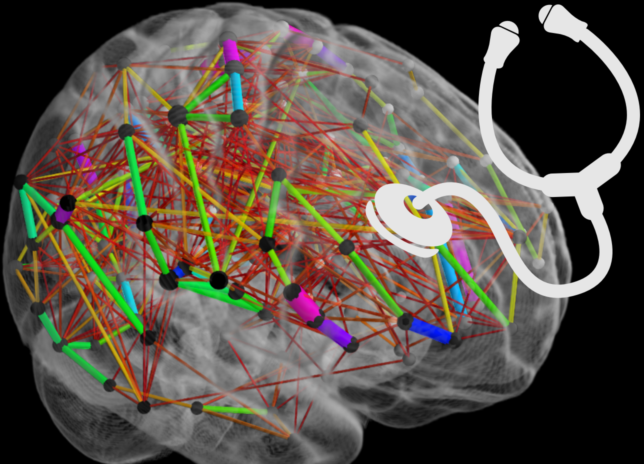
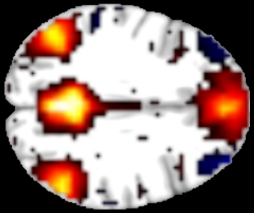
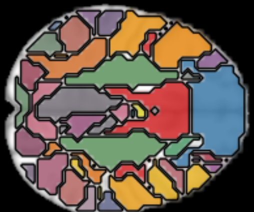
# Statistical markers of pathologies from the brain at rest

Gaël Varoquaux

PARIETAL Inria NeuroSpin



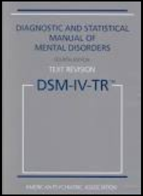




# Probing variations of the mind

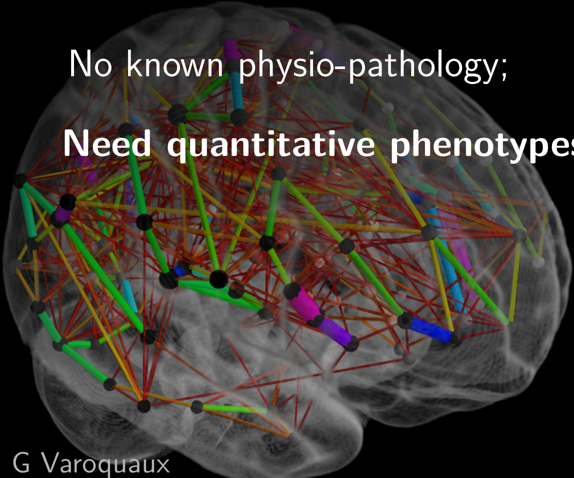
## Psychiatry is defined by symptoms

Diagnostic and Statistical
Manual of Mental Disorders




No known physio-pathology; Autism $\stackrel{?}{=}$ Asperger

**Need quantitative phenotypes of brain function**



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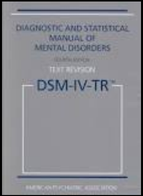
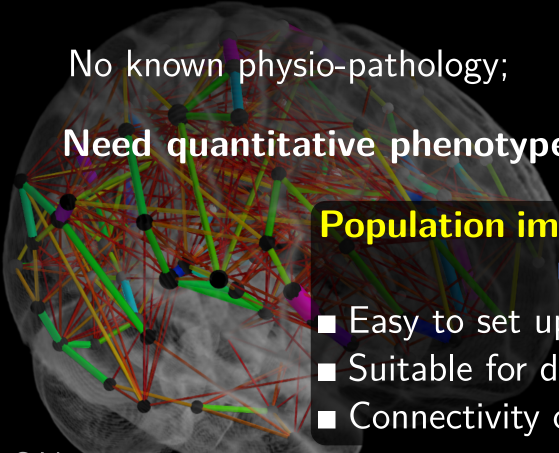


No known physio-pathology; Autism $\stackrel{?}{=}$ Asperger

**Need quantitative phenotypes of brain function**

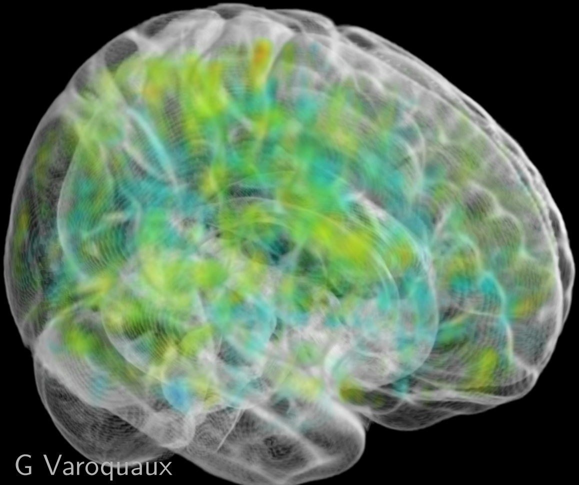
## Population imaging with rest fMRI

UK Biobank [Miller... 2016]

- Easy to set up reproducibly
- Suitable for diminished patients
- Connectivity captures traits

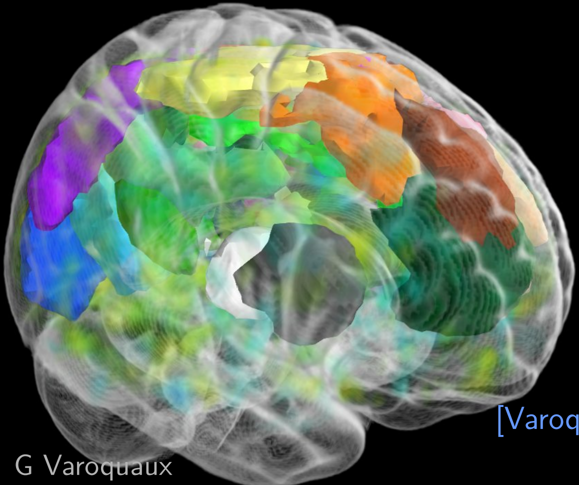
# Functional connectomes: brain graphs

No salient features in rest fMRI



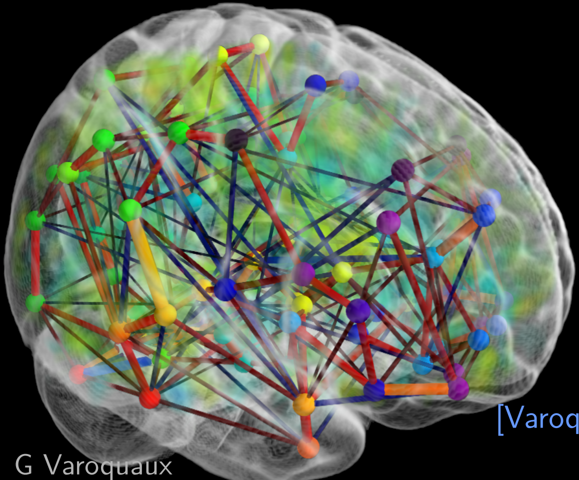
# Functional connectomes: brain graphs

- Define functional regions



[Varoquaux and Craddock 2013]

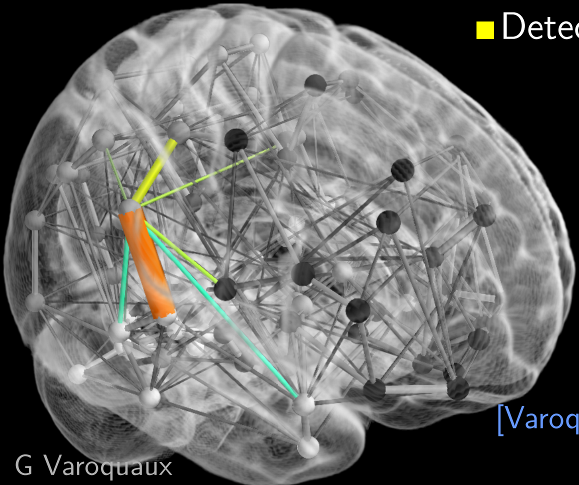
# Functional connectomes: brain graphs



- Define functional regions
- Learn interactions

[Varoquaux and Craddock 2013]

# Functional connectomes: brain graphs



- Define functional regions
- Learn interactions
- Detect differences

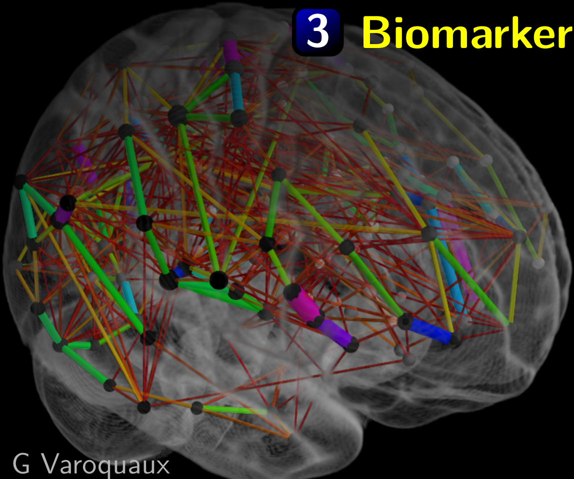
[Varoquaux and Craddock 2013]

# Outline

1 Functional regions

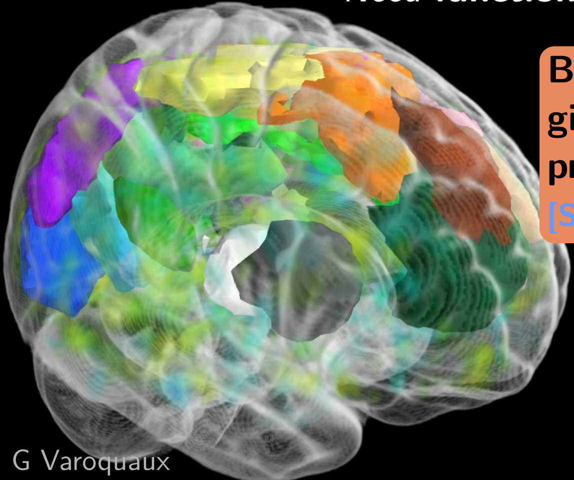
2 The connectome matrix

3 Biomarkers of autism



# 1 Functional regions

Need **functional** regions for nodes



**Bad choice of regions gives wrong graph properties**
[Smith... 2011]

⇒ Spatial analysis

# 1 Functional regions

Available "on the market"

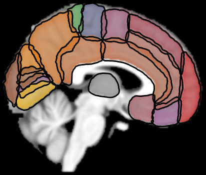
anatomical atlases, functional atlases, region-extraction methods

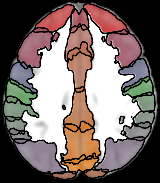
# 1 Functional regions

- Atlases based on anatomy
- Clustering tools
- Models based on linear decompositions

