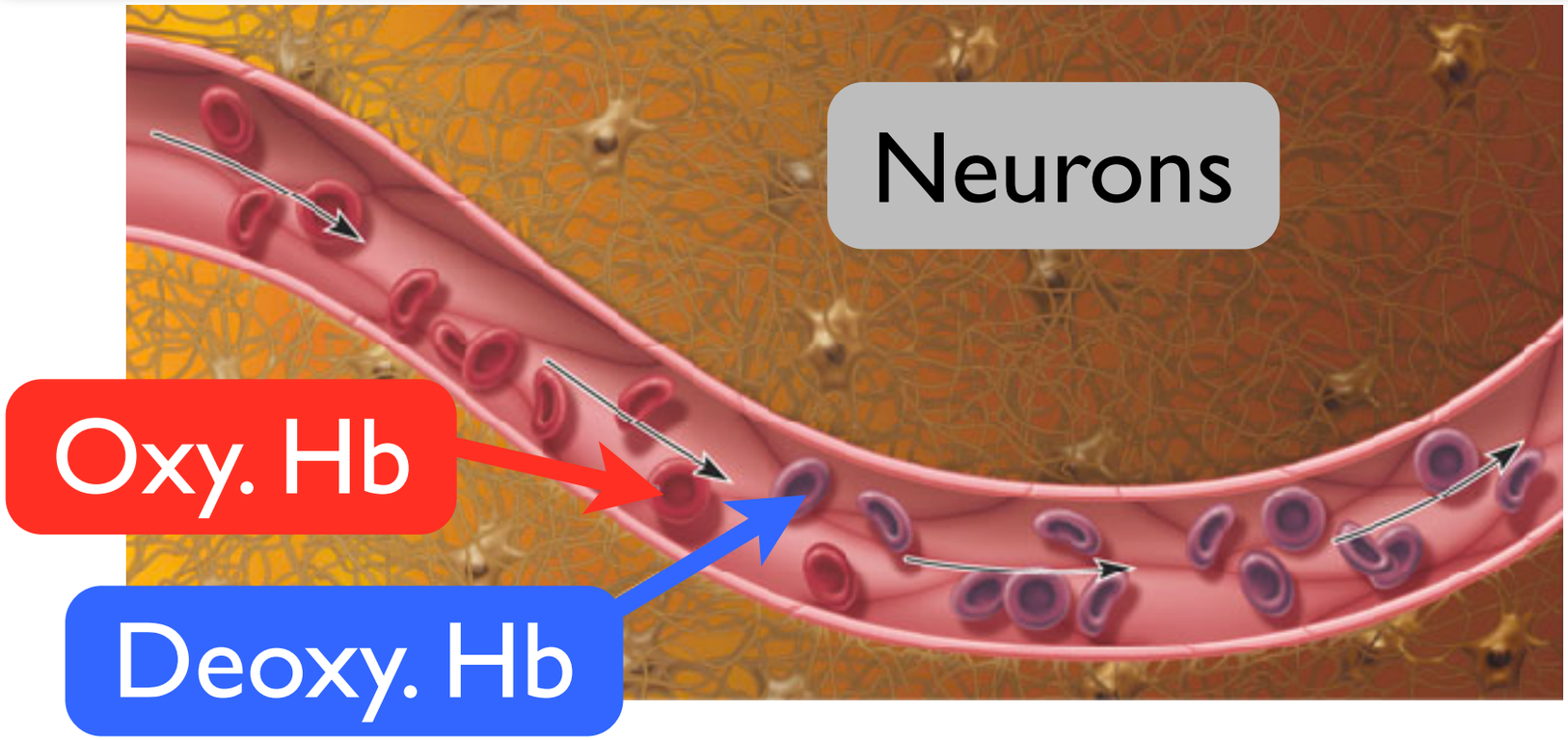
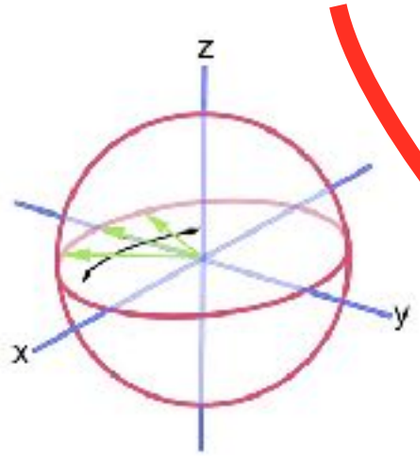
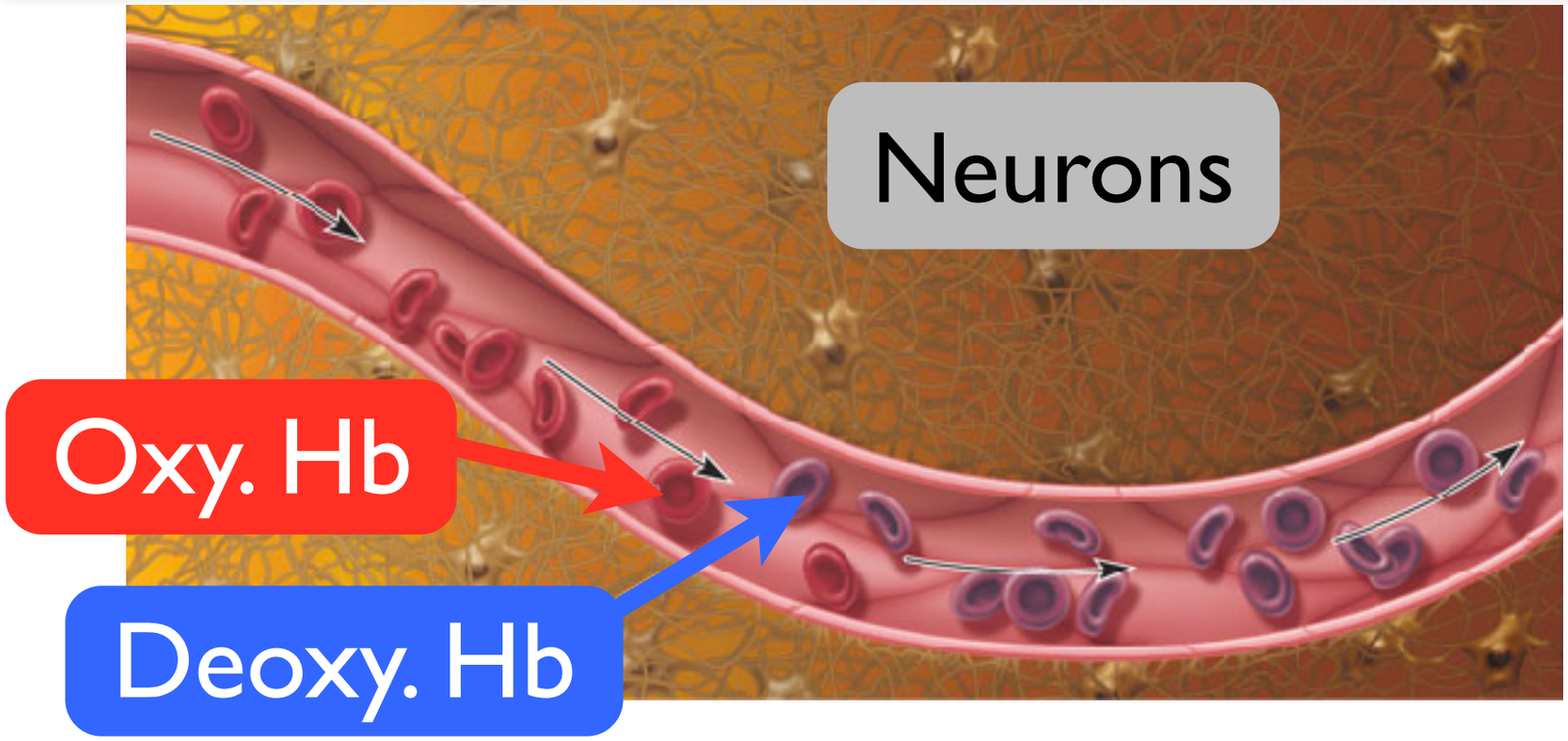


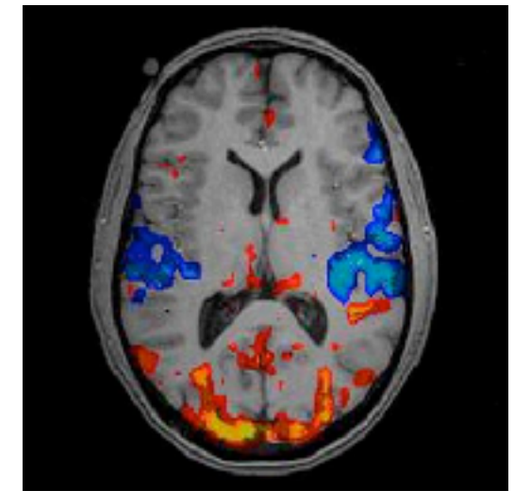



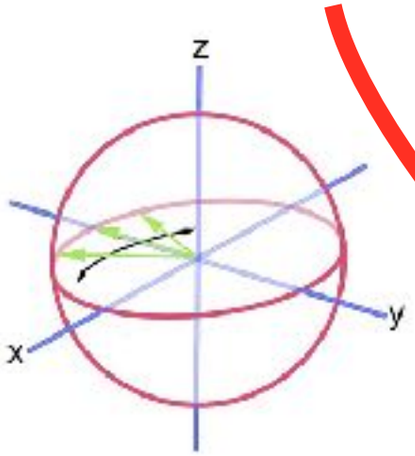

Magnetic resonance imaging

Scanner

# Functional MRI (fMRI)






Magnetic resonance imaging

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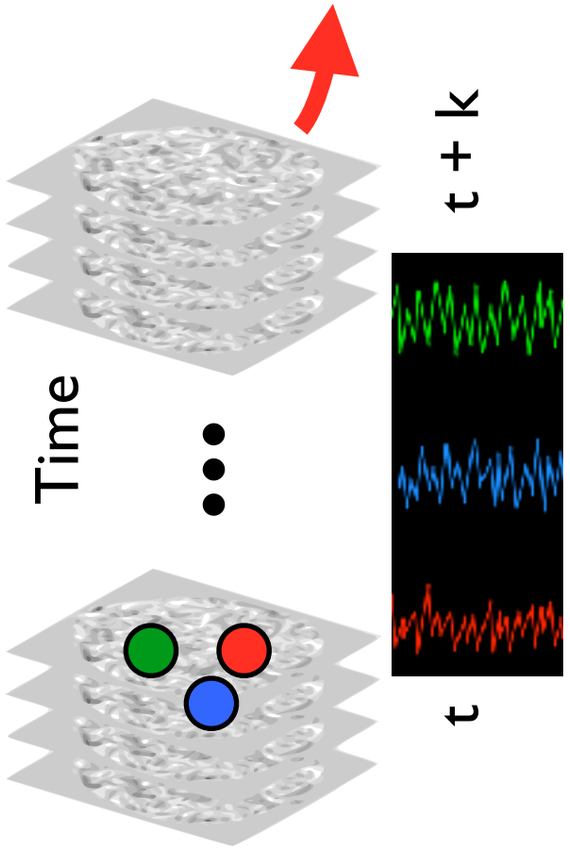
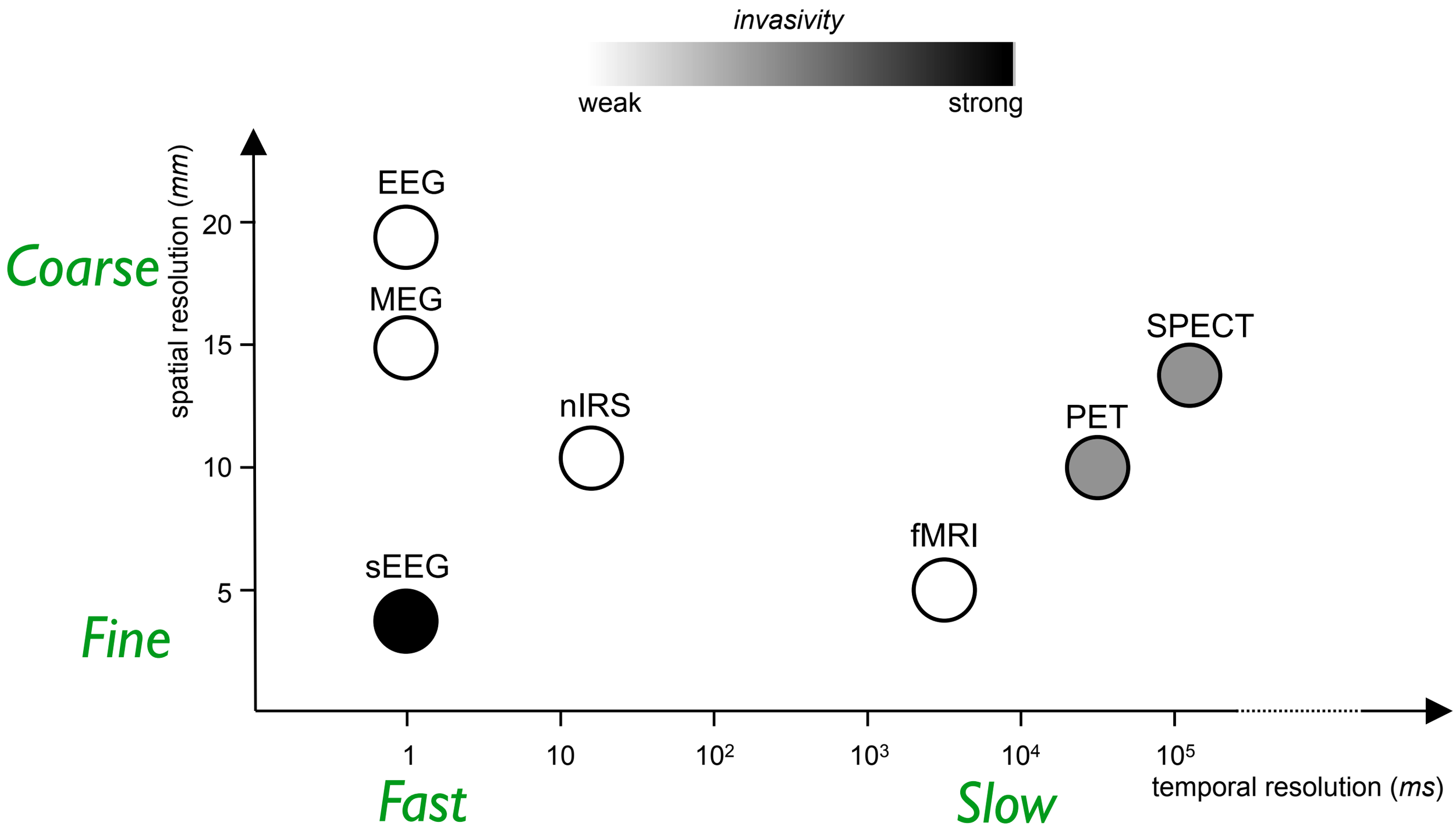


# What is functional brain imaging?



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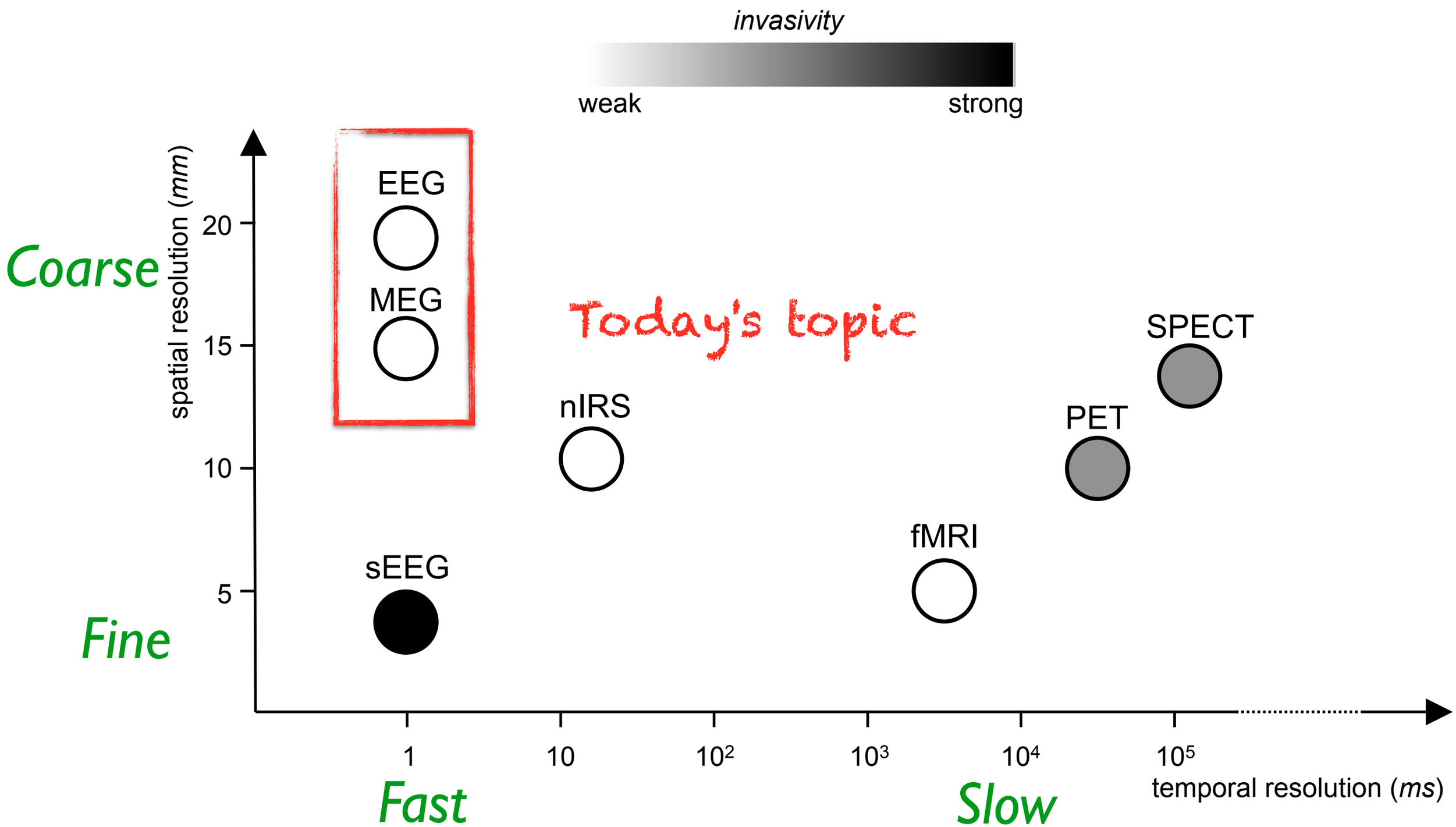
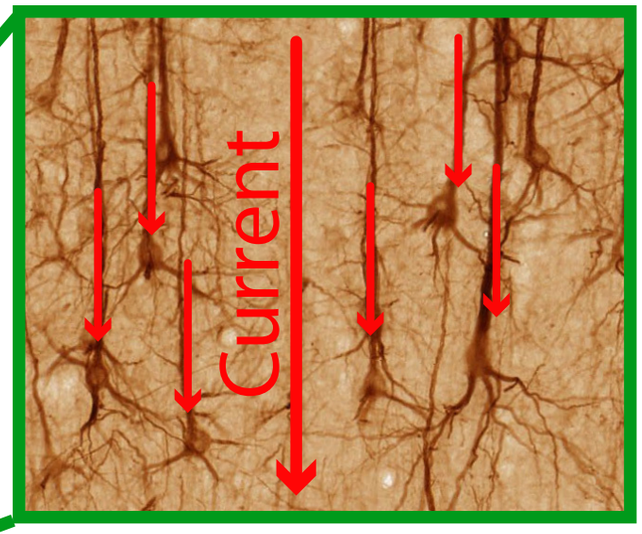
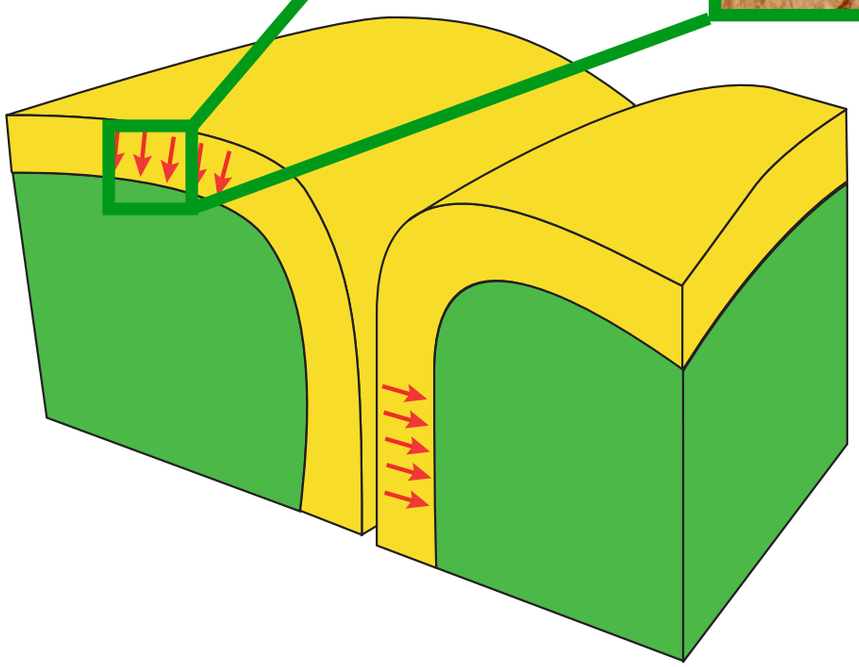


