Charting a Functional Atlas from an fMRI Dataset

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Random Shapes, Tutorials, IPAM 2007

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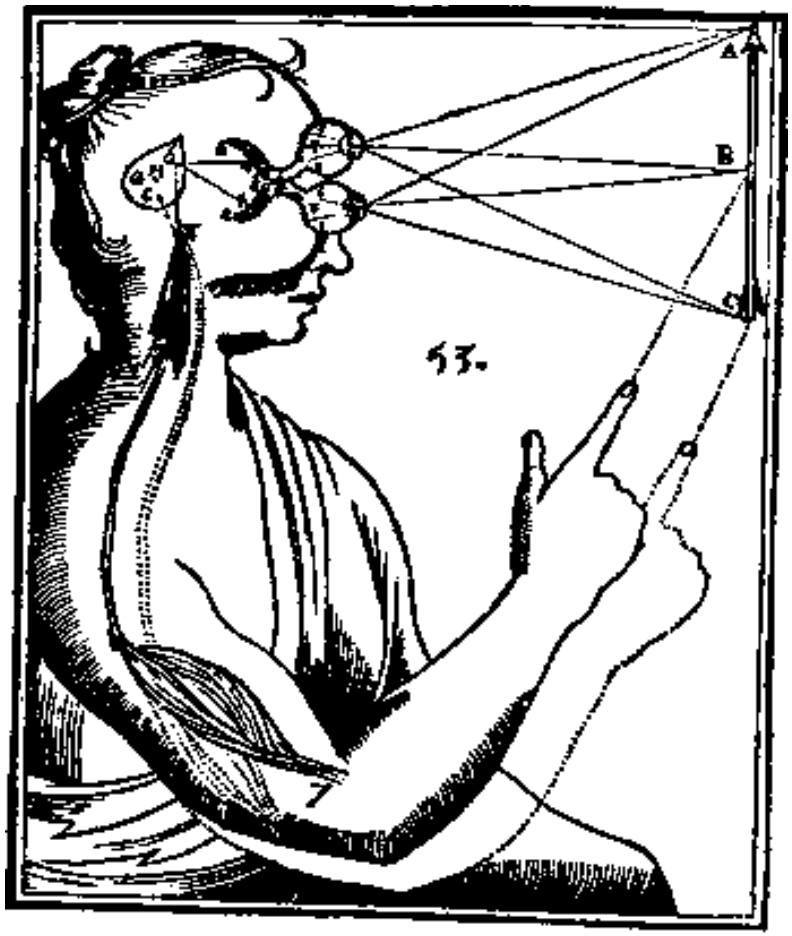
- IPAM Graduate Summer School: Intelligent Extraction of Information from Graphs and High Dimensional Data

Outline

1. Introduction
   - State of the art
2. Exploration of fMRI datasets
   - A random walk on the dataset
   - Synthetic dataset
   - Event-related stimuli
   - Visual stimulus
3. Conclusion

Introduction

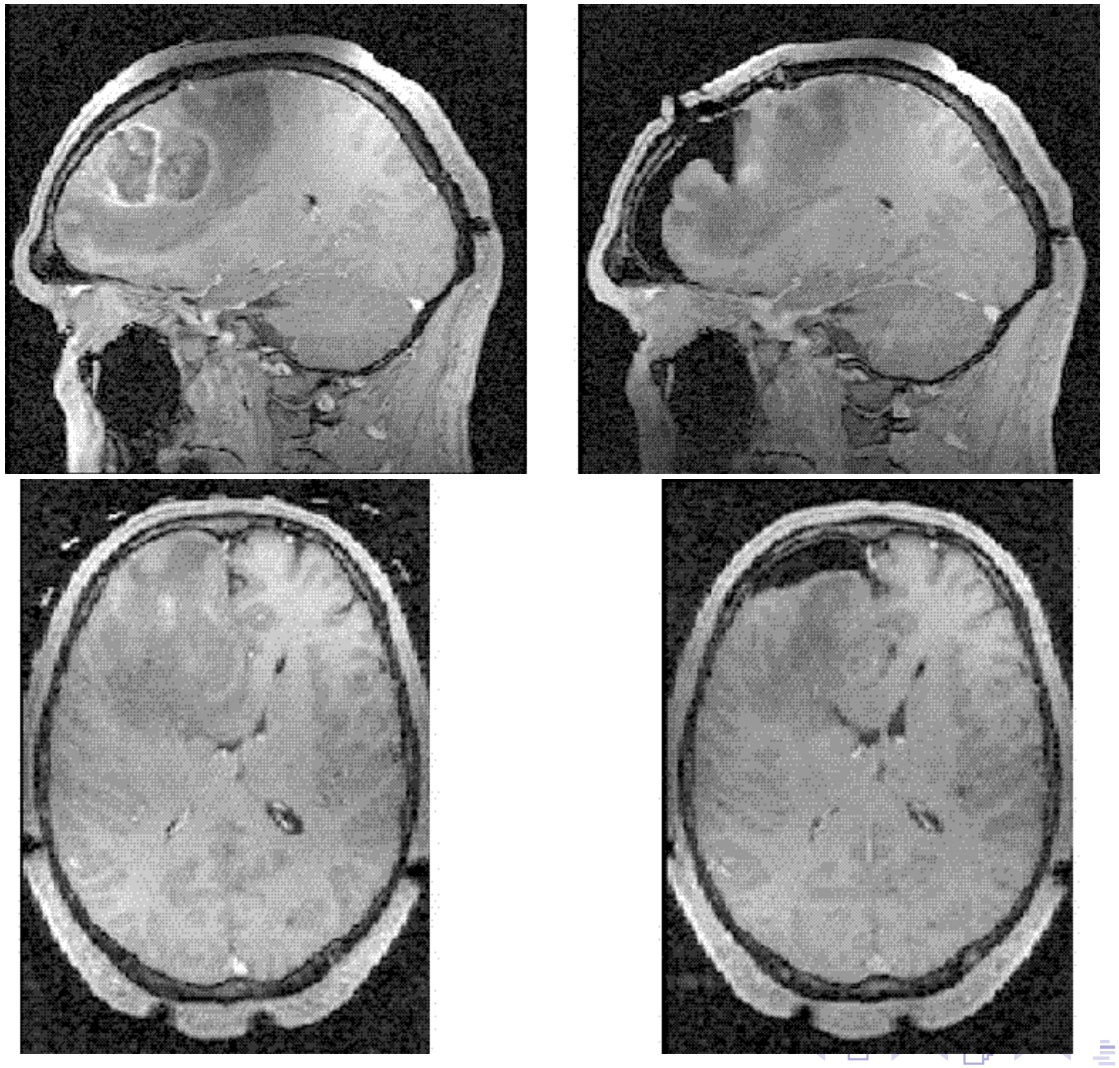
- functional imaging : delineation of functional anatomy in terms of spatial and temporal organization



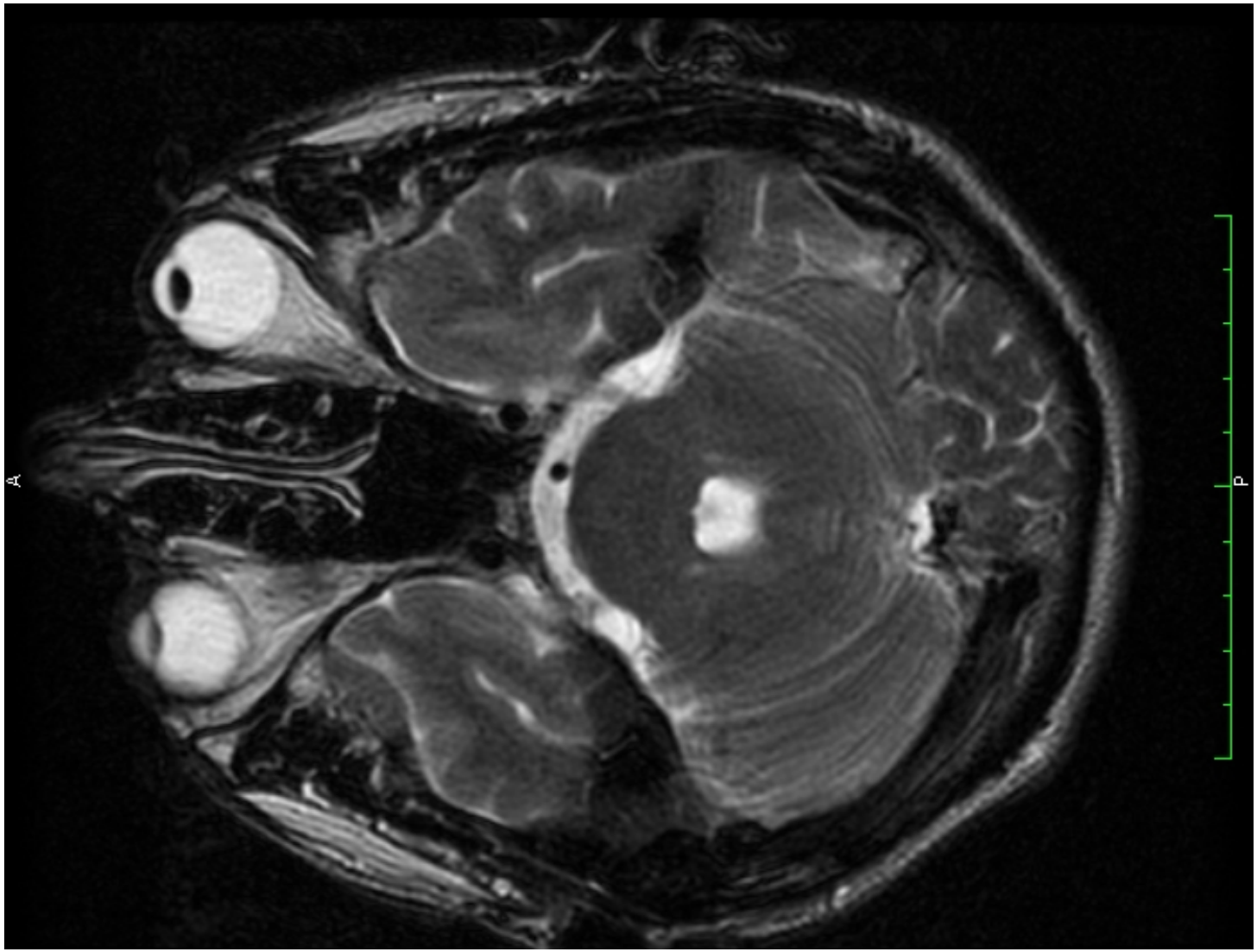
René Descartes *De homine* (1662)

Scientific and Clinical relevance

- cognitive neuroscience
- map a patient's brain before neurosurgery

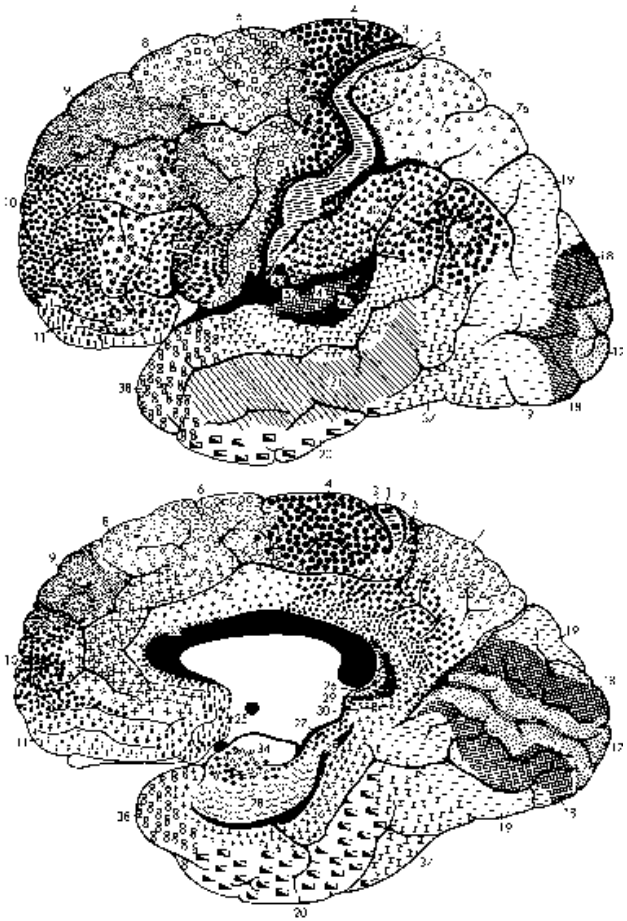


Magnetic Resonance Imaging : anatomy and structure



The dogma of functional brain mapping

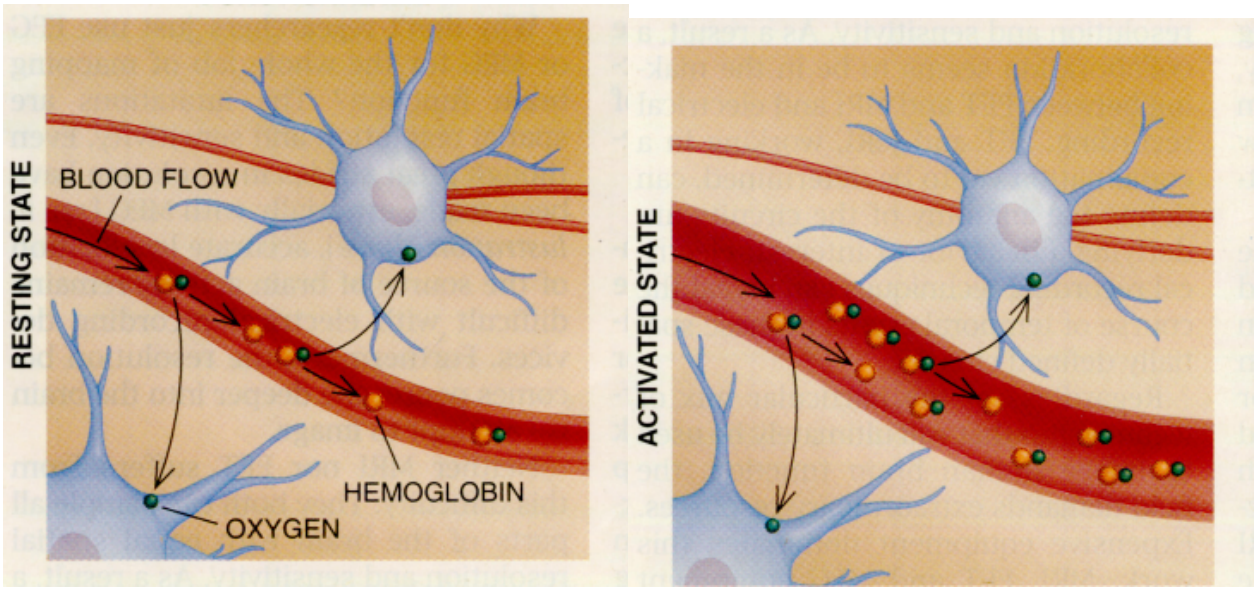
- functional specialization : certain areas are responsible for specific functions