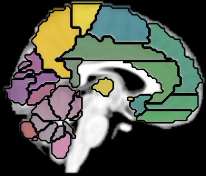
- Anatomical atlases do not resolve functional structures

**Harvard Oxford**

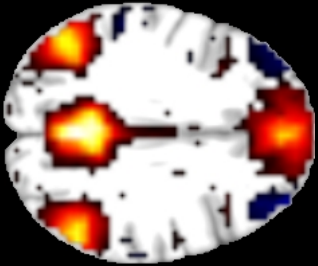




**AAL**

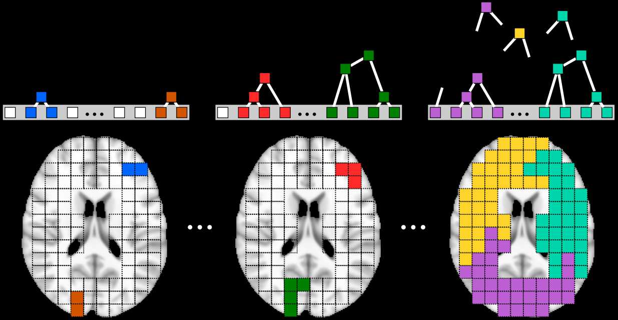


Default mode network: most stable network at rest



# 1 Clustering approaches

- Group together voxels with similar time courses



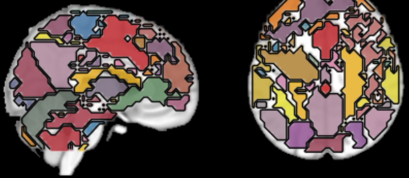
# 1 Clustering approaches

## K-Means

- Fast
- No spatial constraint
  (smooth the data)

  Related to [Yeo... 2011]

KMeans

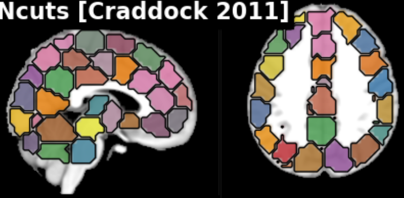


## Normalized cuts

[Craddock... 2012]

- Slow
- Spatial constraints
- Very geometrical

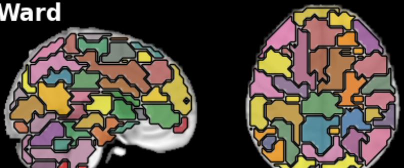
Ncuts [Craddock 2011]



## Ward clustering

- Very fast
  (even with many clusters)
- Spatial constraints

Ward

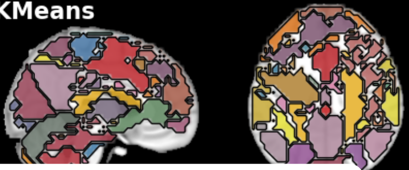


# 1 Clustering approaches [Thirion... 2014]

## K-Means

- Fast
- No spatial constraint
  (smooth the data)

KMeans



**Model selection: empirical results**

Based on cluster stability and fit to data

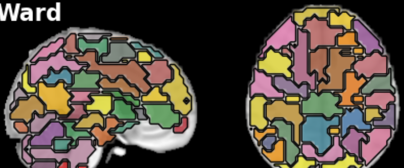
- Large number of clusters: Ward
- Small number of clusters: Kmeans

[Thirion... 2014]

## Ward clustering

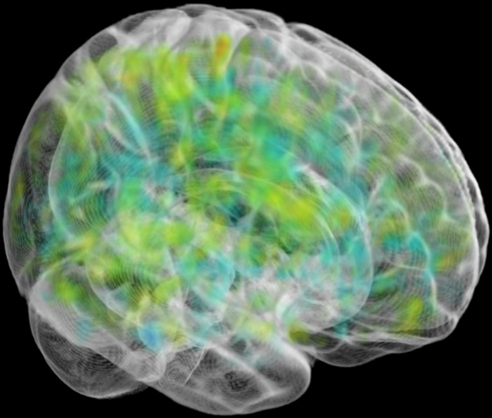
- Very fast
  (even with many clusters)
- Spatial constraints

Ward



**Working hypothesis / model**:
Observing linear mixtures of networks at rest

Time courses



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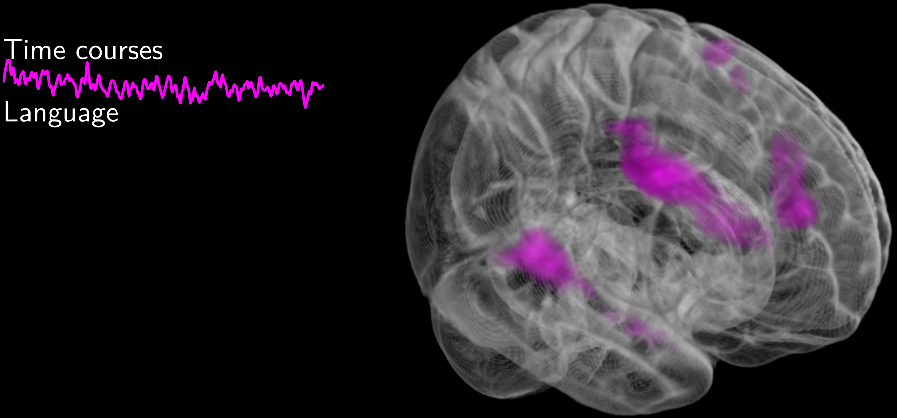

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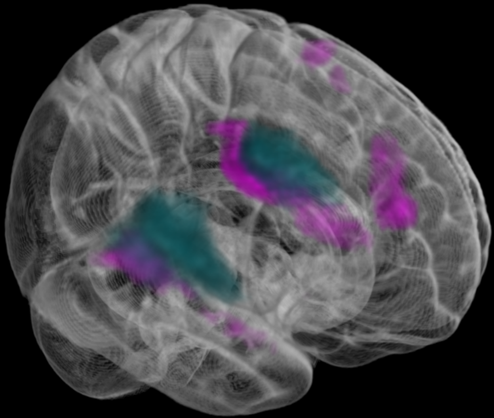

# 1 Mixture models: linear decompositions

**Working hypothesis / model**:

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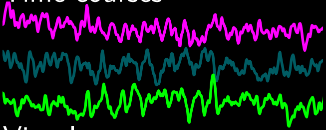
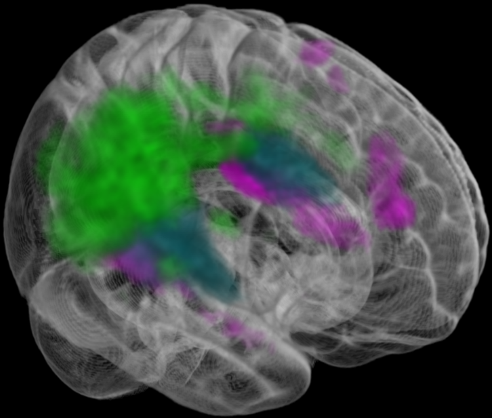


Visual



# 1 Mixture models: linear decompositions

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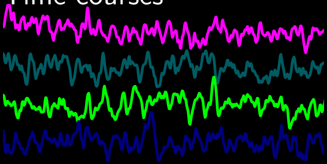
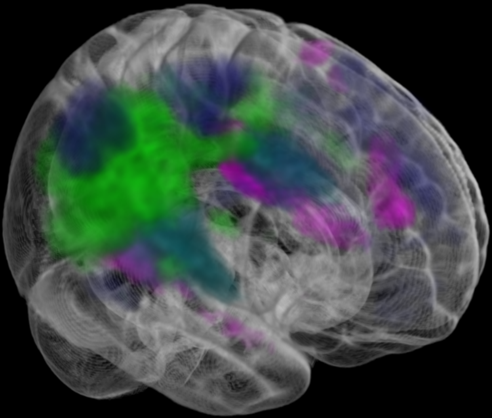


Dorsal Att.



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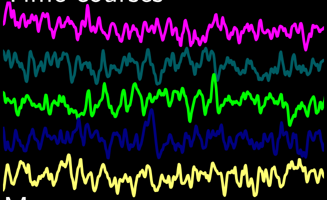
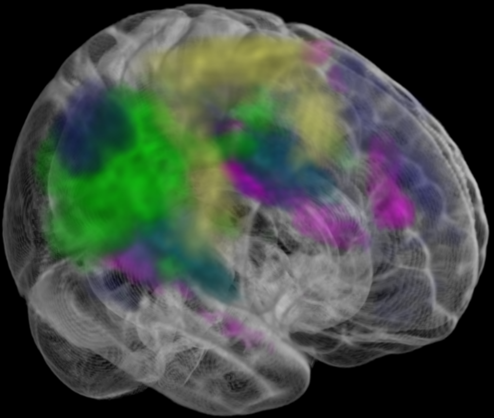


Motor



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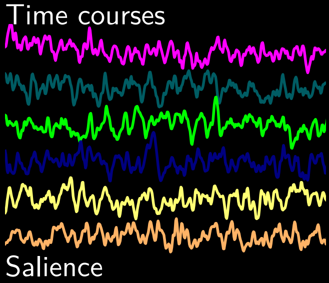


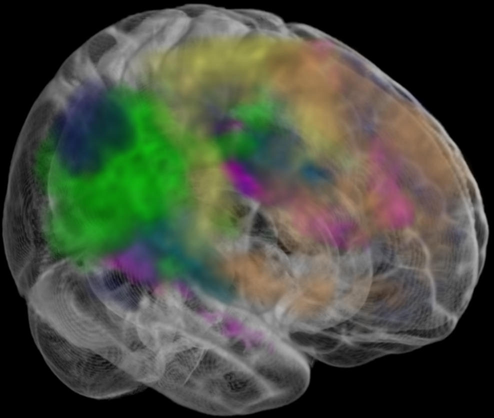

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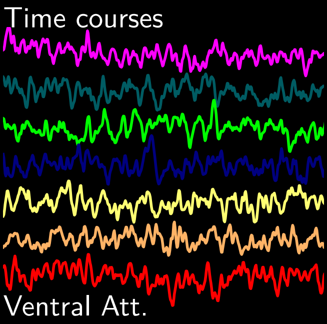


