Statistical inference in high-dimension & application to brain imaging

Imaging and machine learning workshop

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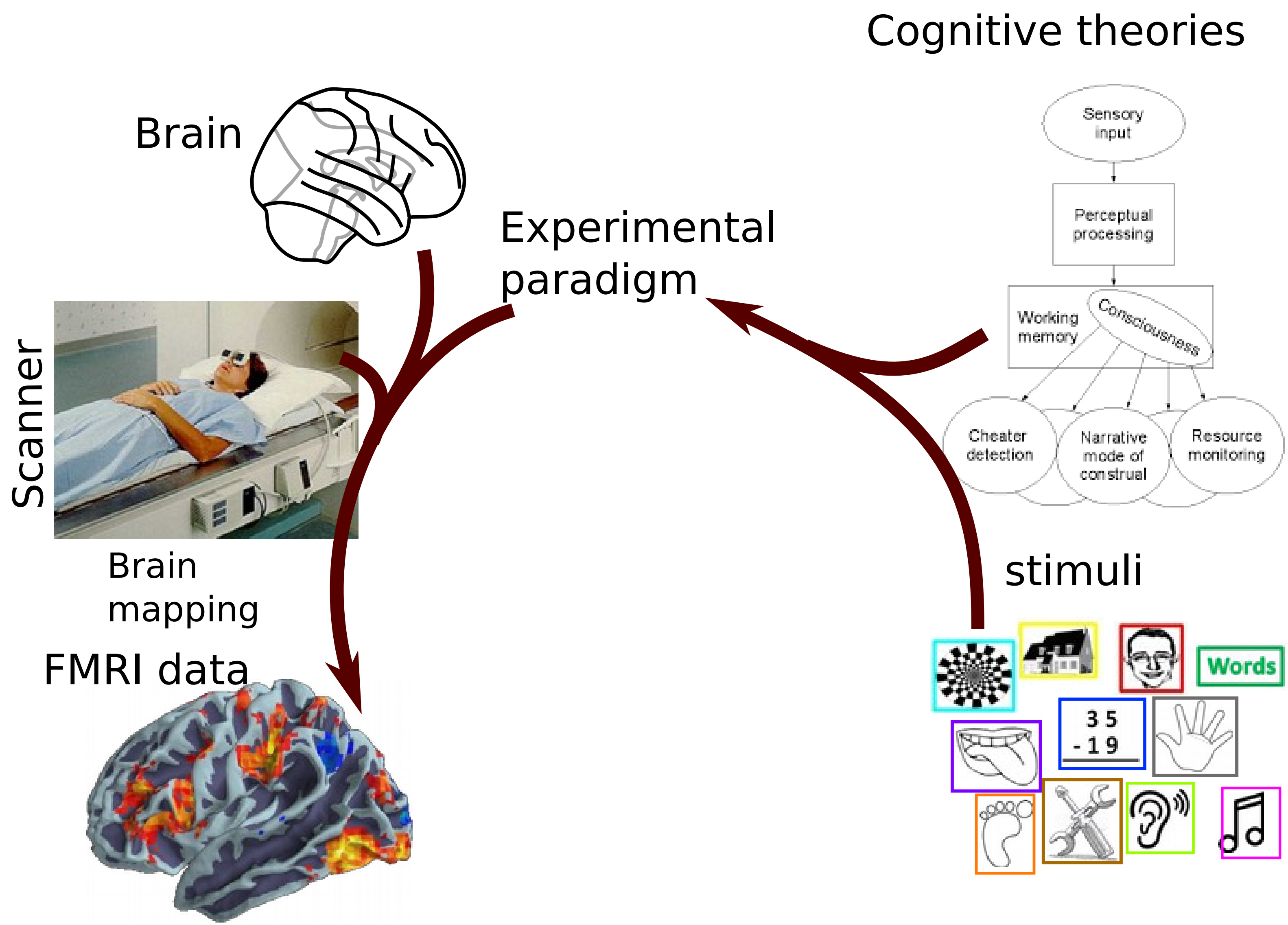
INVENTEURS DU MONDE NUMÉRIQUE

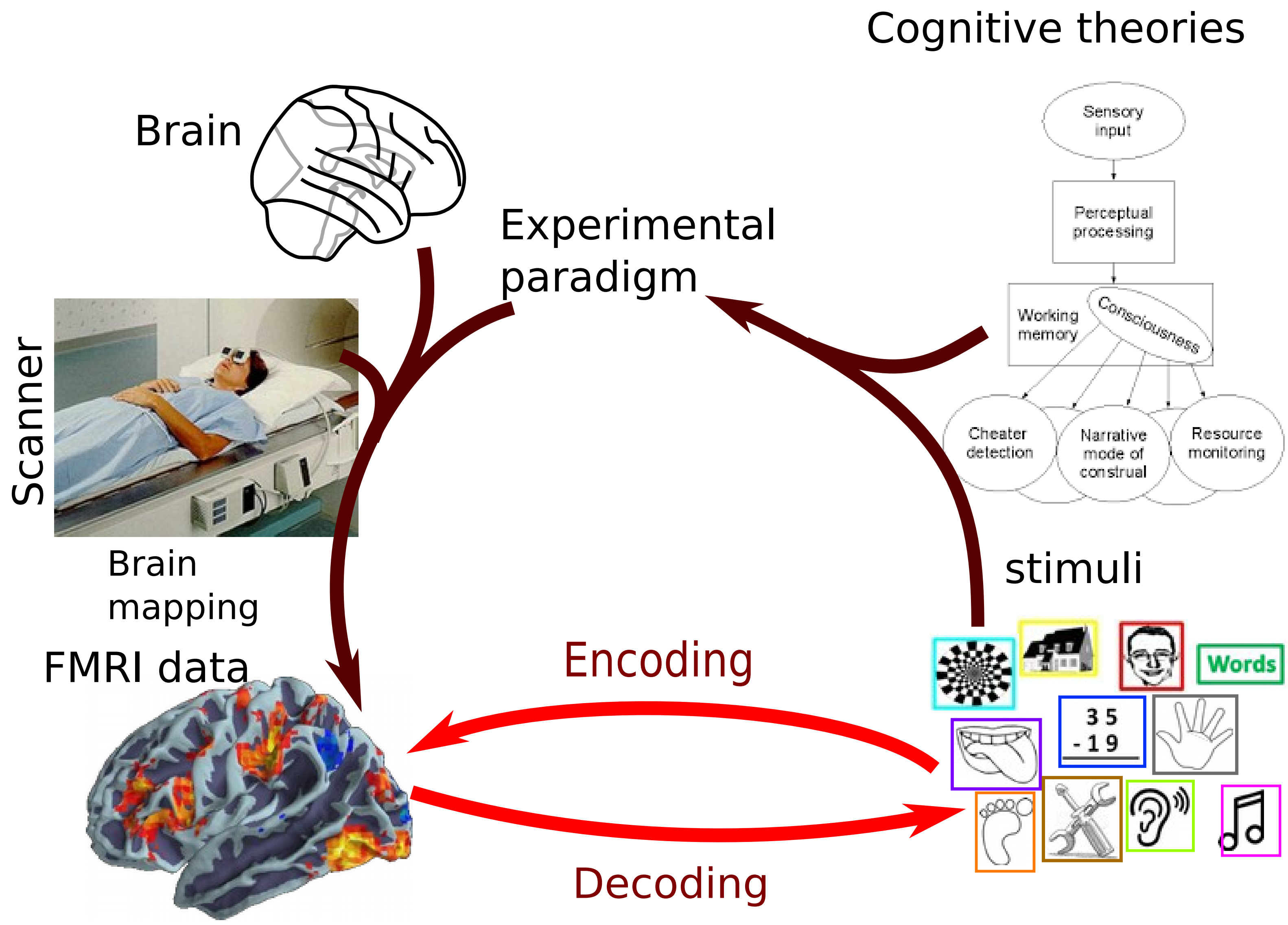
Cognitive neuroscience

How are cognitive activities affected or controlled by neural circuits in the brain ?

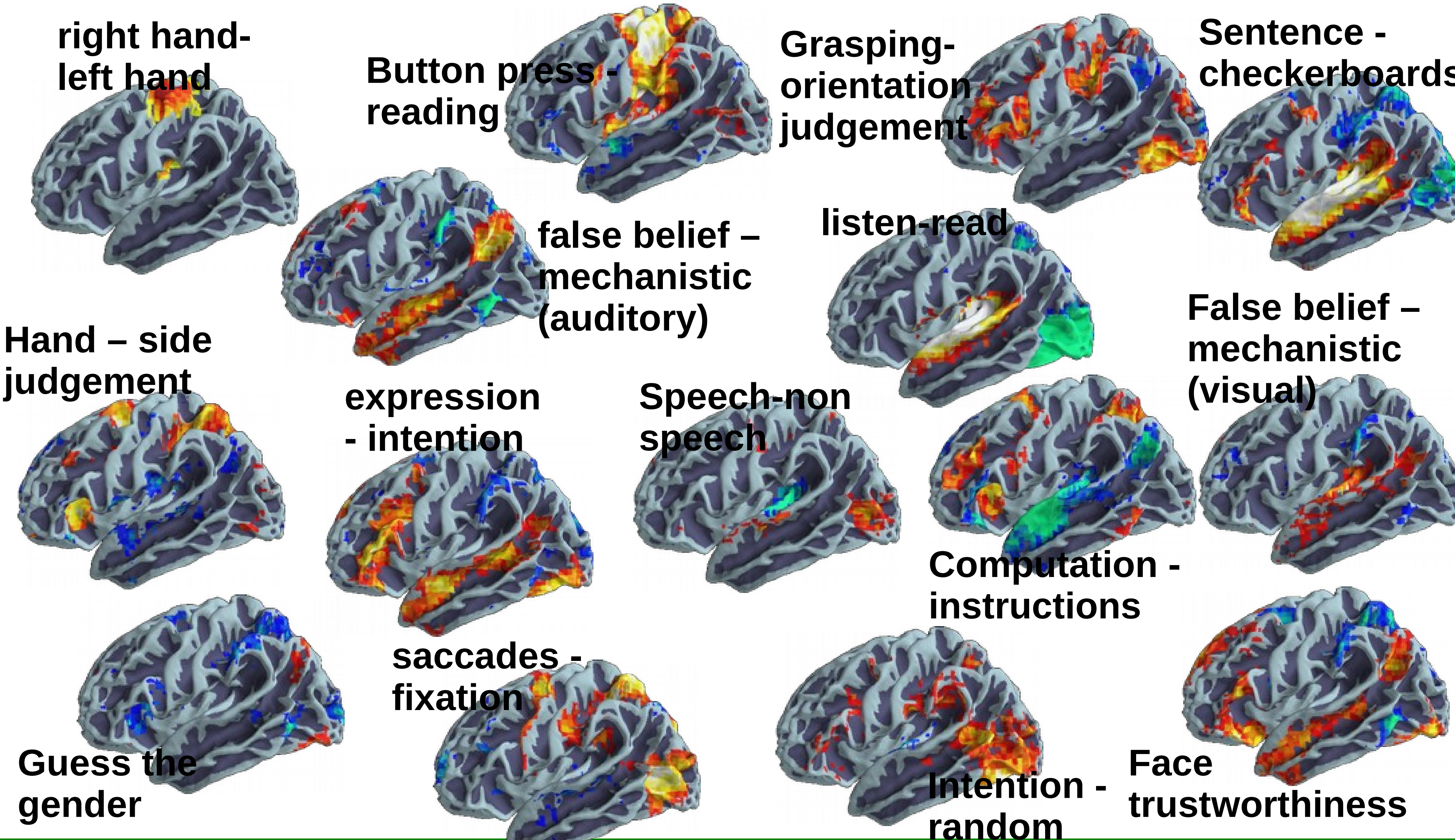
The brain, the mind and the scanner



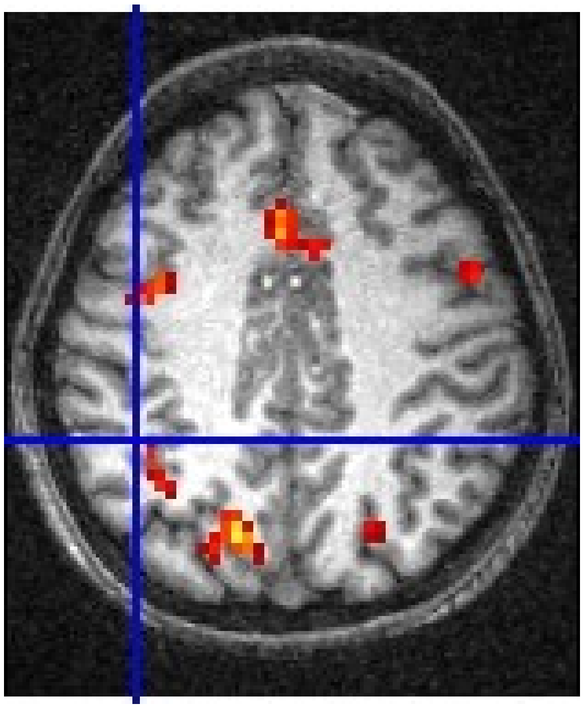
The brain, the mind and the scanner

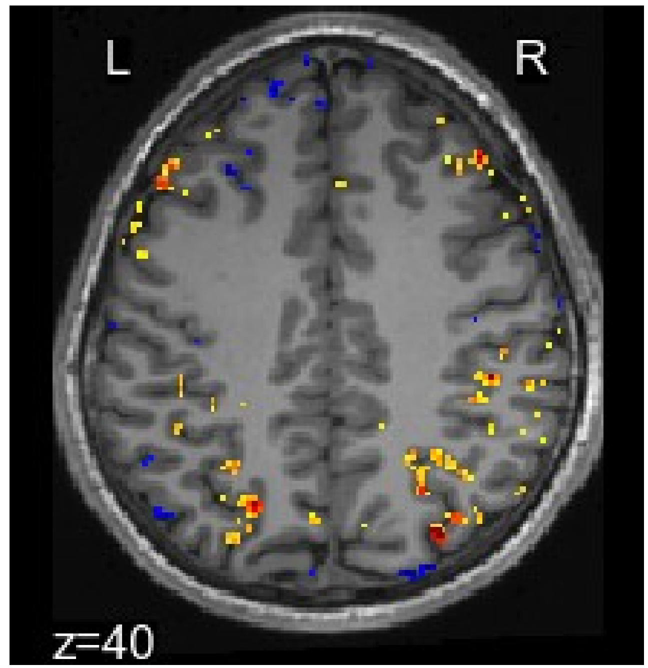


Encoding: mapping cognitive functions to brain activity



Resolution increases





2007:
3 mm

2014:
1.5 mm

2021:
0.5 mm ?