Korbinian Brodmann (1909) : maps based on cytoarchitecture (still used today)

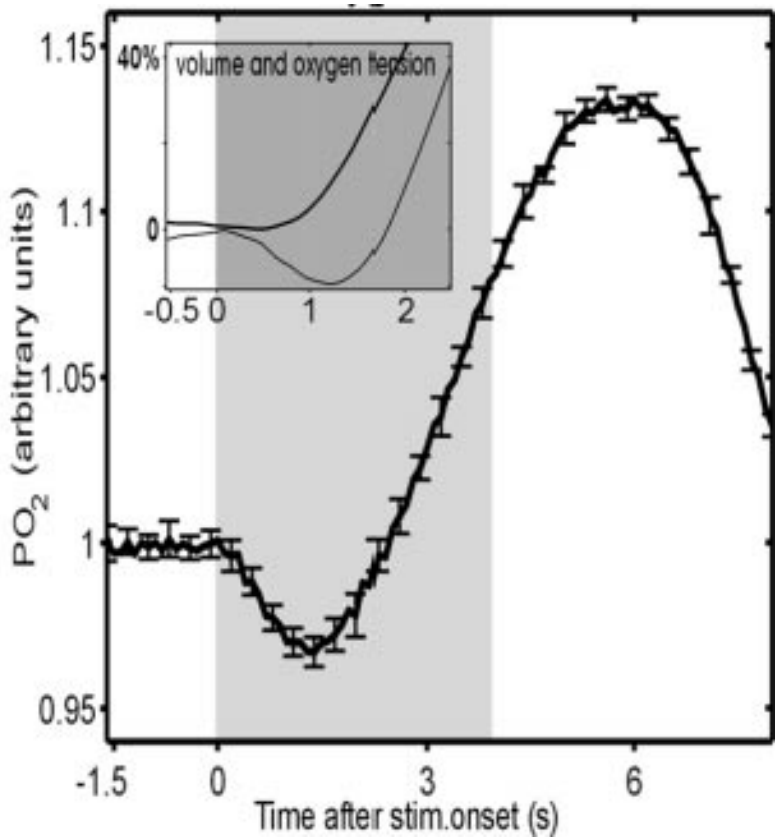
Neuronal activity creates a metabolic/vascular response

- brain = most energy-consuming tissue in the entire body
- glucose + oxygen $\rightarrow$ energy
- hemoglobin $\rightarrow$ oxygen : cerebral blood flow = 20% of cardiac output
  (brain mass = 2 % of total body mass !)
- very dense mesh of capillaries



Oxygen concentration changes in the microcirculation

- $t = 0\ s$ subject is submitted to a stimulation.
- $t = 1.5\ s$ oxygen consumption created by metabolic demand
- $t = 6\ s$ oversupply of oxygenated blood
- fMRI signal (oxygenated hemoglobin) $\neq$ fMRI signal (surrounding tissue)



[Vanzetta and Grinvald, 1999].

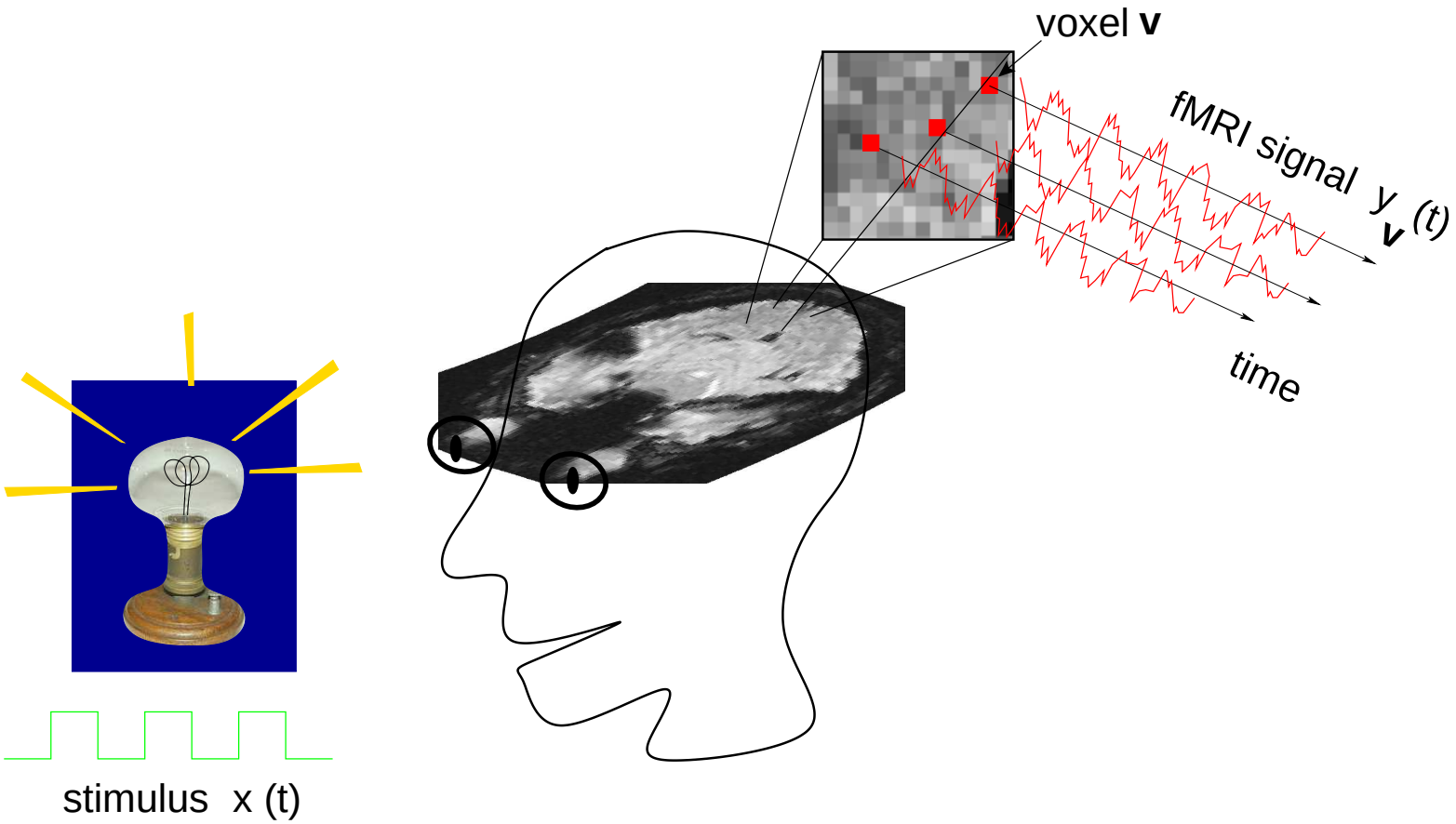
imbalance between oxygen metabolism and oxygen supply

$\rightarrow$ Blood Oxygen Level-Dependent contrast

Functional MRI: time and space

- in plane resolution: 1-3 mm
- interscan interval (TR): 1-3 seconds
- image size: 128 x 128 x 256 voxels
- one voxel: 2 millions neurons
- neuronal activity: 10-100 milliseconds,
  hemodynamic response: 3 seconds (6-9 s for peak)

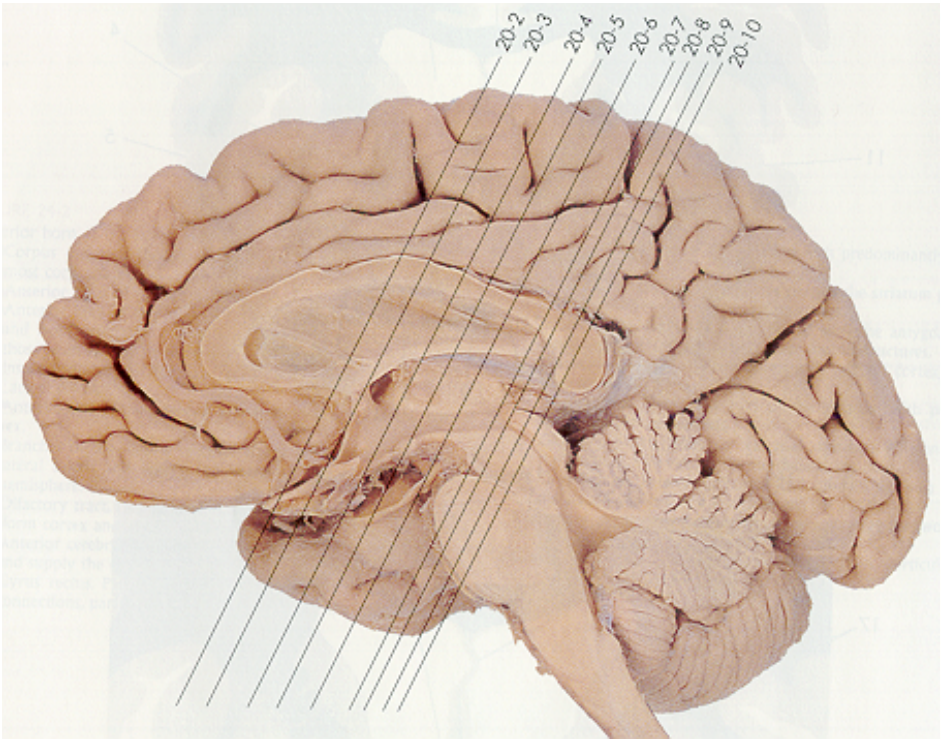
Functional Magnetic Resonance Imaging (fMRI)

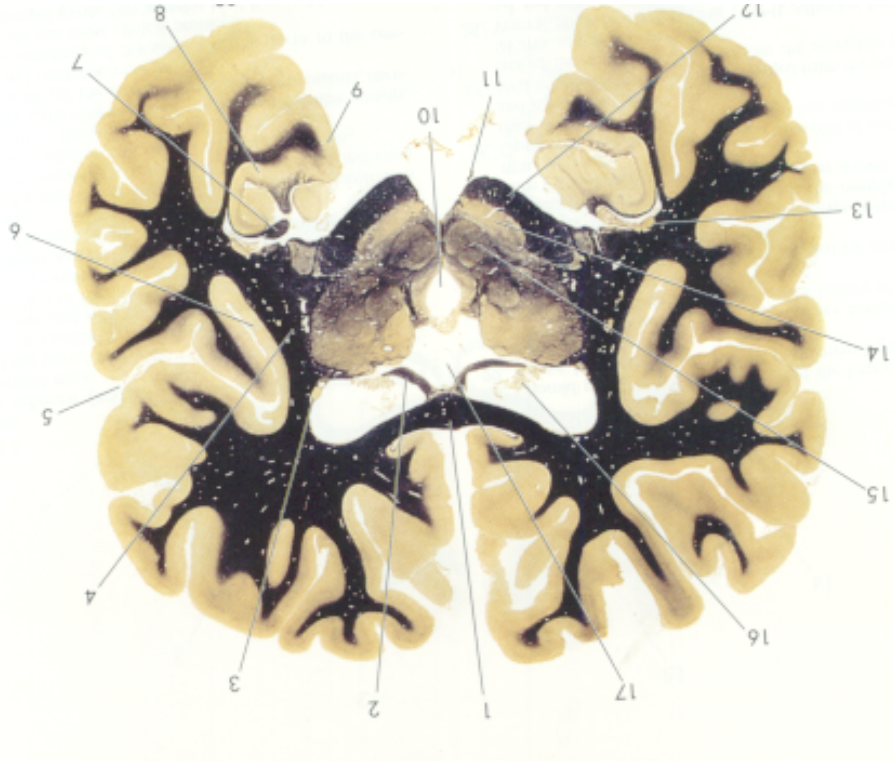


- Goal of the analysis : detect "activated" voxels $\boldsymbol{\nu}$ where changes in the fMRI signal $\mathbf{y}$ are triggered by the stimulus $\mathbf{x}$.

Analysis of fMRI : the scientific questions

1. realignment of image volumes : compensate for head motion
   - estimation of the rigid motion (translation + rotation)
   - realignment : interpolation (lowpass filter)
2. comparison between brains : complexity of the cortex
   - warping to a template reference brain volume
     (stereotaxic atlas of Talairach and Tournoux)





Analysis of fMRI : the scientific questions

3. neighboring voxels can be functionally distant :
   cortex = folded ribbon of gray matter
   - extraction of the cortical surfaces
   - analysis of function performed on the cortical ribbon
4. detection of the activation
   - signal changes = 3-6 %
   - baseline fluctuation (drift)
   - only 5-10 % voxels are activated
   - no ground truth
   - several methods of analysis : none is optimal for all purposes
   - spatio-temporal analysis : correlation in time and space

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Analysis of fMRI data : Univariate statistical models

- General Linear Model [Friston et al., 1995]

$$\mathbf{y_v} = \mathbf{x}\boldsymbol{\beta} + \boldsymbol{\varepsilon}, \quad \boldsymbol{\varepsilon} \sim \mathcal{N}(0, \boldsymbol{\Sigma}) \tag{1}$$

- Linear Time Invariant Model
  [Lange and Zeger, 1997, Genovese, 2000]

$$\mathbf{y_v} = h_{\boldsymbol{v}} * \mathbf{x} \tag{2}$$

limitations :

- $\varepsilon(t)$ correlated ; $\mathrm{var}(\boldsymbol{\varepsilon})$ varies as a function of $\boldsymbol{v}$ [Chen et al., 2003]
- $h_{\boldsymbol{v}}$ depends on brain region, subject, etc.
- spatial correlation ?
- nonlinear relationship between $\mathbf{y_v}$ and $\mathbf{x}$ [Friston et al., 1998, Miller et al., 2001, Rees et al., 1997, Vazquez and Noll, 1998].

Multivariate methods: Principal component analysis

$$\mathbf{Y} = \begin{bmatrix} y_{\mathbf{v}_1}(1) & \cdots y_{\mathbf{v}_1}(T) \\ y_{\mathbf{v}_2}(1) & \cdots y_{\mathbf{v}_2}(T) \\ \vdots & \vdots \\ \vdots & \vdots \\ \vdots & \vdots \\ y_{\mathbf{v}_N}(1) & \cdots y_{\mathbf{v}_N}(T) \end{bmatrix} = U \Lambda V^T$$

$N =$ number of voxels $\gg T =$number of time samples

$U : N \times T$ orthogonal, $\Lambda : T \times T$, diagonal, $V : T \times T$ orthogonal

$$\mathbf{Y} = \sum_{k=1}^{T} \lambda_k U_k V_k^T, \qquad U_k : \text{image}, \; V_k^T : \text{time series}.$$

Multivariate methods: PCA/SVD

limitations :

- components need to be orthogonal
- no clear interpretation of the components
- spatial structure is lost

Independent Component Analysis

Independent component analysis
[B.B.Biswal and Ulmer, 1999, McKeown, 2000]

$$\mathbf{Y}^T = \begin{bmatrix} y_{\mathbf{v}_1}(1) & y_{\mathbf{v}_2}(1) & \cdots\cdots & y_{\mathbf{v}_N}(1) \\ \vdots & \vdots & & \vdots \\ y_{\mathbf{v}_1}(T) & y_{\mathbf{v}_2}(T) & \cdots\cdots & y_{\mathbf{v}_N}(T) \end{bmatrix} = AS$$

- S: K rows of statistically independent maps of size N
- A: $T \times K$, mixing matrix

limitations :

- spatial maps need to be independent
- interpretation of the components ?