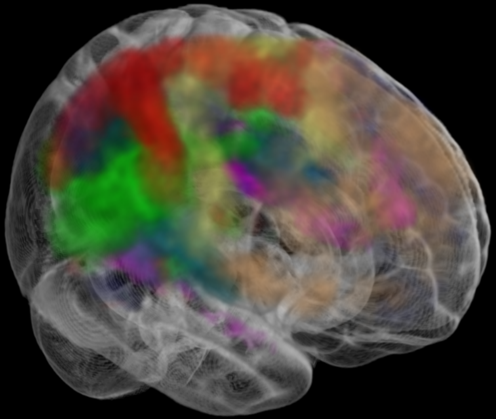

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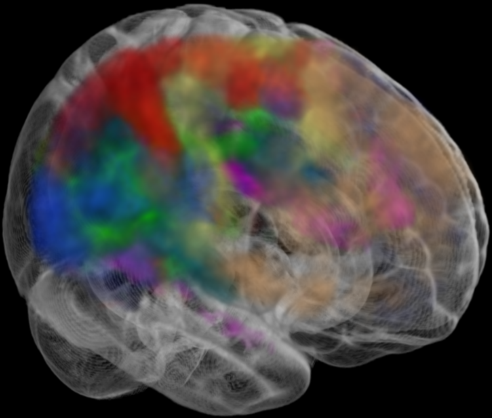

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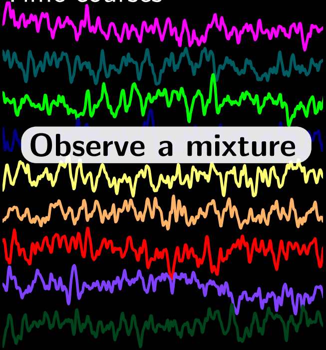
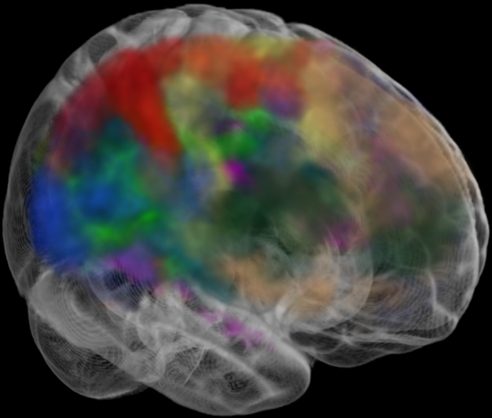
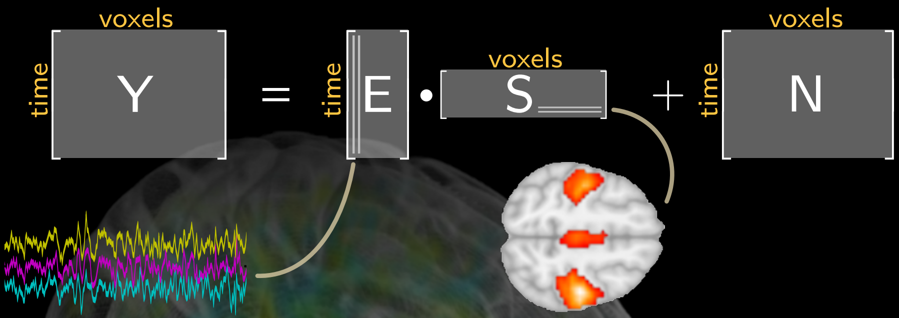


How to unmix networks?

# 1 Spatial modes: ICA decomposition

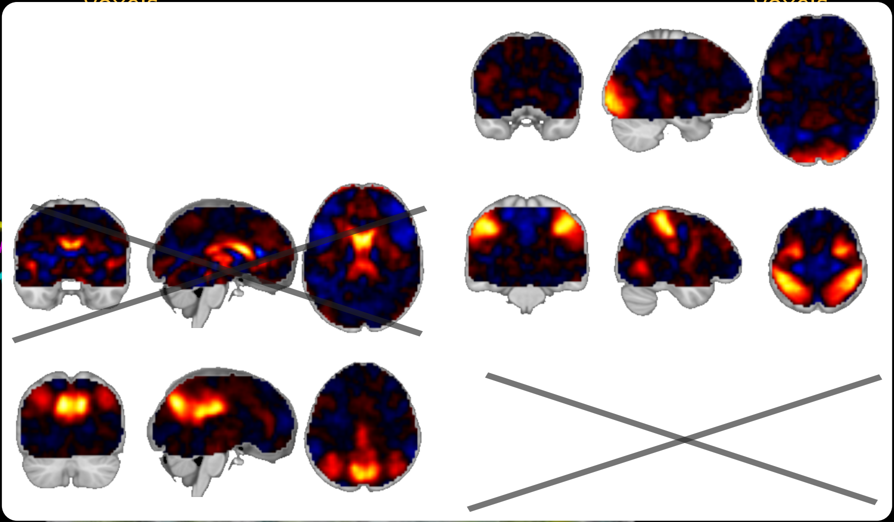



**Decomposing time series into:**

- covarying spatial maps, **S**
- uncorrelated residuals, **N**

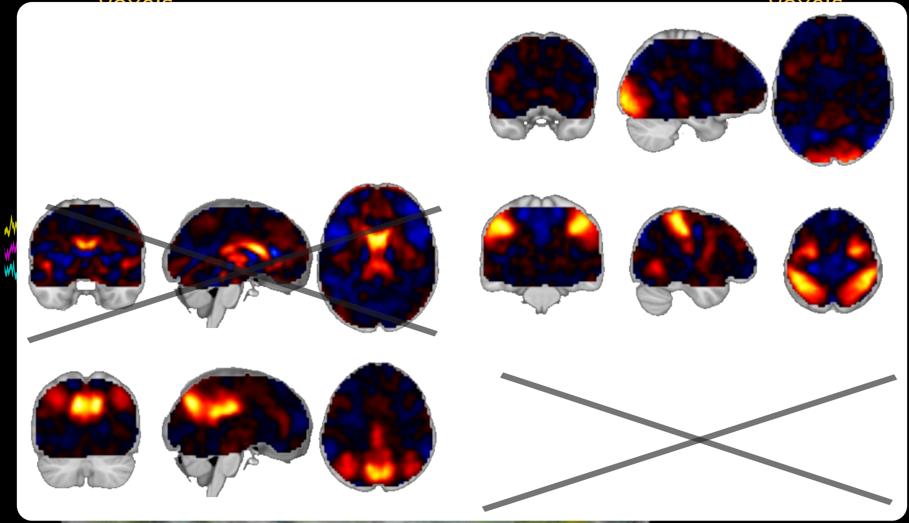
**ICA: minimize mutual information across S**

# 1 Spatial modes: ICA decomposition



**ICA: minimize mutual information across S**

# 1 Spatial modes: ICA decomposition

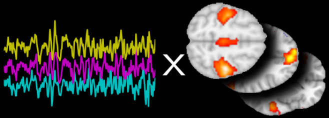


**Sparse decompositions: sparse penalty on maps**

## ICA

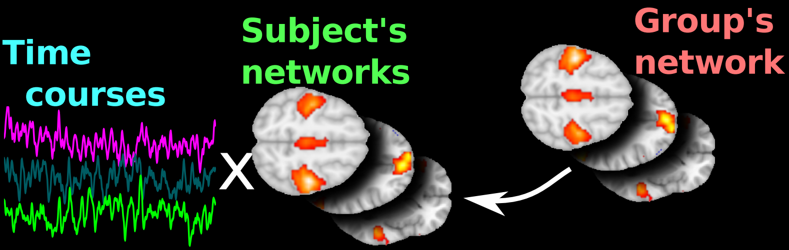
1. Select signal of interest
2. Select "maximaly independent" ICs

## Sparse decomposition



$$\hat{\mathbf{E}}, \hat{\mathbf{S}} = \underset{\mathbf{S},\mathbf{E}}{\operatorname{argmin}} \underbrace{\left\| \mathbf{Y} - \mathbf{E}\,\mathbf{S} \right\|_2^2}_{\text{Data fit}} + \underbrace{\lambda \left\| \mathbf{S} \right\|_1}_{\text{Penalization: sparse maps}}$$

**Joint** estimation of signal space + components




## Multi-Subject Dictionary Learning

$$\underset{\mathbf{E}^s,\mathbf{S}^s,\mathbf{S}}{\operatorname{argmin}} \sum_{\mathit{subjects}} \left( \|\mathbf{Y}^s - \mathbf{E}^s {\mathbf{S}^s}^T\|_{\mathrm{Fro}}^2 + \mu \|\mathbf{S}^s - \mathbf{S}\|_{\mathrm{Fro}}^2 \right) + \lambda\,\Omega(\mathbf{S})$$

Data fit

Subject variability

Penalization: inject structure

[Varoquaux... 2011, Abraham... 2013]

**Create a region-forming penalty:**


$$\underset{\mathbf{E}^s, \mathbf{S}^s, \mathbf{S}}{\operatorname{argmin}} \sum_{subjects} \left( \|\mathbf{Y}^s - \mathbf{E}^s {\mathbf{S}^s}^T\|^2_{\text{Fro}} + \mu \|\mathbf{S}^s - \mathbf{S}\|^2_{\text{Fro}} \right) + \lambda\, \Omega(\mathbf{S})$$

Data fit

Subject variability

Penalization: inject structure

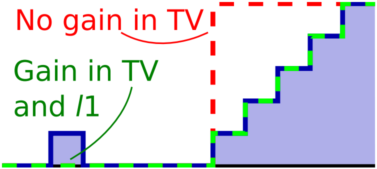
[Varoquaux... 2011, Abraham... 2013]

## Create a region-forming penalty:

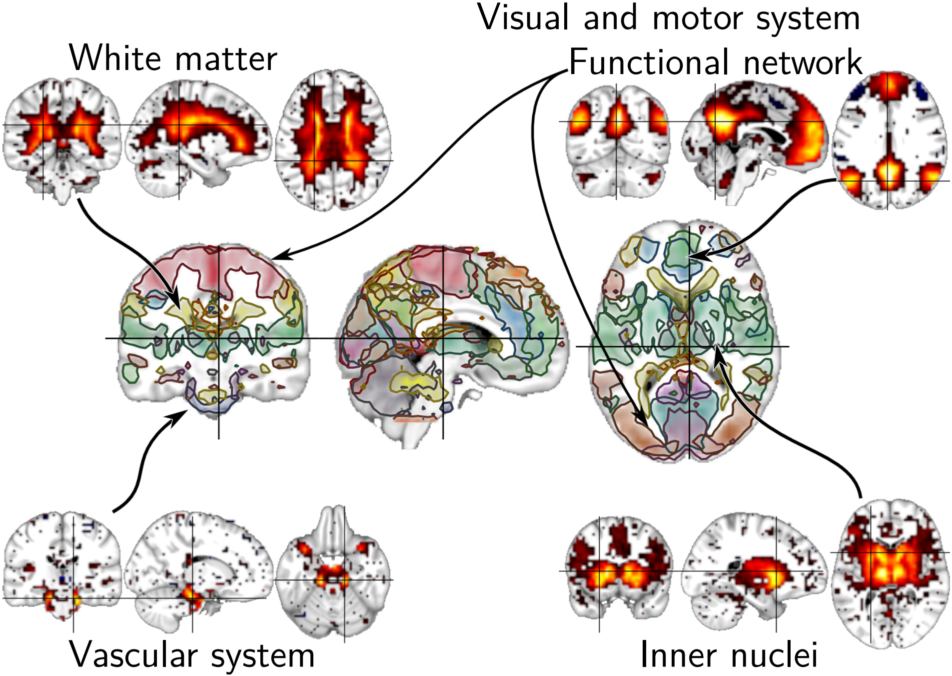

**TV-$\ell_1$ penalty:** $\|\mathbf{w}\|_1 + TV(\mathbf{w})$

- sparse and smooth regions
- TV $\neq$ "piecewise constant"