p = 50,000

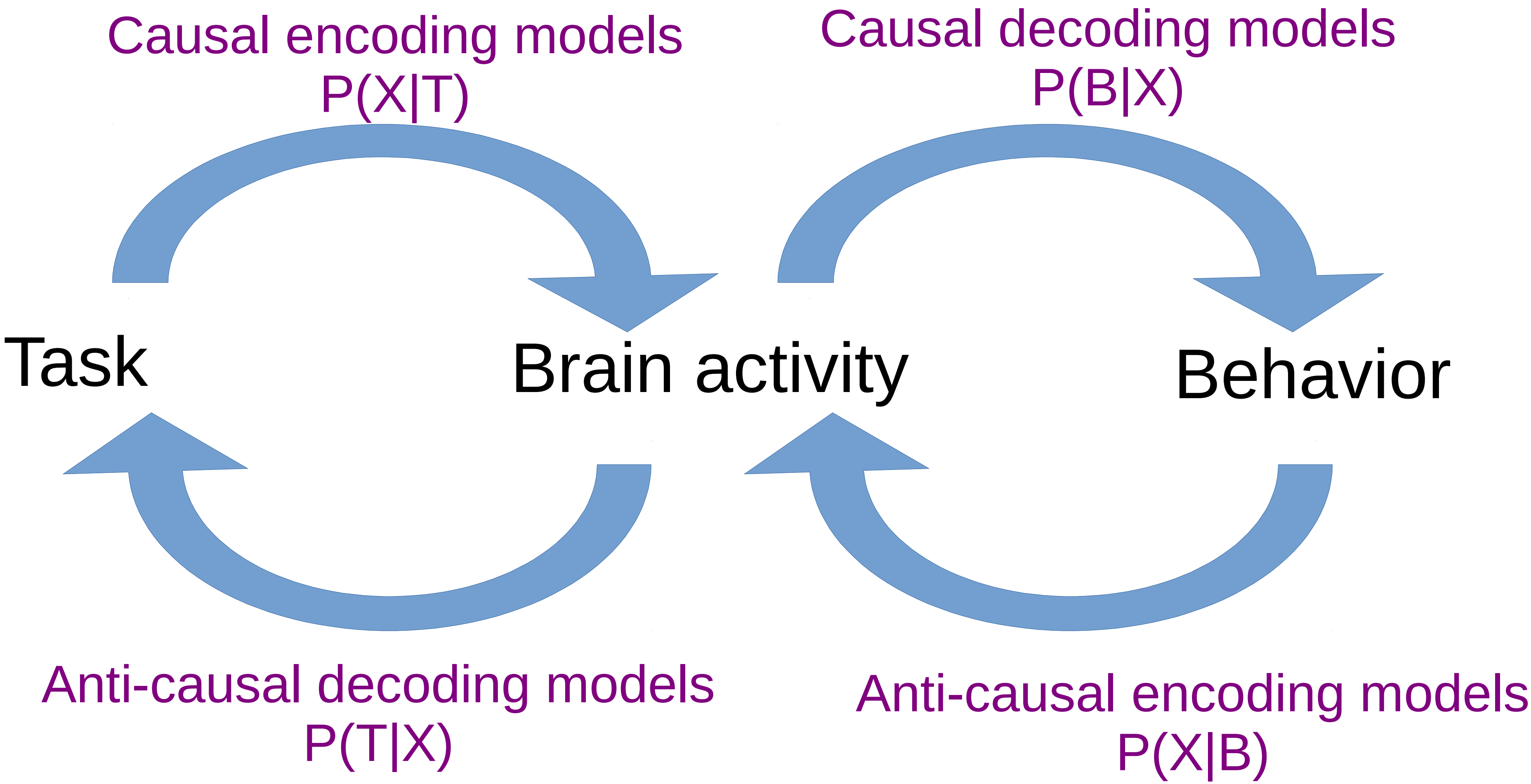
p = 400,000

p = 10^7

better estimators for large-scale brain imaging

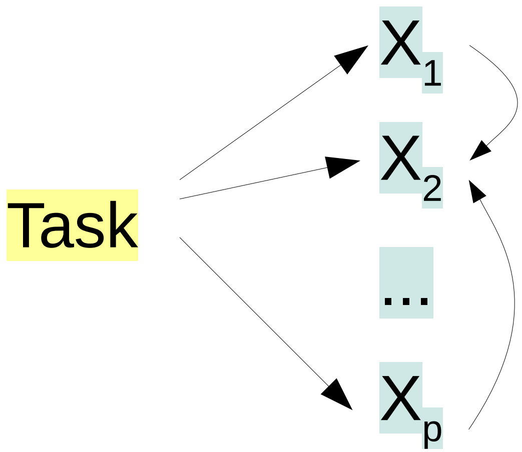
- A causal framework for brain activity decoding
- Dimension reduction for images
- Fast regularized ensembles of models
- Statistical inference for high-dimensional models

Causal reasoning on encoding/decoding



[Weichwald et al Nimg 2015]

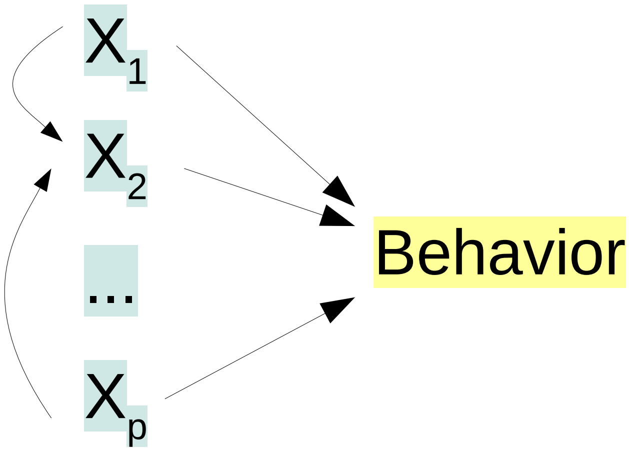
Causal interpretation



$$\mathbf{X_i} \perp\!\!\!\perp \mathbf{T}$$

Encoding: causal
Decoding: anti-causal

$$\mathbf{X_i} \perp\!\!\!\perp \mathbf{T} | (\mathbf{X_j}, \mathbf{j} \neq \mathbf{i})$$



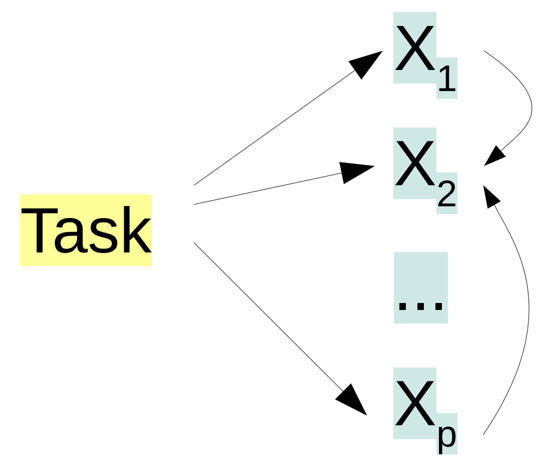
$$\mathbf{X_i} \perp\!\!\!\perp \mathbf{B}$$

Encoding: anti-causal
Decoding: causal

$$\mathbf{X_i} \perp\!\!\!\perp \mathbf{B} | (\mathbf{X_j}, \mathbf{j} \neq \mathbf{i})$$

Causal reasoning on encoding/decoding

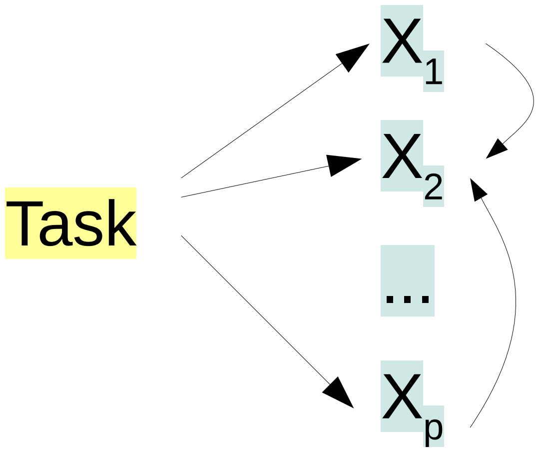
		Feature X_i relevant?		
		Encoding	Decoding	Causal interpretation
Experimental setting	Task	$\times$		$T \perp\!\!\!\perp X_i \Rightarrow X_i$ is no effect of T
		$\checkmark$		$T \not\perp\!\!\!\perp X_i \Rightarrow X_i$ is an effect of T
	Behaviour			



[Weichwald et al. NIMG 2015]

Causal reasoning on encoding/decoding

		Feature X_i relevant?		
		Encoding	Decoding	Causal interpretation
Experimental setting	Task	$\times$		$T \perp\!\!\!\perp X_i \Rightarrow X_i$ is no effect of T
		$\surd$		$T \not\perp\!\!\!\perp X_i \Rightarrow X_i$ is an effect of T
			$\times$	$T \perp\!\!\!\perp X_i \mid \boldsymbol{X} \setminus X_i \Rightarrow$ inconclusive
			$\surd$	$T \not\perp\!\!\!\perp X_i \mid \boldsymbol{X} \setminus X_i \Rightarrow$ inconclusive
	Behaviour			



[Weichwald et al. NIMG 2015]

Causal reasoning on encoding/decoding

Experimental setting		Feature X_i relevant? Encoding	Feature X_i relevant? Decoding	Causal interpretation
	Task	$\times$		$T \perp\!\!\!\perp X_i \Rightarrow X_i$ is no effect of T
	Task	$\surd$		$T \not\perp\!\!\!\perp X_i \Rightarrow X_i$ is an effect of T
	Task		$\times$	$T \perp\!\!\!\perp X_i \mid \mathbf{X} \setminus X_i \Rightarrow$ inconclusive
	Task		$\surd$	$T \not\perp\!\!\!\perp X_i \mid \mathbf{X} \setminus X_i \Rightarrow$ inconclusive
	Behaviour	$\times$		$B \perp\!\!\!\perp X_i \Rightarrow X_i$ is no cause of B
	Behaviour	$\surd$		$B \not\perp\!\!\!\perp X_i \Rightarrow$ inconclusive
	Behaviour		$\times$	$B \perp\!\!\!\perp X_i \mid \mathbf{X} \setminus X_i \Rightarrow$ inconclusive
	Behaviour		$\surd$	$B \not\perp\!\!\!\perp X_i \mid \mathbf{X} \setminus X_i \Rightarrow$ inconclusive

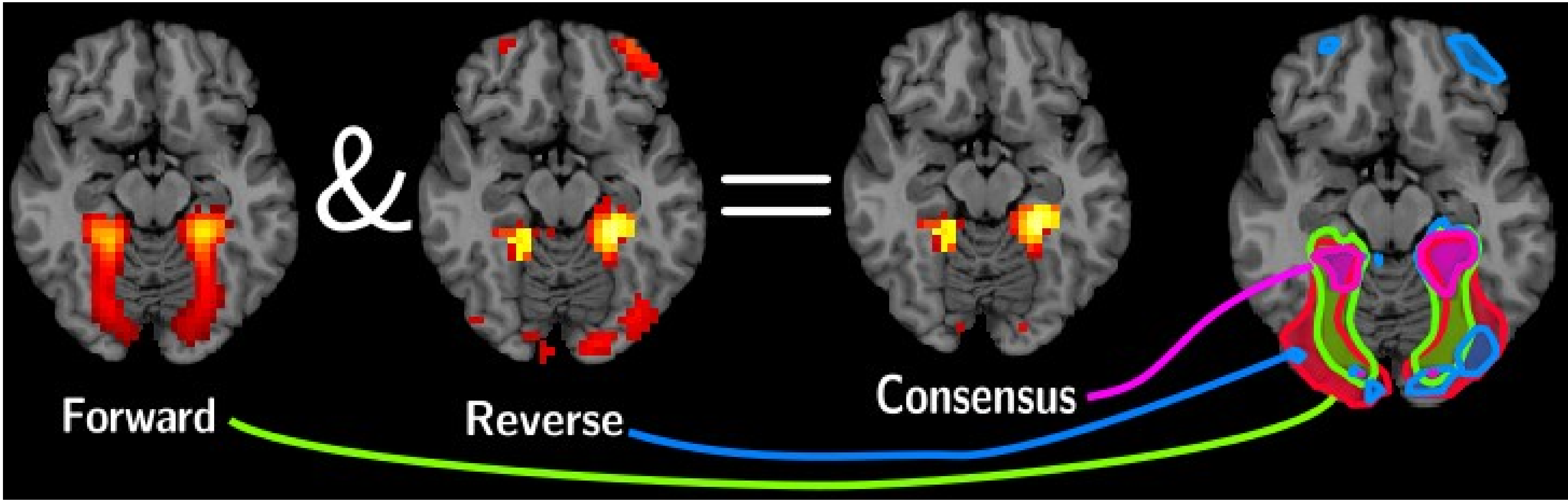
[Weichwald et al. NIMG 2015]