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Algorithm: Construction of the embedding

- [Shen and Meyer, 2005, Shen and Meyer, 2006, Shen and Meyer, 2007],[details given in tutorial 1]

Input:

- $\mathbf{x}_i(t), t = 0, \cdots, T-1, \; i = 1, \cdots, N$,
- σ ; n_n number of nearest neighbors, K: number of eigenfunctions.

Algorithm:

1. construct the graph (and $\boldsymbol{W}$) defined by the n_n nearest neighbors ; compute $\mathbf{P} = \mathbf{D}^{-1}\boldsymbol{W}$
2. find the first K eigenfunctions, $\boldsymbol{\Phi}_k$, of $\mathbf{D}^{\frac{1}{2}}\mathbf{P}\mathbf{D}^{-\frac{1}{2}}$

Output: For all $\mathbf{x}_i$

- new co-ordinates of $\mathbf{x}_i$: $\left\{ \frac{1}{1-\lambda_k} \frac{\boldsymbol{\Phi}_k(i)}{\sqrt{\pi_i}} \right\}, \quad k = 2, \cdots, N$

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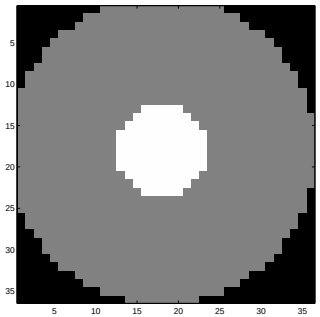
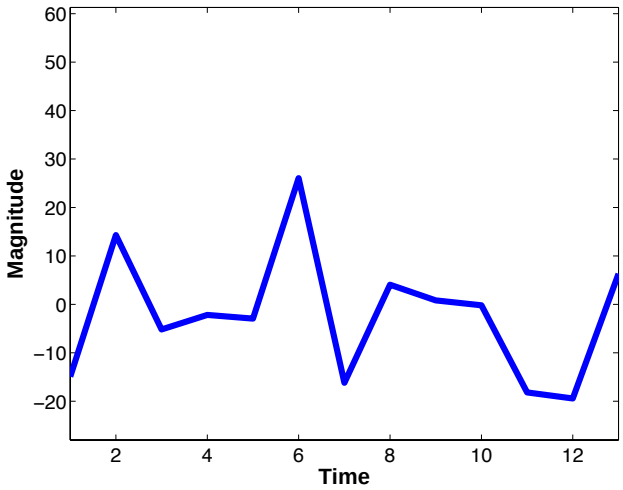
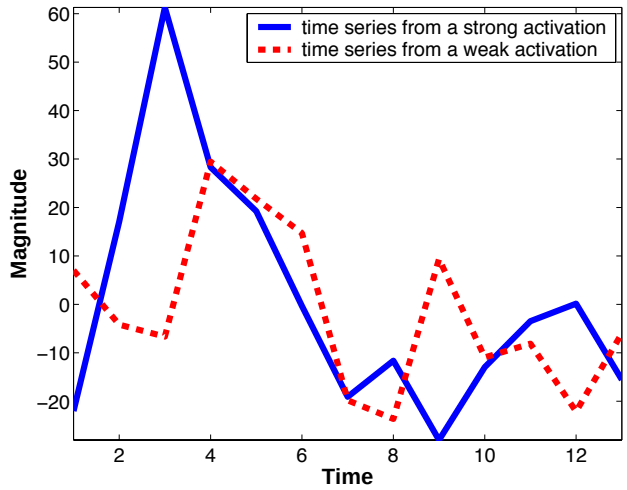
The data

- Idea: blend synthetic activation into real *in vivo* fMRI data
- realistic noise and background time series
- access to ground truth







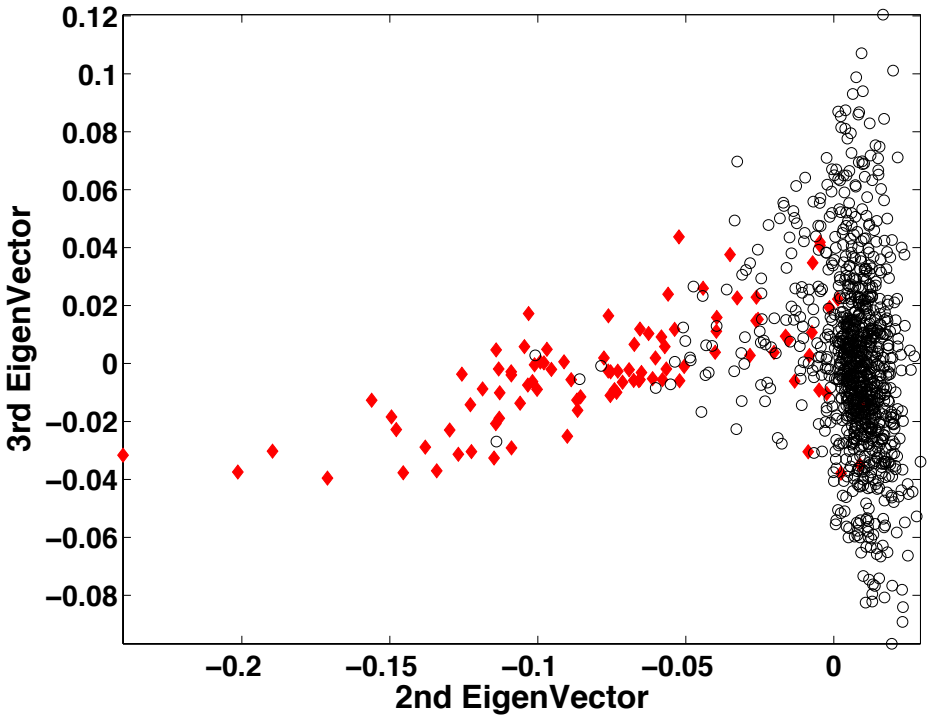
- non activated ring (1067 voxels), time series from *in vivo* fMRI

The data

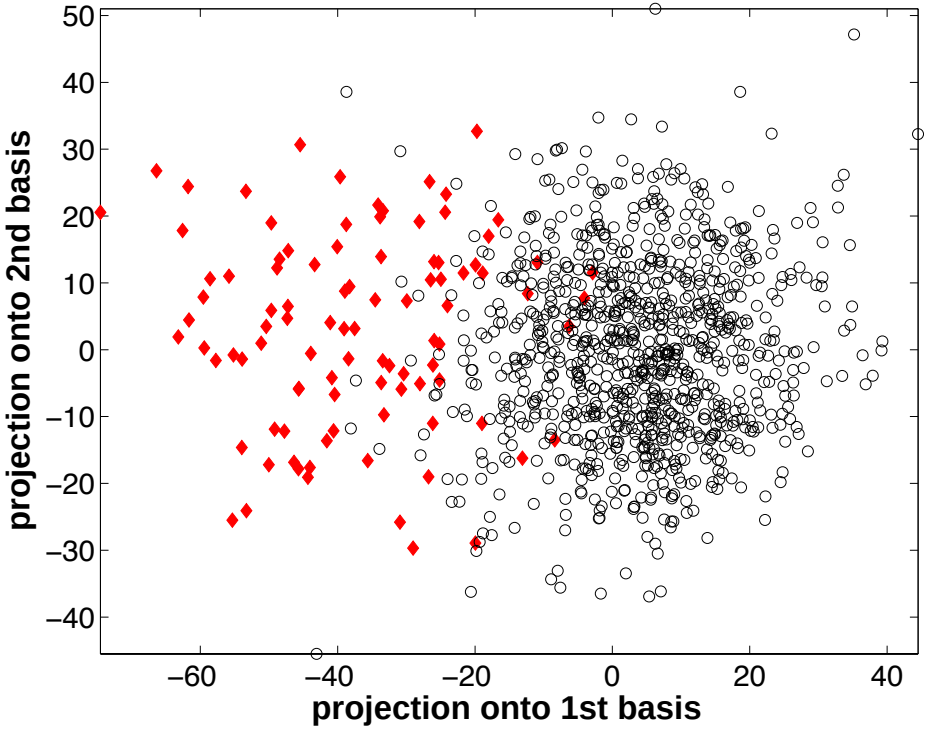
- activated disk (97voxels $\approx 9\%$)
- time series $= \alpha\,(h \star g)(t) + n(t)$, where
- $n(t) = \textit{in vivo}$ fMRI noise
- $h(t) = (t/d_1)^{a_1}\, e^{-(t-d_1)/b_1} - c\; t(t/d_2)^{a_2}\, e^{-(t-d_2)/b_2}$
  - $a_1 = 6,\ c = 0.35,\ a_2 = 12,\ b_2 = 0.9.$
  - $b_1,\ \alpha$ randomly sampled: $b_1 \sim \mathcal{U}[0.8, 1.2], \alpha \sim \mathcal{U}[5, 10].$
- $g(t) = 1$ if $t = 0, 1$; $g(t) = 0$ otherwise.
- generate 20 independent synthetic datasets

Reduction of dimensionality

- Two dimensional parametrization of one dataset



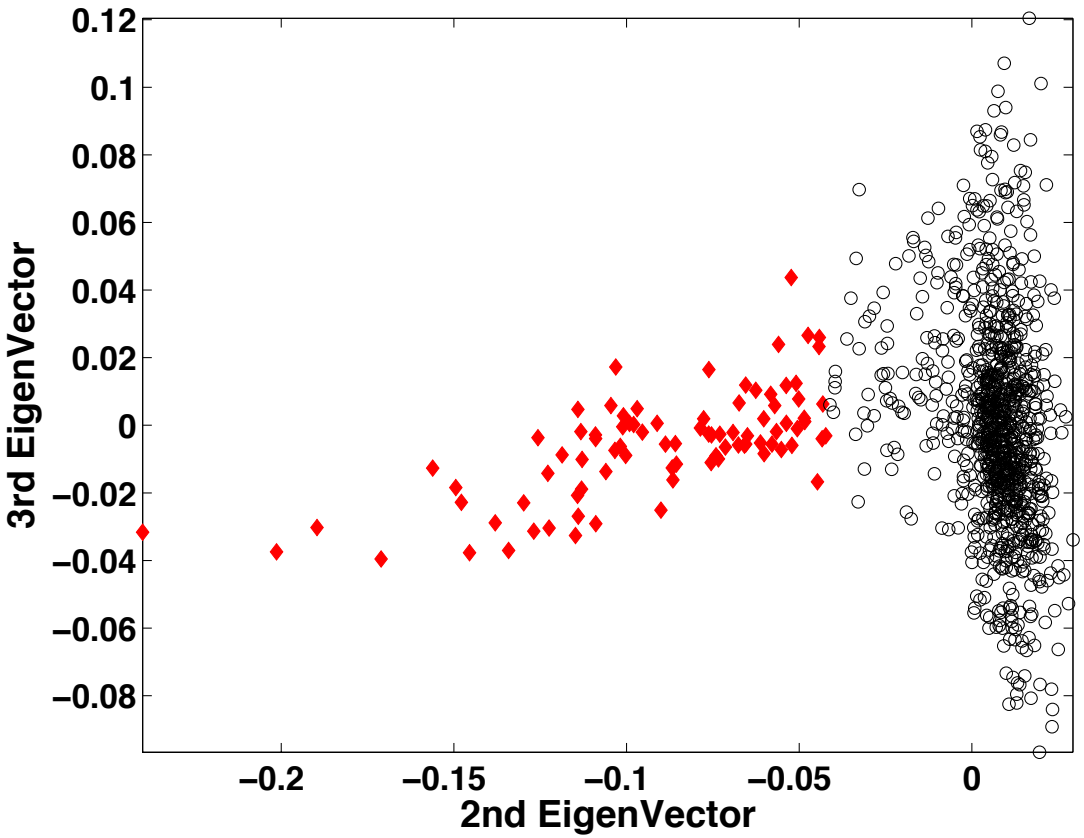
Embedding from $\kappa(i,j)$



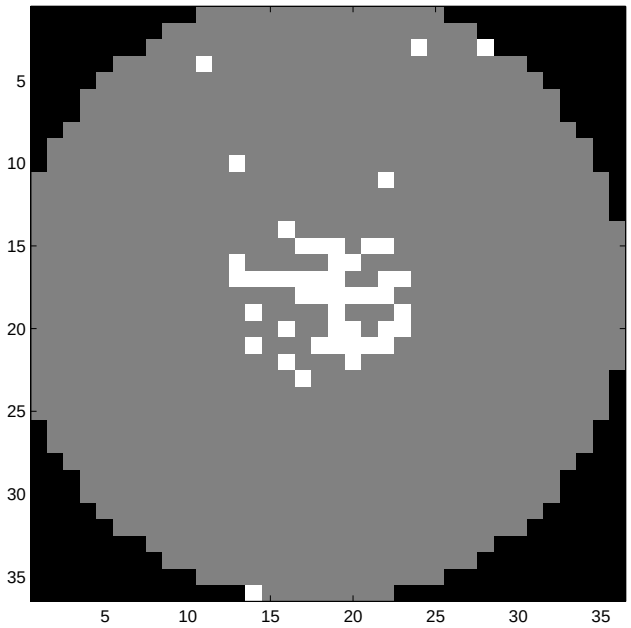
PCA

Clustering

- K-Means clustering with the new parameterization



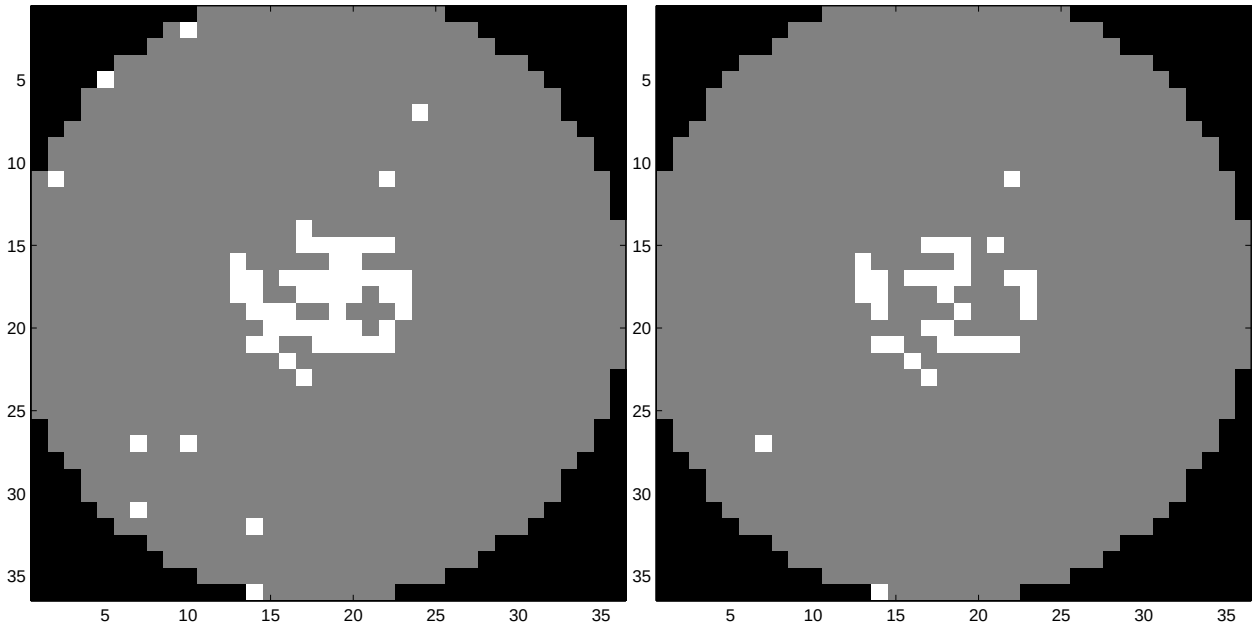
Labels (from K-mean clustering)



activation map

Gold standard

- Linear regression equipped with an oracle: $h(t)$
- Optimal if the noise is white (not true for fMRI)



p-value=0.005 p-value=0.001

Type I and II errors (20 datasets)