[Gramfort... 2013]

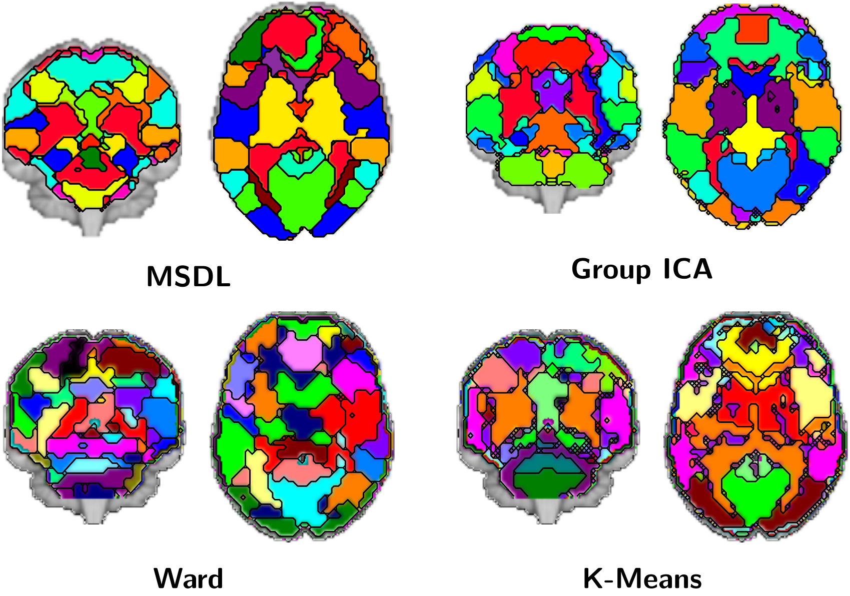



[Varoquaux... 2011, Abraham... 2013]



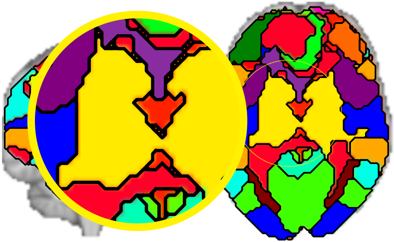

Downloadable from Parietal webpage `http://team.inria.fr/parietal`

# Brain parcellations

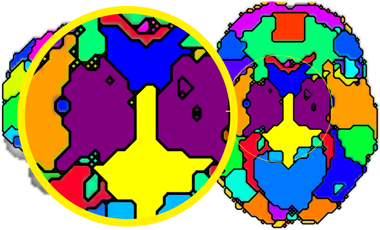



[Abraham... 2013]

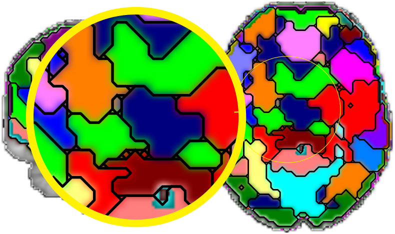
# Brain parcellations



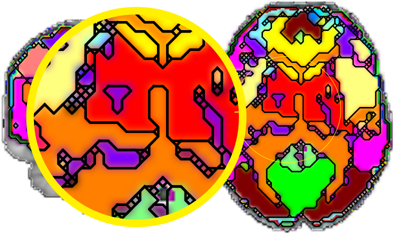
MSDL



Group ICA



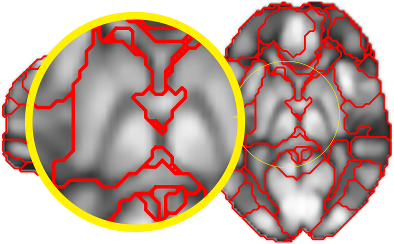
Ward



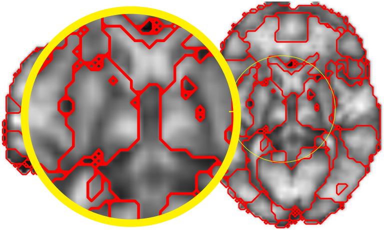
K-Means

[Abraham... 2013]

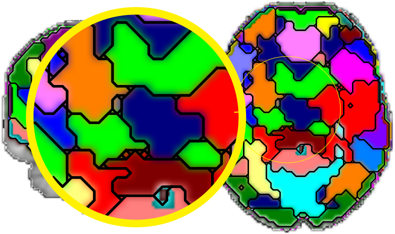
# Brain parcellations



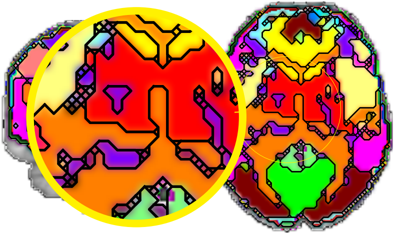
MSDL



Group ICA



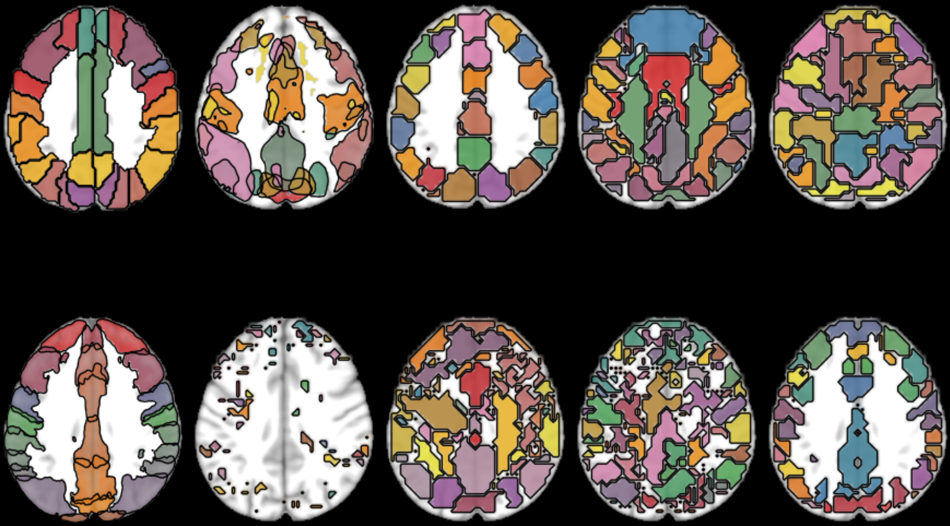
Ward



K-Means

[Abraham... 2013]

# Functional regions



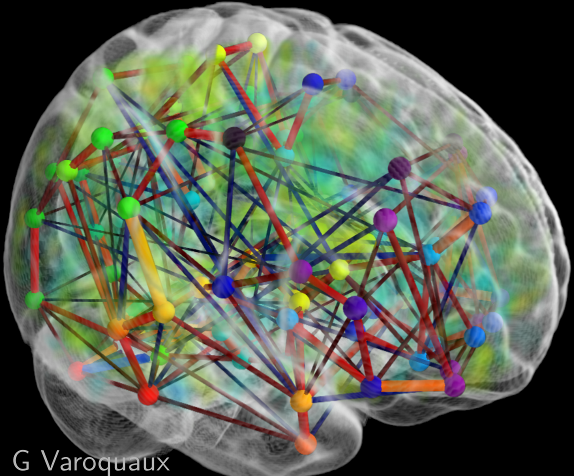
# Functional regions

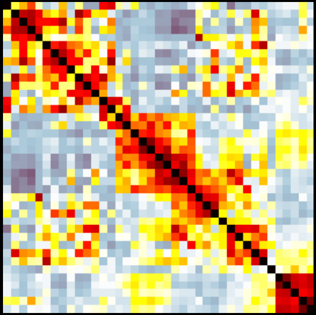
AAL | Smith 2009 ICAs | Craddock 2011 Ncuts | Abraham 2013 TV-MSDL | Ward

Harvard-Oxford | High model order ICA | K-Means | Varoquaux 2011 Smooth-MSDL | Yeo 2011

# 2 The connectome matrix

How to capture and represent interactions?





# 2 Data processing induces structure

**Small-world**:

"*The friends of my friends are my friends*"

**Correlation**:

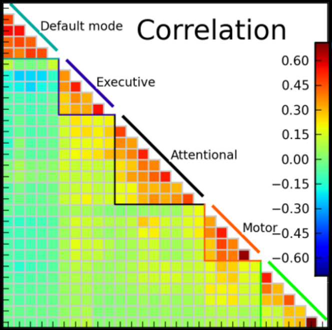
If **A** and **B** are very correlated,
and **C** is correlated with **A**,
**C** is also correlated with **B**

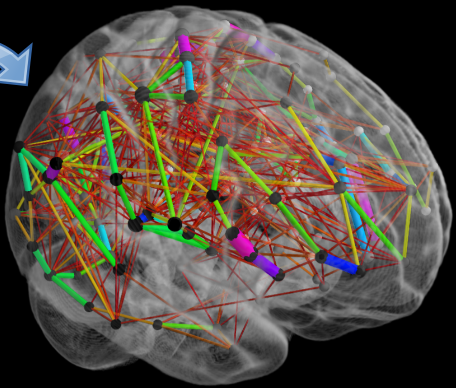
$\Rightarrow$ Thresholded correlations are small-world

[Zalesky... 2012]