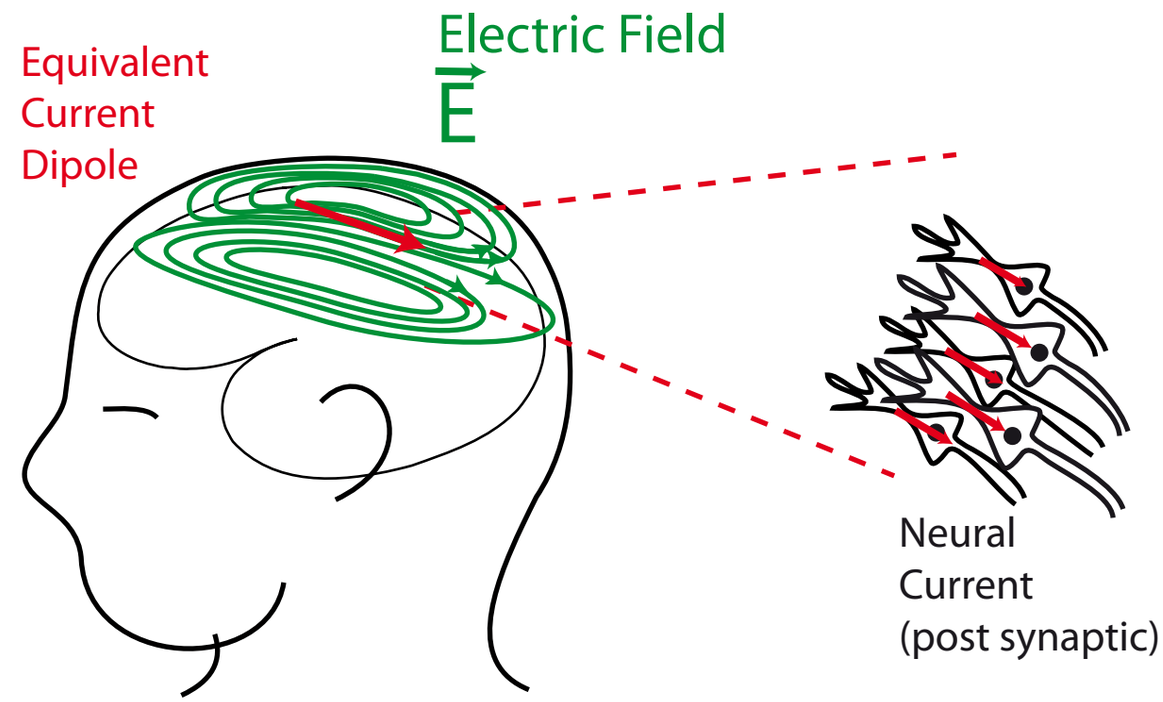
# Neurons as current generators

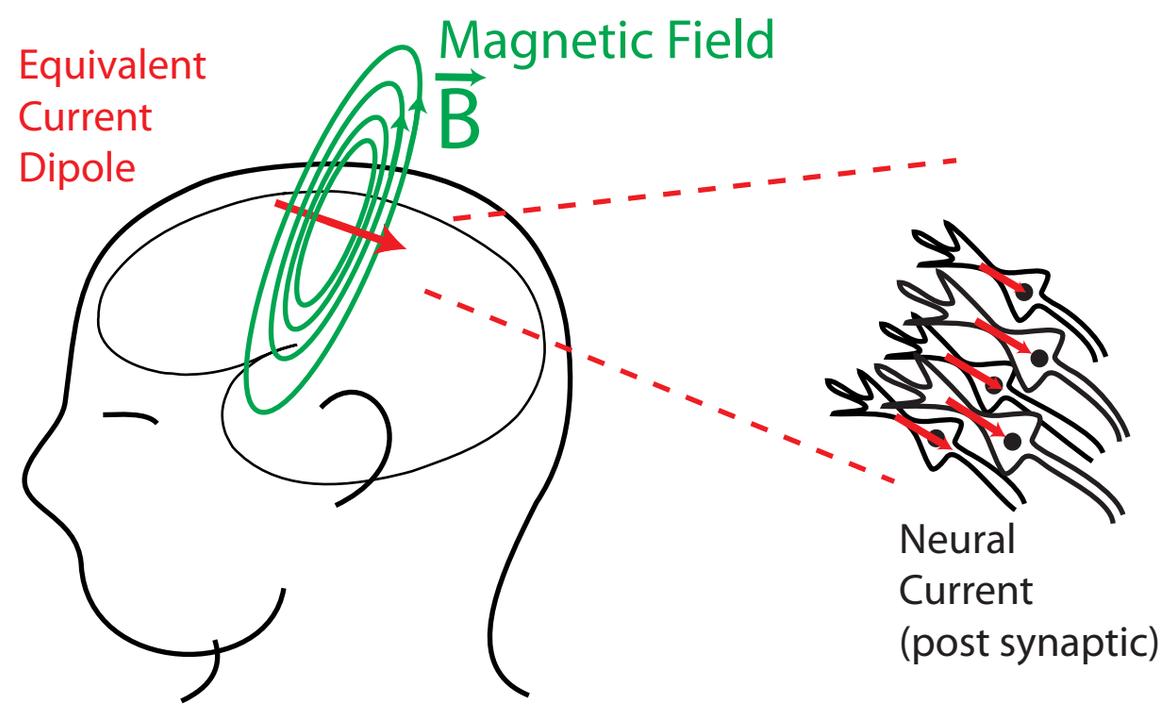
Large cortical pyramidal cells organized in macro-assemblies with their **dendrites normally oriented to the local cortical surface**