Table: Type I error (false alarm)

our approach	$p = 0.001$	$p = 0.005$
0.0037	0.00015	0.002

Table: Type II error (missed activation)

activation strength (α)	5 to 6	6 to 7	7 to 8	8 to 9	9 to 10
our approach	0.4710	0.3632	0.2569	0.1508	0.1108
$p = 0.005$	0.5223	0.3806	0.2265	0.1201	0.0757
$p = 0.001$	0.7567	0.6119	0.4779	0.3324	0.1973

- more false activations than linear model
- missed activation: comparable to $p = 0.005$

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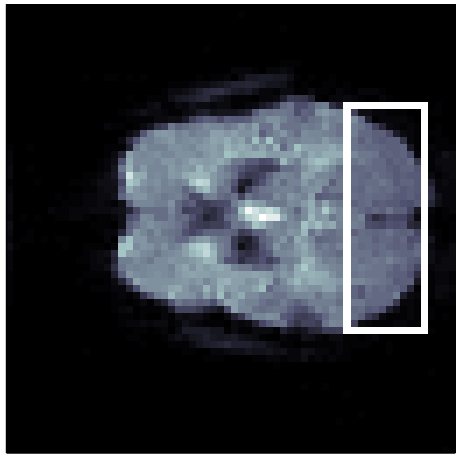
The Data

- fMRI study of age-related changes in functional anatomy [Buckner et al., 2000]
- 1.5 s duration visual stimulus;
  subject pressed a key upon stimulus onset
- TR = 2.68 s; 64×64 images 3.75 x 3.75mm;
  16 contiguous axial slices
- two-trial condition: 2 consecutive stimuli
  with inter-trial interval= 5.36 sec.
- one-trail/two-trial conditions were mixed randomly
- 15 trials per run ; 8 one-trial condition and 7 two-trial condition,
- one run = 128 images

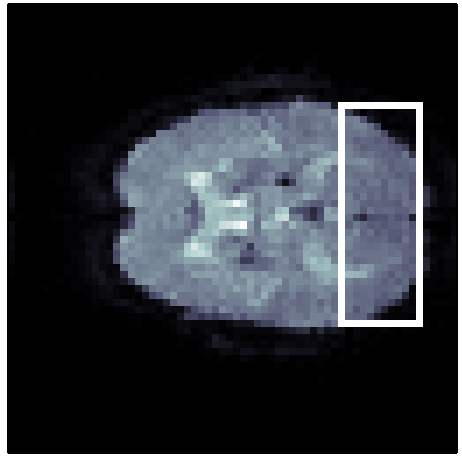
Data pre-processing

- one dataset, single run, 80 year old female with mild dementia
- analysis: posterior region of the brain $\supset$ visual cortex,
- 4 axial slices, about 300 voxels in each slide,
- extract 8 samples ($\approx$ 22 s) for each one/two-trial condition
- average one conditions and two conditions separately
- each voxel give rise to two time series: conditions 1 and 2
- remove linear trend, and run the analysis
- use 2nd, 3rd and 4th eigenvectors to chart the map

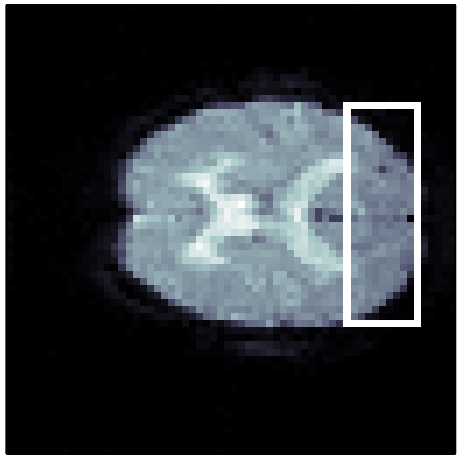
slice 7



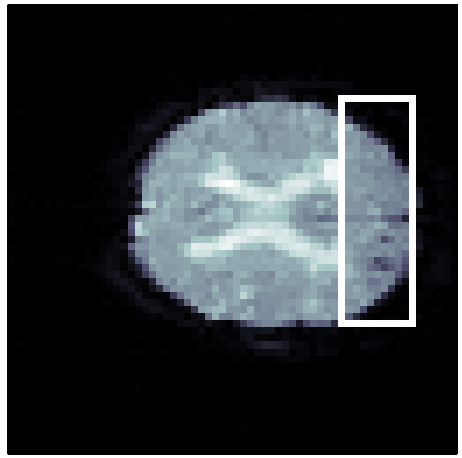
slice 8



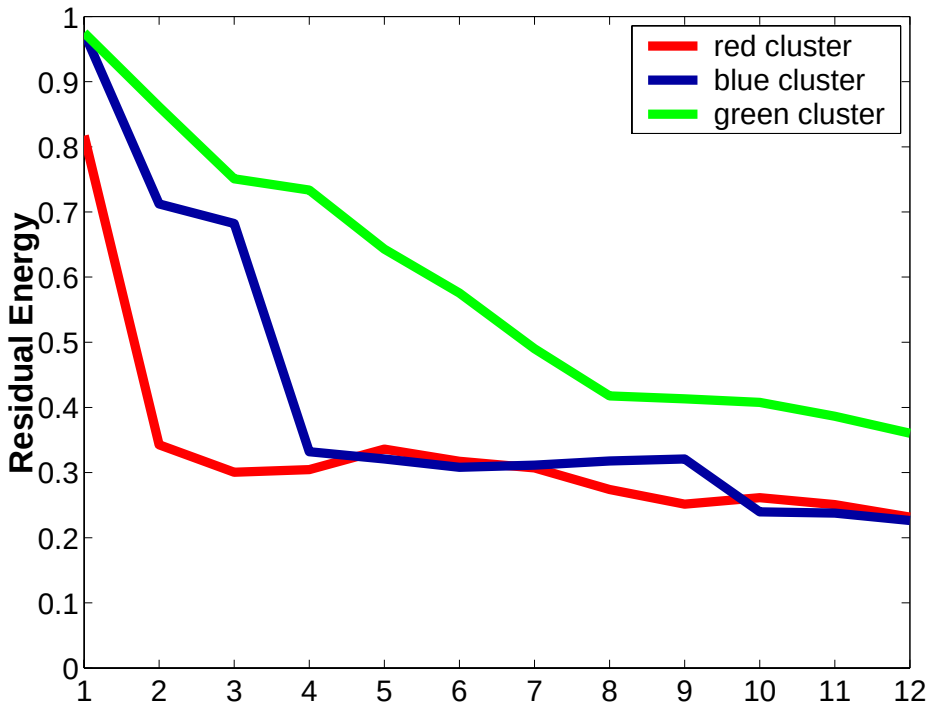
slice 9



slice 10

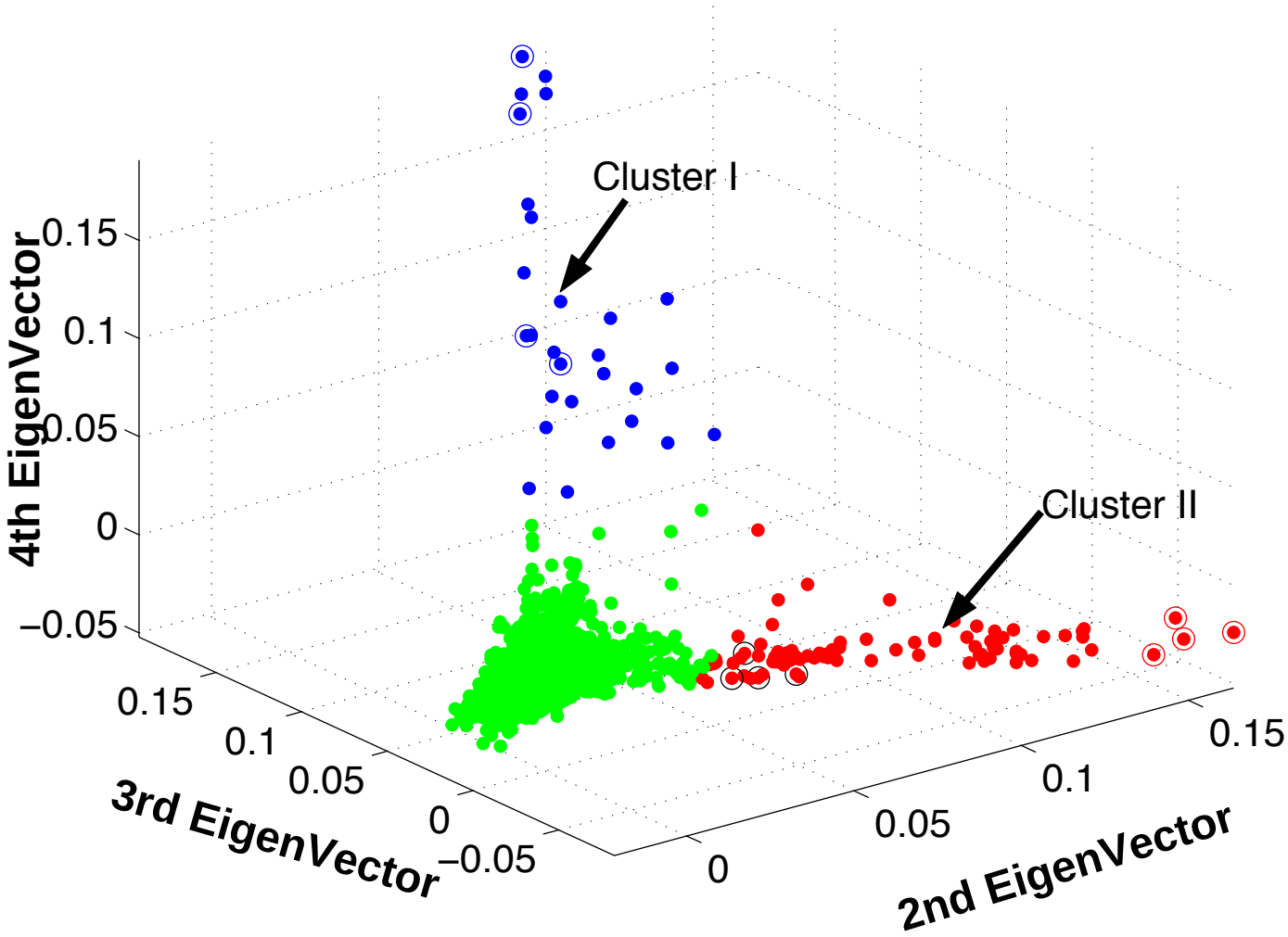


Selection of K



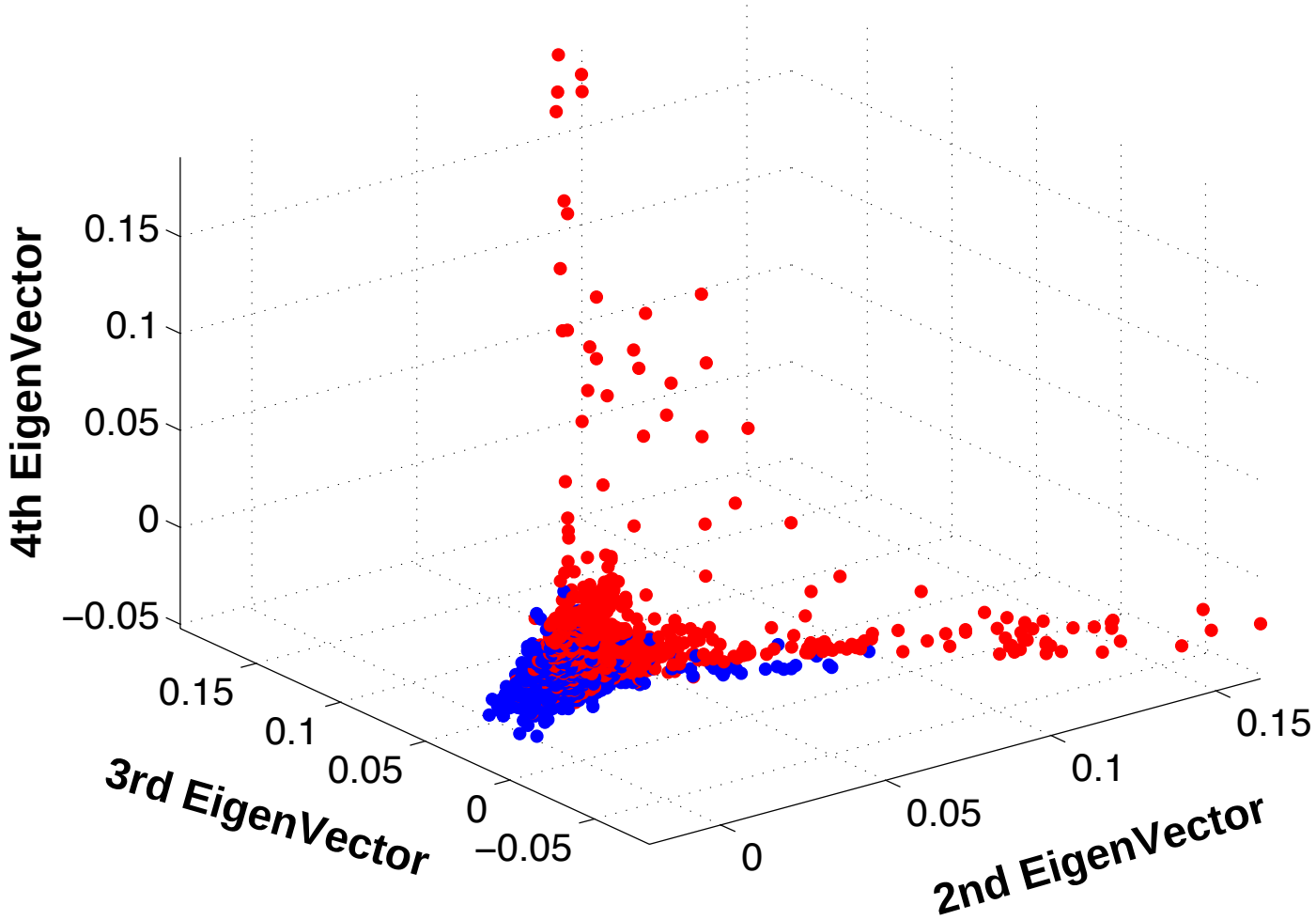
- red and blue clusters are well approximated with $K = 4$ eigenvectors: activated time series,
- green cluster is poorly approximated : background time series