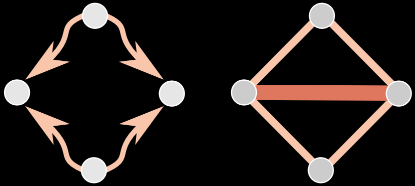
**Need careful statistics**

# 2 From correlations to connectomes

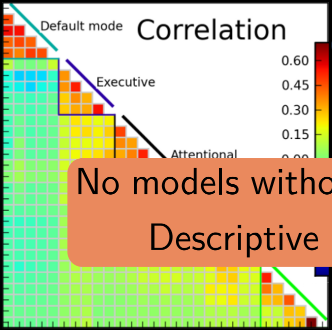


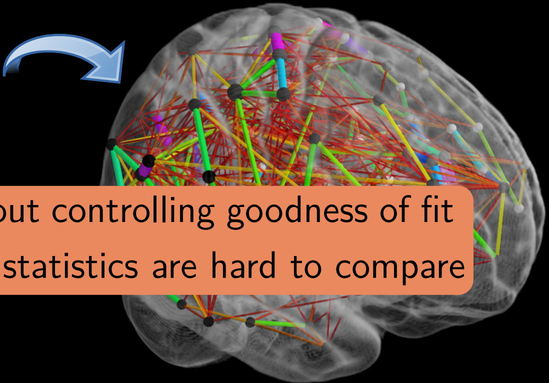



**Threshold?**



# 2 From correlations to connectomes



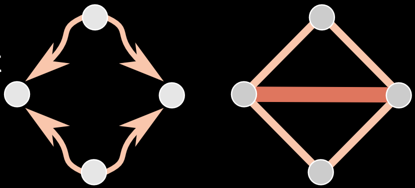



No models without controlling goodness of fit

Descriptive statistics are hard to compare

**Threshold?**

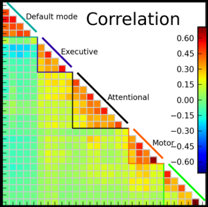
How to check that we are not throwing out the baby with the bath water



# 2 Probabilistic model for interactions

- Simplest **data generating process** = multivariate normal:

$$\mathcal{P}(\mathbf{X}) \propto \sqrt{|\mathbf{\Sigma}^{-1}|}e^{-\frac{1}{2}\mathbf{X}^T\mathbf{\Sigma}^{-1}\mathbf{X}}$$




- Model parametrized by inverse covariance matrix, $\mathbf{K} = \mathbf{\Sigma}^{-1}$: ***conditional*** covariances

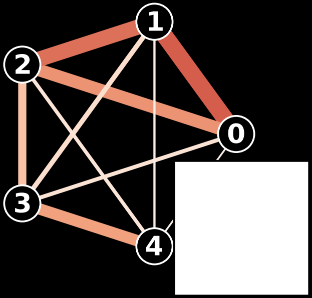
- Goodness of fit:
  likelihood of observed covariance $\hat{\mathbf{\Sigma}}$ in model $\mathbf{\Sigma}$

$$\mathcal{L}(\hat{\mathbf{\Sigma}}|\mathbf{K}) = \log|\mathbf{K}| - \operatorname{trace}(\hat{\mathbf{\Sigma}}\,\mathbf{K})$$

# 2 Correlations: observations and indirect effects

## Observations

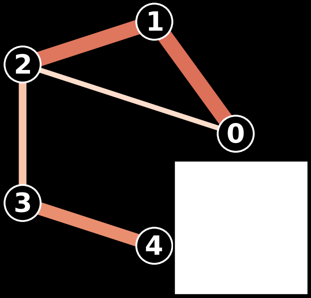
**Correlation**




Covariance:
scaled by variance

## Direct connections

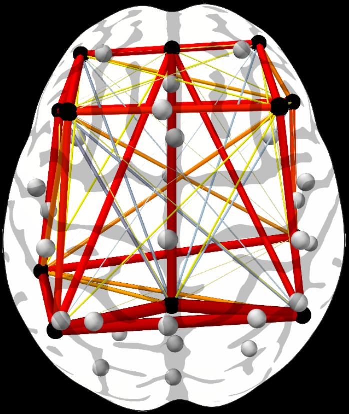
**Partial correlation**




Inverse covariance:
scaled by partial variance

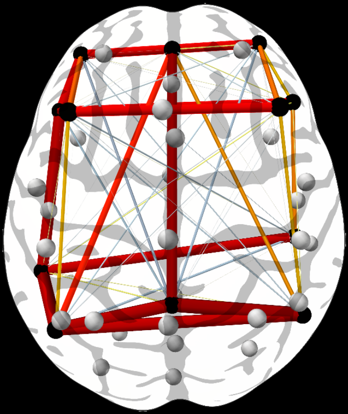
## Observations

Correlation



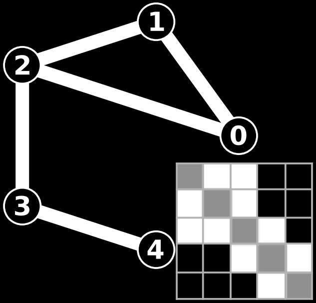
## Direct connections

Partial correlation



## Gaussian graphical models

Zeros in inverse covariance give **conditional independence**




$$\mathbf{\Sigma}^{-1}_{i,j} = 0 \quad \Leftrightarrow \quad \mathbf{x}_i,\ \mathbf{x}_j \text{ independent conditionally on } \{\mathbf{x}_k, k \neq i, j\}$$

## Sparse inverse covariance

Estimator imposes zeros

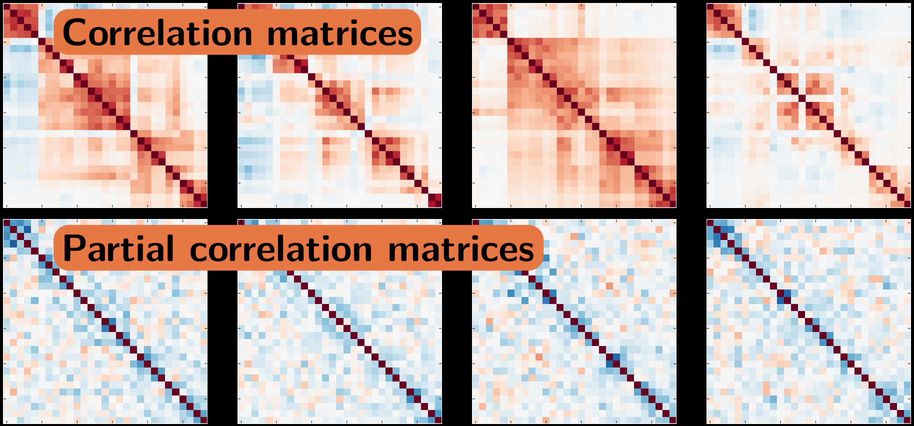
[Smith... 2011, Varoquaux... 2010b]

## Shrunk estimator

Estimates closer to 0

[Varoquaux and Craddock 2013]

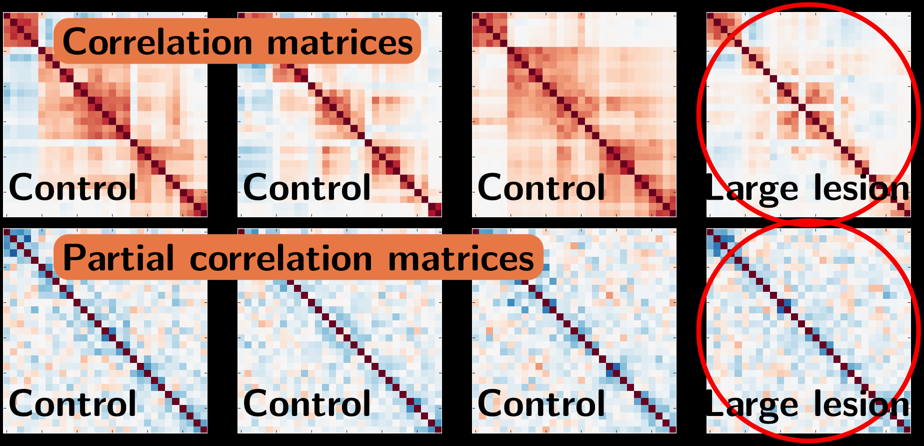
# 2 Differences in correlations across subjects




3 controls, 1 severe stroke patient

**Which is which?**

# 2 Differences in correlations across subjects




- Spread-out variability in correlation matrices
- Noise in partial-correlations

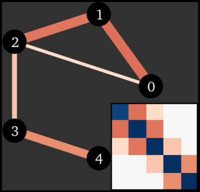
**Strong dependence between coefficients**

[Varoquaux... 2010a]

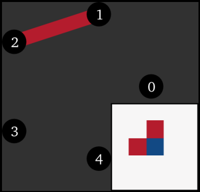
# 2 A toy model of differences in connectivity

- Two processes with different partial correlations

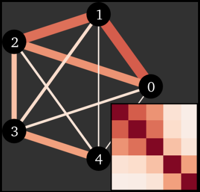
$\mathbf{K}_1$:



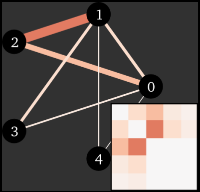

$\mathbf{K}_1 - \mathbf{K}_2$:




$\mathbf{\Sigma}_1$:

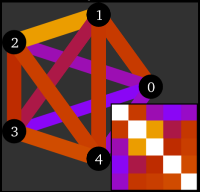



$\mathbf{\Sigma}_1 - \mathbf{\Sigma}_2$:

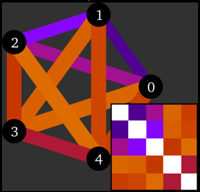



- $+$ jitter in observed covariance

$\mathrm{MSE}(\mathbf{K}_1 - \mathbf{K}_2)$:




$\mathrm{MSE}(\mathbf{\Sigma}_1 - \mathbf{\Sigma}_2)$:

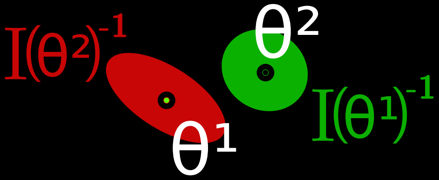



**Non-local effects and non homogeneous noise**

**Estimation error of covariances**

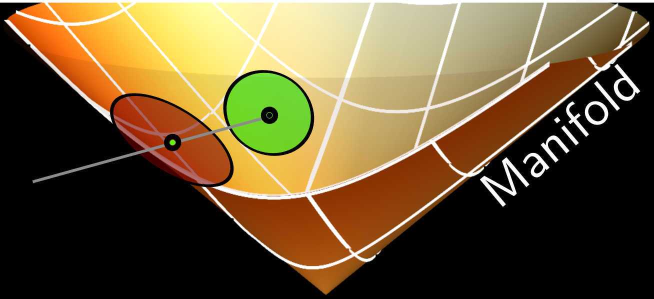
- Assymptotics given by Fisher matrix [Rao 1945]

  Cramer-Rao bounds



**Estimation error of covariances**

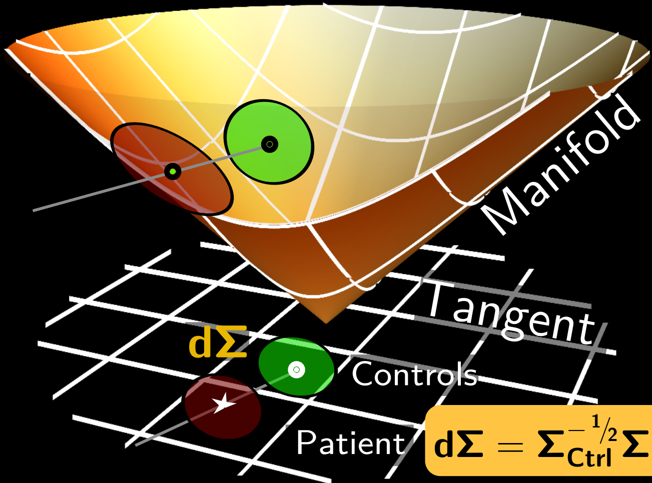
- Assymptotics given by Fisher matrix [Rao 1945]
- Defines a metric on a manifold of models
- With covariances: Lie-algebra structure