$Q = I \times d$
(10 to 100 nAm) with the equivalent current dipole (ECD) model

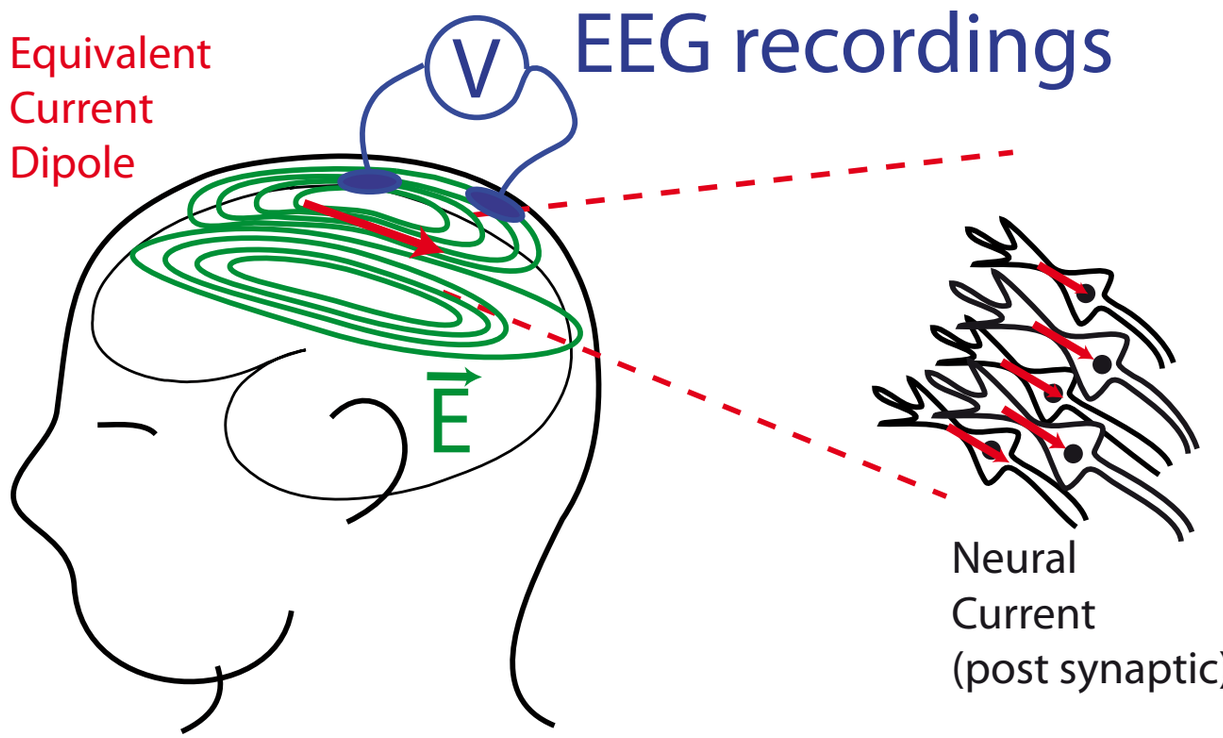


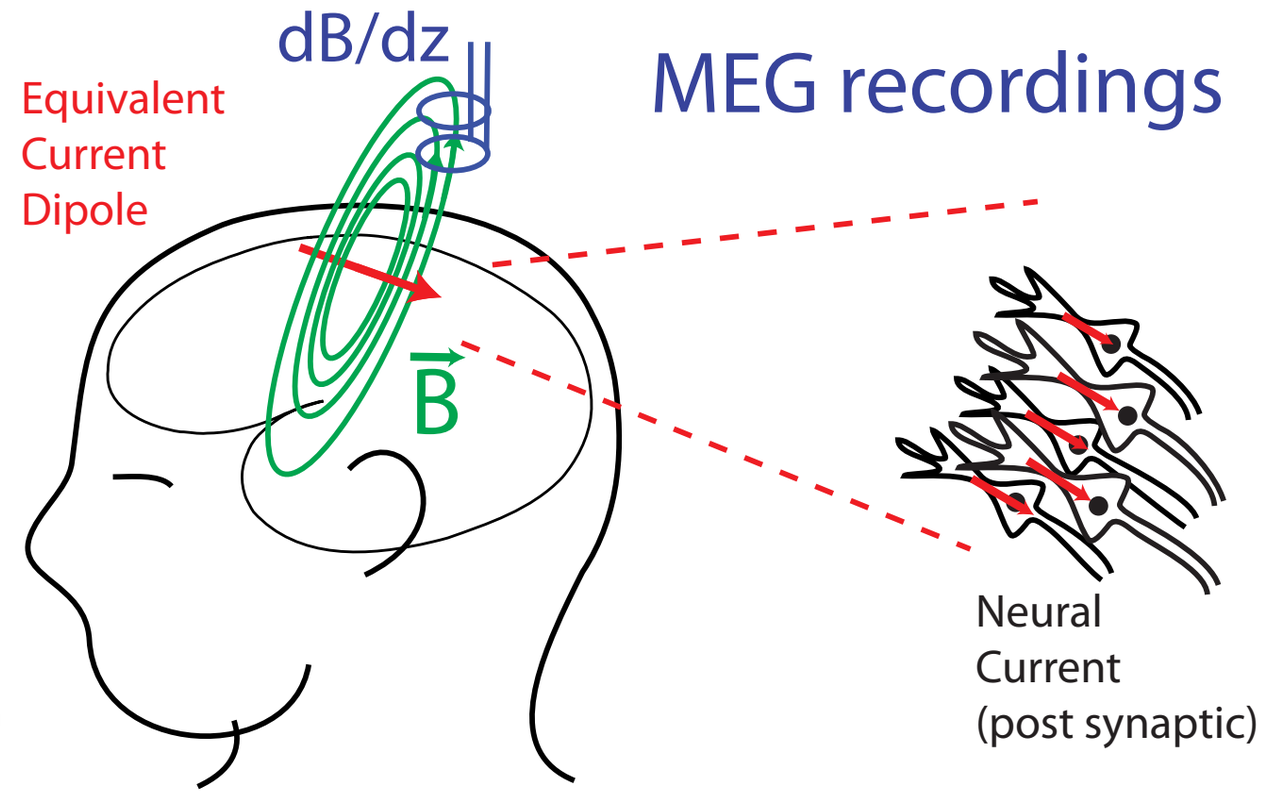



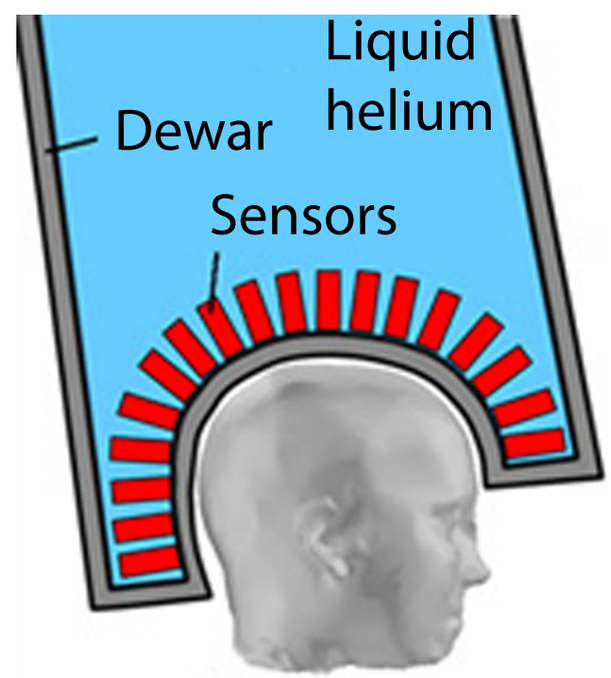



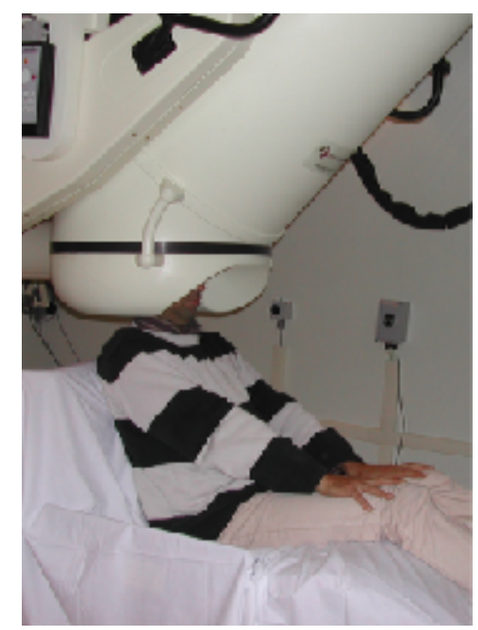
# Electro- & Magneto-encephalography



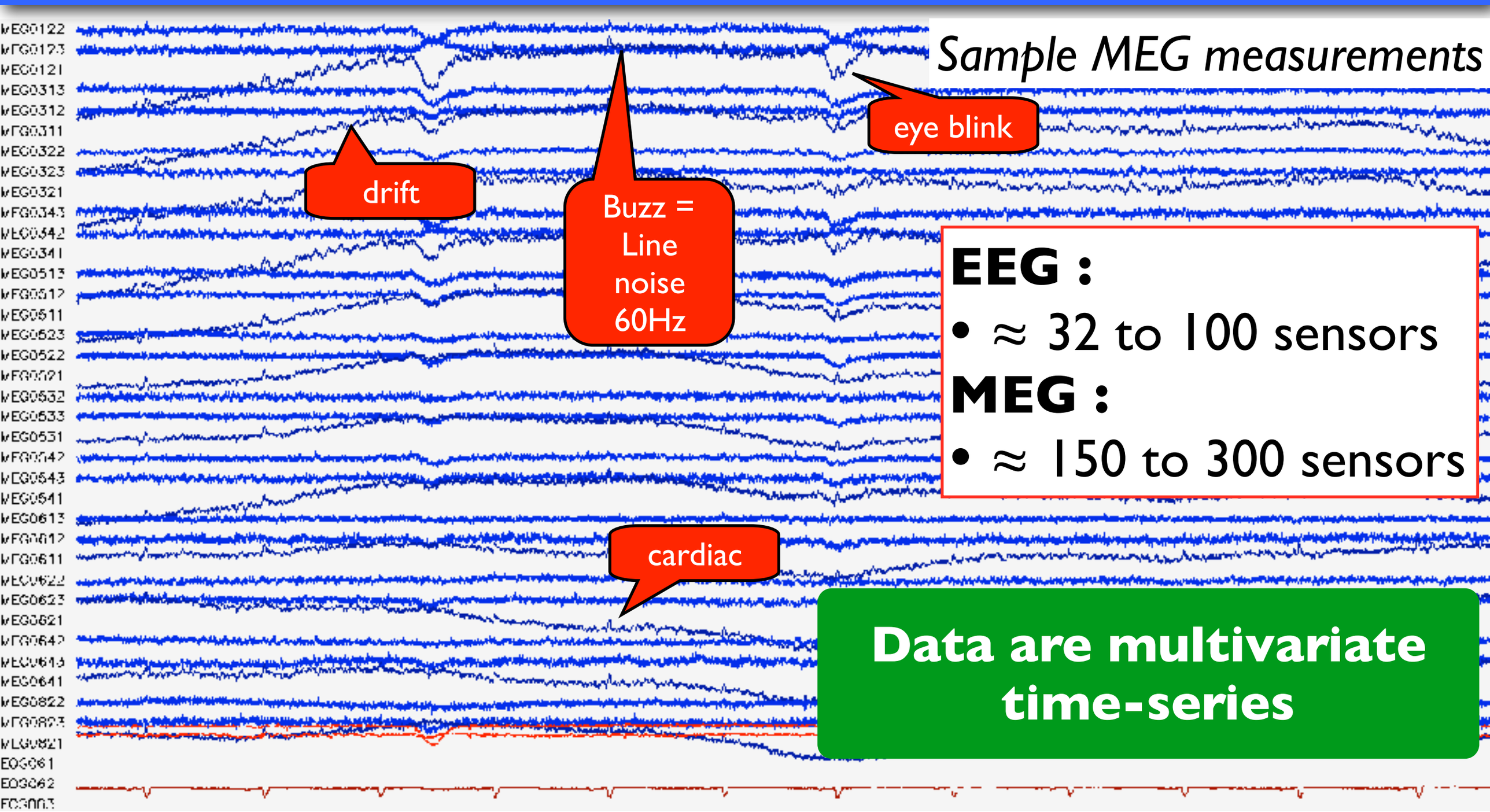

First EEG recordings in 1929 by H. Berger



Hôpital La Timone
Marseille, France

# M/EEG Measurements




**EEG :**

- ≈ 32 to 100 sensors

**MEG :**

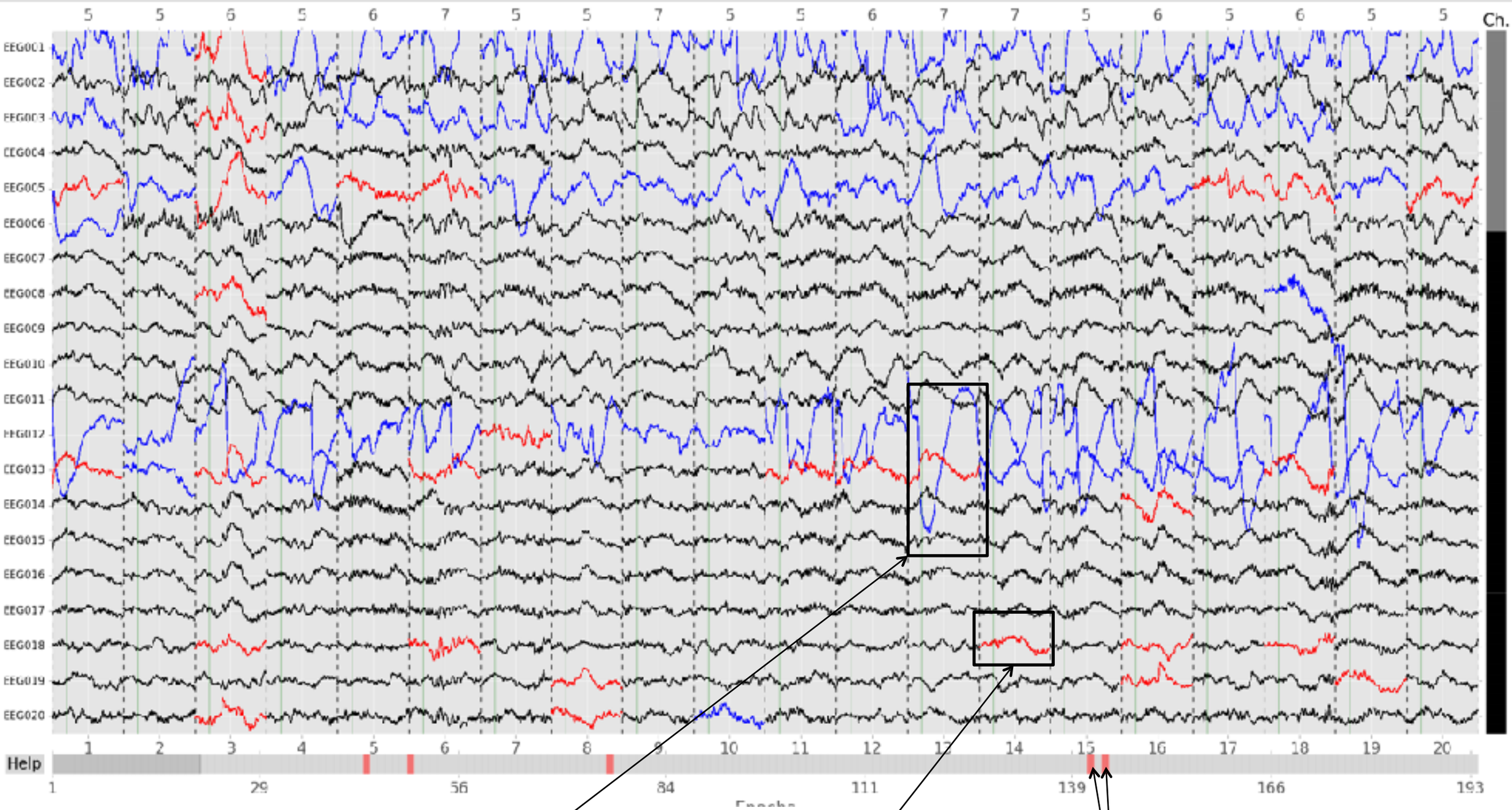
- ≈ 150 to 300 sensors

**Data are multivariate time-series**

Time frame: 10 seconds

≈ 1000 samples / s

# Artifacts everywhere & tedious to manually fix



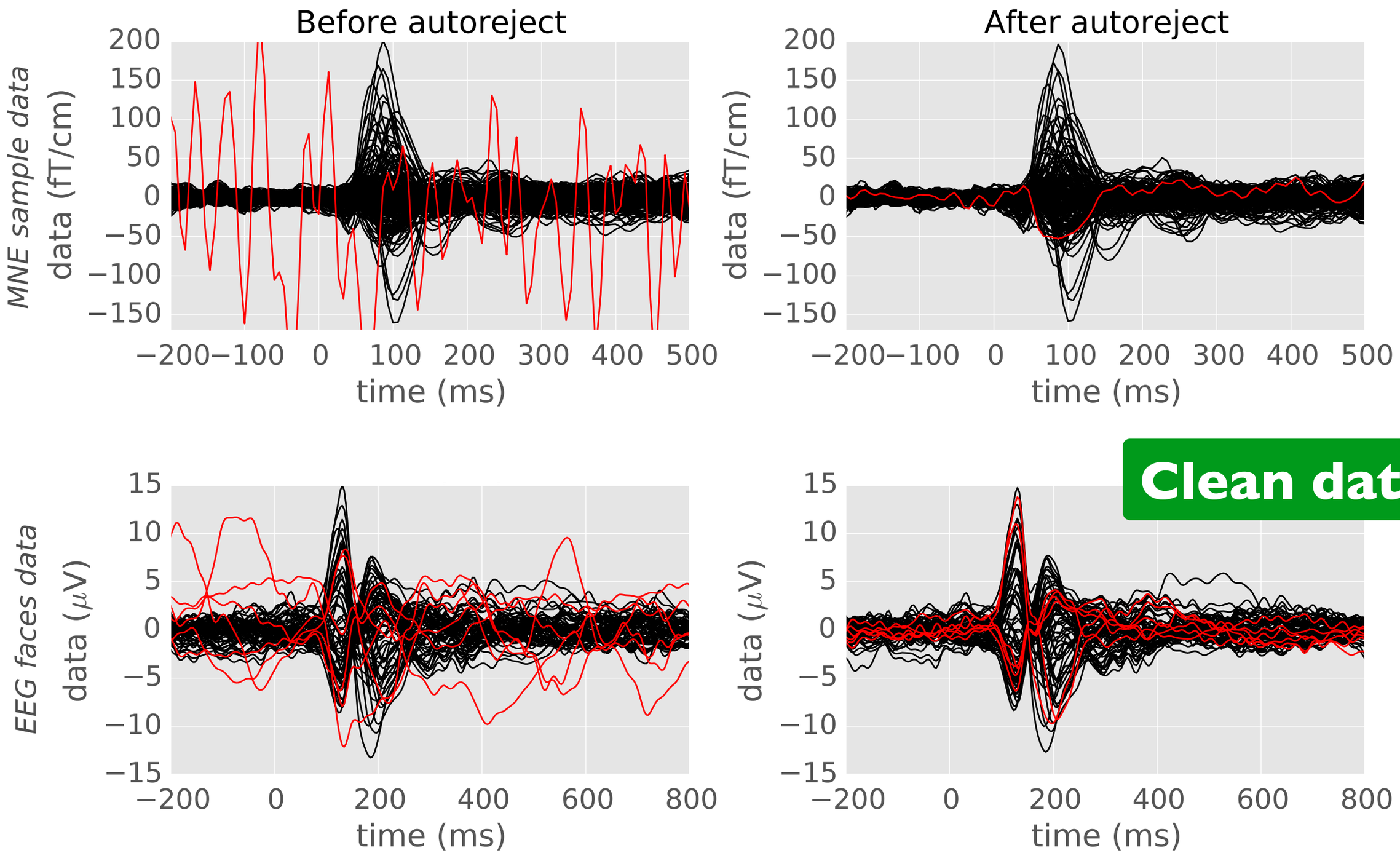

Sensor to be interpolated

Bad sensor but not going to be interpolated

Bad trials

http://autoreject.github.io/auto_examples/plot_visualize_bad_epochs.html

# Automatic artifact cleaning tool

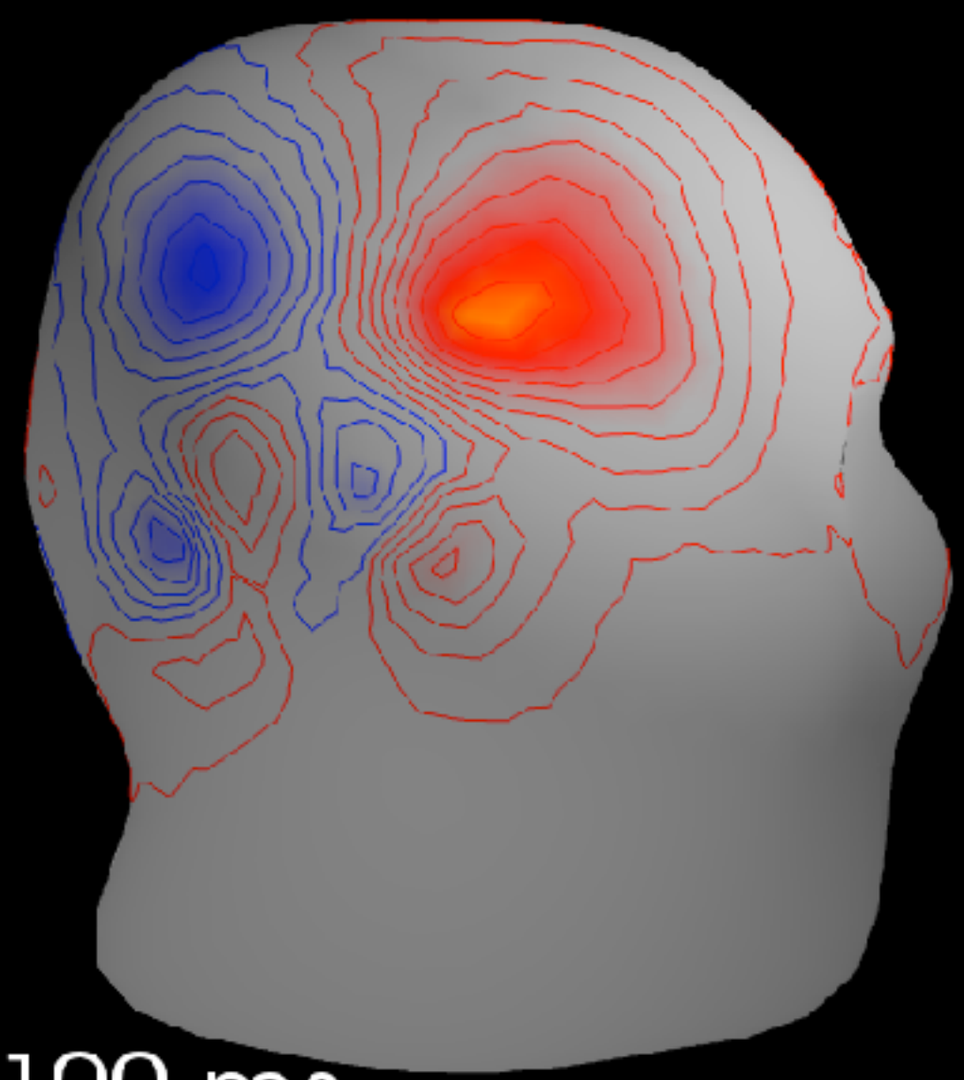



[M Jas, D Engemann, Y Bekhti, F Raimondo, and A Gramfort, "Autoreject: Automated artifact rejection for MEG and EEG.", NeuroImage 2017]

# Imaging the brain at a millisecond time scale with MEG and EEG

## and stats and optimization

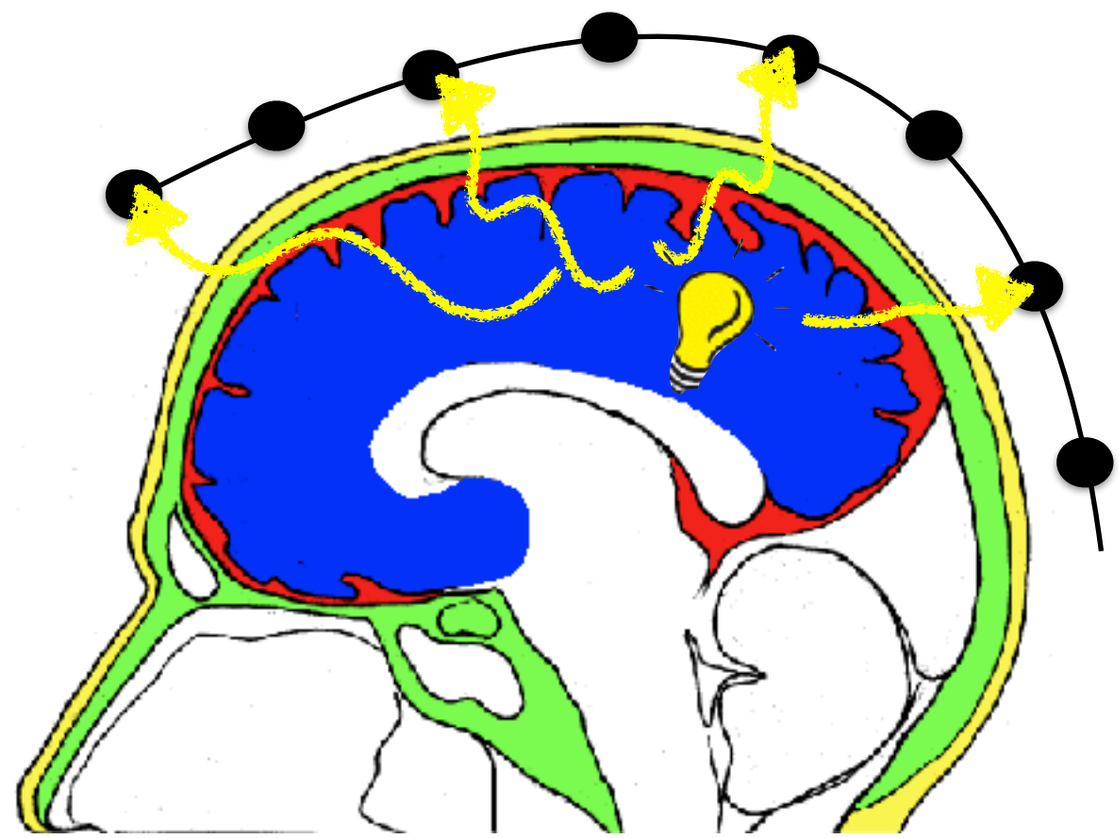
**Find the current generators** that produced the MEG measurements



t = 100 ms

# What do we measure?

$$\nabla \times \vec{B} = \mu_0 \vec{J}$$

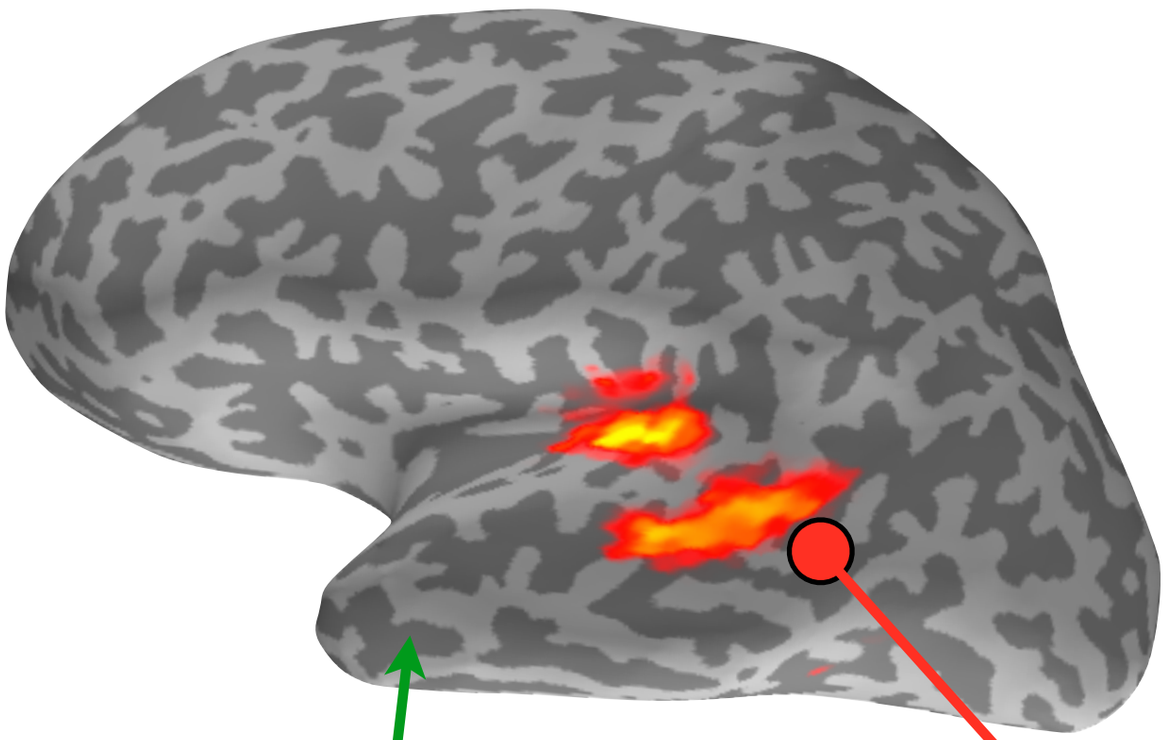


Boundary element method (BEM),
i.e., numerical solver with
approximate solution.

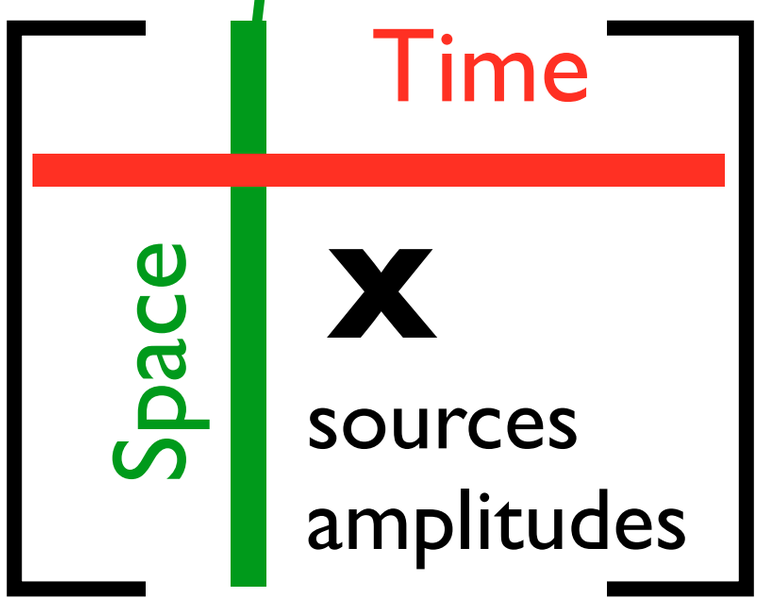
Linear PDE -> Linear forward problem / Fixed design

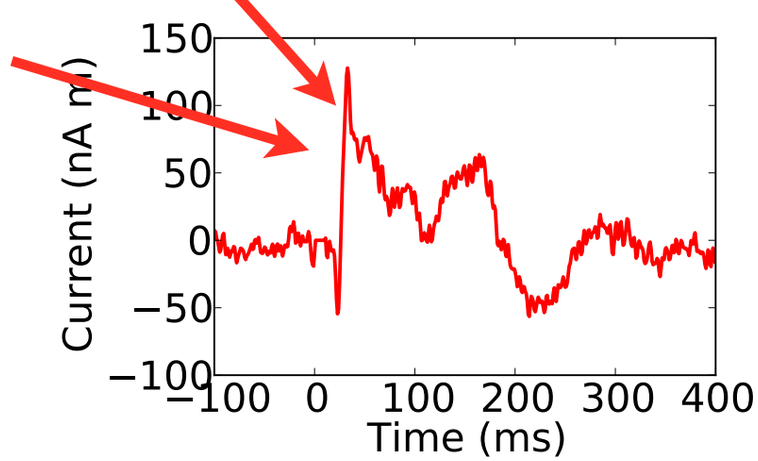
[Geselowitz 67, De Munck 92, Kybic et al. 2005, Gramfort et al. 2010 ]

# The source model



Position 5000 candidate sources over each hemisphere (e.g. every 5mm)