The new parametrization



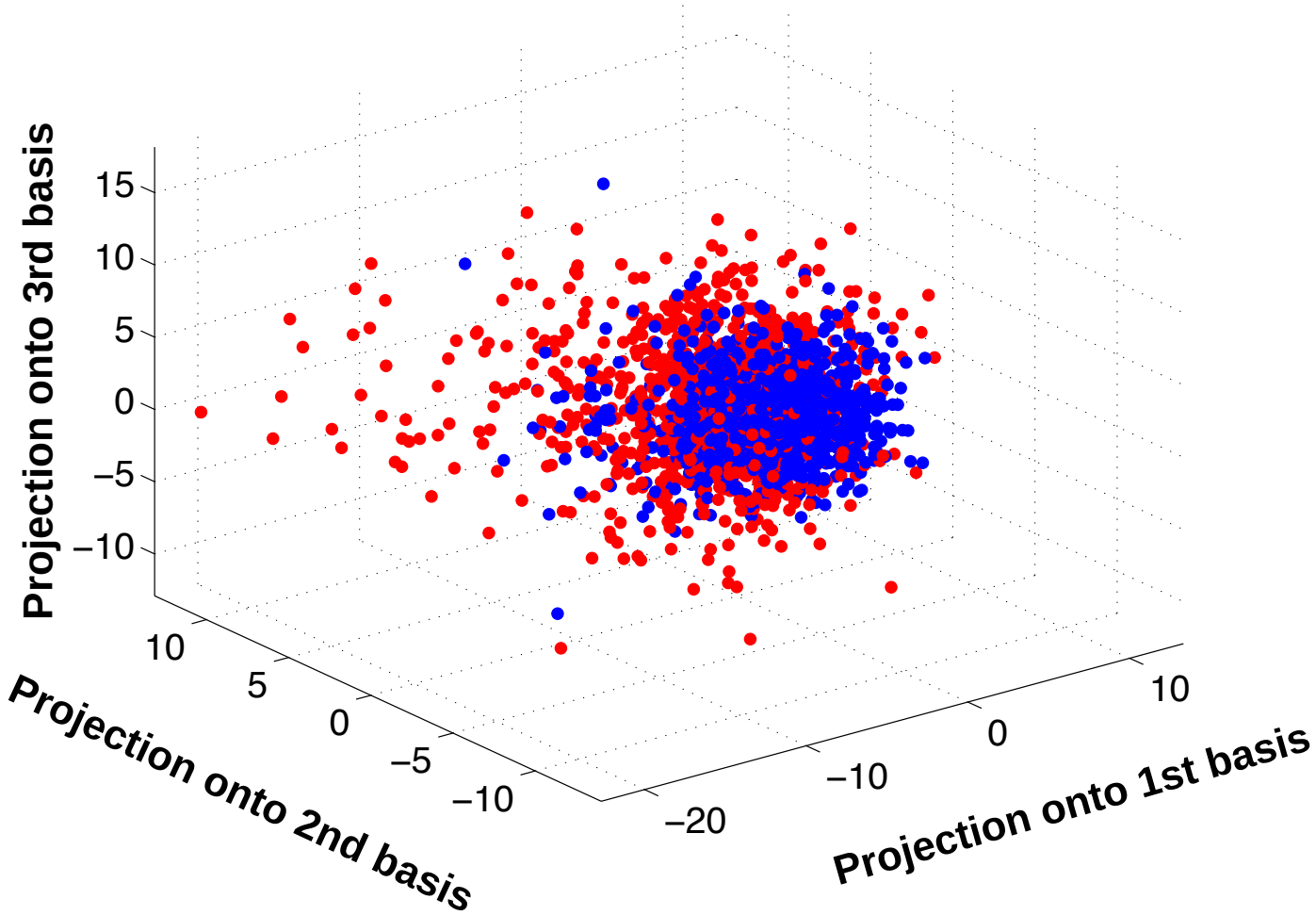
Colors = K-Means clustering into 3 clusters.

Difference between the two conditions



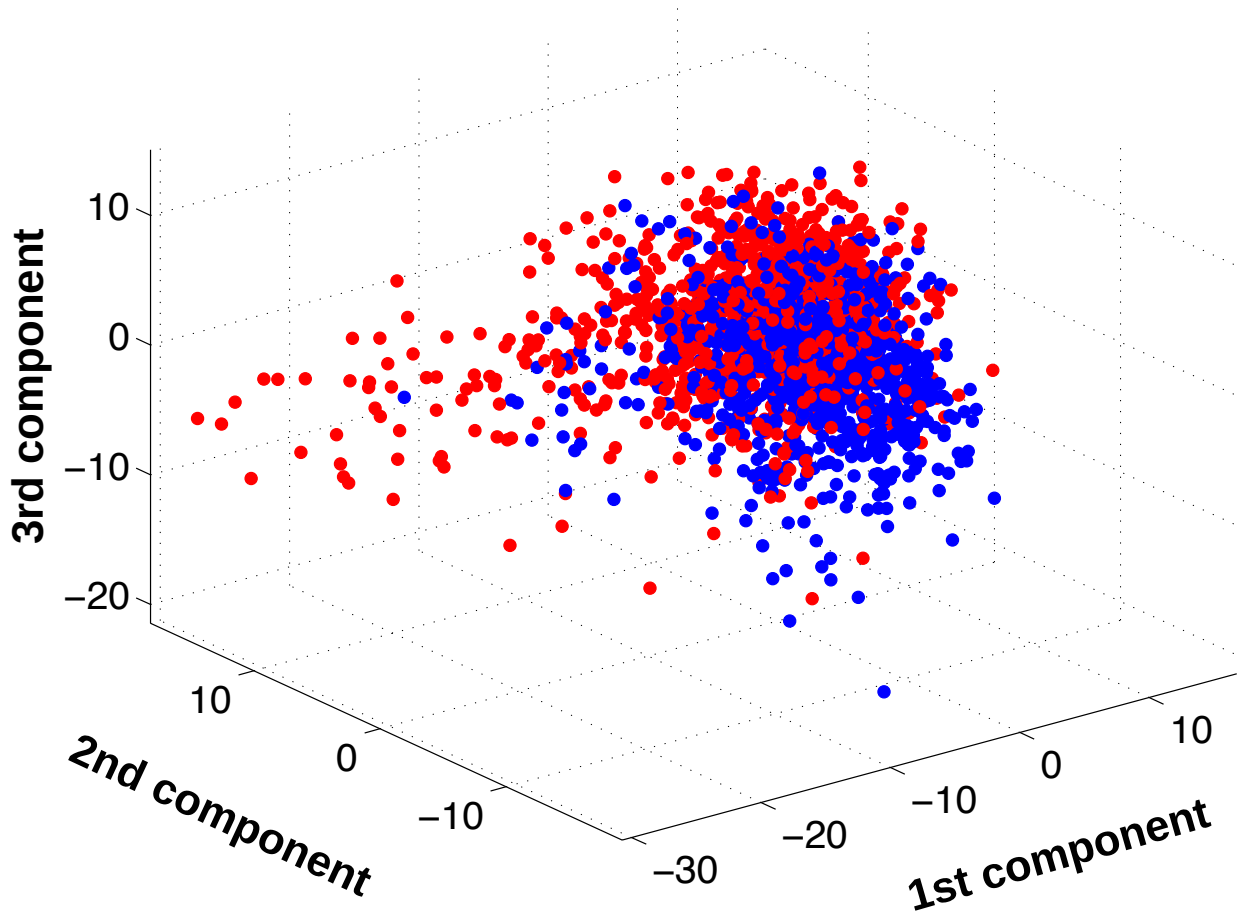
Blue = one-trial condition ; Red = two-trial

Parametrization given by PCA



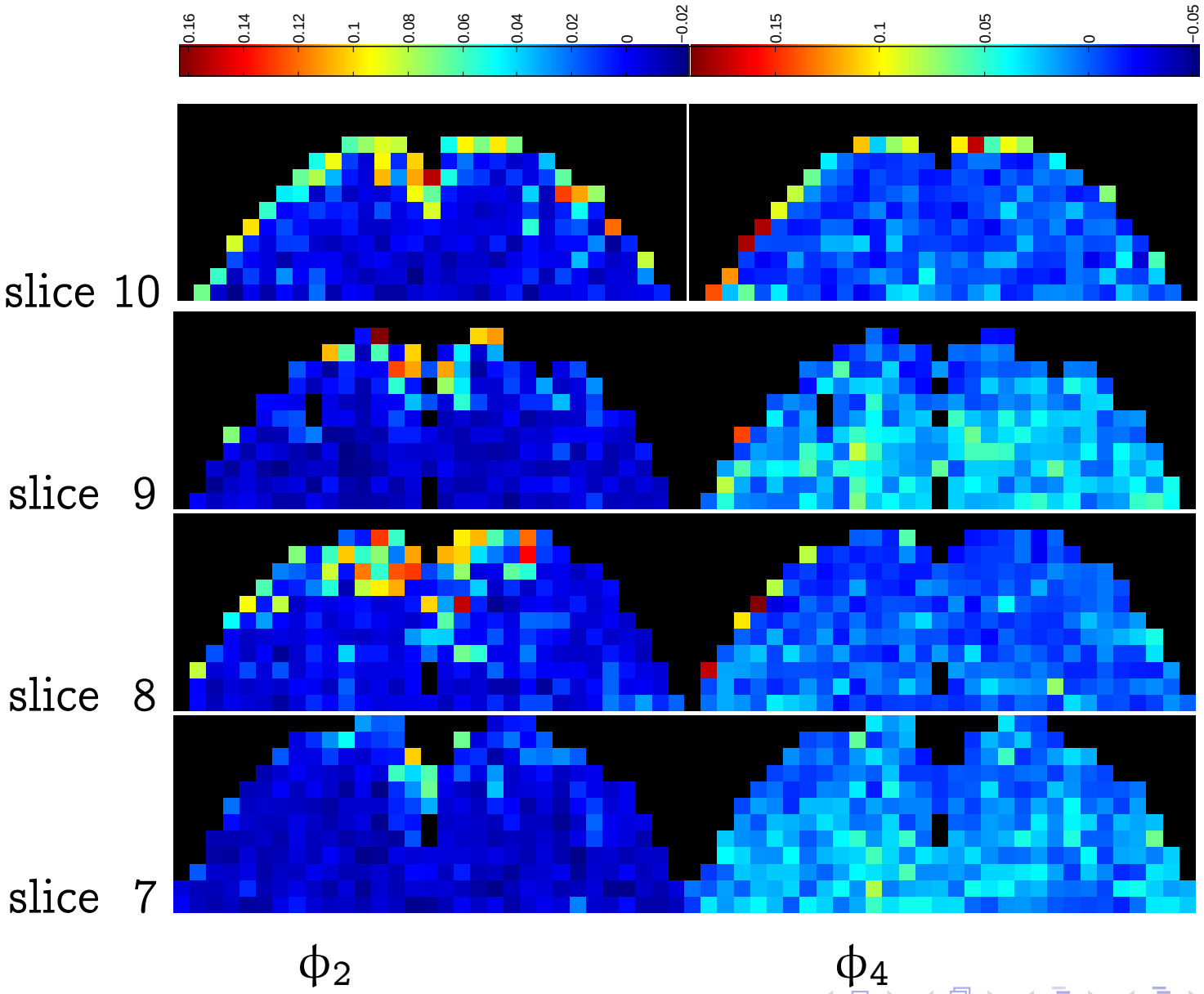
Blue = one-trial condition ; Red = two-trial

Parametrization given by ISOMAP

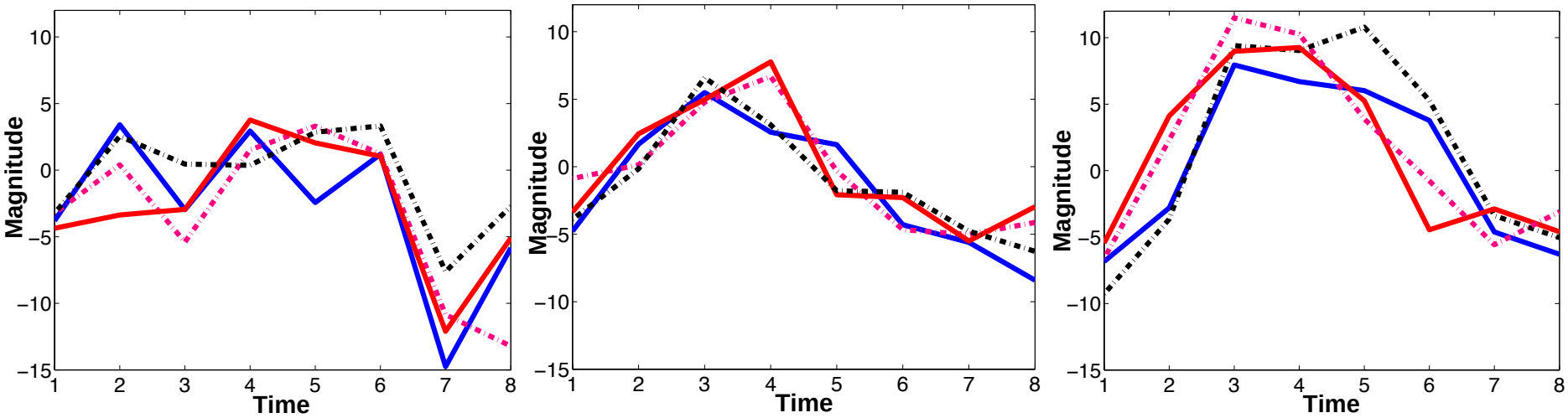


Blue = one-trial condition ; Red = two-trial

So what do the eigenvectors look like ?