## 2 Reparametrization for uniform error geometry

- Disentangle parameters (edge-level connectivities)
- Connectivity matrices form a manifold

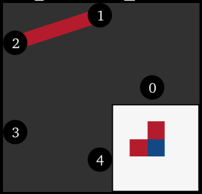
$\Rightarrow$ project to tangent space



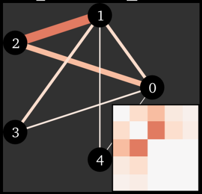

$$\mathbf{d\Sigma} = \mathbf{\Sigma}_{\mathbf{Ctrl}}^{-1/2}\mathbf{\Sigma}_{\mathbf{Patient}}\mathbf{\Sigma}_{\mathbf{Ctrl}}^{-1/2}$$

## The simulations

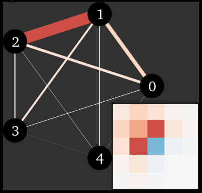
$\mathbf{K}_1 - \mathbf{K}_2$:



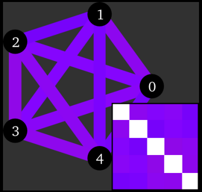

$\mathbf{\Sigma}_1 - \mathbf{\Sigma}_2$:




$\mathbf{d\Sigma}$:

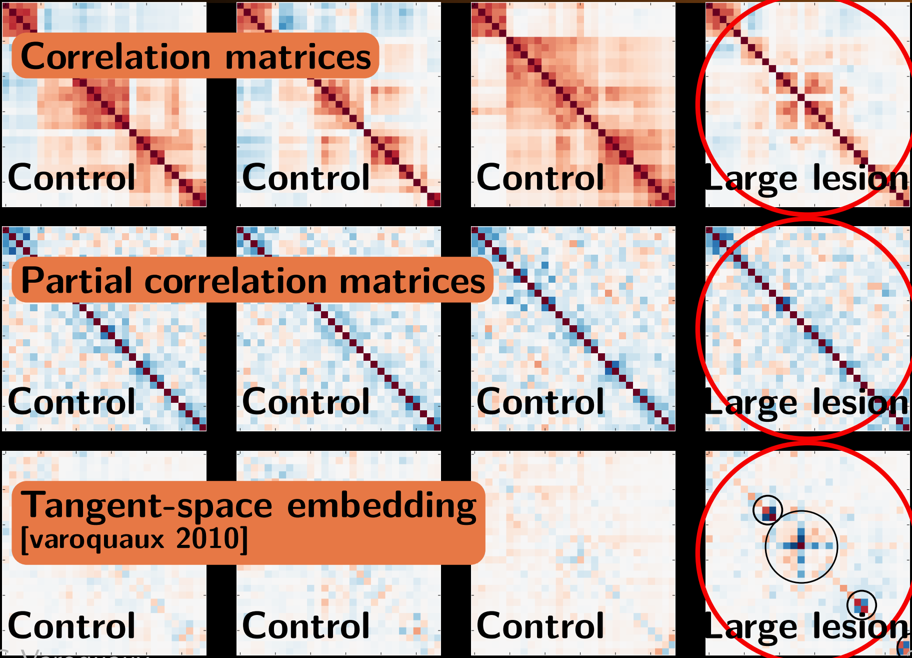



$\mathrm{MSE}(\mathbf{d\Sigma})$:



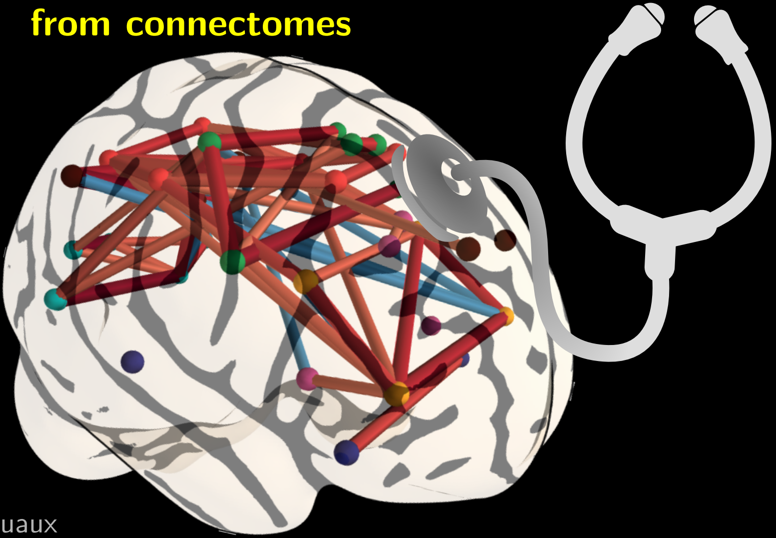

**Semi-local effects and homogeneous noise**

## 2 Which parametrization capture differences



# 3 Biomarkers of autism

## from connectomes

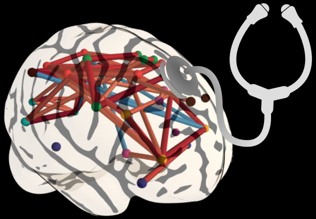


Predicting diagnostic status a good success metric

## Multi-site large autism dataset: ABIDE

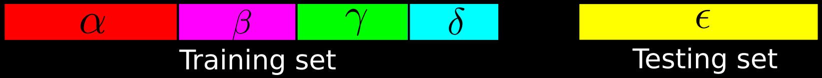
[Di Martino... 2014]

- Autism Spectrum Disorder
  $\Rightarrow$ Patient/Control classification
- 16 sites
- $\sim$ 1000 subjects

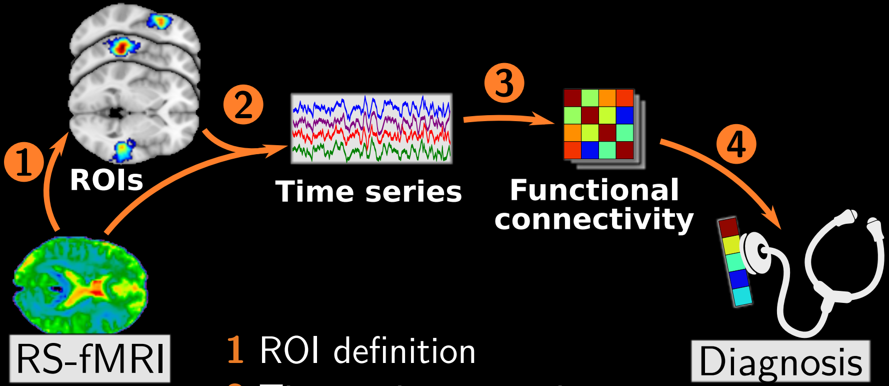


## Biomarkers robust to inter-site variations

- Cross-validation predicting to new sites



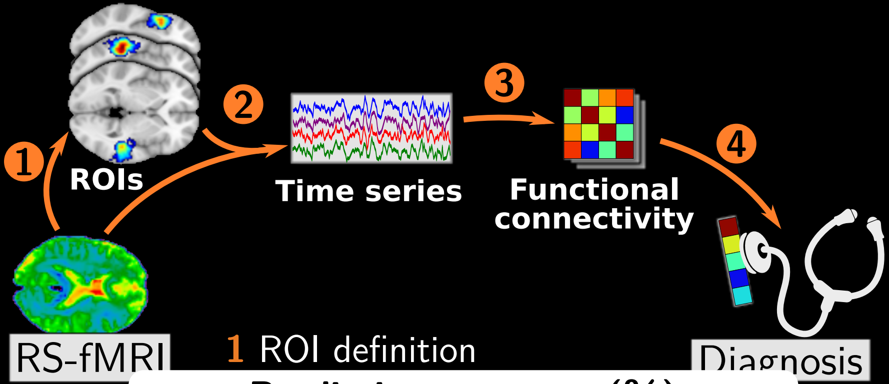
# A connectome classification pipeline




**1** ROI definition
**2** Time-series extraction
**3** Connectivity matrices
**4** Supervised learning

[Abraham... 2016]

# A connectome classification pipeline



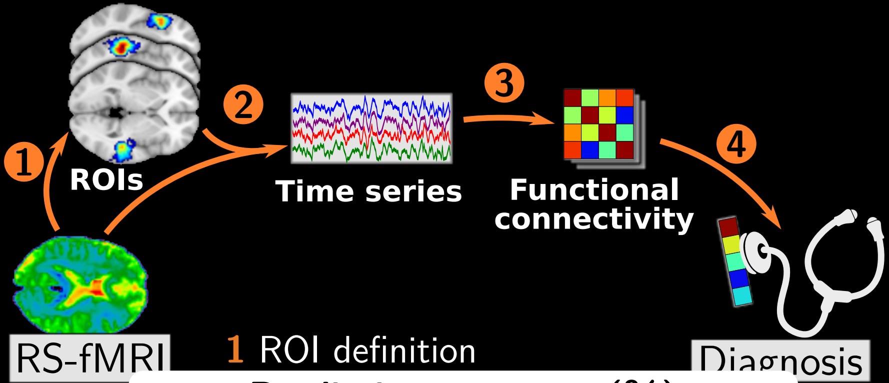

1 ROI definition

**Prediction accuracy (%)**

| | |
|---|---|
| **Seen sites** | **67±3** |
| **Unseen sites** | **67±5** |

016]