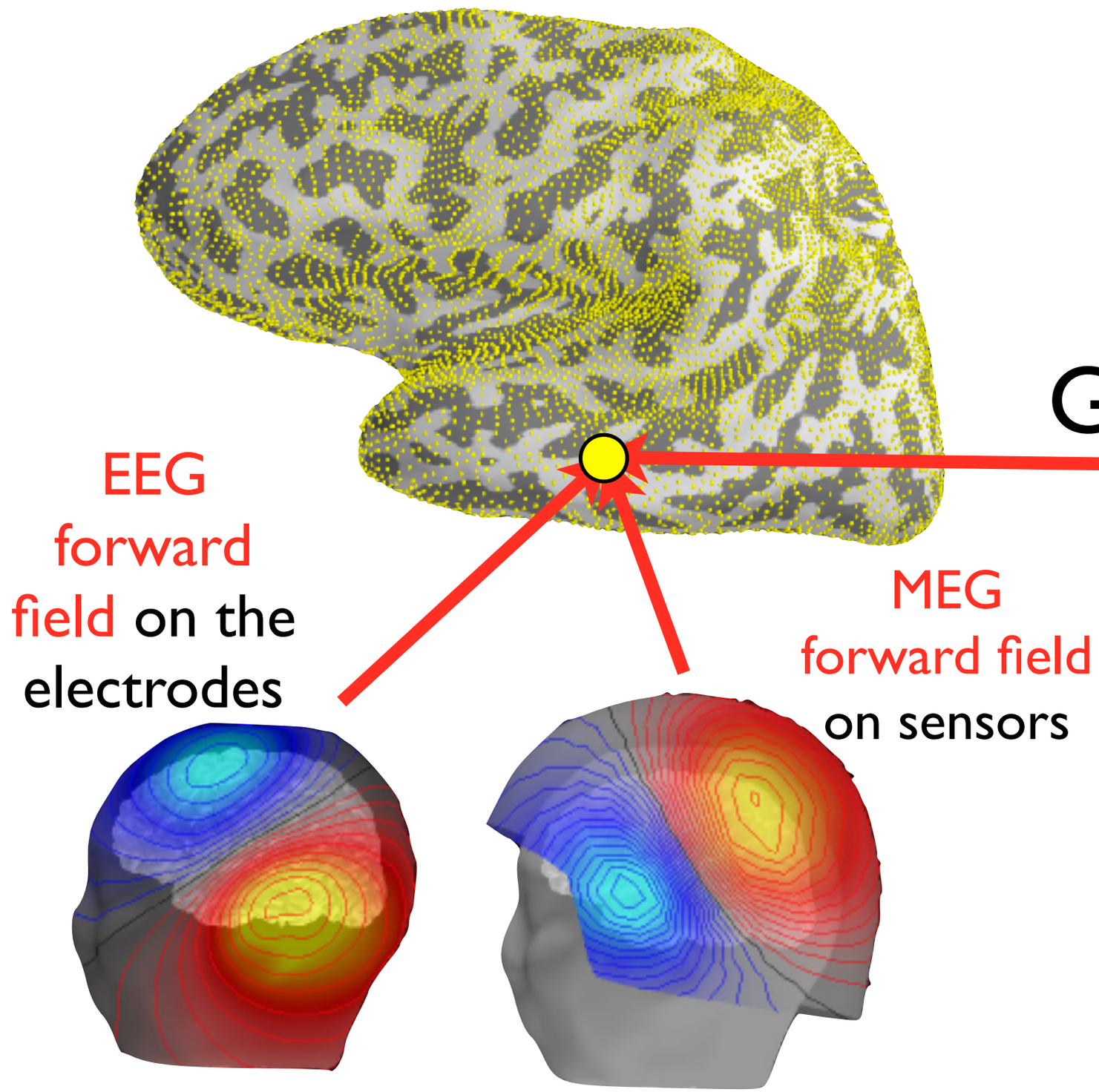




$$\mathbf{X} \in \mathbb{R}^{\mathbf{P} \times \mathbf{T}}$$

*Scalar field defined over time*

[Dale and Sereno 93]

# The source model

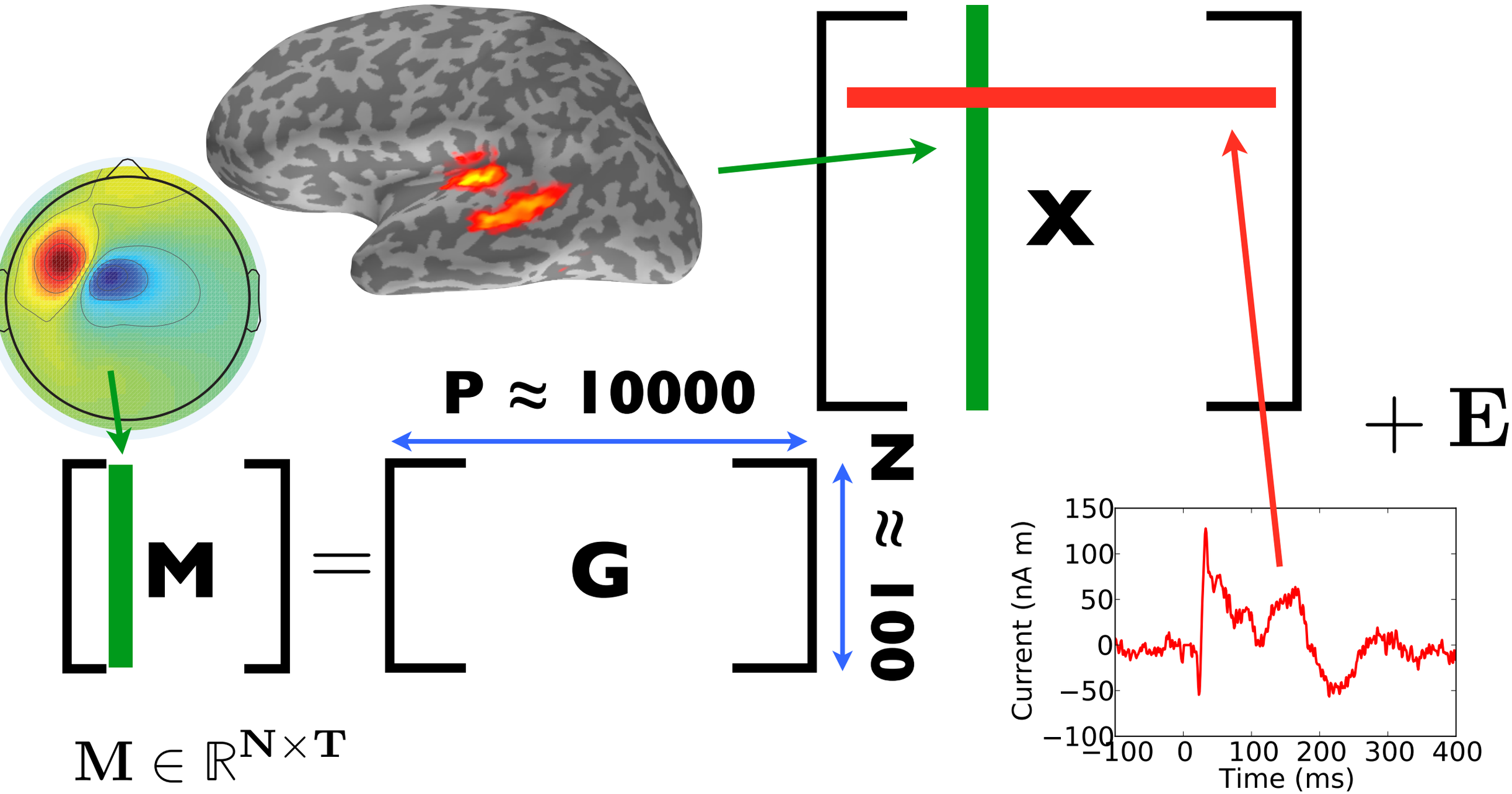



one column = Forward field of one dipole

$$G = \left[\begin{array}{c} G_{EEG} \\ \hline G_{MEG} \end{array}\right] \in \mathbb{R}^{\mathbf{N} \times \mathbf{P}}$$

G is the gain matrix / forward operator obtained by concatenation of the forward fields

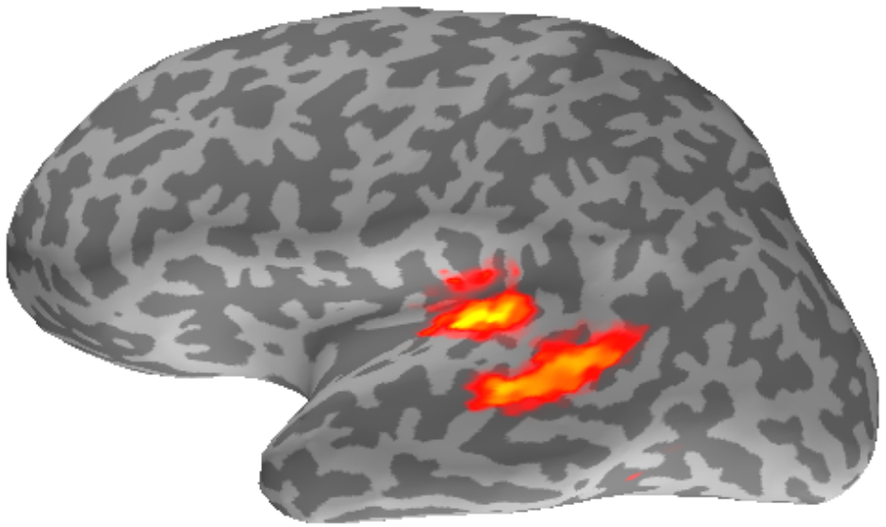
# M = GX+E : An ill-posed problem




$\mathbf{M} \in \mathbb{R}^{\mathbf{N} \times \mathbf{T}}$

**Small "N" large "P" problem**

# $y_t = X\beta_t + e_t$ : An ill-posed problem



Standard statistics notations

$\boldsymbol{\beta_t} \in \mathbb{R}^{\mathbf{P}}$

regression coefficients

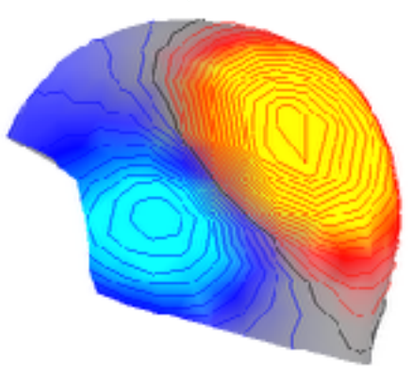
**P ≈ 10000**

$$\mathbf{y_t} = \mathbf{X} \quad \mathbf{N \approx 100}$$

$\in \mathbb{R}^{\mathbf{N}}$ (design matrix)

$+ \mathbf{e_t}$

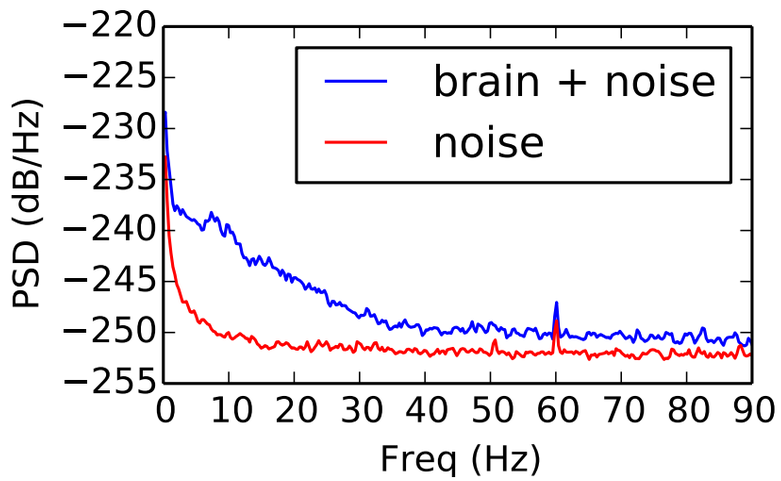
$\in \mathbb{R}^{\mathbf{N}}$



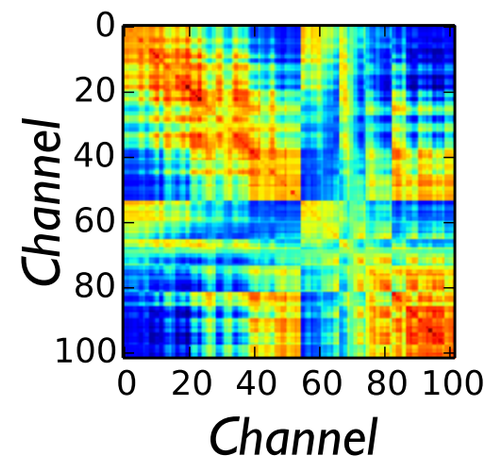
At **each time instant** the M/EEG inverse problem **IS** a **regression** with more variables than observations

# Why is it challenging?

- Complex signal dynamics: oscillations and transients
- Complex noise structure: colored and heteroscedastic



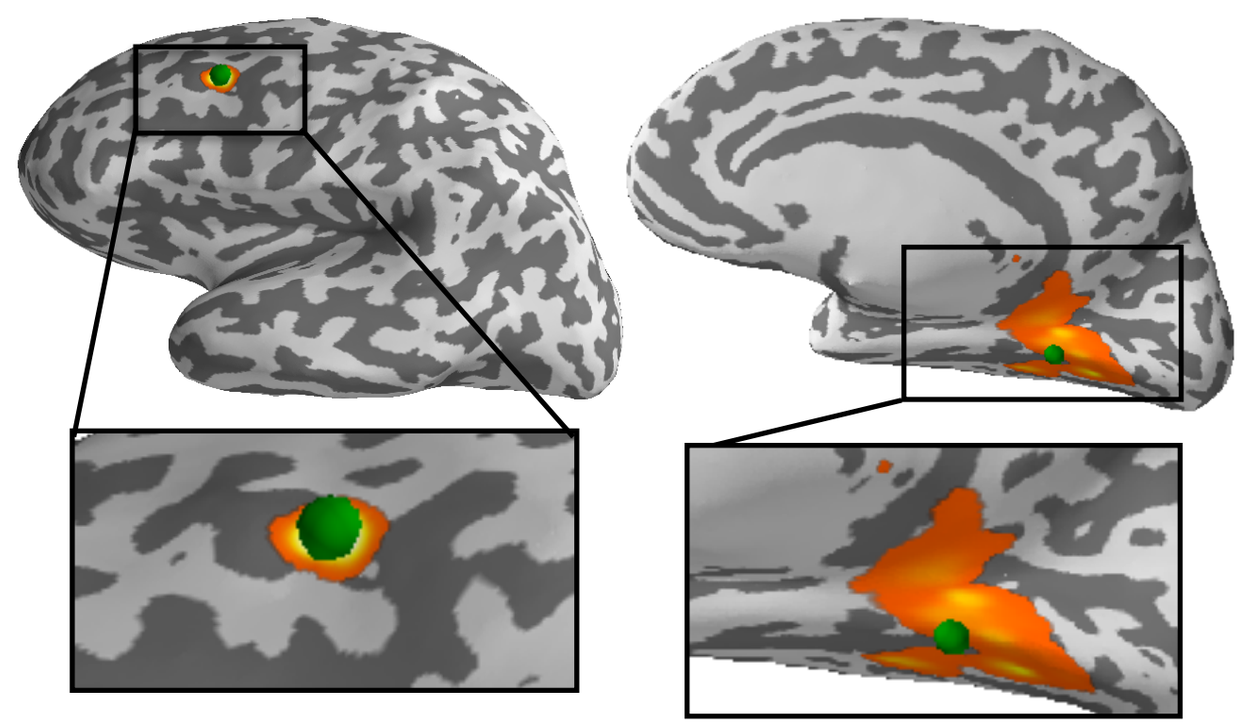

*Spectrum*




*Spatial correlation*

*[Engemann & Gramfort, Neuroimage 2015]*

- Device sensitivity varies with sensor types & source locations



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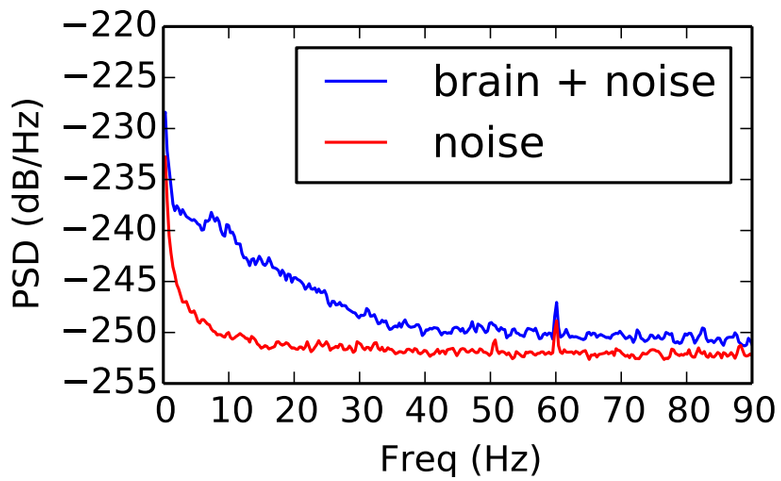
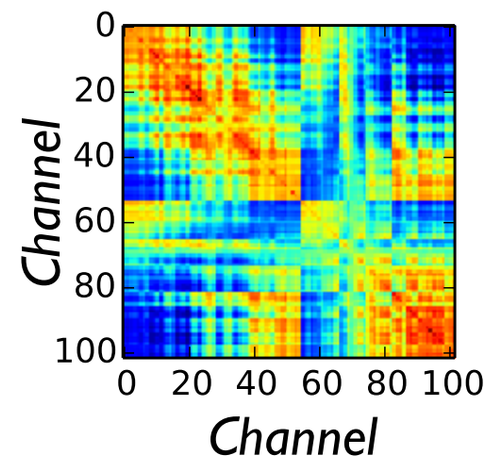



*Spectrum*

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*[Engemann & Gramfort, Neuroimage 2015]*

- Device sensitivity varies with sensor types & source locations

*What not giving up?*
*Clinical use (sleep, epilepsy, stroke, autism) & Cognitive Neurosience, Neuroengineering*

# Variational formulation

$$\mathbf{X}^* = \arg\min_{\mathbf{X}} \|\mathbf{M} - \mathbf{G}\mathbf{X}\|_F^2 + \lambda\phi(\mathbf{X}), \lambda > 0$$

Data fit Regularization

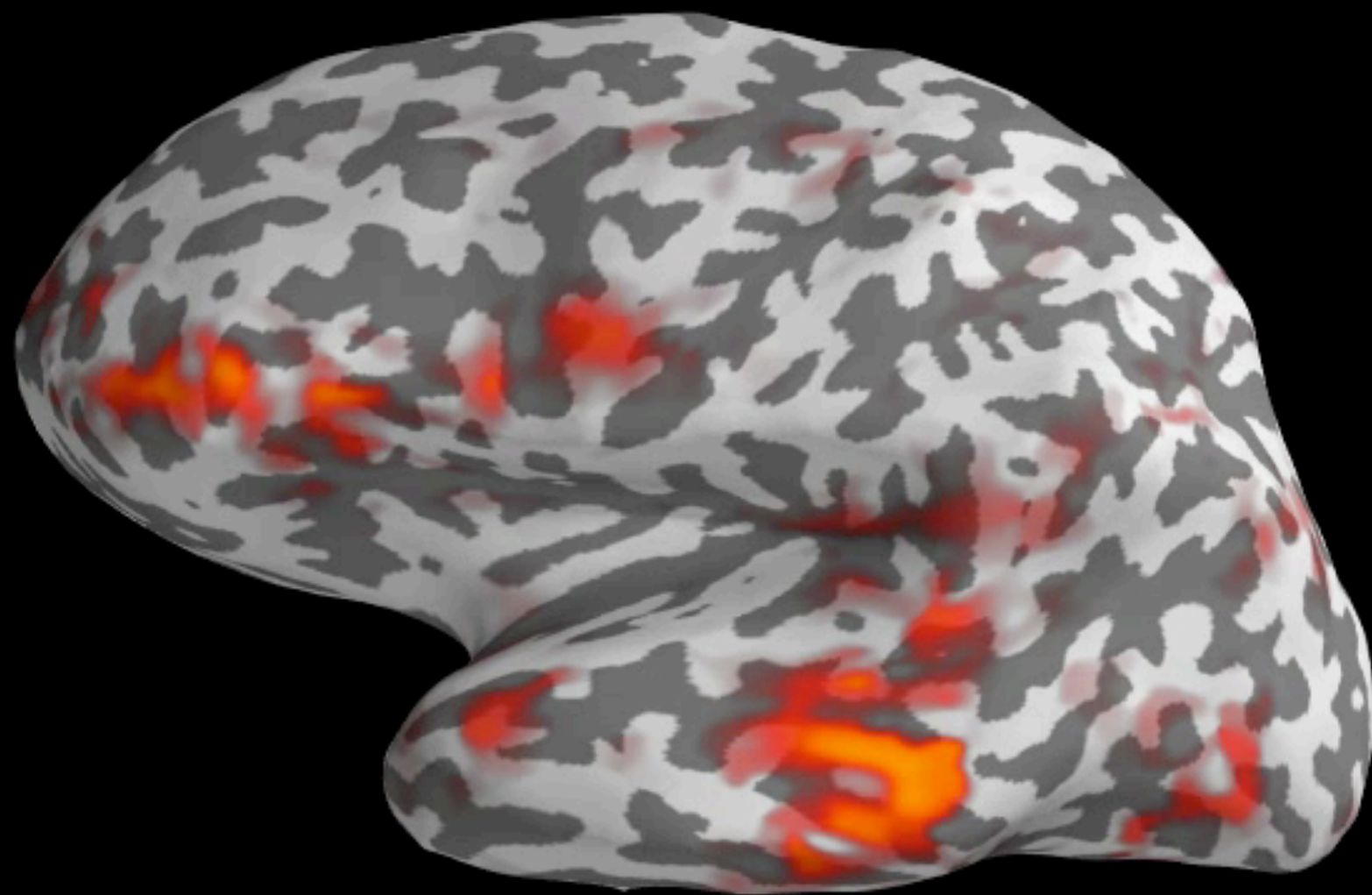
$\lambda$ : Trade-off between the data fit and the regularization

where $\|\mathbf{A}\|_F^2 = \mathbf{tr}(\mathbf{A}^T\mathbf{A})$

**Remark:** We assume here Gaussian i.i.d. homoscedastic noise. For heteroscedastic regression see e.g.

[Massias et al. Heteroscedastic Concomitant Lasso for sparse multimodal electromagnetic brain imaging, Arxiv]