Causal reasoning on encoding/decoding

		Feature X_i relevant? Encoding	Decoding	Causal interpretation
Experimental paradigm	Task	$\times$	$\times$	X_i is no effect of T
		$\surd$	$\times$	X_i is an indirect effect of T
		$\times$	$\surd$	X_i provides context
		$\surd$	$\surd$	X_i is an effect of T
	Behaviour	$\times$	$\times$	X_i is no cause of B
		$\surd$	$\times$	X_i is no direct cause of B
		$\times$	$\surd$	X_i provides context
		$\surd$	$\surd$	inconclusive

[Weichwald et al. NIMG 2015]

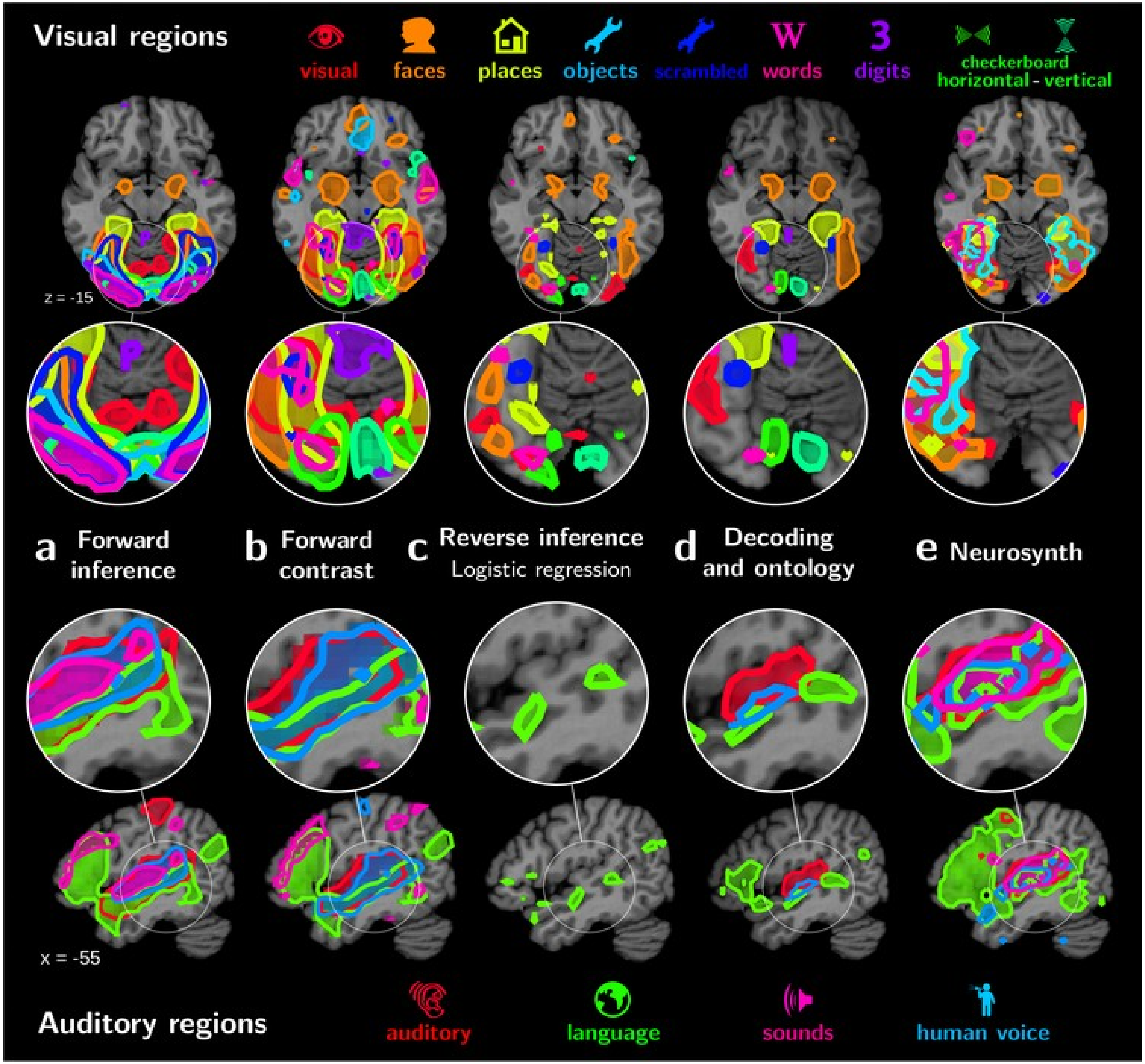
Joint encoding and decoding



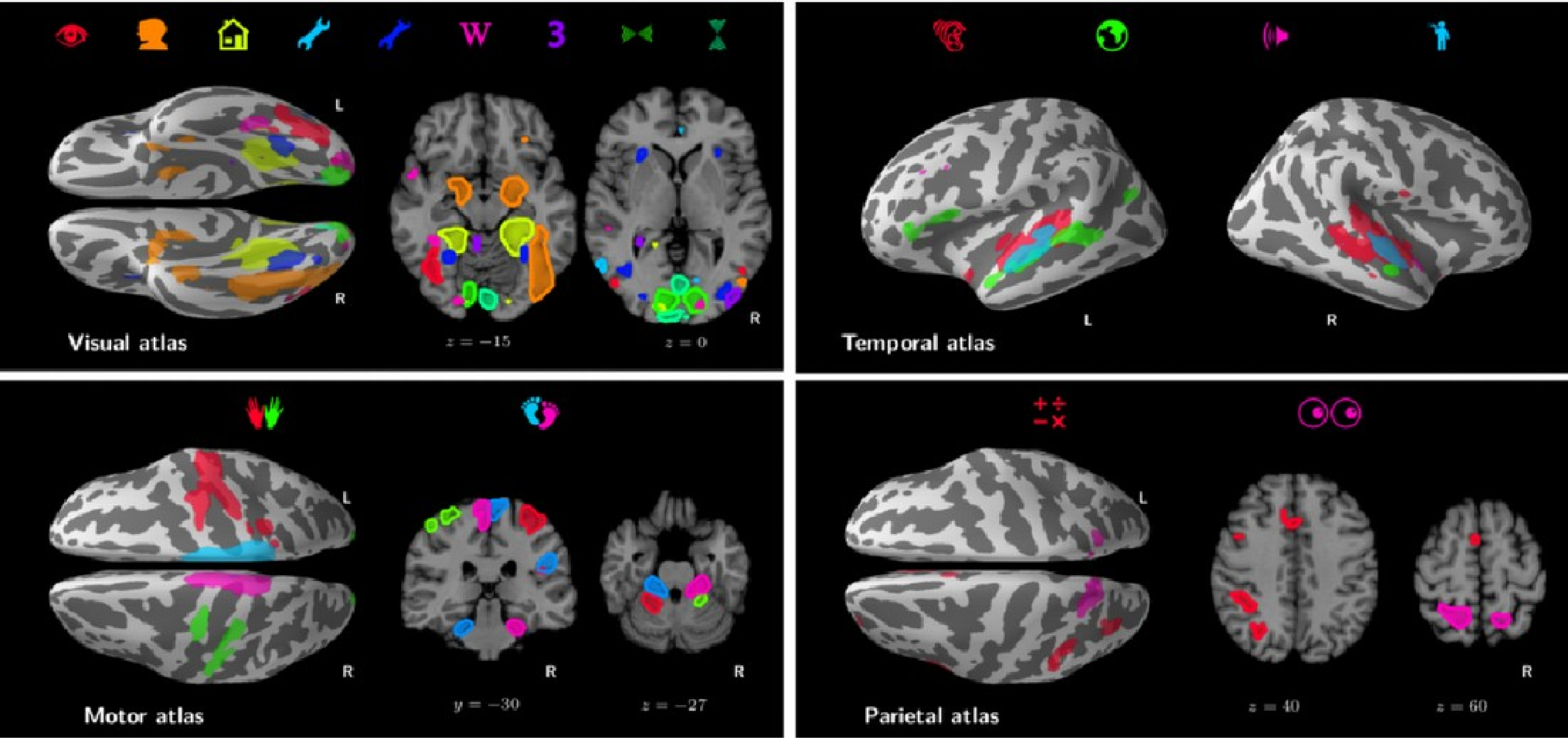
“Encoding” “Decoding”

[Schwartz et al. NIPS 2013, Varoquaux et al. PCB 2018]

Decoding maps



Joint encoding and decoding

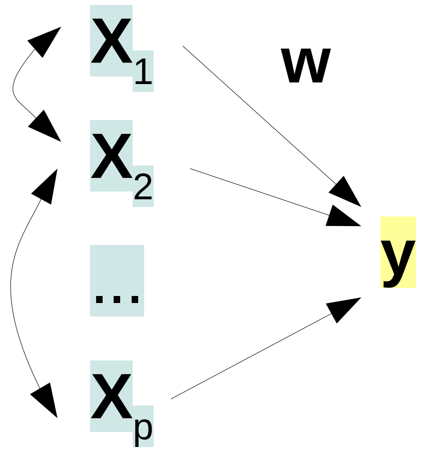


[Schwartz et al. NIPS 2013, Varoquaux et al. PCB 2018]

Statistical associations and causal reasoning

- Problems:
  - Establish non-independence based on finite datasets → statistical tests
  - **Large number of conditioning variables**
  - Encoding models: **Multiple comparison issues**
  - Decoding problem: **statistical tests in multiple regression**

Brain activity decoding



- behavior = f (brain activity)

$$\mathbf{y} = \mathbf{X}\boldsymbol{w}^* + \sigma_* \varepsilon$$

- error vector: $\varepsilon \sim \mathcal{N}(\mathbf{0}, \mathbf{I}_n)$
- noise magnitude: $\sigma_* > 0$

- prediction: find $\hat{\boldsymbol{w}}$ that minimizes $\|\mathbf{X}\hat{\boldsymbol{w}} - \mathbf{X}\boldsymbol{w}^*\|_2$
- estimation: find $\hat{\boldsymbol{w}}$ with control on $|\hat{w}_j - w_j^*|$ for all $j \in [p]$

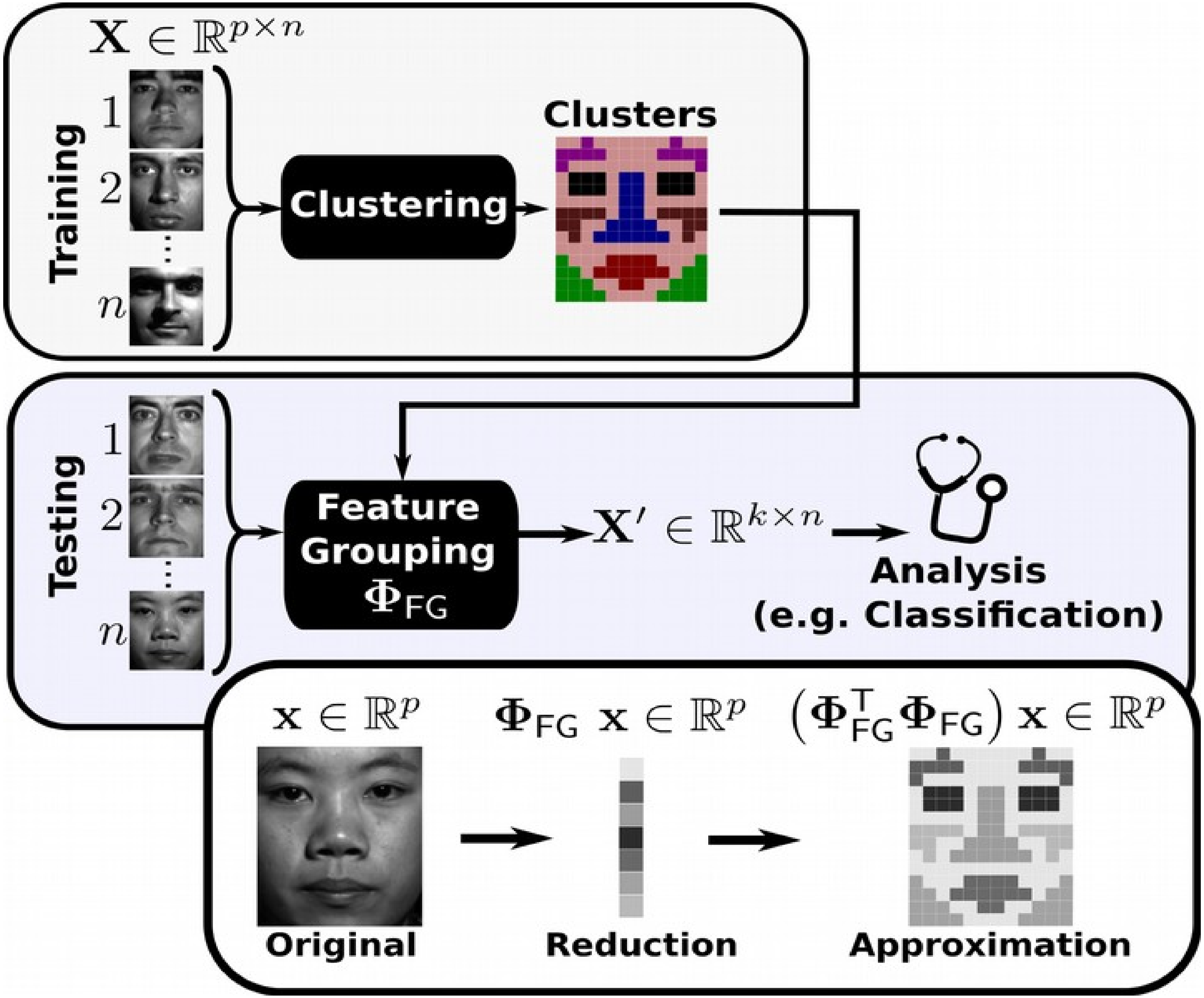
Outline

- A causal framework for brain activity decoding
- Dimension reduction for images
- Fast regularized ensembles of Models
- Statistical inference for high-dimensional models