# A connectome classification pipeline



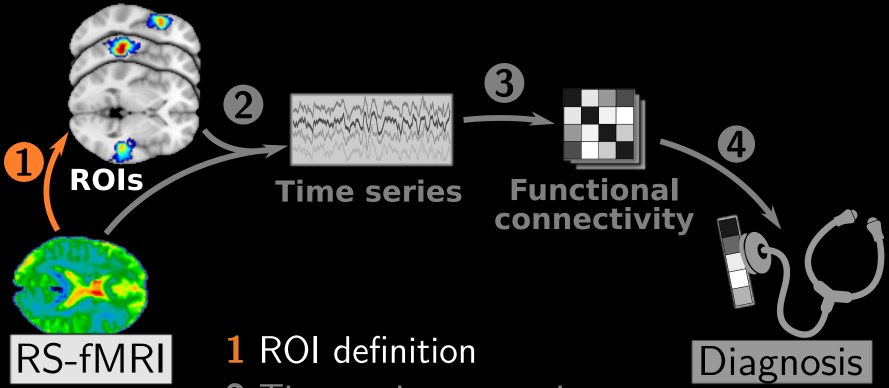

**Prediction accuracy (%)**

| | |
|---|---|
| **Seen sites** | **67±3** |
| **Unseen sites** | **67±5** |

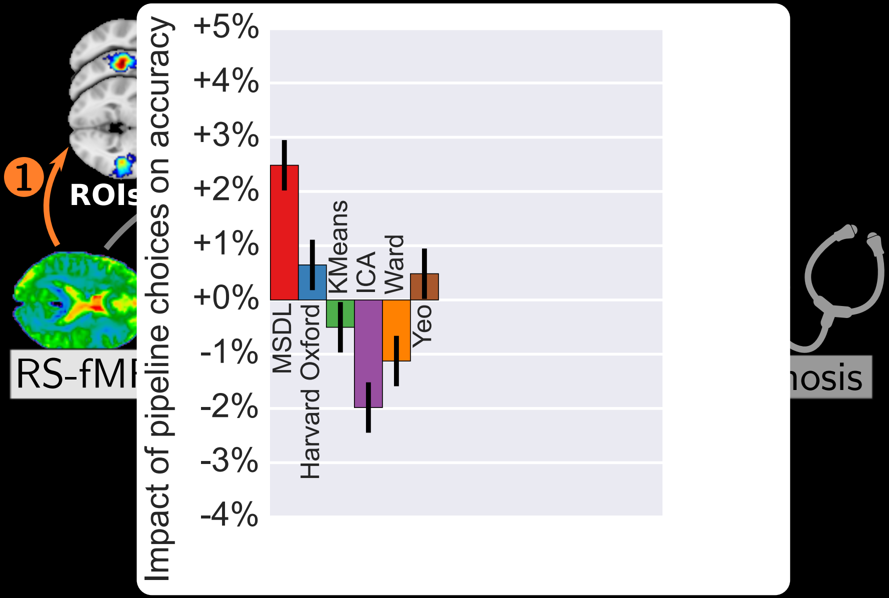
**What is important to predict?**

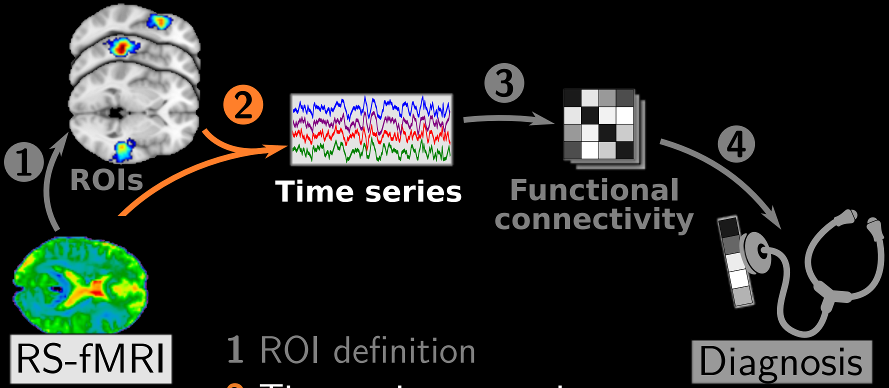
016]

# 3 ROI definition: impact of choice



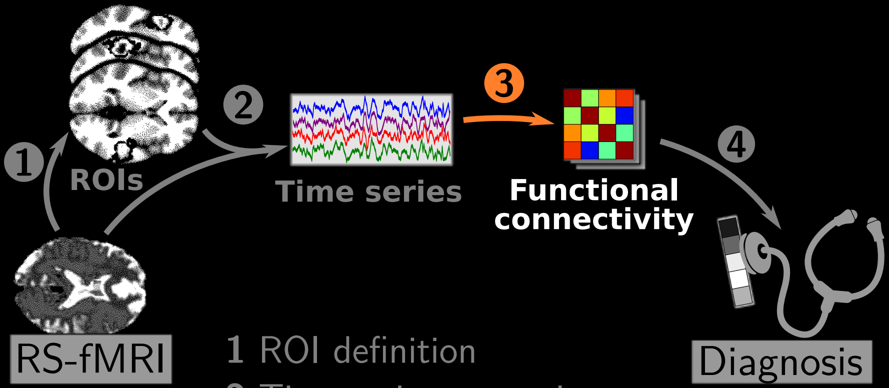

1 ROI definition
2 Time-series extraction
3 Connectivity matrices
4 Supervised learning


ROIs
RS-fMRI
Impact of pipeline choices on accuracy
+5%
+4%
+3%
+2%
+1%
+0%
-1%
-2%
-3%
-4%
MSDL
Harvard Oxford
KMeans
ICA
Ward
Yeo
osis




1 ROI definition
2 Time-series extraction
3 Connectivity matrices
4 Supervised learning

# 3 Functional-connectivity matrix




1 ROI definition
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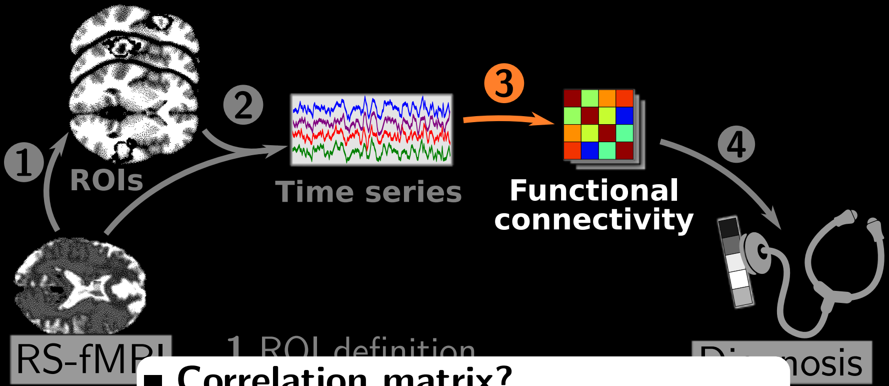
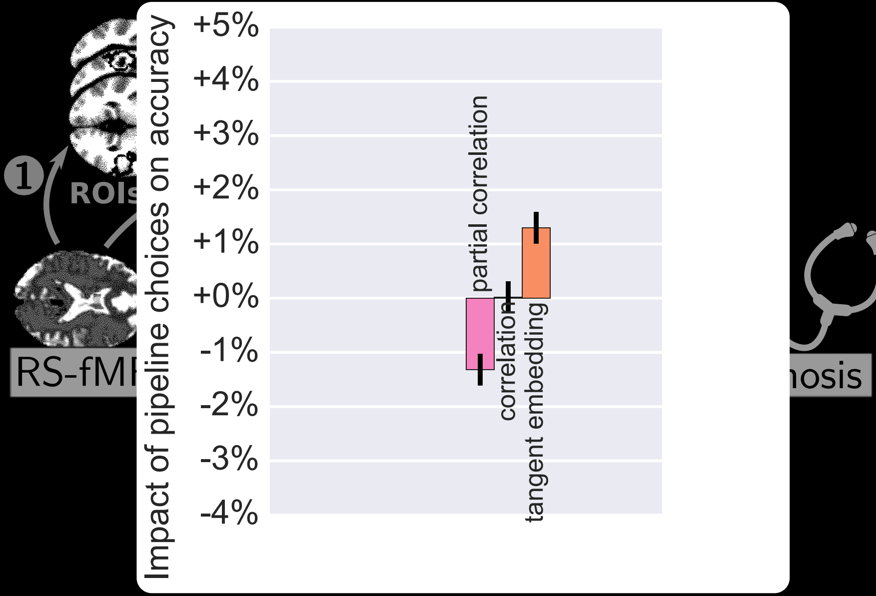
# 3 Functional-connectivity matrix



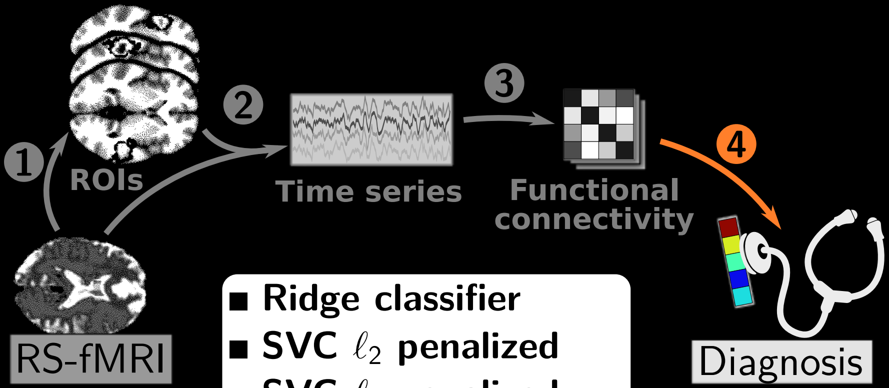

- Correlation matrix?
- Partial correlation matrix?
- Tangent-space embedding?

[Varoquaux... 2010a]