Result obtained with L2 regularization: $\phi(\mathbf{X}) = \|\mathbf{X}\|_F^2$



time=0.00 ms

http://youtu.be/Uxr5Pz7JPrs

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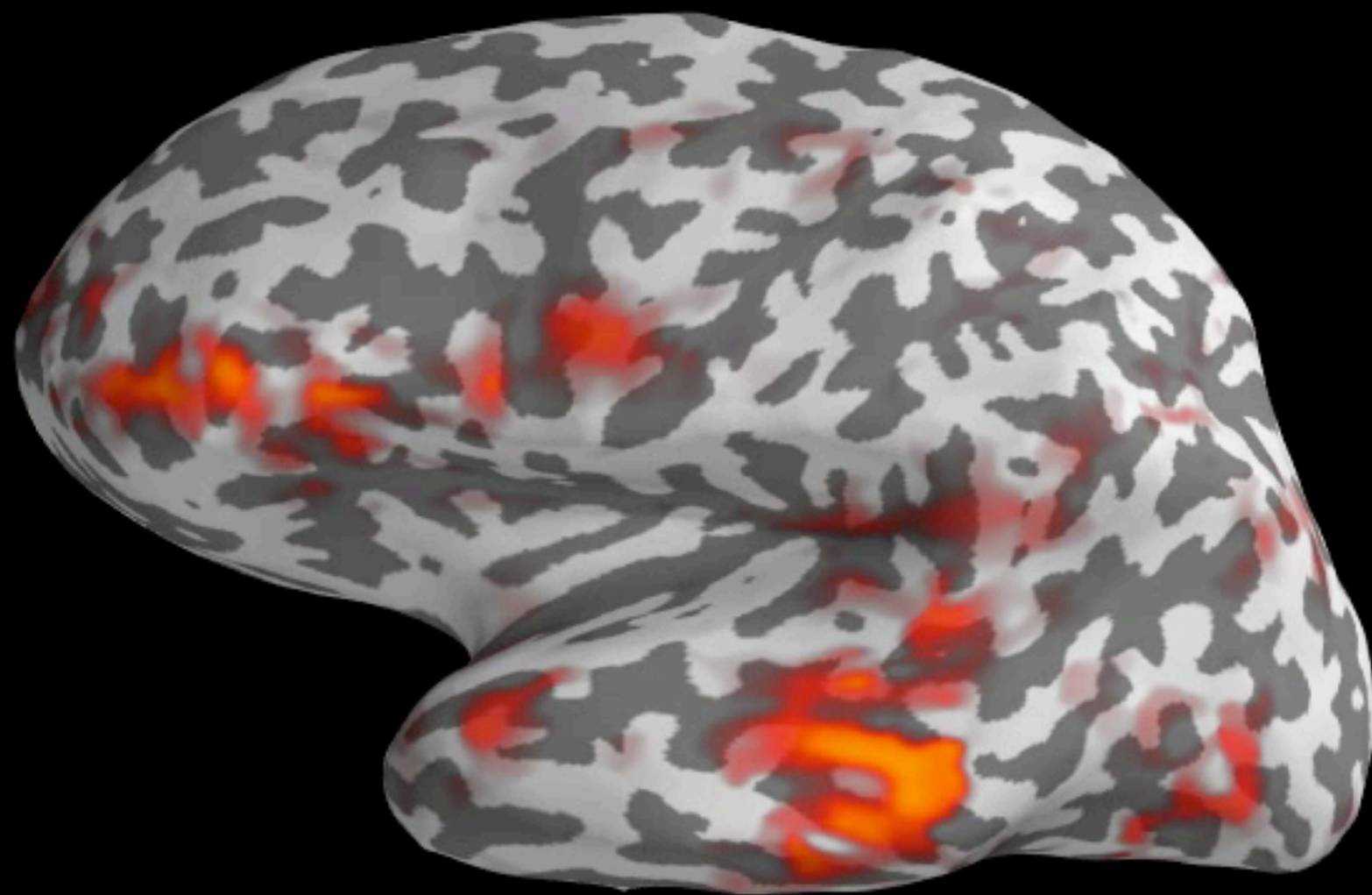

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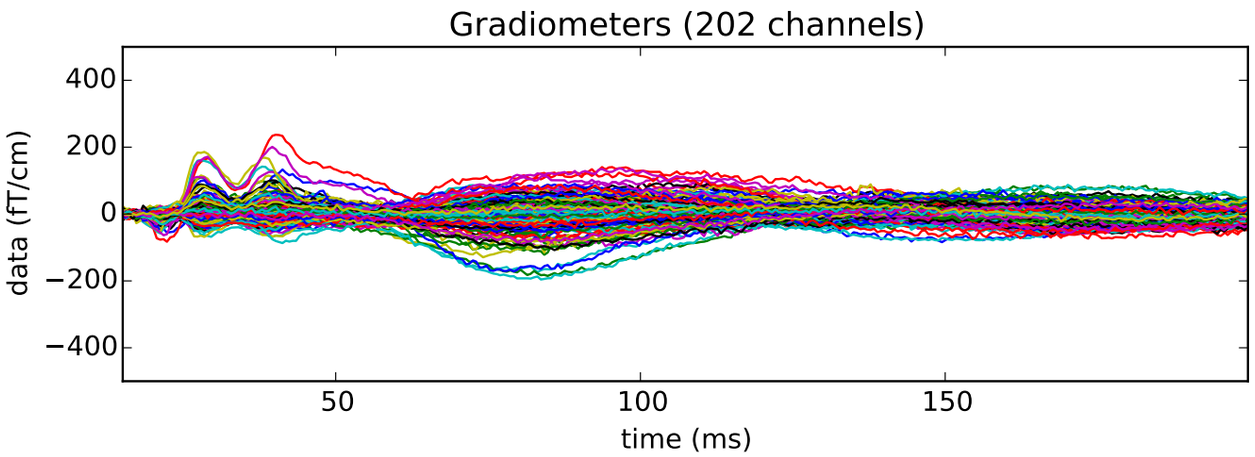
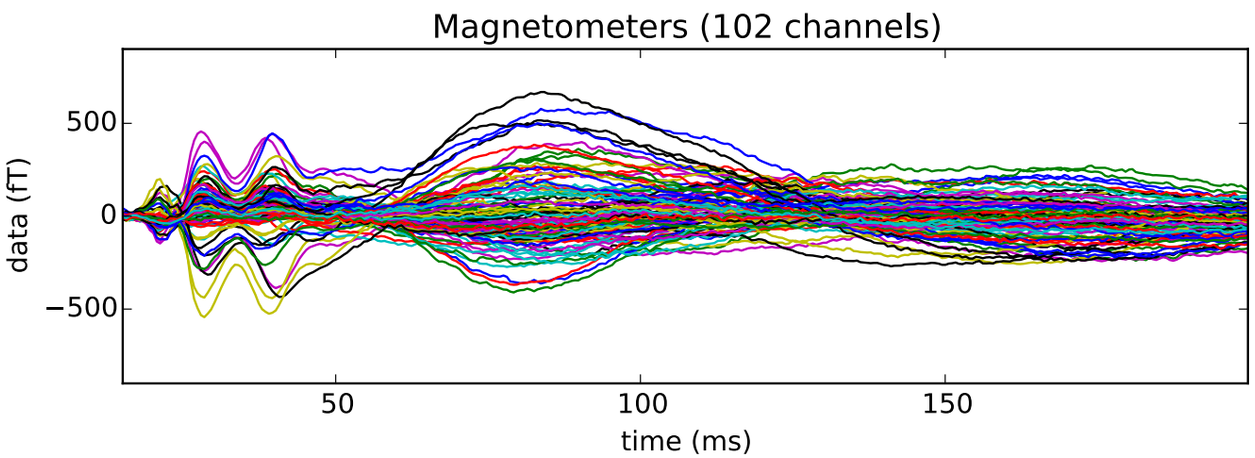
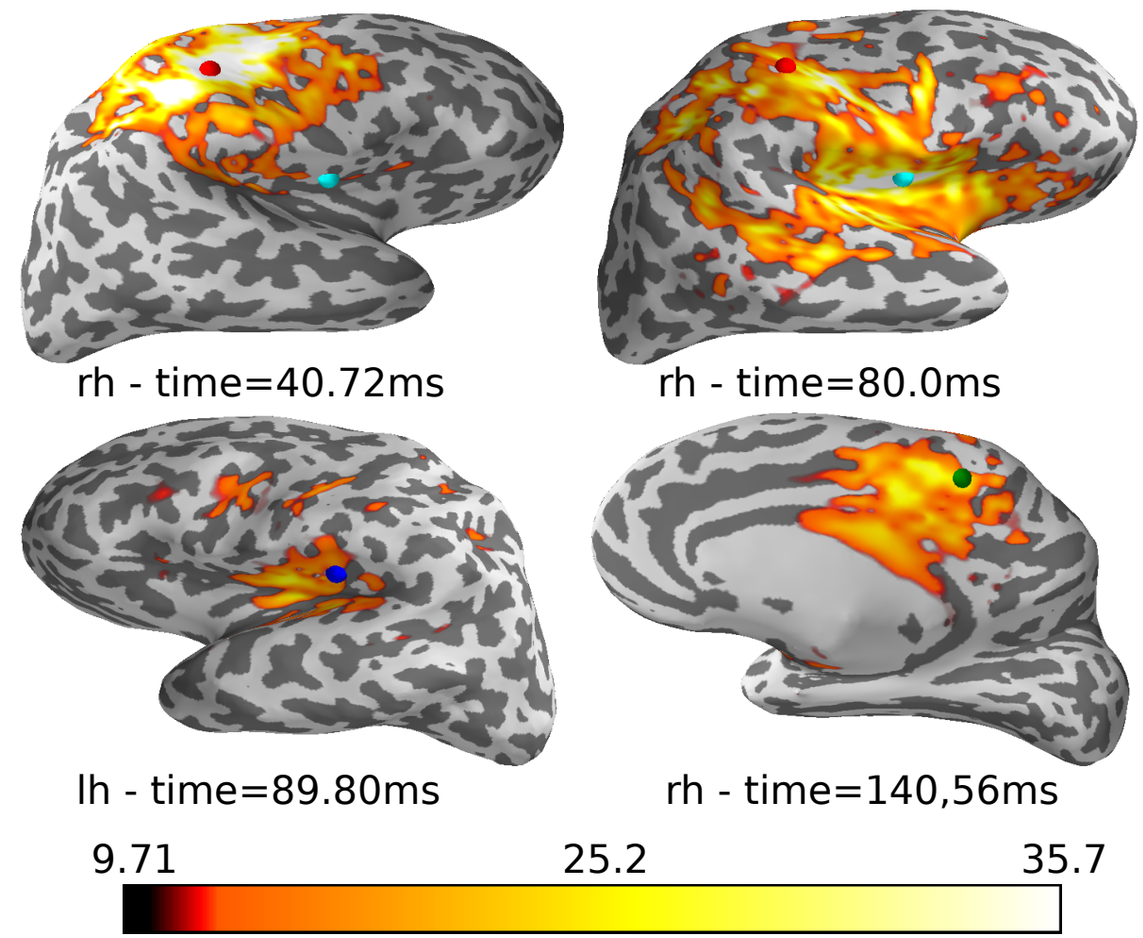
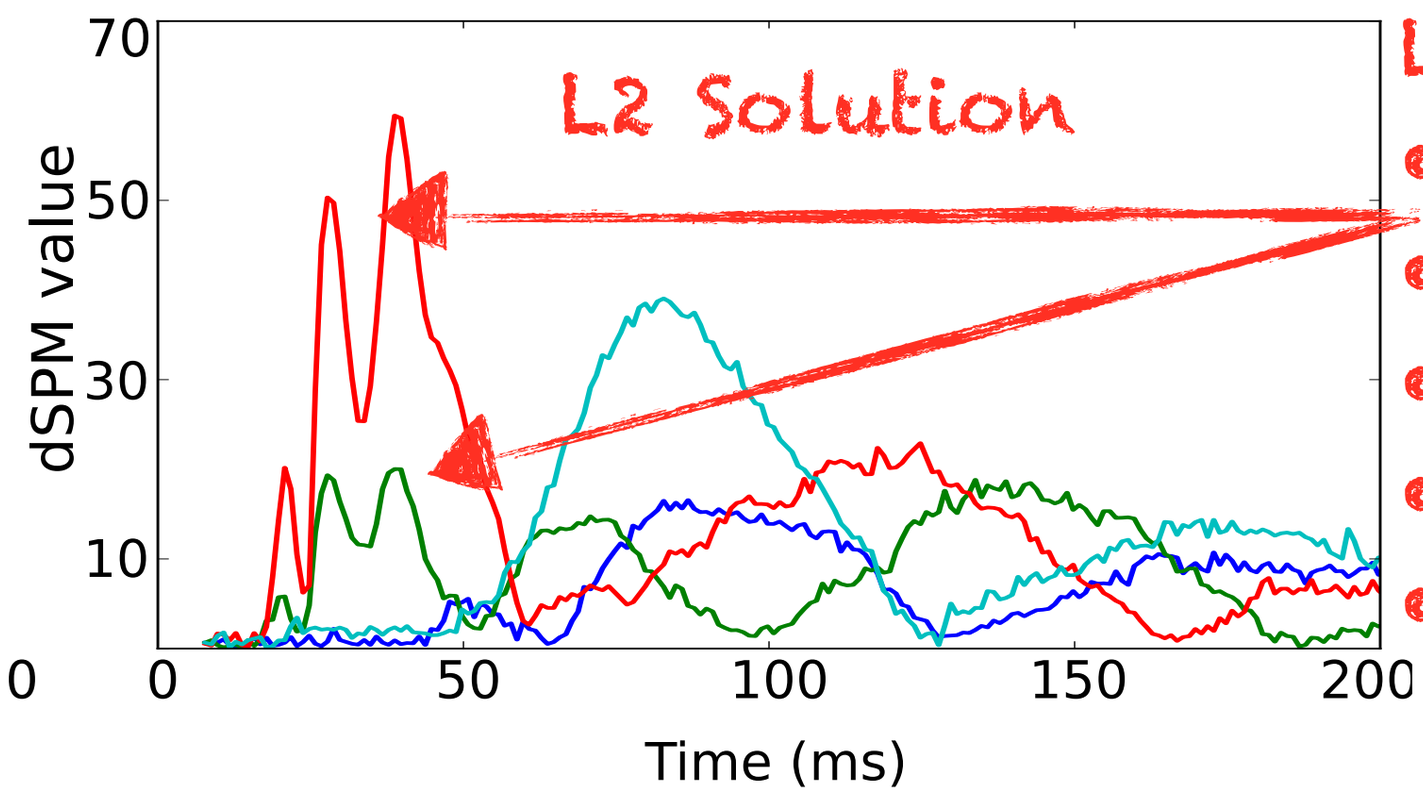