Compression in the image domain

- Reduce the complexity of learning algorithms: $p \rightarrow k \ll p$
- Random projections = fast generic solution, but
  - Sub-optimal for structured signals
  - Not invertible when p and k are large
- Local redundancy $\rightarrow$ feature grouping strategies / clustering: “super-pixels”
  - Fast clustering procedures needed (large-k regime)

Superpixels as an image operator



Crafting good image compression

- Key assumption: signal of interest L-Lipschitz

$$|\mathbf{x}_i - \mathbf{x}_j| \leq L\,\mathrm{dist}_{\mathcal{G}}(v_i, v_j), \quad \forall (i,j) \in [p]^2$$

- Feature grouping matrix $\mathbf{\Phi}_{\mathsf{FG}} \in \mathbb{R}^{k \times p}$

- almost trivially: $\|\mathbf{x}\|^2 - L^2 \sum_{q=1}^{k} |\mathcal{C}_q|^3 \leq \|\mathbf{\Phi}_{\mathsf{FG}}\,\mathbf{x}\|^2 \leq \|\mathbf{x}\|^2$

- Worst case $\|\mathbf{x}\|_2^2 - kL^2 \max_{q \in [k]} \{|\mathcal{C}_q|^3\} \leq \|\mathbf{\Phi}_{\mathsf{FG}}\,\mathbf{x}\|_2^2 \leq \|\mathbf{x}\|_2^2$

Need a fast method to learn balanced clusters

Denoising properties

- Noisy signal model $\mathbf{x} = \mathbf{s} + \mathbf{n}$

$$\mathrm{MSE}_{\mathrm{approx}} \leq L^2 \sum_{q=1}^{k} |\mathcal{C}_q| \, \mathrm{diam}_{\mathcal{G}}(\mathcal{C}_q)^2 + \frac{k}{p} \mathrm{MSE}_{\mathrm{orig}}$$

- Denoising

$$\mathrm{MSE}_{\mathrm{approx}} \leq \mathrm{MSE}_{\mathrm{orig}}$$

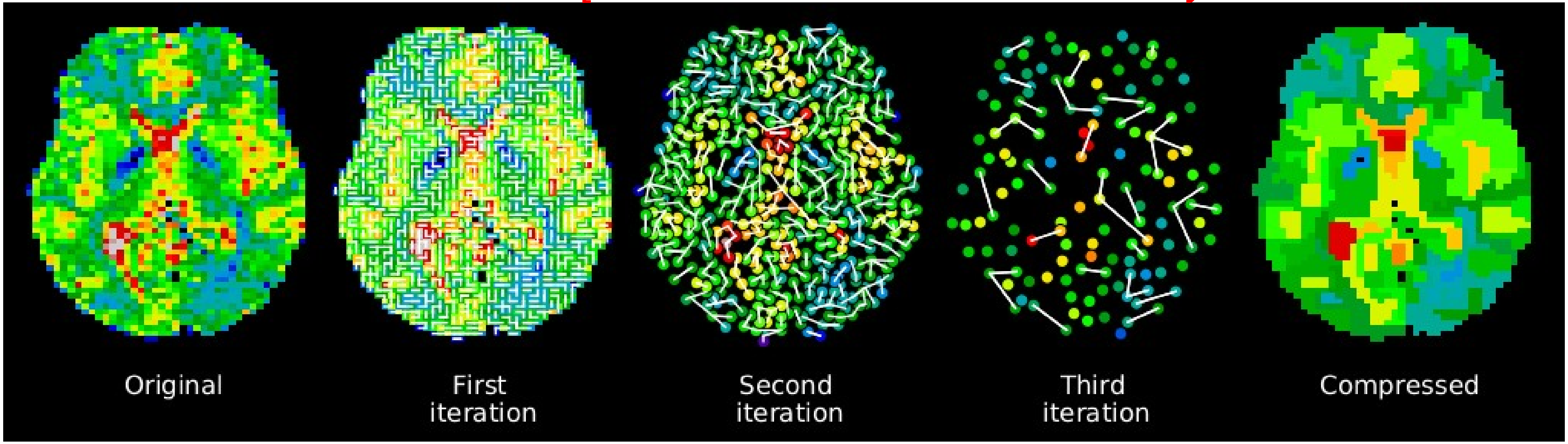
$$L^2 \leq \frac{(p-k)}{\sum_{q=1}^{k} |\mathcal{C}_q| \, \mathrm{diam}_{\mathcal{G}}(\mathcal{C}_q)^2} \sigma^2$$

- Equal-size clusters

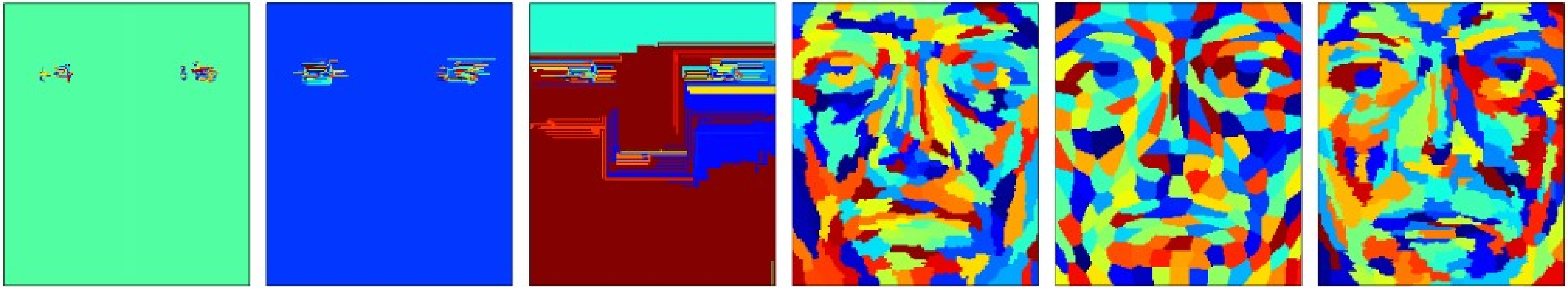
$$\mathrm{MSE}_{\mathrm{approx}} \leq p \left(\frac{L}{k}\right)^2 + \frac{k}{p} \mathrm{MSE}_{\mathrm{orig}} = O\left(\max\left\{\frac{p}{k^2}, \frac{k}{p}\right\}\right)$$

Recursive neighbor Agglomeration

[Thirion et al. Stamlins 2015, Hoyos Idrobo PAMI 2018]

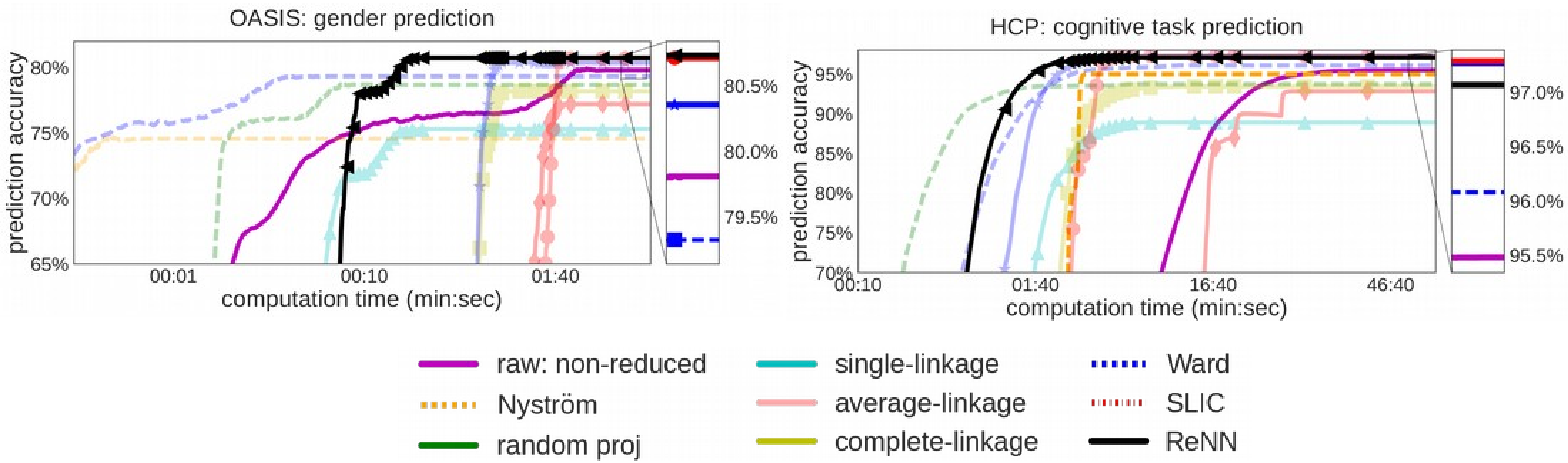


Based on local decisions = fast (linear time) – avoid percolation



(a) single-linkage (b) average-linkage (c) complete-linkage (d) Ward (e) SLIC (f) ReNA

Effect on data analysis tasks



Impressive speed-up and increased accuracy with respect to non-compressed representation

– Clustering has a denoising effect

[Hoyos Idrobo IEEE PAMI 2018]

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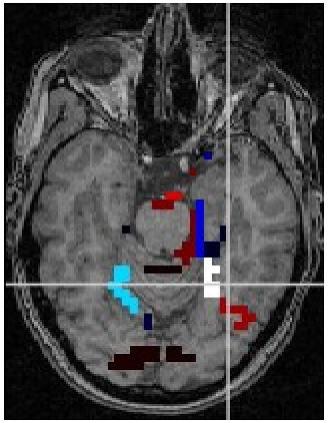
Bagging of clustered models