# 3 Functional-connectivity matrix



# 3 Supervised learning method

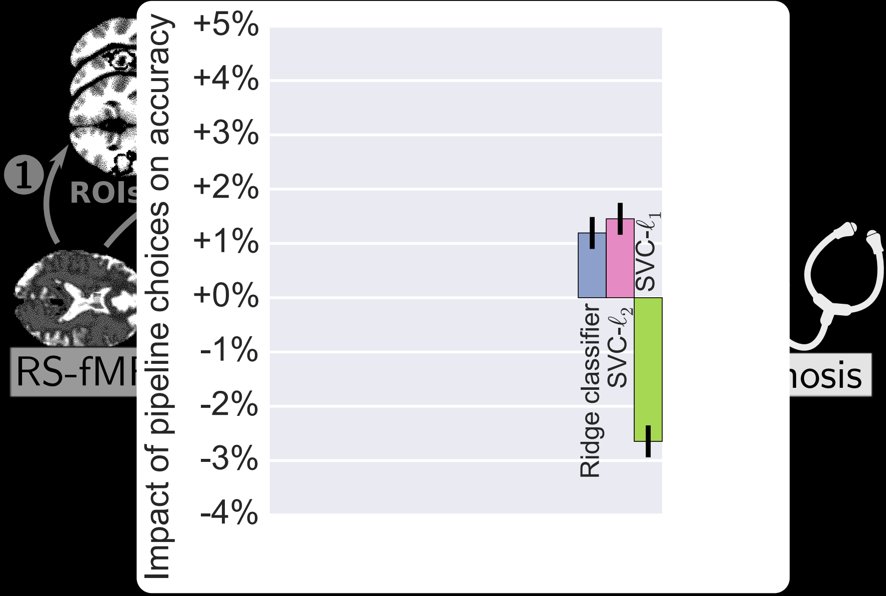



- **Ridge classifier**
- **SVC $\ell_2$ penalized**
- **SVC $\ell_1$ penalized**

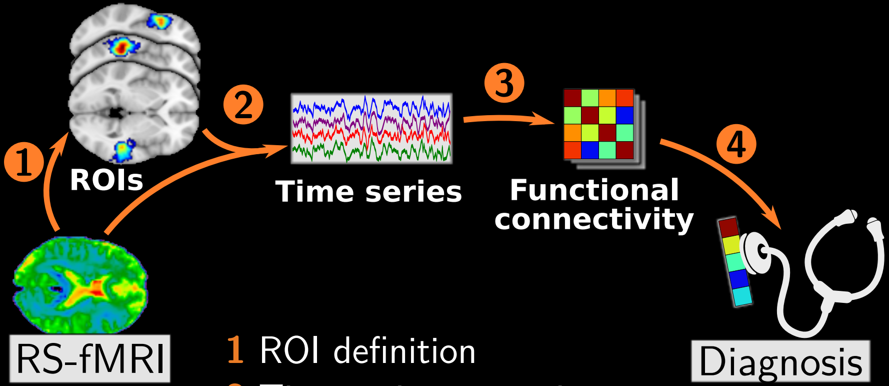
3 Connectivity matrices

4 Supervised learning

# 3 **Supervised learning method**: impact of choice



# Importance of pipeline steps

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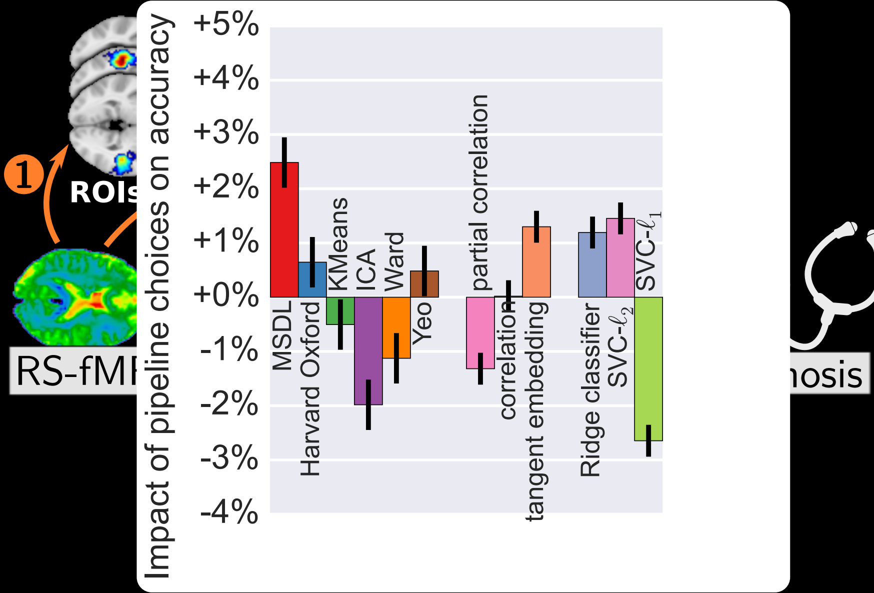
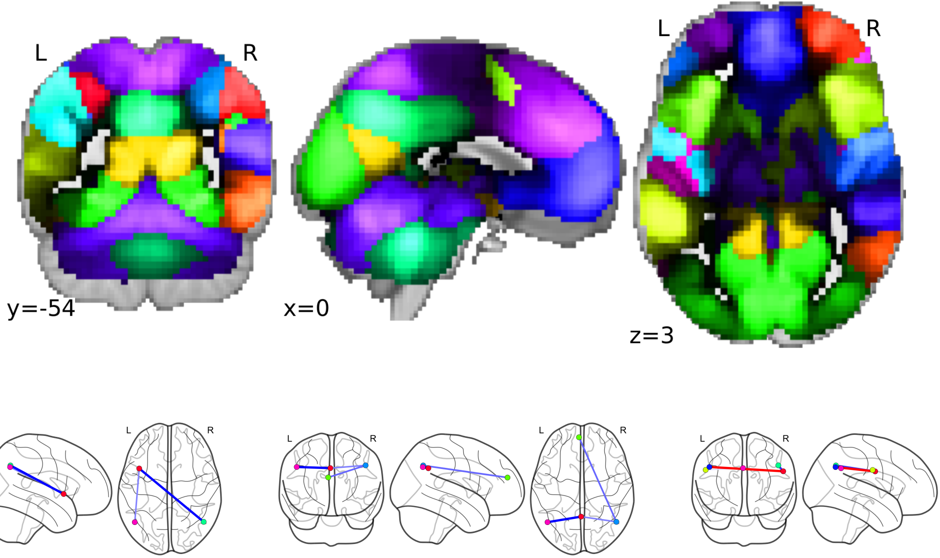
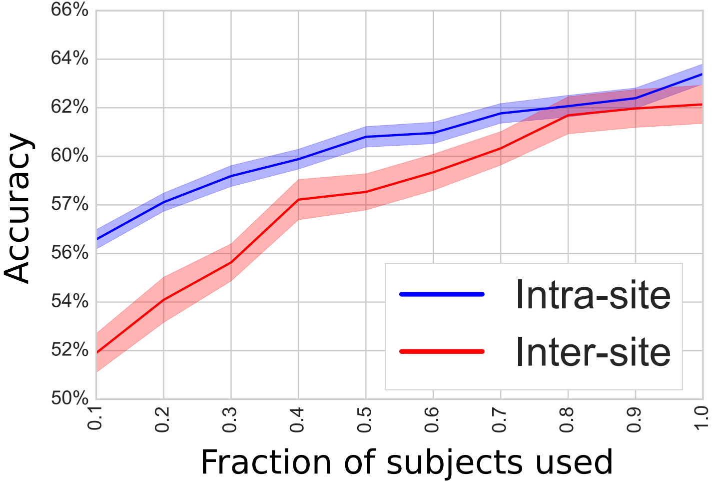


# MSDL atlas



## More data is better

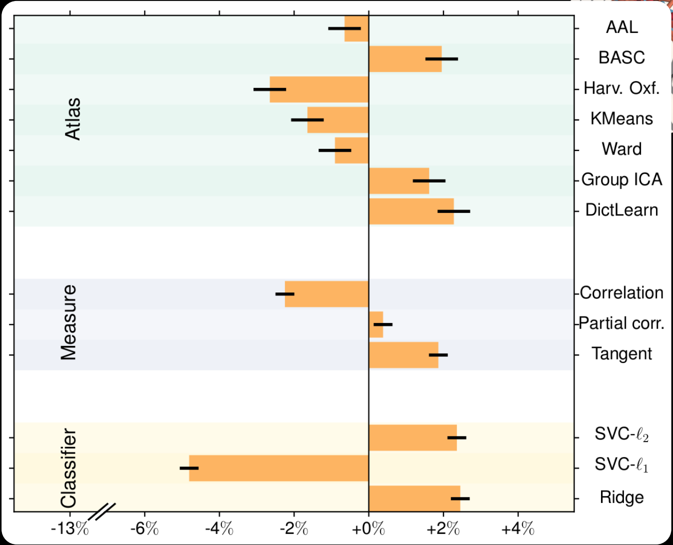


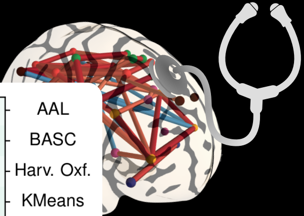

Multivariate processing of a 1Tb of heterogeneous data is worth the trouble

# 3 Results carry over (1) [Dadi... 2016]

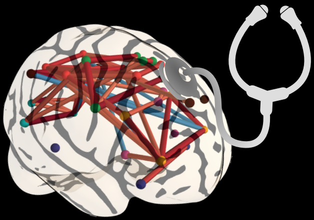
## 3 more cohorts and brain disorders

- Schizophrenia, Alzheimer's, addiction



## 3 Results carry over (2) [Liem... 2016]



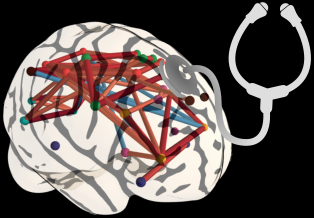
**Brain aging**

- Combines brain connectivity and morphology
- Predicts age with a mean absolute error of 4.3 years
- Prediction error correlates with cognitive impairment

# 3 Psychiatric neurophenotypes from rest-fMRI

## Viable from data accumulation

- ABIDE is a post-hoc aggregate
- Prediction across sites



# 3 Psychiatric neurophenotypes from rest-fMRI

**Viable from data accumulation**

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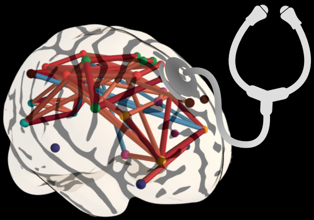

- Not (yet) for clinical diagnostic
- Capture neural signatures of disorders

$\Rightarrow$ **Towards a redefinition of disorders**

**Requires huge data accumulation**

# nilearn: machine learning for neuroimaging

## Make it easy for

- Neuroscientists to use machine learning
- Machine learning research to do neuroimaging

**Design goal**: runs out of the box

## Strong points

- Fast and versatile
- High-quality brain plotting
- Simple syntax

*Meaningful neuroimaging analysis in examples.*

**Try it** – `http://nilearn.github.io`

[Abraham... 2014]

# Statistical markers of pathologies

## Markers from brain graphs

- Choice of regions critical (learn them)
- Valued graphs and estimation error
- Tangent-space embedding
- Standard SVM

# Statistical markers of pathologies

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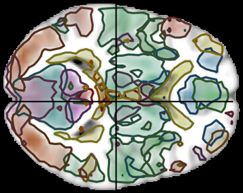

**Dictionary learning MSDL**

Good definitions of regions

Validation is very hard

# Statistical markers of pathologies

## Markers from brain graphs

- Choice of regions critical (learn them)
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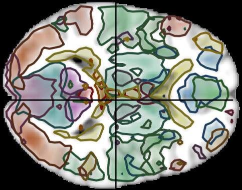


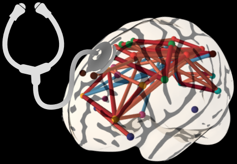
**Dictionary learning MSDL**

Good definitions of regions

Validation is very hard

**Prediction of autism across sites**

[Abraham... 2016]



@GaelVaroquaux

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R. C. Craddock, G. A. James, P. E. Holtzheimer, X. P. Hu, and H. S. Mayberg. A whole brain fMRI atlas generated via spatially constrained spectral clustering. *Human brain mapping*, 33(8): 1914–1928, 2012.

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A. Gramfort, B. Thirion, and G. Varoquaux. Identifying predictive regions from fMRI with TV-L1 prior. In *PRNI*, pages 17–20, 2013.

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