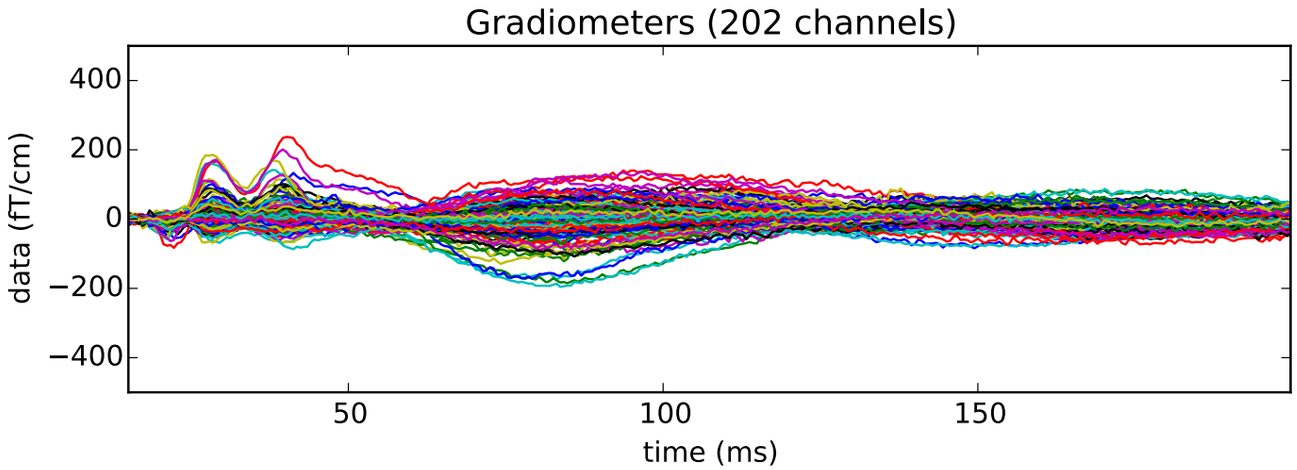



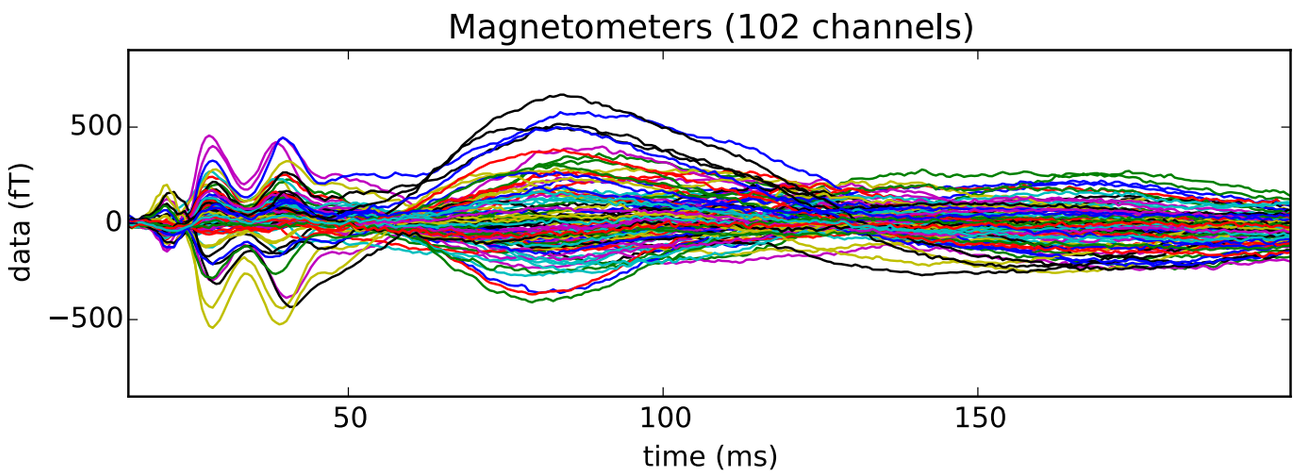



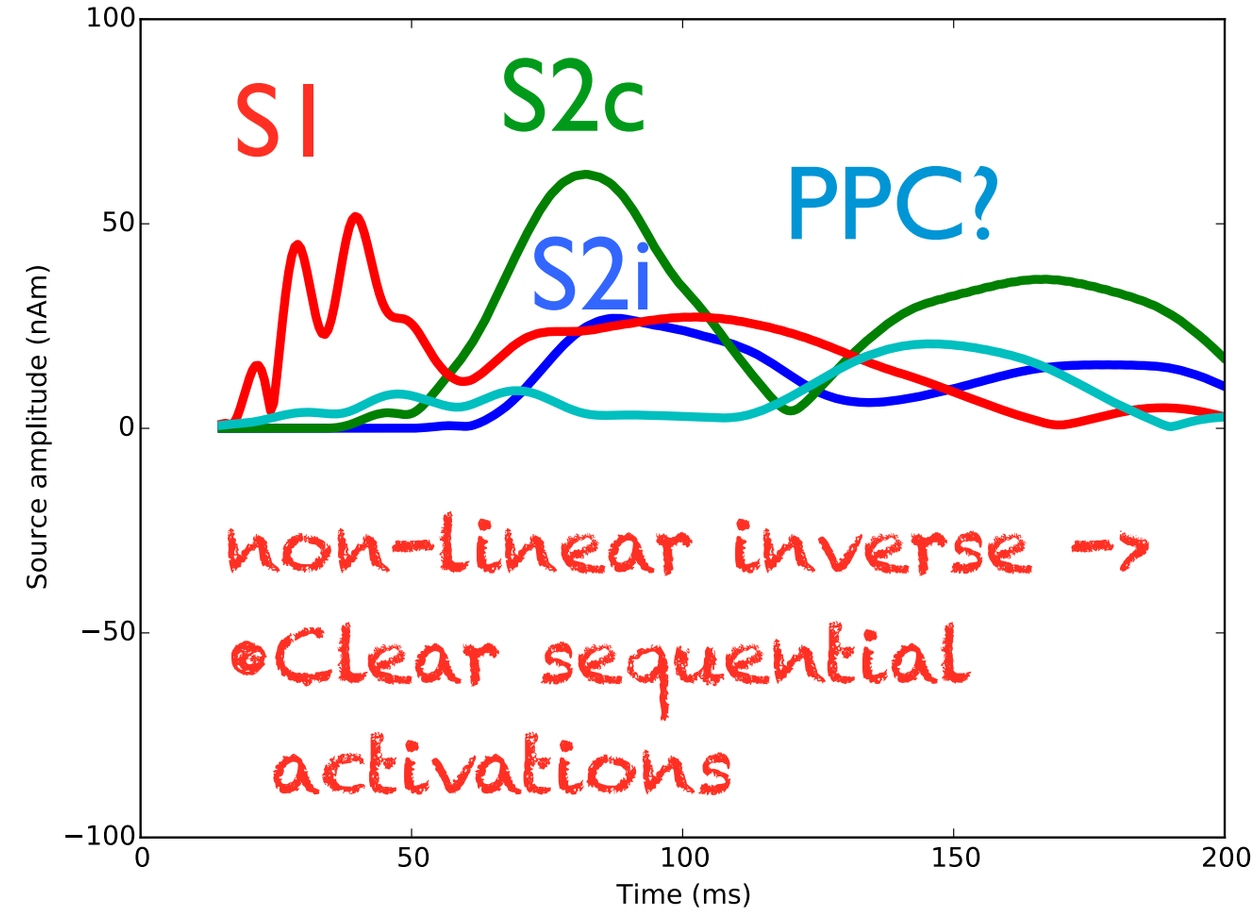

Linear inverse ->

- Imperfect deconvolution
- spatial leakage
- smeared activations
- no temporal smoothing
- but really fast...

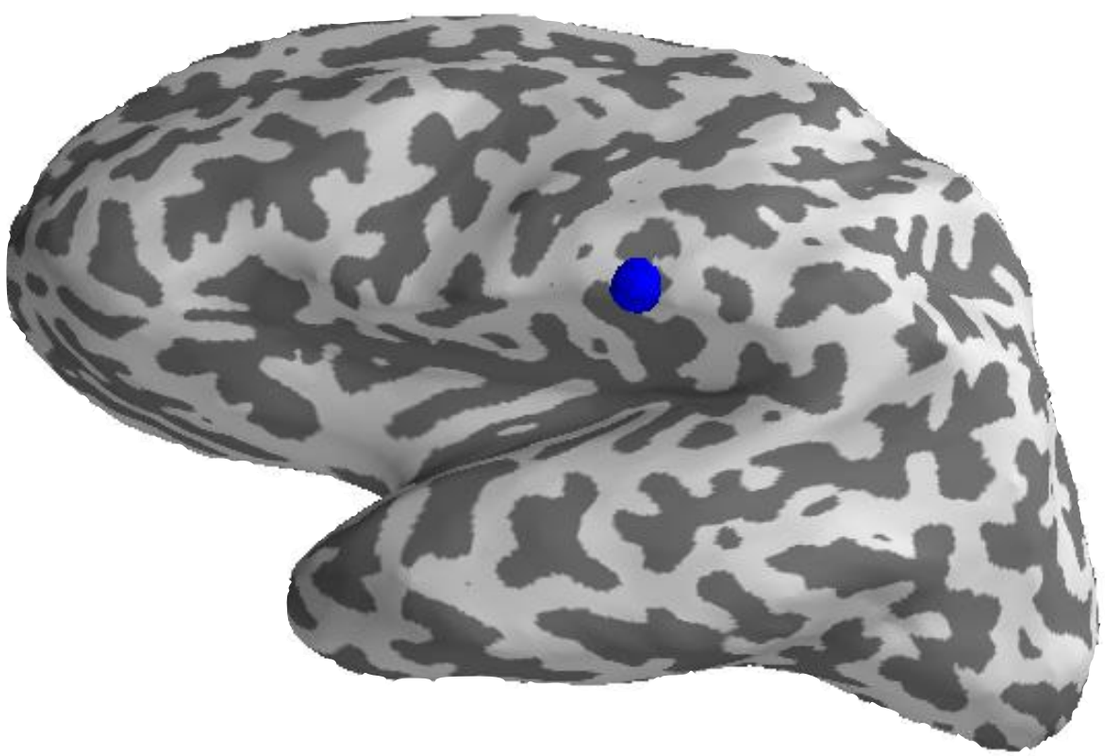
# $\phi(\mathbf{X})$ sparse / non-smooth

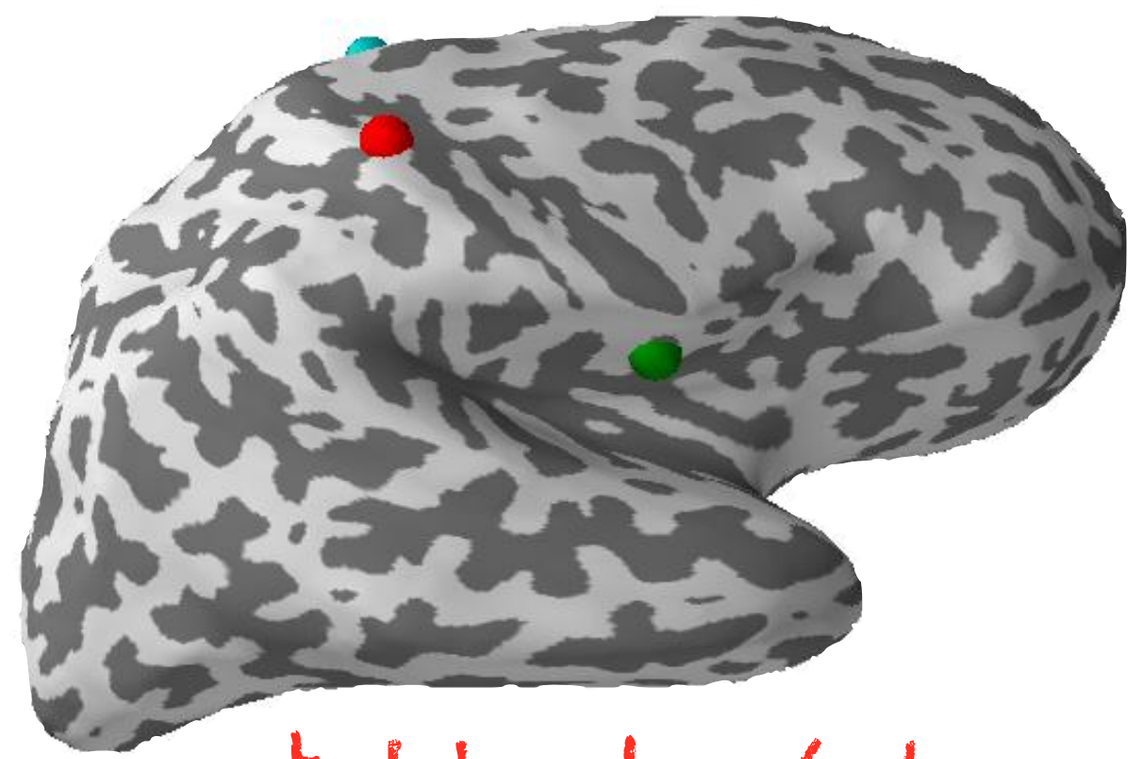


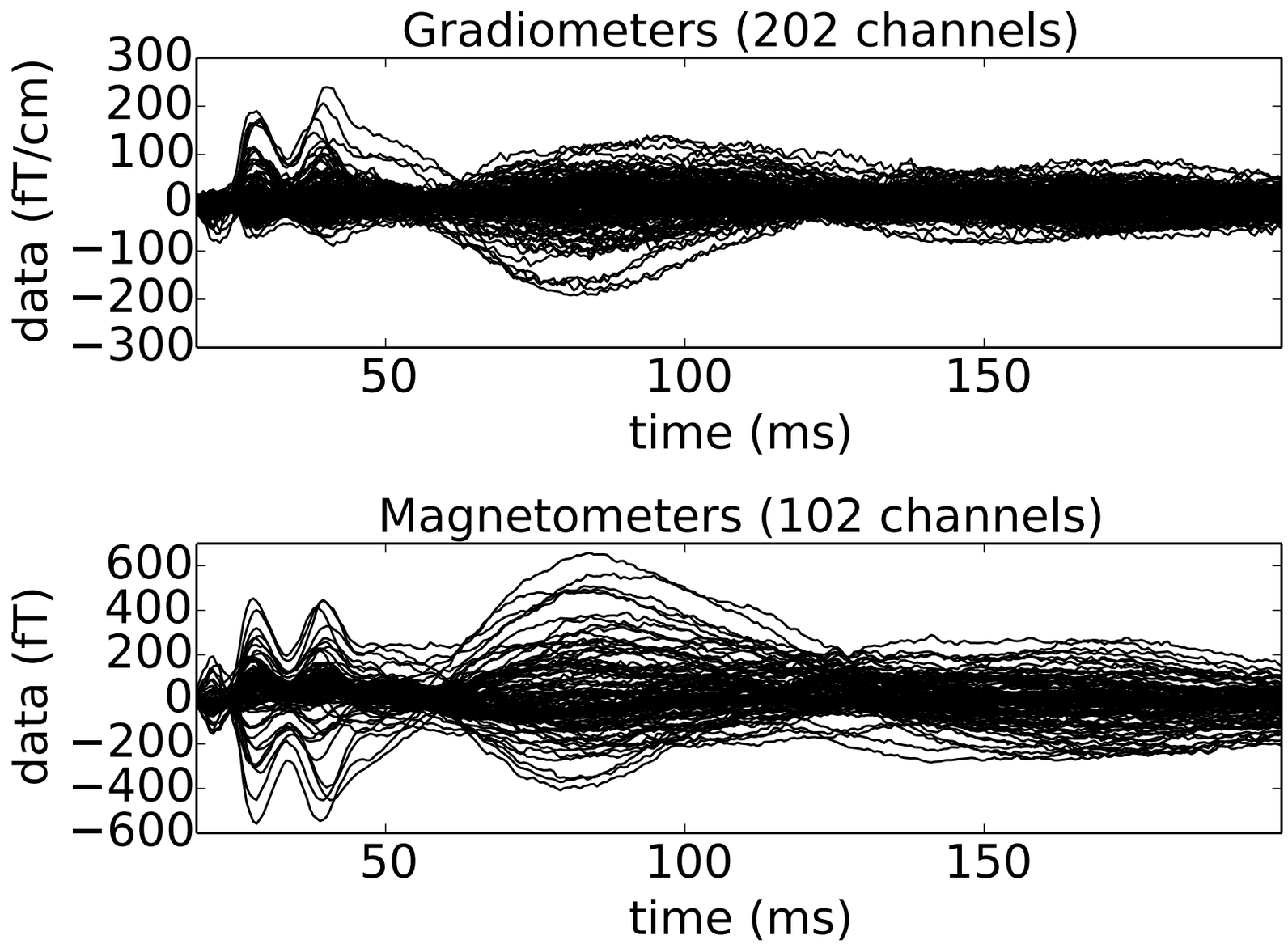

non-linear inverse ->
•Clear sequential activations





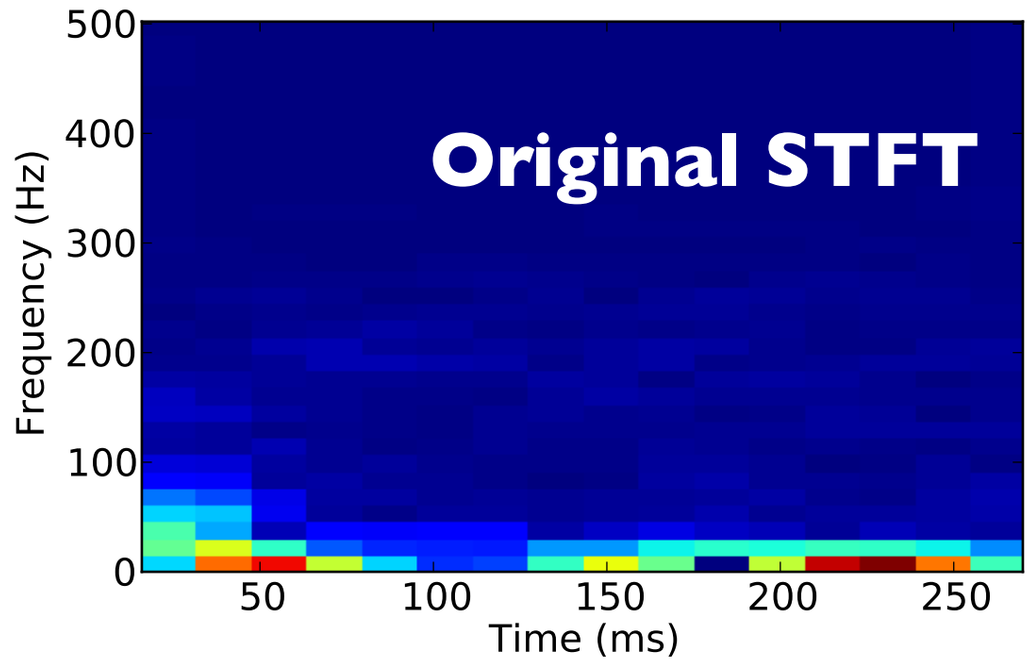
but harder / slower ....