X

Clustering (create contiguous regions)

y

Solve **regression** on cluster-based representation



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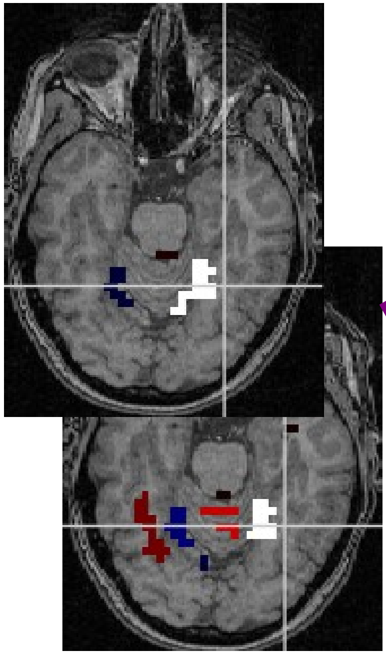
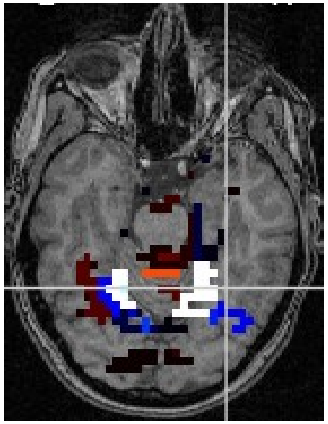


various clusterings

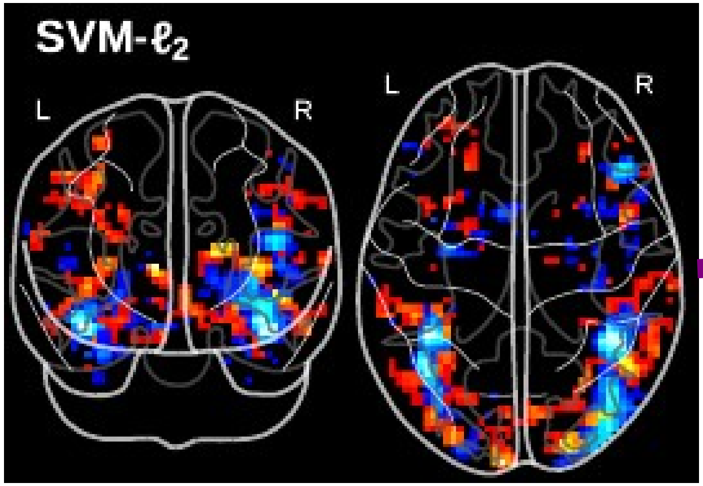
average

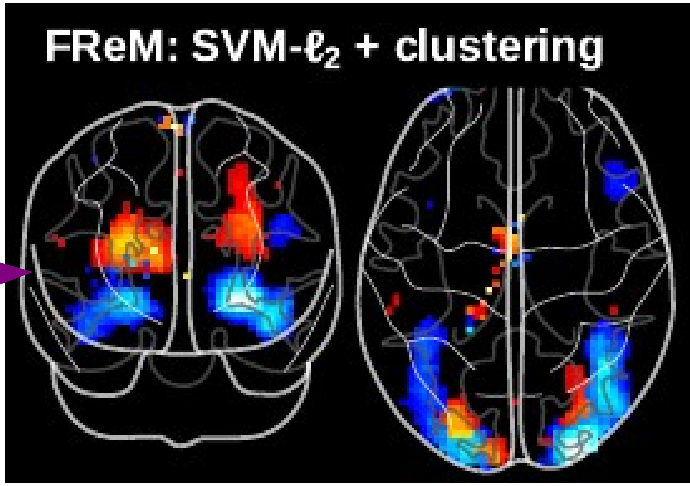


Computationally efficient structure

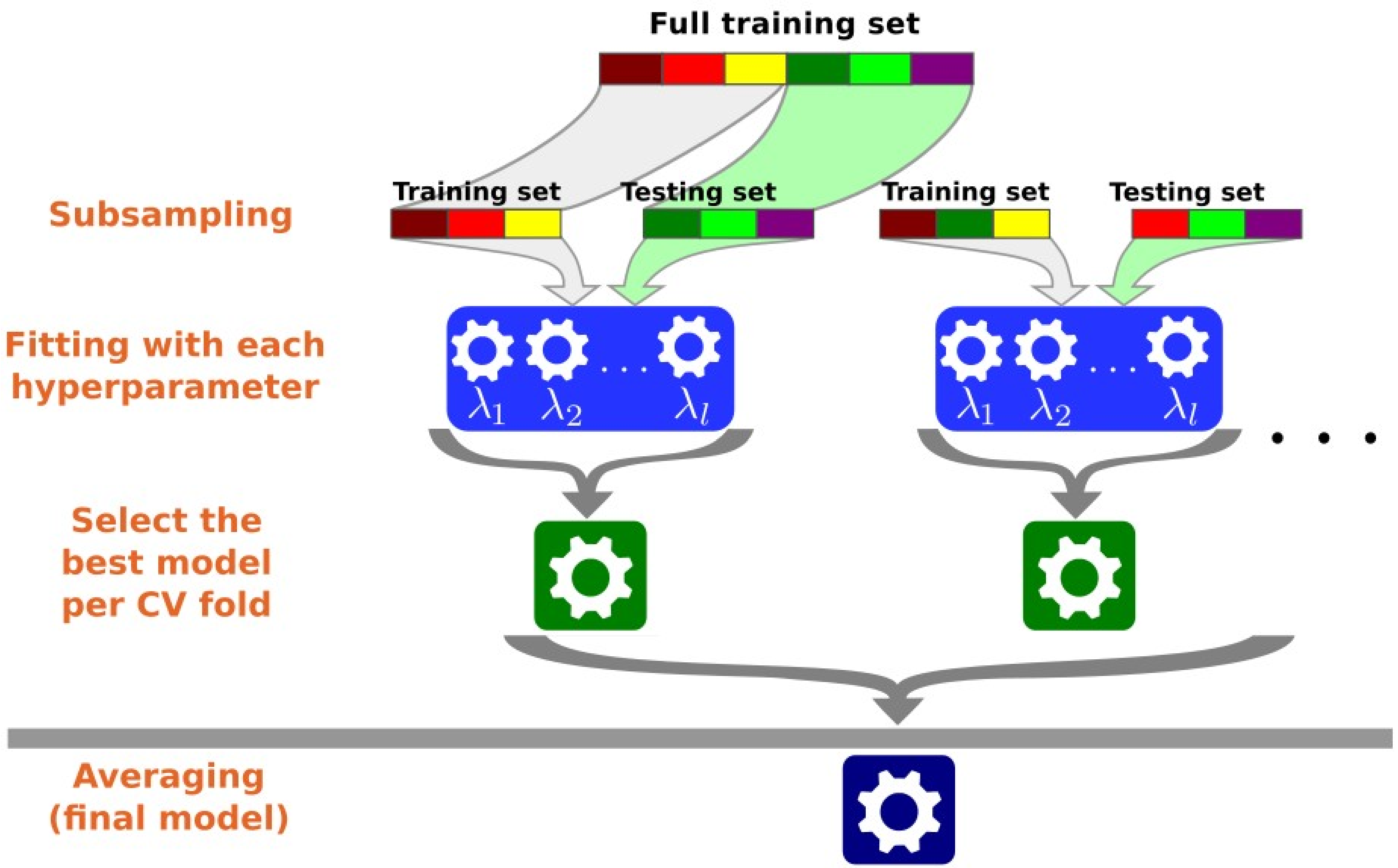
“fast regularized ensembles of models”

State of the art solution: not very stable, but cheap



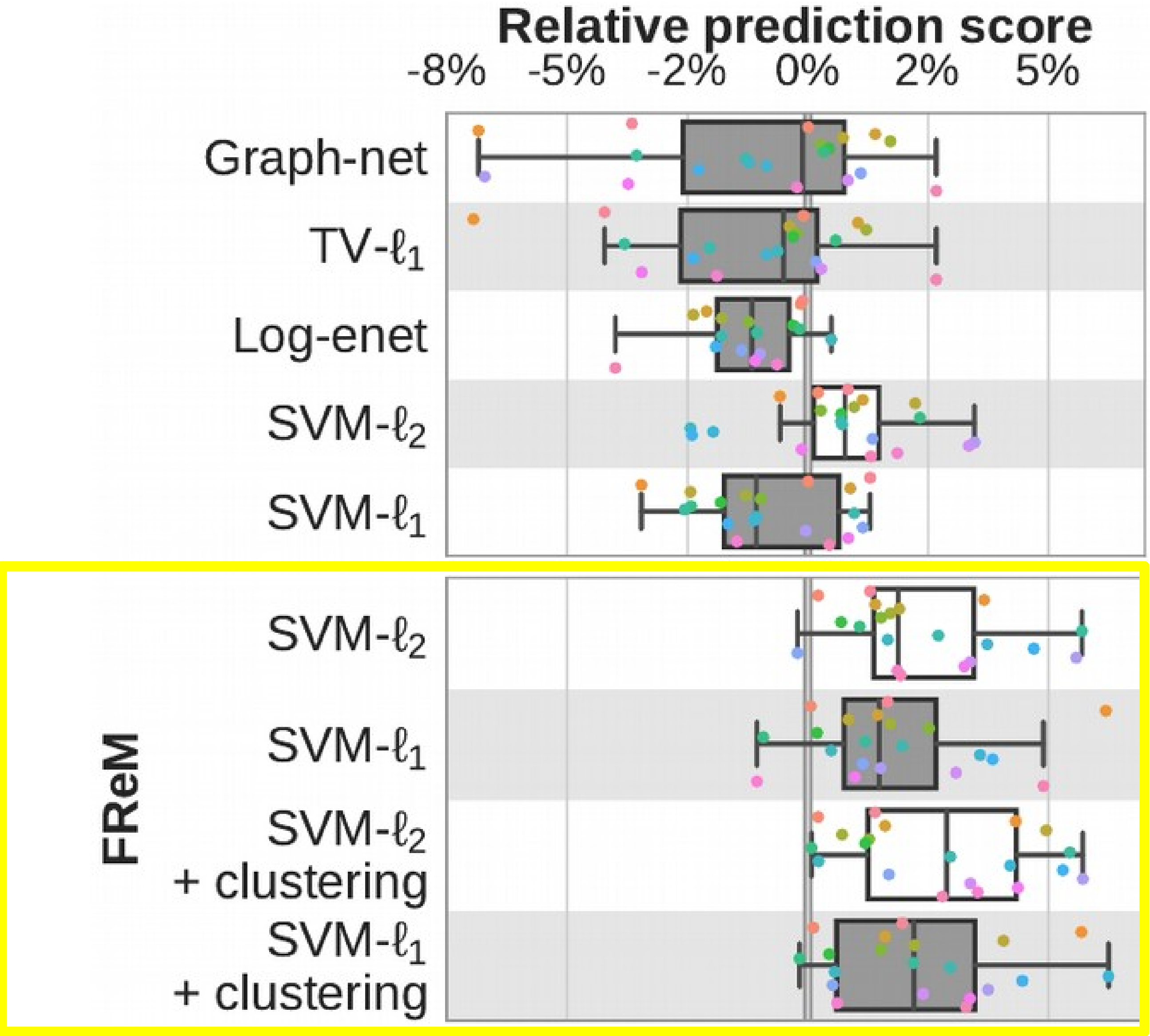


Computationally efficient structure



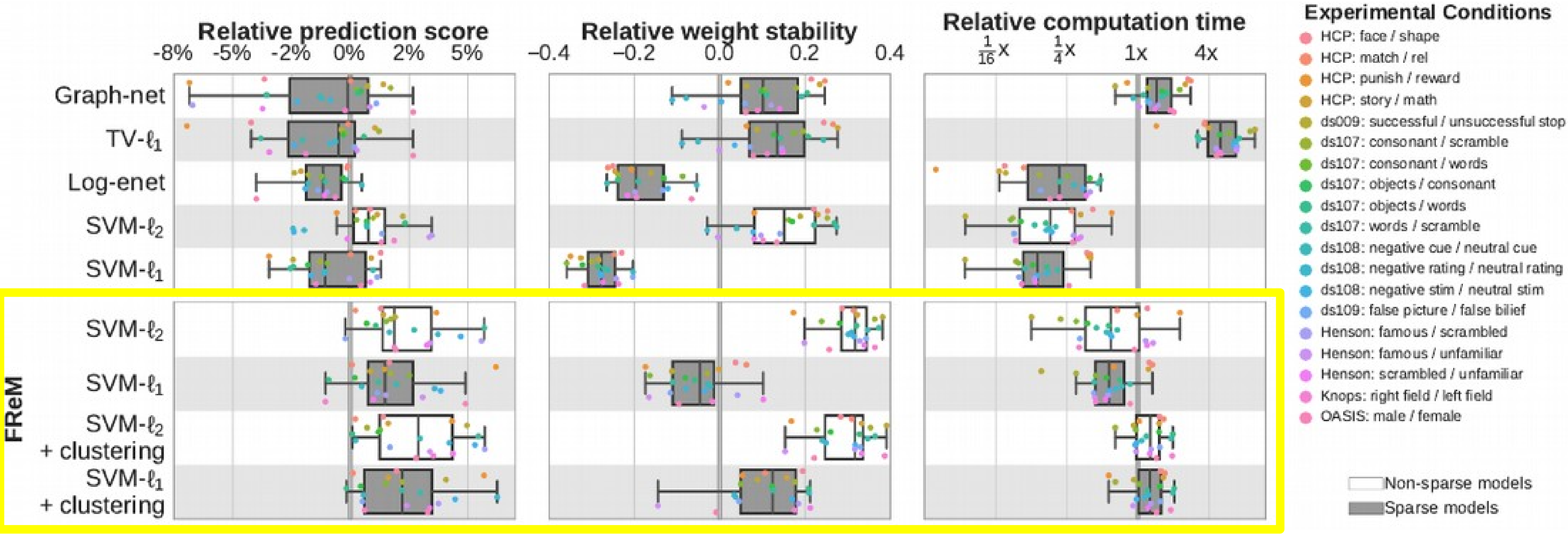
Effect on prediction accuracy

[Hoyos Idrobo et al PRNI 2015, Neuroimage 2017, PAMI 2018]



"fast regularized ensembles of models"

More results



[Hoyos Idrobo et al PRNI 2015, Neuroimage 2017, PAMI 2018]

Outline

- A causal framework for brain activity decoding
- Dimension reduction for images
- Fast regularized ensembles of Models
- Statistical inference for high-dimensional models

Statistical inference on w

- Inference: find {j: $\mathbf{w}_j > 0$} with some statistical guarantees
- Standard solutions for high-dimensional linear models ($p \cong n$)
  - Corrected ridge [Bühlmann 2013]
  - Desparsified Lasso [Zhang & Zhang 2014, Montanari 2014]
  - Multi-split [Meinshausen 2009], knockoffs [Candès 2015+]
- Fail for $p \gg n$