Time series from clusters red and blue



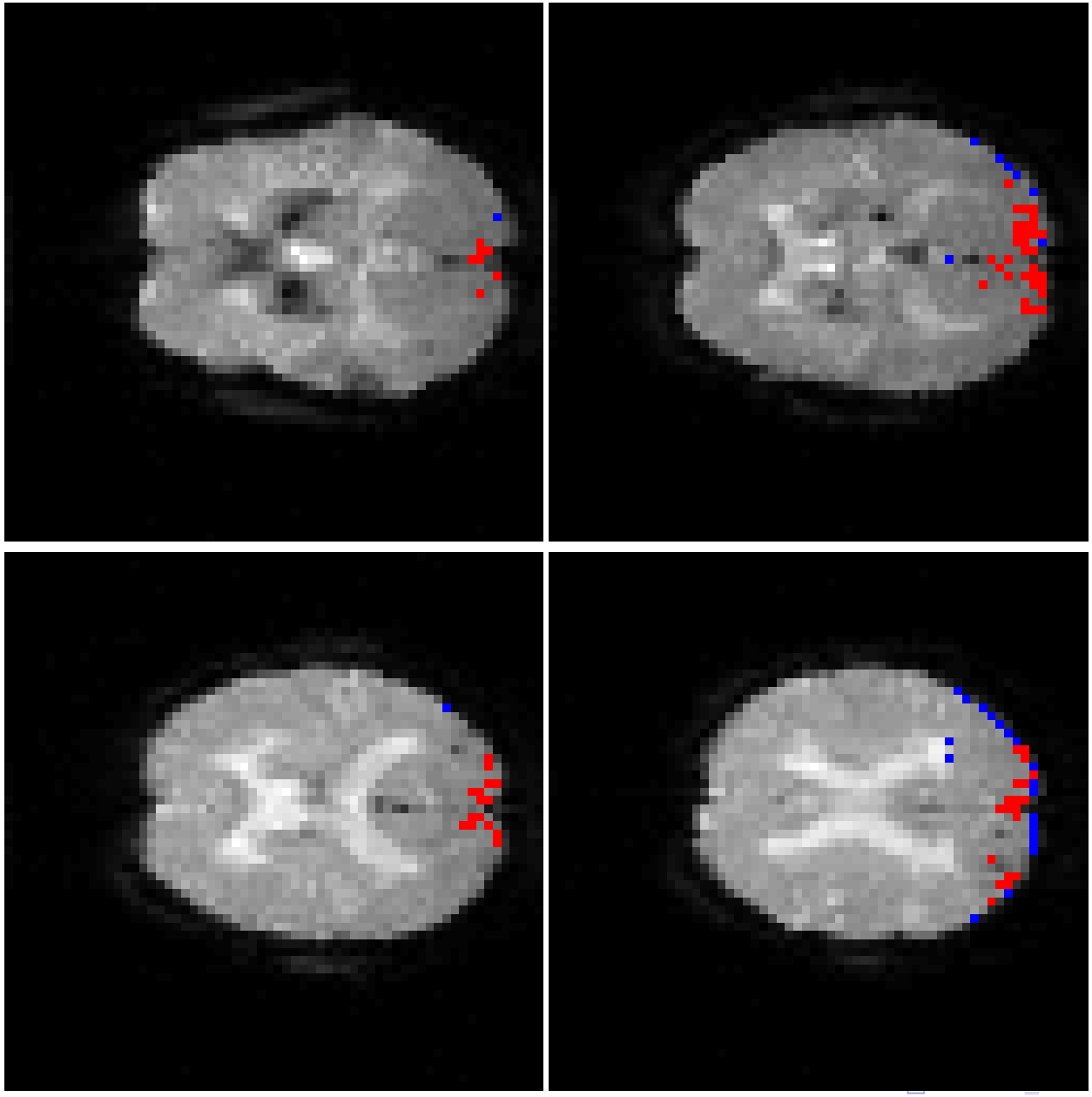
blue cluster

red cluster
(close to background)

red cluster
(tip of the branch)

- two-trial condition elicits a stronger response (superposition of the response)
- as we move further away on the branch, the activation becomes stronger

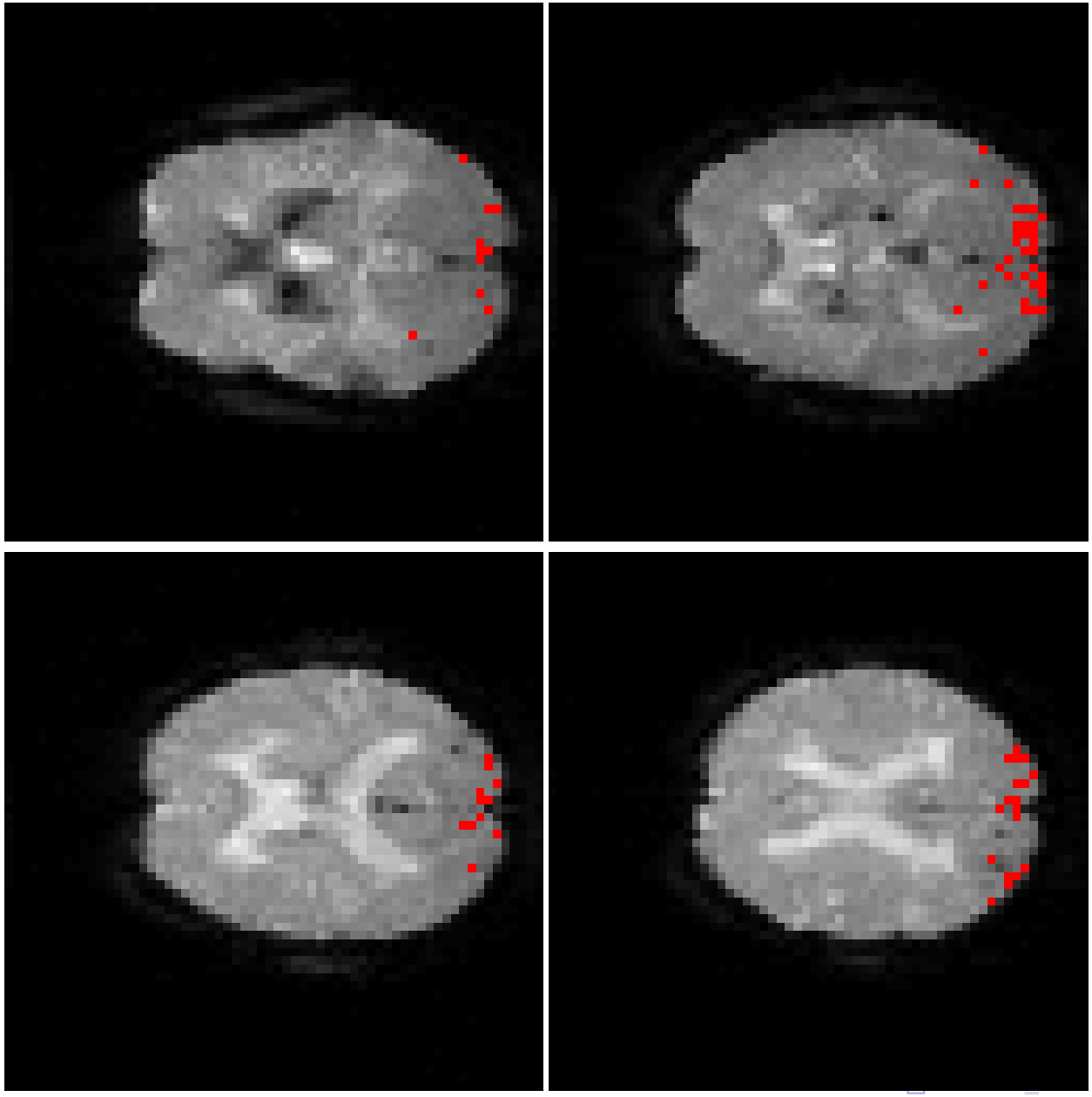
Where are the blue and red clusters ?



Interpretation of the blue and red clusters

- blue time series: dip at t=7, voxels on the border of the brain
- red time series $\approx$ activation pattern, voxels in the visual cortex
- comparison with the linear model:
  - regressor $= h(t) * s(t)$
  - $h(t) = ((t-\delta)/\tau)^2 e^{(t-\delta)/\tau}$, $\delta = 2.5$, $\tau = 1.5$.
  - $s(t) =$ stimulus for the two-trial condition.

Activation map with the linear model



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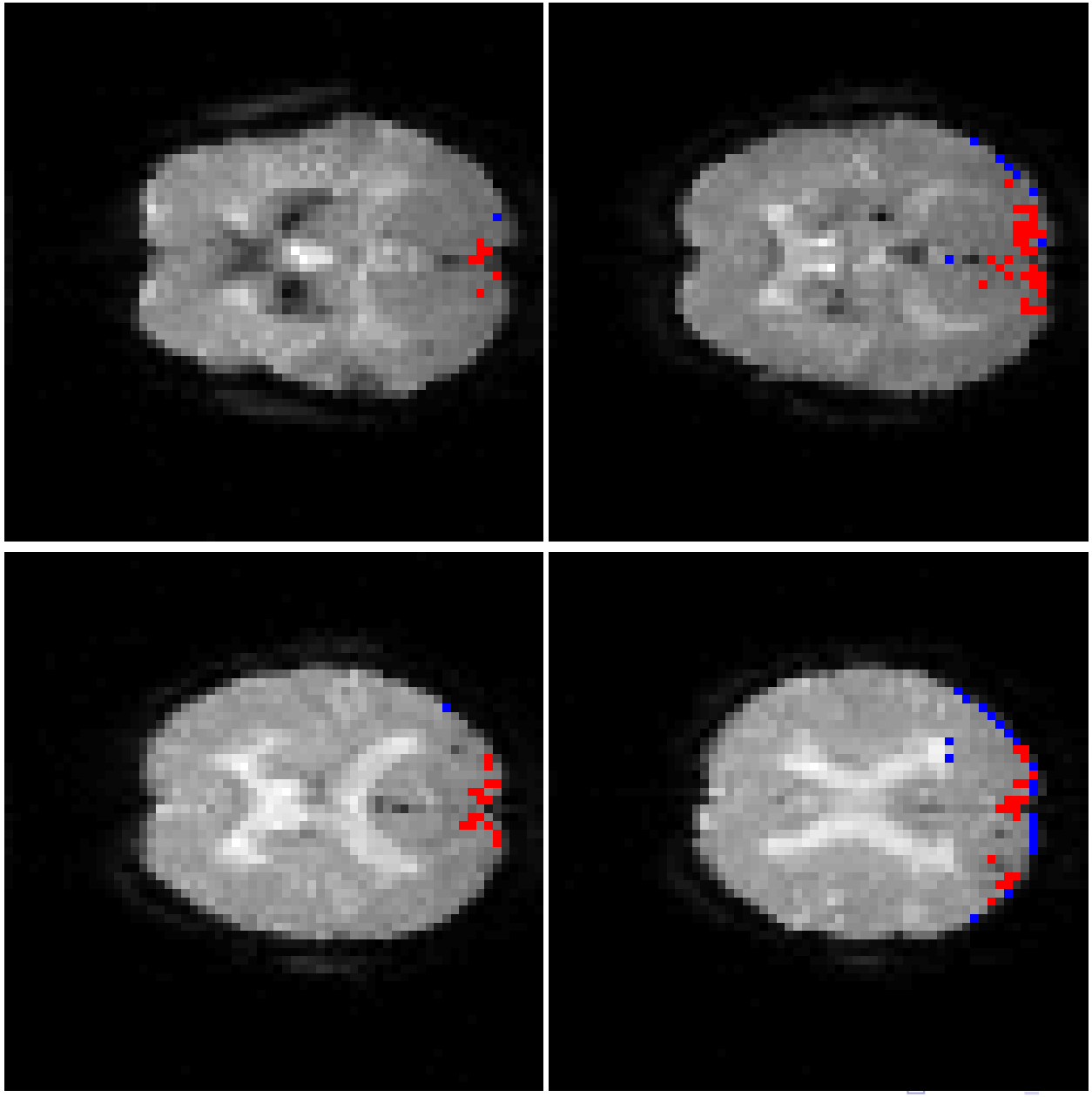

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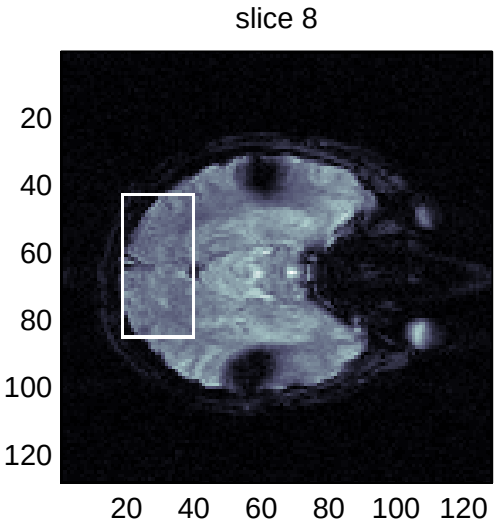
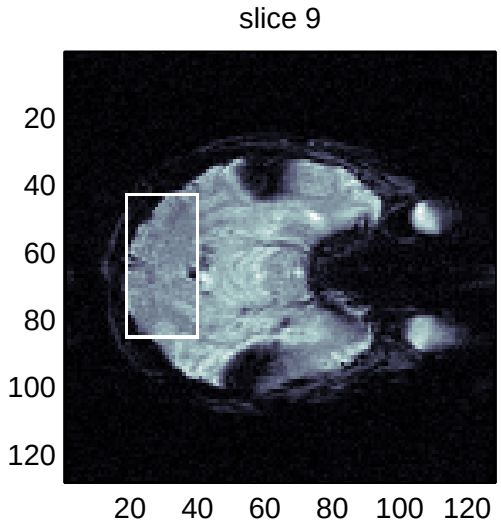
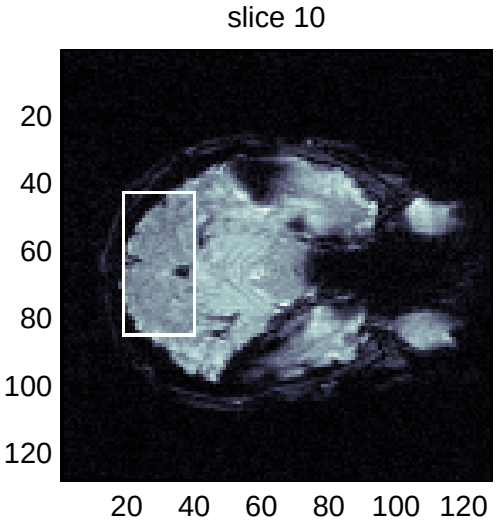
Visual stimulus

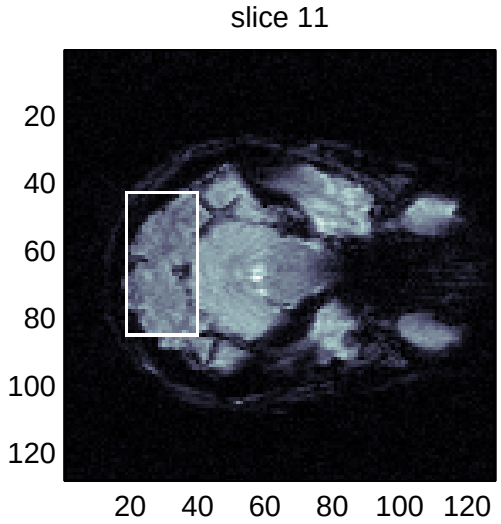
- visual stimulus : flashing checkerboard, 30s ON, 30s OFF
- fMRI images were acquired every 3s, 80 images
- voxel size $1.88 \times 1.88 \times 3$mm, image size 128×128
- region of analysis: 43×22 contains the visual cortex, slices 8 to 11.