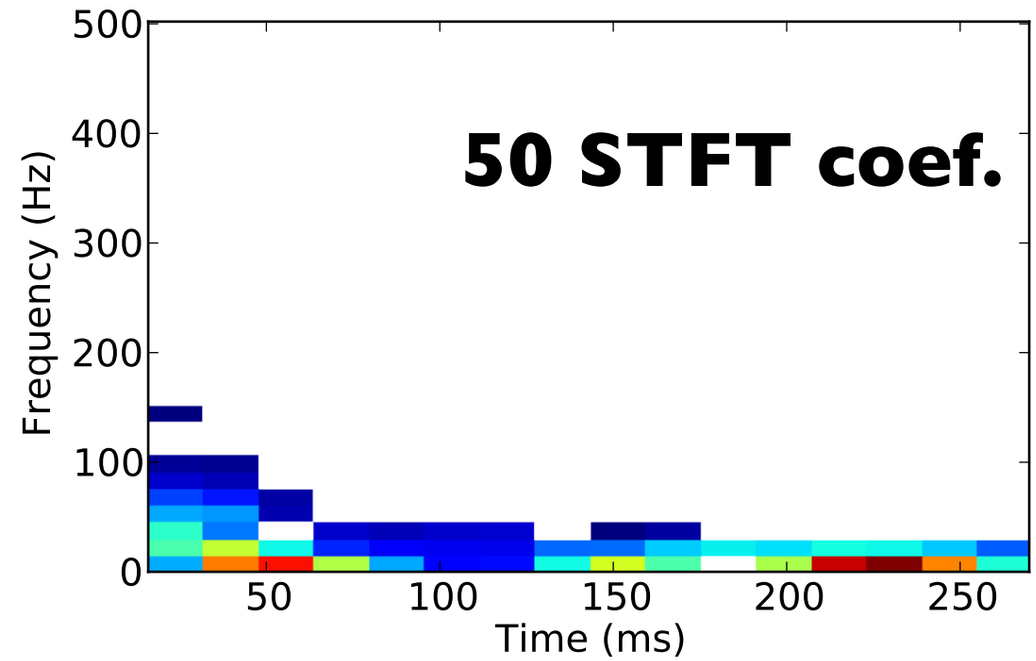
# Data are spatio-temporal

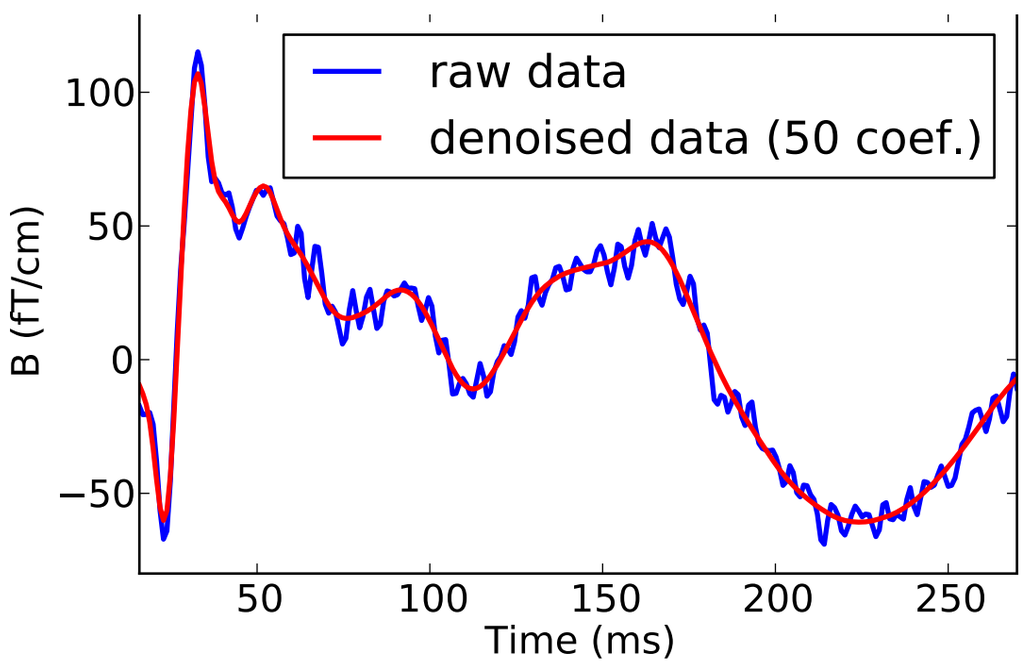



**Challenge: How do you promote sparse solutions with non-stationary sources?**

# Change the represensation



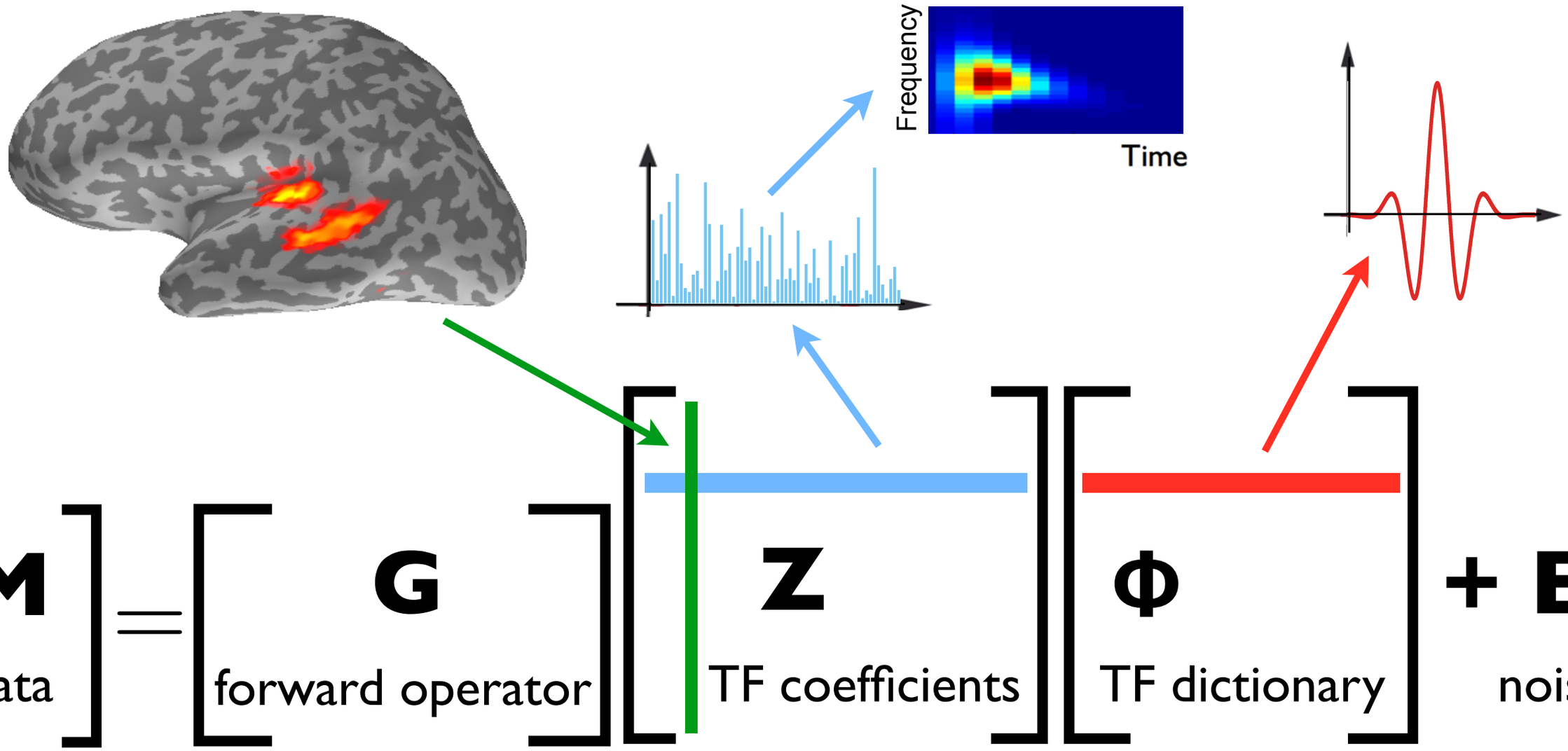



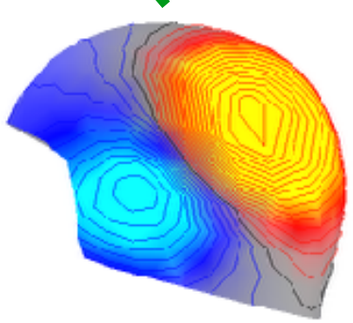




[“Wavelet shrinkage” Donoho & Johnstone 94]
[“Soft thresholding” Donoho 95]
[Application to evoked EEG, O. Bertrand et al. 94]
[Application to ST EEG, Quiroga et al. 03]
etc.

[Moussallam, Gramfort, Richard, Daudet, Signal Processing Letters 2014 ]

# $M = GZ\Phi + E$



**Objective: estimate Z given M**

[Gramfort et al., *Time-Frequency Mixed-Norm Estimates: Sparse M/EEG imaging with non-stationary source activations*, Neuroimage 2013]

# Time-frequency (TF) regularization

**The classical approach** [MNE, dSPM, sLORETA]:

$$\hat{\mathbf{X}} = \arg\min_{\mathbf{X}} \underbrace{\|\mathbf{M} - \mathbf{G}\mathbf{X}\|_F^2}_{\text{data fit}} + \underbrace{\lambda\phi(\mathbf{X})}_{\text{regularization}}, \ \lambda > 0$$

**we propose:**

$$\hat{\mathbf{Z}} = \arg\min_{\mathbf{Z}} \|\mathbf{M} - \mathbf{G}\mathbf{Z}\mathbf{\Phi}^{\mathcal{H}}\|_F^2 + \lambda\phi(\mathbf{Z}), \ \text{then } \hat{\mathbf{X}} = \hat{\mathbf{Z}}\mathbf{\Phi}^{\mathcal{H}}$$

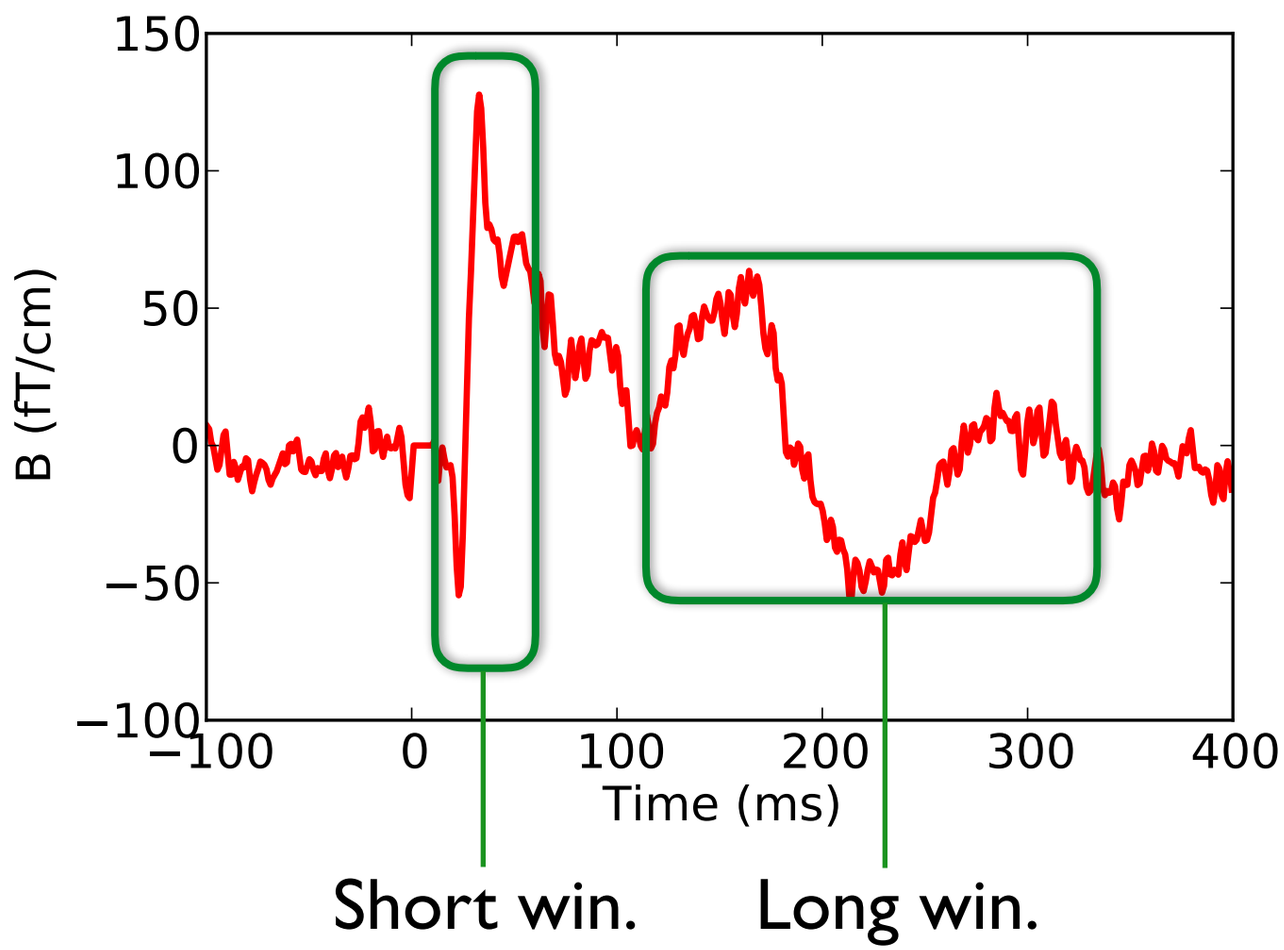
- $\Phi$ : is a **TF dictionary**
- $Z$ : **coefficients** of the **TF transform** of the sources

localization in space, time and frequency in one step

# Multi-scale dictionary

$$\hat{\mathbf{Z}} = \arg\min_{\mathbf{Z}} \|\mathbf{M} - \mathbf{G}\mathbf{Z}\mathbf{\Phi}^{\mathcal{H}}\|_F^2 + \lambda\phi(\mathbf{Z}), \text{ then } \hat{\mathbf{X}} = \hat{\mathbf{Z}}\mathbf{\Phi}^{\mathcal{H}}$$

- $\mathbf{\Phi}$ : union of n **STFT dict. with diff. window lengths**
- $\mathbf{Z}$ : is the combination of **coefficients** of the diff. **TF transforms** of the sources

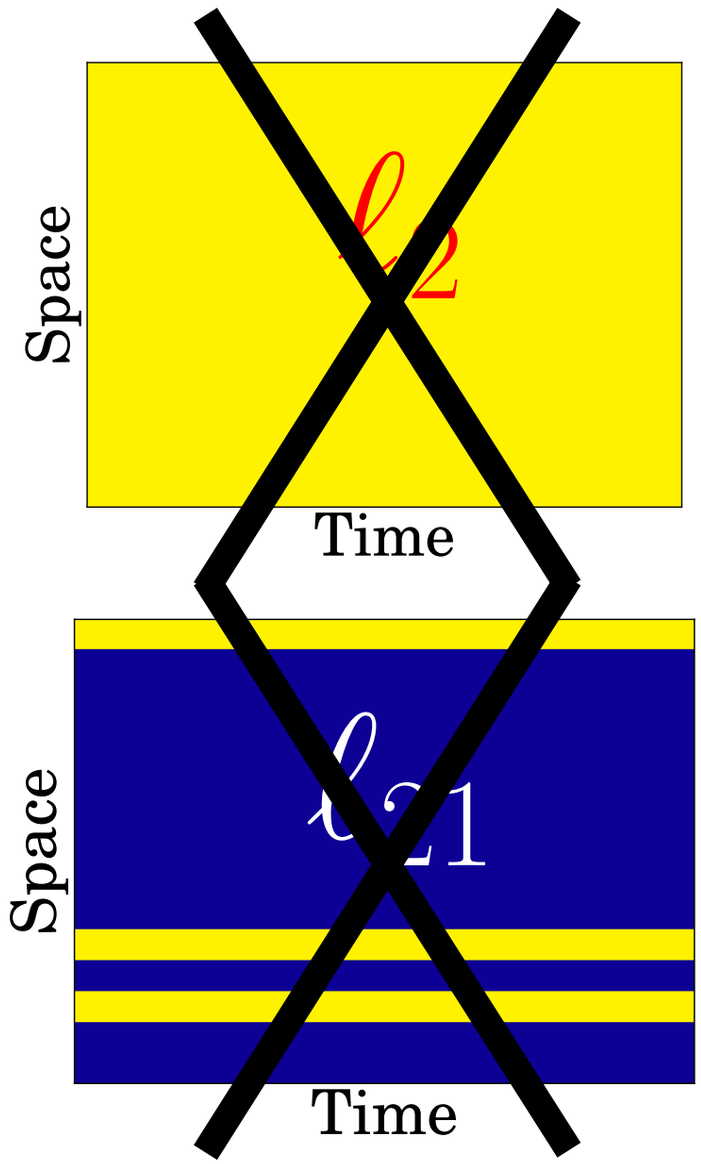


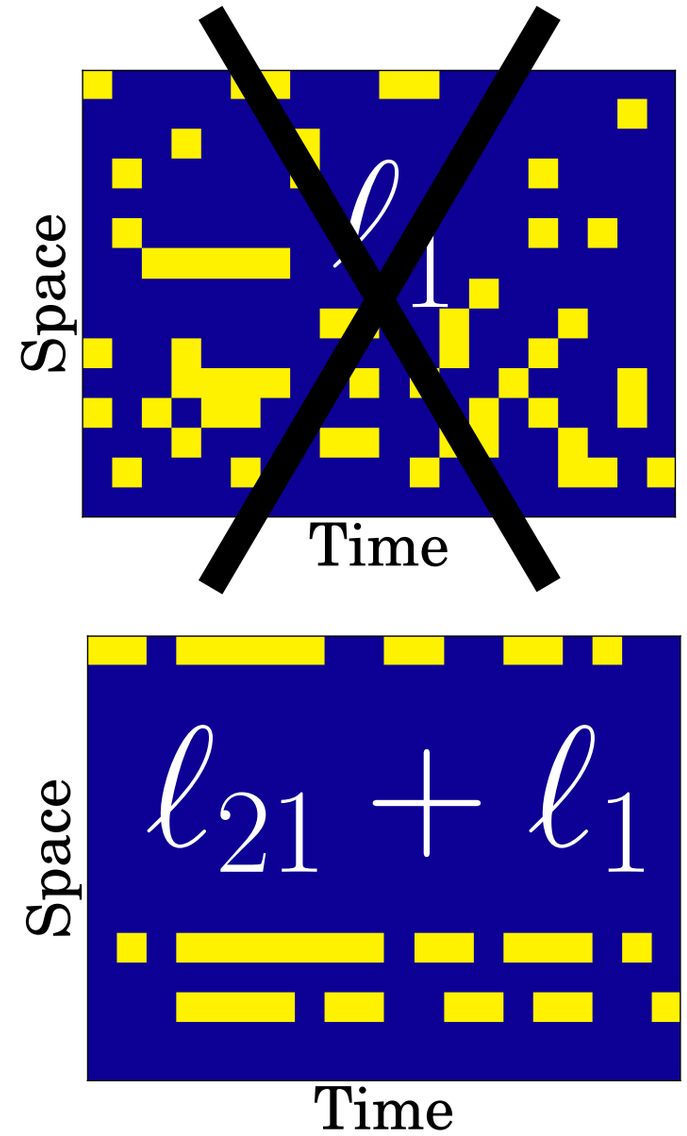

[Bekhti et al. 2016]

cf. [Kowalski et al. 2008]

cf. [Starck et al. 2005]

# What regularization?




Sparse Group Lasso

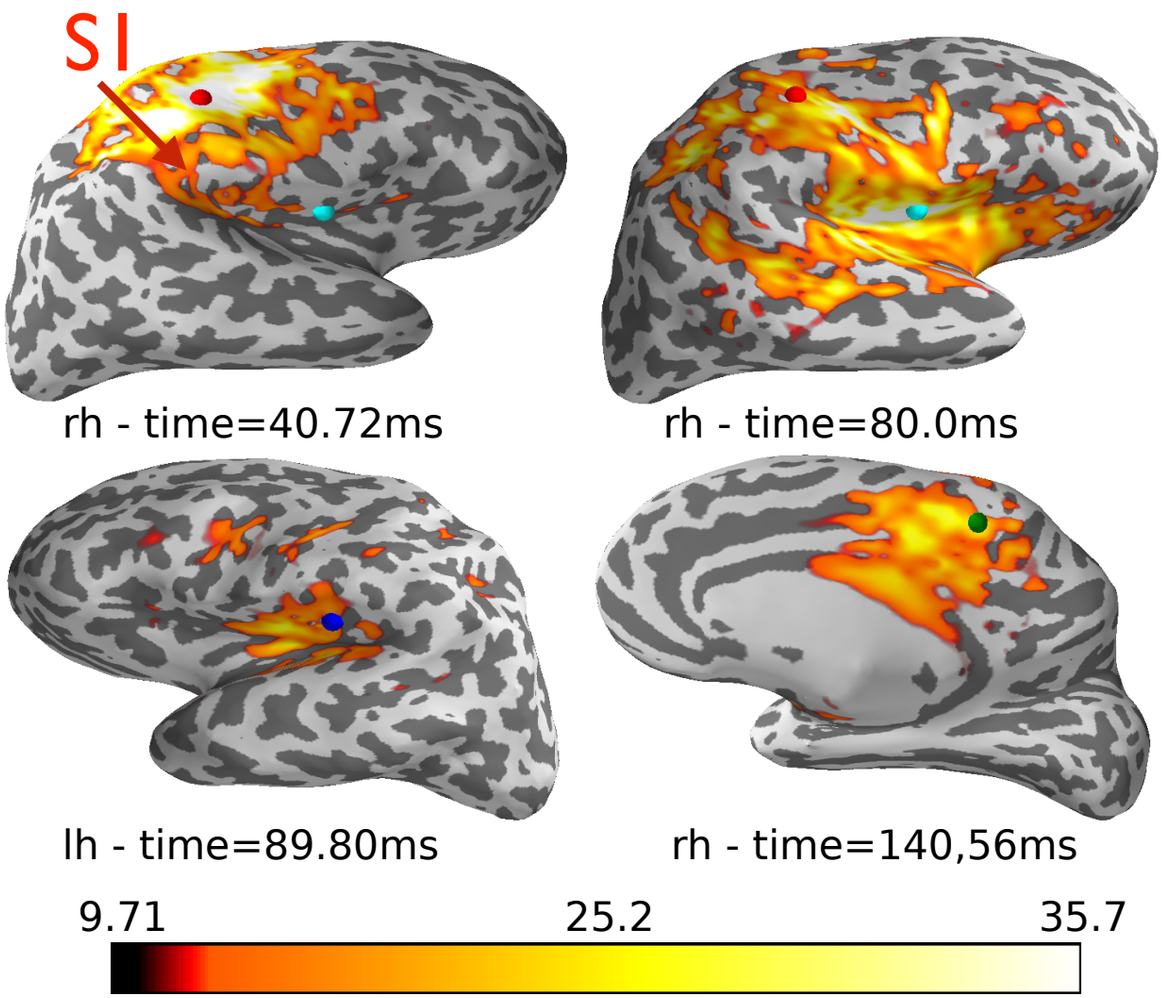
$$\phi(Z) = \lambda(\rho\|Z\|_1 + (1-\rho)\|Z\|_{21})$$

$$\|\mathbf{X}\|_{21} = \sum_i \sqrt{\sum_t |x_{i,t}|^2}$$

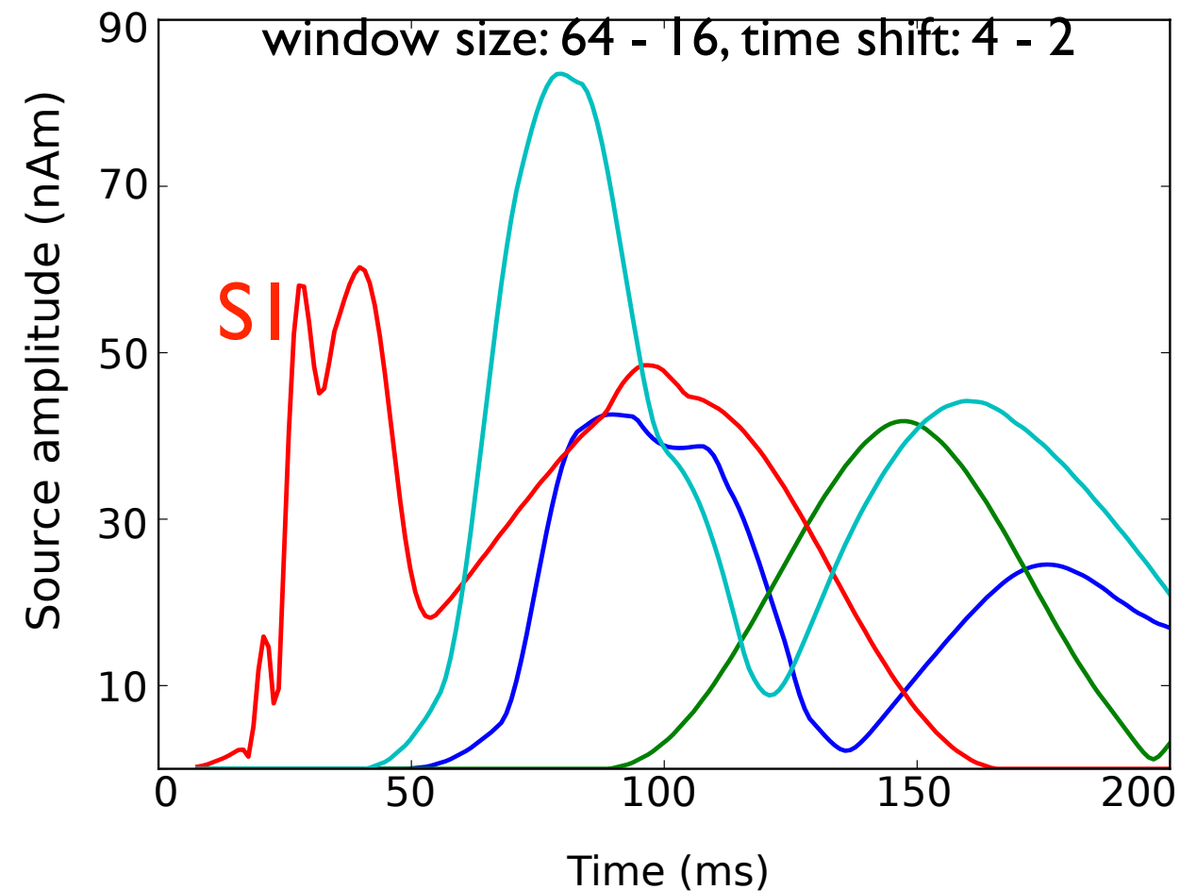
Safe screening for this model in [Ndiaye Fercoq Gramfort Salmon NIPS 2016 ]