Desparsified Lasso

- **Objective:** construct confidence bounds on the coefficients of $\boldsymbol{w}^*$
- **Principle:** [Zhang & Zhang 2014 Series B Stat Meth]
  - construct an unbiased estimator of $\boldsymbol{w}^*$ (generalization of $\hat{\boldsymbol{w}}^{\text{OLS}}$)
  - compute its covariance matrix
- **Heuristic argument:** in low dimension we can prove that:

$$\hat{w}_j^{\text{OLS}} = \frac{\mathbf{z}_j^\top \mathbf{y}}{\mathbf{z}_j^\top \mathbf{x}_j} \quad ,$$

where $\mathbf{z}_j$ is the residual of the OLS regression of $\mathbf{x}_j$ versus $\mathbf{X}^{(-j)}$:

$$\mathbf{z}_j = \mathbf{x}_j - \mathbf{P}_{\mathbf{X}^{(-j)}} \mathbf{x}_j \quad ,$$

where $\mathbf{P}_{\mathbf{X}^{(-j)}}$ is the projection onto $\text{Span}(\mathbf{X}^{(-j)}) \subset \mathbb{R}^{p-1}$

Desparsified Lasso

- **Desparsified Lasso estimator:** when $n < p$, $\mathbf{z}_j$ is the residual of a Lasso-CV regression of $\mathbf{x}_j$ vs $\mathbf{X}^{(-j)}$ and the debiased estimator is:

$$\hat{w}_j = \frac{\mathbf{z}_j^\top \mathbf{y}}{\mathbf{z}_j^\top \mathbf{x}_j} - \sum_{k \neq j} \frac{\mathbf{z}_j^\top \mathbf{x}_k \hat{w}_k^{(init)}}{\mathbf{z}_j^\top \mathbf{x}_j} \quad ,$$

  where $\hat{\boldsymbol{w}}^{(init)}$ is an initial non linear estimator of $\boldsymbol{w}^*$ (*e.g.*, Lasso)

- **Covariance:** the covariance matrix of this estimator is:

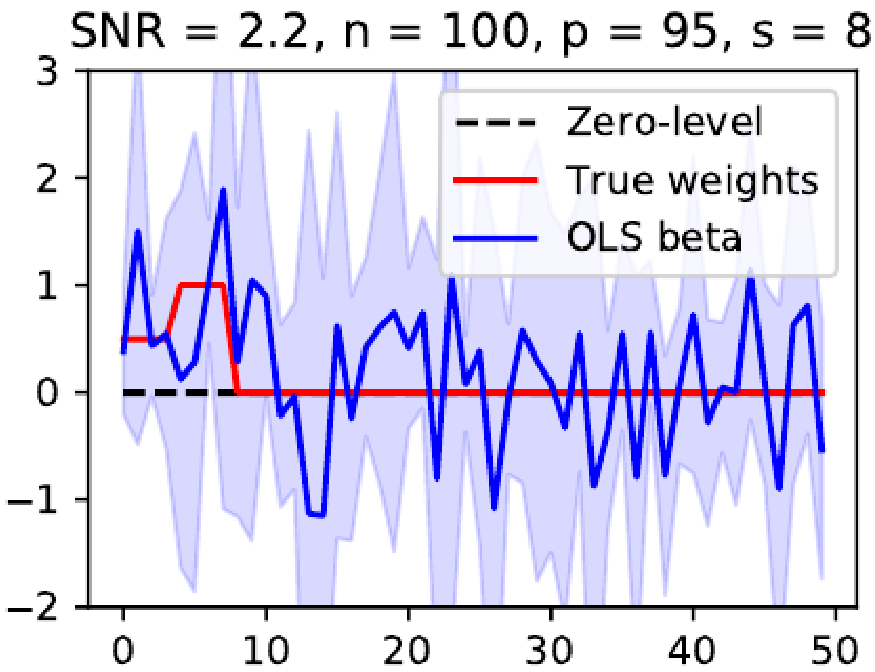
$$\Omega_{jk} = \frac{n \mathbf{z}_j^\top \mathbf{z}_k}{(\mathbf{z}_j^\top \mathbf{x}_j)(\mathbf{z}_k^\top \mathbf{x}_k)}$$

- **Confidence bounds:** under few assumptions (Dezeure et al. [2015]):

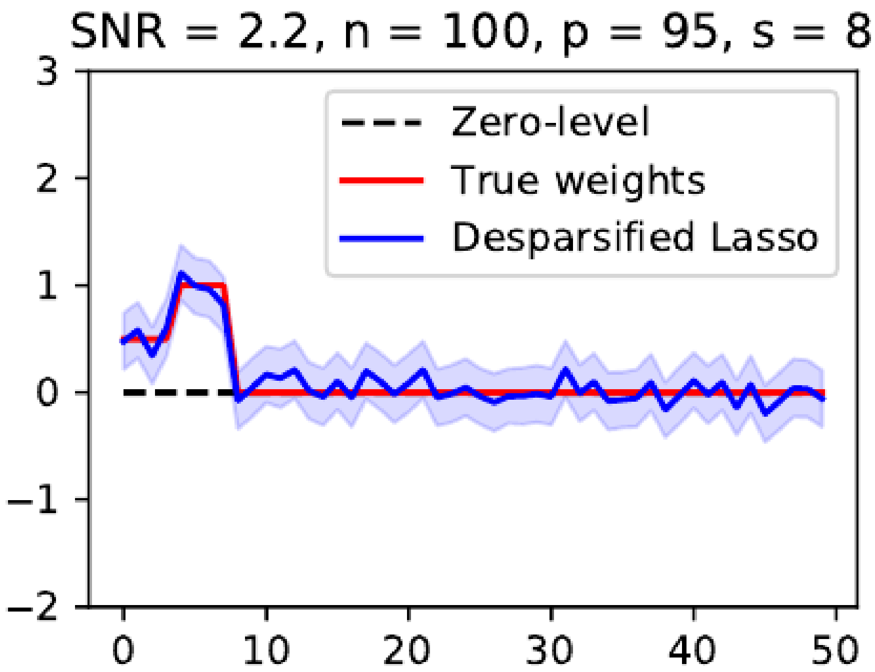
$$\boxed{\sigma_*^{-1} (\Omega_{jj})^{-1/2} (\hat{w}_j - w_j^*) \sim \mathcal{N}(0, 1)}$$

Preliminary assessment

- **Comparing OLS and Desparsified Lasso solutions:**



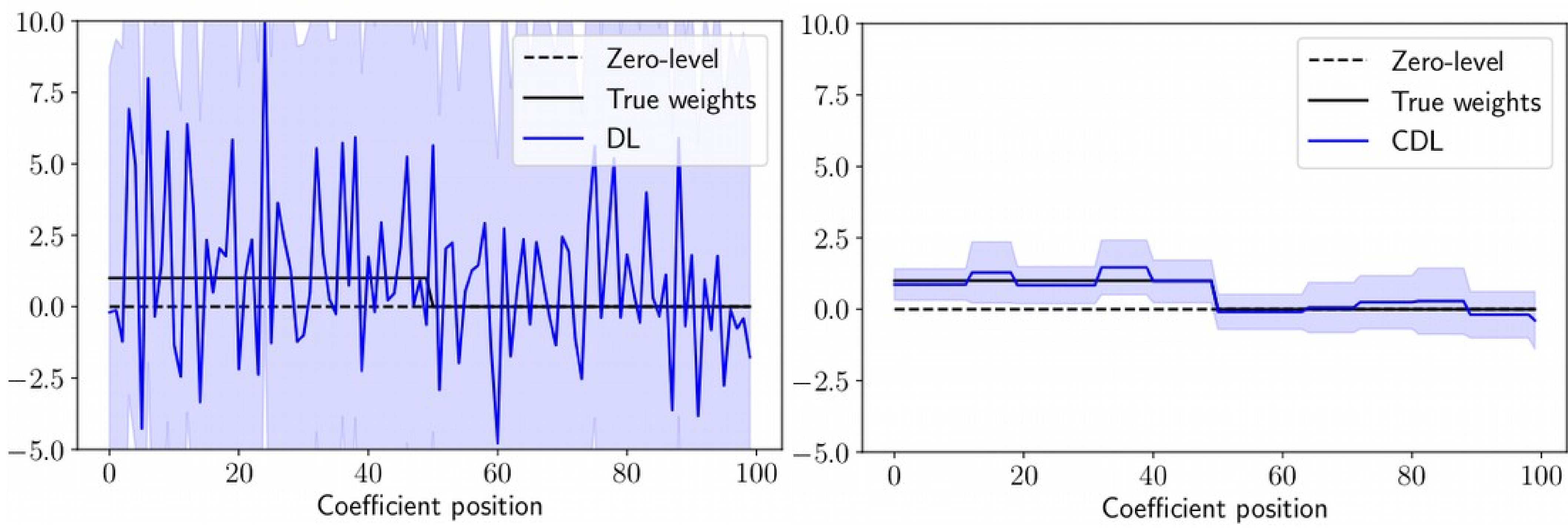
OLS regression when $p \approx n$



Desparsified Lasso when $p \approx n$

Large p → need dimension reduction

p=2000, n=100



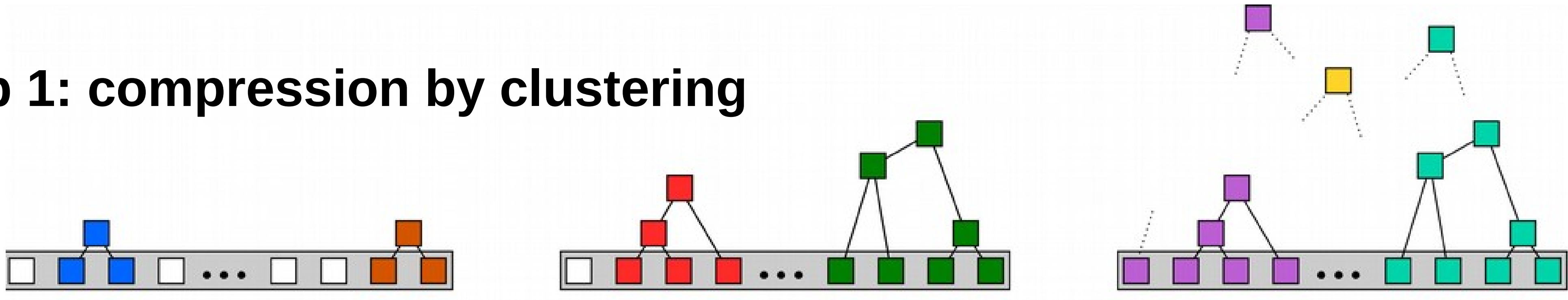
Large p kills statistical power

CDL tames variance

[Chevalier et al. subm. To MICCAI]

Adaptation to brain imaging

Step 1: compression by clustering



Step 2: inference on compressed representations

$$\sigma_*^{-1}(\Omega_{jj})^{-1/2}(\hat{w}_j - w_j^*) \sim \mathcal{N}(0,1)$$

***C**lustered*
***D**esparsified*
***L**asso*

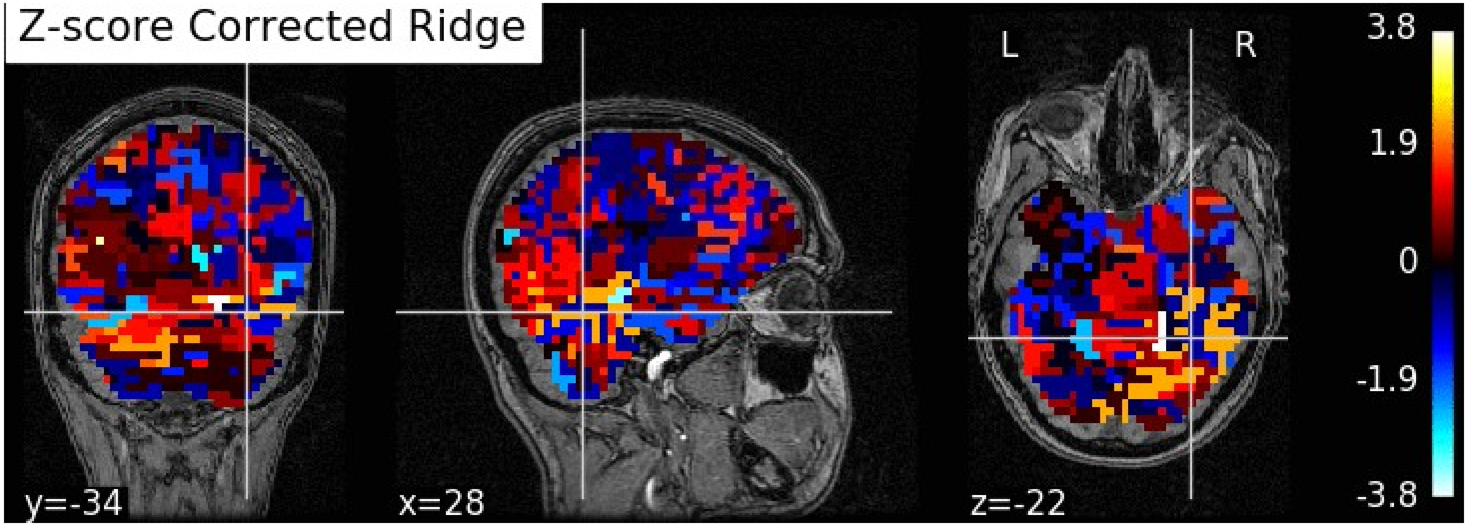
Step 3: ensembling iterate with different parcellations
→ **aggregate p-values** (*see also* FReM)