Visual stimulus: region of analysis

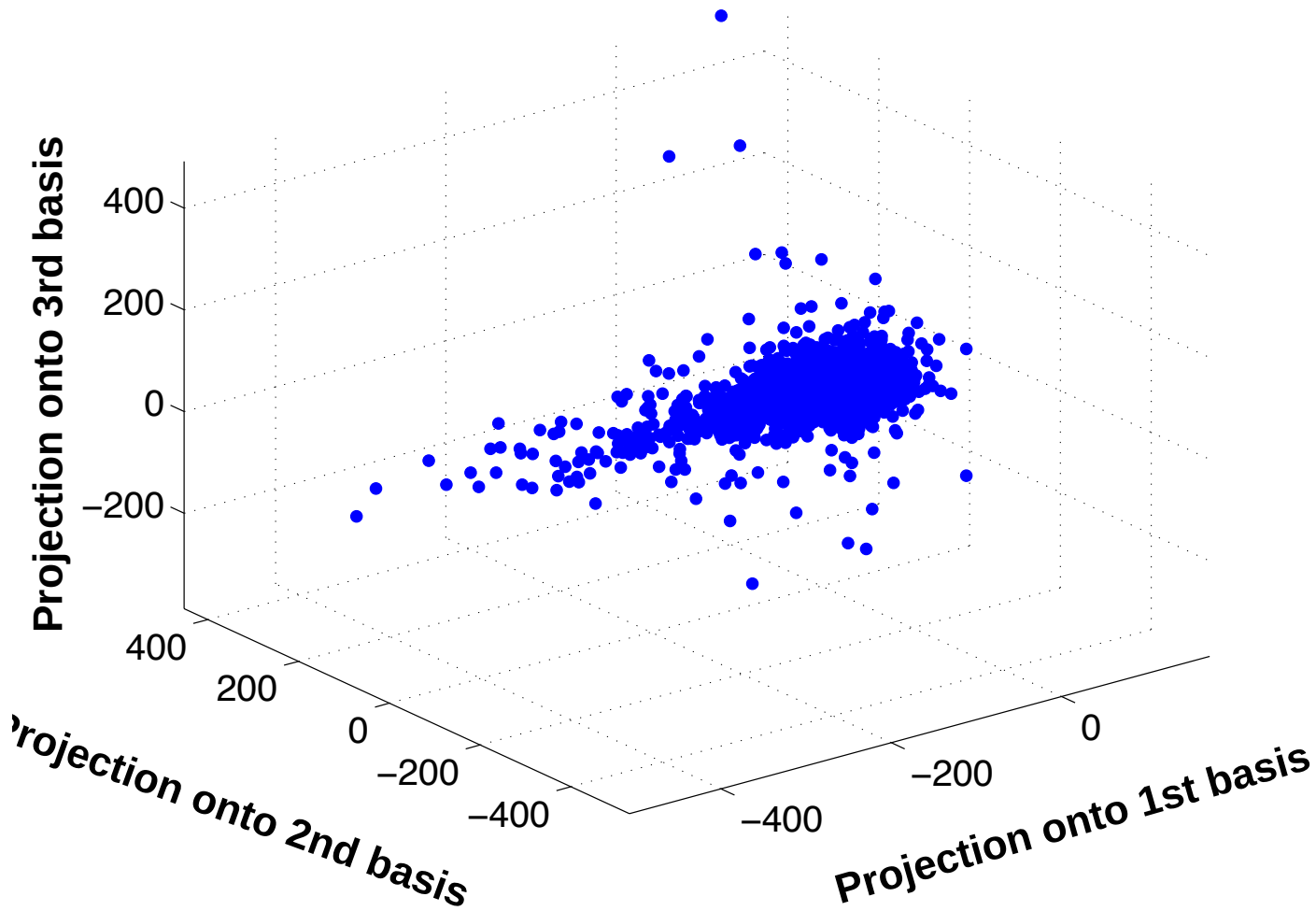




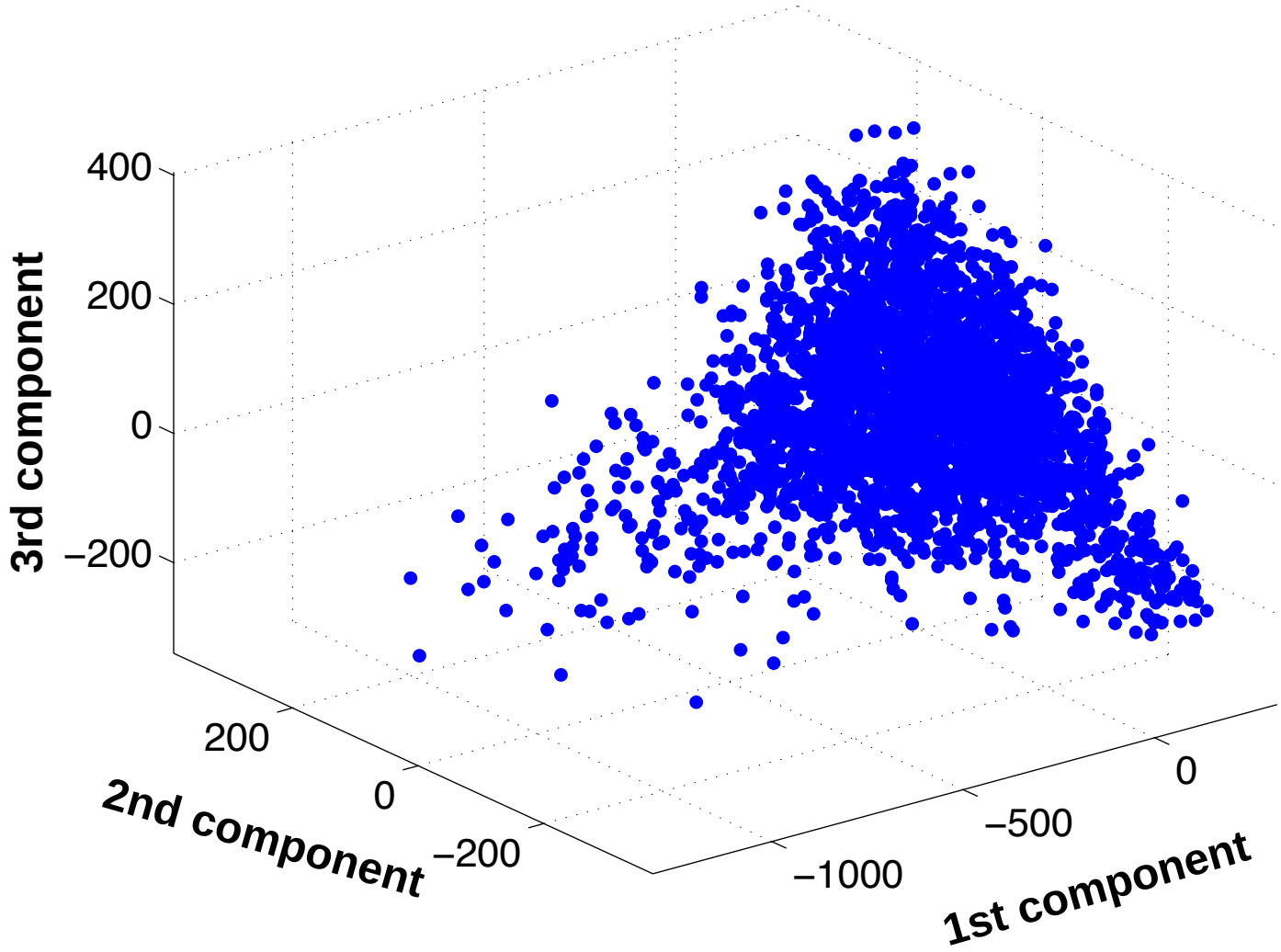




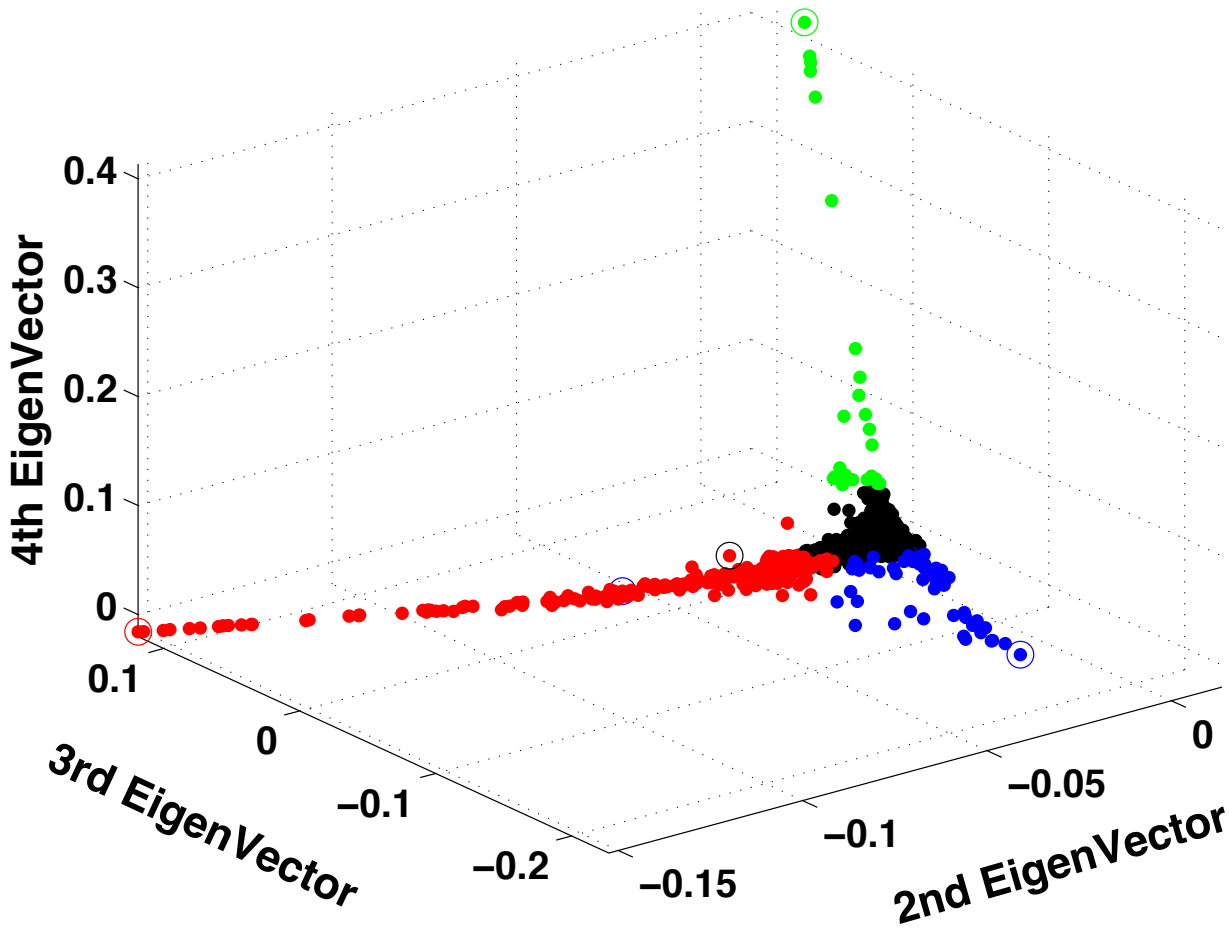
Parametrization given by PCA



Parametrization given by ISOMAP

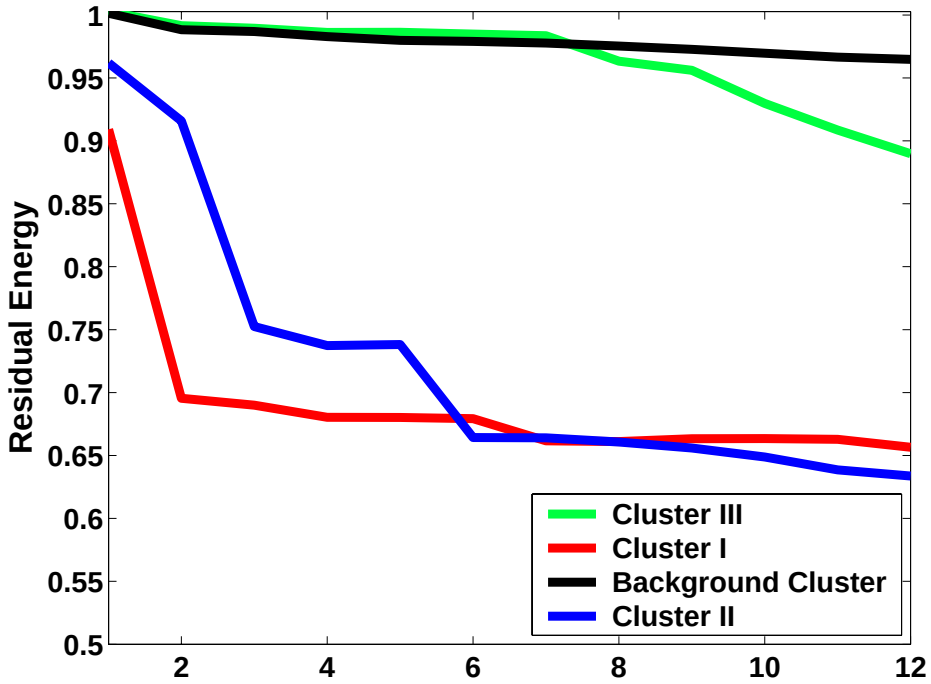


The new parametrization



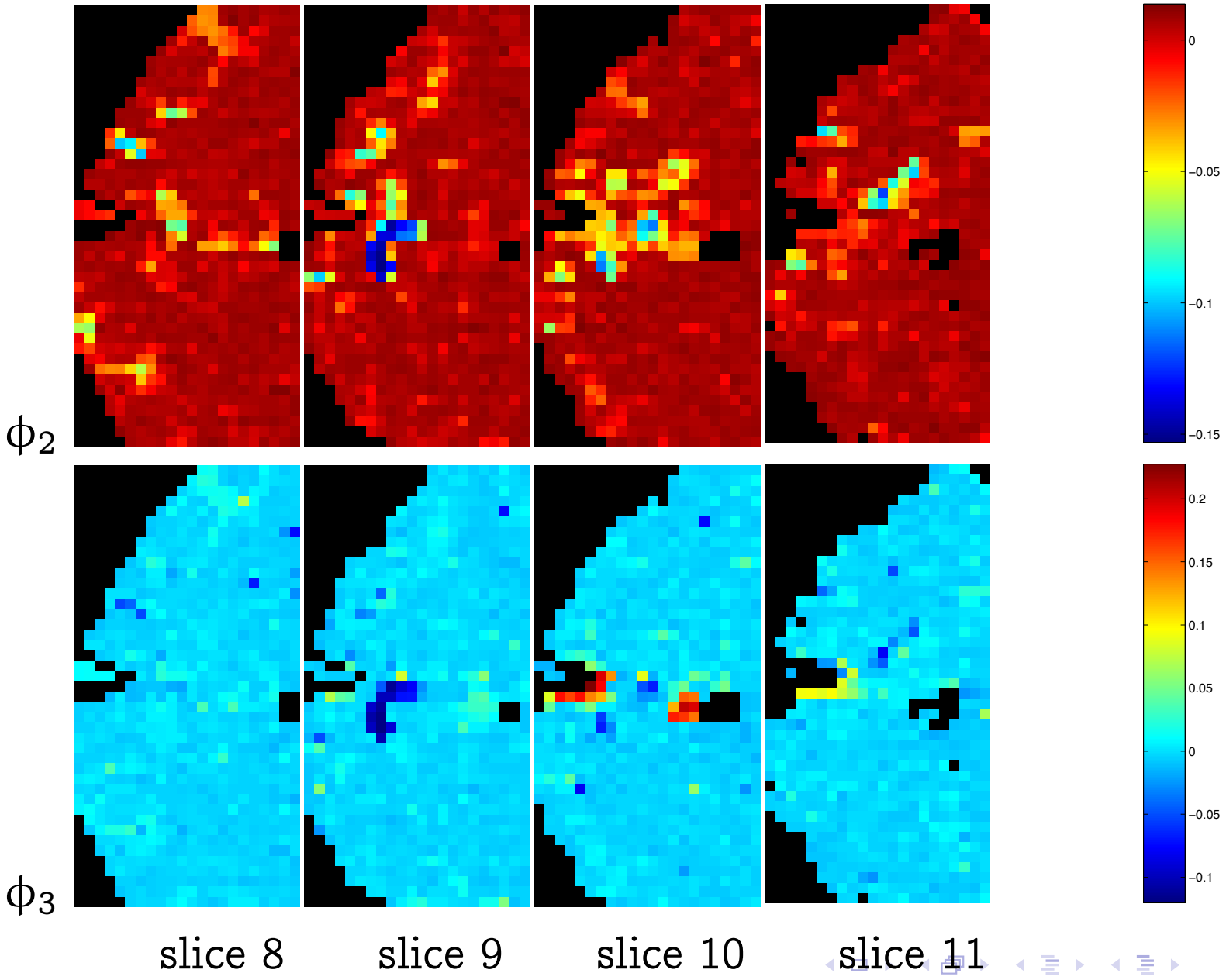
Colors = clustering into 4 clusters.

Choice of K

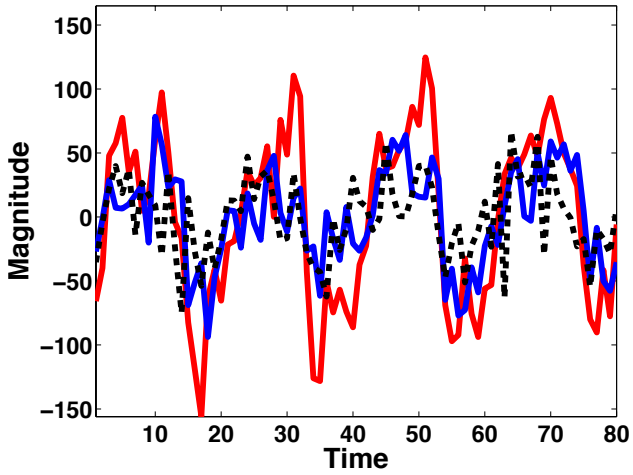


- red and blue clusters are well approximated with $K = 3$ eigenvectors: activated time series,
- green cluster is poorly approximated: weak activation?
- black cluster cannot be well approximated : background time series

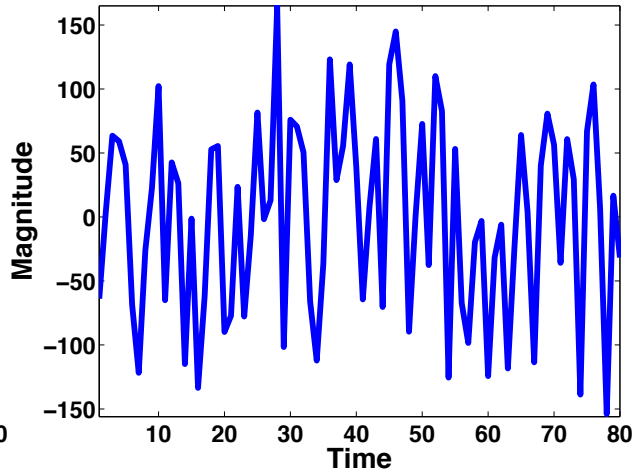
So what do the eigenvectors look like ?



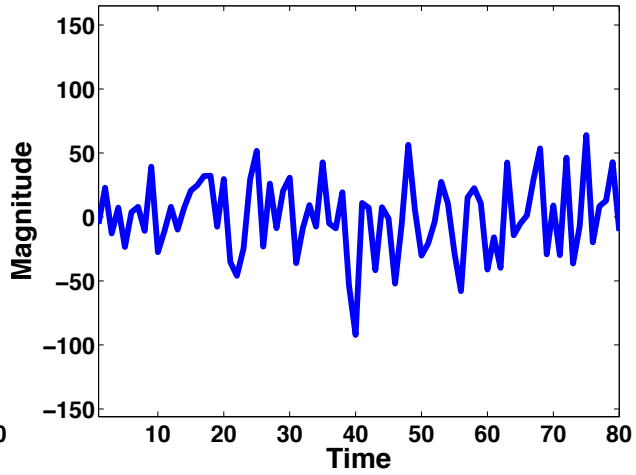
Time series from the three clusters



red cluster



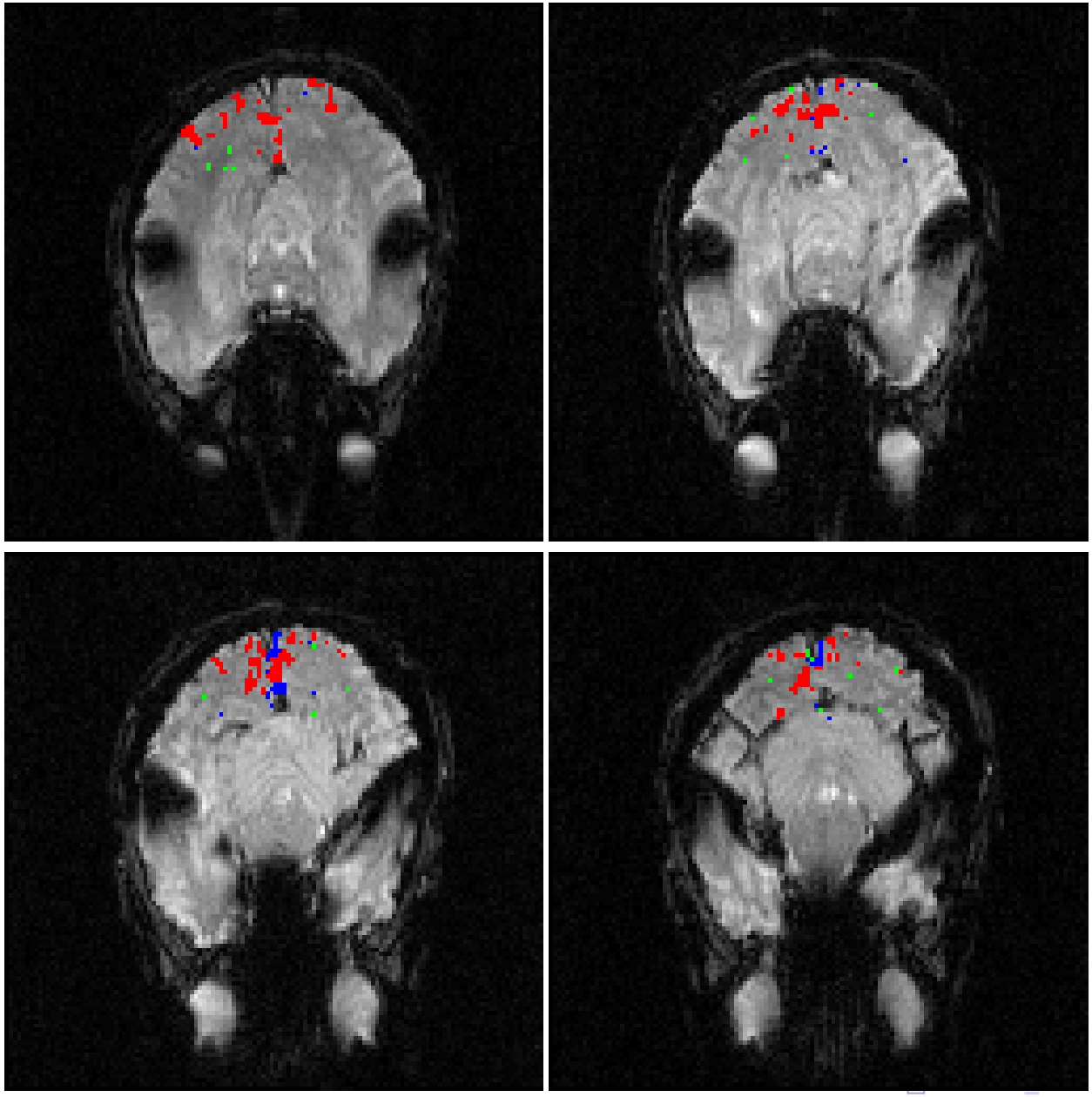
blue cluster



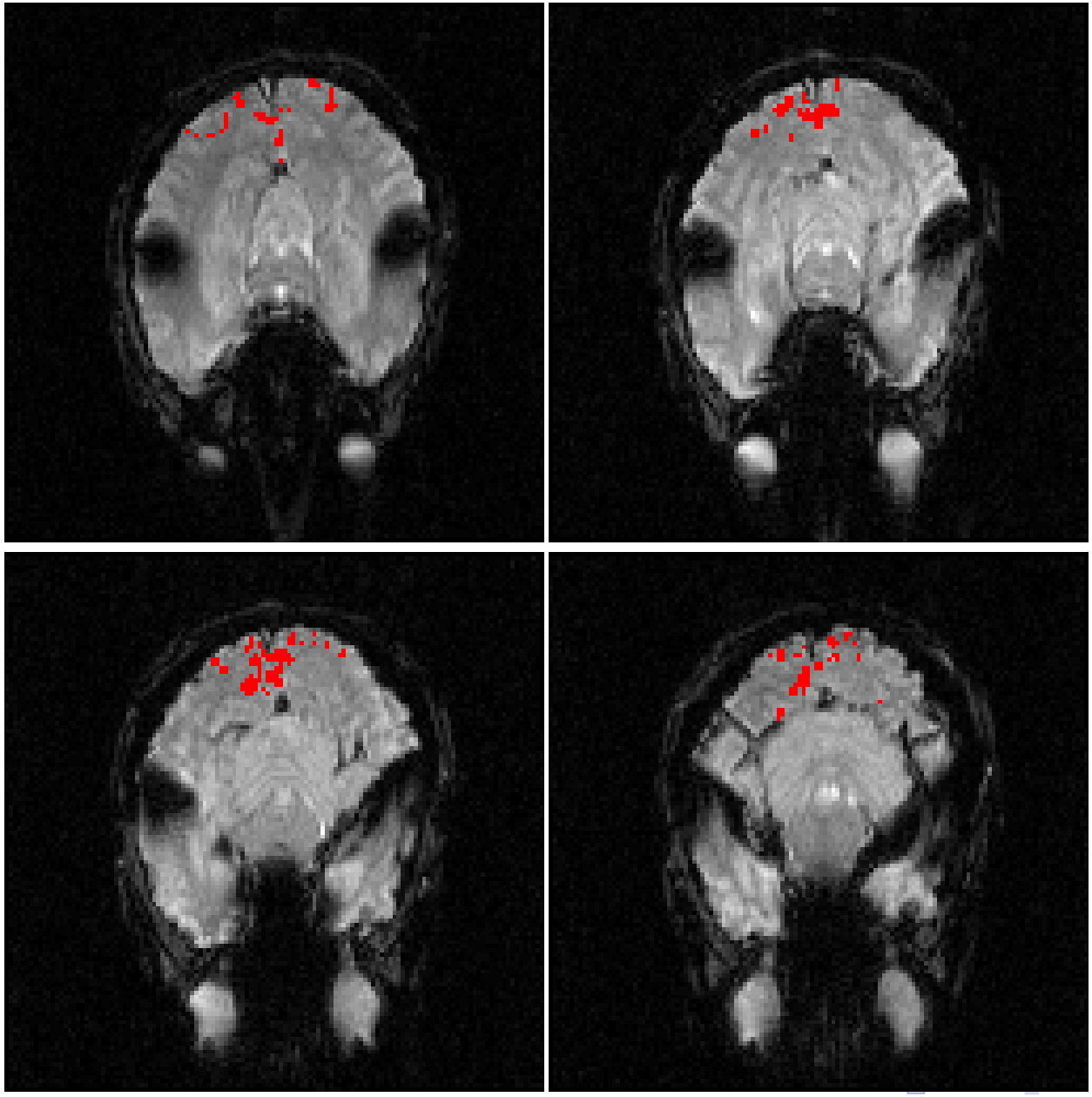
green cluster

- red cluster: typical hemodynamic response to block design stimulus response
- blue cluster: high frequency signal: physiological artifact
- green cluster: weak response to stimulus

Where are the blue, red and green clusters ?



Activation map with the linear model



Conclusion

1. Exploratory analysis of fMRI dataset: construction of a functional map
   - low dimensional representation of the dataset
   - maps are build globally based on the "functional" geometry of the fMRI dataset
   - clustering of the low dimensional representation
   - clear separation of the components into: (1) response to stimulus, (2) coherent physiological signals, (3) artifacts, and (4) background time series
2. Evaluation and comparison to linear and nonlinear techniques.
   - synthetic datasets
   - *in vivo* datasets
3. papers to appear soon on our website: ece.colorado.edu/~fmeyer

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