# Results

Somatosensory - MIND dataset




dSPM




- Clear sequential activations
- No spatial leakage

[Bekhti et al. PRNI 2016]

# Optimization procedure

- Keys to fast solvers:
  - Block coordinate descent it the way !

    eg. [Tseng 2001, Friedman et al. 2007]
  - Gap Safe Screening rules

    [Fercoq et al. ICML 2015, N'Diaye et al. NIPS. 2016]
  - Working set strategies (cf. Blitz method)

    eg. [Johnson et al. ICML 2015]

**Algorithm 2** Coordinate descent (Lasso) with GAP Safe screening

**Input:** $X, y, \epsilon, K, f, (\lambda_t)_{t \in [T-1]}$

Initialization: $\lambda_0 = \lambda_{\max}, \quad \beta^{\lambda_0} = 0$
**for** $t \in [T-1]$ **do** ▷ Loop over $\lambda$'s
  $\beta \leftarrow \beta^{\lambda_{t-1}}$ ▷ previous $\epsilon$-solution
  **for** $k \in [K]$ **do**
    **if** $k \mod f = 1$ **then**
      Construct $\theta \in \Delta_X$, $A^{\lambda_t}(\mathcal{C}) = \{j \in [p] : \mu_{\mathcal{C}}(\mathbf{x}_j) \geqslant 1\}$
      **if** $G_{\lambda_t}(\beta, \theta) \leqslant \epsilon$ **then** ▷ Stop if duality gap small
        $\beta^{\lambda_t} \leftarrow \beta$
        **break**
      **end if**
    **end if**
    **for** $j \in A^{\lambda_t}(\mathcal{C})$ **do** ▷ Soft-Threshold coordinates
      $\beta_j \leftarrow \mathrm{ST}\Big(\frac{\lambda_t}{\|\mathbf{x}_j\|^2}, \beta_j - \frac{\mathbf{x}_j^\top (X\beta - y)}{\|\mathbf{x}_j\|^2}\Big)$
    **end for**
  **end for**
**end for**

**Algorithm 2** Coordinate descent (Lasso) with GAP Safe screening

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Initialization: $\lambda_0 = \lambda_{\max}, \quad \beta^{\lambda_0} = 0$

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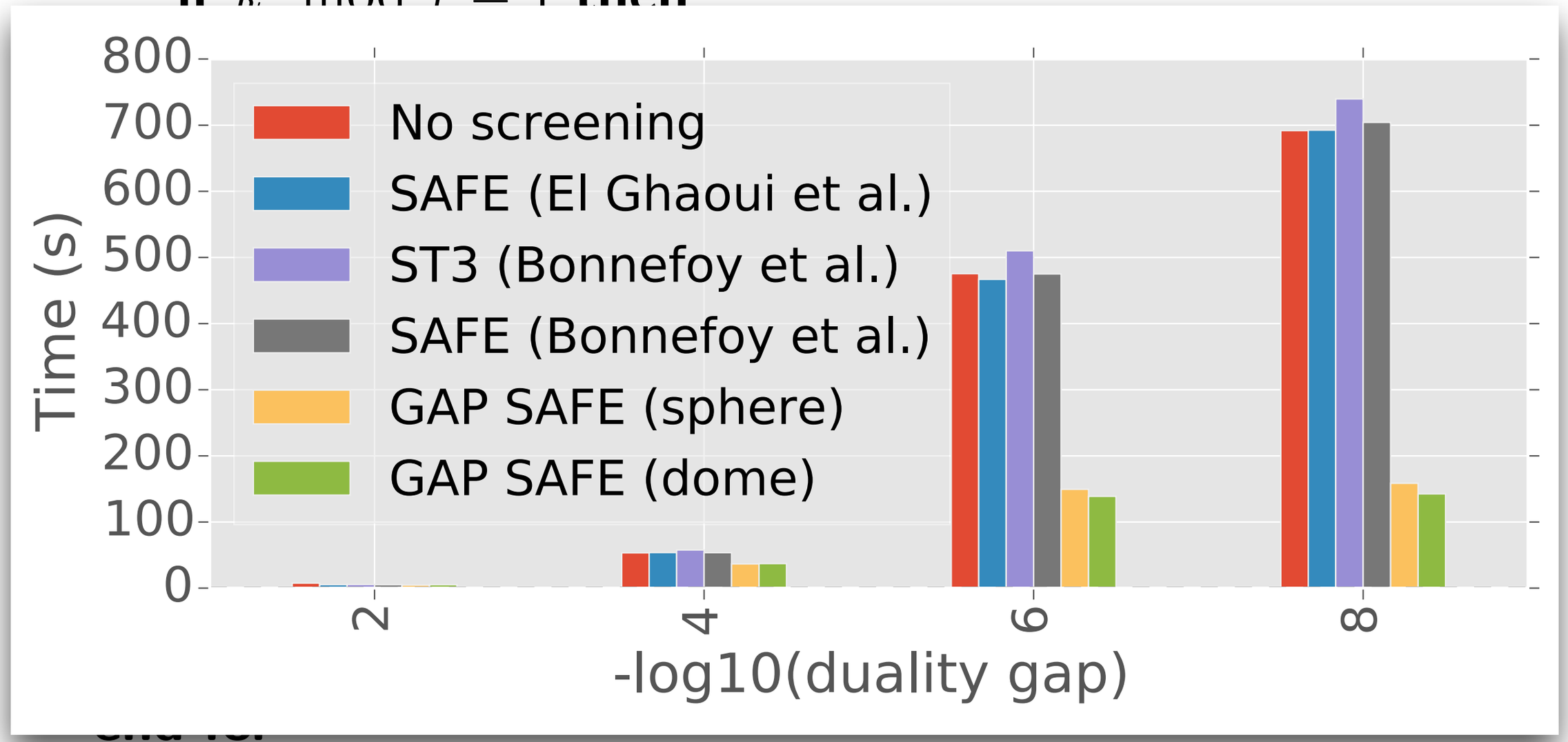
    **if** $k \mod f = 1$ **then**




**end for**

[Fercoq et al. ICML 2015]

# Conclusion / Challenges

- Signals are very weak and can be terribly noisy
- Noise is often physiological (e.g. brain itself) so its statistics are very complex (non-stationarity, heteroscedastic, etc.)
- Data are not so small and studies move towards population for which computation time and automatic processing are the key.
- Brain imaging people need easy access to the tools / software to process their data.

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scikit-learn.org/stable/

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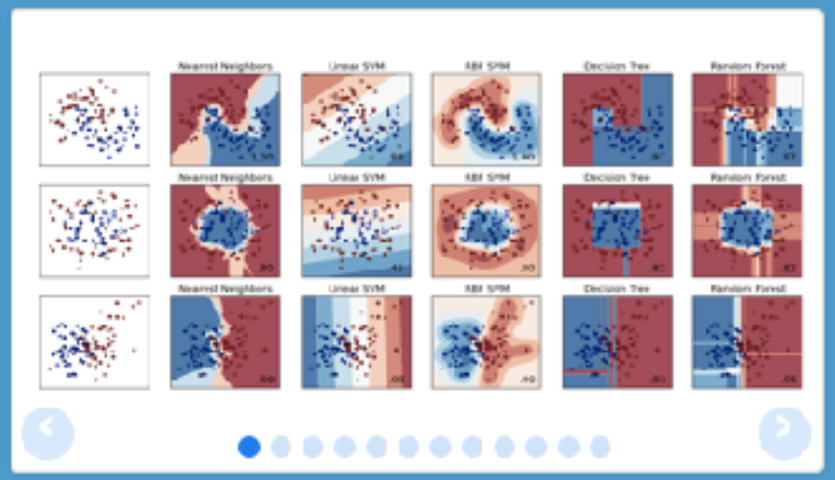


# scikit-learn

*Machine Learning in Python*

- Simple and efficient tools for data mining and data analysis
- Accessible to everybody, and reusable in various contexts
- Built on NumPy, SciPy, and matplotlib
- Open source, commercially usable - BSD license

## Classification

Identifying to which set of categories a new observation belong to.

**Applications**: Spam detection, Image recognition.
**Algorithms**: *SVM*, *nearest neighbors*, *random forest*, ... — *Examples*

## Regression

Predicting a continuous value for a new example.

**Applications**: Drug response, Stock prices.
**Algorithms**: *SVR*, *ridge regression*, *Lasso*, ... — *Examples*

## Clustering

Automatic grouping of similar objects into sets.

**Applications**: Customer segmentation, Grouping experiment outcomes
**Algorithms**: *k-Means*, *spectral clustering*, *mean-shift*, ... — *Examples*

## Dimensionality reduction

Reducing the number of random variables to consider.

**Applications**: Visualization, Increased efficiency
**Algorithms**: *PCA*, *Isomap*, *non-negative matrix factorization*. — *Examples*

## Model selection

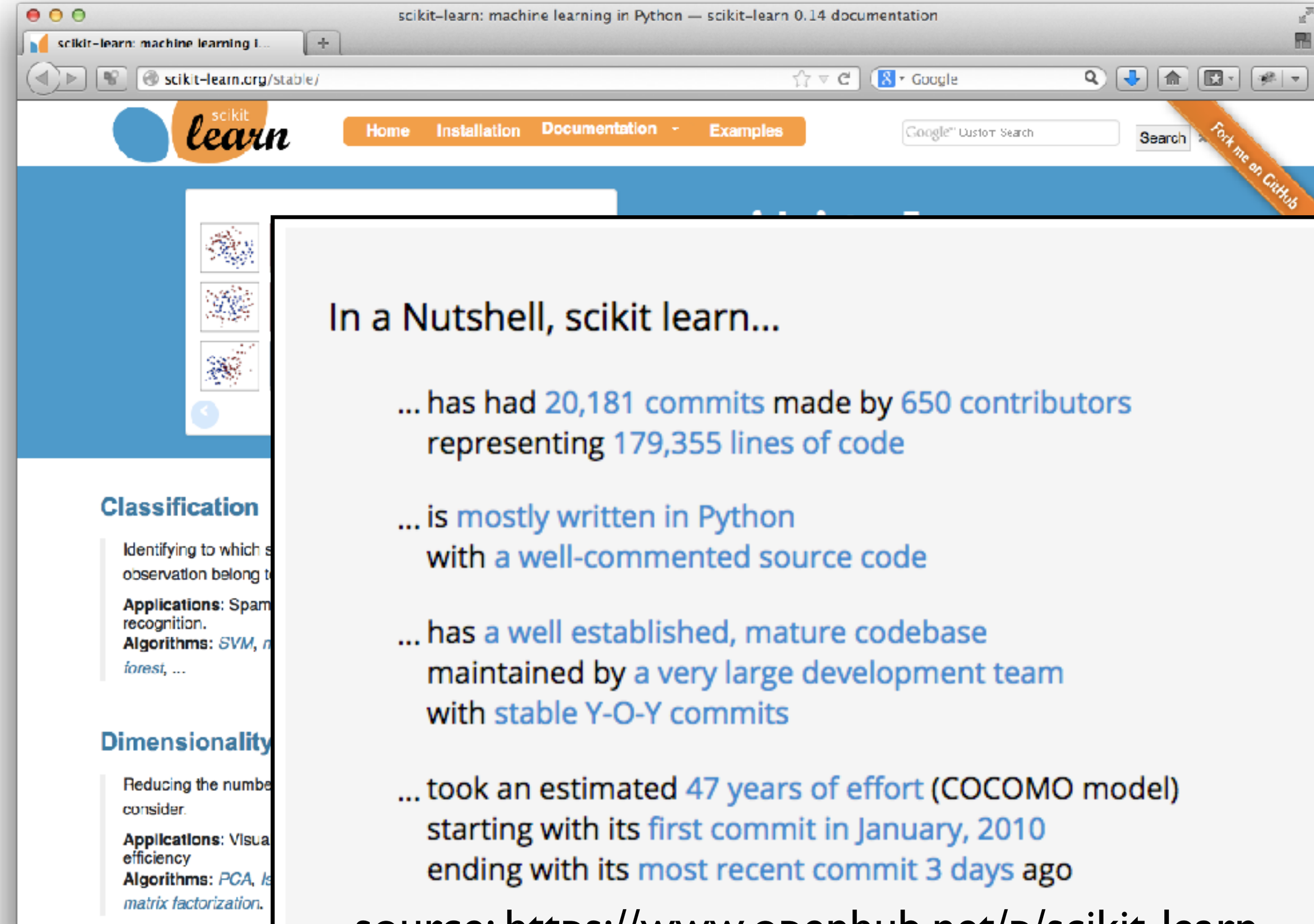
Comparing, validating and choosing parameters and models.

**Goal**: Improved accuracy via parameter tuning
**Modules**: *grid search*, *cross validation*, *metrics*. — *Examples*

## Preprocessing

Feature extraction and normalization.

**Application**: Transforming input data such as text for use with machine learning algorithms.
**Modules**: *preprocessing*, *feature extraction*. — *Examples*




# In a Nutshell, scikit learn...

... has had 20,181 commits made by 650 contributors
representing 179,355 lines of code

... is mostly written in Python
with a well-commented source code

... has a well established, mature codebase
maintained by a very large development team
with stable Y-O-Y commits

... took an estimated 47 years of effort (COCOMO model)
starting with its first commit in January, 2010
ending with its most recent commit 3 days ago

source: https://www.openhub.net/p/scikit-learn

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## Classification

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**Applications**: Spam
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# MNE

MEG + EEG ANALYSIS & VISUALIZATION

http://www.martinos.org/mne

MNE is a community-driven software package designed for for **processing electroencephalography (EEG) and magnetoencephalography (MEG) data** providing comprehensive tools and workflows for:

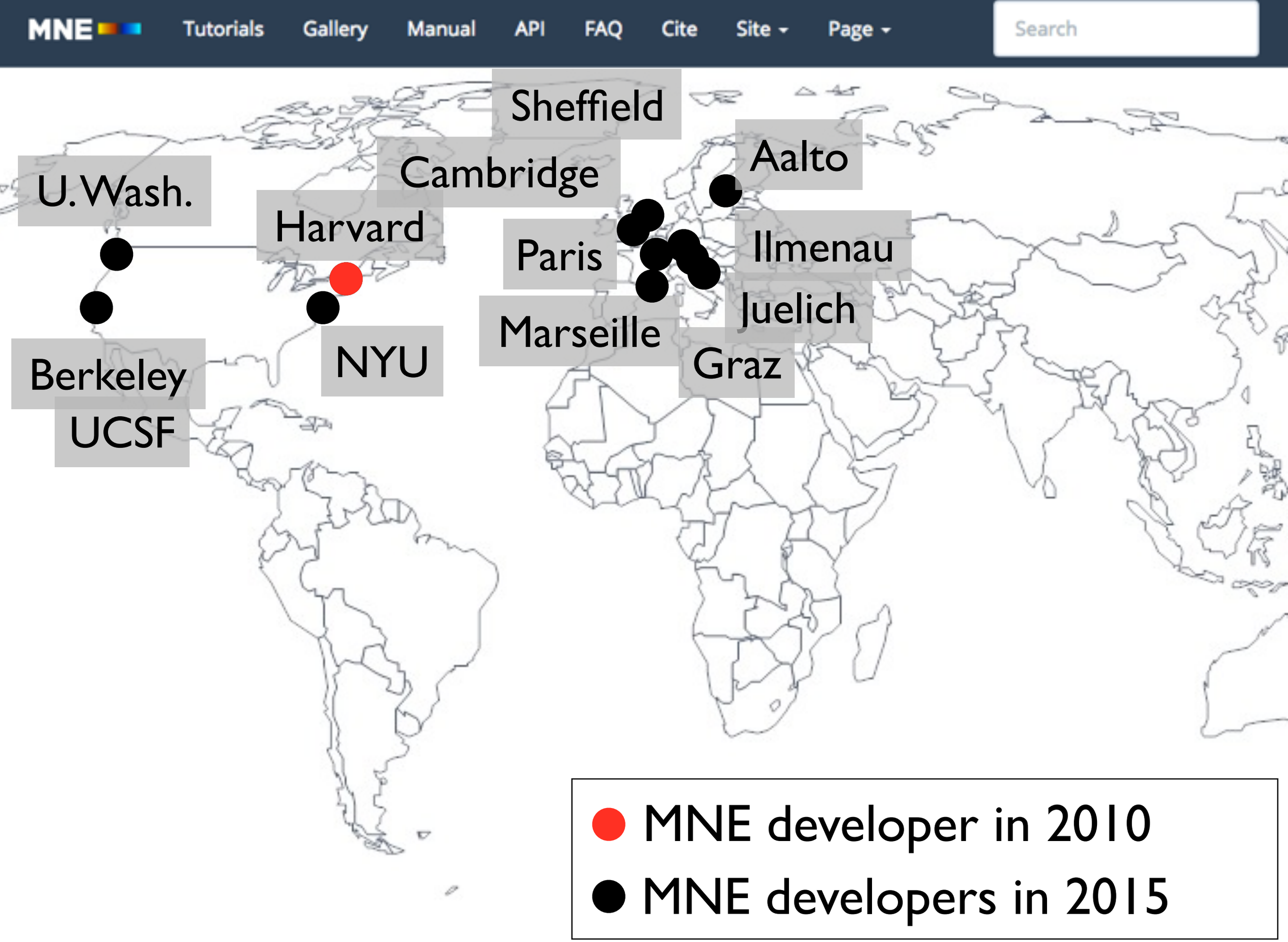
1. Preprocessing
2. Source estimation
3. Time–frequency analysis
4. Statistical testing
5. Estimation of functional connectivity
6. Applying machine learning algorithms
7. Visualization of sensor- and source-space data

MNE includes a comprehensive Python package (provided under the simplified BSD license), supplemented by tools compiled from C code for the LINUX and Mac OSX operating systems, as well as a MATLAB toolbox.

## Documentation

- Getting Started
- What's new
- Cite MNE
- Related publications
- Tutorials
- Examples Gallery
- Manual
- API Reference
- Frequently Asked Questions
- Advanced installation and setup
- MNE with CPP

*MNE software for processing MEG and EEG data*, A. Gramfort, M. Luessi, E. Larson, D. Engemann, D. Strohmeier, C. Brodbeck, L. Parkkonen, M. Hämäläinen, Neuroimage 2013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Harvard
Paris
Ilmenau
Juelich
Marseille
Graz
NYU
Berkeley
UCSF
MNE developer in 2010
MNE developers in 2015

# Thanks !

- M. Hämäläinen
- M. Kowalski
- D. Strohmeier
- J. Haueisen
- Y. Bekhti
- M. Jas
- G. Varoquaux
- B. Thirion
- M. Eickenberg
- F. Pedregosa
- J. Salmon
- O. Fercoq
- E. Ndiaye
- … the scikit-learn contributors
- … the MNE contributors

## Post-docs positions available !

**Contact** http://alexandre.gramfort.net

*GitHub : @agramfort* *Twitter : @agramfort*

**Support** ERC SLAB, ANR THALAMEEG ANR-14-NEUC-0002-01
NIH R01 MH106174, DFG HA 2899/21-1.

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