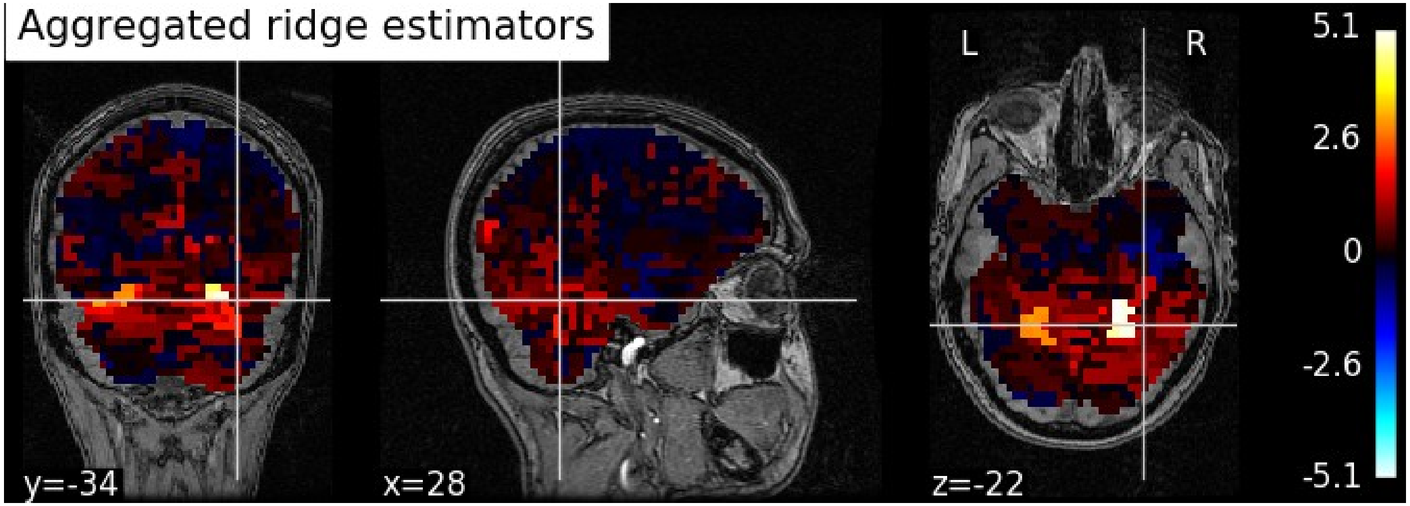
***E**nsemble of*
***C**lustered*
***D**esparsified*
***L**asso*

From CDL to ECDL

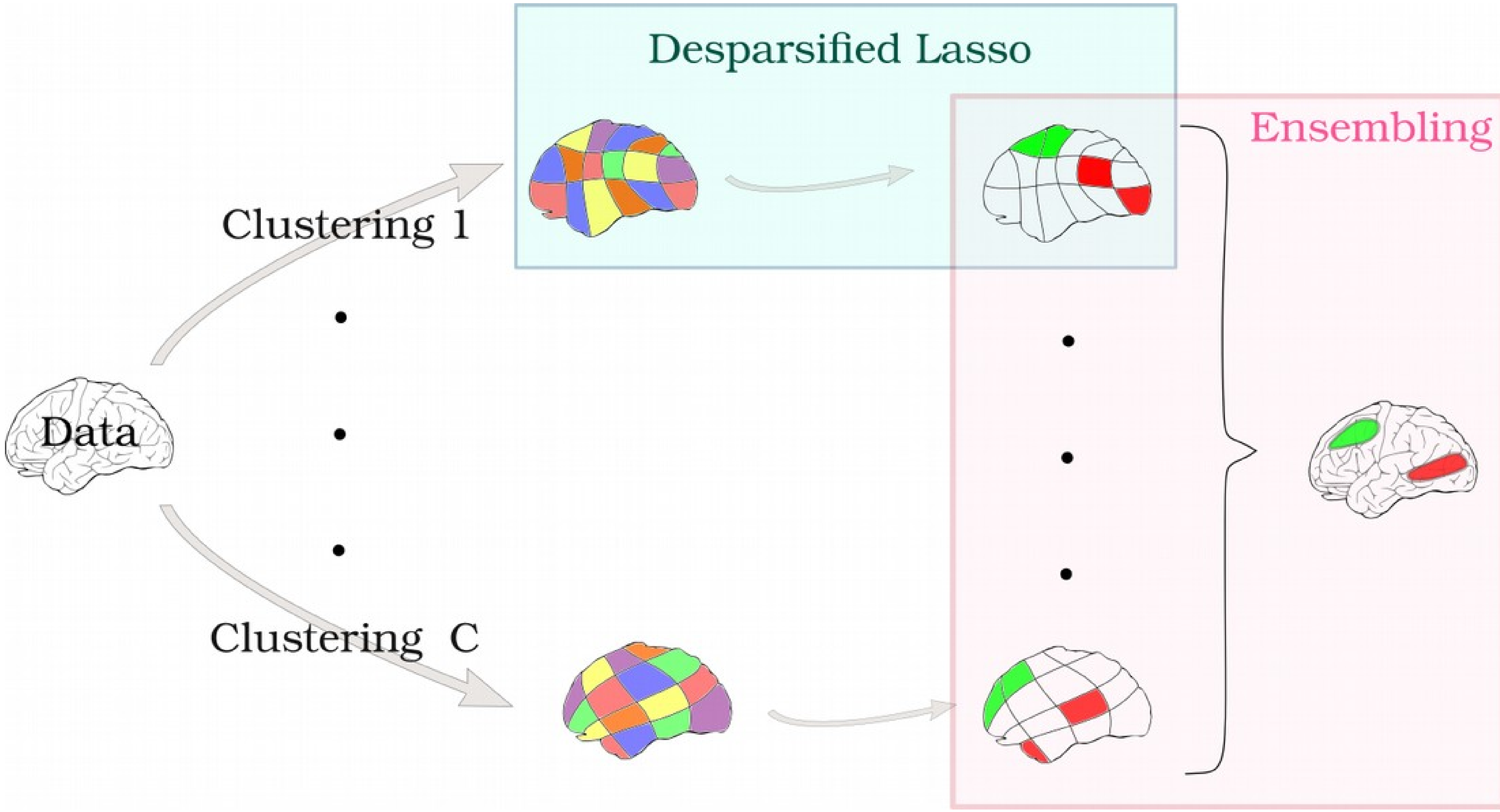
DL p-values
from different
clusterings

aggregation





ECDL for brain imaging



δ-error control

Definition (δ-null region)

The set of covariates that verify the δ-null hypothesis in the true model is called the δ-null region and is denoted by N^δ:

$$N^\delta = \{j \in [p] : \forall k \in [p], d(j,k) \leq \delta \implies \mathbf{w}^*_k = 0\} \quad .$$

Definition (Rejection region)

Given a family of p-values $\hat{p} = (\hat{p}_j)_{j \in [p]}$ and a threshold $\alpha \in (0,1)$, we call rejection region at level α for the family $\hat{p}$ the indexes of covariates whose corresponding p-value are lower than α and denote it by $R_\alpha(\hat{p})$:

$$R_\alpha(\hat{p}) = \{j \in [p] : \hat{p}_j \leq \alpha\} \quad .$$

δ-error control

Definition (δ-type 1 error region)

Given a family of p-values $\hat{p} = (\hat{p}_j)_{j\in[p]}$ and a threshold $\alpha \in (0,1)$, the δ-type 1 error region (or erroneous rejection region with tolerance δ) at level α is the set of covariates indexes belonging both to the δ-null region and to the rejection region at level α:

$$\mathscr{E}_\alpha^\delta(\hat{p}) = N^\delta \cap R_\alpha(\hat{p}) \ .$$

Definition (δ-family wise error rate)

Given a family of p-values $\hat{p} = (\hat{p}_j)_{j\in[p]}$ and a threshold $\alpha \in (0,1)$, the δ-FWER, denoted $FWER_\alpha^\delta(\hat{p})$, is the probability that the δ-type 1 error region at level α is not empty:

$$FWER_\alpha^\delta(\hat{p}) = \mathbb{P}(|\mathscr{E}_\alpha^\delta(\hat{p})| \geq 1) = \mathbb{P}(\min_{j\in N^\delta} \hat{p}_j \leq \alpha) \ .$$

δ-FWER control

Definition (δ-FWER control)

We say that the family of p-values $\hat{p} = (\hat{p}_j)_{j \in [p]}$ *controls the* δ*-FWER if, for all* $\alpha \in (0, 1)$*:*

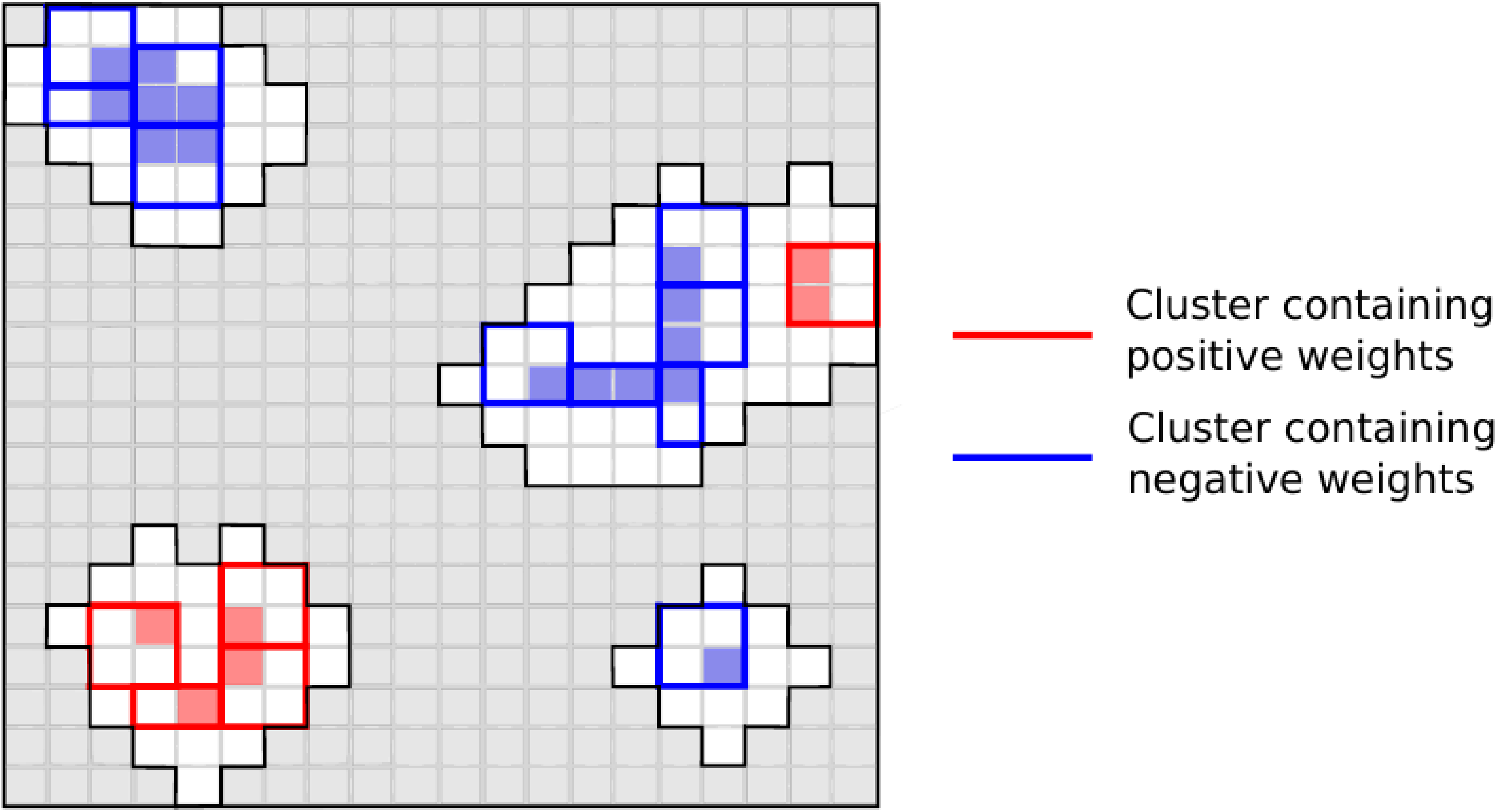
$$FWER_{\alpha}^{\delta}(\hat{p}) \leq \alpha \ .$$

Proposition

Under the assumptions for the vanilla Desparsified Lasso and assumptions on the weight map and on the data structure we have the following result:

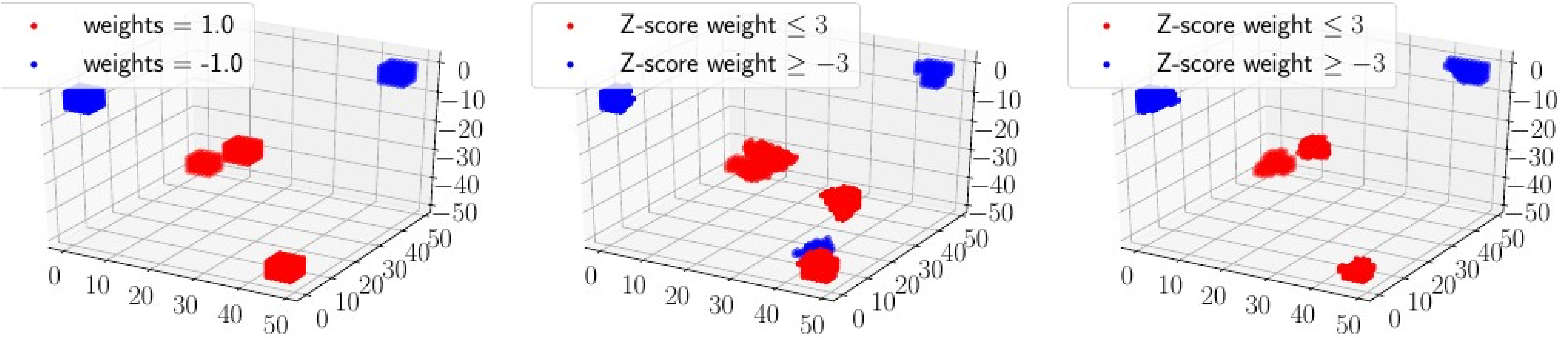
If the diameters of the clusters are all smaller than δ *then the p-value family computed through the ECDL algorithm controls the* δ*-FWER.*

δ-FWER-control



Simulations: ECDL > CDL

- **Parameters:** $n = 400$, $H = 50$, $p = H^3 = 125\,000$, $\sigma_{\mathrm{smth}} = 2$
- **Noise:** $\mathrm{SNR}_y = 3$ by taking $\sigma_* = 8$
- **Hyperparameters:** $C = 500$ and $B = 25$
- **Weights:**



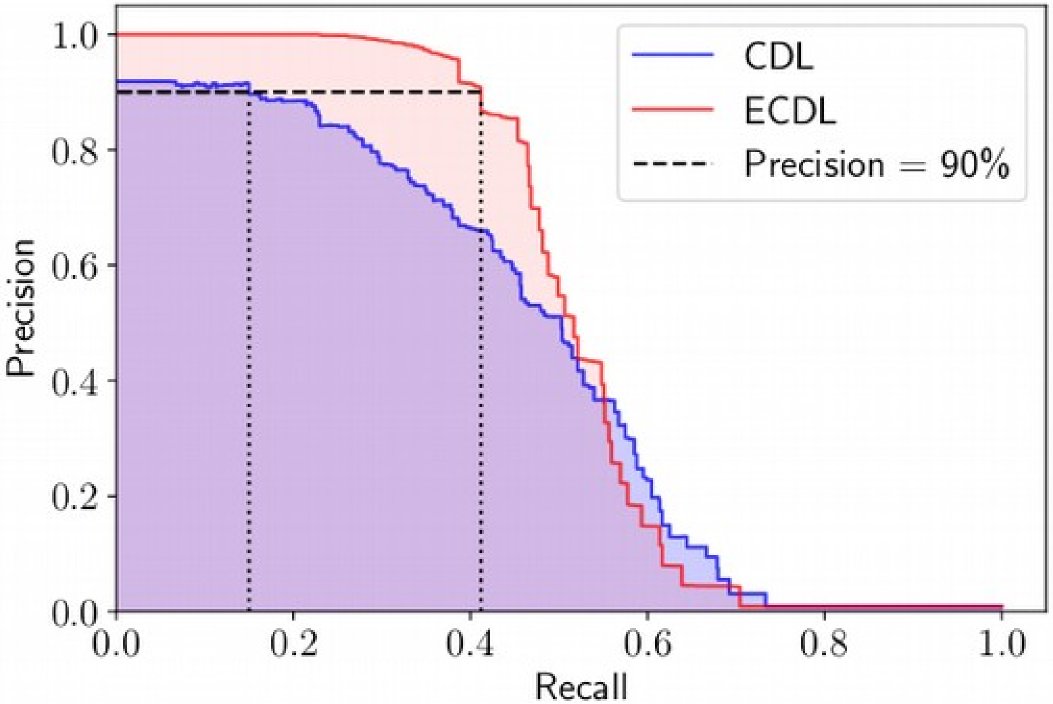
(a) weight vector: $\mathbf{w}^*$ (b) CDL (c) ECDL

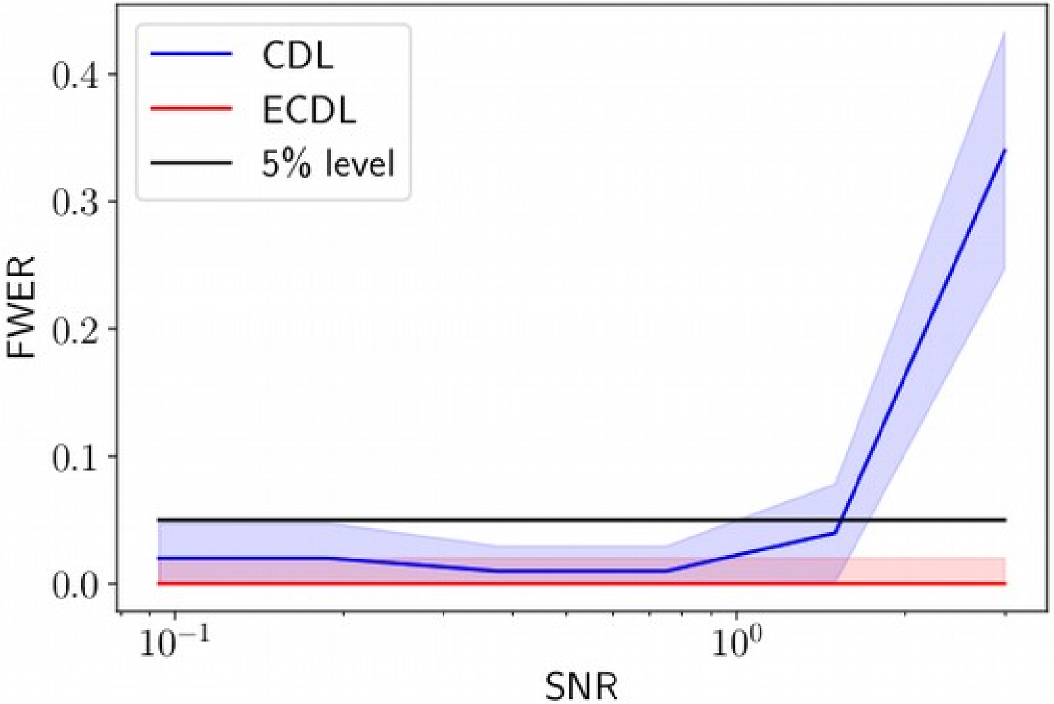
[Chevalier et al. MICCAI 2018]

Experiments: PR and FWER control

$$\text{Recall} = \frac{\text{Number of true positive}}{\text{Size of the active set}} \quad \text{Precision} = \frac{\text{Number of true positive}}{\text{Number of discoveries}}$$

$$\text{FWER} = \text{Prob}(\text{Number of false positive} \geq 1)$$





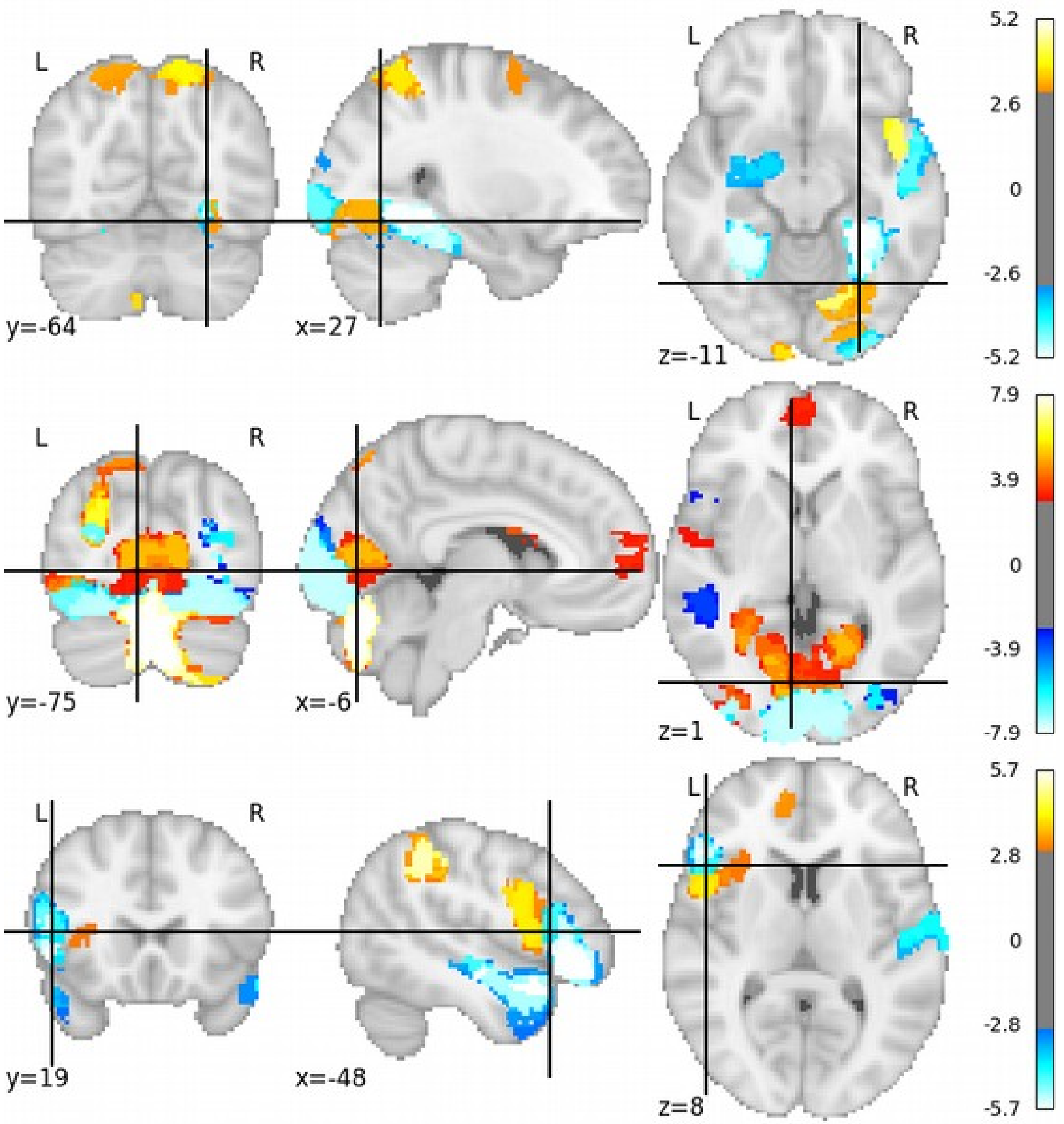
Better PR with ECDL

+ More accurate FWER control

[Chevalier et al. MICCAI 2018]

Effects on real data

HCP dataset, n=900



Social cognition

Visual feature discrimination

Language vs maths

[Nguyen et al. IPMI 2019, Chevalier et al. MICCAI 2018]

Conclusion

- Causal reasoning →
  conditional association analysis
- Large-p data bring challenges:
  - Computation cost
  - Difficulty of statistical inference
- Solutions: ensembling, subsampling, compression
- Efficient stochastic regularizers
- Ongoing comparison with knockoff

[Nguyen et al. IPMI 2019]

WIP

- Classification setting
- Use of bootstrap

[Aydore et al. subm]

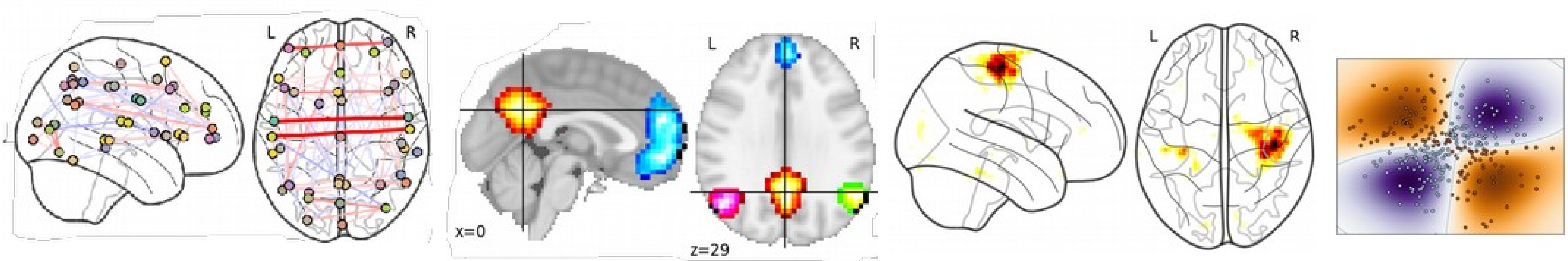
From good ideas to good practices: software

scikits learn machine learning in Python

ni learn

MNE
MEG + EEG ANALYSIS & VISUALIZATION

- Machine learning in Python
- Machine learning for neuroimaging
  http://nilearn.github.io
- BSD, Python, OSS
  - Classification of (neuroimaging) data
  - Network analysis



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